HEMISPHERIC CONTRIBUTIONS TO MOTOR CONTROL AND
ARM PREFERENCE IN UNILATERAL STROKE PATIENTS

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ABSTRACT

Sensorimotor stroke is the leading cause of permanent disability in United States, often resulting in contralesional hemiparesis characterized by weakness, spasticity, and abnormal synergies in the side contralateral to the damaged hemisphere. Brain damage that results from stroke tends to be predominantly unilateral, due to the hemisphere specificity of cerebral circulation. While a great deal of research has focused on understanding the deficits in the contralateral limbs, very little attention has been given to the fact that the hemispheres are not functionally symmetric for sensorimotor processing. Sainburg et al have previously shown that each hemisphere contributes specific mechanisms to the control of both the arms: the left hemisphere for control of movement trajectory, and the right hemisphere for stabilizing the limb in a steady state position. We propose that each hemisphere imparts its specialized control processes to each arm. A clear prediction of this hypothesis is that damage to the right or left hemisphere due to stroke, should produce hemisphere specific deficits in both the ipsilesional and contralesional arms of stroke patients. In a series of three experiments, we tested whether 1) the contralesional arm motor deficits produced by unilateral stroke patients vary based on the hemisphere of damage and severity of impairment, 2) damage to one hemisphere produces hemisphere-specific motor adaptation deficits in both the arms of the stroke patients and 3) Spontaneous arm selection for reaching tasks are dependent on the hemisphere that is damaged. Our results support our hypothesis that left and right hemisphere damage produces hemisphere-specific deficits in motor control that affect motor adaptation in both the ipsilesional and contralesional arms of stroke patients: While
left hemisphere damage produces significantly higher initial direction errors and hand
path curvatures (trajectory measures), right hemisphere damage produces significantly
higher distance and final position errors during reaching movements. In addition, mild to
moderately paretic patients with right hemisphere damage preferred to use their
contralesional arm significantly less than the respective arm of their age matched control
group. In contrast, mild to moderately paretic patients with left hemisphere damage
preferred to use their contralesional right arm to the same extent as the control group’s
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CHAPTER 1
INTRODUCTION

Stroke is the leading cause of permanent disability in the United States (Casper et al., 2003), predominantly due to the contralesional hemiparesis or hemiplegia. Contralesional hemiparesis refers to weakness, abnormal synergies, and spasticity on the side of the body opposite to the damaged hemisphere. Severe stroke might produce contralesional hemiplegia, which refers to total paralysis of the arm, leg on the side opposite to the damaged hemisphere. The deficits occur predominantly in the contralateral side because of the crossed organization of the motor system (Brinkman and Kuypers, 1972; Kuypers, 1964). Thus, damage to one hemisphere produces deficits predominantly on the other side of the body. Several studies have focused on understanding these deficits and on developing novel rehabilitation protocols (Mark and Taub, 2004; Volpe et al., 2001; Whitall et al., 2000) to help improve the motor function of stroke patients. But, there has been very little attention given to the fact that the hemispheres are not functionally symmetric for sensorimotor processing, and that the motor deficits that emerge due to stroke could be different based on the hemisphere that is damaged. In fact, there are several factors that could influence the contralesional motor deficits demonstrated by unilateral stroke patients: hemisphere of damage, lesion location within each hemisphere, severity of impairment of each patient, demographic info of stroke patients, and phase of stroke (chronic or acute). Thus, an understanding of the specific deficits produced by stroke patients is extremely crucial and essential to
maximize recovery following physical rehabilitation. This dissertation research aims to better understand the specific contributions of each hemisphere by examining the motor deficits and arm preference in unilateral stroke patients.

**Contralesional & Ipsilesional deficits following unilateral stroke**

As unilateral stroke predominantly produces contralesional motor deficits, several previous studies in the literature have focused on understanding the specific contralesional deficits produced by unilateral stroke. Several earlier studies have attributed contralesional impairments to reduced agonist and antagonist muscle activations (El-Abd et al., 1993), hyperactive reflexes (Mizrahi and Angel, 1979) or presence of abnormal synergies (Dewald et al., 1995). However, more recent studies have also demonstrated coordination deficits in the contralesional arm of stroke patients (Beer et al., 2000; 2004; Levin, 1996). For example, when patients were asked to perform a simple reaching movement to 16 targets located radially around a start circle, it was observed that the stroke patients made systematic direction errors with their paretic arm, when compared to the non-paretic arm or control group, and such direction errors were attributed to the failure to predictively account for dynamic intersegmental interactions (Beer et al., 2000). Other studies that have largely focused on the kinematics of the contralesional arm performance have also reported problems in coordinating the actions of the elbow and shoulder joints during reaching movements (Cirstea and Levin, 2000; Levin, 1996). However, none of these studies dissociated the contralesional arm performance of stroke patients based on the hemisphere of damage.

Interestingly, several early studies from Haaland and co-workers (1989a; 1989b; 2004) demonstrated that unilateral stroke also produces ipsilesional deficits, albeit not as
strong as contralesional deficits; and were found to vary based on hemisphere of damage.

For example, Haaland and Harrington (1989a) observed that when unilateral stroke patients performed discrete aiming movements with their ipsilesional arm, patients with left hemisphere damage demonstrated longer reaction time, and higher errors in initial movement when compared to healthy controls. In contrast, the patients with right hemisphere damaged group were as accurate as the controls in all the measures. However, when the patients performed a reciprocal tapping task (Haaland and Harrington, 1989b), which required closed-loop processing, it was observed that only patients with right hemisphere damage made larger constant errors. The authors attributed these findings to a lateralization of open-loop control mechanism to the left hemisphere, and a closed-loop control mechanism to the right hemisphere. But, in a later study examining the closed-loop mechanism in a reaching task in which the target location jumped unexpectedly during the movement, with and without visual feedback, the right hemisphere damaged patients were able to correct their movements as well as the controls when the visual feedback was present, but made significantly high final position errors without vision (Haaland et al., 2004). These findings indicate that the right hemisphere damaged patients are able to correct their movements with the use of visual feedback. The authors found these findings to be inconsistent with their proposed hypothesis of lateralized open loop and closed-loop processing to each hemisphere.

Nevertheless, the existence of ipsilesional deficits as demonstrated by these studies reveal that each hemisphere plays a crucial role in contributing to the control of both arms.

Functional neuroimaging studies that followed these behavioral studies provided evidence of ipsilateral activations when the participants performed sequential finger
apposition movements (Kawashima et al., 1996; Kim et al., 1993). For example, in Kim’s study (1993), it was observed that when participants performed sequential finger apposition movements under a Nuclear Magnetic Resonance imaging scanner, there was a significant contralateral activation when right- and left-handed participants performed the task with their right hand. However, the ipsilateral activation (left motor cortex) was significantly high when the left-handed performed the task with their left hand, and even more for the right-handed participants when they performed the task with their left hand. They attributed these findings to a predominant control of the left hemisphere in planning and execution of movements in both the arms. These functional imaging studies provided the initial evidence of a bi-hemispheric contribution to unilateral finger movements. That is, each hemisphere contributes to unilateral planning and execution of movements in both the arms. However, an important question remained: are the contributions from each hemisphere symmetric or is each hemisphere specialized for distinct motor control mechanisms similar to there being specific regions of the brain that are specialized for speech, memory etc.

*Hemisphere-specific control mechanisms*

Our earlier studies in young healthy adults (Bagesteiro and Sainburg, 2002; 2003; Sainburg and Kalakanis, 2000) documented limb specific advantages for the dominant and nondominant arms during simple reaching movements and during inertial load compensation conditions. For example, in the study by (Bagesteiro and Sainburg, 2002), when participants were asked to reach to a target that required high interaction torques at the elbow joint, the dominant arm performed better than the nondominant arm by making significantly lower initial direction errors and hand path curvatures, suggesting a
specialization for the dominant system for intersegmental coordination. Based on these early studies, Sainburg (2002) proposed a model of motor lateralization, which posits that each hemisphere is specialized for distinct control mechanisms: left hemisphere is critical for predicting limb and task dynamics, and the right hemisphere is specialized for stabilizing the limb in the final position through impedance control mechanisms (see Sainburg, 2010 for a review). Our studies in stroke patients examining the ipsilesional arm performance during single (Schaefer et al., 2007) and multi-joint reaching (Schaefer et al., 2009b) movements provided the initial evidence for this model. For example, in the study by Schaefer et al (2009b), stroke patients were asked to perform reaching movements to three targets (lateral, center, medial) that require different intersegmental coordination. These stroke patients were matched in age, gender and education to the control participants, and the stroke groups were matched on the severity of impairment and the specificity of lesion location / volume. It was observed that left, but not right hemisphere damaged group demonstrated deficits in initial direction errors, and hand path curvature when compared to the control group. In contrast, right, but not left hemisphere damaged group demonstrated deficits in final position accuracy when compared to the control group. These results suggest that left hemisphere may be specialized for control of trajectory of reaching movements, whereas right hemisphere may be specialized for stabilizing the limb in final position, as postulated by our model. These studies offered the preliminary evidence for hemisphere-specific deficits in the ipsilesional arm of unilateral stroke patients.

Our next step was to examine if such hemisphere-specific deficits exist when adapting to a visuomotor rotation task. Substantial research has indicated that motor
adaptation or motor learning involves evaluating the costs of different variables such as task error or energetic efficiency (Pouget & Snyder, 2000; Wolpert et al., 2001). Schaefer et al (2009a) used a visuomotor rotation task, where the cursor was dissociated from the finger by 30°, to examine whether each hemisphere relies on different error signals for motor adaptation. As our model posits a right hemisphere specialization for final position accuracy, they predicted that patients with right hemisphere damage should improve initial direction errors during the adaptation phase, but not final position accuracy; and as left hemisphere is thought to be specialized for trajectory of movements, they predicted that patients with left hemisphere damage should improve final position accuracy, but not trajectory measures. Their results demonstrated that left hemisphere damage interfered with the patient’s ability to adapt to the initial direction, but not with the ability to adapt to the final position. In contrast, right hemisphere damage interfered with online corrections to the final position of the limb. These results offered further support to our model by suggesting that the control of trajectory and steady-state limb position may be specialized to the left and right hemispheres, respectively.

It should however be mentioned that most of earlier stroke studies examined only the ipsilesional arm performance of unilateral stroke patients. This was because patients were severely paretic in their contralesional arm, and spasticity, weakness, and high tone could mask the performance asymmetries in the contralesional limb following unilateral stroke; thus making it difficult to isolate the hemisphere-specific deficits from the spasticity or other abnormalities that emerges due to stroke. This could also be why several previous studies (Beer et al., 2000; 2004; Cirstea and Levin, 2000; Levin, 1996) that examined the contralesional arm performance of stroke patients during reaching
movements, have not observed the hemisphere-specific deficits demonstrated by the stroke patients in our ipsilesional studies. However, as each hemisphere has a higher contralateral preponderance due to the crossed organization of our motor system (Kuypers, 1964), we expect that the deficits in the contralesional arm would strongly reflect the deficiencies in the specific control mechanism of the damaged hemisphere. In my dissertation research, we seek to examine whether our model of motor lateralization could predict the contralesional arm motor deficits in unilateral stroke patients. We limit our stroke patients to those with mild to moderate impairment in their contralesional arm so that they have voluntary control of their elbow and shoulder movement, and are able to complete the entire experimental task without being fatigued.

Specific aims of this dissertation

The purpose of this dissertation was to determine the specific contributions of each hemisphere to arm control and arm preference in unilateral stroke patients. Based on our model of motor lateralization (Sainburg, 2005), we expected that damage to each hemisphere would produce distinct deficits in stroke patients: left hemisphere damage may impair the ability to control the trajectory of reaching movements, whereas right hemisphere damage may impair the ability to stabilize the limb in the final position. In our first study, we tested our model by examining the reaching performance of unilateral stroke patients when they performed a three-directional reaching movement with their contralesional arm. In all our studies the stroke patients are matched demographically to the control participants, and the left and right hemisphere damaged stroke groups are matched by the severity of impairment, lesion location and lesion volume.
As our model is bi-hemispheric; that is, each hemisphere contributes to planning and execution of movements in both the arms, damage to one hemisphere should produce hemisphere-specific deficits in both the arms of unilateral stroke patients. In our second study, we tested this by examining the reaching performance of both the arms of unilateral stroke patients when they adapt to a novel visuomotor rotation task, where the cursor will be dissociated by 30° from the arm; and the participants will adapt to this rotation over 160 trials with each arm. Based on our previous studies in stroke patients (Mutha et al., 2011; Schaefer, Haaland and Sainburg, 2009a), and based on our model, we predict that the left hemisphere damaged patients will demonstrate difficulty in adapting to the visuomotor rotation, whereas right hemisphere damage patients will have no difficulty in adapting to the rotation, but may demonstrate difficulty in stabilizing their limb in the final position.

It has been widely understood that when patients fail to use their affected arm, learned non-use sets in, thereby deteriorating the impairment further and losing the gains attained during physical rehabilitation (Mark and Taub, 2004). So, it is essential that patients continue to use their contralesional arm post-rehabilitation to maximize or retain functional outcome. However, several previous studies examining the arm use during activities of daily living (Haaland et al., 2012; Rinehart et al., 2009) have suggested that right hemisphere damaged patients demonstrate decreased contralesional arm (left arm) use when compared to left hemisphere damaged patients using their contralesional arm (right arm). However, activities of daily living may be biased by habitual patterns of doing the task, like opening a jar, which is usually done by the right hand. Our final study was designed to determine if the arm preference in unilateral stroke patients vary based
on hemisphere of damage and target location in workspace. We present a horizontal array of 32 targets in a workspace in front of the stroke patients, and the patients can choose either of their arms to reach to the targets, when they are presented one at a time. This experimental design would give us an opportunity to comprehensively examine whether the arm preference in stroke patients is modulated by hemisphere of damage and if they do, we can also examine if the target location in the workspace plays a crucial role in arm preference. We believe that the findings from this study could be used to structure rehabilitation in a way to facilitate training in the regions of lesser contralesional arm reaches.

Overall, these studies in my dissertation are geared towards understanding the specific contributions of each hemisphere to arm control and arm preference in unilateral stroke patients. We believe that the findings from these studies would be crucial for a better understanding of the motor deficits produced by unilateral stroke, and could be used to develop novel rehabilitation protocols in the future.
CHAPTER 2

CONTRALESIONAL MOTOR DEFICITS AFTER UNILATERAL STROKE

REFLECT HEMISPHERE-SPECIFIC CONTROL MECHANISMS

Introduction

A large body of research has now established that the two cerebral hemispheres show a considerable degree of lateralization, or a specialization for controlling different aspects of behavior. While such neural lateralization has been characterized primarily through studies of perceptual and cognitive processes, behavioral and neuroimaging studies have raised the possibility that the right and left hemispheres play different roles in the motor control of either arm. Based on our work in young healthy individuals, we have proposed a model of motor lateralization in which each hemisphere has become specialized for different aspects of motor control such that the “dominant/left” hemisphere is critical for predicting limb and task dynamics, and the opposite, “nondominant/right” hemisphere is critical for specifying steady state limb positions through impedance control mechanisms (see Sainburg 2010 for a review). Our recent work in patients with unilateral brain damage (Schaefer et al., 2007; 2009a; 2009b; 2012; Mutha et al., 2010; 2011a, b) and findings from other prior studies (Harrington and Haaland, 1991; Haaland et al., 2004; Winstein and Pohl 1995; Bernspang and Fisher, 1995), have provided a confirmation for hemispheric specialization for movement control. For example, our study examining movement coordination in right-handed stroke patients (Schaefer et al., 2009b) showed a clear double dissociation between hemisphere
status (Healthy/Hemisphere Damage) and arm (Right/Left) for different features of movement. Patients with left hemisphere damage (LHD), but not right hemisphere damage (RHD), showed errors in direction and linearity of reaching movements that were associated with poor coordination of intersegmental dynamics. In contrast, RHD patients made well-coordinated and fairly straight movements, but showed large and highly variable final position errors. In more recent studies, we have significantly expanded on these initial results by demonstrating differential deficits in motor adaptation and error correction mechanisms in LHD and RHD stroke patients (Schaefer et al., 2009a, 2012; Mutha et al., 2011b). These studies have consistently revealed a deficit in predictive control following LHD and final position control following RHD, in line with the predictions of our model.

Our stroke studies were initiated as a critical test of this framework of hemispheric specialization for movement. We reasoned that if a hemisphere contributes its specialization to the movements of both arms, then motor deficits following damage to that hemisphere should be evident even if the ipsilesional arm in stroke patients is used to perform the task. Our studies therefore almost always required subjects to use their ipsilesional arm. However, given the crossed organization of the motor system, motor deficits following stroke are most prominent on the contralesional side. Therefore most studies in stroke patients have, unsurprisingly, been dedicated to understanding the nature of these contralesional motor deficits. These studies have shown that while weakness and spasticity are common with contralesional hemiparesis (Bobath, 1990), discoordination is also a major problem, particularly during point-to-point reaching tasks. For example, Beer et al. (2000; 2004) demonstrated systematic direction errors and poor interjoint
coordination with the contralesional arm in a 16-direction center out reaching task. In this task, every four directions comprised a quadrant in task space, and deficits were largest in the two quadrants, where intersegmental coordination requirements were greatest. Similarly, Levin (1996) and Cirstea and Levin (2000), showed that when stroke patients made horizontal plane reaching movements with the paretic arm, their movements were characterized by high variability and poor synchrony between elbow and shoulder joint motions. In light of these significant contralesional deficits, motor rehabilitation following stroke has also focused on improving the functioning of the contralesional arm.

In fact, newer therapeutic approaches such as constraint induced movement therapy (Taub et al., 1993; Mark and Taub, 2004) emphasize forced and repetitive use of the contralesional arm while also preventing use of the ipsilesional arm as a means to improve contralesional arm performance.

Despite such strong emphasis on understanding contralesional deficits and improving contralesional arm function, prior studies have not been coupled with the growing body of work that addresses hemispheric specificity for movement control mechanisms. One potential reason for this could be the concern that spasticity, weakness and variability in degree of impairment in the contralesional limb could mask any performance asymmetries. Nevertheless, understanding whether neural lateralization results in contralesional deficits that differ depending on the hemisphere of damage is of critical importance for assessing the impact of brain damage on function and also for designing rehabilitation protocols specific to the impaired limb. In this study, we ask whether the motor deficits in the contralesional arm of unilateral stroke patients reflect hemisphere-specific control mechanisms. Our model of lateralized control predicts clear
differences in contralesional motor deficits depending on the laterality of stroke, and therefore, this study also serves as a critical test of our model. We overcome the potential limitation of contralesional spasticity and reduced motor abilities by examining patients with only mild-to-moderate hemiparesis, defined by a score of more than 45 (out of a maximum possible 66) on the Fugl-Meyer Assessment of Upper Extremity Function (FM).

**Materials and Methods**

The Institutional Review Boards of the New Mexico Veteran Affairs Healthcare System (NM VA) and Hershey Medical Center (HMC) approved the study protocol. Prior to participation, all subjects gave informed consent according to the Declaration of Helsinki.

*Participants*

Eighteen unilateral stroke patients (9 LHD, 9 RHD; 1 RHD patient tested at HMC, others at NM VA) and twenty healthy control subjects [10 left healthy control subjects (LHC), 10 right healthy control subjects (RHC); all tested at NM VA] participated in this study. All control subjects were right-handed, and the stroke patients were right-handed prior to the incidence of stroke. Handedness was determined using the 10-item version of Edinburg inventory (Oldfield, 1971). All stroke patients were examined at least 6 months after stroke. All the subjects were screened and excluded based on history of (i) substance abuse and/or serious psychiatric diagnosis (e.g., psychosis); (ii) non-stroke neurological diseases for the stroke patients and all neurological diagnoses for the control subjects; and (iii) peripheral movement
restrictions, such as neuropathy or orthopedic disorders. Measures of hemiparesis (Fugl-Meyer et al., 1975), grip strength (Heaton et al., 2004), auditory comprehension (Kertesz, 1982), limb apraxia (Haaland and Flaherty, 1984), and visuospatial perception (Judgment of Line Orientation, Benton et al., 1994) were used to characterize the degree of impairment in stroke patients across different domains. A modified line cancellation test was administered to all subjects to test for visual neglect (Albert, 1973). Patients with 2 or more errors (out 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.

