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Research report

Abnormalities in skilled reaching movements are improved by peripheral anesthetization of the less-affected forelimb after sensorimotor cortical infarcts in rats

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Abstract

Unilateral damage to sensorimotor cortical (SMC) regions can profoundly impair skilled reaching function in the contralesional forelimb. Such damage also results in impairments and compensatory changes in the less-affected/ipsilesional forelimb, but these effects remain poorly understood. Furthermore, anesthetization of the ipsilesional hand in humans with cerebral infarcts has been reported to produce transient functional improvements in the paretic hand [Floel A, Nagorsen U, Werhahn KJ, Ravindran S, Birbaumer N, Knecht S, et al. Influence of somatosensory input on motor function in patients with chronic stroke. Ann Neurol 2004;56:206–12; Voller B, Floel A, Werhahn KJ, Ravindran S, Wu CW, Cohen LG. Contralateral hand anesthesia transiently improves poststroke sensory deficits. Ann Neurol 2006;59:385–8]. One aim of this study was to sensitively assay the bilateral effects of unilateral ischemic SMC damage on performance of a unimanual skilled reaching task (the single pellet retrieval task) that rats had acquired pre-operatively with each forelimb. The second aim was to determine whether partially recovered contralesional reaching function is influenced by anesthetization of the ipsilesional forelimb. Unilateral SMC lesions were found to result in transient ipsilesional impairments in reaching success and significant ipsilesional abnormalities in reaching movements compared with sham-operates. There were major contralesional reaching impairments which improved during a 4 week training period, but movements remained significantly abnormal. Anesthetization of the ipsilesional forelimb with lidocaine at this time attenuated the contralesional movement abnormalities. These findings indicate that unilateral ischemic SMC lesions impair skilled reaching behavior in both forelimbs. Furthermore, after partial recovery in the contralesional forelimb, additional improvements can be induced by transient anesthetization of the ipsilesional forelimb. This is consistent with the effects of unilateral anesthetization in humans which have been attributed to the modulation of competitive interhemispheric interactions. The present findings suggest that such interactions are also likely to influence skilled reaching function in rats.

Keywords: Motor cortex; Ischemia; Behavioral compensation; Skilled reaching; Motor learning; Less-affected forelimb; Interhemispheric competition

1. Introduction

Unilateral lesions to sensorimotor cortical (SMC) regions in rats result in sensory and motor impairments in the contralesional forelimb, including impairments in the fine movements used in reaching and grasping [51,54]. Such damage also results in complex behavioral changes in the "less-affected", ipsilesional forelimb. Subtle deficits in the ipsilesional forelimb have been documented using sensitive measures of skilled reaching movements [18,31,33]. Animals also increase reliance on the ipsilesional forelimb for many behaviors including postural support [25], coordinated limb placement during locomotion [45], reaching and food handling [54,55] in a manner which compensates for impairments in the contralesional forelimb. Because skilled reaching tests in rodents are thought to assay impairments homologous to upper extremity impairments in humans with cerebral strokes, it seems important to understand the nature of the functional impairments and improvements that occur in this task in rats. Whishaw [55] found that recovery of reaching ability in the contralesional forelimb is dependent upon whole-

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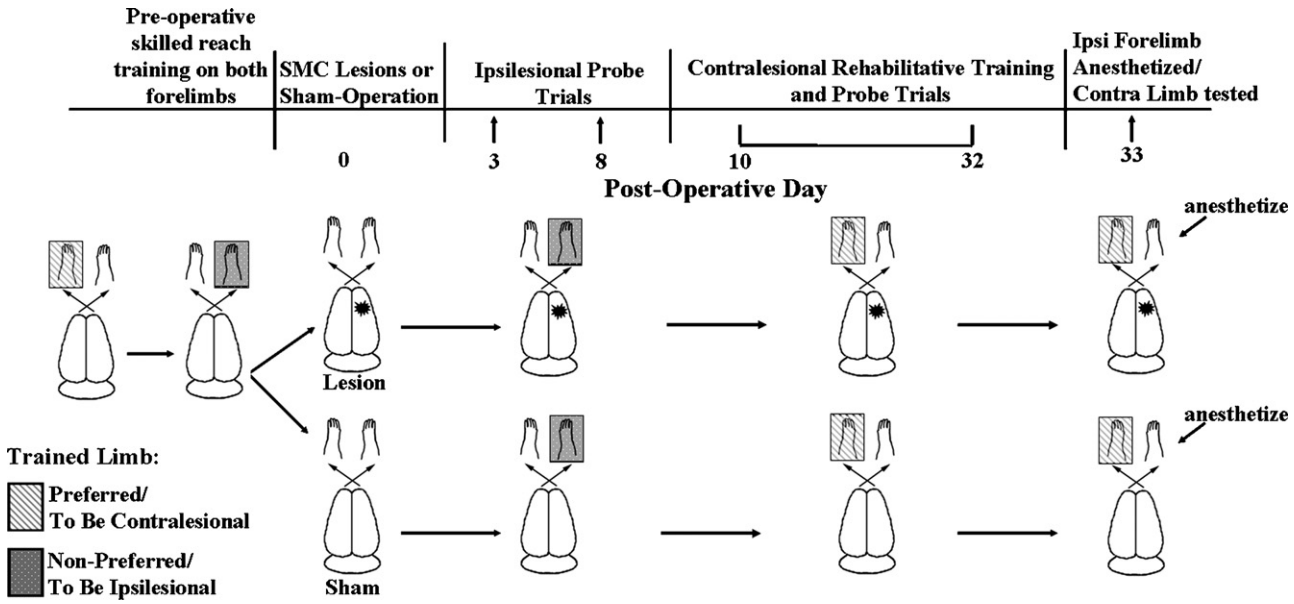

