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RESEARCH ARTICLE

Laterality affects spontaneous recovery of contralateral hand motor function following motor cortex injury in rhesus monkeys

Warren G. Darling · Nicole Helle · Marc A. Pizzimenti · Diane L. Rotella · Stephanie M. Hynes · Jizhi Ge · Kimberly S. Stilwell-Morecraft · Robert J. Morecraft

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Abstract The purpose of this study was to test whether brain laterality influences spontaneous recovery of hand motor function after controlled brain injuries to arm areas of M1 and lateral premotor cortex (LPMC) of the hemisphere contralateral to the preferred hand in rhesus monkeys. We hypothesized that monkeys with stronger hand preference would exhibit poorer recovery of skilled hand use after such brain injury. Degree of handedness was assessed using a standard dexterity board task in which subjects could use either hand to retrieve small food pellets. Fine hand/digit motor function was assessed using a modified dexterity board before and after the M1 and LPMC lesions in ten monkeys. We found a strong negative relationship between the degree of handedness and the recovery of manipulation skill, demonstrating that higher hand preference was associated with poorer recovery of hand fine motor function. We also observed that monkeys with larger lesions within M1 and LPMC had greater initial impairment of manipulation and poorer recovery of reaching skill. We conclude that monkeys with a stronger hand preference are likely to show poorer recovery of contralesional hand fine motor skill after isolated brain lesions affecting the lateral frontal motor areas. These data may be extended to suggest that humans who exhibit weak hand dominance, and perhaps individuals who use both hands for fine motor tasks, may have a more favorable potential for recovery after a unilateral stroke or brain injury affecting the lateral cortical motor areas than individuals with a high degree of hand dominance.

Keywords Brain injury · Hand · Dexterity · Hemispheric dominance

W. G. Darling (✉) · N. Helle · D. L. Rotella · S. M. Hynes
Department of Health and Human Physiology, Motor Control Laboratories, The University of Iowa, Iowa City, IA 52242, USA
e-mail: warren-darling@uiowa.edu

M. A. Pizzimenti
Department of Anatomy and Cell Biology, Carver College of Medicine, The University of Iowa, Iowa City, IA 52242, USA

J. Ge · K. S. Stilwell-Morecraft · R. J. Morecraft
Division of Basic Biomedical Sciences, Laboratory of Neurological Sciences, Sanford School of Medicine, The University of South Dakota, Vermillion, SD 57069, USA

Introduction

Brain damage limited to one hemisphere may result in differing degrees of motor impairment and potential for contralateral hand motor function recovery in humans (McCombe Waller and Whitall 2005; Langan and van Donkelaar 2008). For example, strokes affecting the left hemisphere may cause greater impairments in hand motor function and learning of complex hand motor tasks than strokes affecting the right hemisphere (Kimura and Archibald 1974; Kimura 1977). Yet, when stroke survivors are grouped by pre-ictus hand preference, more recent studies show that right-handed subjects with left hemisphere damage have less impairment and more extensive motor recovery after rehabilitation than right-handed subjects with right hemisphere damage (McCombe Waller and Whitall 2005; Harris and Eng 2006). However, these human studies have not controlled for differences in hemispheric lesion location and size, white versus gray matter lesion involvement, or for magnitude of hand preference (dominance) prior to brain injury. Indeed, all of these factors may uniquely affect the motor recovery process, particularly when

considering the effects of hemispheric dominance on recovery potential.

Hemispheric specialization for control of fine movements may be an important consideration in terms of recovery after motor cortex injury. Clear evidence for such specialization has been demonstrated in right-handed subjects for upper limb pointing movements with the left (dominant) hemisphere being specialized for coordination and right hemisphere for accuracy of movements by both upper limbs (Duff and Sainburg 2007; Schaefer et al. 2007, 2009). Similarly, coordination of multi-finger production of rapid isometric force pulses was better for the dominant hand, but there was no evidence of specialization of the right hemisphere for accuracy of force pulses or stabilization of force steps (Zhang et al. 2006). In contrast, coordination of grip and load forces and minimizing grip/load force ratio appeared to be better for the non-dominant hand in bimanual load force production tasks, suggesting specialization of the right hemisphere for such coordination in right-handed subjects (de Freitas et al. 2007).

Most humans have a very strong tendency to use one hand for many gross and fine motor tasks such as throwing, writing, and picking up small objects. However, humans also show differing degrees of hand preference (Dassonville et al. 1997), and some individuals may use their dominant hand less than others for some tasks. Therefore, understanding how the degree of handedness affects recovery from hemiplegia, as a result of unilateral brain injury, may influence the design and implementation of rehabilitation methods.

In humans, blood oxygen level–dependent functional imaging of the motor cortex was previously shown to be more lateralized to the hemisphere contralateral to the moving hand with increasing degrees of handedness in both right-handed and left-handed subjects (Dassonville et al. 1997). This suggests that a greater degree of hand preference in a fine motor task may be associated with a greater degree of cerebral dominance and interhemispheric inhibition (IHI) for such tasks on the side of the brain contralateral to the preferred hand. Recovery of fine hand motor function after damage to the dominant side of the brain may therefore be closely related to the degree of handedness that existed before damage because IHI would be reduced more after damage to a highly dominant hemisphere than to a weakly dominant hemisphere. That is, a large decrease in IHI to the undamaged hemisphere may result in more skillful movements of the non-dominant hand and greater learned non-use of the dominant hand, thereby causing poor recovery of the dominant hand.

Observations of monkeys and apes indicate a large range of degree of hand preference in fine motor tasks (Spinozzi et al. 2007; Schmitt et al. 2008; Zhao et al. 2012). This is ideal for studying effects of handedness on recovery of fine motor skills after brain damage because this wide gradation of hand preference can be assessed, which is not the case for human studies. Study of motor recovery in animal models with hand function similar to humans following selective injury to the hemisphere opposite the preferred hand may provide important insight into how the degree of hand preference affects motor recovery in patients with stroke or lateral cortical brain trauma. This information may also provide some insight into the issue of lateralization of cortical motor control in these animals.

The purpose of this study was to test whether laterality in the rhesus monkey (*Macaca mulatta*), as indicated by degree of hand preference in a unimanual fine motor task, influences spontaneous recovery of hand motor function after controlled brain injury to lateral frontal lobe motor areas of the hemisphere contralateral to the preferred hand. We hypothesized that monkeys with a high degree of hand preference will be slower to recover use of the preferred hand and exhibit a longer lasting impairment of skilled hand use after such injury than monkeys with a low degree of hand preference. We also examined the effects of lesion volume on recovery of dexterity in these lesions limited to M1 and LPMC because our previous work showed the effects of lesion volume on recovery for a wide range of lesion types (M1 alone, M1 + LPMC, M1 + LPMC + supplementary motor area, and larger non-focal lesions). We hypothesized that spontaneous recovery of dexterity would be poorer with increased lesion size within M1 and LPMC.

Methods

Animals

Ten adult rhesus monkeys (*M. mulatta*) with a wide range of hand preferences served as subjects for these experiments (Table 1). The post-lesion duration over which monkeys were studied varied, because an important purpose of this research was to examine the time-course of reorganization of corticofugal connections in response to brain injury (McNeal et al. 2010) and cellular/molecular events which characterize the recovery process (Nagamoto-Combs et al. 2007, 2010). The monkeys were housed and maintained in a United States Department of Agriculture (USDA)-approved and inspected facility. All behavioral protocols were approved by the University of South Dakota Institutional Animal Care and Use Committee and performed according to USDA, National Institutes of Health and Society for Neuroscience guidelines for the ethical treatment of animals. Prior to testing, each monkey was evaluated by a primate veterinarian and judged to be healthy and free of any neurological deficits.

Table 1 Characteristics of monkeys (in order of ascending degree of hand preference)

Monkey	Age[a] (years)	Sex	Handedness index	Lesion location	GMLV[b]	WMLV[c]	Post-lesion duration (months)
SDM78	10.6	M	2.4 R	M1[d] + LPMC[e]	203.7	55.7	1
SDM70	7.2	M	4.4 R	M1 + LPMC	143.27	7.76	6
SDM48	6.8	F	6.0 R	M1 + LPMC	220.31	23.12	12
SDM79	9.8	M	14.0 L	M1 + LPMC	157.20	34.49	1
SDM55	11.8	M	20.0 L	M1 + LPMC	207.64	20.51	12
SDM45	4.9	M	21.3 R	M1 + LPMC	212.64	23.02	6
SDM49	3.5	M	65.0 R	M1 + LPMC	202.91	53.64	1
SDM80	8.8	M	75.7 L	M1 + LPMC	150.72	10.47	3
SDM74[f]	8.6	M	93.2 R	M1 + LPMC	192.56	16.26	3
SDM64	13.6	F	95.3 L	M1 + LPMC	217.92	43.04	6

LPMC lateral premotor cortex

[a] Age at time of lesion

[b] Gray matter lesion volume

[c] White matter lesion volume

[d] M1—primary motor cortex

[e] Lateral premotor cortex

[f] Performed bimanual task before and after lesion

Apparatus

The monkeys were tested on three different tasks that involved reaching and manipulating food targets: a standard dexterity board (sDB—described in Pizzimenti et al. 2007), a modified dexterity board (mDB—Pizzimenti et al. 2007), and a modified movement assessment panel (mMAP—Darling et al. 2006). The sDB task allowed the monkey to choose which hand to use for acquiring the food targets and was implemented to test magnitude of hand preference (see below). The other two tasks (mDB and mMAP) were used to test motor performance of both hands with devices designed to allow experimenter control over which hand was used to grasp and manipulate food targets without putting restraints on the monkey. We do not report on recovery in the mMAP task in this paper because previous work has shown that strength and direction (right/left) of hand preference may vary with task in rhesus monkeys (Lehman 1980). Thus, we focused on recovery in mDB task which is very similar to the sDB task on which hand preference was evaluated.