Table 2-1 summarizes the characteristics of each subject group. We restricted our patient population to only those with mild-to-moderate hemiparesis, as indicated by a score of more than 45 (out of a maximum possible 66) on FM score (Murphy et al., 2010). This was done to ensure that subjects could still perform the task with their contralesional arm, yet contralesional hemiparesis wasn't so extreme that it masked asymmetries between the arms. Further, we intentionally matched our LHD and RHD patients on the FM score to rule out the possibility that any group differences in arm reaching could be attributed to a difference in the degree of hemiparesis. The four groups were not significantly different on age \((F_{3,34} = 0.61, P = 0.61)\) or education \((F_{3,34} = 2.53, P = 0.07)\). Our groups were also fairly well balanced in terms of number of male and female participants \( \text{Chi-square (3,38) = 3.65; P = 0.30} \), suggesting that sex differences should be accounted for when comparing the LHD and RHD groups, which was the more critical comparison for the current study. However, we should state that our current sample sizes precluded our ability to examine sex as a factor in our analyses.
LHD and RHD subjects did not significantly differ in number of years post stroke (P = 0.28), lesion volume (P = 0.94) or contralesional grip strength (P = 0.18). LHD patients were more apraxic than RHD patients (P = 0.01), consistent with the observations of several prior studies (De Renzi et al., 1980; Haaland and Flaherty, 1984; Ochipa & Gonzalez Rothi, 2000). Auditory language comprehension was also significantly weaker in the LHD group (P = 0.04). However, we made sure that all subjects understood the experimental task they were asked to perform and task performance in general indicated that they did so. None of our participants had visual neglect, and visuospatial perception on Judgment of Line Orientation was not significantly different between the two stroke groups (P = 0.994).

High-resolution T1-weighted magnetic resonance images were obtained in stroke patients that were then normalized to a standard template in Montreal Neurological Institute (MNI) space using unified segmentation and normalization routines in SPM8 (Ashburner and Friston, 2005) and custom MATLAB scripts. Lesions were then reconstructed on the anatomical images in Adobe Photoshop, and the traced lesions were converted back into volumes using custom MATLAB code. Volumes from multiple patients within a group (LHD or RHD) were then overlaid in MRICron (Rorden and Brett, 2000) to create overlap images showing areas of damage common to all patients within a group. Figure 2-1 shows the superimposed lesion locations for all subjects within each stroke group. Colors of the shaded region denote the percentage of subjects in each group with damage in the corresponding area. It should be noted that the lesions are confined to either the left or right hemisphere. Importantly, all LHD and RHD patients had damage in at least one region of the sensorimotor motor system (Brodmann Areas 4,
6, 3, 1, 2 and/or internal capsule). Lesion volume was not significantly different between the two stroke groups (P = 0.94) and intrahemispheric lesion location was similar between the two groups.

**Experimental Setup**

The experimental setup is shown in Figure 2-2. Subjects sat facing a table with either their left or right arm supported over a horizontal surface by an air-jet system to eliminate the effects of gravity and reduce friction. A start circle, targets, and the subject’s fingertip (represented by an on-screen cursor) were displayed on a mirror using an HDTV positioned horizontally above the mirror. The mirror blocked the direct vision of the subject’s arm, but reflected the visual display to give the illusion that the display was in the same horizontal plane as the fingertip. Position and orientation of the forearm and upper-arm segments were sampled using a Flock of Birds (Ascension Technology®) system at 130 Hz. The positions of the index finger tip, lateral epicondyle of the humerus and the acromion, directly posterior to the acromio-clavicular joint were digitized using a stylus that was rigidly attached to a 6-DOF Flock of Birds sensor. As sensor data were received, the 3D position of the above-mentioned landmarks was computed using custom software, with the X-Y plane parallel to the tabletop. We used the computed X-Y coordinates of the fingertip to define the projected cursor position.

**Experimental task**

Stroke patients performed the task using their contralesional arm, and the control subjects used their left or right arm depending on their group – RHC or LHC, respectively. Three targets were presented at a distance of 16 cm from a fixed start position. The start circle was presented at a distance of 40 cm from the front edge of the
table, and 15 cm from the midline of body in the right or left hemispace depending on whether the participants use their right or left arm respectively to perform the task. The targets were oriented 50, 90 and 130 degrees relative to the horizontal edge of the table and were presented in the left hemispace for participants performing the task with their left arm (medial, central and lateral targets respectively) or in the right hemispace for participants performing the task with their right arm (lateral, central and medial targets respectively). Prior to the start of each trial, the cursor and the start circle were displayed on the screen. To initiate the trial, the subject brought the cursor into the start circle and after a 300 ms delay, one of the three targets appeared on the screen along with an audio-visual “go” signal, which cued the subjects to initiate a single, rapid movement toward the target. Feedback of the fingertip position was removed at this point and subjects were asked to reach the target with a minimum speed requirement of 0.5 m/s. The speed criterion was used to emphasize consistent performance, and was not used as a basis for excluding trials during data analysis. If subjects satisfied the speed criterion, they received “points” based on the location of the index finger at the end of movement relative to the center of the target; points were also used for motivational purposes only. Visual feedback about final position of the finger as well as the entire hand trajectory was displayed at the end of every trial. Subjects were asked to return the cursor into the start position to begin a new trial. The target and start position was visible throughout the entire trial, allowing certainty about the visually based target position and distance. The three targets were pseudo-randomly presented over a session of 99 trials, such that no target was presented consecutively.
Data Analysis

Finger, elbow and shoulder positions were calculated from sensor’s position and orientation. The joint angles were then calculated, low-pass filtered at 8 Hz using a 3rd order dual-pass Butterworth filter and differentiated to yield tangential velocity and acceleration. The first 9 trials were considered as practice trials and were not included in the analysis. All remaining trials were included in the analysis, except in the extremely rare case when a subject failed to initiate a movement in response to the “go” signal. Movement start was identified by first determining the peak in the tangential velocity profile and then searching backwards to find the first minimum below 5% of the peak. Movement end was determined as the first minimum below 5% of peak tangential velocity by searching forward from the time of peak velocity to the end of movement.

Dependent Measures

Dependent measures of interest in this study were peak velocity, distance error, final position error, movement duration, absolute initial direction error and absolute direction error at movement end. Peak velocity was the maximum tangential velocity during movement. Distance error was defined as the difference between the target distance and the straight-line distance between the starting and final position of the fingertip, regardless of the path taken. Note that this error was signed: if the target was overshot, the error was positive, while if undershot, the distance error was negative. Final position error was calculated as the distance between the target and finger position at movement end. Movement duration was defined as the time from movement onset to movement end. Absolute initial direction error was calculated relative to the line connecting the start position and the target, and was defined as the angular deviation
between the “target line” and the line from the starting location of the hand to the hand location at peak velocity. Absolute direction error at movement end was calculated as the angular deviation between the ‘target line’ and the line from the starting location of hand to the hand location at movement end. Since the hand trajectory is convex (curved), the hand-path curvature was calculated as the minor axis divided by the major axis of the hand path. The major axis was defined as the largest distance between any two points in the hand path, while the minor axis was defined as the largest distance perpendicular to the major axis (Bagesteiro & Sainburg, 2002, Schaefer et al, 2009).

Statistical Analysis

Performance of LHD patients (contralesional arm: right) was compared to that of the control group that performed the task with their right hand. Performance of RHD patients (contralesional arm: left) was compared to that of the control group that performed the task with their left hand. The individual dependent measures were analyzed using 3-way mixed model ANOVA, with arm (left or right) and group (hemisphere-damaged or healthy control) as between-subject factors and the target (50°, 90° and 130°) as the within-subject factor. The effect of target was considered only when it interacted with group and arm, as the primary aim of this study was to determine if laterality of lesion influences the kinematic measures. When there were significant main or interaction effects, post hoc analyses were performed using tukey HSD test, which corrects for multiple comparisons (Kutner et al., 2004). Statistical significance levels were set to 0.05. All statistical analyses were carried out using JMP® statistical software.
Results

The hand-paths of a representative subject from each control group, LHC and RHC, are shown in Figure 2-3A. Regardless of the hand used, the hand-paths of control subjects tended to be fairly straight and directed toward the target, and terminated close to the target. Although not the focus of this study, we did not observe any major differences between the movement patterns of LHC and RHC subjects, consistent with our recent reports of a reduction in interlimb differences in reaching coordination in healthy older subjects relative to healthy younger subjects (Przybyla et al., 2011; Wang et al., 2011). Figures 2-3 show contralesional hand-paths for representative LHD and RHD patients, separated by level of dysfunction as quantified by the FM score. The differences between the hand-paths of patients and healthy control subjects are apparent in Figure 2-3. In general, stroke patients made movements that were more variable and less accurate than those of healthy control subjects. Importantly, there were substantial differences in the movements of LHD and RHD patients. For instance, as shown in Figure 2-3B, the LHD patient showed systematic and variable direction errors for all three targets, while the RHD patients made straighter movements in the direction of the targets but consistently overshot them. These systematic differences between LHD and RHD patients persisted as impairment level increased (Figures 2-3). Even at the highest level of impairment (Figure 2-3E), the directions of the RHD patients’ movements were more clustered compared to their LHD counterparts.

Figure 2-4 compares these findings and other kinematic parameters across all subjects in each group. For statistical comparison, we performed a 3-way ANOVA with group (healthy control, hemisphere damaged), arm (left, right) and target (lateral, center,
medial) as factors. This analysis did not include FM impairment level as a factor because the test of our primary hypothesis required comparison between the performance of stroke patients and that of control subjects, who could not be classified based on FM impairment level. In general, movement duration was greater in the stroke than the control group ($F_{1,34} = 34.97, P < 0.0001$), and this effect did not vary as function of arm, or an interaction between arm and group, or a 3-way interaction between arm, group and target (range of P value: 0.065 to 0.77). Similarly, peak tangential velocity was significantly lower in the stroke groups than the control groups (Figure 2-4B; ANOVA: $F_{1,34} = 36.17, P < 0.0001$), again, without variation as a function of arm, or an interaction between arm and group, or a 3-way interaction between arm, group and target ($P > 0.08$ in all cases).

However, our ANOVA demonstrated that there was a significant 3-way interaction of arm, group and target for final position error ($F_{2,34} = 3.33, P = 0.04$). This interaction can be seen in Figure 2-4C. Whereas both patient groups showed substantially higher errors than their respective control groups ($P < 0.0001$), the LHD group’s errors depended systematically on movement direction, becoming larger from the medial to lateral target, whereas the RHD group’s errors did not. Regardless of this interaction, the overall amplitude of final position errors for LHD and RHD patients were not significantly different ($P = 0.27$), nor was there a difference between the right and left control groups ($P = 0.99$).

As suggested by the 3-way interaction noted above, the final position errors of RHD and LHD groups were due to different factors: while RHD patients tended to overshoot the targets, LHD patients tended to move the correct distance in the wrong
direction (Figures 2-3). Figure 2-5A compares our measure of distance error across our four groups. Our ANOVA revealed a significant interaction between group and arm ($F_{1,34} = 6.17, P = 0.02$). Post hoc analysis revealed that the RHD stroke patients showed significantly higher distance errors when compared to all other groups ($P < 0.01$). However, there were no significant differences in distance error between LHD patients and the LHC group ($P = 0.99$). In other words, damage to the right, but not left hemisphere produced higher distance errors than those of control subjects.

To assess the deficit in controlling movement direction following LHD, we calculated direction error during the early phases of the movement, at peak velocity. These data across our subject groups are shown in Figure 2-5B. Our ANOVA revealed a significant interaction between group and arm ($F_{1,34} = 4.37, P = 0.04$). Post hoc analysis revealed that LHD ($P = 0.002$), but not RHD ($P = 0.76$) patients had significantly higher initial direction errors compared to their respective control groups. Thus, damage to the left, but not right hemisphere, resulted in significantly higher initial direction errors. The hand-paths of the LHD patients in Figures 2-3B-D suggested that direction errors of LHD patients continued throughout the course of movement. To more carefully examine this possibility, we calculated direction errors at movement end (Figure 2-5C). Again, we observed a significant interaction between group and arm for this measure ($F_{1,34} = 5.06, P = 0.03$), and post hoc analysis indicated that LHD patients produced significantly higher direction errors at movement end than the LHC group ($P < 0.0001$). However, there were no significant differences in the direction error at movement end between the RHD and RHC groups ($P = 0.24$). One might conclude that the persistence of direction errors early and late in the movement trajectory might indicate that movements of LHD patients were
straight. However, note that the mean direction errors of LHD patients at the end of movement (Figure 2-5D) were somewhat higher than at peak velocity (Figure 2-5C), indicating that these errors were not corrected during movement. Thus, the movements curved substantially, but this curvature did not reflect directional corrections, as can be seen in the hand-paths in Figures 2-3B-D. In fact, there was a significant interaction between group and arm ($F_{1,34} = 4.39, P = 0.04$) for hand-path curvature. Post hoc analysis revealed that LHD patients showed significantly larger movement curvature than the LHC participants ($P < 0.0001$). Even though some RHD patients showed some curvature in their movements (Figure 2-3D, 2-3E), as a group, the hand-path curvature wasn’t significantly different from that of healthy control subjects ($P = 0.11$). In other words, only left hemisphere damage resulted in increased movement curvature.

Next, we reasoned that a deficit in accurately specifying movement direction following LHD might also be evident as higher variability in this measure (Schaefer et al., 2007; 2009). As expected, LHD patients showed much larger variable direction errors compared with all other groups (Figure 2-5E). There was a significant interaction between group and arm ($F_{1,34} = 5.28, P = 0.03$), with post hoc analysis showing that the variable direction errors of LHD patients were significantly higher compared to the LHC as well as RHD groups ($P < 0.02$). On the other hand, there were no significant differences in variable direction error between the RHD and RHC groups ($P = 0.37$). In other words, damage to left, but not right hemisphere resulted in high variability in movement direction.

In summary, our analyses revealed a double dissociation between the type of error and the hemisphere of damage: RHD, but not LHD, patients showed substantial deficits
in movement distance. In contrast, LHD, but not RHD, patients showed substantial
deficits in constant and variable measures of movement direction. Final position
inaccuracies were not dissociated by hemisphere of damage, but appear to be produced
by the aforementioned differential deficits.

**Effect of Impairment Level (Degree of Hemiparesis indicated by the FM score)**

We next explored the relationship between the extent of the movement deficits
following LHD and RHD, and the severity of clinical motor dysfunction, as indicated by
the FM score. We divided each of our stroke groups into 2 sub-groups – mildly impaired
(FM score: 58 – 66) and moderately impaired (FM score: 46 – 57), similar to previously
published cut scores (Murphy *et al.*, 2010). Both stroke groups had 5 patients in the
mildly impaired range and 4 patients who were moderately impaired. Age was also
comparable among the mild (LHD: 74.2 ± 8.1, RHD: 62.6 ± 13.5) and moderate groups
(LHD: 61.5 ± 11.5, RHD: 64 ± 7.5). The measures from the previous analysis that
showed an interaction between arm and group were subjected to a mixed model 3-way
ANOVA with damaged hemisphere (left or right), FM impairment level (mild or
moderate), and target (lateral, central and medial) as factors.

Figure 2-6 compares our kinematic measures between the two FM score groups
for RHD and LHD patients. For distance error (Figure 2-6A), our ANOVA showed a
significant main effect of FM impairment level ($F_{1,42} = 8.48, P < 0.01$) and damaged
hemisphere ($F_{1,42} = 12.67, P < 0.001$). However, there was no significant interaction
between FM impairment level and damaged hemisphere ($F_{1,42} = 0.59, P = 0.44$). Thus,
distance error was higher for RHD patients when compared to LHD patients, regardless
of their FM severity.
In terms of initial direction error, Figure 2-6B shows that the difference between LHD and RHD is larger in the moderately impaired group. This conclusion is confirmed by the ANOVA, which revealed a significant interaction between FM impairment level and damaged hemisphere ($F_{1,42} = 5.28, P = 0.03$). In other words, as the level of impairment increased, there was a substantial increase in direction error in LHD, but not in RHD patients.

Similar to initial direction error, our hand-path curvature and variable direction error ANOVAs also showed a significant interaction between damaged hemisphere and FM impairment (curvature: $F_{1,42} = 6.69, P = 0.01$; variable direction error: $F_{1,42} = 14.37, P < 0.001$). As the level of impairment increased, there was a substantial increase in both of these measures for the LHD group, but not RHD group (Figures 2-6C and 2-6D).

In summary, these results suggest a substantial effect of the severity of impairment on the reaching performance of stroke patients. While LHD patients showed increasing variability, hand-path curvature and direction error with increasing contralesional hemiparesis, RHD patients did not show variation in these measures based on impairment level. In addition, the specific RHD deficits in movement distance also did not vary with impairment level.

**Discussion**

There is substantial prior research dedicated to understanding contralesional motor deficits after unilateral stroke and improving contralesional arm performance through rehabilitation. However, none of these studies have examined whether movement deficits in the contralesional arm differ depending on the hemisphere of damage, despite a growing body of work indicating that each hemisphere of the brain might be specialized
for controlling different aspects of movement. Our results indicate compelling differences in contralesional arm performance in unilateral stroke patients depending on the hemisphere of damage. These findings support our predictions that left, but not right, hemisphere damage produces deficits in movement trajectory, while right, but not left hemisphere damage produces deficits in stabilizing the limb at the end of movement. We also show that left hemisphere deficits vary with the severity of impairment. These findings not only broaden the scope of our model of hemisphere specific control, but also have significant implications for understanding the impact of stroke on function as well as for clinical rehabilitation.

Our results expand the findings of prior studies, which revealed significant coordination deficits in the contralesional arm of stroke patients. In particular, the studies of Beer, Dewald and colleagues (2000; 2004) reported a failure to predictively account for dynamic intersegmental interactions when stroke patients performed reaching actions with their paretic arm. Levin and colleagues (Levin, 1996; Cirstea & Levin, 2000) largely focusing on movement kinematics, reported problems in coordinating the actions of shoulder and elbow joints during contralesional arm motion. Kamper et al., (2002) reported contralesional deficits in movement velocity, smoothness, linearity and direction. While earlier studies that examined deficits such as weakness and spasticity attributed contralesional impairments to reduced agonist (El-Abd et al., 1993; Fellows et al., 1994) and antagonist muscle activation (El-Abd et al., 1993; McLellan et al., 1985), hyperactive reflexes (Mizrahi and Angel 1979), peripheral disturbances such as changes in tissue properties (Dietz et al., 1991; Given et al., 1995), or the presence of abnormal synergies (Dewald et al., 1995; Bourbonnais et al., 1989), more recent studies that also
address coordination deficits are beginning to identify inadequacies in movement planning (Beer et al., 2000; Kusoffsky et al., 2001) as a potential source of these problems. Our results agree with these studies that a deficit in predictive control mechanisms gives rise to coordination deficits post-stroke. However, our current and prior results provide specificity regarding the neural substrates underlying these deficits by demonstrating that predictive control of movement trajectory features is disturbed only from damage to the left hemisphere. In fact, damage to right hemisphere regions does not impact on the coordination of movement. In contrast, deficits in controlling movement distance arise from damage to the right hemisphere (Schaefer et al., 2007; 2009b). Whereas Kamper et al (2002) observed deficits in controlling movement distance with the contralesional limb, they did not identify whether such deficits differed depending on the hemisphere of damage. Our current results show that only RHD patients made substantial distance errors, indicating that mechanisms that ensure termination of a movement and stabilization of the arm at a goal location are lateralized to the right hemisphere.

