THE EFFECTS OF BRAIN LATERALIZATION ON MOTOR CONTROL AND ADAPTATION

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Abstract

Lateralization of mechanisms mediating functions such as language and perception is widely accepted as a fundamental feature of neural organization. Recent research has revealed that a similar organization exists for the control of motor actions, in that each brain hemisphere contributes unique control mechanisms to the movements of each arm. We now review current research that addresses the nature of the control mechanisms that are lateralized to each hemisphere and how they impact motor adaptation and learning. In general, the studies reviewed here suggest an enhanced role for the left hemisphere during adaptation, and the learning of new sequences and skills. We suggest that this specialization emerges from a left hemisphere specialization for predictive control – the ability to effectively plan and coordinate motor actions, possibly by optimizing certain cost functions. In contrast, right hemisphere circuits appear to be important for updating ongoing actions and stopping at a goal position, through modulation of sensorimotor stabilization mechanisms such as reflexes. We also propose that each brain hemisphere contributes its mechanism to the control of both arms. We conclude by examining the potential advantages of such a lateralized control system.

Introduction

The study of the neural control of voluntary movement has largely relied on an assessment of dominant (typically, right) arm function under a variety of task conditions, an approach that has led to the elucidation of some key motor control principles. However, the predominant emphasis on examining dominant arm performance has resulted in a somewhat erroneous view of motor control - that the control processes for non-dominant arm function are simply "weaker" analogues of those of the dominant arm. Over the past decade, our laboratories have collaboratively demonstrated that this is not the case. Our studies in young, healthy, individuals have documented specific advantages for each arm for different aspects of a movement, while our examination of patients with brain lesions due to stroke has also revealed that the resulting deficits are different depending on the side of damage. These studies have led to the development of our model of motor lateralization, which we define as an asymmetry in performance between the left and right arms that results from a specialization of each hemisphere for distinct movement control mechanisms. In this review, we address: 1) what control mechanisms are specialized in each hemisphere, 2) how they are integrated for the control and coordination of each arm and 3) how this organization impacts

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motor adaptation and learning, which we define as the improvement in motor performance with practice. We focus primarily on the effects of brain lateralization on motor adaptation, an aspect of learning that is engaged when performing simple movements under novel environmental conditions. Because our model of motor lateralization localizes different types of control processes to different hemispheres, we are able to make predictions about how each controller should adapt to different environments

Hemispheric Specialization

Our model of hemispheric specialization for motor control proposes that each hemisphere has become *specialized* for different motor control mechanisms and contributes its specialization to the control of both arms during functional activities. This model has precedents in other cognitive, language, and memory processes, for which hemispheric specializations have been elaborated through studies of patients with disconnection syndrome, in which the corpus callosum, and sometimes, the anterior commissure have been surgically removed (Gazzaniga, 2000). The foundational work by Sperry and Gazzaniga, pioneered the technique of isolating stimuli to, and requiring responses from, a single hemisphere by exploiting the exclusively crossed nature of visual fields and somasthetic system, and the largely crossed nature of the arm motor systems. This research demonstrated that several perceptual, cognitive, memory, and language functions are localized to the left or the right cerebral hemisphere. Research in patients with unilateral brain lesions and functional imaging studies have corroborated this evidence for hemispheric specialization of a variety of behavioral functions.

More recent research using both physiological techniques and computational modeling has revealed a plausible evolutionary basis to this type of lateralized organization. The need to accommodate increasingly complex and coordinated behaviors during the course of evolution presumeably required the development of more extensive neural circuits to carry out the underlying computations. While this could have been accomplished by expanding brain size, this solution was likely to be costly, both in terms of energy requirements and time required to communicate between distant processing units. To avoid this cost, the apparent solution was to modify neural machinery within one hemisphere in order to develop more efficient local circuits. In fact, newer work has shown that development of local circuits within small regions of the brain are the most efficient mechanism for carrying out neural computations, due largely to the reduced energy requirements and lower transmission times associated with circuits comprised of small neurons (van den Heuvel, Stam, Kahn & Hulshoff Pol, 2009). Thus, by localizing computationally intensive processing to local circuits in a single hemisphere, larger neuron systems could be used to simply carry the products of these computational systems to more distant regions of the brain, including the contralateral hemisphere. The relative decrease in the rate of growth of the corpus callosum (Rilling & Insel, 1999), reduction in the speed of callosal transmission (Aboitiz, Lopez & Montiel, 2003), and increase in intrahemispheric white matter connectivity (Rilling and Insel, 1999, Herculano-Houzel, Mota, Wong & Kaas, 2010) supports this view. This modification likely resulted in the co-opting of neurons previously dedicated to functions that were previously represented bilaterally and symmetrically. As a result, the previously symmetric representation was relegated to the other hemisphere, resulting in development of specialized computational processes within and thereby asymmetry between the hemispheres. The result appears to be a mosaic of computational processes that require the unification across both hemispheres for integrated functional performance.

This description of hemispheric lateralization raises an important question regarding the precise definition of "specialization": does specialization of a hemisphere for a computational process mean that the process is exclusively localized in one hemisphere with

no contribution or duplication of function towards that process from the opposite hemisphere? Alternatively, does specialization imply that both hemispheres contain redundant circuitry for all processes, but that each process is represented more extensively in one hemisphere and less in the other ? Based on previous research on memory and language systems, the answer seems to vary depending on the specific neurobehavioral function, as well as the individual brain. For example, the hemispheric encoding/retrieval asymmetry (HERA) model proposed by Tulving and colleagues (Tulving, Kapur, Craik, Moscovitch & Houle, 1994) attributes encoding of episodic memories to the left hemisphere and retrieval of those memories to the right hemisphere. The HERA model predicts catastrophic episodic memory deficits in split-brain patients because one hemisphere could only carry out one half of the process, storage or retrieval. However, split-brain patients show only mild episodic memory impairments, not catastrophic deficits - each hemisphere the has capacity for both encoding and retrieval of episodes, but each hemisphere carries out the process somewhat differently, the left more elaborative and the right more veridical. In addition, the left hemisphere encodes verbal information better, while the right hemisphere is superior at encoding perceptual stimuli. Thus, hemispheric specialization for a given behavioral function such as episodic memory may be related both to the nature of the stimulus (verbal vs visual) and to the component computational process (encoding or retrieval). In contrast, the neural organization of other functions such as language appears to reflect a stronger form of hemispheric specialization. The left hemisphere, in most individuals, appears necessary to process the rules for language organization or grammar, as well as for storage and retrieval of the words and phrases or lexicon. Studies in patients with disconnection syndrome have indicated that while the right hemisphere can contain a limited lexicon, it is effectively incapable of grammar (Gazzaniga, 2000). These two aspects of language appear to be almost completely specialized to the left hemisphere. It should also be pointed out that in rare cases, patients have been shown to have greater lexical and grammar capabilities in the right hemisphere. Thus, some processes show incomplete hemispheric specialization, while others show complete hemispheric specialization. In addition, different individuals can show different extents of specialization for a particular process.

So how do we integrate these findings to help define hemispheric specialization? First, it is important to identify two potential forms of specialization: 1) weak form: both hemispheres can carry out a process, but one does so with greater efficacy and 2) strong form: only one hemisphere can carry out a particular neural computational process, and the corpus callosum is necessary for integrative function. Given the previous description of how hemispheric specialization may have emerged through evolution, it can be conjectured that as a computationally intensive "new" process emerges in a given hemisphere (for example, left hemisphere), the older process that may have existed symmetrically and redundantly in both hemispheres gives up its neurons to the new process and thus becomes less well represented in that hemisphere (left). Thus, some older computational components may be represented in both hemispheres, although asymmetrically (weak form), whereas the newer processes may only be represented in a single hemisphere (strong form).

Our model of motor lateralization identifies two different computational processes associated with voluntary motor control: 1) predictive control that specifies and accounts for movement dynamics including energetics and 2) impedance control that specifies velocity and position based impedance and is robust against unpredictable perturbations. Both processes are necessary for efficient and robust control of movement. It is possible that predictive control reflects the evolutionarily newer process and we propose that it might be represented only in the hemisphere contralateral to the dominant arm, while the computationally simpler impedance control process may be the older process that is asymmetrically represented in both hemispheres, with greater elaboration in the hemisphere contralateral to the non-dominant arm. In this article, we review studies that tested our

hypothesis of lateralization using studies of healthy adults and stroke patients with unilateral left or right hemisphere lesions. Our lesion studies demonstrate hemisphere-specific deficits in both arms of patients, supporting our hypothesis that both hemispheres are necessary for normal integrated function. However, we are unable at this point to conclusively distinguish between the strong and weak forms of hemispheric specialization for two reasons: 1) first, we do not know if the lesions completely eliminate the circuitry in the damaged hemisphere required for the given process and 2) the two processes that we have identified reflect our best interpretation of the information that we have at this point in time. Our computational model (Yadav & Sainburg, 2011), which uses a hybrid control scheme based on predictive and impedance control mechanisms, supports our experimental findings. However, we cannot distinguish at this point whether our hypothesized neural specializations are accurate or rather reflect proxies for the other underlying computational specializations.

Asymmetric Performance: Motor Lateralization

The asymmetry in motor performance between our arms is a prominent feature of human motor behavior that we suggest corresponds to the asymmetrical representation of predictive and impedance control mechanisms in the two hemispheres. Our aforementioned description of hemispheric specialization does not however predict asymmetrical performance between the two arms in healthy individuals. In fact, if the corpus collosum and anterior commissure allow sharing of the output of each specialized process with the contralateral hemisphere, this model should lead to *symmetrical* performance across the arms. Instead, our data indicate that the asymmetry between the dominant and non-dominant arms in healthy adults reflects the specialization of the hemisphere that is contralateral to each arm. The non-dominant arm performance reflects greater reliance on impedance mechanisms that are robust to perturbations, but less energetically efficient, whereas the dominant arm shows efficient smooth performance that is less-robust to perturbations. This indicates that in healthy individuals, movement patterns of each arm largely reflect the specialization of its contralateral controller. Why this asymmetry in performance arises despite the capability of the corpus callosum to share the output of contralateral and ipsilateral controllers is unclear. One possibility is that the contribution of the ipsilateral controller is less efficacious because it is not updated online via direct sensory projections from the effectors, but has to rely on callosal transfer of sensory information going to the contralateral hemisphere that arrives at a delay. In fact, previous research in deafferented patients has indicated that predictive control of task dynamics is dependent on such updating (Ghez & Sainburg, 1995). Similarly, output signals from the ipsilateral to the contralateral controller may be delayed because of transcalossal transfer, again leading to less effective contributions from the ipsilateral hemisphere. Thus, it is possible that the asynchrony in sensorimotor signals between the contralateral and ipsilateral hemispheres would lead to relative deficits in each arm for the control characteristics of the ipsilateral hemisphere.