Behavioral procedures

Behavioral assessments of upper limb and hand movements for the sDB and mDB tasks have been described previously (Darling et al. 2006; Pizzimenti et al. 2007). Briefly, hand preference was assessed before training began in the mDB task by tabulating hand use data on initial reaches and successful acquisitions of pellets from each well of the sDB task with opportunity to acquire 50 food pellets on each of three consecutive days (Nudo et al. 1992). The monkey could use either hand to retrieve the pellet in this task. A handedness index was derived from the ratio of right hand reaches to left hand initial reaches and a ratio of right hand to left hand retrievals for each of the four wells (Eq. 1—Nudo et al. 1992). The preference score indicates the percentage of trials in which the preferred hand was used on more than 50 % of the trials—i.e., a score of 100 indicates only the preferred hand was used on every trial (100 % of the trials), a score of 50 would mean that the preferred hand was used on 50 % more trials than the *non-preferred hand*, and a score of 0 would mean each hand was used on 50 % of the trials.

$$\mathrm{HI} = (P - 50) \times 2 \quad (1)$$

where HI = handedness index, P average percentage of responses (average of initial reaches and retrievals) made with the preferred hand.

The mDB task was performed every 0.5–3 weeks pre-lesion. The final five pre-lesion experiments were conducted over a 6- to 11-week period and demonstrated relatively stable levels of performance (e.g., Fig. 1—note that average mDB performance scores were consistently over 400 in the last 5 pre-lesion tests) before lesions were made to cortical motor areas. Post-lesion data were collected from both limbs during weekly experimental sessions after the surgery for the first 8 weeks. After the 8th post-lesion week, experiments were performed every other week. Each monkey was food-restricted for 18–24 h prior to

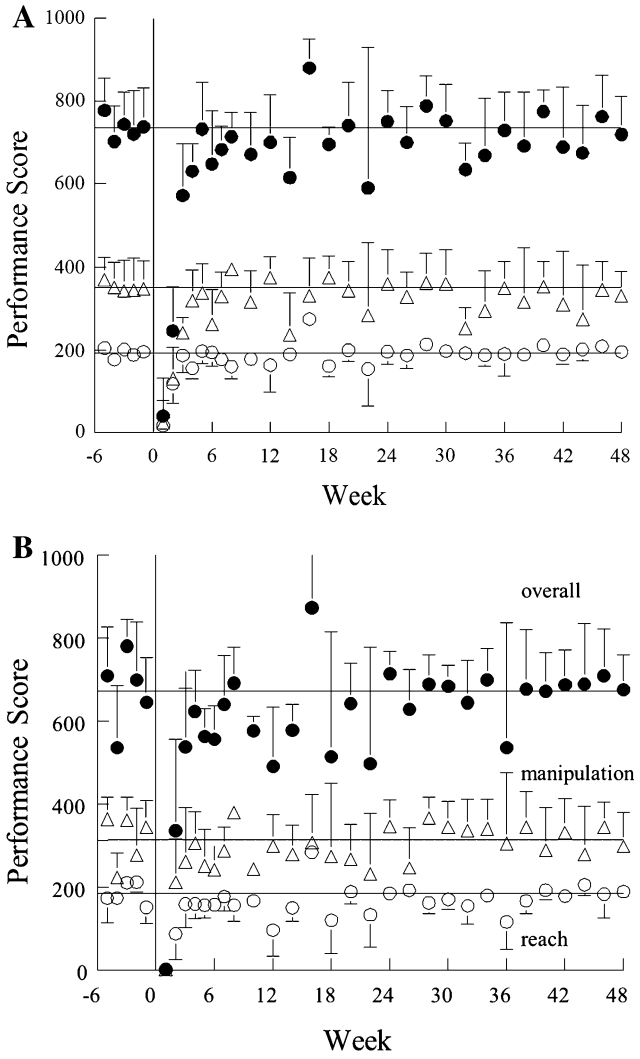

Fig. 1 Performance scores for SDM55 on mDB best well (**a**) and 2nd well (**b**) tasks. Each *plotted* point is the mean performance score for one test session. *Error bars* are 1 SD. The *different symbols* refer to overall (*filled circle*), manipulation (*triangle*), and reach (*open circle*) performance scores. The *horizontal lines* represent mean overall, manipulation, and reach performance scores for the last 5 pre-lesion tests

testing sessions to ensure sufficient motivation for the food-retrieval tasks. This schedule of post-lesion testing was designed to permit study of spontaneous (natural) recovery, rather than more intense daily post-lesion training/task practice as carried out in some previous non-human primate work (e.g., Murata et al. 2008; Kaeser et al. 2011).

For the mDB task, the monkey retrieved small fruit-flavored food pellets from each of 5 wells of the dexterity board. Full testing sessions included five trials for each well (A–E) for both limbs (Pizzimenti et al. 2007). Order of performing with each hand on the different wells was varied among monkeys and on different testing days in pre-lesion tests, but the contralesional hand was always tested first in post-lesion tests.

Surgical procedures

To examine the effects of an isolated injury to frontal cortical motor areas on fine motor control, lesions were made to the arm areas of primary motor cortex (M1) + the adjacent lateral premotor cortex (LPMC) in the hemisphere contralateral to the preferred hand (Table 1). The lesions were created using subpial aspiration to resect the arm areas of M1 and LPMC that were localized using intracortical microstimulation. Extreme care was taken during the aspiration process to avoid extensive, unintended postoperative subcortical white matter damage. This is of particular concern in the white matter territory located beneath the superior precentral sulcus and central sulcus because motor pathways from medial wall origin travel to cortical and subcortical targets in this immediate region (Morecraft et al. 2002; Schmahmann and Pandya 2006). Thus, in each case, at the edge of the lesion site, a portion of the motor cortex residing in close proximity to the superior precentral sulcus and the lower anterior bank of the central sulcus was intentionally spared. In addition to minimizing subcortical injury and sparing medial motor area axons, this approach was taken to ensure a similar lesion design across all cases studied (limited to M1 and LPMC) that would produce a similar experimental state from which each case could recover motor function. Each monkey was administered an antibiotic 24 h prior to surgery and after surgery for 9 consecutive days. Details of the surgical procedures have been outlined previously (Pizzimenti et al. 2007; McNeal et al. 2010).

Data acquisition and analysis

Calibrated video data were acquired from 4 cameras during the mDB task to enable three-dimensional (3D) measurements of positions and motions of the thumb and index tips (Pizzimenti et al. 2007). Locations of the tips of the index finger and thumb were manually digitized using SIMI motion analysis software and used to compute measures of grip aperture (as a measure of finger–thumb coordination) and distance of fingertip and thumb tip from pellet (as measures of reach accuracy) when the finger first touched the dexterity board or food pellet (identified by visual inspection of the video records). Temporal data were used to compute reach duration (time from hand exit of portal to first contact of dexterity board), duration of first manipulation (time from contact with pellet until pellet is acquired in grasp or contact with the pellet is broken), number of manipulation attempts, and total manipulation duration (time from first contact with pellet until pellet is acquired and hand movement toward cage begins).

These 3D measurements, along with temporal data, were then normalized and used to compute an overall

performance score (see Pizzimenti et al. 2007), which provides a relative measure of the monkey's ability to complete the task on each well. A performance score of zero occurred when no attempt was made to retrieve the pellet. The highest performance scores occurred on successful trials when the subject performed with the lowest reach and manipulation durations, highest accuracy (smallest distance between index tip and pellet at initial contact), smallest grip aperture at contact, and fewest numbers of lost contacts of the digit with the pellet with either hand (i.e., 1,000 if a single trial had the best score for each component among pre-lesion trials for both hands). To ensure discrimination between trials where no attempt was made (performance score = 0) and where a failed attempt occurred, failed attempts received a minimum score of 50. We also computed separate reach and manipulation performance scores to assess whether these aspects of the movements were affected differently following brain lesions (see Pizzimenti et al. 2007).

Computation of dependent measures of performance, skill, and recovery

There were five measures of performance scores in the mDB task (one for each of 4 wells and one for the pellet on the flat panel). An overall performance score was computed using scores from the well that the monkey performed with the highest skill during the last 25 pre-lesion trials (i.e., best well) and a 2nd smaller well, in which the monkey performed at about 1/2 the skill level observed with the best well. Skill was measured as the mean performance score divided by the standard deviation of performance scores for 25 consecutive trials (over 5 test sessions—see Pizzimenti et al. 2007). Thus, high skill was demonstrated by high performance scores with low variability. Separate reach and manipulation skill scores were computed (see Pizzimenti et al. 2007).