Nature of motor deficits following left and right hemisphere damage

Before discussing the specific nature of the deficits following left and right hemisphere damage, it should be emphasized that our model of hemispheric specialization (Sainburg, 2010) is bi-hemispheric – we posit that each hemisphere contributes different aspects of control to movements of both arms. Such bi-hemispheric control is consistent with observations from previous neuroimaging studies that motor cortical areas of both brain hemispheres are active during unilateral finger movement (Li et al., 1996; Cramer et al., 1999), finger sequencing (Kim et al., 1993; Kawashima et al.,
and unilateral arm movements (Nirkko et al., 2001). Our prior findings in healthy individuals in which we documented limb specific advantages for the dominant and non-dominant arms (Sainburg and Kalakanis, 2000; Bagesteiro and Sainburg, 2003; Bagesteiro and Sainburg, 2002) and our recent work in the ipsilesional arm of stroke patients (Schaefer et al., 2007; 2009b; 2012; Mutha et al., 2010; 2011b) have supported this bi-hemispheric model of control. In fact, Schaefer et al. (2007; 2009b) have demonstrated that ipsilesional deficits in motor coordination and learning mirror the functional advantages that we had previously reported in the dominant and non-dominant arms of healthy subjects. For example, LHD produced deficits in intersegmental coordination and in direction learning during adaptation to visuomotor rotation, while RHD produced deficits in final position accuracy and position adaptation. In addition, both Desrosiers et al. (1996) and Schaefer et al. (2009b) showed that these deficits are often functionally relevant, and correlate with deficits in clinical movement evaluations that include simulated activities of daily living. In a more recent study, Robertson et al., (2012) revealed coordination deficits in both arms of stroke patients with LHD, during unconstrained reaching movements. While both left and right brain damaged patient groups had reduced scapula protraction in the contralesional paretic arm, scapula protraction was only reduced in the ipsilesional arms of the LHD group. The authors concluded that LHD produced deficits in proximal coordination, a finding that they suggested might be consistent with previous findings of reduced intersegmental coordination in the ipsilesional arm of LHD patients (Schaefer et al., 2009b). Our current findings confirm that these specific ipsilesional deficits also occur in the contralesional hemiparetic arm of both RHD and LHD stroke patients.
While the nature of our previously observed ipsilesional and current contralesional deficits appears similar, two important differences between these studies must be pointed out. First, in the current study, we did not observe a dependence of LHD related trajectory deficits on intersegmental coordination requirements. While deficits in movement direction or hand-path curvature in LHD patients were always larger than those in LHC subjects, our ANOVAs for these measures did not show a significant three-way interaction among group, arm and target. These findings agree with those of Kamper et al. (2002) who showed only a modest dependence of contralesional deficits on movement direction, yet they stand in contrast with our findings in the ipsilesional arm where the magnitude of the deficits almost always increased as intersegmental coordination requirements increased. This raises the interesting question of whether left hemisphere contributions to coordination of ipsilateral arm movements become more critical as the complexity of the movement increases. While we cannot directly answer this question yet, this suggestion is not far from some observations of functional neuroimaging and lesion studies of finger movements. Harrington and Haaland (1991) previously observed that performance of complex heterogeneous arm posture sequences with the ipsilateral arm was more impaired than that of simple, repetitive ones after LHD, but not RHD. Haaland et al. (2004) also showed greater left hemisphere activation during the performance of complex rather than simple finger sequences even when the ipsilateral left hand was used to perform the task. Verstynen et al. (2005) extended these findings by showing that increased ipsilateral left hemisphere contributions did not necessarily require sequential actions, but were present during the performance of any complex finger movement. Whether a similar conclusion can be drawn for arm reaching
movements remains a subject of future investigation. Second, in contrast to our previous ipsilesional studies, final position errors were not significantly different between LHD and RHD patients in the current study. However, it must be stressed that here, LHD final position errors were due to deficits in direction control, while RHD errors resulted from deficits in adequately stopping at the end of movement. While the most impaired LHD patient in our current study (Figure 2-3E) did show some difficulty in stopping at the medial target, this was not observed in other LHD patients (Figure 2-3B-D). These patients did not show any systematic overshoot or undershoot, which would be indicative of a deficit in adequately stopping the movement at the target location. While the movements of the LHD patient in Figure 3E might give the impression of a distance control problem, this was not the case. Note that the movements directed towards the lateral target ended closer to the center target than the lateral target, as a result of large direction errors. However, the average distance of these movements was fairly well matched to the target distance, confirming that final position errors in LHD patients were largely due to initial direction error, but not distance control deficits. In contrast, for RHD patients, directional deviations, if any, were initiated very late in the movement, mostly after the hand had crossed the target (Figures 2-3D, 2-3E). The direction errors made by RHD patients were in fact very small and comparable to control subjects. Thus, the final position errors in the RHD group, were largely due to the patients consistently overshooting the target, as can be seen in Figures 2-3B-E. These findings in RHD patients are consistent with our previous results (e.g., Schaefer et al., 2009b), but we had previously observed intact accuracy (final position errors comparable to controls) in our LHD patients, who tended to correct their movements back to the target position despite
initially deviating from the target direction when moving with the ipsilesional arm. We interpreted such corrections in LHD patients as a contribution of the intact right hemisphere to the ipsilesional, left arm through crossed descending pathways. However, in the current study, following LHD, corrections of the contralesional right arm were ineffective or absent, leading to large errors at the end of movement. This is likely to result from the fact that the intact right hemisphere has limited direct access to the contralesional right arm, which may limit effective corrections and stabilization of the arm at the desired goal location.

While we have emphasized that RHD, but not LHD final position errors arise due to a deficit in controlling movement distance, it is interesting to speculate whether our results could be explained on the basis of differential deficit in LHDs and RHDs solely in estimating or planning movement distance. First, our neuropsychological tests showed that there were no significant differences between LHD and RHD stroke groups in visuospatial perception (Judgement of Line Orientation Test: \( P = 0.994 \)), making it unlikely that visuospatial deficits, if any, played a differential role in estimating target distance as shorter or longer in one group over the other. Second, while a certain component of movement distance appears to be preplanned (Gordon and Ghez, 1987a; 1987b), our recent work has shown that achievement of a target distance relies on “online” (during movement) processes that use sensory information to modulate limb impedance (Mutha et al., 2008). We suggest that it is these impedance mechanisms that are disrupted by RHD, producing a deficit in accurately stopping at a goal location and thereby affecting the achievement of a target distance. In contrast, movement distance in LHD patients was fairly well matched to the target distance. In fact, LHD patients’
distance errors were very small, positive on average, and most importantly, comparable to control subjects. Thus, we do not believe that LHD affected processes that regulate achievement of movement distance. Nevertheless, further research is necessary to comprehensively examine the contributions of distance planning mechanisms to these differential deficits.

While addressing these distinct deficits in LHD and RHD patients, it is imperative to explain why elderly stroke patients demonstrate such differential deficits, when healthy elderly subjects tend to show a reduction in motor lateralization (Przybyla et al., 2011). Prior brain imaging studies have shown that such a reduction in lateralization with aging is a consequence of increased neural recruitment bilaterally, rather than a reduced specialization of one hemisphere. For example, Cabeza (2002) showed that for certain neuropsychological functions that are associated with asymmetric patterns of recruitment in young subjects, older subjects recruit more symmetric patterns of cortical activity. Furthermore, these patterns are associated with sustained performance on the neuropsychological tasks, suggesting that bilateral recruitment is likely compensatory in nature, in light of reduced unilateral neural capacity. This forms the basis of the HAROLD (Hemisphere Asymmetry Reduction in Older Adults) model proposed by Cabeza. In line with these results, we have shown that older adults show more symmetric patterns of motor behavior and interlimb transfer of motor learning (Wang et al., 2011; Przybyla et al., 2011). Taken together, our findings and related imaging findings (Mattay et al., 2002) suggest that as people age, increased symmetry in behavior is not due to a reduction in specialization of one hemisphere, but rather due to an increase in bilateral hemispheric recruitment. However, Adamo et al (2009) reported the emergence of
proprioceptive wrist matching asymmetries with age, suggesting that some new neural asymmetries may develop, while others become diminished with aging. The current findings in the contralesional arm, together with previous findings in the ipsilesional arm (Schaefer et al., 2007; 2009b) support this view by showing that loss of contribution from one hemisphere, either right or left, will reestablish systematic motor asymmetries. If, on the other hand, hemispheric specialization itself had become reduced, motor asymmetries between LHD and RHD patients would not have been observed. We therefore conclude that our current findings support the HAROLD model, and extend it to motor function.

Differentiating Right Hemisphere Deficits in Visuospatial Processing from Motor Control

Right hemisphere damage has previously been shown to produce deficits in cognition and perception, including unilateral neglect (Bottini et al., 2009). It is plausible that the accuracy deficits revealed in the current study for RHD patients could emerge from such perceptual deficits. Pisella et al. (2011) recently argued that the right hemisphere might be dominant for visuo-spatial processing, based on several studies examining optic ataxia, neglect and visual agnosia. For example, in a study focused on correlating the critical neural substrates associated with unilateral visual neglect, Vallar and Perani (1986) recruited 110 stroke patients to participate in a circle cancellation task. The results indicated that damage to right inferior parietal lobe commonly resulted in contralateral visual neglect, which was consistent with later studies documenting visual neglect following right hemisphere damage (Mattingley, 1999; Vallar et al., 1993). In our current study, RHD patients consistently overshot the targets, resulting in large distance errors (Figures 2-3B-E). However, none of our RHD patients had visual neglect, which
rules out the possibility that these errors are a consequence of neglect. It is also unlikely that these errors are attributable to optic ataxia because the hand-paths of RHD patients were fairly accurate in direction, which is not characteristic of this deficit. In addition, several studies have indicated that errors due to optic ataxia are predominant when patients try to grasp or reach to objects located in their peripheral or extra-foveal visual field (Buxbaum and Coslett, 1997; Dijkerman et al., 2006). However, in the current study, the targets were presented close to the center of the subject’s visual field and workspace, and no restrictions were imposed on the gaze direction of the subjects. We conclude that the errors associated with difficulty stopping on targets in the current study are unlikely to result from deficits such as optic ataxia or unilateral visual neglect. Instead, we attribute these errors to a deficit in the specialized role of right hemisphere in controlling limb impedance for stabilizing limb position at the end of movement.

Effect of impairment level on contralesional deficits

Our results show that patients with moderate to mild hemiparesis show motor deficits that vary with the hemisphere of damage, and that these deficits in LHD patients vary with the extent of impairment measured by the FM score. One of the difficulties in developing a more specific understanding of how movement deficits following stroke are affected by lesion location and impairment level has been the paucity of research that has detailed the relationship between the degree of motor impairment and kinematic, kinetic, and/or electrophysiological measures of motor performance. Only a few studies have investigated this association. For example, Kamper et al. (2002) examined the reaching performance of mild-to-severely paretic chronic stroke patients while they made reaching movements to 75 targets. They reported that deficits in a variety of contralesional
performance measures, including velocity, direction error and linearity strongly correlated with impairment level, as measured by the Chedoke-McMaster Stroke Arm Assessment Scale. However, no previous studies have assessed how this dependence might be modulated by the hemisphere of damage. Our current findings indicate that the trajectory based deficits produced by LHD patients increase with the severity of FM impairment, while the severity of impairment does not modulate differences in distance error for RHD patients (Figure 2-6). It is difficult to explain this asymmetric dependence of performance errors on level of impairment. It may simply be the case that variations in level of impairment have a more graded effect on the ability to coordinate the segments of the arm than on the ability to stop at a given location. It is also notable that previous neural activation studies have shown asymmetries related to side of impairment. For example, Zemke (2003) showed that when stroke patients performed a finger-tapping task with their paretic arm, LHD patients had higher contralesional sensorimotor cortex activation than RHD patients. These findings are somewhat consistent with neural activation studies in healthy subjects indicating greater ipsilateral activation when performing sequential finger apposition with the non-dominant as compared with the dominant hand (Kim et al., 1993). Zemke’s findings suggest that the greater recruitment of ipsilateral cortex is maintained following RHD, but not LHD. It is plausible that contralesional arm of RHD patients receives greater contribution from the intact ipsilateral (left) hemisphere, and this may diminish the effect of impairment level on performance measures, like accuracy. However, it is impossible to conclusively explain the asymmetrical effects of RHD and LHD on the relationship between our performance measures and our measures of impairment in the current study.
Implications for Rehabilitation

The finding that contralesional deficits differ depending on the side of hemisphere of damage has important implications for the design of clinical rehabilitation intervention. While approaches such as constraint induced movement therapy (Taub et al., 1993; Mark and Taub, 2004) have shown decreased impairment and improved function through forced use of the contralesional arm, these techniques have not differentiated the type or amount of therapy depending on side of damage. Our results suggest that therapy might be designed to address specific deficits that emerge after left or right hemisphere damage. Such a focused approach is possible through the use of new methodologies that employ advanced robotic and computer based intervention that allows high-resolution analysis of performance during and following therapy (e.g., Volpe et al., 2001). These tools could be used to design specific tasks and modify movement related feedback so as to emphasize certain variables over others. For example, after LHD, task feedback can be modified to amplify errors perpendicular to the desired trajectory while reducing errors in the direction of the desired movement. Such changes would penalize deviations from the desired movement path, while allowing errors in the direction of movement. In contrast, following RHD, tasks that penalize final position errors could be designed. Finally, given the presence of ipsilesional deficits that mirror contralesional problems, bilateral training should be a critical component to therapeutic intervention in unilateral stroke (Whitall et al., 2000; Cunningham et al., 2002; Latimer et al., 2010; Cauraugh et al., 2010). Bilateral training is not only important to facilitate remediation in the ipsilesional arm, but also because unilateral training may not automatically carry-over.
to spontaneous bilateral performance, which is the best predictor of better performance on everyday tasks (Haaland et al., 2012). In fact, recent research has indicated that learning novel kinetic and visuomotor environments with a single arm transfers only partially to bilateral movements, even when the same arm experiences the imposed forces under unilateral and bilateral conditions (Nozaki et al., 2006). Thus, we suggest that it is critical to consider the specific deficits induced by right or left hemisphere lesions and consider bilateral training in order to enhance motor rehabilitation post-stroke.
### TABLE 2-1: Summary of participant information

<table>
<thead>
<tr>
<th>Variable (mean ± SD)</th>
<th>Healthy control</th>
<th>Hemispheren damaged</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Number of Males</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.6 ± 6.3</td>
<td>64.2 ± 9.5</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.0 ± 1.8</td>
<td>14.9 ± 1.8</td>
</tr>
<tr>
<td>Years post stroke(a)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lesion volume (cm^3)(b)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Fugl-Meyer motor score(c)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Visuospatial Perception(d)</td>
<td>25.6 ± 4.38</td>
<td>28.3 ± 3.56</td>
</tr>
<tr>
<td>Language comprehension(e)</td>
<td>80.0 ± 0.0</td>
<td>79.2 ± 2.5</td>
</tr>
<tr>
<td>Limb Apraxia(f)</td>
<td>13.7 ± 1.1</td>
<td>13.4 ± 1.3</td>
</tr>
<tr>
<td>Contralesional Grip strength(g)</td>
<td>50.3 ± 5.9</td>
<td>49.2 ± 8.2</td>
</tr>
</tbody>
</table>

Note: Values are means ± SD

\(a\)Years post-stroke are calculated as time elapsed between incidence of stroke and day of data collection

\(b\)Lesion volume is computed from MRI and CT scans using a computer algorithm

\(c\)Maximum score on the total upper-extremity Fugl-Meyer motor score is 66

\(d\)Visuospatial perception was assessed using the Judgement of Line Orientation test.

\(e\)Language comprehension was assessed using the Western Aphasia Battery

\(f\)Limb apraxia was designated as mean number correct out of 15 items using a validated apraxia battery

\(g\)Grip strength from dynamometer are expressed as standardized \(t\) scores.

\(\ast\)One RHD patient was not administered the Judgement of Line Orientation test.
Figure 2-1: Overlap images showing locations of lesions between right and left hemisphere damaged groups (Color scale of magenta to red shows increasing overlap). Lesions are confined to either left or right hemisphere.

Figure 2-2: Schematic of the experimental setup. Subjects sat facing a mirror onto which the start position and targets were projected using a HDTV, and rested their arms in an air-sled system placed on a glass tabletop.
Figure 2-3: (A) Comparison of hand paths between representative LHC and RHC subjects. (B-E): Comparison of hand paths between left- and right-hemisphere-damaged patients across severity.
of hemiparesis, assessed using the FM score. Each RHD and LHD pair has similar FM scores; FM scores decrease from (B) to (E), indicating increasing degree of hemiparesis.

Figure 2-4: (A) Mean duration and (B) mean peak tangential velocity for right and left arm of control subjects (LHC, RHC) (black) and the contralesional arm of LHD and RHD patients (grey). (C) Final position error for the same groups for the three different targets (lateral, central, medial). Error bars indicate SEM. * indicates significant (p < 0.05) group differences.
Figure 2-5: (A) Mean distance error, (B) mean absolute initial direction error, (C) mean absolute direction error at end of movement, (D) mean hand path curvature, and (E) mean variable direction error at peak velocity for the LHC, LHD, RHC and RHD groups. Error bars indicate SEM. * indicates significant (p < 0.05) group differences.
Figure 2-6: (A) Mean distance error, (B) mean absolute initial direction error, (C) mean hand path curvature, and (D) mean variable direction error at peak velocity of mildly and moderately impaired LHD (black) and RHD (grey) patients. Error bars indicate SEM.
CHAPTER 3

UNILATERAL STROKE PRODUCES HEMISPHERE-SPECIFIC BILATERAL DEFICITS

Introduction:

Unilateral stroke most commonly produces contralesional hemiparesis, which is weakness, spasticity, and abnormal synergies in the side of the body opposite to the damaged hemisphere. Much of the physical rehabilitation post-stroke focuses on the contralesional side (upper or lower limb) as it demonstrates moderate to severe impairment depending on the damage. However, several studies over the years have also indicated that the ipsilesional side of the body also demonstrates deficits post unilateral stroke, although not as severe as the contralateral side (Haaland and Delaney, 1981; Haaland and Harrington, 1989; Winstein and Pohl, 1995). For example, in Haaland & Harrington’s study (1989), stroke patients performed simple reaching movements across different amplitudes with their ipsilateral arm, and their results demonstrated that the stroke patients were slower and less accurate during the initial phase of movements, when compared to the control group, thus demonstrating deficits in the ipsilesional arm of stroke patients. These studies suggested that each hemisphere might contribute to execution of movements in both the limbs. Functional neuroimaging studies that followed these behavioral studies offered further evidence of bi-hemispheric contributions to unilateral finger movements (Kawashima et al., 1996; Kim et al., 1993). For example, in
these studies, the participants were asked to perform sequential apposition movements of the fingers to the thumb, and their brain activity was observed using nuclear magnetic resonance imaging or using positron emission tomography. It was observed that when patients performed these finger-sequencing tasks, there was a predominant contralateral activation in the primary motor area, and an asymmetric ipsilateral activation in the motor and premotor area as well, especially in the left hemisphere. They attributed such ipsilateral activations to contributions of both hemispheres in planning and execution of motor tasks. Further, Verstynen et al (2005) demonstrated that such ipsilateral activation is more pronounced when right-handed participants perform complex sequencing and chord movements (but not tapping movements) with their left hand, than when such movements are performed in the left hand of left-handed participants. These studies suggest a predominant role of left hemisphere (in right-handed participants) in movement planning and execution of contralateral and ipsilateral arm. Thus, the findings of these behavioral and neuroimaging studies suggest that both hemispheres contribute to planning and execution of movements in each limb. However, an important question remained: are the contributions from each hemisphere symmetric? In other words, do both hemispheres contribute identical control mechanisms to either arms, or are each hemisphere specialized for distinct control mechanisms.