Motor adaptation

Motor adaptation has been conceived as a learning process in which subjects "learn" to modify motor output so that errors induced by alterations in the movement environment are reduced to pre-perturbation, baseline levels. Such alterations may occur, for instance, when manipulating various objects or when moving in different dynamical environments (for example, moving in a swimming pool, or walking on a boat deck). In laboratory studies (mostly with the dominant arm) investigating adaptation, common perturbations include the use of prism glasses or visuomotor rotations that introduce a novel mapping between actual hand motion and its visual feedback, and unfamiliar (but predictable) forces that alter the dynamics of the task. The reduction in movement errors over trials of repeated exposure to the perturbation follows an exponential pattern, and removal of the perturbation results in large, persistent after-effects. Adaptation is thought to reflect changes in predictive control,

i.e. movement planning - which we define as a series of steps that transforms information about target and arm location, and task dynamics, into a sequence of movement commands that specify parameters such as movement direction and shape - is enhanced so that the effects of the perturbation are predicted and accounted for, and the motor output is appropriately modified (Sainburg, Ghez and Kalakanis, 1999; Mazzoni and Krakauer, 2006). Computationally, this process is modeled as an iterative update of a "forward" model, defined as a transformation from movement commands to their desired sensory consequences. In this scheme, "sensory prediction errors", or the difference between the predicted and actual sensory feedback drive the updating process, so that the predicted sensory consequences of motor commands coincide with the actual sensory feedback. This process has been shown to occur implicitly (Mazzoni & Krakauer, 2006), although new research suggests that adaptation may also involve explicit, or declarative strategies (Keisler & Shadmehr, 2010) as well as reinforcement mechanisms that are driven by task success (Huang, Haith, Mazzoni & Krakauer, 2011). Additionally, an important component that determines task success when exposed to a perturbation is the ability to make corrections online, during an ongoing trial, so that the hand is brought to the intended target accurately. Whether this component also improves with repeated exposure to the perturbation remains unclear.

Impact of motor lateralization on adaptation

Our discussion of hemispheric lateralization above pointed out research on episodic memory, in which the underlying processes of storage and retrieval were hypothesized to be specialized in each hemisphere (HERA model, Tulving et al, 1994). In addition, studies in patients with disconnection syndrome indicated that hemispheric specialization for episodic memory is related to the type of information that is to be learned (verbal or visual). These two different types of studies revealed two aspects of specialization: hemispheric specialization for memory storage and retrieval, and specialization depending on the type of the memories. We now define a similar distinction in our studies examining the impact of hemispheric specialization on motor adaptation. Our model of motor lateralization proposes hemispheric specialization for two control processes: predictive control that takes account of limb and task dynamics, and impedance control that is robust to unexpected perturbations. Each process requires different input and provides distinct output information, which can influence what features of the task are learned. Our studies examining adaptation to changes in the movement environment are designed to investigate how lateralized control might impact adaptive processes. We must clarify that it is also plausible that the adaptation processes, involving error evaluation, and memory storage and retrieval processes, might themselves be lateralized. The predictions that we make in the studies reviewed in this paper are based on our hypothesis of motor control asymmetry, and not on hypotheses about asymmetry in motor memory storage and retrieval, per se'. However, we do describe results that introduce the question of whether mechanisms underlying error evaluation and learning mechanisms, themselves, might also be lateralized.

To address questions about how asymmetries in control may affect adaptive processes, we assess both the rate and extent of adaptation, as well as patterns of motor generalization. In our earliest study comparing motor adaptation between the two arms in healthy young adults, we compared adaptation of the dominant and non-dominant arms to a 30 degree visuomotor rotation perturbation (Sainburg, 2002). Upon initial exposure to the perturbation, movements of both arms showed large, but similar curvatures, consistent with the requirement to correct for the rotation-induced error and bring the cursor to the displayed target. These errors were reduced over time, as movement trajectories became much more linear and movement direction was improved. Importantly, the pattern of error reduction showed a striking similarity between the right and left arms (Figure 1). There appeared to be

no difference between the rate or the final degree of adaptation, suggesting that visuomotor adaptation, as quantified using these measures, possibly occurred in a similar manner for the two arms.

However, when we examined the transfer of visuomotor learning between the arms, substantial differences occurred which depended on which arm first adapted to the rotation (Sainburg & Wang, 2002; Wang & Sainburg, 2003). In order to compare the transfer of learned information between the arms, two groups of subjects were tested: one group first adapted to the rotation with the right arm, and was then exposed to the same rotation with the left arm This order was reversed for participants in the second group (left arm adapted first, followed by exposure of the right arm). Transfer of learning was defined as the difference in performance of the same arm when it was naively exposed to the rotation and when it experienced the rotation following opposite arm adaptation. For example, right arm performance after left arm learning was compared to the performance of the right arm when it had no prior exposure to the rotation. The results indicated remarkable asymmetries in the pattern of information transfer between right and left arm movements. Initial movement direction, a reflection of predictive control, showed substantial transfer to the right arm following left arm learning, but not from the right arm to the left. In contrast, final position accuracy, which is influenced by sensory feedback during the ongoing movement, was substantially improved in the left arm following right arm adaptation, but not vice versa (Figure 2). In a follow-up study, we showed that strong left-handers displayed the same asymmetrical pattern of transfer, such that opposite arm training benefited the left, dominant, arm in terms of only initial direction and the right, non-dominant, arm only in terms of final position accuracy. Taken together, these results indicated that the dominant arm learned about predictive mechanisms from the non-dominant arm, while the non-dominant arm gained information about achievement of a final position from the dominant arm. Using a similar visuomotor adaptation paradigm, Anguera et al. (2007) also confirmed transfer of position, but not direction information, from the right to the left arm in right-handed subjects. Dizio and Lackner (1995) had also previously reached a similar conclusion when they examined the transfer of learning from the right to the left arm. They had subjects adapt to a Coriolis force field induced by having them reach in an environment that was slowly rotated. The right arm gradually adapted to this velocity dependent force and when the left arm was tested following right arm training, information about final position, but not movement direction or shape, was transferred. Thus, while dominant arm adaptation is viewed largely as an improvement in predictive control, it appears that from exposure to the perturbation, the non-dominant arm learns about processes that ensure accurate achievement of the target position during a trial.

What determines the nature of transfer between the two arm/hemisphere systems? We have hypothesized that evolutionary pressures to accommodate more complexity in motor behaviors [for example, tool use and construction (Marzke, 2009; Marzke & Marzke, 2000)] may have driven each brain hemisphere to become specialized for different aspects of movement control. It is possible that what each hemisphere retrieves from the opposite hemisphere (that has undergone adaptation), depends on that hemisphere's "strength". In other words, each hemisphere learns from the other, only those aspects of performance that it has become specialized for controlling – the left hemisphere for specifying features such as initial movement direction, and the right hemisphere for specifying outcomes such as accuracy. Our research findings have largely supported this idea that each brain hemisphere is specialized for different aspects of motor control. Several studies from our laboratory have shown that in healthy right-handed individuals, the right arm largely outperforms the left arm in terms of the direction and linearity of movement trajectories. Such right arm advantages appear to arise from an enhanced ability to predict arm and task dynamics so that the optimal strategy for a particular action can be planned. Because of advantages in such

predictive control, right arm movements tend to be straighter, smoother and energetically more efficient than those of the left arm (Bagesteiro & Sainburg, 2002; Sainburg, 2002; Sainburg & Kalakanis, 2000; Sainburg & Schaefer, 2004; Schaefer, Haaland, & Sainburg, 2007, 2009b). In contrast, the left arm often shows better accuracy and precision in achieving a desired spatial position. This benefit is particularly pronounced when the ongoing movement is unexpectedly perturbed, or, in other words, the movement has to be updated online when an unfamiliar task condition is introduced (Bagesteiro & Sainburg, 2003; Duff & Sainburg, 2007). It is important to stress that the fact that these findings have been compiled through studies of left and right *arm* motion in healthy individuals should not imply that our model of *hemispheric* specialization is strictly contralateral. Instead, as we alluded to earlier, we propose a hybrid control scheme, in which each hemisphere contributes its specialization to control of movements of each arm (Yadav & Sainburg, 2011). Thus, our model suggests that the left hemisphere provides predictive control mechanisms specifying aspects such as movement direction to movements of both the contralateral and the ipsilateral arms, while the right hemisphere contributes positional control mechanisms during movements of either arm as well. However, given the largely contralateral innervation of our effectors (Brinkman & Kuypers, 1972; Kuypers, 1964; Kuypers & Brinkman, 1970), it is the arm contralateral to a hemisphere that primarily shows the signatures of that hemisphere's specialization in its movement patterns. It is therefore possible that adaptation to a visuomotor rotation, evaluated through predictive control mediated changes in movement direction, proceeds in an identical manner behaviorally for the two arms, but improves such control only in the left hemisphere. On the other hand, it is likely that continuous exposure to the rotation during adaptation provides an opportunity for right hemisphere to enhance its control strategy for achievement of the target position during the ongoing movement. Consistent with this view is the observation that adaptation to novel force environments, achieved by making specific predictions about those forces, proceeds more rapidly with the right arm relative to the left (Duff & Sainburg, 2007; Schabowsky, Hidler, & Lum, 2007). In contrast, the left arm improves final position accuracy but without predictively accounting for the effects of the novel forces (Schabowsky, et al., 2007). This separation of function may be a way of ensuring that neither process is completely compromised - the right hemisphere may ensure accurate task completion while the left hemisphere gradually learns to improve movement planning. Asymmetric interhemispheric transfer of learning may be a consequence of this specialization - why not retrieve features that the accessing hemisphere is already good at, so that performance is better from the very beginning?