A recovery score was computed to reflect the recovery in hand fine motor skill in the mDB task during post-lesion testing. The recovery score was computed by taking the ratio of highest post-lesion skill (computed from the mean and standard deviation of 25 consecutive post-lesion trials over 5 consecutive post-lesion testing sessions in the mDB best well and 2nd well tasks) to pre-lesion skill (i.e., over the last 5 consecutive pre-lesion testing sessions). A recovery score of zero indicates that the monkey showed no recovery (i.e., no attempts to acquire food targets in the mDB task), a score <1.0 indicates that the monkey recovered to a lower skill than in pre-lesion testing and a recovery score >1.0 indicates that the monkey recovered to perform better than pre-lesion skill levels (in terms of higher mean performance scores or lower variability of scores, or both).

We also investigated measures of impairment duration to examine whether recovery began sooner in monkeys with lower degree of hand preference. These measures were post-lesion week of 1st attempt (the week of the first trial in which the monkey reached and touched the food target in the mDB task); post-lesion week of 1st success (the week of the first trial in which the monkey successfully retrieved the food target in the same tasks); and post-lesion week of 5 successes (the first week in which the monkey completed 5 successful consecutive retrievals of the food targets in the same tasks). These measures indicate the duration of severe impairment (i.e., no attempt to acquire the food) and moderate impairment (until successful acquisitions were made). We assessed whether duration and degree of initial impairment and recovery of motor function depended on magnitude of hand preference (handedness index) and lesion volume (total, gray matter, white matter) using linear correlation analyses. For the correlation analyses with lesion volume as the independent variable, we simply assessed which of total, gray matter and white matter lesion volumes had the highest correlation with each dependent variable. We did not apply Bonferroni corrections for the p values from the correlation analyses because we wished to assess possible relationships between the important variables in this small group (10 monkeys for analysis of initial impairment, 7 for analysis of recovery because only 4 weeks for recovery was permitted in three monkeys).

Histological tissue preparation and lesion site analysis

Nissl-stained tissue sections through the lesion site were prepared using standard histochemical methods as formerly described (Morecraft et al. 1992, 2004, 2012). Briefly, to analyze the lesion, Nissl-stained tissue sections spaced 500 μm apart through the lesion site were evaluated using an Olympus BX51 microscope (Leeds Precision, Minneapolis, MN, USA) for gray matter removal and underlying white matter fiber bundle involvement. The subcortical bundles were defined according to the atlas of Schmahmann and Pandya (2006), and gray matter regions (cytoarchitectonic areas 6, 4, 3, 2, and 1) were defined according to the criteria of Morecraft et al. (2004, 2012). After detailed microscopic analysis, the cortical and subcortical limits of each lesion site were plotted onto anatomically homologous Nissl-stained tissue sections from the non-lesioned hemisphere (see Figs. 1 and 3 of Darling et al. 2011) using the microscope and an attached MAC 5000 motorized stage (Ludl Electronic Products, Hawthore, NY, USA) which was attached to Neurolucida data collection software (MBF Bioscience, Williston, VT, USA). Gray matter and white matter lesion site volumes were then calculated using Neurolucida software as previously described (Pizzimenti et al. 2007; Darling et al. 2009).

Results

Lesion site analysis

The descriptions and accompanying figures of the lesion site analysis for all cases except SDM49, SDM74, SDM78, SDM79 and SDM80 have been presented in our previous reports (Darling et al. 2009; McNeal et al. 2010; Nagamoto-Combs et al. 2010). Thus, an account of the histological lesion analysis for these five unreported cases is provided below.

SDM49

With respect to case SDM49, the lesion site was similar to all other animals evaluated in this study in that the gray matter resection was restricted to the arm region of the primary motor cortex (M1) and dorsolateral premotor cortex (LPMCd) (Fig. 2). Specifically, the arm region of M1 was fully removed with the exception of cortex lining the depths of the anterior bank of the central sulcus. The face and leg areas of M1 were fully spared. The lesion from M1 extended rostrally to involve the inferior portion

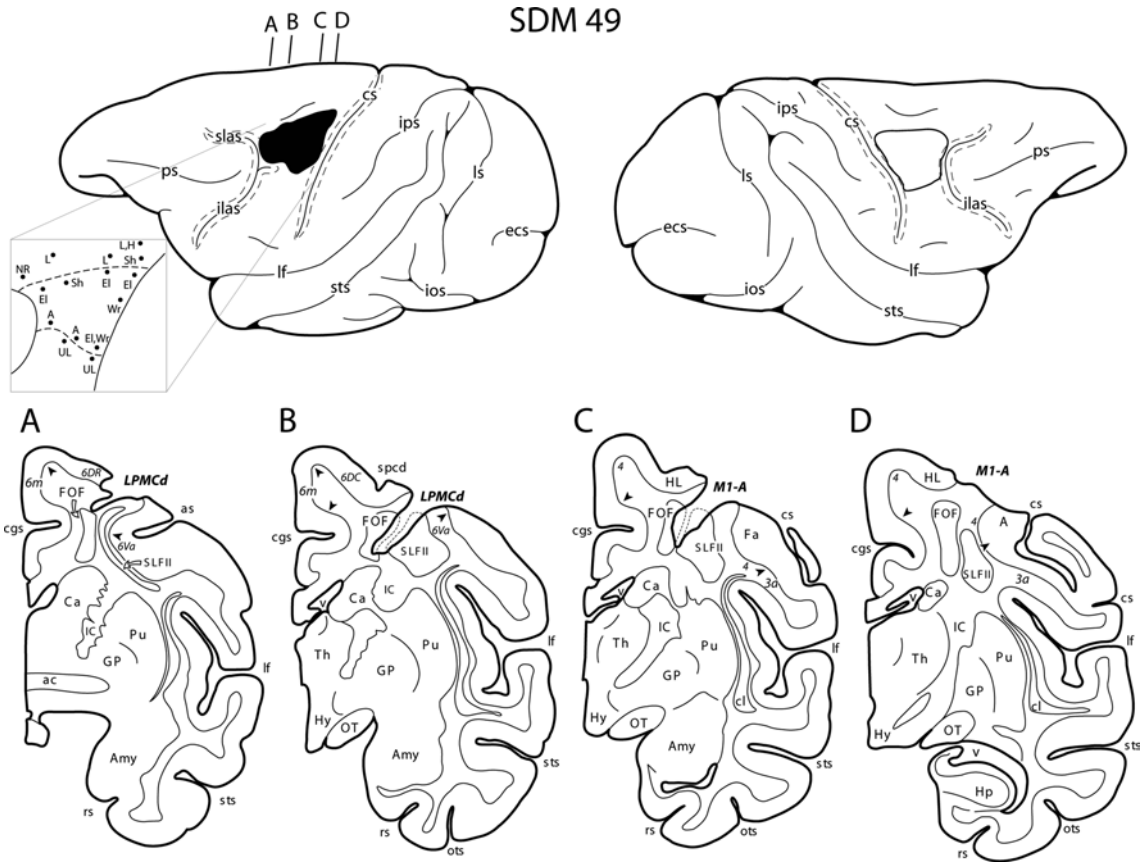

Fig. 2 *Line* drawings of the lateral surface of the cerebral hemispheres of case SDM49 which received an M1 + LPMC lesion. Representative coronal sections through the lesion site are located immediately *below* the *lateral views*. The *left* hemisphere illustrates the location of the cortical lesion (*blackened area*) and the *right* hemisphere the location of the superimposed lesion (*outlined area*) that was used to calculate the respective *gray* and *white* matter lesion volumes using Nissl-stained tissue sections. Coronal *panels***a**–**d** are all through the lesion site on the *left* hemisphere. In each coronal section, the major region of extirpated cortex is identified by the *bold italicized* conventions. Pertinent Brodmann's cytoarchitectonic areas are indicated on the coronal sections immediately below or within the *gray* matter (*small italicized numbers*/*letters*), and the respective boundaries are identified by the *arrow heads*. Identified in the subcortical white matter region are the putative locations of the fronto-occipital fasciculus (FOF) and superior longitudinal fasciculus subcomponent II (SLFII). The pullout illustrates the microstimulation *map* on the *left* hemisphere. On the *map,* each *black dot* represents a stimulation point with the affiliated movement(s) observed following stimulation. *A* arm of M1, *ac* anterior commissure, *Amy* amygdala, *as* spur of arcuate sulcus, *Ca* caudate nucleus, *cgs* cingulate sulcus, *cl* claustrum, *cs* central sulcus, *ecs* ectocalcarine sulcus, *El* elbow, *GP* globus pallidus, *Fa* face of M1, *H* hip, *Hp* hippocampus, *HL* hindlimb of M1, *Hy* hypothalamus, *ic* internal capsule, *ilas* inferior limb of arcuate sulcus, *ios* inferior occipital sulcus, *ips* intraparietal sulcus, *L* leg, *lf* lateral fissure, *LPMCd* dorsal lateral premotor cortex, *ls* lunate sulcus, *M1* primary motor cortex, *NR* no response, *OT* optic tract, *ots* occipitotemporal sulcus, *ps* principal sulcus, *Pu* putamen nucleus, *rs* rhinal sulcus, *Sh* shoulder, *slas* superior limb of arcuate sulcus, *spcd* superior precentral dimple, *sts* superior temporal sulcus, *Th* thalamus, *UL* upper lip, *v* ventricle, *Wr* wrist

of cytoarchitectonic area 6DC of the dorsal lateral premotor cortex. A small portion of the dorsal part of area 6Va of the ventral lateral premotor cortex was removed, whereas cortex lining the banks of the arcuate sulcus was largely spared. This case sustained greater subcortical white matter damage than all other cases reported in this study except SDM78 (Table 1). The additional white matter damage in SDM49 occurred specifically at mid-levels of the resection, where the lesion site dipped inferiorly to involve the lateral part of the frontal occipital fasciculus (FOF) and medial part of subsector II of the superior longitudinal fasciculus (SLF II) (Fig. 2b, c). From this location, the lesion extended inferiorly ending above the body of the caudate nucleus, sparing Muratoff's bundle (MB) located directly above the caudate. Further caudally, subcortical white matter located below the extirpated gray matter was spared (Fig. 2d).

