Experimental Brain Research (2020) 238:205–220
https://doi.org/10.1007/s00221-019-05690-0

RESEARCH ARTICLE

Changes in ipsilesional hand motor function differ after unilateral injury to frontal versus frontoparietal cortices in *Macaca mulatta*

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Received: 13 June 2019 / Accepted: 7 November 2019 / Published online: 13 December 2019

Abstract

We tested the hypothesis that injury to frontoparietal sensorimotor areas causes greater initial impairments in performance and poorer recovery of ipsilesional dexterous hand/finger movements than lesions limited to frontal motor areas in rhesus monkeys. Reaching and grasping/manipulation of small targets with the ipsilesional hand were assessed for 6–12 months post-injury using two motor tests. Initial post-lesion motor skill and long-term recovery of motor skill were compared in two groups of monkeys: (1) F2 group—five cases with lesions of arm areas of primary motor cortex (M1) and lateral premotor cortex (LPMC) and (2) F2P2 group—five cases with F2 lesions + lesions of arm areas of primary somatosensory cortex and the anterior portion of area 5. Initial post-lesion reach and manipulation skills were similar to or better than pre-lesion skills in most F2 lesion cases in a difficult fine motor task but worse than pre-lesion skill in most F2P2 lesion cases in all tasks. Subsequently, reaching and manipulation skills improved over the post-lesion period to higher than pre-lesion skills in both groups, but improvements were greater in the F2 lesion group, perhaps due to additional task practice and greater ipsilesional limb use for daily activities. Poorer and slower post-lesion improvement of ipsilesional upper limb motor skill in the F2P2 cases may be due to impaired somatosensory processing. The persistent ipsilesional upper limb motor deficits frequently observed in humans after stroke are probably caused by greater subcortical white and gray matter damage than in the localized surgical injuries studied here.

Keywords Reach · Grasp · Manipulation · Brain injury

Introduction

A large number of cross-sectional studies in unilateral stroke victims have shown measurable deficits in control of force and speed of ipsilesional upper limb movements (Colebatch and Gandevia 1989; Desrosiers et al. 1996; Yelnik et al. 1996; Hermsdorfer et al. 1999; Kim et al. 2003; Pohl et al. 2003; Yarosh et al. 2004; Wetter et al. 2005; Schaefer et al. 2007; Noskin et al. 2008; Haaland et al. 2009; Baak et al. 2015; Hsu et al. 2018), coordination of reach and grasp (Baak et al. 2015) and control of precision grip (Seo et al. 2009; Hsu et al. 2018). Recent work has also demonstrated clear ipsilesional hand deficits in control of pinch force during lifting and in using active touch to discriminate weight, roughness and shape between about 1–6 weeks post-stroke (Hsu et al. 2018). Notably, post-stroke longitudinal studies of ipsilesional arm/hand function have shown improvements in strength and speed of movement over time but with some persistent, relatively minor residual deficits (Jones et al. 1989; Marque et al. 1997; Laufer et al. 2001; Noskin et al. 2008). These findings are consistent with reports that activity of primary motor cortex (M1) and supplementary motor cortex (SMC or M2) neurons ipsilateral to the moving arm are modulated in accordance with movement kinematics in non-human primates and suggest a role for these areas in

Communicated by John C. Rothwell.

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control of ipsilateral arm movements (Brinkman and Porter 1979; Donchin et al. 1998; Cisek et al. 2003).

Deficits in cortical processing of somatosensory information after stroke may also contribute to ipsilesional hand fine motor deficits (Hsu et al. 2018). A recent report showing that the primary somatosensory cortex (S1) ipsilateral to an active digit muscle is involved in gating sensory information from that digit (Lei and Perez 2017) is consistent with this finding. Observations of Mutha and colleagues illustrating that left hemisphere parietal lesions in human stroke impaired accuracy of left hand movement to a target that was moved to a new position during hand movement is also consistent with impaired somatosensory processing of information from the ipsilesional arm because accurate movements to the new target location require such processing to define limb state when the correction is initiated (Mutha et al. 2014). Also supporting a role for somatosensory processing deficits in ipsilesional hand movement control is the finding that, despite apparent recovery in clinical tests of hand motor function, ipsilesional hand reaching movements were less smooth in stroke patients than in healthy controls (Metrot et al. 2013). Overall, these data suggest that parietal areas in both cerebral hemispheres contribute to processing of sensory information from both upper limbs and to online control of their movements.

Studies in animal models have the advantage over human studies of permitting assessment of motor deficits longitudinally before and after brain injury. Many such studies have focused on the contralesional limb motor function before and after unilateral motor cortex damage (e.g., Travis 1955a, b; Black et al. 1975; Nudo et al. 1996; Gonzalez and Kolb 2003; Marshall et al. 2003; Roitberg et al. 2003; Luke et al. 2004; Carmichael et al. 2005; Gao et al. 2006; O'Bryant et al. 2007; Darling et al. 2009, 2016), but only a few have investigated function of the ipsilesional limb during single limb motor tasks (Brinkman 1984; Bury and Jones 2002; Roitberg et al. 2003; Gonzalez et al. 2004; Luke et al. 2004; Kaeser et al. 2010; Darling et al. 2011). In contrast to the findings from human studies, unilateral lesions of motor cortex may facilitate learning and performance of reach and grasp by the ipsilesional limb in rats (Bury and Jones 2002; Luke et al. 2004) and monkeys (Kaeser et al. 2010; Darling et al. 2011). Specifically, we reported that lesions of frontal lobe motor areas in rhesus monkeys resulted in initial decrements in fine motor performance that increased with lesion size in most monkeys but recovered over time such that the ipsilesional limb usually improved to perform better than prior to the injury (Darling et al. 2011). Acute ipsilesional hand fine motor deficits have been reported in monkeys (Brinkman 1984) and persistent minor ipsilesional forelimb reaching deficits were observed in one rodent study (Gonzalez et al. 2004) following unilateral lesions of motor cortex and in one monkey study following a very large multifocal lesion including cortical and subcortical structures (Roitberg et al. 2003). Thus, most past research in animal models indicates minimal lasting effects of unilateral motor or sensorimotor cortex lesions on ipsilesional upper limb movement control, but with some evidence of persistent minimal deficits.

In the present work, we compared recovery of ipsilesional hand motor skill in monkeys with lesions to M1 and lateral premotor cortex (LPMC) (F2 lesion) to that in monkeys with lesions to M1, LPMC, S1 and anterior part of parietal area 5 (F2P2). We hypothesized that F2P2 lesions encompassing frontoparietal sensorimotor areas would cause greater initial impairments in performance and poorer recovery of ipsilesional dexterous movements than lesions limited to frontal lobe motor cortical areas (F2 lesions) because of possible deficits in processing tactile and proprioceptive information due to the parietal lobe injury. We also hypothesized that changes in reach and manipulation skill after the lesion would be associated with volume of gray and/or white matter lesions. We were especially interested in the effects of lesions to gray matter of the rostral and caudal banks of the central sulcus. These areas contain neurons with direct projections onto motor neurons of upper limb muscles (i.e., rostral bank of the central sulcus, also known as caudal M1 or M1c) and with direct projections from the primary sensory processing area for the upper limb to M1c (i.e., caudal bank of the central sulcus, termed rostral S1 or S1r). Alternatively, greater reductions in trans-callosal inhibition (TCI) to the non-lesioned hemisphere in F2P2 lesioned cases than in F2 lesioned cases may result in better ipsilesional limb motor performance after the lesion.

