Neuroscience Letters 539 (2013) 77–81

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Training following unilateral cervical spinal cord injury in rats affects the contralesional forelimb

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HIGHLIGHTS

- Training the injured side after spinal cord injury influences the other side.
- Training two tasks can affect the performance of each other.
- Rehab training should consider uninjured parts of the nervous system.

ARTICLE INFO

Article history:
Received 26 November 2012
Received in revised form 2 January 2013
Accepted 19 January 2013

Keywords:
Single pellet reaching
Horizontal ladder
Incomplete spinal cord injury
Rehabilitative training
Task-specific recovery

ABSTRACT

Rehabilitative training is an essential component of current therapeutic strategies for spinal cord injured individuals. However, there are still various open questions that need to be answered in order to optimize training strategies. For example, why can animals trained in a single task perform worse compared to untrained animals when tested in untrained tasks. Such results suggest a potential competition among motor tasks over spared neuronal circuitry. Whether training induced competition for neuronal circuitry may also exist between injured and spared circuitries of the ipsi- and contralesional extremity is currently unknown. Here we investigated whether training restricted to the frontlimb ipsilateral to cervical spinal injury (IF) can impact motor performance of the contralesional frontlimb (CF) in a rat model of cervical SCI. We compared CF performance following general motor training of all limbs (horizontal ladder), following specific training of the IF (pellet reaching), as well as following a combination of both training paradigms. Our findings indicate that adding ipsilateral side-specific training to general training can negatively impact performance of the CF, without resulting in any improvement of performance of the IF. In conclusion, our results emphasize that important decisions have to be made when designing rehabilitative training strategies, ideally taking into account more than the primarily affected extremity.

1. Introduction

Currently, rehabilitative training is the most widely used and likely the most effective strategy to improve motor recovery in individuals with spinal cord injury (SCI) [10]. Yet, many important details as to how the effectiveness of training protocols can be maximized remain poorly studied. While the limited translation of improvements after task-specific training into untrained tasks in animal models of SCI as well as in affected humans has received increasing attention [6,8,11], recent reports from animal models suggest that task-specific training may even negatively influence performance in untrained tasks [4]. For example, cats trained to walk on a treadmill did not reach a similar performance level as control animals in a standing test, whereas cats trained to stand performed considerably poorer at walking [2]. Further evidence that task-specific training may adversely impact performance in untrained tasks comes from rat models of incomplete cervical SCI [5]. Here, cervically injured rats trained in a reaching task performed worse at walking across a horizontal ladder than untrained animals.

The observation that training induced improvements in task-specific motor recovery often come at the cost of performance in untrained tasks suggests that training induces a task-specific

Abbreviations: CF, contralesional frontlimb; DT, double training group (trained in reaching as well as on the horizontal ladder); HL, horizontal ladder training group; IF, ipsilesional frontlimb; p.i., post-injury; s.c., subcutaneous; SCI, spinal cord injury; SP, single pellet reaching training group.

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http://dx.doi.org/10.1016/j.neulet.2013.01.043