Previous studies from our lab aimed to address this question by examining interlimb differences in young healthy adults. We hypothesized that the performance advantages of each limb could be translated to the specialization of the contralateral hemisphere. For example, Bagesteiro & Sainburg (2002; 2003) examined the reaching performance of young healthy adults when they performed simple reaching movements,
or reaching movements while adapting to inertial load conditions. These studies demonstrated limb-specific advantages to each arm during reaching movements: the dominant arm appeared to be better in controlling the trajectory of movements, and the nondominant arm appeared to be better in achieving an accurate final position. These studies led to the postulation that the dominant (left) hemisphere may be specialized for control of trajectory or intersegmental coordination, whereas the nondominant (right) hemisphere may be specialized for stabilizing the limb in the final position (Sainburg, 2005). Based on our model, we predicted that patients with left hemisphere damage (LHD) should demonstrate deficits in trajectory measures, whereas patients with right hemisphere damage (RHD) should demonstrate deficits in stabilizing limb in the final position. In agreement with this prediction, our previous stroke studies examining ipsilesional arm performance during single- and multi-joint reaching movements in stroke patients demonstrated that LHD patients produced significantly high direction errors, while RHD patients produced significantly high final position errors in their reaching movements (Schaefer et al., 2007; Schaefer et al., 2009b). Our recent study examining the contralesional arm performance of unilateral stroke patients also revealed findings consistent with our model of motor lateralization (Mani et al., 2013). In addition to these distinct motor control deficits, we have also demonstrated that hemisphere of damage might modulate the motor learning deficits in stroke patients. Specifically, in a previous visuomotor adaptation study with the ipsilesional arm (Schaefer et al., 2009a), these hemisphere-specific deficits were robust for different aspects of adaptation: right hemisphere damaged patients made straight trajectories with large final position errors, whereas left hemisphere damaged patients made highly curved movements with small
final position errors. Our recent study offered further insight by providing crucial evidence that only patients with left parietal damage demonstrate contralesional deficits in adapting to a visuomotor adaptation (Mutha et al., 2011). In contrast, patients with right parietal damage did not demonstrate any deficits in adapting to visuomotor rotations, suggesting that left, but not right parietal regions may be critical for adapting to visuomotor rotation tasks.

It should be mentioned that each of our previous studies in stroke patients examined only one arm of the stroke patients (ipsilesional or contralesional, but not both). If our hypothesis that each hemisphere contributes specific control mechanism to both the arms is true, then a clear prediction of this hypothesis would be to demonstrate that damage to either hemisphere results in hemisphere-specific deficits in both the arms of the same stroke patients. To our knowledge, there has been no previous study that has provided this evidence. Our current study aims to address this question by examining both the ipsilesional and contralesional arm of stroke patients when they adapt to novel visuomotor rotation session. We predict that left, but not right hemisphere damaged patients will demonstrate trajectory based adaptation deficits in both their arms, whereas right, but not left hemisphere damaged patients will demonstrate deficits in stabilizing limb at the final position.

Materials and Methods:

Participants

There were a total of 24 participants in this study: 12 control subjects, and 12 stroke patients (6 LHD and 6 RHD). All the patients were relatively highly functioning (FM
score greater than 55), and all LHD patients had damage to the parietal cortex (as our previous studies have suggested that left parietal region is critical for visuomotor adaptation). To have patients who are highly functioning (because there were 480 trials in this experiment) and also have damage to the left parietal region restricted our sample size. The control and stroke participants were matched on age ($F_{2,21} = 0.60; P = 0.55$), and education ($F_{2,21} = 0.08; P = 0.91$). The stroke groups were matched on the severity of impairment based on Fugl-Meyer upper extremity motor assessment test ($F_{1,10} = 0.08; P = 0.77$).

**Experimental setup:**

The experimental set-up is shown in Figure 3-1. Subjects sat facing a table with either their left or their right arm supported over a horizontal surface by an air-jet system to eliminate the effects of gravity and reduce friction. A start circle, targets and the subject’s fingertip (represented by an on-screen cursor) were displayed on a mirror using a high-definition television positioned horizontally above the mirror. The mirror blocked the direct vision of the subject’s arm, but reflected the visual display to give the illusion that the display was in the same horizontal plane as the fingertip. Position and orientation of the forearm and upper arm segments were sampled using a Flock of Birds (Ascension Technology) system at 130Hz. The positions of the index finger tip, lateral epicondyle of the humerus and the acromion, directly posterior to the acromioclavicular joint were digitized using a stylus that was rigidly attached to a 6-degree of freedom Flock of Birds sensor. As sensor data were received, the 3D position of the aforementioned landmarks was computed using custom software, with the x–y plane parallel to the tabletop. We used the computed x–y coordinates of the fingertip to define
the projected cursor position.

*Experimental task:*

The experiment task consists of reaching to 8 targets distributed radially around a start circle, and these targets are presented in a pseudorandom sequence (Figure 3-1B). Each subject performed two experimental sessions: baseline (80 trials with each arm), rotation session (160 trials with each arm). If the subjects started the baseline session with their left arm, they would start the rotation session also with their left arm, and vice versa. Whether the subjects will use their left or right arm first was randomized. All eight targets will be projected in the same hemispace as the arm, and will be oriented radially at a distance of 12cm from start circle. During the baseline sessions, the relation between finger and cursor will be veridical. However, during the adaptation session, the position of the cursor will be rotated 30° clockwise relative to the start circle, and this session will be used to examine the adaptation of stroke patients to visuomotor rotation.

*Measures*

As there were 160 trials in the rotation session for 8 targets, we grouped these trials as “cycles”. One “cycle” = 8 trials (one trial to each target). Thus, there were 20 cycles for the adaptation session, and 10 cycles for the baseline session (80 trials). We were interested in comparing how the measures varied during the adaptation session. The measures that we used to quantify the performance of the participants are initial direction error (direction error at peak velocity), hand path curvature, final position error, and peak tangential velocity.

*Statistical Analysis*

We split our data into two categories to examine separately the contralesional &
ipsilesional arm performance. For each of these two categories, we performed a 2-way ANOVA on Group (control, stroke) and hand (left or right) on the measures of peak tangential velocity, initial direction error, hand path curvature, and final position error during the entire adaptation session. When warranted, post hoc analyses were performed using Tukey HSD.

Results

Figure 3-3 shows the differences in peak tangential velocity across both the ipsilesional and contralesional arm of stroke groups, when compared to the control group. Our 2-way ANOVA revealed a significant effect of the interaction between group and arm for the ipsilesional (F_{1,34} = 17.67, P < 0.0001) and contralesional arm (F_{1,34} = 4.22, P = 0.04) for the peak tangential velocity. Post hoc analysis showed that the LHD patients demonstrated significantly lower peak tangential velocity than the Controls across both the arms (P < 0.0001). In contrast, the peak tangential velocity of the RHD patients was similar to the Controls (P > 0.22, in both arms). This could indicate that during the adaptation session, LHD patients made significantly slower movements in trying to adapt to the rotation.

Figure 3-4 shows the mean initial direction error across all three groups from the first cycle to the last cycle during the adaptation session across both arms. It appears that the LHD patients had difficulty in adapting to the rotation over the course of the adaptation session, when compared to the Controls. However, the RHD patients seem to adapt nearly as well as the control group. Our ANOVA revealed a significant effect of the interaction between the group and arm in the ipsilesional (F_{1,34} = 10.92, P = 0.001) and
contralesional arm ($F_{1,34} = 8.27, P = 0.004$) for initial direction error. Post hoc analysis revealed that the LHD group made significantly high initial direction errors when compared to the controls ($P < 0.001$, in both arms). In contrast, the direction errors of the RHD patients were similar to the control group ($P > 0.1$, in both cases).

Figure 3-5 shows the mean hand path curvature across all three groups from the first cycle to the last cycle during the adaptation session across both arms. It is evident that the LHD patients made significantly more curvature in their movements during the adaptation session, when compared to the Controls. However, the RHD patients seem to be as good as the control group. Our ANOVA revealed a significant effect of the interaction between the group and arm in the ipsilesional ($F_{1,34} = 13.85, P = 0.0002$) and contralesional arm ($F_{1,34} = 16.47, P < 0.0001$) for hand path curvature. Post hoc analysis revealed that the LHD group made significantly high initial direction errors when compared to the controls and RHD patients in the ipsilesional arm ($P < 0.001$). In contrast, there were no significant differences in the hand path curvature between the RHD and control group for the ipsilesional arm ($P = 0.95$). However, both stroke groups had higher hand path curvature than the control group in the contralesional arm, but the hand path curvature of the LHD group was significantly higher than all the other groups ($P < 0.001$).

Figure 3-6 shows the mean final position error across all three groups from the first cycle to the last cycle during the adaptation session across both arms. It appears that RHD group made more errors in final position when compared to the control group. Our ANOVA revealed that there was a significant effect of the interaction between the group and arm for final position error in the contralesional arm ($F_{1,34} = 6.36; P = 0.01$). Post hoc
analysis indicated that the RHD group made significantly high final position errors than the controls ($P = 0.0016$). In contrast, the final position errors of the LHD group were similar to the controls ($P = 0.99$). However, our ANOVA revealed no significant interaction between the group and arm for final position error in the ipsilesional arm ($F_{1,34} = 1.37; P = 0.24$). This could be because the participants in general made high errors with their left arm, irrespective of the group, thereby nullifying the effect here. As our apriori hypothesis was that RHD patients would make significantly high final position errors with both arms, we performed a secondary analysis comparing each stroke group with the respective control group in a 2-way ANOVA with group (control, LHD or RHD), and arm (left or right) as factors. In RHD vs controls comparison, our ANOVA revealed a significant effect of group ($F_{1,34} = 16.22; P < 0.0001$), and arm ($F_{1,34} = 22.82; P < 0.001$). Post hoc analysis revealed that the RHD group made significantly high errors when compared to the controls ($P < 0.0001$). In contrast, when comparing LHDs and controls, our ANOVA revealed that there was no significant effect of group ($F_{1,34} = 0.09; P = 0.76$). These results clearly suggest that right, but not left hemisphere damage produces deficits in final position. These results are in agreement with our several previous studies, consistent with our model of motor lateralization.

**Correlation of final position errors with direction errors**

As the RHD patients showed significant improvement in their hand path curvatures and initial direction errors over the adaptation session, we examined how these improvements translated to improvements in final position accuracy during the adaptation session. Figure 3-6C shows the correlation between the final position error and the initial direction error made by a representative patient of each stroke group. It appears that the
RHD patient improved his directional accuracy to achieve an improvement in final position error during the adaptation session. In contrast, the LHD patient seems to make similar final position error irrespective of the directional errors they make. A one-way ANOVA revealed a significant effect of group (control, LHD, RHD) for the mean correlation coefficient for the final position error vs initial direction error ($F_{2,45} = 3.43, P = 0.04$). Post hoc analysis using Tukey HSD revealed that the correlation coefficient was significantly weaker for the LHD group when compared to the control group ($P = 0.04$). In contrast, the correlation coefficient of the RHD group was similar to the controls ($P = 0.46$). These results suggest that when RHD patients improved their direction errors, their final position errors improved as well. However, when we compare the correlation coefficient of final position error and direction error at the end of movement, the RHD group had significantly weaker correlation coefficient when compared to the controls ($P = 0.04$). In contrast, the LHD patients had a similar, stronger correlation coefficient as the control group ($P = 0.1$). This suggests that the final position errors made by the RHD patients cannot be attributed to direction errors at the end of movement, but rather these errors are due to the patients overshooting the target, as demonstrated in Figure 3-2.

To summarize, the LHD patients demonstrated significant difficulty in adapting to the rotation, and this effect was not modulated by arm, which indicates that left parietal damage results in motor learning deficits in both the arms of the same stroke patients. In contrast, RHD patients adapted nearly as well as the control group, and these patients had damage in one or more of the sensorimotor regions of the cortex, and it doesn’t seem to affect their adaptation. Thus, our results offer crucial evidence that left hemisphere, in particular, the parietal region appears to be critical for adapting to visuomotor rotation in
BOTH the arms, whereas right hemisphere damage results in deficits in stabilizing both the arms in the final position.

Discussion

The purpose of this study was to investigate whether left or right hemisphere damage produces hemisphere-specific deficits in both the arms of stroke patients. While several previous studies have provided evidence of ipsilesional deficits in unilateral stroke patients (Haaland, 2004; Sunderland, 2000; Weinstein and Pohl, 1995), the nature of these deficits was not clearly understood. Recent studies from our lab provided evidence of hemisphere-specific deficits in the ipsilesional (Schaefer et al., 2009b) and contralesional arm (Mani et al., 2013) of stroke patients. But, whether such hemisphere-specific deficits exist in both the arms of the same patients remained inconclusive. Our current study aimed to address this critical question by examining the reaching performance of both the arms of unilateral stroke patients. Our current findings provide the first and comprehensive evidence for distinct hemispheric contributions to bilateral arm control: LHD patients demonstrate deficits in trajectory measures in both their arms, whereas RHD patients demonstrate deficits in achieving an accurate final position in both their arms.

Hemispheric contributions to bilateral arm control

Functional neuroimaging studies provided the initial evidence of bi-hemispheric contributions to unilateral finger movements (Kawashima et al., 1996; Kim et al., 1993). For example, in these studies, the participants were asked to perform sequential apposition movements of the fingers to the thumb, and their brain activity was observed
using nuclear magnetic resonance imaging or using positron emission tomography. It was observed that when patients performed these finger-sequencing tasks, there was a predominant contralateral activation in the primary motor area, and an asymmetric ipsilateral activation in the motor and premotor area as well, especially in the left hemisphere. They attributed such ipsilateral activations to contributions of both hemispheres in planning and execution of motor tasks. Further, Verstynen et al (2005) demonstrated that such ipsilateral activation is more pronounced when right-handed participants perform complex sequencing and chord movements (but not tapping movements) with their left hand, than when such movements are performed in the left hand of left-handed participants. These studies suggest a predominant role of left hemisphere (in right-handed participants) in movement planning and execution of contralateral and ipsilateral arm. Early behavioral studies in stroke patients also provided evidence consistent with this observation, where it was observed that patients with left, but not right hemisphere damage demonstrated bilateral impairment in measures such as proximal steadiness or distal dexterity (Haaland et al., 1977). However, in studies that followed (Haaland and Delaney, 1981; Haaland and Harrington, 1989; Winstein and Pohl, 1995), ipsilesional deficits were observed in both the arms of unilateral stroke patients. For example, in the study by Haaland & Delaney (1981), they observed ipsilesional deficits in unilateral stroke patients in tasks that required sensorimotor interaction (like grooved pegboard tasks, maze coordination), regardless of the hemisphere of damage. Thus, the findings of these behavioral and neuroimaging studies suggest that both hemispheres contribute to planning and execution of movements in each limb. However, an important question remained: are the contributions from each
hemisphere symmetric? In other words, do both hemispheres contribute identical control mechanisms to both arms, or is each hemisphere specialized for distinct control mechanisms.

Our current findings provide the answer to this critical question: each hemisphere appears to contribute distinct mechanisms to the control of both the arms. While LHD patients demonstrated deficits in intersegmental coordination (trajectory based errors) in both the arms, RHD patients demonstrated deficits in final position accuracy when adapting to a visuomotor rotation, as predicted by our model of motor lateralization (Sainburg, 2010; 2005). Our model is bi-hemispheric, and has been postulated based on several previous studies in young healthy adults. For example, Bagesteiro and Sainburg (2002) demonstrated limb-specific advantages to each arm during reaching movements: the dominant arm appeared to be better in controlling the trajectory of movements, and the nondominant arm appeared to be better in achieving an accurate final position. These previous studies led us to postulate that the dominant (left) hemisphere appears to be specialized for control of trajectory or intersegmental coordination, whereas the nondominant (right) hemisphere appears to be specialized for stabilizing the limb in the final position. Our recent studies examining ipsilesional (Schaefer et al., 2009b) and contralesional arm (Mani et al., 2013) performance during simple reaching movements provided the initial evidence supporting our model: LHD patients produced significantly high direction errors, implying deficits in intersegmental coordination, whereas RHD patients produced high final position errors, implying a deficit in stabilizing limb in final position. However, it should be mentioned that each of these studies examined only one arm of the stroke patients (ipsilesional or contralesional, but not both). If each
hemisphere contributes specific control mechanism to both the arms, then a critical test for such a model would be to demonstrate that damage to either hemisphere results in hemisphere-specific deficits in both the arms of the same stroke patients. To our knowledge, there has been no previous study that has provided this evidence.

Bilateral deficits following unilateral stroke

Over the years, there has been a considerable amount of research focused on understanding the contralesional deficits after unilateral stroke. For example, unilateral stroke has been shown to result in weakness, spasticity, reduced agonist & antagonist muscle activations (El-Abd et al., 1993;), hyperactive reflexes (Mizrahi and Angel, 1979), or presence of abnormal synergies (Dewald et al., 1995) in the contralesional arm of stroke patients. Recent studies have also reported a failure to account for dynamic intersegmental interactions (Beer et al., 2000), and in coordinating the actions of elbow and shoulder joints in the contralesional arm of stroke patients (Cirstea and Levin, 2000; Levin, 1996). However, studies from our lab narrowed down these coordination deficits in the contralesional (Mani et al., 2013) and ipsilesional arm (Schaefer et al., 2007; Schaefer et al., 2009b) of stroke patients to a specialization in left hemisphere, based on our model. However, whether left hemisphere damage contributes to coordination deficits in both the arms of same patients remained inconclusive. Our current findings now provide the first solid evidence for such coordination deficits in both the arms of the same LHD patients. During the adaptation session, the LHD group demonstrate significant errors in direction and hand path curvatures reflecting a deficit in intersegmental coordination, in both their arms, and these deficits seem to persist during the entire visuomotor adaptation session. In contrast, the control and RHD group seemed to adapt
to the visuomotor rotation, and improved their directional errors over the course of the adaptation session. These results are also consistent with earlier studies examining visuomotor adaptation in the ipsilesional (Schaefer et al., 2009a) arm of stroke patients. The higher direction and trajectory errors made by the LHD group in the current study cannot be attributed to these patients making fast movements because our results also indicate that the LHD group took significantly longer duration and had lower peak tangential velocity than both the RHD and control group, in both their arms. However, the inability of the LHD patients to adapt to the visuomotor rotation could also be attributed to the fact that all these patients had damage to the left parietal region, which has been shown previously to be critical for adapting to visuomotor rotations in the contralesional arm (Mutha et al., 2011). Thus, left hemisphere appears to be specialized for control of trajectory of movements, and parietal region, in particular, could be critical for visuomotor adaptation. In addition, we also observe such hemisphere-specific deficits to be present in both the arms of the same stroke patients in our current study - a finding that has significant clinical implications.