Methods

Experimental animals

Ten adult rhesus monkeys, five with lateral frontal motor area lesions (F2 lesion cases) and five with lateral frontoparietal lesions (F2P2 lesion cases), were subjects for these experiments (Table 1). Recovery of contralesional (more impaired) hand motor function of all these cases has been reported on previously (Darling et al. 2016). All survived 6 or 12 months post-lesion to allow adequate time for recovery of upper limb function. Note that ipsilesional hand motor recovery of the F2 lesion cases was presented previously (Darling et al. 2011). The animals were housed, cared for, and maintained in a United States Department of Agriculture (USDA) and Association for Assessment and Accreditation of Animal Laboratory Care (AAALAC) approved and inspected facility. All behavioral and surgical protocols were conducted in accordance with USDA, National Institutes of Health, and Society for Neuroscience guidelines for the ethical treatment

Table 1 Subject characteristics and lesion volumes

Case SDM	Age at time of lesion (years)	Sex	Lesion category	PLD (months)	GMLV (mm^3 %)				WMLV (mm^3)	
					FC	M1c %	PC	S1r %	FC	PC
45	4.9	M	F2	6	212.6	10.7	0.0	0.0	23.02	0.0
48	6.8	F	F2	12	220.3	7.7	0.0	0.0	23.12	0.0
55	11.8	M	F2	12	207.7	27.7	0.0	0.0	20.51	0.0
64	13.6	F	F2	6	217.9	8.0	0.0	0.0	43.03	0.0
70	7.2	M	F2	6	143.2	6.2	0.0	0.0	7.76	0.0
76	>8.0[a]	M	F2P2	7	188.6	6.5	75.2	7.2	16.23	6.9
81	12	F	F2P2	12	108.8	30.3	68.1	19.5	7.40	6.2
83	3.8	F	F2P2	12	181.1	50.2	76.8	34.4	8.16	8.0
87	17	F	F2P2	6	224.0	46.1	102.3	24.4	44.65	11.6
91	7.8	F	F2P2	6	192.6	100.0	76.2	69.9	46.21	6.7

PLD post-lesion duration, *GMLV* gray matter lesion volume, *WMLV* white matter lesion volume, *FC* frontal cortex, *PC* parietal cortex

[a]> 8.0—estimated age

of experimental animals and approved by the University of South Dakota Institutional Animal Care and Use Committee. A primate veterinarian judged all the subjects to be healthy and free of any neurological deficit prior to the lesion based on observations of cage behavior and their ability to grasp various objects. Proximal and distal movements and range of motion at the joints in both upper extremities of all animals were normal except for SDM55. The interphalangeal joints of digit 3 of the right hand were permanently extended, but there were no abnormalities in the left hand. Despite this abnormality, this animal preferred the right hand and ably performed precision grip with digits 1 and 2 of both hands.

Experimental apparati

Fine hand/finger motor function was tested using the modified movement assessment panel (mMAP—Fig. 1a, c) to measure forces applied while acquiring a food target from a flat surface (easiest task) and over straight and curved rods (most difficult task) (Darling et al. 2006), and a modified dexterity board (mDB—Fig. 1b, d) to measure kinematic variables during reaching and grasping small food pellets from wells of different size (Pizzimenti et al. 2007). These devices attach to the monkey's cage and serve to control which hand the monkey can use to successfully perform the tasks without any restraints. The monkeys were able to move freely about the cage between trials.

Data acquisition

Forces applied during manipulation of a ring-shaped food target (usually a carrot chip with a hole punched through the center) in the mMAP task were recorded at 200 samples/s using Datapac 2k2 (Run Technologies). Movements of the hand were recorded using a single digital video camera (Sony, model DCR-DVD301) placed directly in front of the cage to allow for post-testing assessment of success/failure and qualitative ratings of movement strategy.

Four digital video cameras interfaced with the SIMI Motion data acquisition package (SIMI Reality Motion Systems, Unterschleissheim, Germany) to record hand movements at 100 frames/s during the mDB task to assess kinematic variables as described previously (Pizzimenti et al. 2007). Video data collection began when the portal door was opened to allow the monkey to reach toward the food pellet and continued until the pellet was either retrieved into the cage, knocked off of the platform, or a 60 s time limit had expired. A calibration frame and direct linear transformation software were used to provide three dimensional data on thumb-tip, index-tip and target (pellet) locations to assess duration and accuracy of each monkey's reach and grip aperture (thumb–index-tip distance) when the index-tip or thumb first touched the pellet or the Plexiglas plate holding the pellet itself. The video data were also analyzed visually to extract manipulation duration (time from first pellet contact until the pellet was acquired successfully or the monkey lost the pellet from grasp and did not attempt again) and the number of times the monkey lost contact with the pellet and attempted again to acquire it. These were used to compute a performance score as described in Pizzimenti et al. (2007).

Behavioral procedures

The behavioral tasks used to assess motor function have been described extensively in previous reports (Pizzimenti et al. 2007; Darling et al. 2009, 2011; McNeal et al. 2010). Briefly,

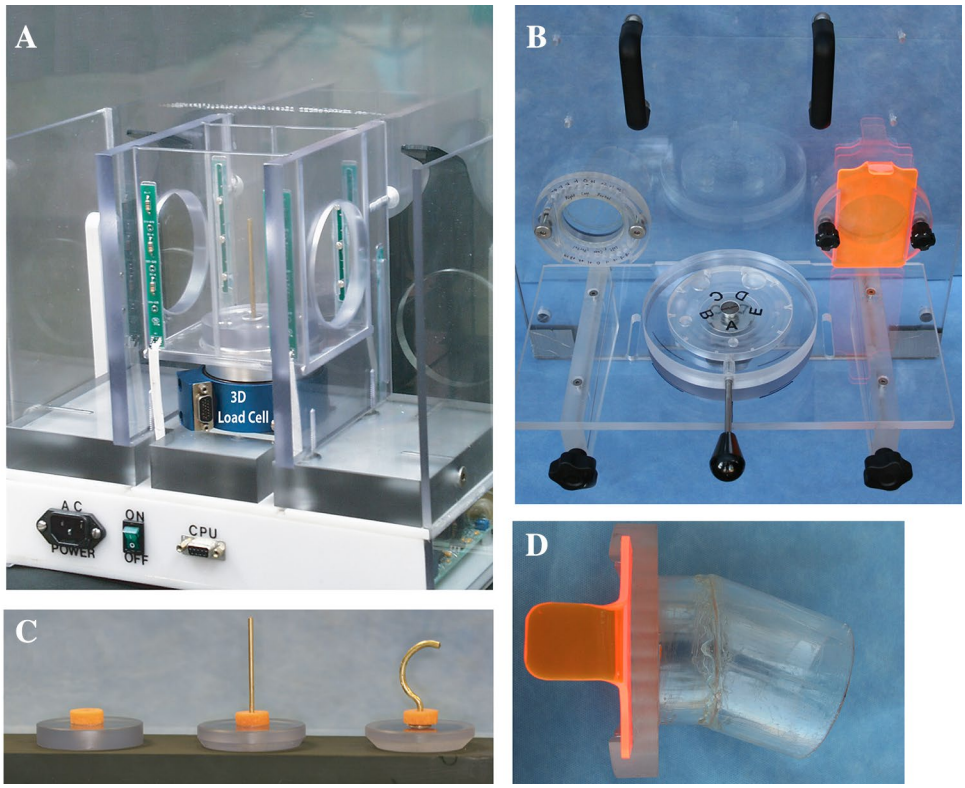

Fig. 1 Pictures of the experimental apparati. **a** The modified Movement Assessment Panel (mMAP) with the 3D load cell and below it in **b** is shown the food target (carrot chip with hole in center) and three levels of difficulty (flat surface, straight rod, curved rod—note that the metal curve is directed away from the monkey in the cage). See Darling et al. (2006) for a complete description of the mMAP device. **c** The modified dexterity board (mDB) device with a round Plexiglas plate that can be rotated to put each well in a consistent location for each hand and then locked in place. **d** An adjustable chute that projects into the monkey's cage to ensure that the monkey can successfully acquire the food pellet with only with the hand we are testing. See Pizzimenti et al. (2007) for a complete description of this device

the monkey was food-restricted for 18–24 h prior to each testing session. A "standard" rectangular dexterity board was initially used to assess the preferred hand and strength of hand preference for each monkey (Nudo et al. 1992; McNeal et al. 2010) followed by training on the mMAP and mDB tasks. Full testing sessions included blocks of five trials with each hand on each of five wells in the mDB task (i.e., 25 trials per hand in total in a single testing session) and on each of the three difficulty levels in the mMAP task (i.e., 15 trials per hand in total in a single testing session). Pre-lesion data were collected every 1–3 weeks, with the total number of pre-lesion test sessions varying according to each monkey's ability to learn the task and perform consistently. The final five consecutive pre-lesion experiments that demonstrated relatively stable levels of performance were considered indicative of consistent good performance and used to determine readiness for lesions to cortical motor areas (see Results). Post-lesion data were collected during weekly experimental sessions for the first 2 months after the surgery after which tests were conducted every 2 weeks.

Surgical procedure

Preoperative, surgical and postoperative procedures were the same as those described previously for lesions of frontal lobe motor areas (Darling et al. 2009; McNeal et al. 2010; Morecraft et al. 2015a). Briefly, a craniotomy was made over the frontoparietal region exposing the lateral cortical surface. Intracortical microstimulation (ICMS) was then used to identify the arm areas of M1 and LPMC in all cases and also of S1 and rostral area 5 in F2P2 lesion cases. Detailed topographical maps of the movement representations are provided in previous reports (McNeal et al. 2010; Morecraft et al. 2015a; Darling et al. 2016). Arteries supplying these areas, including the Rolandic artery were cauterized to block surface blood flow to these cortices. Following a 5–10 min waiting period the corresponding gray matter was removed with aspiration. All lesions were placed in the hemisphere contralateral to the preferred limb and the planned surgical lesions targeted the arm areas of primary motor cortex (M1) + the adjacent lateral premotor cortex (LPMC) (category F2 lesion) and M1 + LMPC + primary somatosensory cortex (S1) + rostral part of parietal area 5 (category F2P2 lesion). Figure 2 illustrates the lesions of all ten monkeys. Extensive descriptions of these lesions based upon histological analysis and verification are included in our previous reports (Darling et al. 2009, 2016; McNeal et al. 2010; Morecraft et al. 2015a).

