

Electrical stimulation of motor cortex in the uninjured hemisphere after chronic unilateral injury promotes recovery of skilled locomotion through ipsilateral control

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Partial injury to the corticospinal tract (CST) causes sprouting of intact axons at their targets, and this sprouting correlates with functional improvement. Electrical stimulation of motor cortex augments sprouting of intact CST axons and promotes functional recovery when applied soon after injury. We hypothesized that electrical stimulation of motor cortex in the intact hemisphere after chronic lesion of the CST in the other hemisphere would restore function through ipsilateral control. To test motor skill, rats were trained and tested to walk on a horizontal ladder with irregularly spaced rungs. Eight weeks after injury, produced by pyramidal tract transection, half of the rats received forelimb motor cortex stimulation of the intact hemisphere. Rats with injury and stimulation had significantly improved forelimb control compared to rats with injury alone and achieved a level of proficiency similar to uninjured rats. To test whether recovery of forelimb function was due to ipsilateral control, we selectively inactivated the stimulated motor cortex using the GABA agonist muscimol. The dose of muscimol we used produces strong contralateral but no ipsilateral impairments in naïve rats. In rats with injury and stimulation, but not those with injury alone, inactivation caused worsening of forelimb function; the initial deficit was reinstated. These results demonstrate that electrical stimulation can promote recovery of motor function when applied late after injury and that motor control can be exerted from the ipsilateral motor cortex. These results suggest that the uninjured motor cortex could be targeted for brain stimulation in people with large unilateral CST lesions.

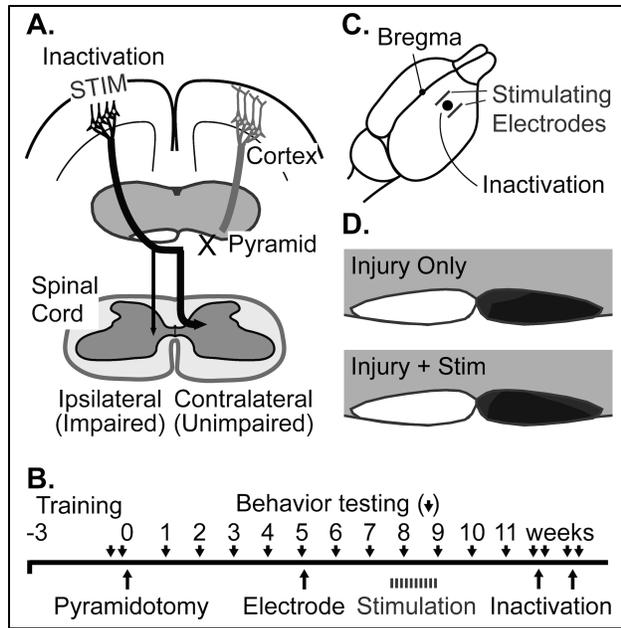


Figure 1. Methods. 1A. Experimental schema. Eight weeks after CST lesion (X), the motor cortex (M1) in the uninjured hemisphere is electrically stimulated (STIM). M1 in the uninjured hemisphere was inactivated at the end of the efficacy trial. 1B. Experimental timeline. 1C. Position of stimulating electrodes and inactivation. Electrode wires were bent into an ‘L’ shape and run parallel over the forelimb area of the motor cortex. The anterior–posterior position of the angle of the L-shaped electrodes was in line with bregma, and the lateral positions were 2 mm and 3.5 mm, respectively. The electrodes extended anterior from bregma to 4 mm anterior to bregma, which covers the caudal forelimb area of M1. D. Pyramid lesions. The injury site was examined with myelin-stained cross sections through the lesion site. Select lesions were verified with PKC γ staining of the CST below the lesion. Lesions of individual rats are represented by light gray profiles over the white pyramid. Four animals in each group had complete lesions, and one animal in each group had minor sparing.

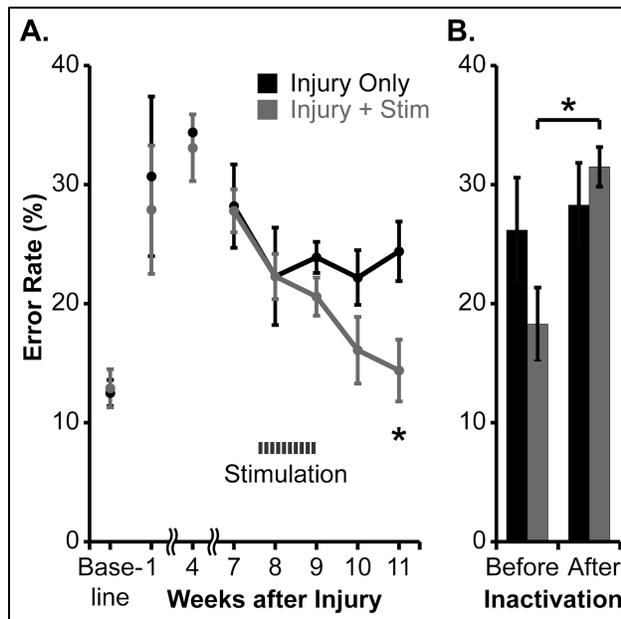


Figure 2. M1 electrical stimulation after chronic injury improves locomotor skill through ipsilateral control. 2A. Recovery of skilled walking in the impaired forelimb. Rats were trained to cross a horizontal ladder with irregularly spaced rungs until they achieved a baseline error rate below 20%. After CST lesion, the error rates increased in the affected forelimb to a similar degree in rats with injury only (black) and rats with injury and stimulation (gray; $n=5$ per group). Until the start of stimulation (weeks 1-7) the error rates in the two groups were not different. After the start of stimulation (weeks 8-11) the groups differed significantly (repeated measures ANOVA, with Bonferroni post hoc correction, asterisk, $p=0.03$). 2B. Loss of behavioral recovery with ipsilateral motor cortex inactivation. A subset of rats ($n=3$ per group) was subjected to motor cortex inactivation ($n=6$ inactivations per group). The error rate in the initially impaired forelimb ipsilateral to stimulation is plotted before and after inactivation. In the rats with injury only, inactivation did not change the error rate. In rats with injury and stimulation, inactivation of the stimulated motor cortex reinstated their initial deficit (paired t -test, $p=0.01$), demonstrating that their improved motor performance with electrical stimulation was due to control from the ipsilateral and stimulated motor cortex.