Previous studies have demonstrated that left hemisphere damage could result in unilateral neglect in the right hemispace (Beis et al., 2004). However, the trajectory based deficits observed in LHD patients cannot be attributed to unilateral visual neglect because none of the stroke patients in our study demonstrated neglect in a modified line cancellation task (Albert, 1973). In addition, several recent studies have suggested that right, but not left hemisphere damage produces contralateral visual neglect (Bottini et al., 2009; Pisella et al., 2011). Even earlier studies by Valler et al. (1986; 1993) have offered evidence that only patients with right inferior parietal damage demonstrate contralateral
visual neglect. Thus, the trajectory-based deficits in LHD patients cannot be attributed to unilateral visual neglect. Also, the final position errors of the LHD patients were as good as the control group during the entire adaptation session, suggesting that these patients had no problems in identifying and reaching accurately to the target. In contrast, the RHD patients made significantly high final position errors than the controls & LHD groups in both their arms during the entire adaptation session, despite making straighter movements as the control group. This finding is in agreement with our previous results examining ipsilesional arm performance of stroke patients (Schaefer et al., 2007; Schaefer et al., 2009a; 2009b), consistent with our model of motor lateralization. However, the movements made by RHD patients were similar in peak tangential velocity and duration when compared to the controls. Thus, the high final position errors made by the RHD group cannot be attributed to fast movements, but rather reflects the deficits in the limb-stabilizing mechanism of the damaged right hemisphere.

Overall, our current findings suggest that left hemisphere damage produces deficits in intersegmental coordination in both the arms, whereas right hemisphere damage produces deficits in stabilizing the limb in the final position in both the arms. Thus, our current findings in combination with our previous studies in unilateral stroke patients provide substantial and crucial evidence for ipsilateral hemispheric contributions to bilateral deficits in stroke patients.

Clinical Implications

It has been well documented that motor learning in the contralesional arm of stroke patients is one of the most critical aspects for a successful rehabilitation (Krakauer, 2006). Our current findings provide evidence that left hemisphere damage produces
deficits in adapting to novel visuomotor rotation tasks, suggesting a motor learning
deficit predominantly in LHD patients. In contrast, RHD patients do not demonstrate any
motor learning deficit, but demonstrate significantly larger errors in final position
accuracy, as predicted by our model of motor lateralization. Thus, our study brings out
distinct hemisphere-specific deficits in both the arms of unilateral stroke patients based
on the hemisphere of damage, suggesting that it’s not only just the contralesional arm that
demonstrates deficits, but the ipsilesional arm as well. We suggest that physical
rehabilitation should focus on addressing the deficits in the both the contralesional and
ipsilesional arm of stroke patients. Bilateral arm training for unilateral stroke patients
might be particularly useful, as it has been shown to improve bilateral arm performance
post rehabilitation (Whitall et al., 2000; Latimer et al., 2010). However, it has also been
suggested that only patients with left, but not right hemisphere damage demonstrate
improvements in their paretic arm following bilateral arm training (Waller and Whitall,
2005). For example, in the study by Waller and Whitall (2005), LHD patients
demonstrated improvements in elbow flexion, shoulder adduction, shoulder extension,
and Wolf Motor Arm test. In contrast, RHD patients did not demonstrate improvements
in any of these measures. Thus, it appears that hemisphere of damage plays a crucial role
in the outcome post-rehabilitation. Therefore, it is crucial that physical rehabilitation
protocols should be designed by taking into account the specific deficits produced by
stroke patients in both the arms, as demonstrated by our current study.
Figure 3-1: (A) Experimental setup; (B) Experimental task - During the baseline session the relation between the cursor and finger is veridical. During the adaptation session, the cursor was dissociated by 30° in the clockwise direction from the finger; (C) Lesion overlay of stroke groups.
Figure 3-2: Representative hand paths of subjects from each group. It can be observed that the LHD patient does not adapt to the rotation, and keeps making curved hand paths even in the last cycle, but achieves accurate final position. In contrast, the RHD subject adapts to the rotation, but makes high final position errors consistently.

Figure 3-3: Peak Tangential Velocity of all three groups in both the arms during the visuomotor rotation session.
Figure 3-4: (A) Mean ± SE for the initial direction error across all cycles in the adaptation session for the three groups: Controls (grey), LHD (black), and RHD (black). (B) Initial direction error across both the arms between the stroke and control groups during the entire adaptation session.
Figure 3-5: (A) Mean ± SE hand path curvature of the three groups: Controls (grey), LHD (black) and RHD (black) across all the cycles of the adaptation session. (B) Mean hand path curvature across both the arms between the stroke and control group during the entire adaptation session.
Figure 3-6: (A) Mean final position error across all three groups (Controls: grey, Stroke:
black) during the adaptation session. (B) Comparison of final position error between the three groups across all cycles during the adaptation session. (C) Mean final position error of each cycle of the adaptation session is plotted as a function of mean initial direction error of each cycle of the adaptation session for representative LHD and RHD patients. Each dot represents one cycle; Corresponding $r^2$ values are displayed in the bottom right corner of each scatterplot.
CONTRALESIONAL ARM PREFERENCE DEPENDS ON HEMISPHERE OF DAMAGE AND TARGET LOCATION IN UNILATERAL STROKE PATIENTS

Introduction

Stroke is the leading cause of permanent disability in the United States (Casper et al., 2003), often producing hemiparesis on the side of the body opposite to the side of the damaged hemisphere (i.e. contralesional). Unilateral stroke can often lead to patients avoiding using their contralesional arm for activities of daily living, and relying more on their ipsilesional arm. For example, Vega-Gonzalez & Granat (2005) reported that right-handed stroke patients use the ipsilesional arm more frequently than the affected arm due to contralesional hemiparesis. It is clinically important to address arm preference in chronic stroke patients because it has been shown that movement practice plays a critical role in sustaining and improving gains in performance developed during rehabilitation (Langhorne, Bernhardt & Kwakkel, 2011). In addition, learned non-use can negatively impact recovery, when patients avoid using the contralesional arm. Constraint induced movement therapy was developed to combat this learned non-use of the paretic arm after stroke with the goal of facilitating recovery (Taub & Morris, 2001). However, there could be several factors that influence arm choice in stroke patients. Haaland and colleagues (2012) found that arm use was influenced by laterality of stroke in right-handers. When performing simulated instrumental activities of daily living (IADLs) patients with left hemisphere damage (LHD) used their contralesional arm significantly more than patients with right hemisphere damage (RHD), which was attributed to the fact that the LHD
group’s contralesional arm was their preferred arm. However, as the dominant arm more frequently performs unilateral IADL tasks, these results may be biased due to using an IADL task.

The choice to use the contralesional or ipsilesional arm may also depend on the spatial requirements of the task. For example, in a recent study, we showed that healthy young adults presented with targets throughout the reachable workspace most often chose the ipsilateral arm to reach toward a target on the same side of the workspace. However, the dominant arm was chosen more frequently for targets near midline (Przybyla et al., 2013; Coelho et al., 2013). Thus, workspace location of the target appears to play a significant role in arm selection. Previous studies examining arm preference in stroke patients (Rexroth et al., 2005; Bernspang & Fisher, 1995) have not examined the influence of workspace location, as their focus was mostly on the functional outcome of the task. In addition, our recent studies in stroke patients have also showed that left and right hemisphere damage produces dissociable deficits in both the contralesional (Mani et al., 2013) and ipsilesional arm (Schaefer et al., 2009b) during reaching tasks. Thus, it stands to reason that the hemisphere of damage might also play a pivotal role in arm selection. In the current study, we examine whether patients with left or right hemisphere damage show different patterns of arm selection for a reaching task to targets that cover the horizontal plane workspace. The patients were matched for severity of motor impairment and lesion characteristics, and all patients were right hand dominant prior to stroke. Thus, we are able to directly determine whether the hemisphere of damage and the location of the targets influence arm selection patterns in a simple reaching task.
Materials and Methods

The Institutional Review Boards of the New Mexico Veteran Affairs Healthcare System and Hershey Medical Center approved the study protocol. Prior to participation, all subjects gave informed consent according to the Declaration of Helsinki (World Medical Association, 2002).

Participants

A total of 30 subjects participated in this study [16 healthy controls, 7 left hemisphere damaged (LHD) patients, 7 right hemisphere damaged (RHD) patients]. All control subjects self-reported current right-handedness, and all stroke patients self-reported right-handedness prior to stroke. All stroke patients were examined at least 6 months after stroke. Subjects were excluded if they had a history of or current (i) substance abuse or other significant psychiatric diagnosis (e.g., psychosis); (ii) non-stroke neurological diagnoses for the stroke patients and all neurological diagnoses for the control subjects; or (iii) peripheral movement restrictions, such as neuropathy or orthopedic disorders. Measures of hemiparesis (Fugl-Meyer et al., 1975), and auditory comprehension (Kertesz, 1982) were used to characterize the degree of impairment in stroke patients across different domains. None of the stroke patients in our study demonstrated unilateral visual neglect, as confirmed by performance on the line cancellation task (Albert, 1973).

Experimental setup and task

The experimental setup is shown in Figure 4-1. Subjects sat facing a table with both their left and right arm supported over a horizontal surface by an air-jet system to eliminate the effects of gravity and reduce friction. This support allowed patients to
perform the task with both arms, without demonstrating or reporting fatigue. Two start circles, targets, and the subject’s fingertips (represented by an on-screen cursor) were displayed on a mirror using an HDTV positioned horizontally above the mirror. The mirror blocked the direct vision of the subject’s arm, but reflected the visual display to give the illusion that the display was in the same horizontal plane as the fingertip. Position and orientation of the forearm and upper-arm segments were sampled using a Flock of Birds (Ascension Technology®) system at 130 Hz. The positions of the index finger tip, lateral epicondyle of the humerus and the acromion, directly posterior to the acromio-clavicular joint were digitized using a stylus that was rigidly attached to a 6-DOF Flock of Birds sensor. As sensor data were received, the 3D position of the above-mentioned landmarks was computed using custom software, with the X-Y plane parallel to the tabletop. We used the computed X-Y coordinates of the fingertip to define the projected cursor position.

The experimental task involved reaching to 32 targets, presented one at a time, across the workspace in front of the subject (Figure 4-1). Prior to the start of each trial, the two start circles and cursors (representing the fingertip of each arm) were displayed on the screen. Each start circle required the arm to be positioned at 30° shoulder flexion and 75° elbow flexion, as depicted in Figure 4-1. To initiate the trial, the subject brought both the cursors into the start circles and after a 500 ms delay, one of the targets appeared on the screen along with an audio-visual “go” signal, which cued the subjects to initiate a single, rapid movement toward the target. The subjects were free to choose whichever arm they wanted to perform the reaching movement. Once the trial was completed, the subjects returned their fingertips to the start positions to begin a new trial. The 32 targets
were pseudo-randomly presented over a session of 512 trials, such that no target was presented consecutively.

**Measures**

To quantitatively determine the preference for using the dominant or premorbidly-dominant right arm, right arm preference was computed as a ratio of the number of reaches performed using the right arm to the number of reaches performed using the left arm for each subject (Figure 4-3A). We also quantified the percentage of contralesional arm reaches to all targets (Figure 4-3B) and to the targets on the body’s midline, which were equidistant from either arm’s starting location (Figure 4-3C) in the stroke patients. In order to assess the effect of workspace region on arm choice, we computed the average frequency of right and left arm reaches to each target across subjects and used these data to identify the midline of reaching frequency (RF Midline) using a linear approximation to points in space that yielded 50% of right arm reaches at each row of targets (see Figure 4-4). We also quantified the offset of the RF Midline from the body’s midline at each row of targets. This RF Midline offset was computed as a percentage of the distance from the midline of the body and the extreme left or right target at each row (Przybyla et al., 2013).

**Statistical Analysis**

The arm choice between the three groups (control, LHD, RHD) was analyzed using a one-way ANOVA with group as the factor and right arm preference as the dependent measure. Contralesional arm reaching performances between LHD and RHD groups were analyzed using a one-way ANOVA with laterality of damage (left or right) as a factor and the percentage of contralesional arm use as the dependent measure. RF
Midline Offset was analyzed using a 2-way ANOVA with row (1/2/3/4) and group (control, LHD, RHD) as factors. When warranted, post-hoc analyses were performed using Tukey HSD test, which corrects for multiple comparisons (Kutner, 2004). Statistical significance levels were set to 0.05. All statistical analyses were carried out using the software JMP (SAS Institute Inc., USA).

Results

Table 4-1 shows that all three groups (control, LHD, RHD) were matched for age ($F_{2,27} = 1.52; P = 0.23$) and education ($F_{2,27} = 0.96; P = 0.39$). The stroke groups (LHD, RHD) were not significantly different for upper extremity motor impairment (Fugl-Meyer motor score (FM): $F_{1,12} = 0.72; P = 0.41$), or time post-stroke ($F_{1,12} = 0.28; P = 0.61$). The FM scores of the patients in this study ranged from 46 to 64, indicating moderate to mild motor impairment. Figure 4-2 shows the superimposed lesion locations for all subjects within each stroke group. All lesions were confined to either the left or right hemisphere. All patients had damage in at least one region of the sensorimotor system (Broadmann areas 4,6,3,1,2, internal capsule), and the intrahemispheric lesion locations were similar, though slightly more posterior in the LHD group. Lesion volumes were not significantly different between the two groups ($F_{1,12} = 0.02; P = 0.92$).

Figure 4-3 shows the patterns of arm choices for all 3 groups across all targets (4-3A), and comparing only the stroke groups’ contralesional reaches (all targets, 4-3B or only the 4 midline targets, 4-3C). Figure 4-3A shows that the RHD group chose their right arm substantially more than did the control and LHD groups across all targets as confirmed by a significant main effect of group ($F_{2,27} = 3.43, P = 0.04$). Post hoc analyses
indicated that the right arm preference of the RHD group was significantly greater than the control group (P = 0.04), and because of the nature of the ratio measure (right hand/left hand) this finding also shows that the RHD group used their left arm significantly less than the control group. In addition, there was no significant difference between the control and LHD groups (P = 0.97). These findings indicate that the LHD group chose to use their contralesional, right arm as often as the control group used their right arm, despite mild to moderate paresis. In contrast, the RHD group chose to use their contralesional, non-dominant arm less than control subjects chose to use their left, non-dominant arm across the entire workspace.

Figure 4-3B directly compares the choice to reach with the contralesional arm between LHD and RHD groups to all targets. The percentage of contralesional arm reaches for the RHD group was lower than that of the LHD group. Because the midline targets were equidistant from both the right and left hand start positions, these targets had no geometrical or biomechanical bias. We, thus separately compared contralesional reaches to these symmetrically positioned targets (Figure 4-3C). This comparison revealed that the RHD group used their contralesional arm less than the LHD group, which was confirmed by ANOVA, which showed statistically significant main effect of group for all targets (F_{1,40} = 4.93; P = 0.03) and midline targets (F_{1,12} = 27.9; P = 0.0002). This result suggests that the preference of using the dominant arm is preserved in LHD patients, while RHD patients reach more with the dominant arm than do control subjects.

To examine the effect of workspace location on hand choice, we evaluated the reach percentage of each arm to each target across all 3 groups, as shown in Figure 4-4. We then calculated the midpoint of reach frequency for each target row, and the reach
frequency midline indicates the interpolated location in space, in which 50% of the reaches would be made with left arm and 50% with the right arm. One can think of this as the point in space in which a subject switched their reaching preference to the other hand. Our ANOVA revealed a significant effect of group ($F_{2,108} = 9.81; P < 0.0001$) for RF midline offset. Post-hoc analysis revealed that the RF midline offset was significantly leftward for the RHD group, when compared to the control and LHD groups ($P < 0.0058$, in both cases). However, the RF midline offset of the LHD group was not significantly different from the control group ($P = 0.79$). This indicates that the RHD patients reached significantly further across the midline than did the control group. In contrast, the LHD patients reached with their contralesional right arm across midline to the same extent as the control group. We conclude that in right-handers, the side of hemisphere damage interacts with premorbid hand preference following stroke. If the nondominant arm is contralesional (RHD patients), the preference to use that arm drops significantly, whereas if the dominant arm is contralesional (LHD patients), the patients’ preference to use that arm is retained.

**Discussion**

Previous studies (Haaland et al., 2012; Rinehart et al., 2009) that have examined arm use during IADL tasks have suggested that right and left hemisphere damaged patients tend to use their contralesional arm to different extents. However, ADL tasks do not allow one to examine the influence of workspace location on arm preferences. In addition, premorbid patterns of ADL performance could strongly bias arm use patterns in such tasks. In the current study, we presented an arm choice paradigm, in which subjects
had the option to reach with either arm to each of 32 targets that were distributed throughout the reachable horizontal plane workspace. Our results indicated that the laterality of hemispheric damage has a substantial impact on the choice to use the contralesional arm, such that LHD patients are more likely to choose their contralesional arm, than are RHD patients. Thus, the hemisphere that is damaged has a substantial impact on the patient’s choice to use the contralesional arm, and this choice is also modulated by the location of the target in the workspace. The RHD group used their right (ipsilesional) arm substantially more than the controls to reach across the midline to the left hemispace, but the LHD group’s decision to use their right (contralesional) arm was similar to that of control participants.

*The influence of side of lesion on limb choices*

Our mildly hemiparetic stroke groups (RHD and LHD) and our control participants reached to an array of 32 targets, that covered the reachable horizontal plane workspace. Our findings revealed a consistent bias of RHD patients against reaching with the non-dominant contralesional arm. Because our groups were matched for degree of motor impairment and lesion size and their lesion locations were fairly similar, our findings are not likely to have resulted from the degree of hemiparesis or intrahemispheric lesion characteristics. The tendency to avoid use of the contralesional arm in RHD patients was modified substantially by workspace region. While almost all targets in the far right or far left of the workspace were reached using the right arm for right space and left arm for left space, the dominant arm bias of RHD patients was strongest in the midline regions. In contrast, for LHD patients, their arm choices were similar to that of our healthy age matched control group despite right hemiparesis. The
tendency of RHD patients to avoid using the contralesional non-dominant arm is consistent with previous findings during simulated activities of daily living (Haaland et al., 2012). The current results extend these findings to show that this tendency is not due to the nature of daily living activities, but persists for simple reaching movements. In addition, we show that workspace location modulates these choices, especially in RHD patients. Specifically, the RHD patients are likely to use their contralesional arm only in the left side of the workspace. Thus, the location of objects in the workspace can counteract the tendency of these patients to avoid the use of the contralesional non-dominant arm. We expect that this information can be important in structuring rehabilitation experiences to encourage spontaneous contralesional arm choices in patients with right hemisphere damage.

The influence of workspace location

Previous studies that have examined arm preference across the workspace have shown that healthy adults generally prefer to make ipsilateral reaches, avoiding crossing the midline (Peters, 1996; Gabbard & Rabb, 2000). The rationale for this is that reaches that cross midline require more energy (Carey et al., 1996), although some have also attributed the tendency to the greater demands of intrahemispheric visual-motor processing (Verfaellie & Heilman, 1990). However, even in healthy adults this reaching pattern appears to be asymmetric, with the dominant arm making slightly more reaches into the contralateral hemispace (Przybyla et al., 2013; Stins et al., 2001; Gabbard & Rabb, 2000). In the current study, our findings for healthy aged matched control subjects are generally in agreement with these previous studies. However, the percentage of reaches into the contralateral hemispace with the dominant right arm were not as high as
that observed for young adults in several previous studies (Stins et al., 2001; Bryden et al., 2000), even those with the same array of targets as we presented in our current study (Przybyla et al., 2013). This difference in reaching pattern between young (Przybyla et al., 2013) and older adults (current study) could be attributed to the reported reduction in motor performance and motor transfer asymmetries with aging (Przybyla et al., 2011; Wang et al., 2011). Consistent with this idea, neuroimaging studies have shown that, as people age, there is a considerable reduction of hemispheric asymmetry (Cabeza, 2002).

The current study shows that the hemisphere of damage modulated the pattern of arm choices across the horizontal plane workspace (Figure 4-4). RHD patients used their right, dominant arm to reach across the midline to the contralateral hemispace significantly more than did the age matched control subjects. This difference seems to persist irrespective of the distance from the body required for the reach. In contrast, the pattern of reaches for the LHD patients was similar to that of the age matched control group. These findings suggest that when the non-dominant arm was contralesional (as for the RHD group), the patients’ preference to use that arm to reach to targets was substantially reduced, compared to when the contralesional arm was dominant.