Histological procedures

Following the predetermined survival/recovery period (Table 1), each monkey was deeply anesthetized with an overdose of pentobarbital (50 mg/kg or more) and perfused

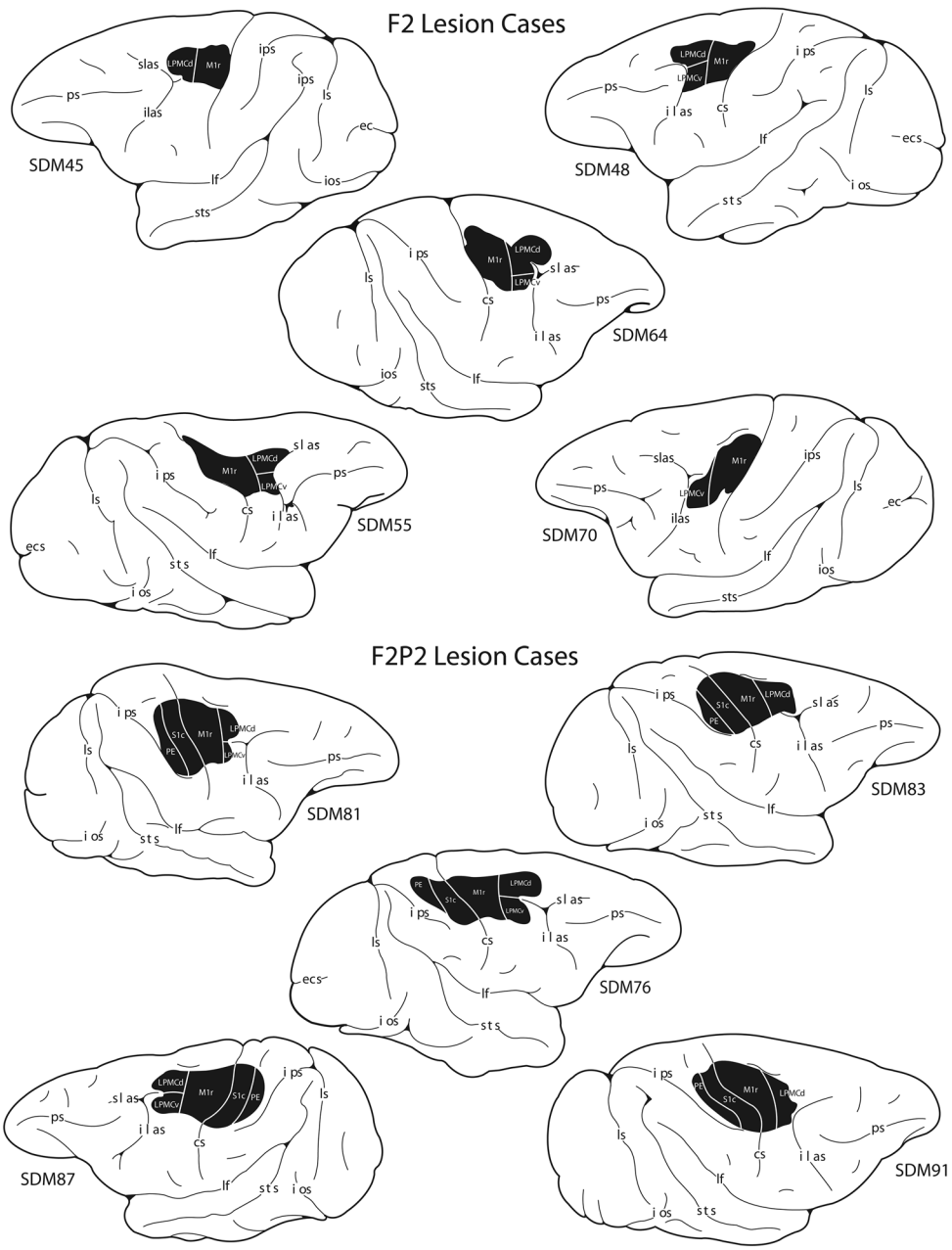

Fig. 2 Line drawings of the lateral surface of the cerebral cortex showing the lesion site locations (blackened area) in the five frontal and five frontoparietal lesion cases. Detailed descriptions of the histological and cytoarchitectonic characteristics of each lesion are provided in previous reports along with microstimulation maps of the cortical surface that were used to guide the placement of each lesion (Darling et al. 2009, 2016; McNeal et al. 2010; Morecraft et al. 2015a).*cs* central sulcus, *ecs* ectocalcarine sulcus, *ilas* inferior limb of the arcuate sulcus, *ios* inferior occipital sulcus, *ips* intraparietal sulcus, *lf* lateral fissure, *ls* lunate sulcus, *ots* occipito-temporal sulcus, *ps* principal sulcus, *slas* superior limb of the arcuate sulcus, *sts* superior temporal sulcus

transcardially with 0.9% saline, followed by 2 L of 4% paraformaldehyde in 0.1 M phosphate buffer at pH 7.4 (PB), then 1 L each of 10% and 30% sucrose in 0.1 M PB for cryoprotection. The brain was removed, then blocked into cortical, brainstem and spinal cord components. The tissue was placed in 30% sucrose in 0.1 M PB for 2–5 days at 4 °C and then processed for histochemical visualization of the cortical lesion (Morecraft et al. 2001, 2002, 2007). To accomplish this, the cortical tissue was frozen sectioned in the coronal plane on a sliding microtome (American Optical 860, Buffalo, NY, USA) at a thickness of 50 µm in cycles of 10, forming ten complete series of evenly spaced tissue sections, respectively. To identify the cytoarchitectonic organization of each brain, one complete series of tissue sections was processed for Nissl substance using our previously described histochemical methods (Morecraft et al. 1992; Morecraft and Van Hoesen 1992) and used for the lesion volume analysis in the present report.

Estimation of lesion volume

The methods for estimating gray and white matter lesion volume were described previously (Pizzimenti et al. 2007; Darling et al. 2009). Briefly, localization of the cortical injury

site was accomplished using brightfield illumination on a BX-51 Olympus microscope (Leeds Precision Instruments, Minneapolis, MN) attached to a high-resolution MAC 5000 motorized stage (Ludl Electronic Products, Hawthorne, NY, USA). The microscope was joined to a Neurolucida and Stereo Investigator neuroanatomical software system (Microbrightfield, Colchester, VT, USA) in a Dell Precision Tower 5810. Using the data collection system, each Nissl-stained coronal section through the lesion site was traced including the locations of the lesion site boundaries and spared gray matter/white matter borders. Anatomically matched Nissl-stained coronal sections from the non-lesioned hemisphere of the same animal were then plotted in the identical manner and the lesion site was digitally transferred onto the non-lesioned hemisphere. Cytoarchitectonic criteria used to evaluate the caudal frontal cortex and rostral parietal cortex were based upon the reports of Pandya and colleagues (Barbas and Pandya 1987; Morecraft et al. 2012, 2015b). White matter lesion volume was performed using a similar method in which the external boundary of the white matter region of interest coincided with the plane of interface between layer VI and the subcortical white matter. The internal boundaries of the white matter region of interest corresponded to the width and depth of the injury as determined from Nissl-stained sections through the lesioned hemisphere. The white matter boundaries obtained from the lesioned hemisphere were then transferred to the matching coronal section in the non-lesioned hemisphere. Subcortical structures and fiber pathways that were spared and damaged were identified using the atlas and nomenclature of Schmahmann and Pandya (2006). The Cavalieri estimator probe in the Stereo Investigator software (MBF Bioscience, Williston VT, USA) was then used to calculate respective gray and white matter lesion volumes.

