Review

Passive cycling in neurorehabilitation after spinal cord injury: A review

Raffaele Nardone^{1,2,3}, Andrea Orioli², Stefan Golaszewski¹, Francesco Brigo^{2,4}, Luca Sebastianelli ⁵, Yvonne Höller ¹, Vanessa Frey^{1,3}, Eugen Trinka^{1,3}

¹Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria,

²Department of Neurology, Franz Tappeiner Hospital, Merano, Italy, ³Spinal Cord Injury and Tissue Regeneration Center, Paracelsus Medical University, Salzburg, Austria, ⁴Department of Neurological and Movement Sciences. Section of Clinical Neurology, University of Verona, Italy, ⁵Department of Neurorehabilitation, Hospital of Vipiteno, Italy

Context/Objective: Passive cycling (PC) may represent a potential alternative neurorehabilitation program for patients who are too weak or medically unstable to repeatedly practice active movements. We review here the most important animal and human studies addressing PC after spinal cord injury (SCI).

Methods: A MEDLINE search was performed using following terms: “passive”, “cycling”, “pedaling”, “pedalling”, “spinal cord injury”.

Results: Experimental studies revealed that PC modulated spinal reflex and reduced spasticity. PC also reduced autonomic dysreflexia and elicited cardio-protective effects. Increased levels of mRNA for brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor and neurotrophin-4 were found. In contrast, human studies failed to show an effect of PC on spasticity reduction and did not support its application for prevention of cardiovascular disease-related secondary complications.

Conclusion: Available evidence to support the use of PC as standard treatment in patients with SCI is still rather limited. Since it is conceivable that PC motion could elicit sensory inputs to activate cortical structures and induce cortical plasticity changes leading to improved lower limb motor performance, further carefully designed prospective studies in subjects with SCI are needed.

Keywords: Spinal cord injury, Passive, Cycling, Exercise.

Introduction

Traumatic spinal cord injury (SCI) disrupts ascending and descending pathways that carry information between the brain and the spinal, leading to severe impairments of motor, sensory and autonomic function at and below the site of injury.¹ However, the central nervous system (CNS) is capable of significant plasticity after SCI,^{2,3} and rehabilitative interventions after neural injury affect this plasticity at different levels. Rehabilitation strategies focus on influencing CNS plasticity to regain function rather than on repairing lost connections.^{4,5} Cortical map plasticity changes after somatosensory deafferentation can also be induced by increasing the activity of corresponding cortical areas through enhanced sensory experience.⁶

Moreover, investigations in rat models^{7,8} and in patients with incomplete SCI^{9–12} revealed that cortical reorganization and functional recovery can be promoted by training the non-affected portions of the body or by doing exercise therapies applied to the affected body in order to improve the residual functions below the level of the lesion. The mechanisms mediating this recovery are not fully understood, but activity-dependent plasticity is likely to play a major role.¹³ On the other hand, sensory inflow originating mostly from large diameter afferents (Ia fibers) plays an important role in inducing essential functional and morphological plastic changes, both in the developmental stages of the CNS and in adulthood.¹⁴ In fact, the pattern of sensory inflow produces changes in synaptic efficacy between the Ia afferents and the alpha motoneurons.

Cycling requires coordinated lower limb muscle activities similar to those necessary for ambulation.

Correspondence to: Raffaele Nardone, Department of Neurology – “F. Tappeiner” Hospital – Merano/o, Via Rossini, 5, 39012 Merano (BZ) – Italy. E-mail address: raffaele.nardone@asbmeran-o.it

Indeed, during cycling exercise agonist and antagonist muscles are contracted reciprocally and in a pattern similar to that required for walking.¹⁵

However, for patients who are too weak or medically unstable to repeatedly practice active movements, passive exercise, and in particular passive cycling (PC), may represent a potential alternative program.

We review here the most important studies published in the field of PC and rehabilitation in subjects with SCI.

Methods

A comprehensive review of computerized literature databases and searches to find unpublished trials were performed to minimize publication bias.

The MEDLINE, accessed by Pubmed (1966 – November 2015) and EMBASE (1980–November 2015) electronic databases were searched using following free terms and medical subject headings (MeSH) combined in multiple search strategies: “passive”, “cycling”, “pedaling”, “pedalling”, “spinal cord injury”.

The search was limited to studies written in English. Full-text articles were retrieved for the selected titles, and reference lists of the retrieved articles were searched for additional publications. In case of missing or incomplete data, principal investigators of included trials were contacted and additional information requested. Two review authors (YH and FB) screened the titles and abstracts of the initially identified studies to determine if they satisfied the selection criteria. The two reviewers independently assessed the methodological quality of each study and risk of bias, focusing on blinding and other potential sources of bias. Any disagreement was resolved through consensus. The search strategy described above yielded 35 results. Only original articles (and not single case reports, letters or review articles) reporting data on studies using than that of PC in subjects with SCI were considered eligible for inclusion. Therefore, 18 papers were provisionally selected and contributed to this review: the earliest was published in 1999 and the most recent in 2015. A flow-chart (Fig. 1) illustrates the selection/inclusion process.