These findings bring up the question of whether this pattern of choices would occur during more natural activities of daily living. More recently, Haaland and coworkers (Haaland et al., 2012; Rinehart et al., 2009) investigated arm use during simulated activities of daily living in stroke patients. In these studies, patients performed instrumental activities of daily living (IADL), including tasks such as writing checks, using a telephone, and meal preparation. The performance in these IADL tasks was assessed using either the Arm Motor Ability Test (Kopp et al., 1997) or the Functional
Impact Assessment (Sadek et al., 2011) and duration of contralesional and ipsilesional arm movements was quantified separately using accelerometers. Both studies reported that the RHD patients used their ipsilesional arm significantly more often than the LHD patients, while one (Haaland et al., 2012) reported that RHD patients used their contralesional arm less than LHD patients. It should be stressed that many of these tasks are normally performed unilaterally by the dominant arm, and therefore might show a bias based on premorbid task practice. However, taken together with our current study, we can conclude that RHD reduces the tendency to spontaneously choose the contralesional left arm for reaching or while performing activities of daily living. In contrast, left hemisphere damage has little effect on arm choices, when the severity of motor impairment is mild to moderate. The study by Haaland et al (2012) suggest that the asymmetry in this pattern may persist with more severe impairments. Based on these findings, we suggest that the side of hemisphere damage may play a significant role in the degree to which the effects of physical rehabilitation are transferred from the clinic to the home setting, where patients make spontaneous choices about arm use.

Implications for Rehabilitation

The current findings might be important in structuring rehabilitation for patients with unilateral stroke. Our findings, taken together with the literature reviewed above, indicate that right-handed patients with right hemisphere stroke show a strong tendency to avoid using their contralesional, nondominant arm. It is important to note that neither our study nor previous studies have systematically examined left-handed stroke patients; therefore we cannot directly generalize our findings to this group. Nevertheless, we consider our findings important because of the impact that this trend may have on
contralesional impairment during and following rehabilitation after stroke. It has been well established that when patients do not use their paretic arm, learned nonuse develops, which is associated with further motor deterioration (Taub & Morris, 2001). Our current findings may be a result of the greater tendency of the RHD group to avoid spontaneously using the nondominant arm, especially as our stroke patients were in the chronic stage of recovery (at least 6 months post stroke). Our results suggest that the previous findings (Harris & Eng, 2006) in hemiparetic stroke patients showing greater motor deficits in the contralesional nondominant as compared to the contralesional dominant arm may be related to this tendency to avoid spontaneously using the nondominant paretic arm and learned non-use.

To sustain and improve gains in performance developed during rehabilitation, it is critical for patients to continue to use the contralesional arm in non-supervised settings. In fact, regardless of intervention technique, it appears that movement practice may be the single most critical determinant in the efficacy of movement training interventions (Langhorne et al., 2011). Good et al (2011) recently conducted a meta-analysis, which indicated that physical rehabilitation programs of greater intensity and longer duration tended to produce better outcomes (Langhorne & Duncan, 2001). Unfortunately, due to current reimbursement limitations, patients rarely spend more than a few weeks in intensive rehabilitation centers following stroke. This emphasizes the importance of the spontaneous choices that individuals make to use the contralesional arm in unsupervised settings. We now suggest that occupational and physical therapists pay particular attention to encouraging right hemisphere damaged patients to choose the contralesional arm in the therapeutic environment. It is plausible that shaping these choices through
successive approximations of workspace location might develop patterns that can be carried out in more natural settings. For example, placing objects in the far left of the workspace would tend to produce spontaneous left-hand reaches. Gradually moving the objects toward the midline during successive reaches might encourage habitual patterns of choice that may be carried out in more natural settings. Techniques such as constraint-induced therapy could be combined with these manipulations to further offset the RHD patients’ tendency to avoid using the contralesional arm (Treger et al., 2012; Wolf et al., 2008; Caimmi et al., 2007; Krakauer, 2006).

**Limitations in our current study and future directions**

We designed this study to determine whether the hemisphere of damage influences one’s choice to use the contralesional or ipsilesional arm, following stroke. We hypothesized that left and right hemisphere damage might produce asymmetrical influences on limb choices, based on previous reports, indicating differential effects of left and right hemisphere lesions on motor control (Mani et al., 2013; Schaefer et al., 2009b) and use (Haaland et al., 2012) of each arm. We limited our subjects’ selection to those patients with moderate to low hemiparesis (Fugl-Meyer score > 45), so that all patients could successfully reach to all targets in the workspace. We also restricted movements to a two-dimensional surface, in order to reduce potential mechanical asymmetries associated with different limb elevation postures (Ellis et al., 2006) and to reduce the potential for fatigue. Finally, we restricted our patient population to premorbid right-handed patients. This was done for two reasons: First, we matched patients for lesion size and location, as well as impairment level, between our groups. This type of matching precluded our ability to include left-handers, because there were simply not
enough left-handed patients in our database to differentiate by lesion characteristics and by impairment level. Second, our previous research upon which we based our hypotheses was similarly restricted to right-handers. Overall, our current study has certain limitations, which raise important questions for future research. These include questions regarding the generality of our results to unconstrained movement conditions, and to left-handed patient groups. However, we believe that our findings provide strong evidence that the side of brain damage has a substantial impact on spontaneous choices to use the contralesional arm following sensorimotor stroke.

Figure 4-1: Schematic of the experimental setup. Subjects sat facing a mirror onto which the start position and targets were projected using a HDTV, and rested their arms in an air-sled system placed on a glass tabletop. The top-view of the experimental interface depicting targets and start circles is also shown.
Figure 4-2: Overlap images showing locations of lesions for the (A) right and (B) left hemisphere damaged groups; Color scale of magenta to yellow shows increasing overlap.
Figure 4-3: (A) Comparison of mean right arm preference (ratio of right arm reaches to left arm reaches) across the three groups (control, LHD, RHD) for all targets. (B) Comparison of contralesional arm reaches between LHD and RHD patients to all targets, and (C) to midline targets (the 4 targets located on the midline of the body).
Figure 4-4: Reach Frequency to each target for each group: (A) Control, (B) LHD and (C) RHD (Dark shade: right arm reach frequency; Lighter shade: left arm reach frequency). The line depicts the Reach Frequency midline for each group. (D) Comparison of Reach Frequency Offset across each group by the row number.

Table 4-1: Demographic information of subjects

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>LHD</th>
<th>RHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>16</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.37 ± 6.11</td>
<td>65.42 ± 6.6</td>
<td>61.85 ± 11.39</td>
</tr>
<tr>
<td>Education</td>
<td>15.3 ± 2.49</td>
<td>16.0 ± 3.05</td>
<td>14.0 ± 3.05</td>
</tr>
<tr>
<td>Fugl Meyer score</td>
<td>N/A</td>
<td>60.57 ± 3.95</td>
<td>58.29 ± 5.88</td>
</tr>
<tr>
<td>Lesion volume (cm³)</td>
<td>N/A</td>
<td>114.47 ± 132.30</td>
<td>120.81 ± 79.82</td>
</tr>
<tr>
<td>Years post-stroke</td>
<td>N/A</td>
<td>3.52 ± 2.01</td>
<td>4.88 ± 6.54</td>
</tr>
</tbody>
</table>
The purpose of this dissertation was to examine whether the arm preference and upper extremity motor deficits of unilateral stroke patients vary based on the hemisphere of damage. We expected that the motor deficits in the contralesional and ipsilesional arm of stroke patients would reflect the deficits of the specific control mechanisms of the damaged hemisphere, based on our model of motor lateralization (Sainburg, 2002). Specifically, we predicted that left but not right hemisphere damage should produce deficits in the trajectory measures of reaching, whereas right but not left hemisphere damage should produce deficits in stabilizing the limb in the final position. In addition, based on differential contributions of each hemisphere to arm control and from previous studies that have observed differences in arm use pattern during activities of daily living (Rinehart et al., 2009; Haaland et al., 2012), we expected that left hemisphere damaged patients would prefer to use their contralesional arm to a greater extent than that of the right hemisphere damaged patients. Our three studies supported our hypothesis by revealing hemisphere-specific deficits in both the contralesional and ipsilesional arm of unilateral stroke patients: left hemisphere damaged patients demonstrated significantly high errors in trajectory measures, whereas right hemisphere damaged patients demonstrated significantly high final position errors. In addition, we also observed that the contralesional arm preference of unilateral stroke patients was also modulated by hemisphere of damage and workspace location of the target.
The aim of the first study was to determine whether the contralesional motor deficits produced by unilateral stroke patients reflect deficits in the hemisphere-specific control mechanisms. In a three-directional reaching task, we observed that left but not right hemisphere damaged patients made significantly high errors in initial direction and hand path curvatures, whereas right but not left hemisphere damaged patients made significantly high distance errors, due to overshooting the target. However, in contrast to our previous studies examining the ipsilesional arm performance in stroke patients (Schaefer et al., 2007; 2009b), in our current study, both the stroke groups made significantly high final position errors when compared to their respective control group. A closer inspection of the hand paths made by stroke patients revealed that the final position errors made by the left hemisphere damaged patients was because of their inability to correct their movements, which were deviating away from the target (directional errors). In contrast, the hand path directions of the right hemisphere damaged patients were in line with the target direction, but they were not able to stop accurately at the target, thereby resulting in large overshoots causing high final position errors. It was also observed that the hemisphere-specific deficits demonstrated by left hemisphere damaged patients also varied with the severity of impairment, with the moderately impaired group demonstrating much higher errors in trajectory measures when compared to the mildly impaired left hemisphere damaged group, whereas the severity of impairment did not modulate the differences in distance error for patients with right hemisphere damage. It is difficult to explain this asymmetrical dependence of performance errors on the severity of impairment, evaluated by using Fugl-Meyer upper extremity motor assessment test (Fugl-Meyer et al., 1975). It might simply be because the
variations in severity of impairment may have a more graded effect on the ability to coordinate segments of the arm than on the ability to stop at a given location. However, the disparity between the performance measures and clinical measures of impairment requires further research.

The aim of our second study was to determine whether damage to one hemisphere produces hemisphere-specific deficits in both the arms of unilateral stroke patients. In this experiment, stroke patients and control participants adapted to a visuomotor rotation over 160 trials with each arm. Our results revealed that the left but not right hemisphere damaged group demonstrated significantly high initial direction errors and hand path curvatures with both their arms when compared to the controls. In contrast, the right but not left hemisphere damaged group demonstrated significantly high final position errors with both their arms when compared to the controls. In addition, the high final position errors made by the right hemisphere damaged group did not correlate with the direction errors at the end of movement, suggesting that these final position errors were due to overshoots rather than deficits in adapting to the rotation. These findings directly support our hypothesis by indicating that each hemisphere contributes specific mechanisms to the control of each arm, and are also consistent with our previous study examining ipsilesional arm adaptation to visuomotor rotation (Schaefer et al., 2009a). To our knowledge, this is the first study to demonstrate that damage to either hemisphere produces hemisphere-specific deficits in both the ipsilesional and contralesional arm of stroke patients, which has crucial implications for clinical rehabilitation.

The aim of our third study was to determine whether contralesional arm preference in stroke patients is influenced by hemisphere of damage and target location in
the workspace. Several previous studies in the literature have examined the arm use pattern in unilateral stroke patients when they performed activities of daily living (Rinehart et al., 2009; Haaland et al., 2012), and they observed that the arm use pattern was modulated by hemisphere of damage, with the left hemisphere damaged group using their contralesional arm to a greater extent than the right hemisphere damaged group. However, as these tasks resemble daily activities, they are influenced by premorbid habitual patterns of executing these tasks, and are biased to the premorbid dominant arm (right arm). Our current study was designed to overcome such limitations and comprehensively examine arm preference in chronic stroke patients by having them reach to a horizontal plane array of 32 targets, which was presented one at a time, in a pseudo-random sequence. Our results indicate that the left hemisphere damaged group prefers to reach using their contralesional arm much more than the right hemisphere damaged group’s preference to use their contralesional arm, when comparing across all the targets. Even when comparing only the midline targets, which had no geometrical or biomechanical bias, the contralesional arm reaches made by right hemisphere damaged patients was much lower than the contralesional arm reaches made by left hemisphere damaged group. In addition, our results also revealed that the target location in the workspace modulated the reaching preference in the stroke groups, with the right hemisphere damaged patients using their ipsilesional right arm more frequently to cross over the midline into their contralesional hemispace; thereby making much fewer reaches with their contralesional arm. Thus, our findings demonstrate that when the contralesional arm is premorbidly dominant (left hemisphere damaged group), the preference to use that arm is similar to the control group, in mild to moderately impaired
patients. However, when the contralesional arm is premorbidly non-dominant (right hemisphere damaged group), the preference to use that arm decreases significantly, even in mild to moderately impaired patients.

*Future directions and clinical implications*

The finding that the contralesional and ipsilesional deficits depending on the side of damage has crucial implications for the design of clinical rehabilitation intervention.

We suggest that physical rehabilitation should focus on addressing the deficits in the both the contralesional and ipsilesional arm of stroke patients. Bilateral arm training for unilateral stroke patients might be particularly useful, as it has been shown to improve bilateral arm performance post rehabilitation (Whitall et al., 2000; Latimer et al., 2010). However, it has also been suggested that only patients with left, but not right hemisphere damage demonstrate improvements in their paretic arm following bilateral arm training (Waller and Whitall, 2005). For example, in the study by Waller and Whitall (2005), LHD patients demonstrated improvements in elbow flexion, shoulder adduction, shoulder extension, and Wolf Motor Arm test. In contrast, RHD patients did not demonstrate improvements in any of these measures. Thus, it appears that hemisphere of damage plays a crucial role in the outcome post-rehabilitation. In addition, our findings indicating a declined preference of RHD patients to use their contralesional arm might warrant the use of Constraint Induced Physical Therapy as a rehabilitation paradigm for RHD patients (Mark and Taub, 2004). In future, we suggest that rehabilitation protocols could be designed to address the specific deficits that emerge after left or right hemisphere damage. For example, for left hemisphere damaged patients, task feedback can be modified to amplify errors perpendicular to the desired trajectory while reducing errors in
the direction of the desired movement. Such changes would penalize deviations from
desired movement while allowing errors in direction of movement. In contrast, following
right hemisphere damaged patients, tasks that penalize final position errors could be
designed. Overall, we suggest that stroke rehabilitation should not adapt a ‘one-size-fits-
all’ approach in implementing a particular physical rehabilitation for stroke patients.
Rather, it is crucial that physical rehabilitation protocols be designed by taking into
account the hemisphere of damage, and the specific deficits demonstrated by stroke
patients in both the arms.
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APPENDIX

CONTRALESIONAL MOTOR DEFICITS AFTER UNILATERAL STROKE REFLECT HEMISPHERE-SPECIFIC CONTROL MECHANISMS
Contralesional motor deficits after unilateral stroke reflect hemisphere-specific control mechanisms

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We have proposed a model of motor lateralization, in which the left and right hemispheres are specialized for different aspects of motor control: the left hemisphere for predicting and accounting for limb dynamics and the right hemisphere for stabilizing limb position through impedance control mechanisms. Our previous studies, demonstrating different motor deficits in the ipsilesional arm of stroke patients with left or right hemisphere damage, provided a critical test of our model. However, motor deficits after stroke are most prominent on the contralesional side. Post-stroke rehabilitation has also, naturally, focused on improving contralesional arm impairment and function. Understanding whether contralesional motor deficits differ depending on the hemisphere of damage is, therefore, of vital importance for assessing the impact of brain damage on function and also for designing rehabilitation interventions specific to laterality of damage. We, therefore, asked whether motor deficits in the contralesional arm of unilateral stroke patients reflect hemisphere-dependent control mechanisms. Because our model of lateralization predicts that contralesional deficits will differ depending on the hemisphere of damage, this study also served as an essential assessment of our model. Stroke patients with mild to moderate hemiparesis in either the left or right arm because of contralateral stroke and healthy control subjects performed targeted multi-joint reaching movements in different directions. As predicted, our results indicated a double dissociation; although left hemisphere damage was associated with greater errors in trajectory curvature and movement direction, errors in movement extent were greatest after right hemisphere damage. Thus, our results provide the first demonstration of hemisphere specific motor control deficits in the contralesional arm of stroke patients. Our results also suggest that it is critical to consider the differential deficits induced by right or left hemisphere lesions to enhance post-stroke rehabilitation interventions.

Keywords: lateralization; stroke; motor control; reaching movements; impairment

Introduction

A large body of research has now established that the two cerebral hemispheres show a considerable degree of lateralization or a specialization for controlling different aspects of behaviour. Although such neural lateralization has been characterized primarily through studies of perceptual and cognitive processes, behavioural and neuroimaging studies have raised the possibility that the...
right and left hemispheres play different roles in the motor control of either arm. Based on our work in young healthy individuals, we have proposed a model of motor lateralization, in which each hemisphere has become specialized for different aspects of motor control, such that the ‘dominant/left’ hemisphere is critical for predicting limb and task dynamics, and the opposite, ‘non-dominant/right’ hemisphere is critical for specifying steady-state limb positions through impedance control mechanisms (see Sainburg, 2010 for a review). Our recent work in patients with unilateral brain damage (Schaefer et al., 2007, 2009a, b; Mutha et al., 2010, 2011a, b; Schaefer et al., 2012) and findings from other previous studies (Haaland and Harrington, 1989; Harrington and Haaland, 1991; Bernspang and Fisher, 1995; Weinstein and Pohl, 1995; Haaland et al., 2004) have provided a confirmation for hemispheric specialization for movement control. For example, our study examining movement coordination in right-handed stroke patients (Schaefer et al., 2009b) showed a clear double dissociation between hemisphere status (healthy/hemisphere damage) and arm (right/left) for different features of movement. Patients with left hemisphere damage, but not right hemisphere damage, showed errors in direction and linearity of reaching movements that were associated with poor coordination of intersegmental dynamics. In contrast, patients with right hemisphere damage made well-coordinated and fairly straight movements, but they showed large and highly variable final position errors. In more recent studies, we have significantly expanded on these initial results by demonstrating differential deficits in motor adaptation and error correction mechanisms in left and right hemisphere damage stroke patients (Schaefer et al., 2009a; Mutha et al., 2011b; Schaefer et al., 2012). These studies have consistently revealed a deficit in predictive control after left hemisphere damage and final position control after right hemisphere damage, in line with the predictions of our model.

Our stroke studies were initiated as a critical test of this framework of hemispheric specialization for movement. We reasoned that if a hemisphere contributes its specialization to the movements of both arms, then motor deficits after damage to that hemisphere should be evident even if the ipsilesional arm in stroke patients is used to perform the task. Our studies, therefore, almost always required subjects to use their ipsilesional arm. However, given the crossed organization of the motor system, motor deficits after stroke are most prominent on the contralesional side. Therefore, most studies in stroke patients have, unsurprisingly, been dedicated to understanding the nature of these contralesional motor deficits. These studies have shown that although weakness and spasticity are common with contralesional hemiparesis (Bobath, 1990), coordination is also a major problem, particularly during point-to-point reaching tasks. For example, Beer et al. (2000, 2004) demonstrated systematic direction errors and poor interjoint coordination with the contralesional arm in a 16-direction centre-out reaching task. In this task, all four directions comprised a quadrant in task space, and deficits were largest in the two quadrants where intersegmental coordination requirements were greatest. Similarly, Levin (1996) and Cirstea and Levin (2000) showed that when stroke patients made horizontal plane reaching movements with the paretic arm, their movements were characterized by high variability and poor synchrony between elbow and shoulder joint motions. In light of these significant contralesional deficits, motor rehabilitation after stroke has also focused on improving the functioning of the contralesional arm. In fact, newer therapeutic approaches, such as constraint-induced movement therapy (Taub et al., 1993; Mark and Taub, 2004), emphasize forced and repetitive use of the contralesional arm while also preventing use of the ipsilesional arm as a means to improve contralesional arm performance.