Data analysis

Force data from the mMAP task were analyzed visually in Datapac 2k2 along with the accompanying video data to identify the first touch of the carrot chip or plate/rod supporting the carrot chip to the end of force application (i.e., when the carrot chip was removed from plate supported by the load cell or the rod) and to identify trial outcome. The force, duration and outcome data were used to compute a performance score (Eqs. 1 and 2) for manipulation on each trial normalized to each monkey's abilities in terms of the range of durations and impulses observed during pre-lesion testing as described previously (Darling et al. 2009). Skill on the mMAP curved rod task was computed as mean performance score/s.d. of performance scores over five consecutive test sessions in the pre-lesion phase (from the last 5 pre-lesion test sessions) and during the post-lesion phase to identify the highest skill attained during recovery over five consecutive test sessions. The ratio of highest post-lesion skill to skill over the last five pre-lesion trials was used as a measure of recovery of manipulation skill.

$$\mathrm{TAImp}(n) = \int |F_x|\mathrm{d}t + \left|F_y\right|\mathrm{d}t + |F_z|\mathrm{d}t, \tag{1}$$

TAImp (n) is the total absolute impulse of trial n, $\int$ is the integral over duration of trial t with respect to time (dt), F_x is the force applied in left/right direction, F_y is the force applied in anterior–posterior direction, F_z is the force applied in vertical direction.

If outcome $\geq$ 2 (i.e., successful grasp and lift/manipulation of the carrot chip) then

$$\mathrm{PS}_{\mathrm{mMAP}}(n) = \left\{ \begin{array}{r} 100 * ((\mathrm{TAImp}(n) - \mathrm{Min\ TAImp})/\mathrm{TAImp\ range}) + \\ 100 * ((\mathrm{Dur}(n) - \mathrm{MinDur})/\mathrm{Dur\ Range}) \end{array} \right\} * \mathrm{Outcome}(n) \tag{2}$$

$$\text{if } \mathrm{PS}_{\mathrm{mMAP}}(n) < 200 \text{ then } \mathrm{PS}_{\mathrm{mMAP}}(n) = 200$$

Else

$$\mathrm{PS}_{\mathrm{mMAP}}(n) = \left\{ \begin{array}{r} 100 * ((\mathrm{MaxTAImp} - \mathrm{TAImp}(n))/\mathrm{TAImp\ Range}) \\ +100 * ((\mathrm{MaxDur} - \mathrm{Dur}(n))/\mathrm{DurRange}) \end{array} \right\} * \mathrm{Outcome}(n)$$

$$\text{If } \mathrm{PS}_{\mathrm{mMAP}}(n) > 200 \text{ then } \mathrm{PS}_{\mathrm{mMAP}}(n) = 200$$

$$\text{If } \mathrm{PS}_{\mathrm{mMAP}}(n) < 50 \text{ then } \mathrm{PS}_{\mathrm{mMAP}}(n) = 50$$

where $PS_{mMAP}(n)$ is the performance score on mMAP trial *n,* Outcome(*n*) is the success on trial *n* (0 for no attempt with the correct hand, 1 for unsuccessful attempt with the correct hand, 2 if the carrot chip is successfully grasped and lifted over the rod but then dropped and not removed from the food chamber, 3 if the carrot chip is successfully grasped and lifted over the rod but then dropped and removed from the food chamber, 4 for successful acquisition without dropping the carrot chip), MinTAImp is the minimum single trial pre-lesion total absolute impulse within a difficulty level for either hand, MaxTAImp is the maximum single trial pre-lesion total absolute impulse within a difficulty level for either hand, TAImp Range is the MaxTAImp–MinTAImp, Dur(*n*) is the duration of trial *n,* MinDur is the minimum single trial duration during pre-lesion tests with either hand within a difficulty level, MaxDur is the maximum single-trial duration during pre-lesion tests with either hand within a difficulty level, DurRange is the MaxDur–MinDur.

Movements of the reaching hand in the mDB task were recorded with four digital video cameras (Basler, model A602fc) and analyzed using a data acquisition and analysis package (SIMI Reality Motion Systems, Unterschleissheim, Germany). Calibration of the four cameras was carried out with a rigid calibration frame using direct linear transformation methodology. The hand/digit movements were analyzed to assess trial outcome as well as accuracy and speed of reaching and manipulation/grasp of the pellet. These data were used to compute an overall performance score (Eq. 3) for each trial and a performance score for reaching (based on duration, accuracy and grip aperture of the reach—Eq. 4) and manipulation (based number of times contact with the food pellet was lost and duration—Eq. 5) on each trial normalized to each monkey's abilities (e.g., duration of reach and manipulation, accuracy of reach) during the pre-lesion phase as described previously (Pizzimenti et al. 2007). The best well (with the highest overall pre-lesion skill over the last five pre-lesion trials defined as described above using performance scores in the mDB tasks for each well) and a second smaller well (with pre-lesion skill about ½ that of the best well) were identified and the highest post-lesion recovery of skill was analyzed for these wells. Recovery of both reach skill and manipulation skill was analyzed as the ratio of highest post-lesion skill over five consecutive post-lesion tests to pre-lesion skill over the last five pre-lesion tests.

$$PS_{(n)} = m_{(n)} \times [100 \times (\text{Rdur} + \text{Gapp} + \text{Mdur} + \text{Acc} + C)] \quad (3)$$

$$RS_{(n)} = m_{(n)} \times [100 \times (\text{Rdur} + \text{Gapp} + \text{acc})] \quad (4)$$

$$MS(n) = m(n) \times [100 \times (\text{Mdur} + C)] \quad (5)$$

where: $PS_{(n)}$ is performance score of trial *n*, $RS_{(n)}$ is reach score of trial *n,* $MS_{(n)}$ is manipulation score of trial *n,* $m_{(n)}$ is the multiplier (0 for no attempt, 1 for failure, 2 for successful retrieval of the pellet),

$$\text{Rdur} = \frac{(\text{maximum prelesion reach duration} - \text{reach duration on trial } n)}{(\text{maximum} - \text{minimum prelesion reach duration})}$$

$$\text{Gapp} = \frac{(\text{maximum prelesion grip aperture at touchdown} - \text{grip aperture on trial } n)}{(\text{maximum} - \text{minimum prelesion grip aperture})}$$

$$\text{Mdur} = \frac{(\text{maximum prelesion manipulation duration} - \text{manipulation duration on trial } n)}{(\text{maximum} - \text{minimum prelesion manipulation duration})}$$

$$\text{Acc} = \frac{(\text{maximum prelesion pellet - index distance touchdown} - \text{pellet - index distance on trial } n)}{(\text{maximum} - \text{minimum prelesion pellet - index distance})}$$

$$\text{C} = 1/(1 + \text{ number of times contact is broken between a digit and the pellet on trial } n).$$

Temporal aspects of recovery were assessed by identifying the post-lesion week of consistent success (on all 5 trials) in the mMAP curved rod task and the mDB task (any well). We also assessed reaching and manipulation skill as the mean performance score divided by the standard deviation of performance scores over five consecutive testing sessions (i.e., 25 trials over an approximately 5 week period). Skill was measured during the last five pre-lesion tests, first five post-lesion tests and the five consecutive tests with highest skill during the post-lesion period. The ratios of post-lesion to pre-lesion skill were used as measures of initial and long-term effects of the injury (and additional task practice), respectively. These skill measures were computed for the mMAP curved-rod task (mMAP manipulation skill) and for two wells on the mDB task (reach skill and manipulation skill): (1) the well with the highest overall (reach and manipulation) skill during pre-lesion and (2) a smaller (second) well with a skill about ½ that of the skill on the best well.

Statistical analysis

Initial post-lesion deficits in motor skill (ratio of skill in the first 5 post-lesion tests to skill in the last 5 pre-lesion tests) and skill recovery (ratio of highest skill observed during the post-lesion phase to pre-lesion skill) by each monkey were computed. These ratios were compared for the two lesion groups using separate three-way (group × task × time) repeated measures analyses of variance to test whether recovery of reach skill and manipulation skill differed between the two groups in the different mDB tasks (best well, second well). Because one monkey (SDM76) performed very inconsistently and with many no-attempts in the mMAP curved rod task after the lesion, recovery of skill on this task was analyzed using two-way (group × time) repeated measures analysis of variance with only four cases in the F2P2 lesion group.

We explored hypotheses related to recovery of post-lesion skill and lesion volume using simple linear correlation. We considered gray and white matter lesion volumes and percentage of M1c and S1r lesion volumes in separate analyses due to the small population studied. We did not correct for multiple *t* tests of these correlation coefficients in this exploratory analysis.