Fig. 1. Schematic diagram illustrating the experimental design and the time course of behavioral testing.

body compensatory changes and this includes compensatory ways of using the ipsilesional forelimb to assist in movements of the impaired forelimb. However, it is unknown whether compensation with the ipsilesional forelimb is a necessary chronic contributor to improvements in reaching performance with the contralesional forelimb. Furthermore, recent findings in humans suggest that sensory and motor function of one hand can be improved by ischemic nerve block of the opposite hand [48,50]. This effect is thought to be due to modulation of interhemispheric inhibition and it points to a potential target for therapeutic interventions [49], but it is has not been established to occur in rats. Thus, one purpose of the present study was to test whether partially recovered reaching performance with the contralesional forelimb after unilateral SMC lesions is enhanced or impaired by peripheral anesthetization of the ipsilesional limb.

Another purpose of the present study was to sensitively analyze bilateral changes in reaching performance after unilateral SMC lesions. Focal SMC lesions can *enhance* skilled reaching in a task that animals learn to perform with the ipsilesional forelimb after the lesion compared to intact animals learning the same task [5,10,22,29]. This effect co-exists with subtle ipsilesional abnormalities in the movements used for reaching [23] and may be linked to neuronal growth promoting effects of denervation and enhanced excitability in the contralesional motor cortex [3,5,10,22,23,29]. In humans, transient virtual lesions of the motor cortex created using repetitive transcranial magnetic stimulation also enhance the performance of a motor task with the ipsilesional hand [27,47]. However, Gonzalez et al. [18] found reductions in skilled reaching success rates in the forelimb ipsilateral to relatively large unilateral frontal cortex lesions using a task that the animals had acquired prior to the injury (see also [33,55]). It may be that enhancement in ipsilesional forelimb reaching function can only be detected after small lesions that do not produce very major ipsilesional deficits [23]. It is also possible that lesion-induced facilitation in skill learning does not generalize to performance of skills that were well learned prior to the injury, even after relatively small cortical lesions. This latter possibility was tested in the present study.

In this study, rats were trained to be proficient in a unimanual skilled reaching with each forelimb. Endothelin-1, a vasoconstricting peptide, was then used to induce ischemic SMC lesions of the forelimb representation region of one hemisphere. Quantitative and qualitative changes in reaching performance were then assessed in each forelimb. To promote improvements in the reaching function of the contralesional forelimb, rats received a period of rehabilitative reach training of this limb, an approach that has previously been found to be effective in improving function [7,13,37,42] and promoting reorganization of movement representations in the peri-lesion cortex [28,36]. The ipsilesional forelimb was then anesthetized to test its effects on reaching performance of the impaired forelimb. Fig. 1 summarizes the experimental design.

2. Materials and methods

2.1. Animals

Seventeen male Long–Evans hooded rats were used in this study. Rats were obtained at 1 month of age from a breeding colony of the Animal Resources Center at the University of Texas at Austin ($n=7$) or from Charles Rivers Laboratories ($n=10$). Rats were housed in clear Plexiglas cages in pairs or triplets, were on a 12:12 h light:dark cycle and were given water *ad libitum*. Rats were ~100 days old at the onset of training. Beginning a few days before training, rats were restricted to 14–15 grams of chow per animal given at the end of each day to ensure that they were not sated at the time of the reach training. Animals were assigned to two groups: one group received unilateral ischemic lesions in the forelimb representation area of the SMC ($n=9$) and the second group received a sham operation ($n=8$). The mean ± S.E.M. weekly weight change during the experiment was $-0.27 \pm 0.33\%$ in the lesion group and $1.58 \pm 1.52\%$ in the sham group. Assignments were random with the exception that groups were matched as closely as possible for pre-operative