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Sensorimotor cortex injury effects on recovery of contralesional dexterous movements in *Macaca mulatta*

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ABSTRACT

The effects of primary somatosensory cortex (S1) injury on recovery of contralateral upper limb reaching and grasping were studied by comparing the consequences of isolated lesions to the arm/hand region of primary motor cortex (M1) and lateral premotor cortex (LPMC) to lesions of these same areas plus anterior parietal cortex (S1 and rostral area PE). We used multiple linear regression to assess the effects of gray and white matter lesion volumes on deficits in reaching and fine motor performance during the first month after the lesion, and during recovery of function over 3, 6 and 12 months post-injury in 13 monkeys. Subjects with frontoparietal lesions exhibited larger deficits and poorer recovery as predicted, including one subject with extensive peri-Rolandic injury developing learned nonuse after showing signs of recovery. Regression analyses showed that total white matter lesion volume was strongly associated with initial post-lesion deficits in motor performance and with recovery of skill in reaching and manipulation. Multiple regression analyses using percent damage to caudal M1 (M1c), rostral S1 (S1r), LPMC and area PE as predictor variables showed that S1r lesion volumes were closely related to delayed post-lesion recovery of upper limb function, as well as lower skill level of recovery. In contrast, M1c lesion volume was related primarily to initial post-lesion deficits in hand motor performance. Overall, these findings demonstrate that frontoparietal injury impairs hand motor function more so than frontal motor injury alone, and results in slower and poorer recovery than lesions limited to frontal motor cortex.

1. Introduction

The contribution of cortical processing of somatosensory information to recovery of dexterous movements after precentral motor cortex injury has rarely been studied and, consequently, is poorly understood. Because the cortical territory served by the middle cerebral artery (MCA) is most commonly affected in stroke, damage frequently occurs to one or both of the major motor and sensory areas, specifically the primary motor cortex (M1) and primary somatosensory cortex (S1). Moreover, other adjacent areas of the frontal and parietal lobes including lateral premotor cortex (LPMC) and posterior parietal cortex (PPC) may also be involved after MCA stroke but the effect of such large lesions on motor recovery has not been a focus of contemporary studies in non-human primates. Indeed, it has been reported that the parietal lobe is the most frequently injured part of the cortical mantle after MCA stroke (Yoo et al., 1998) but injury confined to the precentral motor region continues to be the focus of experimental study (Dancause et al., 2006; Eisner-Janowicz et al., 2008; Moore et al., 2012). Functionally, the anterior and posterior parietal lobe regions are known to play a critical role in processing of somatosensory information for perception (Kaas, 2012) and for control of hand/digit movements for reaching and grasping (Kaas, 1993). Thus, there are ample reasons to study the effects of extensive lesions involving peri-Rolandic sensorimotor areas on recovery of dexterous hand/digit movements, which often recover poorly in stroke patients.

Rarely recognized but classical experimental lesion studies reporting the effects of isolated resection of S1, and larger parietal lobe lesions encompassing both S1 and the PPC in monkeys have shown that such lesions do not cause acute paralysis as is observed after M1 resection, but result in more persistent motor deficits such as hypotonia/weakness, ataxia and reliance on vision when attempting to perform precise upper extremity motor tasks (Kennard and Kessler, 1940; Peele, 1944). Similarly, studies in stroke patients report that functional recovery of hand movements is often poor when localized injury involves the parietal lobe and causes somatosensory dysfunction (Abela et al., 2012; Freund, 2003; Stern et al., 1971; Zeman and Yiannikas, 1989), with recovery associated with changes in gray matter volume of perilesional premotor cortex and subcortical areas including thalamus, caudate

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nucleus and cerebellum (Abela et al., 2015). In support of these observations is a recent case study of an individual who underwent left S1 resection to manage intractable seizures (Richardson et al., 2016). It was found that this patient had persistent impairments in maintaining right hand power grip force without vision and in initiation of grip forces to visual targets, but feedforward control of grip force during active movement to prevent slip of an object held in precision grip was intact. It seems consistent in the literature that practice of motor tasks and use of vision can ameliorate some of the motor deficits following parietal cortex injury (Carey et al., 2002; Jeannerod et al., 1984; Smania et al., 2003).

We recently reported that frontoparietal lesions in rhesus monkeys caused impaired fine hand/digit grasping and manipulation movements with varying degrees of recovery that are accompanied by striking changes in descending projections from spared medial premotor cortex (Morecraft et al., 2015). Notably, in contrast to our previous observations showing that lesions limited to precentral frontal motor areas results in an enhanced supplementary motor cortex corticospinal projection (CSP) in the form of increased terminal boutons (McNeal et al., 2010), we found that additional lesion of adjacent parietal cortex results in decreased numbers of supplementary motor cortex CSP boutons to neurons controlling hand/digit motion (Morecraft et al., 2015). Thus, parietal cortex may exert trophic influences on frontal lobe motor areas, and contribute to maintaining or enhancing the CSP from those gray matter areas. This may, in part, explain why patients with peri-Rolandic frontoparietal damage show poor recovery of distal upper extremity movements.