Results

Use of the ipsilesional hand for movements such as reaching and grasping of the cage bars for climbing and postural support appeared to be smooth, accurate and at normal speed during observations of cage behavior in all cases in the days immediately following the lesion. These observations contrasted with those of the contralesional hand which was clearly impaired in all these activities as we have previously reported for these same lesioned animals (Darling et al. 2009; Morecraft et al. 2015a). However, some impairment of ipsilesional fine hand motor function was observed as failed attempts or no attempts in some cases in the mDB best and second well tasks and the mMAP curved-rod task in the first post-lesion motor testing session at 1 week after the lesion (Table 2). Among the F2 lesion cases, SDM55 and SDM70 had failed attempts in the mDB best well and second well tasks. Also, SDM55 had one failed attempt and four no-attempts in the mMAP curved-rod task. Among the F2P2 lesion cases SDM76 had failed attempts in the mDB best well and second well tasks and SDM91 had failed attempts

Table 2 Failed attempts, successes and no attempts in the first post-lesion tests of ipsilesional hand motor function at 1 week post-lesion

Case SDM	Lesion	mDB best well			mDB second well			mDB any well			mMAP crvd rod		
		FA	S	NA	FA	S	NA	FA	S	NA	FA	S	NA
45	F2	1	4	0	0	5	0	0	5	0	0	5	0
48	F2	0	4	1	0	5	0	0	5	0	0	5	0
55	F2	1	4	0	3	2	0	0	5	0	1	0	4
64	F2	0	5	0	0	5	0	0	5	0	0	5	0
70	F2	2	3	0	2	3	0	1	4	0	0	5	0
Mean (F2 cases)		0.8	4	0.2	1	4	0	0.2	4.8	0	0.2	4	0.8
76	F2P2	1	4	0	1	4	0	0	5	0	0	5	0
81	F2P2	0	5	0	0	5	0	0	5	0	0	5	0
83	F2P2	0	5	0	0	5	0	0	5	0	0	5	0
87	F2P2	0	5	0	0	5	0	0	5	0	0	5	0
91	F2P2	0	5	0	0	5	0	0	5	0	2	3	0
Mean (F2P2 cases)		0.2	4.8	0	0.2	4.8	0	0	5	0	0.4	4.6	0

FA failed attempts, *S* successful acquisitions, *NA* no attempt

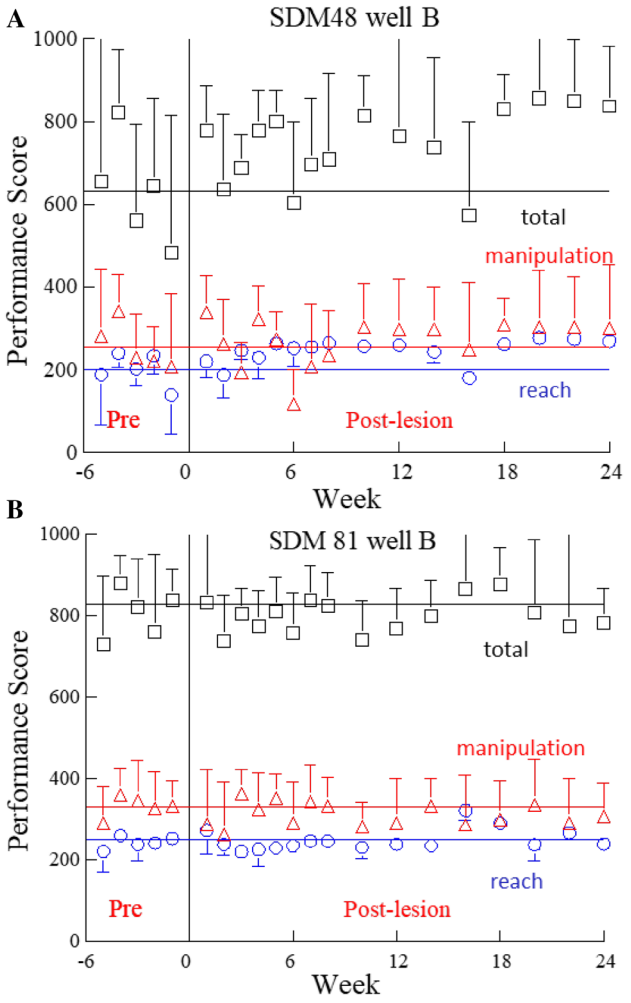

Fig. 3 Pre- and post-lesion mean performance scores on the 13 mm diameter well B of the mDB test by two monkeys. SDM48 (**a**) is a representative F2 lesion case and SDM81 (**b**) is a representative F2P2 lesion case. Each plotted point shows the mean overall performance score (black squares), manipulation performance score (red triangles) or reach performance score (blue circles) for a single monkey in a single testing session on the smaller well (with a pre-lesion skill equal to about ½ that of the best well). Error bars are 1 standard deviation (SD). The solid horizontal lines show the average performance scores over the last five pre-lesion tests

in the mMAP curved-rod task. Consistent with observations of cage behavior, all F2 and F2P2 lesion cases were successful in all attempts on either one well of the mDB task or in the mMAP curved-rod task (Table 2).

Performance scores over the post-lesion period varied from week-to-week and were often better than during the prelesion phase (e.g., Figs. 3a, 4a), but some monkeys exhibited post-lesion performance that was similar to the last tests of the pre-lesion phase (Figs. 3b, 4b). Considering performance score components, average reach and manipulation durations in the mDB second well task were similar to the last five pre-lesion tests (Fig. 5a, b). There was also improvement in the mMAP curved-rod task in the first five post-lesion tests with similar (F2P2 cases) or reduced (F2 cases) manipulation duration and total impulse compared to the last five pre-lesion tests (Fig. 5c, d). In subsequent post-lesion weeks, reach and manipulation durations in the mDB second well task decreased to lower than pre-lesion values in the F2 lesion group but only to about equal to pre-lesion values in the F2P2 lesion group (Fig. 5a, b). However, in the mMAP curved-rod task manipulation duration and impulse decreased to clearly below pre-lesion levels in both groups (Fig. 5c, d).

Despite some difficulties in the first post-lesion test 1 week after the lesion, there were improvements in initial post-lesion reach and manipulation skill over weeks 1–5 post-lesion compared to pre-lesion skill in the F2 lesion group, especially in the difficult second (smaller) well mDB task (indicated by a post/pre-lesion skill ratio > 1.0 in Fig. 6a, b). In contrast, most F2P2 lesion cases had poorer post-lesion skill in the first five post-lesion weeks in all tasks (indicated by a lower post/pre-lesion skill ratio < 1.0 in Fig. 6a, b). Over subsequent post-lesion tests, post-lesion reach skill improved in both groups (time main effect: $F_{1,8} = 13.43$, $p = 0.006$), but with a trend to higher levels especially in the difficult mDB second well task (Fig. 7a, b; well main effect: $F_{1,8} = 4.14$, $p = 0.076$). Statistical analysis showed that the F2 lesion group recovered better than the F2P2 cases in terms of reach skill (Figs. 3a, 6a; group main effect: $F_{1,8} = 5.41$, $p = 0.048$, $p < 0.05$). Indeed, all lesion cases improved to above pre-lesion levels in reach skill in either the best well or second well task by at least 20% (Fig. 7a). There were no significant interaction effects ($p > 0.211$).

Manipulation skill showed similar trends to reach skill during recovery after the lesion. Initial post-lesion manipulation skill in the mDB second well task and mMAP curved-rod task was below pre-lesion levels in most F2P2 cases but were equal to or above pre-lesion levels in most F2 cases (Fig. 6b). Subsequently, manipulation skill improved to above pre-lesion levels in most lesion cases (Fig. 7b; mDB task; time main effect: $F_{1,8} = 24.59$, $p = 0.001$; mMAP curved-rod task: $F_{1,7} = 22.34$, $p = 0.002$). The F2 lesion group showed more improvement in the mDB second well task than in the best well task (Figs. 6b, 7b; group × well interaction: $F_{1,8} = 8.97$, $p = 0.017$; $p = 0.013$ for post hoc comparison of second well to best well tasks) and also a trend to better recovery than the F2P2 lesion group ($p = 0.057$ for comparison of F2 group to F2P2 lesion group for the mdB second well task). There were no other significant interactions ($p > 0.225$). Manipulation skill on the mMAP curved-rod task improved similarly in the two groups (Fig. 7b; group main effect: $F_{1,7} = 0.007$, $p = 0.934$; time main effect: $F_{1,7} = 22.34$, $p = 0.002$; group × time interaction: $F_{1,7} = 2.23$, $p = 0.179$).