Effects of lateralized control on adaptation following stroke

Our model of lateralized movement control mechanisms offers clear predictions regarding the consequences of unilateral stroke, on adaptation. Improvement in predictive control, reflected by improvement in movement direction and linearity in a visuomotor adaptation paradigm, should be impaired following left, but not right hemisphere damage. In contrast, right, but not left hemisphere damage should produce deficits in correcting ongoing actions in response to the rotation. Importantly, as stated above, because our scheme is not simply a contralateral one, but proposes that each hemisphere contributes its mechanism to each arm's motion, deficits after unilateral stroke should be evident in contralesional *and* ipsilesional arm movements. Schaefer et al (2009a) recently tested this prediction by having left or right hemisphere damaged stroke patients (LHD and RHD respectively) adapt to a 30 degree visuomotor rotation with their ipsilesional arm. Clear, but distinct deficits were observed following left and right hemisphere damage relative to the performance of healthy control subjects who performed the same task with either their left or their right arm (Figure 3). Even after experiencing the rotation for over 200 trials, the movements of LHD patients remained significantly more curved and misdirected initially relative to those of the control

participants. However, LHD did not disrupt the ability to achieve the target position during the trial. In fact, on the first few trials of the rotation block when trajectory errors due to the rotation were the largest, these patients were able to successfully correct their movements and showed movement accuracy that was actually better than the control group. In contrast, RHD subjects had no difficulty adapting to the rotation, as evidenced by their gradual, but similar improvement in movement direction and trajectory straightness relative to healthy controls. However, RHD patients showed a significant deficit in correcting ongoing movements in response to the rotation. As a result, final position errors were significantly larger during the first few trials of the rotation block. These errors did decrease over time, but this reduction was strongly associated with improvements in movement direction with rotation adaptation, so that online corrections were no longer necessary. Thus, LHD, but not RHD adversely impacted direction adaptation, while RHD, but not LHD, impaired online control for achieving a position.

These findings raise an interesting question: what if subjects are required to adapt to position perturbations such as visuomotor gains rather than directional deviations? Such tasks require the modification of movement distance so that the cursor can reach the desired target. Vectorial planning models suggest that movement distance, like movement direction, is largely preplanned (). However, our research has shown that achievement of the planned distance, i.e. stopping at a desired goal position, also incorporates the use of sensory feedback during movement to modulate the output of our stabilization mechanisms (Mutha, Boulinguez, & Sainburg, 2008; Yadav & Sainburg, 2011). It is therefore unclear whether gain adaptation can be fully accounted for by modifications in distance planning strategies, i.e. through changes in predictive control, for which we have proposed a left hemisphere specialization, or, whether such adaptation also relies on alterations in strategies that regulate achievement of that distance, which we suggest are lateralized to the right hemisphere. This conundrum is evident in the findings of Palluel-Germain et al (2011) who tested LHD patients in a gain adaptation paradigm. Although these LHD patients did not show a deficit in gain adaptation as a group, significant individual differences were observed. While some LHD subjects showed a strong deficit in adapting to the altered gain, others did not, which they suggested was possibly related to the volume of damage to the supramarginal gyrus of the left inferior parietal lobe. Unfortunately, these authors did not test RHD subjects, but they speculated that perhaps RHD subjects, as a group, would show a larger deficit in gain adaptation, in light of our findings of a right hemisphere specialization for achievement of a goal position. Thus, while LHD did impact upon visuomotor gain adaptation on an individual subject level, the effect of RHD on this process remains speculative.

Neural substrates critical for adaptation

What neural substrates within the left hemisphere are critical for motor adaptation? We recently investigated this question using a visuomotor adaptation paradigm. Interestingly, the focus of a large number of adaptation studies has been on the role of the cerebellum. There is no doubt that cerebellar damage impairs adaptation (Bastian, 2008; Martin, Keating, Goodkin, Bastian, & Thach, 1996; Smith & Shadmehr, 2005; Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). However, the precise role of the cerebellum remains unclear. Several studies have shown that net cerebellar activity decreases as errors decrease during adaptation (Flament, Ellermann, Kim, Ugurbil, & Ebner, 1996; Imamizu et al., 2000; Nezafat, Shadmehr, & Holcomb, 2001; Seitz et al., 1994). These studies have suggested that cerebellar activity may be error related. We and others (Fiez, Petersen, Cheney, & Raichle, 1992; Flament, et al., 1996; Ojakangas & Ebner, 1994; Taylor, Klemfuss, & Ivry, 2010) have envisaged that the role of the cerebellum may be to provide the error signals necessary for adaptation to occur, while the process of adaptation may occur elsewhere. A

computational model was recently proposed by Tanaka et al (2009) based on this idea - errors derived from the cerebellum could be relayed to posterior parietal cortex, where the process of adaptation could occur. This paper showed that experimentally-observed visuomotor adaptation and generalization patterns could be reproduced using a population-coding model in which adaptation induced changes in the synaptic weights between narrowly tuned, parietal like neurons and units in the motor cortex. Importantly, models that utilized tuning properties of motor cortical or cerebellar neurons could not reproduce behavioral data.

This result reinforces the findings from a large number of functional neuroimaging studies that have shown consistent activation of parietal cortical regions during adaptation. However, these studies have been inconsistent with regard to whether parietal regions within one or both hemispheres are critical for adaptation, with studies arguing in favor of only left (Danckert, Ferber, & Goodale, 2008), only right (Ghilardi et al., 2000; Krakauer et al., 2004) or bilateral (Diedrichsen, Hashambhoy, Rane, & Shadmehr, 2005; Graydon, Friston, Thomas, Brooks, & Menon, 2005; Grefkes, Ritzl, Zilles, & Fink, 2004) parietal regions being important for adaptation. Case studies of patients with bilateral parietal damage have also been equivocal - one reported a strong adaptation deficit (Newport, Brown, Husain, Mort, & Jackson, 2006), but another study in a patient with bilateral optic ataxia, a disorder that usually occurs following bilateral superior parietal damage, concluded that adaptation was intact (Pisella et al., 2004). Thus, collectively, the results from imaging and lesion studies have been quite controversial. We recently examined patients with focal strokes to left or right parietal regions in a typical visuomotor adaptation paradigm (Mutha, et al., 2011). Our patients had only mild contralesional hemiparesis and therefore were able to use their contralesional arm to perform the task. Their performance was compared that of healthy control subjects using their left or right arm. Given our previous findings that LHD, but not RHD, impaired the ability to correct initial movement direction and curvature, we predicted that parietal damage in the left hemisphere would produce stronger deficits in this task. Our data confirmed this prediction. While patients with right parietal damage improved movement direction in a manner similar to controls, left parietal damaged patients showed a clear disruption in adjusting their movement direction by accounting for the novel task condition. This study thus confirmed a critical role for left parietal regions for updating our prior visuomotor representations and modifying movement plans accordingly.

Shadmehr and Holcomb (1997) had previously arrived at a similar result when they investigated the consolidation of motor adaptation using positron emission tomography (PET), although, they did not focus on the lateralization of neural activation patterns. When initially exposed to unfamiliar forces while moving the right arm, an area of activation in the dorsolateral prefrontal cortex of the right hemisphere was observed. This activation decreased as adaptation occurred. The authors therefore suggested that this right frontal activation was related to the early learning of the novel dynamics. However, when subjects completely adapted to the force field and were tested with the same arm in the same field after a delay of ~5.5 hours, the neural activation profile was dramatically different. Parietal and premotor regions in the left hemisphere demonstrated strong activation during the retest. Shadmehr and Holcomb (1997) argued that while left premotor activation was perhaps associated with retrieval processes, left parietal activation most likely reflected where the learned information were represented. Krebs et al (1998) also reported that initial exposure to a novel force field was associated with activation of regions in the right hemisphere, but, as learning progressed, regions in the left hemisphere became more active. Supporting this idea, Della-Maggiore et al (2004) showed that disrupting neural processing in left parietal cortex with transcranial magnetic stimulation interfered with the learning of novel dynamics imposed using a force field similar to that used by Shadmehr and Holcomb (1997). Unfortunately, these studies did not ask participants to perform movements with their left

arm, and so a direct conclusion of left, but not right hemisphere influence on adaptation, regardless of the arm moved, could not be drawn. Our study, which suggested a critical role for left parietal regions, only tested the contralesional arm in left or right parietal damaged patients and thus suffered from the same limitation.

In order to address this issue, we investigated the effects of focal frontal and parietal damage in the left or right hemisphere during visuomotor adaptation in stroke patients who performed the task with their ipsilesional arm (Mutha, Sainburg, & Haaland, 2012). This study had two aims: first, we wished to confirm that if parietal processes that mediate adaptation are lateralized in the left hemisphere, deficits in this process would be evident following left, but not right parietal damage, even in the ipsilesional arm. Second, we examined the effects of right and left frontal damage when these patients were exposed to a novel visuomotor condition. We were thereby able to test the suggestion of Shadmehr and Holcomb (1997) that right frontal regions may be associated with early stages of learning. As expected, left parietal damage prevented improvement in movement direction in response to the rotation. While these participants did improve somewhat in the first few movements under the novel conditions, their performance quickly reached an asymptote and movement errors on the last few trials remained substantially larger than those of healthy controls (Figure 4, left panel). After-effects, a reflection of an updated internal representation of the perturbation, were also considerably smaller in the left parietal damaged patients. We did not assess later recall of learning, and therefore could not investigate the role of left frontal regions in the retrieval of learning, as suggested by Shadmehr and Holcomb (1997). Left frontal damaged patients did not show significant deficits during adaptation itself, and the magnitude of their after-effects was comparable to that of controls. In contrast, right frontal damage patients showed a clear deficit in updating their ongoing actions when they were first exposed to the rotation. These patients often terminated their movements after making their previously practiced baseline movements, without correcting for the direction errors associated with the visuomotor rotation. As a result, movement accuracy in these patients remained substantially poor during the first few trials of the rotation block relative to that of healthy controls (Figure 4, right panel). These patients however, did not show a deficit adapting their initial movement direction, changes in which followed the same profile as control subjects. Additionally, the magnitude of their after-effects was large and comparable to that of controls. Further, when hand and cursor motion were matched during the after-effect block, these patients made movements in the previously adapted direction, but again showed a deficit in updating their movements to bring the cursor to the target. Thus, our data indicated that right frontal damage did not impair learning of the rotation, but these regions were likely involved in updating the ongoing action during the trial so that the task goal of bringing the cursor to the target could be accurately completed. These results in our right hemisphere damaged patients are consistent with the recent research that has suggested an important role of these regions, along with their connections to the basal ganglia, in "response switching" or action "reprogramming" (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron & Poldrack, 2006; Mars, Piekema, Coles, Hulstijn, & Toni, 2007; Neubert, Mars, Buch, Olivier, & Rushworth, 2010; Swann et al., 2009). While these studies employed cognitive tasks to examine action updating in response to novel stimuli, our results suggest that such online responses in cognitive or motor tasks might engage similar neural substrates in right frontal regions.