Despite such strong emphasis on understanding contralesional deficits and improving contralesional arm function, previous studies have not been coupled with the growing body of work that addresses hemispheric specificity for movement control mechanisms. One potential reason for this could be the concern that spasticity, weakness and variability in degree of impairment in the contralesional limb could mask any performance asymmetries. Nevertheless, understanding whether neural lateralization results in contralesional deficits that differ depending on the hemisphere of damage is of critical importance for assessing the impact of brain damage on function and also for designing rehabilitation protocols specific to the impaired limb. In this study, we ask whether the motor deficits in the contralesional arm of unilateral stroke patients reflect hemisphere-specific control mechanisms. Our model of lateralized control predicts clear differences in contralesional motor deficits depending on the laterality of stroke; therefore, this study also serves as a critical test of our model. We overcome the potential limitation of contralesional spasticity and reduced motor abilities by examining patients with only mild to moderate hemiparesis, defined by a score &gt;45 (of a maximum possible 66) on the Fugl-Meyer Assessment of Upper Extremity Function.

Materials and methods

The Institutional Review Boards of the New Mexico Veteran Affairs Healthcare System and Hershey Medical Centre approved the study protocol. Before participation, all subjects gave informed consent according to the Declaration of Helsinki.

Participants

Eighteen unilateral stroke patients (nine with left hemisphere damage, nine with right hemisphere damage; one patient with right hemisphere damage tested at Hershey Medical Centre, others at New Mexico Veteran Affairs Healthcare System) and 20 healthy control subjects (10 left healthy control subjects, 10 right healthy control subjects; all tested at New Mexico Veteran Affairs Healthcare System) participated in this study. All control subjects were right-handed, and the stroke patients were right-handed before the incidence of stroke. Handedness was determined using the 10-item version of the Edinburgh Inventory (Oldfield, 1971). All stroke patients were examined at least 6 months after stroke. All the subjects were screened and excluded based on history of: (i) substance abuse and/or serious psychiatric diagnosis (e.g. psychosis); (ii) non-stroke neurological diseases for the stroke patients and all neurological diagnoses for the control subjects; and (iii) peripheral movement restrictions, such as neuropathy or orthopaedic disorders. Measures of hemiparesis (Fugl-Meyer et al., 1975), grip strength (Heaton et al., 2004), auditory comprehension (Kertesz, 1982), limb apraxia (Haaland and Flaherty, 1984) and visuospatial perception (Judgement of Line Orientation, Benton et al., 1994)
were used to characterize the degree of impairment in stroke patients across different domains. A modified line cancellation test was administered to all subjects to test for visual neglect (Albert, 1973). Patients with two or more errors (of the 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.

Table 1 summarizes the characteristics of each subject group. We restricted our patient population to only those who had mild to moderate hemiparesis, as indicated by a Fugl-Meyer score of 45 (of a maximum possible 66) (Murphy et al., 2010). This was done to ensure that subjects could still perform the task with their contralesional arm, yet contralesional hemiparesis was not so extreme that it masked asymmetries between the arms. Further, we intentionally matched our patients with left and right hemisphere damage on the Fugl-Meyer score to rule out the possibility that any group differences in arm reaching could be attributed to a difference in the degree of hemiparesis. The four groups were not significantly different in age ($F(3,34) = 0.61$, $P = 0.61$) or education ($F(3,34) = 2.53$, $P = 0.07$). Our groups were also fairly well balanced in terms of number of male and female participants (Table 1; $ \chi^2(3,38) = 3.65$, $P = 0.30$), suggesting that sex differences should be accounted for when comparing the left and right hemisphere damage groups, which was the more critical comparison for the current study. However, we should state that our current sample sizes precluded our ability to examine sex as a factor in our analyses. Subjects with left and right hemisphere damage did not significantly differ in number of years post-stroke ($P = 0.28$), lesion volume ($P = 0.94$) or contralesional grip strength ($P = 0.18$). Patients with left hemisphere damage were more apraxic than patients with right hemisphere damage ($P = 0.01$), consistent with the observations of several previous studies (De Renzi et al., 1980; Haaland and Flaherty, 1984; Ochipa and Gonzalez Rothi, 2000). Auditory language comprehension was also significantly weaker in the group with left hemisphere damage ($P = 0.04$). However, we made sure that all subjects understood the experimental task they were asked to perform, and task performance in general indicated that they did so. None of the participants had visual neglect, and visuospatial perception on Judgement of Line Orientation test was not significantly different between the two stroke groups ($P = 0.994$). High-resolution T1-weighted MRI scans were obtained from stroke patients and were then normalized to a standard template in Montreal Neurological Institute space using unified segmentation and normalization routines in SPM8 (Ashburner and Friston, 2005) and custom MATLAB scripts. Lesions were then reconstructed on the anatomical images in Adobe Photoshop, and the traced lesions were converted back into volumes using custom MATLAB code. Volumes from multiple patients within a group (left or right hemisphere damage) were then overlaid in MRicron (Rorden and Brett, 2000) to create overlap images showing areas of damage common to all patients within a group. Figure 1 shows the superimposed lesion locations for all subjects within each stroke group. Colours of the shaded region denote the percentage of subjects in each group with damage in the corresponding area. It should be noted that the lesions are confined to either the left or the right hemisphere. Importantly, all patients with left and right hemisphere damage had damage in at least one region of the sensorimotor motor system (Brodmann areas 4, 6, 3, 1, 2 and/or internal capsule). Lesion volume was not significantly different between the two stroke groups ($P = 0.94$), and intrahemispheric lesion location was similar between the two groups.

### Experimental set-up

The experimental set-up is shown in Fig. 2. Subjects sat facing a table with either their left or their right arm supported over a horizontal surface by an air-jet system to eliminate the effects of gravity and reduce friction. A start circle, targets and the subject’s fingertip (represented by an on-screen cursor) were displayed on a mirror using a high-definition television positioned horizontally above the mirror. The mirror blocked the direct vision of the subject’s arm, but reflected the visual display to give the illusion that the display was in the same
horizontal plane as the fingertip. Position and orientation of the fore-
arm and upper arm segments were sampled using a Flock of Birds
(Ascension Technology) system at 130 Hz. The positions of the
index finger tip, lateral epicondyle of the humerus and the acromion,
directly posterior to the acromioclavicular joint were digitized using a
stylus that was rigidly attached to a 6-degree of freedom Flock of
Birds sensor. As sensor data were received, the 3D position of
the aforementioned landmarks was computed using custom software,
Motor deficits depend on hemisphere of damage

with the x–y plane parallel to the tabletop. We used the computed x–y coordinates of the fingertip to define the projected cursor position.

Experimental task

Stroke patients performed the task using their contralesional arm, and the control subjects used their left or right arm depending on their group—right- or left healthy control subjects, respectively. Three targets were pseudo-randomly presented over a new trial. The start circle was presented at a distance of 40 cm from the front edge of the table and 15 cm from the midline of body in the right or left hemispace depending on whether the participants use their right or left arm, respectively, to perform the task. The targets were oriented 50°, 90° and 130° relative to the horizontal edge of the table and were presented in the left hemispace for participants performing the task with their right arm (medial, central and lateral targets, respectively) or in the right hemispace for participants performing the task with their right arm (lateral, central and medial targets, respectively). Before the start of each trial, the cursor and the start circle were displayed on the screen. To initiate the trial, the subject brought the cursor into the start circle and after a 300 ms delay, one of the three targets appeared on the screen along with an audio-visual ‘Go’ signal, which cued the subjects to initiate a single rapid movement towards the target. Feedback of the fingertip position was removed at this point, and subjects were asked to reach the target with a minimum speed requirement of 0.5 m/s. The speed criterion was used to emphasize consistent performance and was not used as a basis for excluding trials during data analysis. If subjects satisfied the speed criterion, they received ‘points’ based on the location of the index finger at the end of movement relative to the centre of the target; points were also used for motivational purposes only. Visual feedback about final position of the finger and the entire hand trajectory was displayed at the end of every trial. Subjects were asked to return the cursor into the start position to begin a new trial. The target and start position were visible throughout the entire trial, allowing certainty about the visually based target position and distance. The three targets were pseudo-randomly presented over a session of 99 trials, such that no target was presented consecutively.

Data analysis

Finger, elbow and shoulder positions were calculated from sensor’s position and orientation. The joint angles were then calculated, low-pass filtered at 8 Hz using a third order dual-pass Butterworth filter and differentiated to yield tangential velocity and acceleration. The first nine trials were considered as practice trials and were not included in the analysis. All remaining trials were included in the analysis, except in an extremely rare case when a subject failed to initiate a movement in response to the ‘Go’ signal. Movement start was identified by first determining the peak in the tangential velocity profile and then searching backwards to find the first minimum <5% of the peak. Movement end was determined as the first minimum <5% of peak tangential velocity by searching forwards from the time of peak velocity to the end of movement.

Dependent measures

Dependent measures of interest in this study were peak velocity, distance error, final position error, movement duration, absolute initial direction error and absolute direction error at movement end. Peak velocity was the maximum tangential velocity during movement. Distance error was defined as the difference between the target distance and the straight-line distance between the starting and final position of the fingertip, regardless of the path taken. Note that this error was signed if the target was overshoot, the distance error was positive, whereas if the target was undershot, the distance error was negative. Final position error was calculated as the distance between the target and finger position at movement end. Movement duration was defined as the time from movement onset to movement end. Absolute initial direction error was calculated relative to the line connecting the start position and the target, and was defined as the angular deviation between the ‘target line’ and the line from the starting location of the hand to the hand location at peak velocity. Absolute direction error at movement end was calculated as the angular deviation between the ‘target line’ and the line from the starting location of hand to the hand location at movement end. As the hand trajectory is convex (curved), the hand-path curvature was calculated as the minor axis divided by the major axis of the hand path. The major axis was defined as the largest distance between any two points in the hand path, whereas the minor axis was defined as the largest distance perpendicular to the major axis (Baggesteiro and Sainburg, 2002; Schaefer et al., 2009b).

Statistical analysis

Performance of patients with left hemisphere damage (contralesional arm: right) was compared with that of the control group that performed the task with their right hand. Performance of patients with right hemisphere damage (contralesional arm: left) was compared with that of the control group that performed the task with their left hand. The individual dependent measures were analysed using three-way mixed model ANOVA, with arm (left or right arm) and group (hemisphere-damaged or healthy control group) as between-subject factors and the target (lateral, center and medial) as the within-subject factor. The effect of target was considered only when it interacted with group and arm, as the primary aim of this study was to determine whether laterality of lesion influences the kinematic measures. When there were significant main or interaction effects, post hoc analyses were performed using Tukey’s honestly significant difference test, which corrects for multiple comparisons (Kutner et al., 2004). Statistical significance levels were set to 0.05. All statistical analyses were carried out using JMP® statistical software.

Results

The hand-paths of a representative subject from each control group are shown in Fig. 3A. Regardless of the hand used, the hand-paths of control subjects tended to be fairly straight and directed towards the target and terminated close to the target. Although it was not the focus of this study, we did not observe any major differences between the movement patterns of left- and right healthy control subjects, consistent with our recent reports of a reduction in interlimb differences in reaching coordination in healthy older subjects relative to healthy younger subjects (Przybyla et al., 2011; Wang et al., 2011). Figure 3B-E shows contralesional hand-paths for representative patients with left or right hemisphere damage, separated by the level of dysfunction as quantified by the Fugl-Meyer score. The differences between the hand-paths of patients and healthy control subjects are apparent in Fig. 3. In general, stroke patients made movements that were more variable and less accurate than those of healthy control subjects.
Figure 3 (A) Comparison of hand-paths between representative left healthy (LHC) and right healthy control (RHC) subjects. (B–E) Comparison of hand-paths between patients with left (LHD) and right hemisphere damage (RHD) across severity of hemiparesis assessed using the Fugl-Meyer score. Each right and left hemisphere damage pair has similar Fugl-Meyer (FM) scores; Fugl-Meyer scores decrease from B to E, indicating increasing degree of hemiparesis.
Importantly, there were substantial differences in the movements of patients with left and right hemisphere damage. For instance, as shown in Fig. 3B, the patient with left hemisphere damage showed systematic and variable direction errors for all three targets, whereas the patients with right hemisphere damage made straighter movements in the direction of the targets, but consistently overshot them. These systematic differences between patients with left and right hemisphere damage persisted as impairment level increased (Fig. 3B–E). Even at the highest level of impairment (Fig. 3E), the directions of the movements of patients with right hemisphere damage were more clustered, when compared with their counterparts with left hemisphere damage.

Figure 4 compares these findings and other kinematic parameters across all subjects in each group. For statistical comparison, we performed a three-way ANOVA with group (healthy control group, hemisphere damaged group), arm (left, right) and target (lateral, central, medial) as factors. This analysis did not include Fugl-Meyer impairment level as a factor because the test of our primary hypothesis required comparison between the performance of stroke patients and that of control subjects, who could not be classified based on Fugl-Meyer impairment level. In general, movement duration was greater in the stroke than the control group [$F(1,34) = 34.97, P < 0.0001$], and this effect did not vary as function of arm, or an interaction between arm and group, or a three-way interaction between arm, group and target (range of $P$-value: 0.065–0.77). Similarly, peak tangential velocity was significantly lower in the stroke groups than the control groups [Fig. 4B; ANOVA: $F(1,34) = 36.17, P < 0.0001$] again, without variation as a function of arm, or an interaction between arm and group, or a three-way interaction between arm, group and target ($P > 0.08$ in all cases).

However, our ANOVA demonstrated that there was a significant three-way interaction of arm, group and target for final position error [$F(2,34) = 3.33, P = 0.04$]. This interaction can be seen in Fig. 4C. Although both patient groups showed substantially higher errors than their respective control groups ($P < 0.0001$), the left hemisphere damage group’s errors depended systematically on movement direction, becoming larger from the medial to lateral target, whereas the right hemisphere damage group’s errors did not. Regardless of this interaction, the overall amplitude of final position errors for patients with left hemisphere damage and right hemisphere damage was not significantly different ($P = 0.27$) nor was there a difference between the right and left control groups ($P = 0.99$).
As suggested by the three-way interaction noted previously, the final position errors of right and left hemisphere damage groups were because of different factors: patients with right hemisphere damage tended to overshoot the targets, whereas patients with left hemisphere damage tended to move the correct distance in the wrong direction (Fig. 3B–E). Figure 5A compares our measure of distance error across our four groups. Our ANOVA results revealed a significant interaction between group and arm $[F(1,34) = 6.17, P = 0.02]$. Post hoc analysis revealed that the stroke patients with right hemisphere damage showed significantly higher distance errors when compared with all other groups ($P < 0.01$). However, there were no significant differences in distance error between patients with left hemisphere damage and the left healthy control group ($P = 0.99$). In other words, damage to the right, but not left hemisphere, produced higher distance errors than those of control subjects.

To assess the deficit in controlling movement direction after left hemisphere damage, we calculated direction error during the early phases of the movement, at peak velocity. These data across our subject groups are shown in Fig. 5B. Our ANOVA results revealed a significant interaction between group and arm $[F(1,34) = 4.37, P = 0.04]$. Post hoc analysis revealed that patients with left hemisphere damage ($P = 0.002$), but not patients with right hemisphere damage ($P = 0.76$), had significantly higher initial direction errors compared with their respective control groups. Thus, damage to the left, but not right hemisphere, resulted in significantly higher initial direction errors.

The hand-paths of the patients with left hemisphere damage in Fig. 3B–D suggested that direction errors of patients with left hemisphere damage continued throughout the course of movement. To more carefully examine this possibility, we calculated direction errors at movement end (Fig. 5C). Again, we observed a significant interaction between group and arm for this measure $[F(1,34) = 5.06, P = 0.03]$, and post hoc analysis indicated that patients with left hemisphere damage produced significantly higher direction errors at the movement end than the left healthy control group ($P < 0.0001$). However, there were no significant differences in the direction error at the movement end between the right hemisphere damage and right healthy control groups ($P = 0.24$). One might conclude that the persistence of direction errors early and late in the movement trajectory might indicate that movements of patients with left hemisphere damage were straight. However, the mean direction errors of patients with left hemisphere damage at the end of movement (Fig. 5D) were somewhat higher than at peak velocity (Fig. 5C), indicating that these errors were not corrected during movement. Thus, the movements curved substantially, but this curvature did not reflect directional corrections, as can be seen in the hand-paths in Fig. 3B–D. In fact, there was a significant interaction between group and arm $[F(1,34) = 4.39, P = 0.04]$ for hand-path curvature. Post hoc analysis revealed that patients with left hemisphere damage showed significantly larger movement curvature than the left healthy control participants ($P < 0.0001$). Although some patients with right hemisphere damage showed some curvature in their movements (Fig. 3D and E), as a group, the hand-path curvature was not significantly different from that of healthy control subjects ($P = 0.11$). In other words, only left hemisphere damage resulted in increased movement curvature.

Next, we reasoned that a deficit in accurately specifying movement direction after left hemisphere damage might also be evident as higher variability in this measure (Schaeler et al., 2007, 2009). As expected, patients with left hemisphere damage showed much larger variable direction errors compared with all other groups (Fig. 5E). There was a significant interaction between group and arm $[F(1,34) = 5.28, P = 0.03]$, with post hoc analysis showing that the variable direction errors of patients with left hemisphere damage were significantly higher compared with the left healthy control and right hemisphere damage groups ($P < 0.02$). On the other hand, there were no significant differences in variable direction error between the right hemisphere damage and right healthy control groups ($P = 0.37$). In other words, damage to left hemisphere, but not right hemisphere, resulted in high variability in movement direction.

In summary, our analyses revealed a double dissociation between the type of error and the hemisphere of damage: right hemisphere damage, but not left hemisphere damage, patients showed substantial deficits in movement distance. In contrast, left hemisphere damage, but not right hemisphere damage, patients showed substantial deficits in constant and variable measures of movement direction. Final position inaccuracies were not dissociated by hemisphere of damage, but seem to be produced by the aforementioned differential deficits.

### Effect of impairment level

We next explored the relationship between the extent of the movement deficits after left and right hemisphere damage, and the severity of clinical motor dysfunction, as indicated by the Fugl-Meyer Assessment of Upper Extremity Function score. We divided each of our stroke groups into the following two subgroups: mildly impaired (Fugl-Meyer score of 58–66) and moderately impaired (Fugl-Meyer score of 46–57), similar to previously published cut scores (Murphy et al., 2010). Both stroke groups had five patients in the mildly impaired range and four patients who were moderately impaired. Age was also comparable among the mild (left hemisphere damage: 74.2 ± 8.1, right hemisphere damage: 62.6 ± 13.5) and moderate groups (left hemisphere damage: 61.5 ± 11.5, right hemisphere damage: 64 ± 7.5). The measures from the previous analysis that showed an interaction between arm and group were subjected to a mixed model three-way ANOVA with damaged hemisphere (left or right), Fugl-Meyer impairment level (mild or moderate) and target (lateral, central and medial) as factors.

Figure 6 compares our kinematic measures between the two Fugl-Meyer score groups for patients with right and left hemisphere damage. For distance error (Fig. 6A), our ANOVA results showed a significant main effect of Fugl-Meyer impairment level $[F(1,42) = 8.48, P < 0.01]$ and damaged hemisphere $[F(1,42) = 12.67, P < 0.001]$. However, there was no significant interaction between Fugl-Meyer impairment level and damaged hemisphere $[F(1,42) = 0.59, P = 0.44]$. Thus, distance error was higher for patients with right hemisphere damage when compared...
Figure 5 (A) Mean distance error, (B) mean absolute initial direction error, (C) mean absolute direction error at end of movement, (D) mean hand path curvature and (E) mean variable direction error at peak velocity for the left healthy control (LHC), left hemisphere damage (LHD), right healthy control (RHC) and right hemisphere damage (RHD) groups. Error bars indicate standard error of the mean. *Significant (P < 0.05) group differences.
with patients with left hemisphere damage, regardless of their Fugl-Meyer severity.