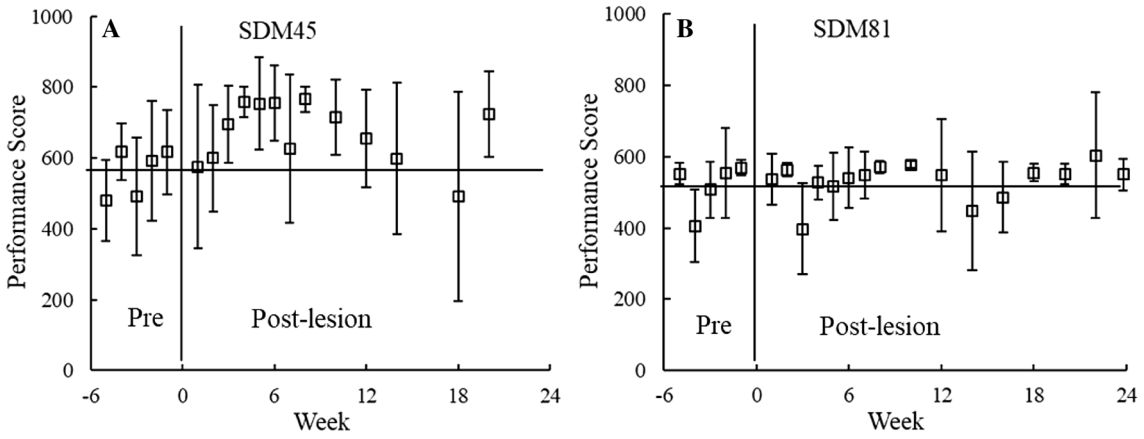

Fig. 4 Pre- and post-lesion mean performance scores on the mMAP curved-rod task by two monkeys. SDM45 (left) is a representative F2 lesion case and SDM81 (right) is a representative F2P2 lesioned case. Each plotted point shows the mean performance score for a single monkey in a single testing session. Error bars are 1 standard deviation (SD). The solid horizontal lines show the average performance score over the last five pre-lesion tests. Note that in the mMAP test there is only one performance score computed from duration and forces applied during manipulation of the target carrot chip over the curved rod. Reach duration and accuracy are not measured because the device requires a complex movement path from inside the cage to the target

Post-lesion recovery of ipsilesional hand motor skill was generally poorly correlated with lesion volume. Among all cases, recovery of reach and manipulation skill was not correlated with total lesion volume or with gray or white matter lesion volume (range of correlation coefficients: − 0.3 to 0.3, $p > 0.2$). Similarly, there were no significant associations of skill recovery with percentage of lesion volume to M1c among all cases (range of correlation coefficients: − 0.47 to 0.14, $p > 0.09$). Surprisingly, among F2P2 cases recovery of manipulation skill was positively associated with parietal white matter lesion volume (Fig. 8, $p < 0.05$) indicating that larger lesions were associated with better recovery of skill. Indeed, SDM87 had the largest parietal white matter lesion and best recovery of manipulation skill in the mDB and mMAP tasks whereas three cases with parietal white matter lesion volume about ½ that of SDM87 all had much poorer recovery of manipulation skill. Similar, but weaker, positive associations of manipulation skill were also observed with parietal gray matter lesion volume and with percentage of S1r lesion volume ($p < 0.1$). Interestingly, SDM91 had much larger percentage lesions of M1c and S1r arm/hand areas than SDM87 and also poorer recovery of manipulation skill (Fig. 8), suggesting that larger gray matter lesions to the banks of the central sulcus result in poorer recovery of ipsilesional hand motor function.

Discussion

Our current findings confirm our previous report that ipsilesional upper limb motor function demonstrates good recovery following unilateral frontal cortex lesions in rhesus monkeys (Darling et al. 2011), extending those findings to cases in which lesions include the anterior parietal lobe. The ipsilesional upper limb typically recovers motor function to better than pre-lesion levels in most cases following unilateral frontal and frontoparietal lesions. Higher than pre-lesion skill in both reaching and manipulation was observed in all frontal and frontoparietal lesion cases in at least one of the mDB best well, mDB second well or mMAP curved-rod tasks. It is important to recognize that the monkeys were not trained to the highest possible skill level during pre-lesion training, thereby permitting continued effects of task practice to occur post-lesion. Possible mechanisms underlying the recovery to higher than pre-lesion skill levels include additional task practice and increased use of the ipsilesional hand in the cage for various activities after the injury due to reduced trans-callosal inhibition (TCI) from the lesioned hemisphere, which may disinhibit contralesional M1 and thereby permit greater practice-induced post-lesion improvement in ipsilesional upper limb motor function. However, the F2 lesion cases demonstrated higher skill earlier in the post-lesion period and overall higher post-lesion skill than F2P2 lesion cases. This suggests that the most likely explanation for poorer post-lesion upper limb motor function in F2P2 than in F2 lesion cases is due the additional parietal lobe damage producing sensory processing deficits and, perhaps, loss of corticospinal projections from anterior parietal lobe. Overall, these findings demonstrate that, in contrast to findings in humans who have suffered stroke, the non-human primate CNS is able to reorganize after unilateral frontal and frontoparietal lesions to allow excellent recovery and even further improvement of ipsilesional upper limb function.

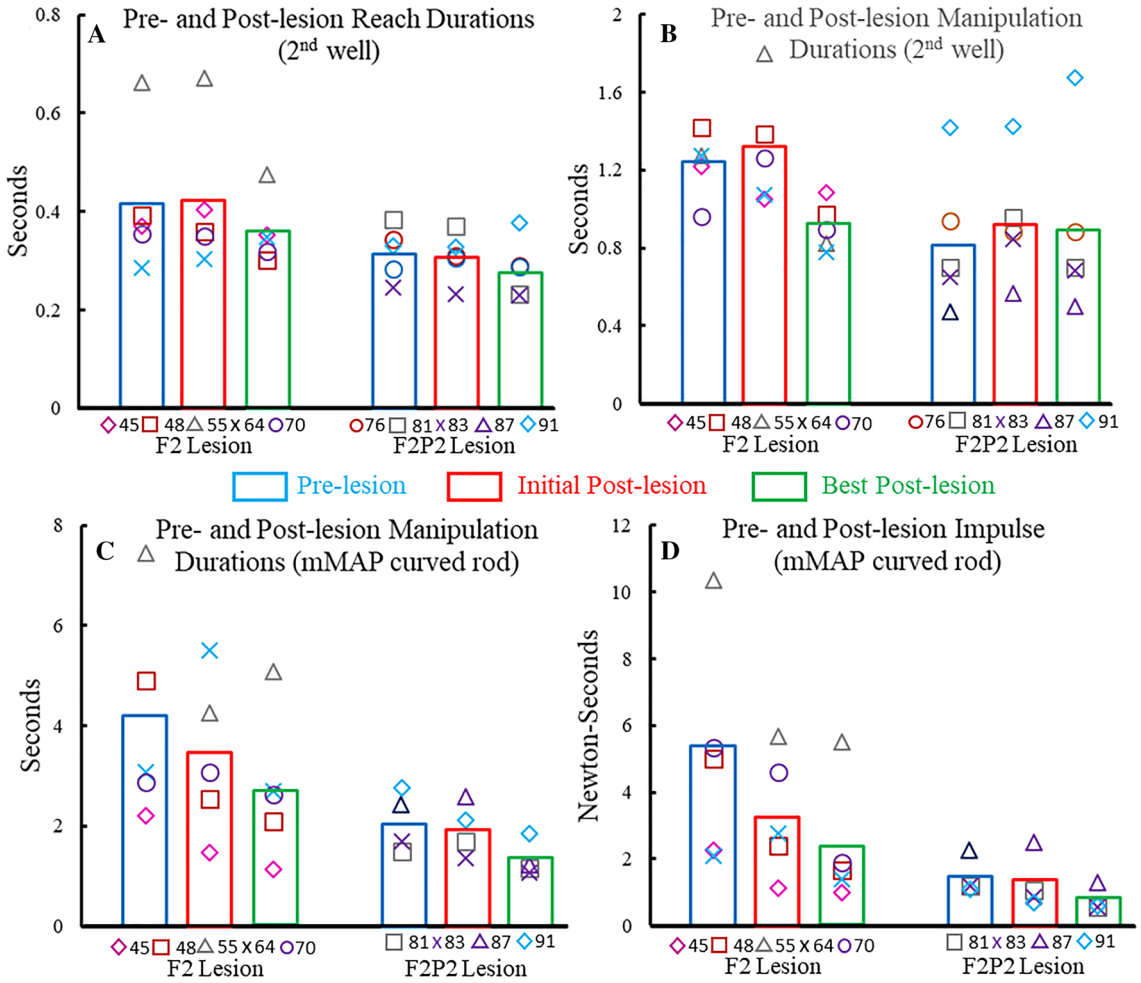

Fig. 5 Pre- and post-lesion reach and manipulation durations and manipulation impulse. Note that decreases in duration and impulse indicate improved performance (i.e., decreased duration, decreased total force application over time). Average reach durations and manipulation durations in the mDB second well task over five consecutive tests are shown in **a**, **b**. Average manipulation durations and manipulation total absolute impulse in the mMAP curved-rod task are shown in **c**, **d**. Each bar represents the averages for the F2 or F2P2 lesion groups over the last five pre-lesion tests (pre-lesion, blue), first five post-lesion tests (initial post-lesion, red) and best five consecutive post-lesion tests (with highest skill). Symbols are data for each case in the group. Note that in the mMAP task there are only data for four cases in the F2P2 lesion group. Note also that the ordinate axes differ on each graph

The better ipsilesional hand recovery in rhesus monkeys is probably related to the focal nature of the lesions to a circumscribed region of cortical gray matter with white matter damage limited to immediately below the gray matter lesion, whereas there is usually much greater damage to subcortical white and gray matter structures in human MCA stroke.