Impact of lateralization on other forms of learning

The studies that we have reviewed so far have highlighted a special role for the left hemisphere specialization for movement adaptation in response to predictable perturbations. Does the left hemisphere also play a special role in other forms of learning? If so what is that role? For example, is a left hemisphere specialization evident during tasks that require

the learning of new movement sequences or improvement in motor performance through repeated practice when no explicit perturbation is applied. Kimura (1977) tested left and right hemisphere damaged stroke patients on a task that required learning of a sequence of hand movements. Left hemisphere damaged patients were quite impaired on acquisition of the movement sequence, taking more than twice as long to learn with either hand relative to right hemisphere damaged patients. This deficit in the left hemisphere damaged patients was observed regardless of whether they moved their ipsilesional or their contralesional arms, thus indicating a larger role for the left hemisphere in the learning of new motor sequences. Jason (1985) also arrived at a similar conclusion, when he showed a deficit in learning a sequence of actions in patients with focal excisions of the left frontal and left temporal cortices. Interestingly, Mateer and Kimura (1977) suggested that this specialization may not be limited to arm movements, but may in fact be more general, based upon their observation that left, but not right, hemisphere damage disrupted learning of a sequence of nonverbal oral movements.

The serial reaction time task (Nissen & Bullemer, 1987; Robertson, 2007) has also been useful in terms of highlighting a left hemisphere specialization for learning movement sequences. In this task, subjects are required to press keys corresponding to the spatial locations of targets presented successively. A set of targets is often presented in a sequential order unbeknownst to the subjects, and learning of the sequence is characterized by smaller response times as compared to a randomized presentation of the targets. When the task is thought to be learned implicitly, i.e. without gaining explicit awareness of sequence order, a strong increase in the activity of left motor and premotor cortices, along with supplementary motor regions can be observed (Grafton, Hazeltine, & Ivry, 1995; Hazeltine, Grafton, & Ivry, 1997; Sadato, Campbell, Ibanez, Deiber, & Hallett, 1996). For instance, Grafton et al (1995) required subjects to learn a sequence of movements with their right hand under two conditions: one when development of explicit knowledge of the sequence was prevented using an attentional distractor task and second, when attentional interference was absent and subjects could (and a majority of them did) gain awareness of the sequence. They observed that sequence learning, without awareness of the sequence order, was associated with larger blood flow responses largely in the left, contralateral areas including sensorimotor cortex, supplementary motor area, anterior frontal regions and parietal cortex, and bilateral putamen. In contrast, when explicit awareness of the sequence was gained, increase in activity in the ipsilateral, right hemisphere regions, particularly right dorsolateral prefrontal and premotor cortices, was seen. Hazeltine et al (1997) made very similar observations in a serial reaction time task using color-coded rather than spatially cued stimuli. Further, Grafton et al (1998) noted that parietal activity was independent of the effector used during learning (hand or arm), reflecting representation of the learned knowledge at a high, abstract level. In order to confirm a left hemisphere specialization for sequence learning, Grafton and colleagues performed a follow-up experiment in subjects performing the task with their left hand (Grafton, Hazeltine, & Ivry, 2002). Brain regions associated with learning with the left arm exhibited a striking similarity to those identified for right hand learning, particularly the left supplementary motor area. Increased activity was also noted in left premotor and inferior parietal regions, and sensorimotor cortex bilaterally. Left hand learning was also associated with activation in more widespread areas of the frontal and temporal lobes. Thus, by demonstrating strong overlap of activated regions in the left hemisphere during sequence learning with the left and right hands, these experiments by Grafton and colleagues confirmed a special role for the left hemisphere in this process.

Several recent studies, particularly those by Ghilardi and colleagues (Ghilardi, Moisello, Silvestri, Ghez, & Krakauer, 2009; Moisello et al., 2009) have argued that in a typical serial reaction time task, it is difficult to gauge what exactly the reduced response times reflect – learning of the order of sequence elements, or improvement in some aspect motor

performance. Rather than requiring key presses as is done in a typical serial reaction time task, these researchers have examined the learning of whole arm movement sequences and asserted that learning of sequence order may not occur completely implicitly, and gradual changes in actual task performance, such as an improvement in spatial accuracy of the movements, may be a more accurate reflection of implicit learning mechanisms. Improvement of task performance itself may comprise of several component processes including learning of the visuomotor mapping between position of the visual stimulus and the required response, planning and executing the correct response, and predicting future events. Which of these processes does the left hemisphere contribute to, and more importantly, in a role different from the right hemisphere? While the answer to this question is uncertain, we posit that a left hemisphere specialization for predictive control, as discussed earlier, contributes to improvement in performance during sequence learning. Specifically, this predictive control specialization may result in better planning and execution of the sequential movements, resulting in enhanced movement kinematics that reflect some kind of optimization process.Moisello et al. (2009) have suggested that such optimization of performance is complete only after the entire sequence order has been learned.

A recent study by Schambra et al (2011) may provide support to this argument of a left hemisphere role in optimization of performance with learning. These authors examined if there exists a hemispheric specialization for "skill" learning, as quantified by changes in a variable derived from the combination for movement error rate and movement time. Importantly, the task used did not involve adaptation to a perturbation that knocked people off their baseline performance levels, but rather required improvements in an existing relationship between movement speed and accuracy, i.e. an optimization of motor performance. Three groups of participants trained with their left hand while three other groups trained with their right hand on a task that required subjects to squeeze a force transducer to move a cursor on a screen through an array of five targets, with each target requiring a different force. Each group received anodal transcranial direct current stimulation over motor cortex of the left or the right hemisphere, which facilitates motor performance (Fritsch et al., 2010; Reis et al., 2009), or sham stimulation. The proposition was that if a hemisphere is specialized for such learning, augmenting the function of that hemisphere by appropriately stimulating it should result in greater performance improvement in both arms compared to when the opposite hemisphere was stimulated. In general, left hemisphere stimulation produced a bigger improvement in performance relative to sham or right hemisphere stimulation when data from both hands were combined (Figure 5A). When each hand was examined separately, left hemisphere stimulation resulted in a clear improvement in performance with the right hand compared to right hemisphere or sham stimulation. For the left hand, there was a trend for a larger enhancement in performance with left rather than right or sham stimulation (Figure 5B). This study therefore suggests that a left hemisphere advantage may exist for motor learning, quantified through changes in motor performance in a non-adaptation paradigm. The findings from this study are in line with our findings demonstrating a left hemisphere specialization for predictive control via visuomotor adaptation and transfer studies. However, while our studies have emphasized a critical role for parietal regions in returning performance to baseline levels in the context of adaptation, the study by Schambra et al (2011) suggests that refinements in motor performance beyond baseline levels may involve motor cortical regions of the left hemisphere. The mechanisms by which such refinements occur require further investigation.

It is important to highlight one study that has argued against such a hemispheric specialization for motor learning. Winstein et al (1999) tested left and right hemisphere damaged stroke patients using their ipsilateral arm to learn to produce a pattern presented on the screen. Their analysis indicated that there was no interaction of group with arm-used

during the learning phase. Thus, with practice, both groups improved similarly relative to initial performance. However, the magnitude of learning itself was quite small in this study - root mean squared error decreased only by about 5 degrees relative to initial error. Another point worthy of consideration regarding this study is that participants were not provided concurrent visual feedback about their movements. Only knowledge of results was provided at the end of each trial. Recent research (Shabbott & Sainburg, 2010) has suggested that simultaneous visual and proprioceptive information is important for motor learning, at least in the context of visuomotor adaptation. The question of whether greater amount of learning would be observed and hemispheric differences would emerge if online visual feedback would have been provided in the study of Winstein et al (1999), remains open.

Implications of lateralized control

This review, necessarily selective, has focused largely on studies that have provided evidence in favor of an enhanced role for the left hemisphere for different learning processes. Adaptation paradigms have been particularly informative in terms of understanding how our internal representations of the body and the environment are updated so that motor planning is improved. Other paradigms such as sequence and skill learning may provide insight in the future about whether these representations are refined or whether some other mechanisms play a role in enhancing movement planning and execution. The studies reviewed here suggest that there might exist a left hemisphere specialization for these processes of adaptation, learning of sequences and skills. Why might this be the case? As stated earlier, we suggest that this specialization may arise from a more general left hemisphere specialization for planning of movements. Thus, even though these processes might be quite different computationally, the common feature when learning these different tasks is the requirement to improve the planning and execution of future actions. A general left hemisphere specialization for this operation may underlie the improvement in performance seen in learning tasks. This thought is consistent with several studies in patients that that have documented that left, more than right, hemisphere damage results in ideomotor apraxia, a disorder where observed spatiotemporal motor deficits are thought to arise from impaired planning due to damage to internal representations (Haaland, Harrington, & Knight, 2000; Ochipa & Gonzalez Rothi, 2000; Rothi, Ochipa, & Heilman, 1991). Networks in the left hemisphere have been implicated for the planning of actual tool use (Johnson-Frey, Newman-Norlund, & Grafton, 2005) as well as the planning of their pantomimes (Kroliczak & Frey, 2009), regardless of the hand used. Further, the left hemisphere is thought to be involved in the selection of actions (Schluter, Krams, Rushworth, & Passingham, 2001) and left parietal regions in particular are thought to play a critical role in motor attention (Castiello & Paine, 2002; Rushworth, Krams, & Passingham, 2001; Rushworth, Nixon, Renowden, Wade, & Passingham, 1997). More recent work also suggests that stimulation of left but not right parietal cortex can affect decisions of which hand to use for a particular task (Oliveira, Diedrichsen, Verstynen, Duque, & Ivry, 2010). Collectively, these results point towards a bigger role for the left hemisphere in planning motor actions. This idea fits well with the suggestion that over the course of evolution, the left hemisphere became specialized for "the control of well-established patterns of behavior under ordinary and familiar circumstances" (MacNeilage, Rogers & Vallortigara, 2009). These authors suggest that as actions became routine and more automatic, their control passed to the left hemisphere. While they do not specify what specific components of control the left hemispheric gained, it is intriguing that our suggestion of left-hemisphere mediated planning, derived almost exclusively using tasks involving "routine" reaching actions, is in line with their proposition.