In terms of initial direction error, Fig. 6B shows that the difference between left and right hemisphere damage is larger in the moderately impaired group. This conclusion is confirmed by the ANOVA results, which revealed a significant interaction between Fugl-Meyer impairment level and damaged hemisphere \((F(1,42) = 5.28, P = 0.03)\). In other words, as the level of impairment increased, there was a substantial increase in direction error in patients with left hemisphere damage, but not in patients with right hemisphere damage.

Similar to initial direction error, our hand-path curvature and variable direction error ANOVA results also showed a significant interaction between damaged hemisphere and Fugl-Meyer impairment [curvature: \(F(1,42) = 6.69, P = 0.01\); variable direction error: \(F(1,42) = 14.37, P < 0.001\)]. As the level of impairment increased, there was a substantial increase in both of these measures for the group with left hemisphere damage, but not for the group with right hemisphere damage (Fig. 6C and D).

In summary, these results suggest a substantial effect of the severity of impairment on the reaching performance of stroke patients. Although patients with left hemisphere damage showed increasing variability, hand-path curvature and direction error with increasing contralesional hemiparesis, patients with right hemisphere damage did not show variation in these measures based on impairment level. In addition, the specific right hemisphere damage deficits in movement distance also did not vary with impairment level.

**Discussion**

There is substantial research dedicated to understanding contralesional motor deficits after unilateral stroke and improving contralesional arm performance through rehabilitation. However, none of these studies have examined whether movement deficits in the contralesional arm differ depending on the hemisphere of damage, despite a growing body of work indicating that each hemisphere of the
brain might be specialized for controlling different aspects of movement. Our results indicate compelling differences in contralesional arm performance in unilateral stroke patients depending on the hemisphere of damage. These findings support our predictions that left hemisphere, but not right hemisphere, damage produces deficits in movement trajectory, whereas right hemisphere, but not left hemisphere, damage produces deficits in stabilizing the limb at the end of movement. We also show that left hemisphere deficits vary with the severity of impairment. These findings not only broaden the scope of our model of hemisphere-specific control but also have significant implications for understanding the impact of stroke on function and for clinical rehabilitation.

Our results expand the findings of previous studies, which revealed significant coordination deficits in the contralesional arm of stroke patients. In particular, the study of Beer et al. (2000, 2004) reported a failure to predictively account for dynamic intersegmental interactions when stroke patients performed reaching actions with their paretic arm. Levin (1996) and Cirstea and Levin (2000) largely focused on movement kinematics and reported problems in coordinating the actions of shoulder and elbow joints during contralesional arm motion. Kamper et al. (2002) reported contralesional deficits in movement velocity, smoothness, linearity and direction. Although earlier studies that examined deficits, such as weakness and spasticity, attributed contralesional impairments to reduced agonist (El-Abd et al., 1993; Fellows et al., 1994) and antagonist muscle activation (Mellman et al., 1985; El-Abd et al., 1993), hyperactive reflexes (Mizrahi and Angel, 1979), peripheral disturbances, such as changes in tissue properties (Dietz et al., 1991; Givens et al., 1995), or the presence of abnormal synergies (Bourbonnais et al., 1989; Dewald et al., 1995); more recent studies that also address coordination deficits are beginning to identify inadequacies in movement planning (Beer et al., 2000; Kusoffsky et al., 2001) as a potential source of these problems. Our results agree with these studies that a deficit in predictive control mechanisms gives rise to coordination deficits post-stroke. However, our current and previous results provide specificity regarding the neural substrates underlying these deficits by demonstrating that predictive control of movement trajectory features is disturbed only from damage to the left hemisphere. In fact, damage to right hemisphere regions does not impact on the coordination of movement. In contrast, deficits in controlling movement distance arise from damage to the right hemisphere (Schaefer et al., 2007, 2009b). Although Kamper et al. (2002) observed deficits in controlling movement distance with the contralesional limb, they did not identify whether such deficits differed depending on the hemisphere of damage. Our current results show that only patients with right hemisphere damage made substantial distance errors, indicating that mechanisms that ensure termination of a movement and stabilization of the arm at a goal location are lateralized to the right hemisphere.

Nature of motor deficits after left and right hemisphere damage

Before discussing the specific nature of the deficits after left and right hemisphere damage, it should be emphasized that our model of hemispheric specialization (Sainburg, 2002; 2005; 2010) is bi-hemispheric—we posit that each hemisphere contributes different aspects of control to movements of both arms. Such bi-hemispheric control is consistent with observations from previous neuroimaging studies that motor cortical areas of both brain hemispheres are active during unilateral finger movement (Li et al., 1996; Cramer et al., 1999), finger sequencing (Kawashima et al., 1993; Kim et al., 1993) and unilateral arm movements (Nikko et al., 2001; Weinstein et al., 1997). Our previous findings in healthy individuals in which we documented limb-specific advantages for the dominant and non-dominant arms (Sainburg and Kalakanis, 2000; Bagesteiro and Sainburg, 2002, 2003) and our recent work in the ipsilesional arm of stroke patients (Schaefer et al., 2007, 2009b; Mutha et al., 2010, 2011b; Schaefer et al., 2012) have supported this bi-hemispheric model of control. In fact, Schaefer et al. (2007, 2009b) have demonstrated that ipsilesional deficits in motor coordination and learning mirror the functional advantages that we had previously reported in the dominant and non-dominant arms of healthy subjects. For example, left hemisphere damage produced deficits in intersegmental coordination and in direction learning during adaptation to visuomotor rotation, whereas right hemisphere damage produced deficits in final position accuracy and position adaptation. In addition, Desrosiers et al. (1996) and Schaefer et al. (2009b) showed that these deficits are often functionally relevant, and that they correlate with deficits in clinical movement evaluations that include simulated activities of daily living. In a more recent study, Robertson et al. (2012) revealed coordination deficits in both arms of stroke patients with left hemisphere damage, during unconstrained reaching movements. Although left and right brain damaged patient groups had reduced scapula protraction in the contralesional paretic arm, scapula protraction was only reduced in the ipsilesional arms of the group with left hemisphere damage. The authors concluded that left hemisphere damage produced deficits in proximal coordination, a finding that they suggested might be consistent with previous findings of reduced intersegmental coordination in the ipsilesional arm of patients with left hemisphere damage (Schaefer et al., 2009b). Our current findings confirm that these specific ipsilesional deficits also occur in the contralesional hemiparetic arm of right and left hemisphere damage stroke patients.

Although the nature of our previously observed ipsilesional and current contralesional deficits seems similar, two important differences between these studies must be pointed out. First, in the current study, we did not observe a dependence of left hemisphere damage-related trajectory deficits on intersegmental coordination requirements. Although deficits in movement direction or hand-path curvature in patients with left hemisphere damage were always larger than those in left healthy control subjects, our ANOVA results for these measures did not show a significant three-way interaction among group, arm and target. These findings agree with those of Kamper et al. (2002) who showed only a modest dependence of contralesional deficits on movement direction, yet they stand in contrast with our findings in the ipsilesional arm where the magnitude of the deficits almost always increased as intersegmental coordination requirements increased. This raises the interesting question of whether left hemisphere contributions
to coordination of ipsilateral arm movements become more critical as the complexity of the movement increases. Although we cannot directly answer this question yet, this suggestion is not far from some observations of functional neuroimaging and lesion studies of finger movements. Harrington and Haaland (1991) previously observed that performance of complex heterogeneous arm posture sequences with the ipsilateral arm was more impaired than that of simple repetitive ones after left hemisphere damage, but not right hemisphere damage. Haaland et al. (2004) also showed greater left hemisphere activation during the performance of complex rather than simple finger sequences, even when the ipsilateral left hand was used to perform the task. Verstynen et al. (2005) extended these findings by showing that increased ipsilateral left hemisphere contributions did not necessarily require sequential actions, but were present during the performance of any complex finger movement. Whether a similar conclusion can be drawn for arm reaching movements remains a subject of future investigation.

Second, in contrast to our previous ipsilesional studies, in the current study, final position errors were not significantly different between patients with left and right hemisphere damage. However, it must be stressed that here, left hemisphere damage final position errors were because of deficits in direction control, whereas right hemisphere damage errors resulted from deficits in adequately stopping at the end of movement. Although the most impaired patient with left hemisphere damage in our current study (Fig. 3E) did show some difficulty in stopping at the medial target, this was not observed in other patients with left hemisphere damage (Fig. 3B–D). These patients did not show any systematic overshoot or undershoot, which would be indicative of a deficit in adequately stopping the movement at the target location. Although the movements of the patient with left hemisphere damage in Fig. 3E might give the impression of a distance control problem, this was not the case. Note that the movements directed towards the lateral target ended closer to the centre target than the lateral target as a result of large direction errors. However, the average distance of these movements was fairly well matched to the target distance, confirming that final position errors in patients with left hemisphere damage were largely because of initial direction error, but not distance control deficits. In contrast, for patients with right hemisphere damage, directional deviations, if any, were initiated late in the movement, mostly after the hand had crossed the target (Fig. 3D and E). The direction errors made by patients with right hemisphere damage were in fact small and comparable with control subjects. Thus, the final position errors in the group with right hemisphere damage were largely because of the patients consistently overshooting the target, as can be seen in Fig. 3B–E. These findings in patients with right hemisphere damage are consistent with our previous results (e.g. Schaef er et al., 2009b), but we had previously observed intact accuracy (final position errors comparable with control subjects) in our patients with left hemisphere damage, who tended to correct their movements back to the target position despite initially deviating from the target direction when moving with the ipsilesional arm. We interpreted such corrections in patients with left hemisphere damage as a contribution of the intact right hemisphere to the ipsilesional, left arm through crossed descending pathways. However, in the current study, after left hemisphere damage, corrections of the contralesional right arm were ineffective or absent, leading to large errors at the end of movement. This might result from the fact that the intact right hemisphere has limited direct access to the contralesional right arm, which could limit effective corrections and stabilization of the arm at the desired goal location.

Although we have emphasized that the final position errors after right, but not left hemisphere damage, arise because of a deficit in controlling movement distance, it is interesting to speculate whether our results could be explained on the basis of differential deficit in left and right hemisphere damages solely in estimating or planning movement distance. First, our neuropsychological tests showed that there were no significant differences between stroke groups with left and right hemisphere damage in visuospatial perception (Judgement of Line Orientation Test: P = 0.994), making it unlikely that visuospatial deficits, if any, played a differential role in estimating target distance as shorter or longer in one group over the other. Second, although a certain component of movement distance seems to be preplanned (Gordon and Ghez, 1987a, b), our recent work has shown that achievement of a target distance relies on ‘online’ (during movement) processes that use sensory information to modulate limb impedance (Mutha et al., 2008). We suggest that it is these impedance mechanisms that are disrupted by right hemisphere damage, producing a deficit in accurately stopping at a goal location and thereby affecting the achievement of a target distance. In contrast, movement distance in patients with left hemisphere damage was fairly well matched to the target distance. In fact, distance errors in patients with left hemisphere damage were small, positive on average and, most importantly, comparable with control subjects. Thus, we do not believe that left hemisphere damage affected processes that regulate achievement of movement distance. Nevertheless, further research is necessary to comprehensively examine the contributions of distance planning mechanisms to these differential deficits.

Although we addressed these distinct deficits in patients with left and right hemisphere damage, it is imperative to explain why elderly stroke patients demonstrate such differential deficits, when healthy elderly subjects tend to show a reduction in motor lateralization (Przybyla et al., 2011). Previous brain imaging studies have shown that such a reduction in lateralization with ageing is a consequence of increased neural recruitment bilaterally, rather than a reduced specialization of one hemisphere. For example, Cabeza (2002) showed that for certain neuropsychological functions that are associated with asymmetric patterns of recruitment in young subjects, older subjects recruit more symmetric patterns of cortical activity. Furthermore, these patterns are associated with sustained performance on the neuropsychological tasks, suggesting that bilateral recruitment is likely to be compensatory in nature, in light of reduced unilateral neural capacity. This forms the basis of the HAROLD (hemisphere asymmetry reduction in older adults) model proposed by Cabeza (2002). In line with these results, we have shown that older adults show more symmetric patterns of motor behaviour and interlimb transfer of motor learning (Przybyla et al., 2011; Wang et al., 2011). Taken together, our findings and related imaging findings (Mattay et al., 2002) suggest that as people age, increased symmetry in behaviour is not because of
a reduction in specialization of one hemisphere, but rather because of an increase in bilateral hemispheric recruitment. However, Adamo et al. (2009) reported the emergence of proprioceptive wrist matching asymmetries with age, suggesting that some new neural asymmetries may develop, whereas others become diminished with ageing. The current findings in the contralesional arm, together with previous findings in the ipsilesional arm (Schaef er et al., 2007, 2009b) support this view by showing that loss of contribution from one hemisphere, either right or left, will re-establish systematic motor asymmetries. If, on the other hand, hemispheric specialization itself has become reduced, motor asymmetries between patients with left and right hemisphere damage would not have been observed. We, therefore, conclude that our current findings support the HAROLD model, and extend it to motor function.

Differentiating right hemisphere deficits in visuospatial processing from motor control

Right hemisphere damage has previously been shown to produce deficits in cognition and perception, including unilateral neglect (Bottini et al., 2009). It is plausible that the accuracy deficits revealed in the current study for patients with right hemisphere damage could emerge from such perceptual deficits. Pisella et al. (2011) argued that the right hemisphere might be dominant for visuospatial processing, based on several studies examining optic ataxia, neglect and visual agnosia. For example, in a study focused on correlating the critical neural substrates associated with unilateral visual neglect, Vallar and Perani (1986) recruited 110 stroke patients to participate in a circle cancellation task. The results indicated that damage to the right inferior parietal lobe commonly resulted in contralateral visual neglect, which was consistent with later studies documenting visual neglect after right hemisphere damage (Vallar et al., 1993; Mattingley, 1999). In the current study, patients with right hemisphere damage consistently overshot the targets, resulting in large distance errors (Fig. 3B–E). However, none of our patients with right hemisphere damage had visual neglect, which rules out the possibility that these errors are a consequence of neglect. It is also unlikely that these errors are attributable to optic ataxia because the hand-paths of patients with right hemisphere damage were fairly accurate in direction, which is not characteristic of this deficit. In addition, several studies have indicated that errors because of optic ataxia are predominant when patients try to grasp or reach to objects located in their peripheral or extra-foveal visual field (Buxbaum and Coslett, 1997; Dijkerman et al., 2006). However, in the current study, the targets were presented close to the centre of the subject’s visual field and workspace, and no restrictions were imposed on the gaze direction of the subjects. We conclude that the errors associated with difficulty stopping on targets in the current study are unlikely to result from deficits, such as optic ataxia or unilateral visual neglect. Instead, we attribute these errors to a deficit in the specialized role of right hemisphere in controlling limb impedance for stabilizing limb position at the end of movement.

Effect of impairment level on contralesional deficits

Our results show that patients with moderate to mild hemiparesis show motor deficits that vary with the hemisphere of damage, and that these deficits in patients with left hemisphere damage vary with the extent of impairment measured by the Fugl-Meyer score. One of the difficulties in developing a more specific understanding of how movement deficits after stroke are affected by lesion location and impairment level has been the paucity of research that has detailed the relationship between the degree of motor impairment and kinematic, kinetic and/or electrophysiological measures of motor performance. Only a few studies have investigated this association. For example, Kamper et al. (2002) examined the reaching performance of mild to severely paretic chronic stroke patients while they made reaching movements to 75 targets. They reported that deficits in a variety of contralesional performance measures, including velocity, direction error and linearity, strongly correlated with impairment level, as measured by the Chedoke-McMaster Stroke Arm Assessment Scale. However, no previous studies have assessed how this dependence might be modulated by the hemisphere of damage. Our current findings indicate that the trajectory-based deficits produced by patients with left hemisphere damage increase with the severity of Fugl-Meyer impairment, whereas the severity of impairment does not modulate differences in distance error for patients with right hemisphere damage (Fig. 6). It is difficult to explain this asymmetric dependence of performance errors on level of impairment. It may simply be the case that variations in level of impairment have a more graded effect on the ability to coordinate the segments of the arm than on the ability to stop at a given location. It is also notable that previous neural activation studies have shown asymmetries related to side of impairment. For example, Zemke (2003) showed that when stroke patients performed a finger-tapping task with their paretic arm, patients with left hemisphere damage had higher contralesional sensorimotor cortex activation than patients with right hemisphere damage. These findings are somewhat consistent with neural activation studies in healthy subjects, indicating greater ipsilateral activation when performing sequential finger apposition with the non-dominant hand as compared with the dominant hand (Kim et al., 1993). Zemke’s (2003) findings suggest that the greater recruitment of ipsilateral cortex is maintained after right hemisphere damage, but not left hemisphere damage. It is plausible that the contralesional arm of patients with right hemisphere damage receives greater contribution from the intact ipsilateral (left) hemisphere, and this may diminish the effect of impairment level on performance measures, like accuracy. However, it is impossible to conclusively explain the asymmetrical effects of right and left hemisphere damage in the relationship between our performance measures and clinical measures of impairment in the current study.

Implications for rehabilitation

The finding that contralesional deficits differ depending on the side of hemisphere of damage has important implications for the design of clinical rehabilitation intervention. Although approaches,
such as constraint-induced movement therapy (Taub et al., 1993; Mark and Taub, 2004), have shown decreased impairment and improved function through forced use of the contralesional arm, these techniques have not differentiated the type or amount of therapy depending on side of damage. Our results suggest that therapy might be designed to address specific deficits that emerge after left or right hemisphere damage. Such a focused approach is possible through the use of new methodologies that exploit advanced robotic and computer-based intervention that allows high-resolution analysis of performance during and after therapy (e.g. Volpe et al., 2001). These tools could be used to design specific tasks and modify movement-related feedback so as to emphasize certain variables over others. For example, after left hemisphere damage, task feedback can be modified to amplify errors perpendicular to the desired trajectory while reducing errors in the direction of the desired movement. Such changes would penalize deviations from the desired movement path while allowing errors in the direction of movement. In contrast, following right hemisphere damage, tasks that penalize final position errors could be designed. Finally, given the presence of ipsilesional deficits that mirror contralesional problems, bilateral training should be a critical component to therapeutic intervention following right hemisphere damage, tasks that penalize final position errors could be designed. Finally, given the presence of ipsilesional deficits that mirror contralesional problems, bilateral training should be a critical component to therapeutic intervention in unilateral stroke (Whitall et al., 2000; Cunningham et al., 2002; Cauraugh et al., 2010; Latimer et al., 2010). Bilateral training is not only important to facilitate remediation in the ipsilesional arm but also because unilateral training may not automatically carry-over to spontaneous bilateral performance, which is the best predictor of better performance on everyday tasks (Haaland et al., 2012). In fact, recent research has indicated that learning novel kinetic and visuomotor environments with a single arm transfers only partially to bilateral movements, even when the same arm experiences the imposed forces under unilateral and bilateral conditions (Nozaki et al., 2006). Thus, we suggest that it is critical to consider the specific deficits induced by right or left hemisphere lesions and consider bilateral training to enhance motor rehabilitation post-stroke.

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1. **Mani S**, Sainburg RL. Unilateral stroke produces hemisphere-specific bilateral deficits. (In preparation for submission)

2. **Mani S**, Przybyla A, Haaland KY, Good DC, Sainburg RL. Contralesional arm preference varies based on hemisphere of damage and workspace location of target. *Neurorehab and Neural Repair*, 2013 (In review)


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