It is curious that recovery of in the mDB and mMAP tasks was not similar for the F2 and F2P lesion cases. Both groups showed similar levels of recovery of manipulation skill in the mDB best well task and in the difficult mMAP curved-rod task but the F2 lesion group exhibited generally better recovery in the mDB second well task. Similar recovery of F2 and F2P2 lesion cases in the best well task may be related to the larger best well allowing both index and thumb to enter the well and less precise index-tip motion to move the pellet to the thumb-tip. In contrast, the smaller second well allows only the index-tip to enter such that the pellet had to be moved more carefully to the thumb-tip located outside of the well. Recovery in the difficult mMAP curved-rod task may be more closely related to strength due to the larger forces required and the carrot chip being much larger than the pellet used in the mDB task. We previously observed that recovery of the contralesional hand in this task among F2 lesion cases was closely correlated to the strength of the projection from ipsilesional M2 to motor neurons in lamina IX of C5-T1 controlling muscles of the contralateral hand (McNeal, 2010 #7478). It is doubtful that strength of the ipsilesional hand is affected differently after F2

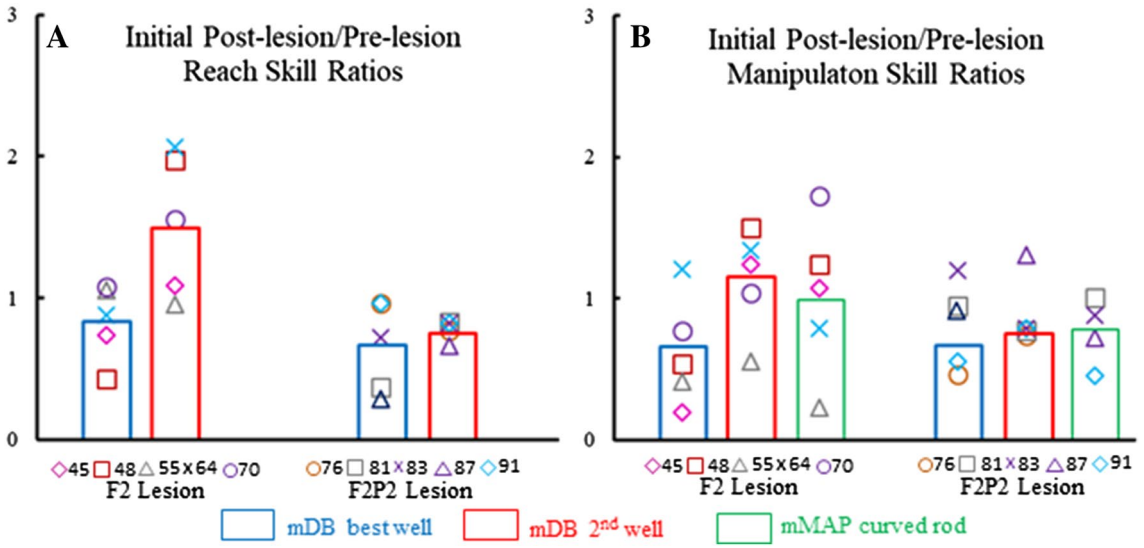

Fig. 6 Initial post-lesion reach (**a**) and manipulation (**b**) skill for F2 and F2P2 lesion cases. Each bar is the mean ratio of skill over the first five post-lesion tests/mean of skill over the last five pre-lesion tests for five F2 and four or five F2P2 lesion cases (5 cases for mDB task, 4 cases for mMAP manipulation skill ratios). Each plotted point represents data from a single case within each lesion group

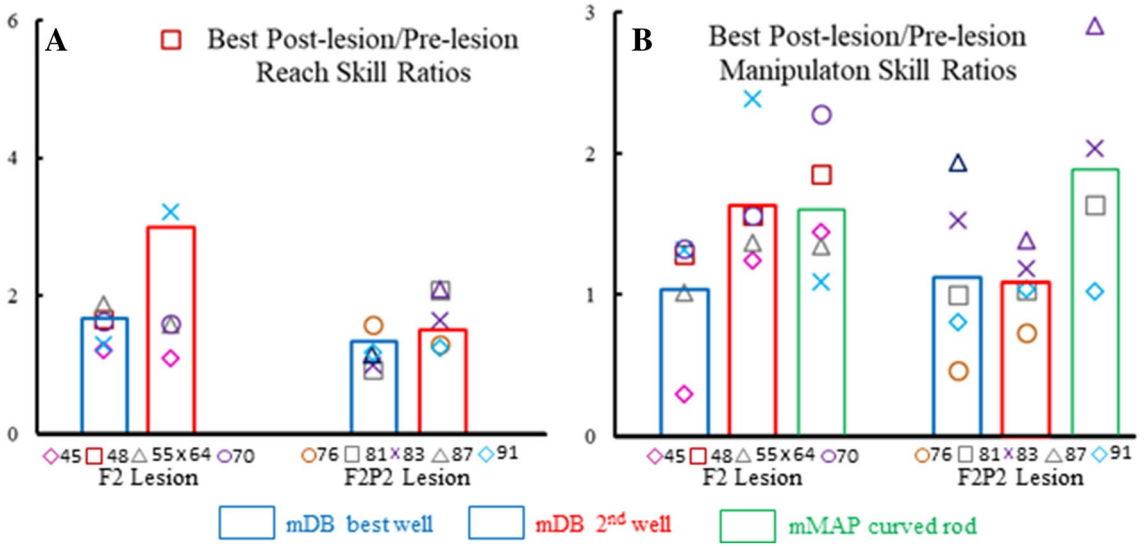

Fig. 7 Best post-lesion/pre-lesion reach (**a**) and manipulation (**b**) skill ratios for F2 and F2P2 lesion cases. Each bar is the mean ratio of best post-lesion skill over five consecutive tests to pre-lesion skill (last 5 pre-lesion tests) for five F2 and four or five F2P2 lesion cases (5 cases for mDB task, 4 cases for mMAP manipulation skill ratios). Each plotted point represents data from a single case within each lesion group. Note that the ordinate axis differs for **a**, **b**

and F2P2 lesions as the contralateral projection from contralesional M1 is likely to be minimally affected by these lesions.

Role of changes in use of the two hands

Increased use of the ipsilesional hand coupled with minimal use of the contralesional hand during cage behaviors and motor testing is one potential behavioral cause of improved hand motor function. There was certainly greatly reduced post-lesion contralesional hand use in the cage during the first post-lesion week and in the first few post-lesion motor tests as we have reported previously (Darling et al. 2009, 2016). We also observed increased reliance on the ipsilesional hand for most tasks performed in the cage during the first post-lesion week as well as very good use of the ipsilesional hand in the first post-lesion motor testing session in both F2 and F2P2 monkeys (Table 2,

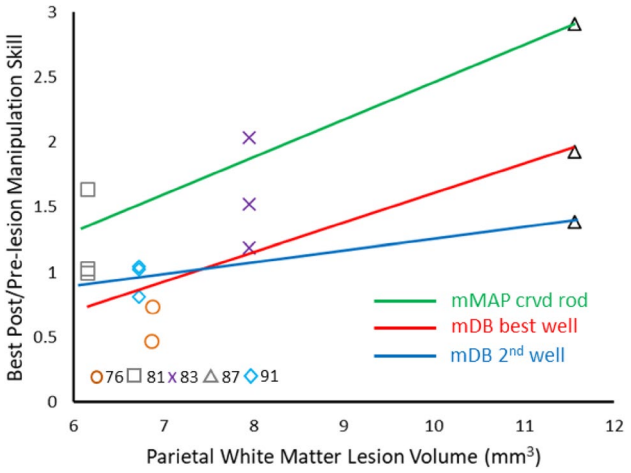

Fig. 8 The ratio of best post- to pre-lesion ipsilesional hand manipulation skill increased with parietal white matter lesion volume in the mDB and mMAP tasks. Linear correlation coefficients were 0.91 for the mMAP curved-rod task ($p=0.045$), 0.84 for the mDB second well task ($p=0.037$) for the mDB second well task and 0.78 ($p=0.06$) for the mDB best well task

note that 9 of 10 cases had successful acquisitions on all trials in at least one well of the mDB task and 8 of 10 had successful acquisitions on all trials in the difficult mMAP curved-rod task). In subsequent motor testing sessions all monkeys successfully acquired food targets in nearly all trials of the mDB best well and second well tasks as well as the mMAP curved rod task when forced to use the ipsilesional hand. Furthermore, we have previously reported on testing for learned nonuse (LNU) of the contralesional hand in three of the five F2 lesion cases (SDM55, SDM64, SDM70) (Darling et al. 2013). All three F2 lesion cases studied with LNU tests in which the animal could use either hand to acquire small food targets from a flat surface, used the ipsilesional hand in over 70% of trials of all LNU tests throughout the post-lesion period. This greater use of the ipsilesional hand in cage behaviors and in the initial motor tests during the post-lesion period may explain the improvements of ipsilesional hand fine motor skill after the lesion, perhaps due to effects of neuroplastic reorganization of descending pathways to subcortical, brainstem and spinal cord motor areas.