Interestingly, MacNeilage et al (2009) have also suggested that the role of the right hemisphere may have been to detect and respond to unexpected stimuli in the environment.

Consistent with this suggestion, as briefly reviewed earlier, we have reported that the left arm in healthy controls shows better movement accuracy, particularly when the ongoing movement is perturbed. Studies in stroke patients have also revealed that damage to the right hemisphere produces specific deficits in achieving a desired spatial location, when moving the contralesional or the ipsilesional arm. We suggest that in the context of reaching movements, this specialization for responding to unexpected environmental events based on available feedback, may have led to a feedback mediated mode of control that modulates sensorimotor stabilization mechanisms such as reflexes to accurately stop at a goal position.

In line with these ideas, Yadav and Sainburg (2011) have recently developed a serial hybrid control model in which movements of both arms are initiated with a predictive, optimal control strategy and terminated with a stabilization, or "impedance" controller. When this model was fit to experimentally observed right and left arm movements of healthy young right-handers, left arm movements were characterized by an early switch in from the predictive to impedance control policy, while dominant arm movements were characterized by a late switch. These findings were consistent with the hypothesized contributions of right and left hemispheres to the control of each arm. Thus, the role of the each hemisphere appears to be clearly distinct during the control of purposeful movements.

Acknowledgments

References

Aboitiz F, Lopez J, Montiel J. Long distance communication in the human brain: timing constraints for inter-hemispheric synchrony and the origin of brain lateralization. Biol Res. 2003; 36:89–99. [PubMed: 12795208]

Anguera JA, Russell CA, Noll DC, Seidler RD. Neural correlates associated with intermanual transfer of sensorimotor adaptation. Brain research. 2007; 1185:136–151. [PubMed: 17996854]

Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci. 2007; 27:3743–3752. [PubMed: 17409238]

Aron AR, Poldrack RA. Cortical and subcortical contributions to Stop signal response inhibition: Role of the subthalamic nucleus. J Neurosci. 2006; 26:2424–2433. [PubMed: 16510720]

Bagesteiro LB, Sainburg RL. Handedness: dominant arm advantages in control of limb dynamics. J Neurophysiol. 2002; 88:2408–2421. [PubMed: 12424282]

Bagesteiro LB, Sainburg RL. Non-dominant arm advantages in load compensation during rapid elbow joint movements. Journal of Neurophysiology. 2003; 90:1503–1513. [PubMed: 12736237]

Bastian AJ. Understanding sensorimotor adaptation and learning for rehabilitation. Curr Opin Neurol. 2008; 21:628–633. [PubMed: 18989103]

Blakemore SJ, Goodbody SJ, Wolpert DM. Predicting the consequences of our own actions: the role of sensorimotor context estimation. J Neurosci. 1998; 18:7511–7518. [PubMed: 9736669]

Brinkman J, Kuypers HG. Splitbrain monkeys: cerebral control of ipsilateral and contralateral arm, hand, and finger movements. Science. 1972; 176:536–539. [PubMed: 4624322]

Castiello U, Paine M. Effects of left parietal injury on covert orienting of attention. Journal of Neurology, Neurosurgery, and Psychiatry. 2002; 72:73–76.

Conditt MA, Gandolfo F, Mussa-Ivaldi FA. The motor system does not learn the dynamics of the arm by rote memorization of past experience. Journal of Neurophysiology. 1997; 78:554–560. [PubMed: 9242306]

Danckert J, Ferber S, Goodale MA. Direct effects of prismatic lenses on visuomotor control: an event-related functional MRI study. Eur J Neurosci. 2008; 28:1696–1704. [PubMed: 18973586]

Danion F, Sarlegna FR. Can the human brain predict the consequences of arm movement corrections when transporting an object? Hints from grip force adjustments. J Neurosci. 2007; 27:12839–12843. [PubMed: 18032655]

Della-Maggiore V, Malfait N, Ostry DJ, Paus T. Stimulation of the posterior parietal cortex interferes with arm trajectory adjustments during the learning of new dynamics. J Neurosci. 2004; 24:9971–9976. [PubMed: 15525782]

Desmurget M, Grafton S. Forward modeling allows feedback control for fast reaching movements. Trends Cogn Sci. 2000; 4:423–431. [PubMed: 11058820]

Diedrichsen J, Hashambhoy Y, Rane T, Shadmehr R. Neural correlates of reach errors. J. Neurosci. 2005; 25:9919–9931. [PubMed: 16251440]

Dizio P, Lackner JR. Motor adaptation to Coriolis force perturbations of reaching movements: endpoint but not trajectory adaptation transfers to the nonexposed arm. Journal of Neurophysiology. 1995; 74:1787–1792. [PubMed: 8989414]

Duff SV, Sainburg RL. Lateralization of motor adaptation reveals independence in control of trajectory and steady-state position. Experimental Brain Research. 2007; 179:551–561.

Fiez JA, Petersen SE, Cheney MK, Raichle ME. Impaired non-motor learning and error detection associated with cerebellar damage. A single case study. Brain. 1992; 115:155–178. [PubMed: 1559151]

Flament D, Ellermann JM, Kim SG, Ugurbil K, Ebner TJ. Functional magnetic resonance imaging of cerebellar activation during the learning of a visuomotor dissociation task. Human brain mapping. 1996; 4:210–226. [PubMed: 20408199]

Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, Lu B. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010; 66:198–204. [PubMed: 20434997]

Gazzaniga MS. Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? Brain. 2000; 123:1293–1326. [PubMed: 10869045]

Ghez C, Sainburg RL. Proprioceptive control of interjoint coordination. Can J Physiol Pharmacol. 1995; 73:273–284. [PubMed: 7621366]

Ghilardi M, Ghez C, Dhawan V, Moeller J, Mentis M, Nakamura T, Eidelberg D. Patterns of regional brain activation associated with different forms of motor learning. Brain Res. 2000; 871:127–145. [PubMed: 10882792]

Ghilardi MF, Moisello C, Silvestri G, Ghez C, Krakauer JW. Learning of a sequential motor skill comprises explicit and implicit components that consolidate differently. Journal of neurophysiology. 2009; 101:2218–2229. [PubMed: 19073794]

Gordon J, Ghilardi MF, Ghez C. Accuracy of planar reaching movementsIIndependence of direction and extent variability. Experimental Brain Research. 1994; 99:97–111.

Grafton ST, Hazeltine E, Ivry R. Functional mapping of sequence learning in normal humans. Journal of Cognitive Neuroscience. 1995; 7:497–510.

Grafton ST, Hazeltine E, Ivry R. Abstract and effector-specific representations of motor sequences identified with PET. Journal of Neuroscience. 1998; 18:9420–9428. [PubMed: 9801380]

Grafton ST, Hazeltine E, Ivry RB. Motor sequence learning with the non-dominant left hand. A PET functional imaging study. Experimental Brain Research. 2002; 146:369–378.

Graydon FX, Friston KJ, Thomas CG, Brooks VB, Menon RS. Learning-related fMRI activation associated with a rotational visuo-motor transformation. Brain Res Cogn Brain Res. 2005; 22:373–383. [PubMed: 15722208]

Grefkes C, Ritzl A, Zilles K, Fink GR. Human medial intraparietal cortex subserves visuomotor coordinate transformation. Neuroimage. 2004; 23:1494–1506. [PubMed: 15589113]

Grimshaw GM. Integration and interference in the cerebral hemispheres: relations with hemispheric specialization. Brain & Cognition. 1998; 36:108–127. [PubMed: 9520310]

Haaland KY, Harrington DL, Knight RT. Neural representations of skilled movement. Brain. 2000; 123:2306–2313. [PubMed: 11050030]

Hazeltine E, Grafton ST, Ivry R. Attention and stimulus characteristics determine the locus of motor-sequence encoding a PET study. Brain. 1997; 120:123–140. [PubMed: 9055803]

Herculano-Houzel S, Mota B, Wong P, Kaas JH. Connectivity-driven white matter scaling and folding in primate cerebral cortex. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:19008–19013. [PubMed: 20956290]

Huang VS, Haith A, Mazzoni P, Krakauer JW. Rethinking motor learning and savings in adaptation paradigms: model-free memory for successful actions combines with internal models. Neuron. 2011; 70:787–801. [PubMed: 21609832]

Imamizu H, Miyauchi S, Tamada T, Sasaki Y, Takino R, Putz B, Kawato M. Human cerebellar activity reflecting an acquired internal model of a new tool. Nature. 2000; 403:192–195. [PubMed: 10646603]

Jason GW. Manual sequence learning after focal cortical lesions. Neuropsychologia. 1985; 23:483–496. [PubMed: 4033903]

Johnson-Frey SH, Newman-Norlund R, Grafton ST. A Distributed Left Hemisphere Network Active During Planning of Everyday Tool Use Skills. Cerebral Cortex. 2005; 15:681–695. [PubMed: 15342430]

Keisler A, Shadmehr R. A shared resource between declarative memory and motor memory. Journal of Neuroscience. 2010; 30:14817–14823. [PubMed: 21048140]

Kimura D. Acquisition of a motor skill after left-hemisphere damage. Brain. 1977; 100:527–542. [PubMed: 589430]

Krakauer JW, Ghilardi MF, Mentis M, Barnes A, Veytsman M, Eidelberg D, Ghez C. Differential cortical and subcortical activations in the learning of rotations and gains for reaching: a PET study. J Neurophysiol. 2004; 91:924–933. [PubMed: 14523069]

Krakauer JW, Pine ZM, Ghilardi MF, Ghez C. Learning of visuomotor transformations for vectorial planning of reaching trajectories. J Neurosci. 2000; 20:8916–8924. [PubMed: 11102502]

Krebs HI, Brashers-Krug T, Rauch SL, Savage CR, Hogan N, Rubin RH, Alpert NM. Robot-aided functional imaging: application to a motor learning study. Hum.Brain Mapp. 1998; 6:59–72. [PubMed: 9673663]

Kroliczak G, Frey SH. A common network in the left cerebral hemisphere represents planning of tool use pantomimes and familiar intransitive gestures at the hand-independent level. Cereb Cortex. 2009; 19:2396–2410. [PubMed: 19181695]

Kuypers HG. The Descending Pathways to the Spinal Cord, Their Anatomy and Function. Prog Brain Res. 1964; 11:178–202. [PubMed: 14300477]

Kuypers HG, Brinkman J. Precentral projections to different parts of the spinal intermediate zone in therhesus monkey. Brain Research. 1970; 24:29–48. [PubMed: 4099987]

Mars RB, Piekema C, Coles MG, Hulstijn W, Toni I. On the programming and reprogramming of actions. Cerebral Cortex. 2007; 17:2972–2979. [PubMed: 17389629]

Martin TA, Keating JG, Goodkin HP, Bastian AJ, Thach WT. Throwing while looking through prisms. I. Focal olivocerebellar lesions impair adaptation. Brain. 1996; 119:1183–1198. [PubMed: 8813282]

Marzke MW. Upper-limb evolution and development. Journal of Bone and Joint Surgery. American volume. 2009; 914(Suppl):26–30.