SDM 74

On the lateral surface, the lesion site involved area 6DC anterior to the precentral sulcus and extended rostrally to involve the caudal part of area 6DR above the superior limb of the arcuate sulcus (Fig. 3). The ablation also included cortex forming part of the dorsal bank of the arcuate sulcus. From this location, the lesion extended slightly inferiorly to involve cortex forming the banks of the arcuate spur, caudal bank of the upper part of the inferior limb of the

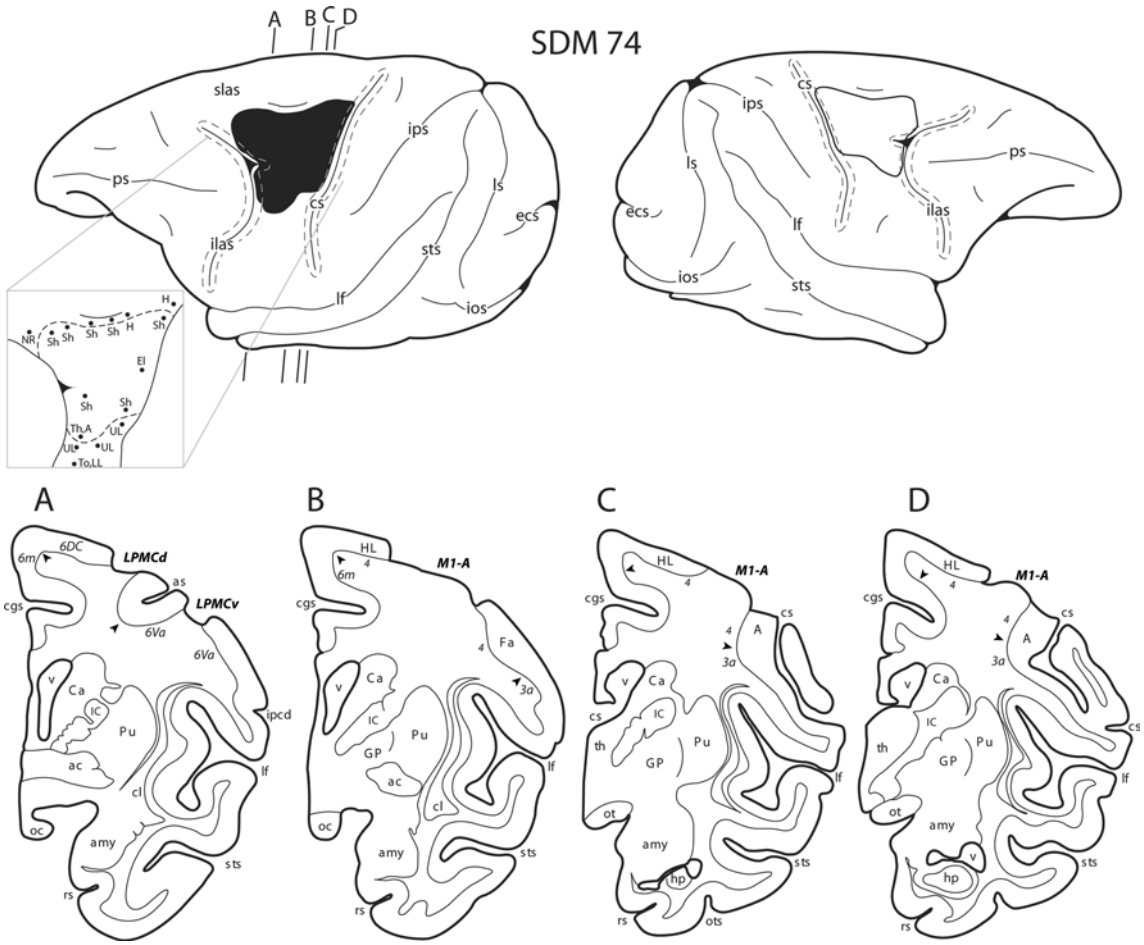

Fig. 3 *Line* drawings of the lateral surface of the cerebral hemispheres of case SDM74 which received an M1 + LPMC lesion. Representative coronal sections through the lesion site are located immediately *below* the *lateral views*. The *left* hemisphere illustrates the location of the cortical lesion (*blackened area*) and the *right* hemisphere the location of the superimposed lesion (*outlined area*) that was used to calculate the respective gray and white matter lesion volumes. Coronal *panels***a**–**d** are all through the lesion site on the *left* hemisphere. In each coronal section, the major region of extirpated cortex is identified by the *bold italicized* conventions. Pertinent Brodmann's cytoarchitectonic areas are indicated on the coronal sections immediately *below*, within, or *above* the *gray* matter (*small italicized numbers/letters*), and the respective boundaries are identified by the *arrow heads*. The pullout illustrates the microstimulation *map* on the *left* hemisphere. On the *map, each black dot* represents a stimulation point with the affiliated movement(s) observed following stimulation. *H* hip, *LL* lower lip, *OC* optic chiasm, *To* tongue. For other abbreviations, see Fig. 2

arcuate sulcus, and a small part of adjacent area 6Va. The lesion extended caudally to effectively remove all of area 4 located on the lateral surface. At the level of the central sulcus, area 4 forming the convexity of the precentral gyrus, including the upper one-third to one-half of the anterior bank of the sulcus, was removed. This case sustained very little white matter damage that was limited to the region directly below the gray matter resection avoiding involvement of all major subcortical white matter bundles.

SDM78

Gray matter removal was restricted to the arm regions of M1 and LPMC as determined by comparing the reconstructed lesioned hemisphere with the superimposed intracortical stimulation map (Fig. 4). Caudally, the lesion involved the upper part of area 4 lining the anterior bank of the central sulcus but spared part of area 4 in the lower half of the sulcus (Fig. 4d). Rostrally, gray matter removal involved the entire portion of area 4 on the gyral surface and the inferior part of area 6DC including the caudal and inferior most part of area 6DR. The gray matter lesion abutting the arcuate sulcus extended into the sulcus to include a small portion of cortex lining the dorsal part of the sulcus. Subcortical white matter damage was mostly limited to the general region directly below the gray matter resection. However, at coronal levels just caudal to the anterior commissure, the white matter lesion extended inferiorly to

