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NEURAL REPAIR

Getting back on your hindlimbs

> volitional and adaptable locomotion had been restored and maintained even in the absence of ongoing stimulation

Around half of individuals with spinal cord injury (SCI) will experience complete loss of volitional movement below the site of injury. At most SCI sites, however, a small proportion of spinal nerve fibres remain intact, but are insufficient to enable movement. Asboth et al. now show that in a rodent model of severe SCI, a combination of electrochemical activation of lumbar motor circuits and gravity-assisted physical training results in neural reorganization that restores volitional locomotion.

The authors induced severe spinal contusions in the thoracic region of rodent spinal cord, which resulted in severance of more than 90% of white matter tracts and hindlimb paralysis. Rodents were allowed to recover for 1 week before therapeutic intervention.

In contused rats, the authors used electrochemical treatment (consisting of application of serotonin receptor agonists and epidural electrical stimulation of lumbar spinal segments) to induce automatic locomotion. To encourage voluntary hindlimb movement, the authors placed rats in an adjustable robotic harness that supported their body weight against gravity and allowed bipedal locomotion on a treadmill or other surface (gravity-assisted system). When combined with electrochemical neuromodulation, training on the gravity-assisted system for 9 weeks resulted in contused rats regaining weight-bearing locomotion and maintenance of balance; crucially, this was maintained, albeit to a lesser extent, in the absence of electrochemical stimulation. Rats subject to electrochemical treatment without training did not recover locomotion. Moreover, unlike untrained rats, trained rats receiving electrochemical neuromodulation could complete a staircase-climbing task, suggesting that volitional and adaptable locomotion had been restored and maintained even in the absence of ongoing stimulation.

The authors then investigated the supraspinal pathway driving this locomotion in contused mice. Although there were no intact projections from the motor cortex across the injury site, optogenetic activation of contralateral motor cortex pyramidal cells, combined with pharmacological activation of lumbar circuits, could still produce weight-bearing (volitional) locomotion. Therefore, another descending pathway must be driving locomotion in these mice.

Retrograde neuroanatomical tracing from the lumbar spine to the brain in mice 1 week after contusion revealed that the most abundant neurons to bridge the contusion site were glutamatergic neurons from the ventral gigantocellular reticular nuclei (vGi). Selective silencing of these neurons in contused mice abolished locomotion induced by optogenetic stimulation of motor cortex with lumbar neuromodulation, suggesting that the motor cortex might signal via vGi to drive volitional locomotion in these mice.

To investigate whether SCI triggers reorganization of this motor cortex–vGi–spinal circuit, the authors examined selectively labelled leg motor cortex–vGi projection neurons in contused and trained rats. In contrast to untrained or unlesioned rats, the density of these fibres was doubled, and these axons formed numerous synaptic contacts with vGi neurons projecting to lumbar spinal regions. Further remodelling was found in the spinal cord, which showed tripling of the density of vGi projection neurons below the injury site. These projections formed close associations with spinal neurons that amplify descending motor input. vGi projection neurons were found to have sprouted in ventral laminas, which contain neurons crucial for locomotion.

Temporary inactivation of vGi neurons that projected across the injury site reversibly abolished volitional locomotion in contused, trained rats. That volitional locomotion can be switched on and off by inactivation and reactivation of the vGi neurons indicates that the reorganized vGi projections play a crucial role in the recovery of volitional locomotion.

Together, these findings suggest that physical rehabilitation, when combined with electrochemical stimulation of lumbar locomotor circuits, results in remodelling of rodent CNS locomotor circuits that promote functional recovery after SCI, and might have important implications for rehabilitation following SCI in humans

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