Marzke MW, Marzke RF. Evolution of the human hand: approaches to acquiring, analysing and interpreting the anatomical evidence. Journal of Anatomy. 2000; 197:121–140. [PubMed: 10999274]

Mateer C, Kimura D. Impairment of nonverbal oral movements in aphasia. Brain & Language. 1977; 4:262–276. [PubMed: 851856]

Mazzoni P, Krakauer JW. An implicit plan overrides an explicit strategy during visuomotor adaptation. J Neurosci. 2006; 26:3642–3645. [PubMed: 16597717]

Messier J, Kalaska JF. Differential effect of task conditions on errors of direction and extent of reaching movements. Exp Brain Res. 1997; 115:469–478. [PubMed: 9262201]

Miall RC, Christensen LO, Cain O, Stanley J. Disruption of state estimation in the human lateral cerebellum. PLoS Biol. 2007; 5:e316. [PubMed: 18044990]

Miall RC, Wolpert DM. Forward models for physiological motor control. Neural Networks. 1996; 9:1265–1279. [PubMed: 12662535]

Moisello C, Crupi D, Tunik E, Quartarone A, Bove M, Tononi G, Ghilardi MF. The serial reaction time task revisited: a study on motor sequence learning with an arm-reaching task. Experimental brain research. 2009; 194:143–155.

Mutha PK, Boulinguez P, Sainburg RL. Visual modulation of proprioceptive reflexes during movement. Brain Res. 2008; 1246:54–69. [PubMed: 18926800]

Mutha PK, Sainburg RL, Haaland KY. Left parietal regions are critical for adaptive visuomotor control. J Neurosci. 2011; 31:6972–6981. [PubMed: 21562259]

Mutha PK, Sainburg RL, Haaland KY. Critical neural substrates for correcting unexpected trajectory errors and learning from them. Brain. (in press).

Neubert FX, Mars RB, Buch ER, Olivier E, Rushworth MF. Cortical and subcortical interactions during action reprogramming and their related white matter pathways. Proc Natl Acad Sci U S A. 2010; 107:13240–13245. [PubMed: 20622155]

Newport R, Brown L, Husain M, Mort D, Jackson SR. The role of the posterior parietal lobe in prism adaptation: Failure to adapt to optical prisms in a patient with bilateral damage to posterior parietal cortex. Cortex. 2006; 42:720–729. [PubMed: 16909632]

Nezafat R, Shadmehr R, Holcomb HH. Long-term adaptation to dynamics of reaching movements: a PET study. Experimental Brain Research. 2001; 140:66–76.

Nissen MJ, Bullemer P. Attentional requriements of learning: Evidence from performance measures. Cognitive Psychology. 1987; 19:1–32.

Ochipa C, Gonzalez Rothi LJ. Limb apraxia. Semin Neurol. 2000; 20(4):471–478. [PubMed: 11149703]

Ojakangas CL, Ebner TJ. Purkinje cell complex spike activity during voluntary motor learning: relationship to kinematics. Journal of Neurophysiology. 1994; 72:2617–2630. [PubMed: 7897479]

Oliveira FT, Diedrichsen J, Verstynen T, Duque J, Ivry RB. Transcranial magnetic stimulation of posterior parietal cortex affects decisions of hand choice. Proc Natl Acad Sci U S A. 2010; 107:17751–17756. [PubMed: 20876098]

Palluel-Germain R, Jax SA, Buxbaum LJ. Visuo-motor gain adaptation and generalization following left hemisphere stroke. Neuroscience Letters. 2011; 498:222–226. [PubMed: 21605626]

Pisella L, Michel C, Grea H, Tilikete C, Vighetto A, Rossetti Y. Preserved prism adaptation in bilateral optic ataxia: strategic versus adaptive reaction to prisms. Exp Brain Res. 2004; 156:399–408. [PubMed: 15133651]

Reeves WH. Concept formation, problem-solving and the right hemisphere. International Journal of Neuroscience. 1985; 28:291–295. [PubMed: 4093265]

Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, Krakauer JW. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106:1590–1595. [PubMed: 19164589]

Rilling JK, Insel TR. Differential expansion of neural projection systems in primate brain evolution. Neuroreport. 1999; 10:1453–1459. [PubMed: 10380962]

Robertson EM. The serial reaction time task: implicit motor skill learning? Journal of Neuroscience. 2007; 27:10073–10075. [PubMed: 17881512]

Rothi LJG, Ochipa C, Heilman KM. A Cognitive Neuropsychological Model of Limb Praxis. Cognitive Neuropsychology. 1991; 8:443–458.

Rushworth MF, Krams M, Passingham RE. The attentional role of the left parietal cortex: the distinct lateralization and localization of motor attention in the human brain. J.Cogn Neurosci. 2001; 13:698–710. [PubMed: 11506665]

Rushworth MF, Nixon PD, Renowden S, Wade DT, Passingham RE. The left parietal cortex and motor attention. Neuropsychologia. 1997; 35:1261–1273. [PubMed: 9364496]

Sadato N, Campbell G, Ibanez V, Deiber MP, Hallett M. Complexity affects regional cerebral blood flow change during sequential finger movements. Journal of Neuroscience. 1996; 16:2693–2700.

Sainburg RL. Evidence for a dynamic-dominance hypothesis of handedness. Experimental Brain Research. 2002; 142:241–258.

Sainburg, RL. Lateralization of Goal-Directed Movement. In: Elliott, D.; Khan, M., editors. Vision and Goal-Directed Movement: Neurobehavioral Persectives. Champaign, IL: Human Kinetics; 2010. p. 219-238.

Sainburg RL, Ghez C, Kalakanis D. Intersegmental dynamics are controlled by sequential anticipatory, error correction, and postural mechanisms. J Neurophysiol. 1999; 81:1040–1056.

Sainburg RL, Kalakanis D. Differences in control of limb dynamics during dominant and non-dominant arm reaching. J Neurophysiol. 2000; 83:2661–2675. [PubMed: 10805666]

Sainburg RL, Schaefer SY. Interlimb differences in control of movement extent. J Neurophysiol. 2004; 92:1374–1383. [PubMed: 15115793]

Sainburg RL, Wang J. Interlimb transfer of visuomotor rotations: independence of direction and final position information. Experimental Brain Research. 2002; 145:437–447.

Sarlegna FR, Malfait N, Bringoux L, Bourdin C, Vercher JL. Force-field adaptation without proprioception: can vision be used to model limb dynamics? Neuropsychologia. 2010; 48:60–67. [PubMed: 19695273]

Schabowsky CN, Hidler JM, Lum PS. Greater reliance on impedance control in the non-dominant arm compared with the dominant arm when adapting to a novel dynamic environment. Experimental Brain Research. 2007; 182:567–577.

Schaefer SY, Haaland KY, Sainburg RL. Ipsilesional motor deficits following stroke reflect hemispheric specializations for movement control. Brain. 2007; 130:2146–2158. [PubMed: 17626039]

Schaefer SY, Haaland KY, Sainburg RL. Dissociation of initial trajectory and final position errors during visuomotor adaptation following unilateral stroke. Brain Research. 2009a; 1298:78–91. [PubMed: 19728993]

Schaefer SY, Haaland KY, Sainburg RL. Hemispheric specialization and functional impact of ipsilesional deficits in movement coordination and accuracy. Neuropsychologia. 2009b; 47:2953–2966. [PubMed: 19573544]

Schambra HM, Abe M, Luckenbaugh DA, Reis J, Krakauer JW, Cohen LG. Probing for hemispheric specialization for motor skill learning: a transcranial direct current stimulation study. Journal of Neurophysiology. 2011; 106:652–661. [PubMed: 21613597]

Schluter ND, Krams M, Rushworth MF, Passingham RE. Cerebral dominance for action in the human brain: the selection of actions. Neuropsychologia. 2001; 39:105–113. [PubMed: 11163368]

Seitz RJ, Canavan AG, Yaguez L, Herzog H, Tellmann L, Knorr U, Homberg V. Successive roles of the cerebellum and premotor cortices in trajectorial learning. Neuroreport. 1994; 5:2541–2544. [PubMed: 7696599]

Shabbott BA, Sainburg RL. Learning a visuomotor rotation: simultaneous visual and proprioceptive information is crucial for visuomotor remapping. Experimental Brain Research. 2010; 203:75–87.

Shadmehr R, Holcomb HH. Neural correlates of motor memory consolidation. Science. 1997; 277:821–825. [PubMed: 9242612]

Shadmehr R, Mussa-Ivaldi FA. Adaptive representation of dynamics during learning of a motor task. Journal of Neuroscience. 1994; 14:3208–3224. [PubMed: 8182467]

Shadmehr R, Smith MA, Krakauer JW. Error correction, sensory prediction, and adaptation in motor control. Annual Review of Neuroscience. 2010; 33:89–108.