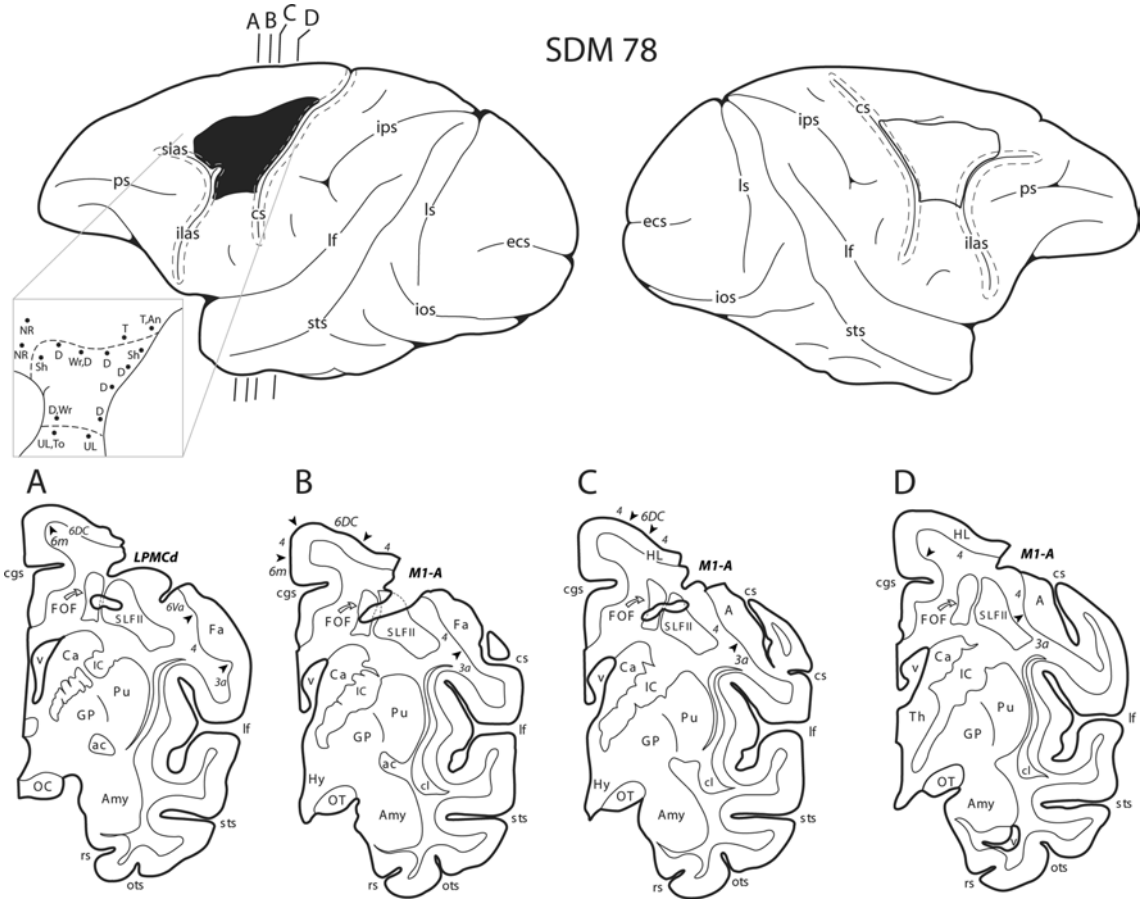

Fig. 4 *Line* drawings of the lateral surface of the cerebral hemispheres of case SDM78 which received an M1 + LPMC lesion. Representative coronal sections through the lesion site are located immediately below the *lateral views*. The *left* hemisphere illustrates the location of the cortical lesion (*blackened area*) and the *right* hemisphere the location of the superimposed lesion (*outlined area*) that was used to calculate the respective gray and white matter lesion volumes. Coronal *panels***a**–**d** are all through the lesion site on the *left* hemisphere. In each coronal section, the major region of extirpated cortex is identified by the *bold italicized* conventions. Pertinent Brodmann's cytoarchitectonic areas are indicated on the coronal sections immediately *below*, within, or *above* the gray matter (*small italicized numbers/letters*), and the respective boundaries are identified by the *arrow heads*. Identified in the subcortical white matter region are the putative locations of the FOF and SLFII. The pullout illustrates the microstimulation *map* on the *left* hemisphere. On the *map, each black dot* represents a stimulation point with the affiliated movement(s) observed following stimulation. *An* ankle, *D* digit. For other abbreviations, see Fig. 2

involve the white matter territory corresponding to the dorsomedial part of the SLF II, as well as the mid-sector of the fronto-occipital fasciculus (FOF) (Fig. 4a, b).

SDM79

Gray matter removal in case SDM79 was limited to the arm regions M1 and LPMC (Fig. 5). Specifically, the lesion involved removal of area 4 on the lateral surface, sparing part of area 4 in the lower region of the central sulcus (Fig. 5b–d). Rostrally, the lesion involved the inferior half of area 6DC and spread anteriorly to involve a small section of caudal area 6DR. Cortex lining the arcuate sulcus was spared. Subcortical white matter damage was largely limited to the adjacent underlying white mater with the exception of some involvement anteriorly of the superior longitudinal fasciculus II (SLF II). Specifically, the lesion occupied the dorsomedial sector of the SLF II territory (Fig. 5a, b).

SDM80

The gray and white matter lesions in case SDM80 formed the second smallest lesion of all cases studied (only SDM70 had a smaller lesion) (Fig. 6; Table 1). The gray matter of the M1 and LPMC arm areas was removed on the lateral

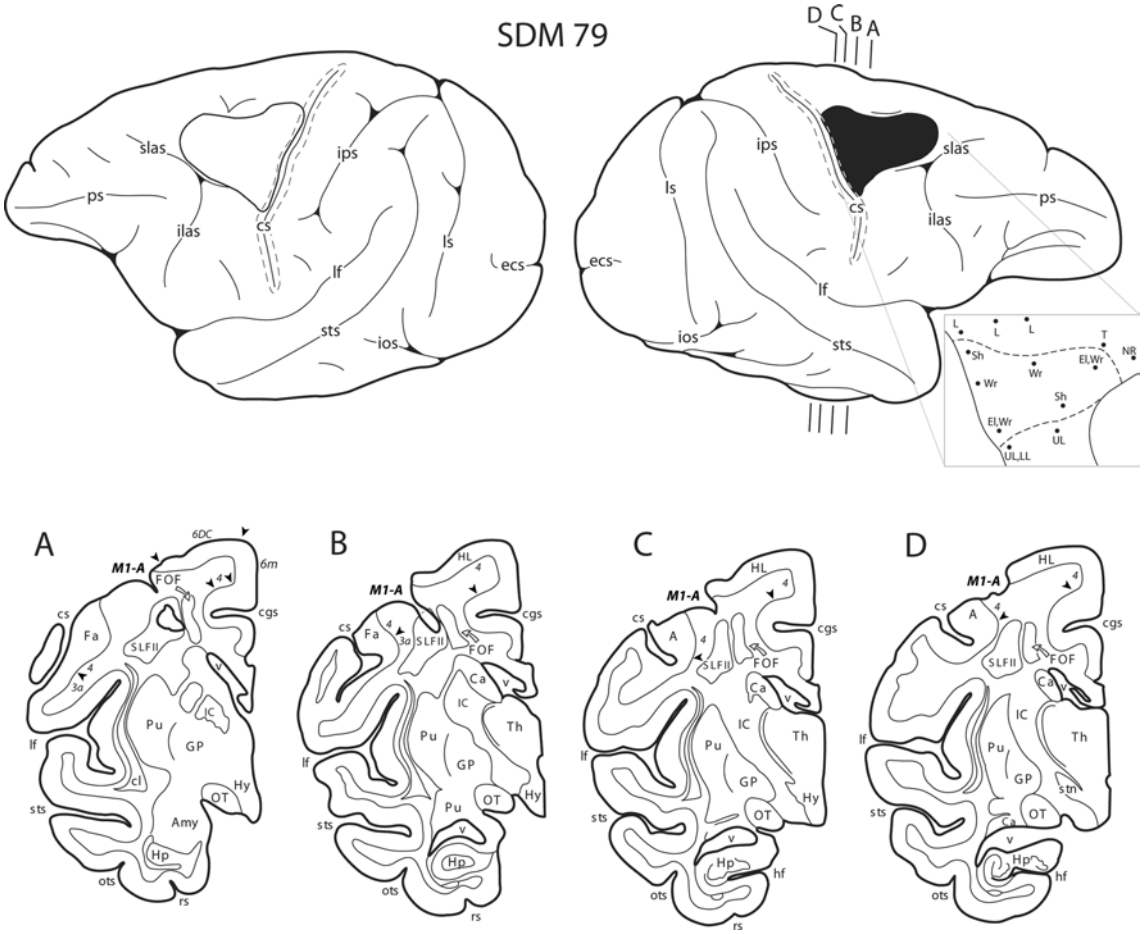

Fig. 5 *Line* drawings of the lateral surface of the cerebral hemispheres of case SDM79 which received an M1 + LPMC lesion. Representative coronal sections through the lesion site are located immediately *below* the *lateral views*. The *right* hemisphere illustrates the location of the cortical lesion (*blackened area*) and the *left* hemisphere the location of the superimposed lesion (*outlined area*) that was used to calculate the respective *gray* and *white* matter lesion volumes. Coronal *panels***a**–**d** are all through the lesion site on the *right* hemisphere. In each coronal section, the major region of extirpated cortex is identified by the *bold italicized* conventions. Pertinent Brodmann's cytoarchitectonic areas are indicated on the coronal sections immediately *below*, within, or *above* the *gray* matter (*small italicized numbers/letters*), and the respective boundaries are identified by the *arrow heads*. Identified in the subcortical white matter region are the putative locations of the FOF and SLFII. The pullout illustrates the microstimulation *map* on the *right* hemisphere. On the *map, each black dot* represents a stimulation point with the affiliated movement(s) observed following stimulation. *LL* lower lip, *stn* subthalamic nucleus, *T* tail. For other abbreviations, see Figs. 2 and 3