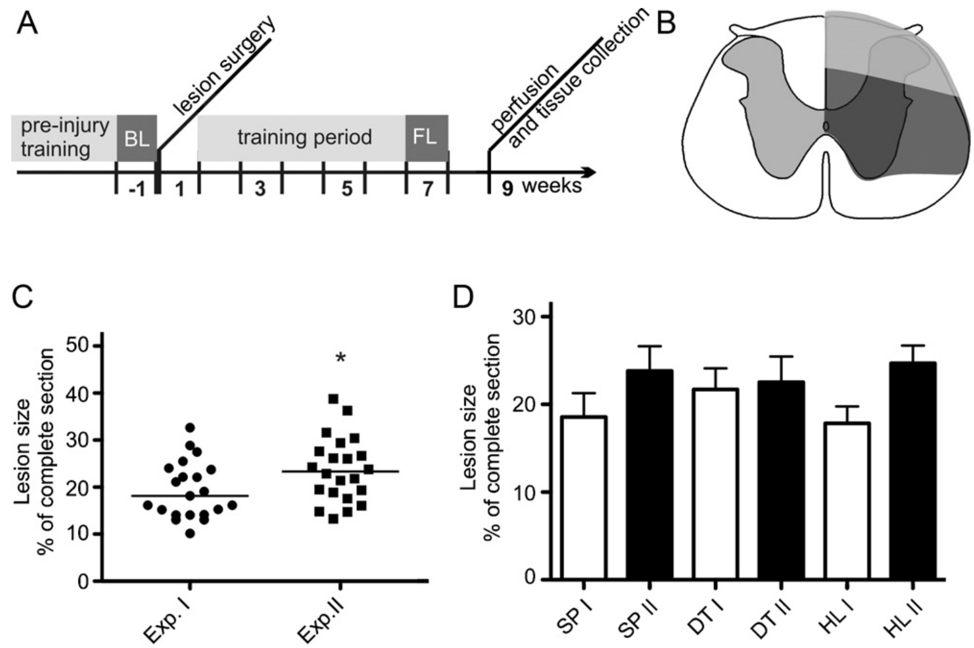

Fig. 1. Experimental flow and lesion analysis. (A) Once rats learned how to perform the single pellet reaching task, they were assessed in this task as well as on the horizontal ladder to yield pre-injury baseline levels (BL). Rehabilitative training, specific to training group, started at day seven following a cervical dorsalquadrant lesion. Animals were trained for five weeks, followed by final testing (FL) and perfusion. (B) Smallest (light gray) and largest (dark gray) lesion extent are indicated in a schematic spinal cord cross section. (C) Overall, lesion sizes (as a percentage of the complete spinal cross section) in the second experiment were significantly larger than lesion sizes in the first experiment ($p = 0.034$, horizontal lines mark group median). (D) Lesion sizes do not significantly differ among training groups (white bars: experiment I; black bars: experiment II). Therefore, we can confidently attribute group differences in recovery to the training regime. SP: single pellet; DT: double training; HL: horizontal ladder. Error bars indicate standard error of the mean, asterisks indicates $p < 0.05$.

rewiring of neural circuits in the central nervous system. If training leads to the commitment of neural networks to produce a certain functional outcome, the circuitry that remains available for untrained tasks may be limited. Based on this concept, how much should training be focused on the circuitry primarily affected by an incomplete injury? This question should be considered in a bigger picture than just the affected limb(s). The idea that neuronal circuitry not directly involved in the primary injury can be affected by an injury to the central nervous system has recently been described [13].

After incomplete SCI, it is conceivable that spared circuitry may mediate compensatory movements to increase the overall functional versatility in every-day life. Considering the emerging evidence for negative aspects of task-specific rewiring after SCI, a critical view on a rehabilitation concept focused solely on the affected extremity may be warranted for individuals with incomplete cervical SCI. Here, we address the question whether training involving the contralesional frontlimb (CF) may be beneficial in overall performance and how training restricted to the primarily affected frontlimb (ipsilesional frontlimb = IF) following unilateral incomplete SCI can impact performance of the CF. This will contribute to defining interactions between training and spared neuronal circuitry on a behavioral level. Knowledge of these interactions will be crucial for designing an optimized training regime to achieve maximal motor function in the clinical setting, taking into account both extremities.

2. Materials and methods

2.1. Animals and experimental groups

Forty-seven female Lewis rats weighing 180–200 g were group housed and kept at a 12 h:12 h light/dark cycle. They were fed ad libitum except for the day preceding a reaching session when food was reduced to 10 g/rat for all rats across all experimental groups. Weights were closely monitored to ensure weight stability over time. Forty-eight hours after lesion surgery, forelimb deficits on the side of the lesion were subjectively categorized upon close observation of overground walking (light: paw placement deficits subtle; moderate: obvious paw placement deficits, involving the wrist joint; severe: forelimb placement deficits involving the forearm and affecting walking). Based on this score, animals were assigned to three groups to ensure equal distribution of deficit severities. One group ($n = 16$) received post-injury (p.i.) training in single pellet reaching (SP group), a second group ($n = 16$) received p.i. training in the horizontal ladder task (HL group) and a third group ($n = 15$) received training in both tasks (double task group DT). The study includes two identically designed experiments with 24 and 23 animals each to allow for adequate training intensity/duration (see design and timeline in Fig. 1A). All experimental procedures were approved by the University of Alberta Health Science Animal Care and Use Committee.

2.2. Spinal cord injury

All animals received a cervical dorsalquadrant spinal lesion unilateral to their preferred paw (as established during pre-injury reaching training). Once rats were anesthetized with isoflurane, their body temperature was maintained at 37 °C with a heating blanket throughout the surgery. After exposure of the spinal cord between C3 and C4, a custom-made microblade was lowered 1 mm into the spinal cord at the midline and then moved laterally to create a unilateral dorsalquadrant lesion. Finally, muscle layers were sutured and the skin was closed with staples. Post-operatively, hydration was restored by saline injections and pain was managed by s.c. injections of buprenorphine (0.05 mg/kg, Temgesic, Schering-Plough, Kirkland, QC, Canada). Animals were kept on a heating blanket until fully awake.