In the current report we examined the effects of lesion volume and location within lateral frontal and parietal sensorimotor areas on impairment of fine hand/digit function over the first month post-lesion, and on extended recovery of such function over 3, 6 and 12 months. Previously we demonstrated that initial deficits and recovery of fine hand motor function were strongly correlated with frontal lesion volume involving a wide range of lesions including M1, LPMC, supplementary motor cortex (M2, or the equivalent of MII, SMC, or SMA-proper as used in the literature) (Luppino et al., 1993; Wiesendanger and Wiesendanger, 1984; Woolsey et al., 1952), pre-supplementary motor cortex (pre-SMA), cingulate motor cortex, and medial prefrontal cortex that included both focal and non-focal lesions (Darling et al., 2009). In the present study we assessed hand motor recovery in 7 monkeys with focal lesions limited to M1 and LPMC and in 6 monkeys with combined lesions to M1, LPMC and the anterior parietal lobe (S1, including the rostral-most part of area PE) because this cortical territory is often damaged after MCA stroke in humans (Carrera et al., 2007; Rasmussen et al., 1992; Yoo et al., 1998). Importantly, the medial cortex, including M2, pre-SMA, cingulate motor areas and medial prefrontal region are typically spared following isolated MCA stroke. We hypothesized that lateral peri-Rolandic lesions including the parietal lobe would cause slower and less complete recovery than lateral lesions affecting only frontal lobe motor areas. Moreover, we quantified the percentage of the total volume damage to M1 and S1 controlling arm/hand movements, to test the hypothesis that increasing volume (as a percentage of total volume) of lesions affecting the gray matter surrounding the central sulcus results in greater fine hand motor deficits and slower/less complete recovery. We also tested whether volume of lesions to LPMC and rostral area PE contributed to poorer recovery as these regions are involved in processing of visual and somatosensory information for coordination of reaching and grasping.

2. Methods

2.1. Experimental animals

Thirteen adult rhesus monkeys (*Macaca mulatta*) were subjects for these experiments, 7 with lesions limited to the hand/arm area of M1 and LPMC (Category F2 lesion) (Fig. 1) and 6 with lesions of the hand/arm area of M1, LPMC, S1 and rostral part of area PE of the superior parietal lobule (Category F2P2 lesion) (Figs. 2, 3, 4) (Table 1). The animals were housed, cared for, and maintained in a United States Department of Agriculture (USDA) approved and inspected facility. All behavioral and surgical protocols were approved by the University of South Dakota (USD) Institutional Animal Care and Use Committee (IACUC), and conducted in accordance with USDA, National Institutes of Health, and Society for Neuroscience guidelines for the ethical treatment of experimental animals. Prior to beginning the study, each monkey was evaluated by a primate veterinarian and judged to be healthy and free of any neurological deficit. Proximal and distal movements and range of motion at the joints in both upper extremities of all animals were normal with the exception of SDM55. In this case the interphalangeal joints of digit 3 were permanently extended. However, this animal was able to perform precision opposition with digits 1 and 2 to successfully acquire the food rewards in the motor tests.

2.2. Experimental apparati

The equipment used to test fine hand motor function has been previously described (modified dexterity board or mDB and modified movement assessment panel or mMAP) (Darling et al., 2006, 2009; Pizzimenti et al., 2007). Both devices were attached to the monkey's cage and controlled, without restraint, which hand the monkey used to perform the tests (Fig. 5). Each hand was tested both pre- and post-lesion. The monkeys were allowed to move freely about the cage between trials in both tests and palatable food targets were used to minimize training effects. Using the mDB device we assessed duration and accuracy of targeted reaching, manipulation duration as well as the number of times the digit lost contact with the target (a small food pellet inside wells of varying diameter). Using the mMAP device we measured forces applied during grasp and manipulation of a carrot chip (or, in one monkey, a type of cereal due to its preference for the cereal over a carrot chip) from a flat surface or over straight and curved rods.

2.3. Video and force data acquisition

2.3.1. mMAP task

Forces applied during manipulation of the carrot chip in the mMAP task (Fig. 5A,B) were recorded at 200 samples/s using Datapac 2k2 (Run Technologies). Movements of the hand during the mMAP task were recorded using a single digital video camera (Sony, model DCR-DVD301) placed directly in front of the cage. These recordings were used for qualitative ratings of the movement strategy and to assess success/failure of the animal on each trial.

2.3.2. mDB task

Quantitative video recordings of hand movements during the mDB task (Fig. 5C,D) were used to assess spatial and temporal variables (e.g., accuracy and duration of the initial reach, grip aperture at touchdown of the hand, etc.) as described previously (Darling et al., 2009). These recordings used four digital video cameras interfaced with the SIMI Motion data acquisition package (SIMI Reality Motion Systems, Unterschleissheim, Germany). 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 retrieved into the cage, the pellet was knocked off of the platform, or a 60 s time limit had expired. Video collection was manually triggered and single trial video clips of each trial were manually created and verified. Details of the video collection protocol, data acquisition, and data analysis of the mDB task are provided in our previous work (Pizzimenti et al., 2007).

2.4. Behavioral procedures

Details of the behavioral protocols used in the current investigation have been described previously. Before the motor testing sessions,