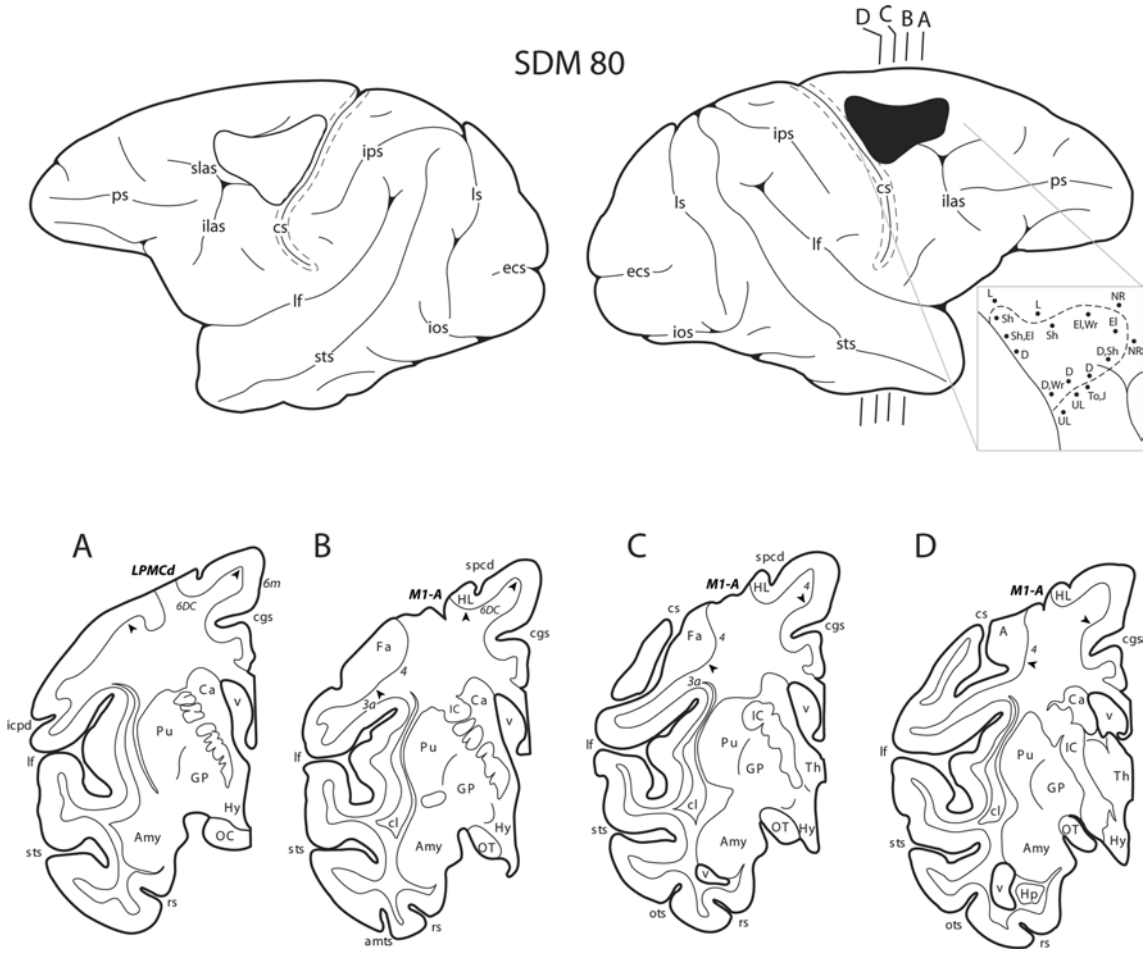

Fig. 6 *Line* drawings of the lateral surface of the cerebral hemispheres of case SDM80 which received an M1 + LPMC lesion. Representative coronal sections through the lesion site are located immediately *below* the *lateral views*. The *right* hemisphere illustrates the location of the cortical lesion (*blackened area*) and the *left* hemisphere the location of the superimposed lesion (*outlined area*) that was used to calculate the respective *gray* and *white* matter lesion volumes. Coronal *panels***a**–**d** are all through the lesion site on the *right* hemisphere. In each coronal section, the major region of extirpated cortex is identified by the *bold italicized* conventions. Pertinent Brodmann's cytoarchitectonic areas are indicated on the coronal sections immediately *below* or *above* the *gray* matter (*small italicized numbers/letters*), and the respective boundaries are identified by the *arrow heads*. The pullout illustrates the microstimulation *map* on the *right* hemisphere. On the *map, each black dot* represents a stimulation point with the affiliated movement(s) observed following stimulation. *ipcd* Inferior precentral dimple. For other abbreviations, see Figs. 2, 3 and 4

convexity sparing the cortex in both the central sulcus caudally and arcuate sulcus rostrally. White matter involvement was very minimal, involving only the subjacent white matter layer located immediately below the vacated gray matter region. All major subcortical bundles (i.e., SLF and FOF) were spared.

Behavioral analysis

As we have shown previously, performance scores on the mDB task were fairly stable before the lesions and declined immediately after the lesion, but then gradually increased as the monkeys recovered upper limb function (e.g., Fig. 1, also see Fig. 4C of Darling et al. 2009). Similar to our previous reports (Darling et al. 2009; McNeal et al. 2010), all monkeys in the present study were clearly impaired with flaccid paresis of the contralateral upper limb for the first few days post-lesion and then started to gradually recover hand function. They were all able to perform the motor tasks successfully after the lesion, with varying levels of skill, including cases SDM49, SDM78, and SDM79 with only 4 post-lesion weeks for recovery (Table 2).

Impairment over the first few weeks after the lesion was dependent on lesion volume but not degree of hand preference. Correlation analysis showed that the post-lesion duration until the first attempt on any well (and 2nd well) was positively correlated with total (gray + white matter) lesion volume ($p < 0.029$), indicating that larger lesions

Table 2 Post-lesion duration of impairment in the mDB task for each monkey (listed in order of ascending degree of hand preference)

Monkey	1st attempt		Post-lesion week of 1st success		Consistent success	
	Any well	2nd well	Best well	2nd well	Best well	2nd well
SDM78	2	2	2	2	2	2
SDM70	1	1	1	2	2	4
SDM48	2	2	2	3	5	6
SDM79	1	2	2	2	2	NA
SDM55	1	2	2	2	4	4
SDM45	1	1	1	1	1	1
SDM49	2	2	2	2	2	2
SDM80	1	1	2	2	2	3
SDM74	1	1	1	1	1	1
SDM64	4	4	4	4	6	5

were associated with longer duration of severe impairment as expected. However, this correlation was due primarily to a threshold effect as all monkeys with total lesion volume below 236 mm^3 had their first attempt at the first post-lesion week, while those with larger lesion volumes (243–260 mm^3) had their first attempt in the 2nd (SDM48, SDM78, SDM49) or 4th (SDM64) post-lesion week (Fig. 7a). There were trends, but no significant correlations, of lesion volume with post-lesion duration until the first success ($p = 0.07$) or until consistent success ($p = 0.09$). There were also no significant correlations of handedness index with post-lesion weekly duration until the first attempt and first success (best well, 2nd well, any well) ($p > 0.14$). Most monkeys were successful at least once in the first post-lesion week in which they made an attempt, indicating that the monkeys did not attempt the task until there was a high probability of success. Duration of recovery to consistent successful performance was also not correlated with handedness index in the mDB best well and 2nd well tasks ($p > 0.299$).

Performance score deficits over the first 4 post-lesion weeks depended on lesion volume but not degree of hand preference. Average reach and manipulation performance scores over the first 4 post-lesion weeks decreased relative to the last 5 pre-lesion tests by variable amounts among the 10 monkeys. Ratios of post to pre-lesion reach (mDB best well task, $p = 0.05$) and manipulation (mDB best well, $p = 0.05$ and 2nd well tasks, $p = 0.033$, Fig. 7b) mean performance scores over the first four post-lesion weeks were negatively correlated with total lesion volume, indicating greater performance deficits with larger lesion volumes. However, these deficits were not correlated with handedness index (Fig. 8, $p > 0.36$). Although the monkey with the highest handedness index (SDM64)

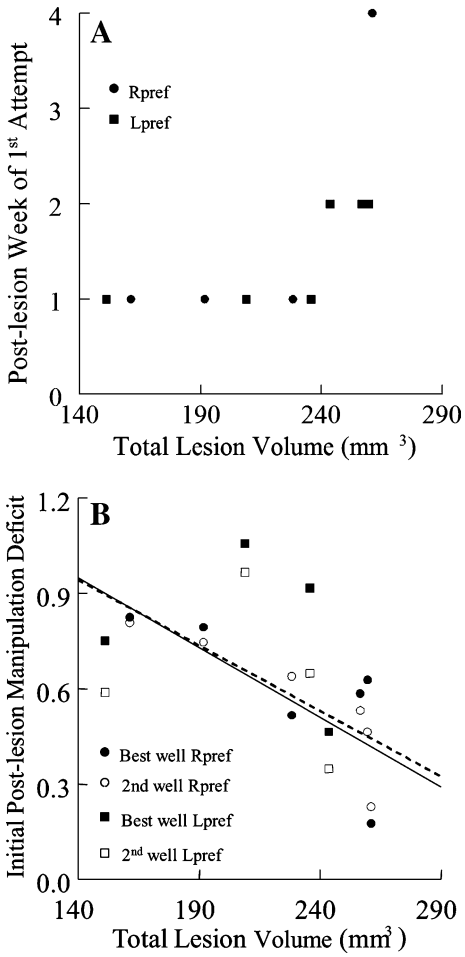

Fig. 7 *Scatterplots* showing post-lesion week of first attempt (with touch of the pellet) in the mDB task on any well (**a**) and initial post-lesion manipulation performance score deficits on the mDB (**b**) tasks (best and 2nd well) versus total lesion volume. Each *plotted* point in **b** is the ratio of average performance score over the first 4 post-lesion weeks divided by average performance score over the last 5 pre-lesion weeks for a single monkey. The *dashed vertical line* in **a** shows total lesion volume of 240 mm The *plotted lines* in **b** (*dashed line* for best well, *solid line* for 2nd well) show best fit linear regression lines. *Circles* show data for monkeys with *right* hand preference (Rpref), and *squares* for monkeys with *left* hand preference (Lpref) in **b**

showed the largest initial performance score declines (77–98 % in reach and manipulation performance scores), another monkey with a slightly lower handedness index (SDM74—HI = 93.2) had little change in average reach and manipulation performance scores during the first 4 post-lesion weeks (6 % decline to 5 % improvement). Notably, SDM74 had a much smaller white matter lesion volume than SDM64, which may account for the lower motor impairment experienced by this monkey. However, SDM49 also had a large white matter lesion volume and relatively high handedness index (65), but had much lower post-lesion declines (i.e., 32–41 %) in mDB reach