Smith MA, Shadmehr R. Intact ability to learn internal models of arm dynamics in Huntington's disease but not cerebellar degeneration. Journal of Neurophysiology. 2005; 93:2809–2821. [PubMed: 15625094]

Swann N, Tandon N, Canolty R, Ellmore TM, MCEvoy LK, Dreyer S, Aron AR. Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci. 2009; 29:12675–12685. [PubMed: 19812342]

Tanaka H, Sejnowski TJ, Krakauer JW. Adaptation to visuomotor rotation through interaction between posterior parietal and motor cortical areas. J Neurophysiol. 2009; 102:2921–2932. [PubMed: 19741098]

Taylor JA, Klemfuss NM, Ivry RB. An explicit strategy prevails when the cerebellum fails to compute movement errors. Cerebellum. 2010; 9:580–586. [PubMed: 20697860]

Tompkins CA, Flowers CR. Perception of emotional intonation by brain-damaged adults: the influence of task processing levels. Journal of Speech & Hearing Research. 1985; 28:527–538. [PubMed: 4087888]

Tseng YW, Diedrichsen J, Krakauer JW, Shadmehr R, Bastian AJ. Sensory prediction errors drive cerebellum-dependent adaptation of reaching. J Neurophysiol. 2007; 98:54–62. [PubMed: 17507504]

Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proceedings of the National Academy of Sciences of the United States of America. 1994; 91:2016–2020. [PubMed: 8134342]

van den Heuvel MP, Stam CJ, Kahn RS, Hulshoff Pol HE. Efficiency of functional brain networks and intellectual performance. J Neurosci. 2009; 29:7619–7624. [PubMed: 19515930]

Vindras P, Desmurget M, Viviani P. Error parsing in visuomotor pointing reveals independent processing of amplitude and direction. Journal of Neurophysiology. 2005; 94:1212–1224. [PubMed: 15857965]

Vindras P, Viviani P. Altering the visuomotor gain. Evidence that motor plans deal with vector quantities. Exp Brain Res. 2002; 147:280–295. [PubMed: 12428136]

Wang J, Sainburg RL. Mechanisms underlying interlimb transfer of visuomotor rotations. Exp Brain Res. 2003; 149:520–526. [PubMed: 12677333]

Wang J, Sainburg RL. Adaptation to visuomotor rotations remaps movement vectors, not final positions. J.Neurosci. 2005; 25:4024–4030. [PubMed: 15843604]

Winstein CJ, Merians AS, Sullivan KJ. Motor learning after unilateral brain damage. Neuropsychologia. 1999; 37:975–987. [PubMed: 10426521]

Wolpert DM, Flanagan JR. Motor prediction. Curr Biol. 2001; 11:R729–R732. [PubMed: 11566114]

Yadav V, Sainburg RL. Motor lateralization is characterized by a serial hybrid control scheme. Neuroscience. 2011; 196:153–167. [PubMed: 21889579]

Yeo, RA.; Thoma, RJ.; Gangestad, SW. Human handedness: a biological perspective. In: Segalowitz, SJ.; Rapin, I., editors. Handbook of Neuropsychology. 2 nd Edition. Vol. Vol. 8. Elsevier Science BV; 2002. p. 331-365.

Zago M, Lacquaniti F. Internal model of gravity for hand interception: parametric adaptation to zero-gravity visual targets on Earth. Journal of Neurophysiology. 2005; 94:1346–1357. [PubMed: 15817649]
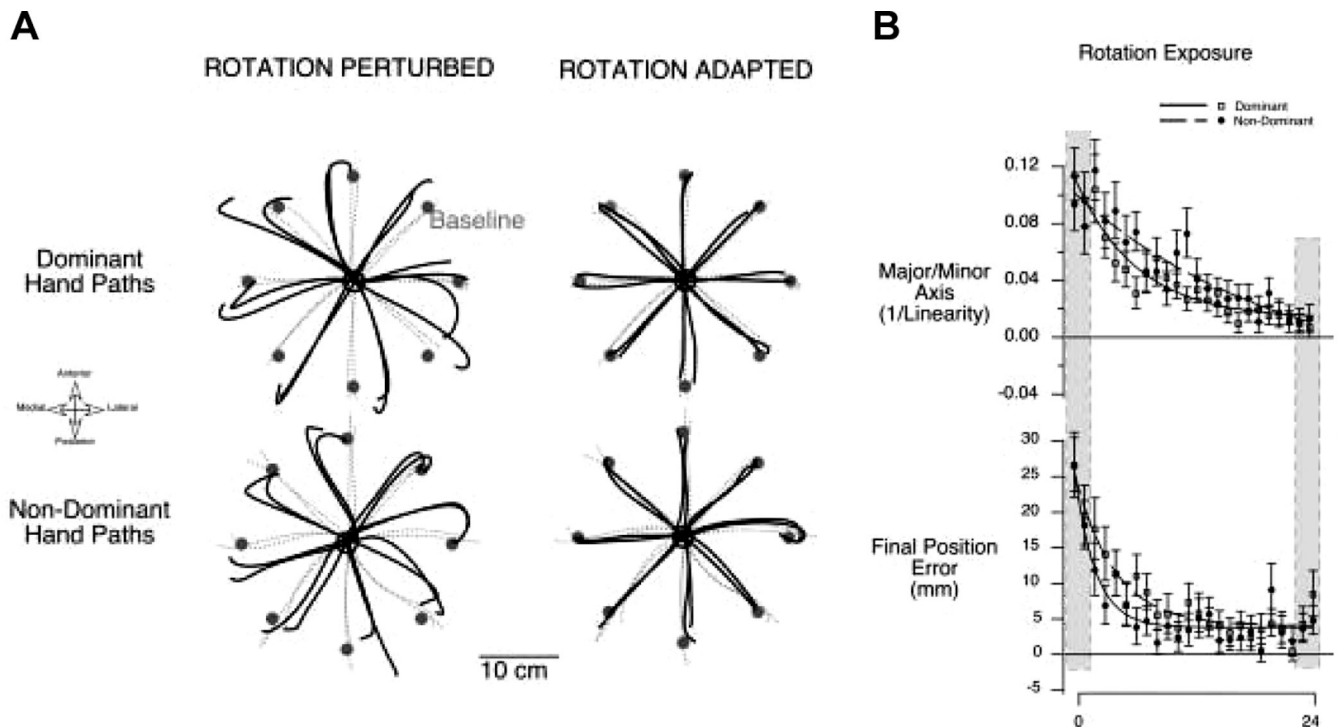
A