Role of sensory processing deficits

The generally slower and poorer recovery of the ipsilesional hand motor function of F2P2 lesion cases may be due to subtle subclinical somatosensory processing deficits that would require sensitive tests to identify. If this were the case, one would expect that greater extent of parietal lobe damage would produce greater deficits in post-lesion improvement/recovery of ipsilesional hand manipulation skill in F2P2 lesion cases. Although counter-intuitive, we observed positive relationships between these skill measures and parietal lobe white matter (Fig. 8) and gray matter lesion volume in the mMAP curved rod and mDB tasks. This suggests larger lesions of parietal lobe and its underlying white matter are associated with better post-lesion improvement of ipsilesional hand manipulation skill within the F2P2 lesion group. This finding is consistent with the idea that reduction of TCI from ipsilesional onto contralesional parietal lobe enhances processing of ipsilesional hand sensory inputs during grasp but would seem to contradict our finding of poorer improvement of ipsilesional limb motor function in F2P2 lesion than in F2 lesion cases that had no parietal lesion. Considering possible effects of M1c and S1r gray matter lesions on recovery of ipsilesional hand manipulation skill, it is noteworthy that SDM91 had the largest such lesions (Table 1) and much poorer recovery of manipulation skill than SDM87. However, SDM87 had a larger parietal white matter lesion and much better post-lesion ipsilesional hand manipulation skill than SDM91 (Fig. 8), consistent with reduced TCI onto contralesional parietal lobe. On a related issue, some work in neurologically intact humans has shown that TMS activation of different parts of posterior parietal cortex (PPC) in one hemisphere can excite or inhibit motor cortex excitability of the other hemisphere (Koch et al. 2009). Thus, loss of excitatory connections from ipsilesional parietal lobe onto contralesional motor cortex in F2P2 cases may counteract loss of TCI from ipsilesional motor cortex and thereby explain the overall poorer post-lesion ipsilesional hand motor function in F2P2 than in F2 lesion cases

Role of transcallosal inhibition

The observed improvement of reach and manipulation skill to better than pre-lesion skill levels in both lesion groups is consistent with the idea that reduced TCI from the lesioned hemisphere allows improved control over the ipsilesional limb by the contralesional hemisphere. One would expect that the additional parietal lobe lesion in F2P2 lesion cases would result in lower TCI on the contralesional hemisphere than in F2 lesion cases. Theoretically, this should result in better ipsilesional hand motor performance in the F2P2 lesion cases. However, as discussed above, recovery was generally faster and to higher skill levels in the F2 lesion cases, thereby contradicting this theory. Thus, in monkey it is possible that additional parietal lobe damage does not reduce TCI onto the contralesional motor cortex more than a lesion limited to frontal lobe motor areas. Alternatively, the effects of reduced TCI on contralesional motor cortex excitability may be limited such that a lesion of the frontal

lobe motor areas reduces TCI sufficiently to have a maximal effect on ipsilesional upper limb motor function.

Role of changes in corticospinal projections

Corticospinal projections from spared frontal lobe motor areas may also contribute to improved ipsilesional hand motor function after the lesion. We have shown previously that neuroplastic responses that upregulate ipsilesional M2 (iM2) CSP and contralesional M1 (cM1) CSP connections into contralesional C5–T1 spinal segments may support recovery of contralesional hand function after F2 lesions (McNeal et al. 2010; Morecraft et al. 2016). However, such positive neuroplastic responses to the contralesional spinal cord are inhibited in F2P2 lesion cases, one likely mechanism contributing to their poorer contralesional hand motor recovery (Morecraft et al. 2015a, 2016). Similar inhibitory effects on the neuroplastic responses of iM2 CSP and cM1 CSP to the ipsilesional spinal cord in F2P2 lesion cases may contribute to poorer post-lesion ipsilesional hand motor skill of these cases. Concerning the spared iM2 ipsilateral CSP (iCSP), our previous reports (McNeal et al. 2010; Morecraft et al. 2015a) show that the estimated number of boutons in C5–T1 of this projection is highly variable among monkeys and not different between controls and lesion cases (i.e., number of boutons range from about 4000–53,000 in controls, about 1700–35,000 in F2 lesion cases, and about 11,000–35,000 boutons in F2P2 cases—see Tables 3 and 6 of McNeal et al. (2010) for controls and F2 lesion cases and Table 7 of Morecraft et al. 2015a for F2P2 lesion cases). Thus, it is doubtful that remodeling of the iM2 iCSP contributes to poorer post-lesion manipulation skill in F2P2 cases. Upregulation of the cM1 iCSP in F2 lesion cases but not in F2P2 cases may provide an explanation for better ipsilesional hand post-lesion manipulation skill in F2 than in F2P2 cases because of the importance of this projection for control of ipsilesional hand/finger motion. Another potential explanation or contributor to poorer ipsilesional post-lesion manipulation skill in F2P2 cases is loss of ipsilateral S1 CSP from the lesioned hemisphere in F2P2 cases affecting tactile and proprioceptive feedback from the ipsilesional upper limb. It has been shown that there is a moderate ipsilateral S1 CSP in monkeys which primarily targets lamina V and VI (Ralston and Ralston 1985). Further, Liu and colleagues recently showed that behavioral responses to light touch are impaired after bilateral pyramidotomy and following selective ablation of S1 and S2 CSP neurons in mice using high-efficiency retrograde lentiviral vectors (Liu et al. 2018). If applicable in the non-human primate model, the loss of the S1 CSP in our F2P2 cases may also adversely affect recovery of grasp and manipulation of small objects. Finally, responses to proprioceptive inputs from the ipsilesional upper limb may also be more impaired in F2P2 cases, thereby affecting control of reaching movements.

Conclusions

Overall, we show that localized sensorimotor cortex lesions in rhesus monkeys do not cause long-term impairment in skilled use of the ipsilesional upper extremity. Moreover, continued minimal task practice through occasional motor testing along with greater use of the ipsilesional hand for daily fine motor tasks may be sufficient for continued improvement of upper limb motor skill. These findings are consistent with our previous report on effects of frontal lobe motor area injury on ipsilesional hand motor function but contrast with those in humans that report long-term ipsilesional hand motor deficits following unilateral stroke affecting sensorimotor cortex and/or subcortical gray matter (e.g., basal ganglia, thalamus) and white matter (e.g., internal capsule, cerebral peduncle) areas involved in the motor system (Jones et al. 1989; Marque et al. 1997; Laufer et al. 2001; Noskin et al. 2008). A novel finding of the present work was that isolated frontoparietal lesions resulted in poorer post-lesion recovery and improvement of hand motor skill in the acute phase and over 6–12 months post-lesion than in cases with lesions limited to frontal lobe motor areas, although both types of lesions generally resulted in improved post-lesion skill. Subtle somatosensory processing impairments are the most likely cause of the poorer recovery/improvement of post-lesion ipsilesional hand function following frontoparietal lesions. The mechanisms underlying the ability of rhesus monkeys to substantially improve ipsilesional hand motor function with additional minimal task practice after frontoparietal injury are not clear but may involve changes in terminal density of spared descending projections to brainstem and/or spinal cord sensory and motor processing areas. This may also be a consequence of lost corticospinal projections from the anterior parietal lobe which have recently been shown to be involved in modulating tactile processing at the spinal cord level (Liu et al. 2018).

Acknowledgements Supported by National Institutes of Health Grants NS 046367 and NS 097450.

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