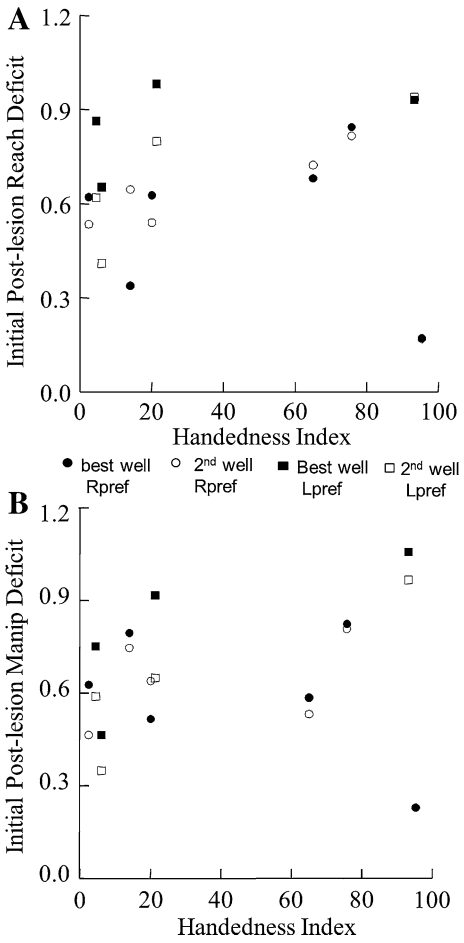

Fig. 8 *Scatterplots* showing performance deficits in the first 4 post-lesion weeks in the mDB best well (*filled symbols*) and 2nd well (*open symbols*) tasks for reaching (**a**) and manipulation (**b**) versus handedness index. Each *plotted* point is the ratio of average performance score over the first 4 post-lesion weeks divided by average performance score over the last 5 pre-lesion weeks for a single monkey. *Circles* are data for monkeys with *right* hand preference (Rpref) and *squares* for monkeys with *left* hand preference (Lpref)

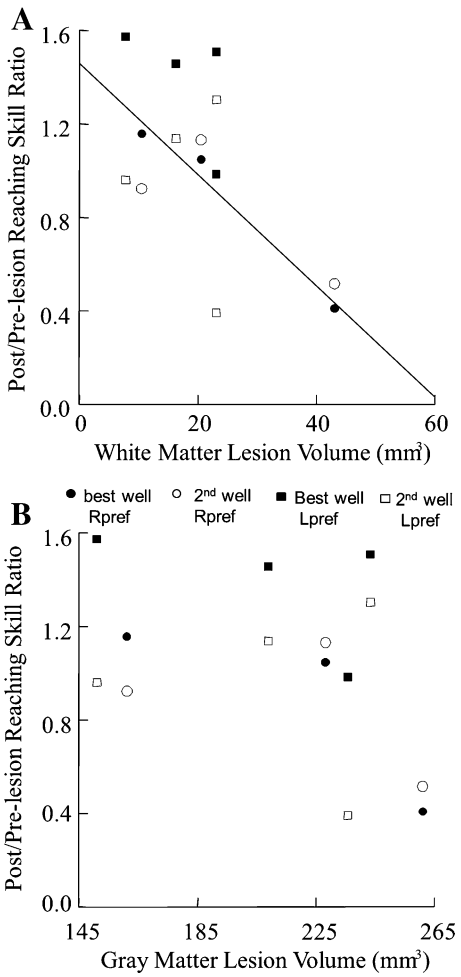

Fig. 9 *Scatterplots* showing recovery of reaching skill versus *white***a** and *gray***b** matter lesion volume. Each *plotted* point is the ratio of highest post-lesion skill over any period of 5 consecutive tests to skill to the last 5 pre-lesion tests in one monkey on the best well (*filled symbols*) and 2nd well (*open symbols*). The *plotted line* in **a** shows the best fit linear regression line for the relationship between recovery of reaching skill on the best well task and white matter lesion volume. *Circles* are data for monkeys with *right* hand preference (Rpref), and *squares* for monkeys with *left* hand preference (Lpref)

and manipulation performance scores over the first four post-lesion weeks than SDM64.

Recovery of skill in reaching, but not manipulation, depended on lesion volume, but only recovery of manipulation skill depended on degree of hand preference. Notably, all 7 monkeys with recovery durations longer than 4 weeks (i.e., excluding SDM49, SDM78, SDM79) showed good recovery in that the ratio of post-lesion to pre-lesion reaching and manipulation skill exceeded 40 % in both best and 2nd well mDB tasks. SDM49 also showed good recovery of skill in the mDB task as mean performance scores at 1 month after the lesion were comparable to those in the last 5 pre-lesion tests, but this monkey is not included in the correlation analyses presented here due to the short recovery time. Recovery of reaching skill in the mDB best well task was negatively correlated with white (Fig. 9a, $r = -0.82$, $p = 0.013$) but not gray (Fig. 9b, $p = 0.16$) matter lesion volume. However, there was no evidence of dependence of recovery of manipulation skill in the mDB best well or 2nd well tasks on gray or white matter lesion volume ($p > 0.15$). Recovery of reaching skill in the mDB task was not correlated with handedness index (Fig. 10a, $p > 0.17$). However, recovery of manipulation skill was strongly negatively correlated with handedness index in the mDB 2nd well task (Fig. 10b, $r = -0.9$, $p = 0.003$), but not in the mDB best well task (Fig. 10b—$p = 0.138$). Although this high negative correlation with handedness index in the difficult mDB 2nd well task was essentially a two-point correlation (Fig. 10b), it demonstrates that the three monkeys with high handedness indexes (75–95)

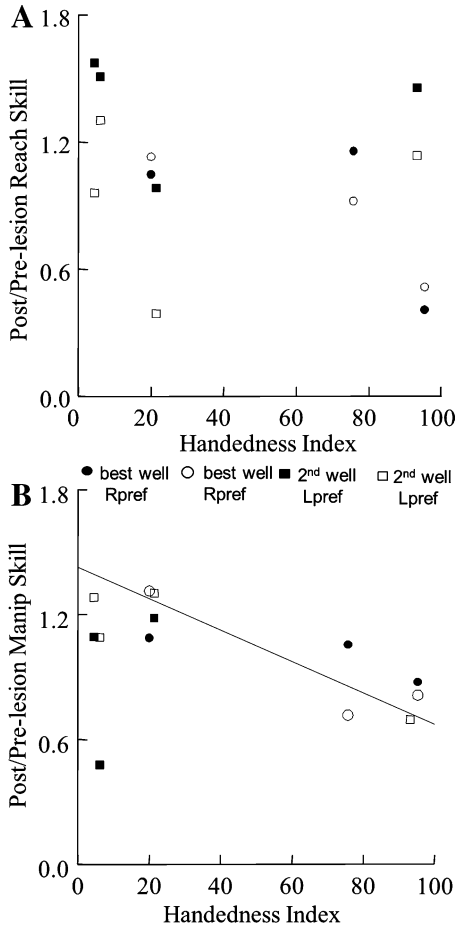

Fig. 10 *Scatterplots* showing post/pre-lesion skill ratios of the mDB best well (*filled circles*) and 2nd well (*open circles*) tasks for reaching (**a**) and manipulation (**b**) versus handedness index. Each *plotted* point is the ratio of highest post-lesion skill over any period of 5 consecutive tests to skill over the last 5 pre-lesion tests in one monkey (*filled symbols* for best well, *open symbols* for 2nd well). The *plotted line* in **b** shows best fit linear regression line for the 2nd well task. Note that data for SDM74 are not shown in **b** for the best well task because of the very high ratio (7.4) showing substantially better skill was achieved after the lesion. *Circles* are data for monkeys with *right* hand preference (Rpref) and *squares* for monkeys with *left* hand preference (Lpref)

recovered relatively poorly (i.e., to 60–80 % of pre-lesion manipulation skill) in comparison with the four monkeys with low handedness indexes (2–21) that all recovered to higher than pre-lesion manipulation skill.

Discussion

The results of this study show that pre-lesion degree of hand preference strongly influences recovery of contralesional hand fine motor skill in a difficult task after a lesion to the upper limb areas of M1 and LPMC. Specifically, a clear negative relationship was observed between handedness index and recovery of manipulation skill in the mDB 2nd well task, which required greater manipulation ability than for the mDB best well task due to smaller diameter of the 2nd well, making it more difficult to manipulate and grasp the food pellet. Importantly, the finding that recovery of manipulation skill did not depend on lesion volume emphasizes the important role of handedness and, presumably, of associated hemispheric dominance and IHI. Notably, recovery of manipulation skill in monkeys with high pre-lesion hand preference was very good in that they recovered to near pre-lesion levels in the 2nd well task, but was clearly poorer than in monkeys with a low hand preference as they recovered to better than pre-lesion skill. Lesion volume also influenced recovery in terms of duration of persistence of a severe deficit in the mDB task (i.e., no attempt to perform the motor task to acquire food targets despite high motivation due to pre-testing food restriction) and recovery of reaching skill.