ROTATION PERTURBED   ROTATION ADAPTED

B

Rotation Exposure

Figure 1.
(A) Dominant (right) and Non-dominant (left) arm handpaths for an individual subject when first exposed to the visuomotor rotation and following adaptation are shown in black. Two pre-exposure baseline movements to each of the eight targets are shown in gray. **(B)** Change in mean handpath curvature and final position error across all subjects for the right (solid) and left (dotted) arms during the rotation exposure trials. Cycles of trials are shown on the x-axis; each cycle comprises eight movements, one to each of the eight targets shown in **A**. Adaptation profiles for curvature and error are very similar for both arms. Figures adapted from Sainburg (2002).
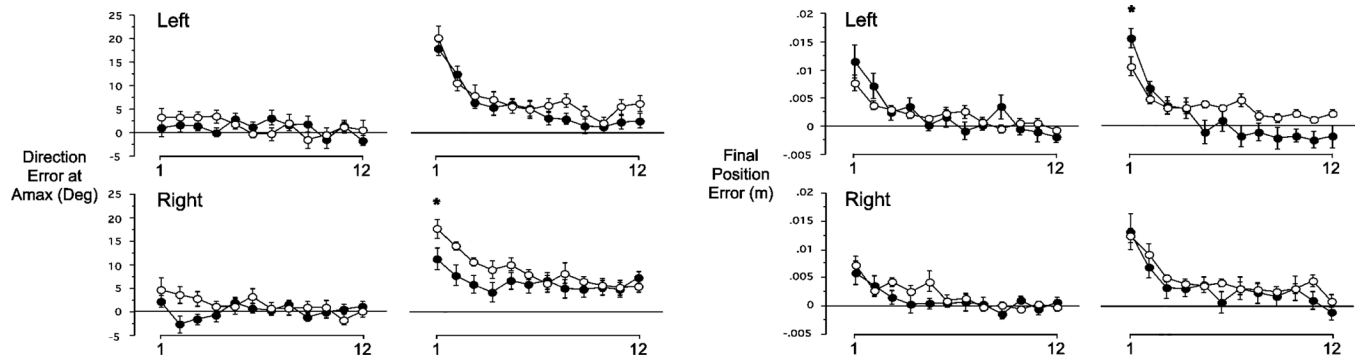
Figure 2.
Initial direction error and final position error for the left and right arms. Filled circles represent the group that adapted to the rotation first with their left arm and were then exposed to the same rotation with their right arm. Open circles represent the group that adapted first with their right arm and were then exposed to the rotation with their left arm. Differences between the group indicate the effects of opposite arm training. For example, following opposite arm training, direction error, but not final position error, made with the right arm (filled circles) is smaller than when the right arm experiences the rotation without left arm training (open circles). Cycles of trials are shown on the x-axis; each cycle comprises sixteen movements, two each to the eight targets presented as in Figure 1A. Figures adapted from Sainburg and Wang (2002).
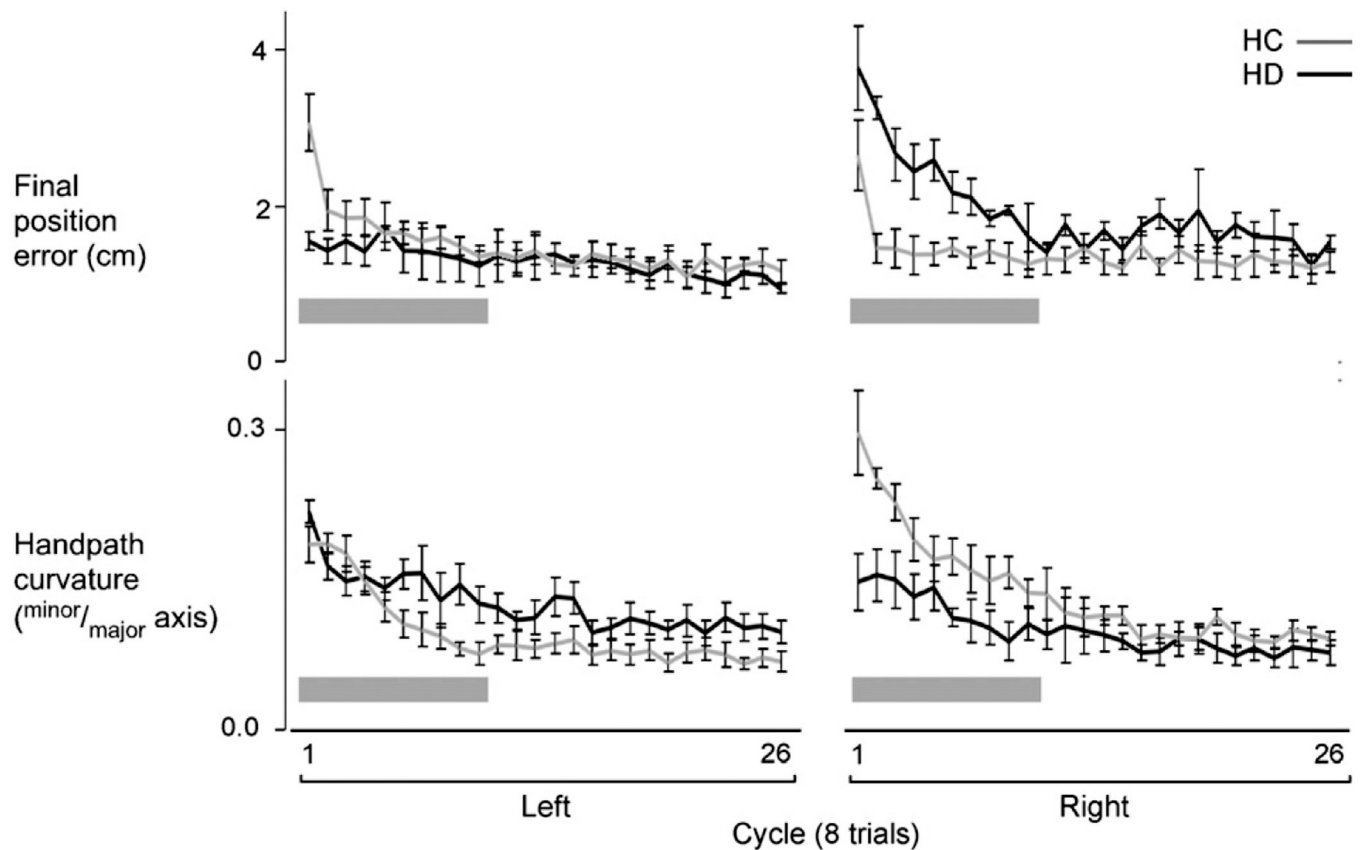
Figure 3.
Change in mean final position error and handpath curvature during the rotation exposure session for the left and right arms of all healthy control subjects (gray) and the ipsilesional arms of all left and right hemisphere damaged subjects (black). Left controls and left hemisphere damaged groups are on the left, while right controls and right hemisphere damaged groups are on the right. Cycles, as defined for Figure 1B, are on the x-axis. Final position errors are small for the left hemisphere damaged group from the beginning of the rotation exposure while handpath curvature remains larger during the entire session relative to the control group performing with the left arm. In contrast, errors are significantly larger for the right hemisphere damaged group, but their curvatures are smaller (i.e., movements are straighter) than the right control group throughout the rotation session. Figures adapted from Schaefer et al (2009a)
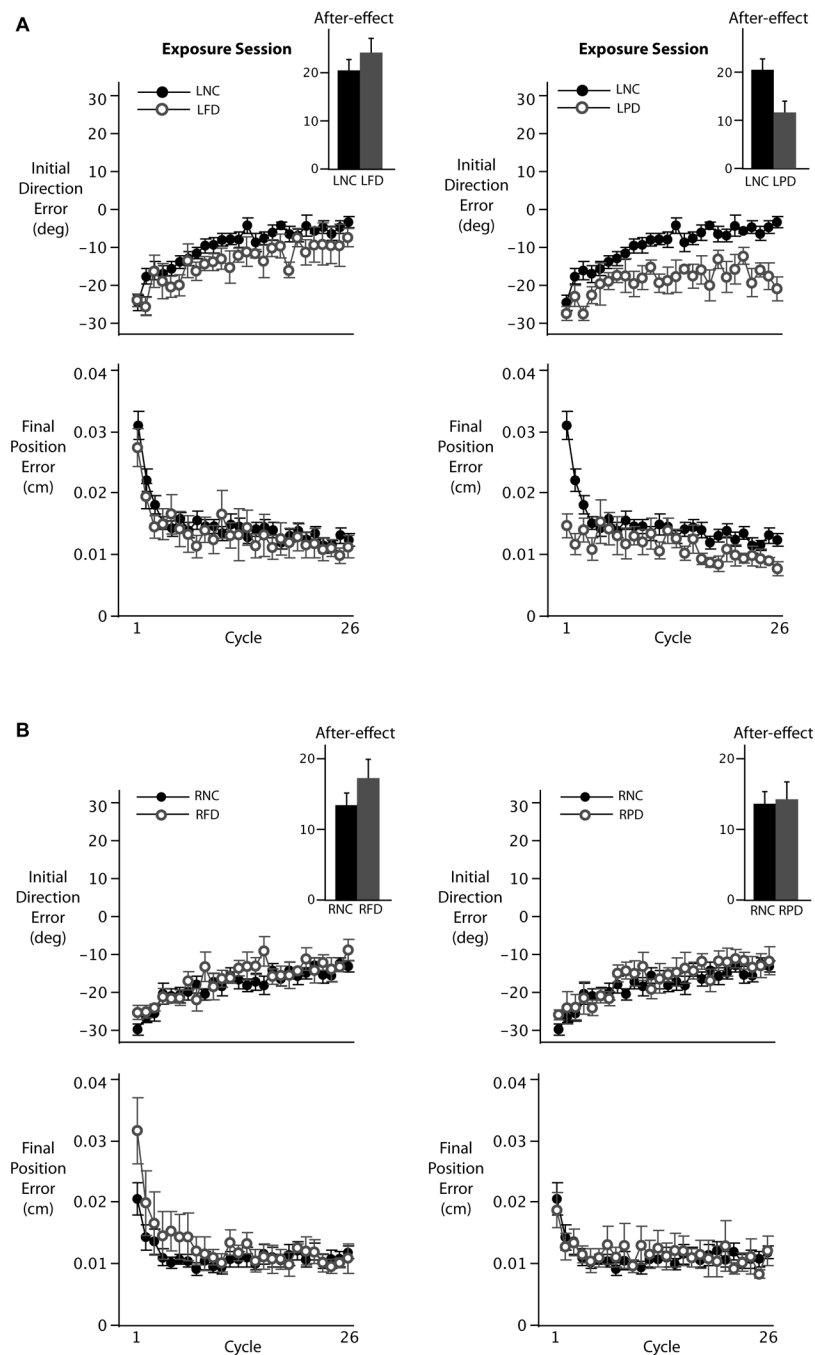
Figure 4.
(A) Change in initial movement direction error and final position error in the left frontal damage (LFD), left parietal damage (LPD) and left healthy control (LNC) groups during the rotation exposure session. Cycles, as defined for figure 1B, are on the x-axis. All subjects in these groups used their left arm to perform the task. Only the LPD group showed a deficit in adapting initial direction, but their final position errors remained consistently low relative to the LNC group. **(B)** Change in initial movement direction error and final position error in the right frontal damage (RFD), right parietal damage (RPD) and right healthy control (RNC) groups during the rotation exposure session. Cycles, as defined for figure 1B, are on

the x-axis. All subjects in these groups used their right arm to perform the task. Neither stroke group showed a deficit in adapting initial direction, and their after-effects (shown in insets) were comparable to controls. However, final position errors were substantially larger in only the RFD group relative to controls during the early part of the rotation session. Figures adapted from Mutha et al (in press)
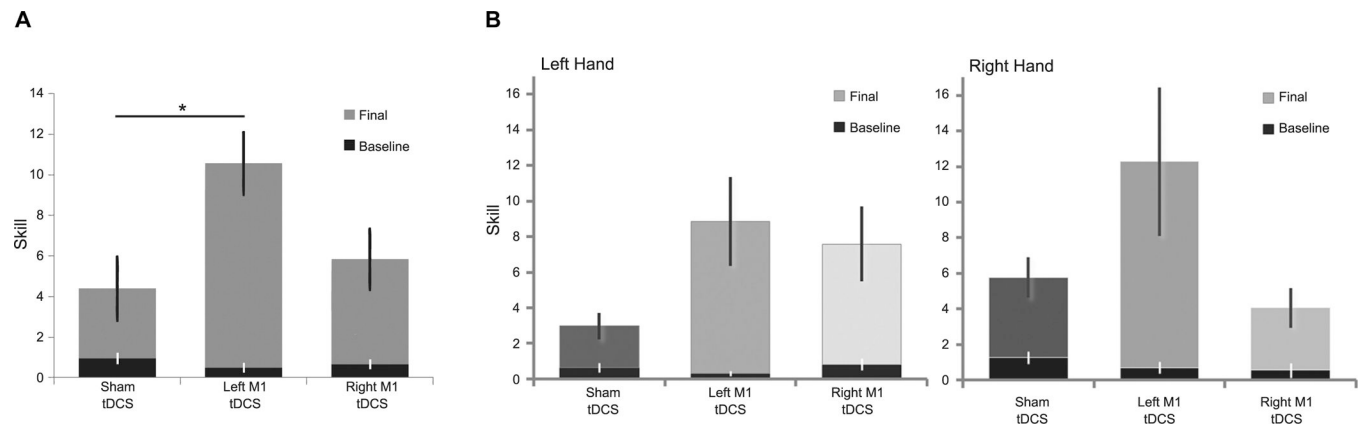
A

B

Figure 5.
(A) Effect of transcranial direct current stimulation on motor skill improvement when data from the left and right arms is combined. Baseline skill was comparable across the three groups. Left motor cortical stimulation significantly improved skill relative to sham stimulation, but right motor cortex stimulation did not. **(B)** When each hand is separately analyzed, left motor cortex stimulation led to a bigger change in skill relative to right motor cortex stimulation in the right as well as in the left hand. Thus, enhancement of left hemisphere activity leads to a bigger improvement in skill compared to right hemisphere stimulation, independent of effector. Figures adapted from Schambra et al (2011)