The ten monkeys in our study exhibited a wide range of handedness indexes and lesion volumes (Table 1). In particular, one monkey (SDM64) exhibited a high handedness index of 95.3 and also showed the longest duration impairment (i.e., until 1st attempts, successful acquisitions, and consistent success in these motor tasks) after the lesion and the poorest recovery in these fine motor tasks. This provides some support for our hypothesis that monkeys with a high degree of handedness would be more incapacitated in use of the preferred hand after damage to the contralateral motor areas than those with a very low degree of handedness. However, the larger lesion in this monkey suggests an important role for lesion size also. Several other findings provide additional support for the conclusion that degree of hand preference is important in recovery. For example, SDM49 and SDM78 both had larger white matter lesions than SDM64 but showed faster recovery in terms of post-lesion duration until consistent successful acquisitions in the mDB best well and 2nd well tasks. This suggests that, despite large lesions, a lower hand preference may allow faster recovery of hand function after cortical motor injury. Moreover, we observed previously that a monkey with much larger gray and white matter lesions than SDM64, but lower handedness index, recovered to higher skill levels in the mDB 2nd well task [see data for SDM50 in Tables 1 and 2 of (Darling et al. 2009)]. Such findings provide additional support for the idea that lower motor-related hemispheric dominance may allow better recovery of upper limb motor function.

We were surprised that recovery of manipulation skill was not inversely correlated with lesion volume as we observed previously in a group of monkeys with a larger range of lesion volumes spanning more cortical motor areas (i.e., lesions of M1 only, M1 + LPMC (M1 + LPMC + SMA, multi-focal lesions affecting also

pre-SMA and cingulate motor areas) (Darling et al. 2009). Kaeser et al. (2011) also reported an inverse relationship between lesion volume within motor cortex and recovery of performance in a similar task, although their Fig. 4a shows that recovery was similar for lesions larger than 40 mm^3 (i.e., three monkeys with lesions of 15–40 mm^3 showed the expected inverse relationship but two other monkeys with lesion volumes of 60 and 100 mm^3 exhibited similar recovery to the monkey with the 40 mm^3 lesion). All of the lesion volumes in our monkeys greatly exceeded 100 mm^3 and extended into LPMC, thus our results do not contradict those of Kaeser et al. (2011). Interestingly, greater white matter lesion volume appeared to be associated with more lasting deficits in reaching skill in the present work (Fig. 9), indicating a double-dissociation between recovery of skill in reaching versus manipulation and their dependence, respectively, on lesion size versus strength of hand preference. Thus, for lesions confined to the regions of M1 and LPMC controlling the contralateral upper limb, it appears that increasing lesion volume has remarkably little effect on lasting impairment of hand fine motor function but does negatively impact gross upper limb motor function (reaching). This lack of effect of lesion volume in M1 and LPMC on recovery of manipulation skill may be partially due to the fact that these lesions spared the caudal M1 hand area located deep in the central sulcus, as we have discussed previously (Darling et al. 2009). These findings suggest that response to rehabilitation of the upper limb after damage to the motor cortex contralateral to the preferred/dominant hand may not be predictable from lesion size because strength of pre-lesion hand/hemispheric dominance appears to play an important role in recovery of grasping skill, which is a primary goal of upper limb rehabilitation.

Research suggesting lasting impairment of upper limb motor function after M1 lesions that damage the caudal M1 hand region has used cynomolgus macaques rather than rhesus macaques and report lower success rate and slower task performance after M1 lesions (Liu and Rouiller 1999; Kaeser et al. 2011). The slower task performance is possibly due to slower and less accurate reaching as well as poorer manipulation skills (separate reaching and manipulation performance scores were not reported). However, given that the cynomolgus macaques were able to acquire some of the food pellets from the wells of the dexterity board, there was apparently some recovery of grasping ability despite the damage to the caudal M1 hand area. It should also be noted that cynomolgus macaques use a different form of precision grip, actually more like key grip between the thumb pad and radial side of the index, than rhesus macaques which mostly use precision grip between the pads of the thumb and index.

Previous work suggests that a high degree of handedness is correlated with a greater degree of cerebral dominance in the hemisphere contralateral to the preferred hand in humans (Dassonville et al. 1997). If this is also the case for rhesus monkeys, a higher degree of hand preference may be a disadvantage for recovery of fine motor skill after an injury to a potentially more dominant hemisphere (as shown in this report), because this hemisphere was relied on heavily for coordinating fine motor tasks of the contralesional arm. However, of 26 rhesus monkeys on which we have tested hand preference with the sDB task (some of these data are unpublished), 16 exhibited handedness indexes of 60 (i.e., used the preferred hand 60 % more often than the non-preferred hand in a fine motor task) or below, suggesting lower hemispheric lateralization in this species than in humans who, on a fine motor task, would most likely use the same hand for all trials unless instructed to use the other hand. Moreover, IHI, which may help to maintain hemispheric dominance in motor tasks by suppressing undesired activity of the opposite hemisphere (Pal et al. 2005), is lower when hand preference is weak (Dassonville et al. 1997) and is also lower in musicians who are trained to use both hands at high skill levels (Ridding et al. 2000) but exhibit a strong hand preference for daily fine motor tasks (Hughes and Franz 2007). Like rhesus monkeys, musicians may also recover high levels of hand function after damage to cortical motor areas (Wohrle and Haas 2007) or damage to the descending fibers of those areas (Toole et al. 2007) perhaps because of lower IHI. Collectively, these observations indicate that lower IHI may result in activity of both hemispheres during unimanual motor activities (i.e., less laterality in hemispheric activation), leading to less cerebral dominance and less interference with recovery of hand function after a lesion affecting one hemisphere or its descending motor output pathways. However, it should also be recognized that reduced laterality can be characteristic of neurological disorders such as autism and schizophrenia (e.g., Dragovic and Hammond 2005; Anderson et al. 2011), suggesting that reduced laterality is not always beneficial and may be a factor in neurological disorders.

Although performance scores on the motor tasks decreased immediately following the lesion, all of the monkeys recovered ability to successfully perform the tasks in the weeks following the brain injury. The fact that most monkeys were able to successfully perform the tasks at near pre-lesion (or higher) skill levels after recovery suggests that there may be residual input from other areas of the brain that help to control arm and hand movements. One possible mechanism is accessing motor memory for the learned task, which may be located in undamaged areas of cortex or subcortical structures, and can be preserved over time (Walton et al. 2008). Although the stored

motor commands for a task would presumably be based on use of the damaged cortical areas in movement control, it is possible that these commands can be implemented through other brain areas as recovery occurs. Motor areas of the non-human primate brain immediately adjacent to or even relatively distant from the lesion may be taking on duties of the lesioned area to compensate for the damage inflicted by the lesion (Nudo et al. 1996; McNeal et al. 2010). Such functional reorganization of the undamaged motor cortical areas may take place regardless of the level of cerebral dominance. Another possible mechanism is that residual input from the undamaged contralesional hemisphere may assist in the recovery of the contralesional arm motor control. Dassonville et al. (1997) found an inverse relationship between the degree of handedness and the extent of ipsilateral activation in the motor cortex. In other words, a high degree of handedness is subserved by activation of the motor cortex, which is mostly contralateral to the moving hand, whereas a low degree of handedness is associated with activation of motor cortices in hemispheres both contralateral and ipsilateral to the moving hand. Thus, monkeys with lower handedness indexes are likely to have greater residual input from the ipsilateral motor areas and may therefore show a faster and greater recovery.

The interpretations of the current study rely on handedness index as a valid measure of hand and hemispheric dominance. Previous studies of handedness in rhesus monkeys have used both gross (e.g., reaching) and fine motor tasks (Lehman 1978a, b, 1980; Hopkins et al. 1989, 1992), but it has been suggested that only fine motor tasks, as we used here, produce reliable hand preferences (Hopkins et al. 1989, 1992). Since all tasks involved in the current study required fine hand/digit movements, including the test of hand preference, it is likely that the measured handedness indexes are reliable and can be considered measures of cerebral dominance at least in terms of fine hand/digit movement control.

In conclusion, we found that monkeys with stronger laterality, as indicated by hand preference in a dexterity board task, tend to show poorer recovery of hand motor function after a lesion to the arm areas of primary motor cortex (M1) and the adjacent lateral premotor cortex contralateral to the preferred hand. These findings support our initial hypothesis that recovery following frontal motor cortex injury would be inversely correlated with magnitude of hand preference. These observations also suggest that humans with weaker hemispheric dominance, and perhaps individuals who use both hands for some fine motor tasks (e.g., musicians—Toole et al. 2007; Wohrle and Haas 2007), may have a more favorable prognosis for recovery of motor function after a stroke than humans with strong hemispheric dominance.

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