Non-human experimental studies

Several studies have assessed the effects of PC on measures of locomotor outcome, electrophysiological measures of spasticity, such as the H-reflex, the extensor monosynaptic reflex (MSR) and the stretch reflex (SR), or changes in motoneuron excitability in experimental animal models undergoing SCI. Moreover, the effects of PC on autonomic dysreflexia (AD), cardiometabolic responses (such as left ventricular dimensions, myocardial contractility and collagen deposition), gene

expression of neurotrophic factors, and myofiber size and composition have been investigated.

In some studies, the combination of PC with other treatment options or drugs (modafinil, quipazine) has been evaluated.

The effects of hind-limb PC on AD have been investigated in forty-five male Wistar rats with SCI at level T3. Hind-limb PC reduces in the rats the severity of AD, as measured by means of pressor response to colorectal distension, and this effect is correlated with changes in primary afferent morphology, while effects on the peripheral vasculature were rather limited, as evaluated by means of in vitro myography assessments of the superior mesenteric artery.¹²

By using the same experimental model, West *et al.* also investigated the cardio-metabolic responses to SCI to determine whether hind-limb PC elicits a cardio-protective effect.¹⁶ After SCI, rats exhibited a rapid and sustained reduction in left ventricular dimensions and function that manifested as reduced contractility, increased myocardial collagen deposition, and upregulated transforming growth factor beta-1 (TGFβ1) and mothers against decapentaplegic homolog 3 (Smad3) mRNA. For the rats that received hind-limb PC, the initial reduction in left ventricular dimensions and function at day 7 post-SCI were completely reversed; moreover, GFβ1 and Smad3 were down-regulated. Conversely, myocardial contractility and collagen deposition remained unchanged.

In another study in adult spinalized rats, the combination of PC exercise, a cellular graft of neural and glial restricted precursor (NRP/GRP) cells, and chronic treatment with quipazine (a piperazine drug used in scientific research) on behavioral outcomes was examined and compared with the individual treatments.¹⁷ The use of quipazine in combination with PC lead to a greater functional recovery than PC alone. In fact, the rats that underwent the combination therapy were able to perform uncoordinated weight-supported stepping without a body weight support system and were capable of supporting their own weight in stance during open field locomotion testing.

A recent study aimed to characterize the flexor and extensor MSR response pre- and post the application of quipazine in chronic complete spinally transected rats that either underwent daily PC for 3 months or did not receive PC.¹⁸ The extensor MSR showed a hyperreflexive response to afferent stimuli and did not respond to quipazine injection. After daily PC, an attenuated hyperexcitability was observed, and the MSR amplitude significantly increased following quipazine injection. For both chronic spinal transection groups, the flexor MSR amplitudes were not altered following

Figure 1 Flow-chart showing the selection/inclusion process

quipazine injection, whereas in the control group, the flexor MSR amplitude increased significantly in response to quipazine.

In adult rats that received a low thoracic spinal transection and PC exercise for 1 or 4 weeks, the gene expression in the lumbar spinal cord as well as the specific response of motoneurons, intermediate gray and proprioceptive sensory neurons was examined to identify potential molecular processes involved in activity dependent plasticity after SCI.¹⁹ Following SCI, motoneurons and intermediate gray displayed small change in mRNA expression, but acute and prolonged exercise increased levels of mRNA for brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor and neurotrophin-4. In dorsal root ganglion neurons, mRNAs for neurotrophic factors and their receptors were largely unaffected by either injury or exercise, while caspase mRNA expression was increased by injury and decreased by exercise. Therefore, exercise affects expression of genes involved in plasticity and apoptosis in a cell specific manner.

In another study, a combined neurophysiological and novel biomechanical approach was used to assess the effects of passive exercise and the administration of the wakefulness-promoting agent modafinil on spasticity following complete T-10 transection in rats.²⁰ Animals were divided into 3 groups and provided daily PC exercise, oral modafinil, or no intervention. After 6 weeks, animals were tested for wind-up of the SR during repeated dorsiflexion stretches of the ankle. H-reflexes were tested in a subset of animals. Both torque and

gastrocnemius electromyography showed evidence of SR wind-up in the transection only group that was significantly different from both treatment groups; H-reflex frequency dependent depression was also restored to normal levels in both treatment groups. The results provide experimental support for the efficacy of PC exercise and modafinil in the treatment of spasticity in this model.

Loss of descending inhibition due to a spinal cord transection reduces H-reflex habituation at a relatively low frequency (10 Hz). PC exercise of the affected hind limbs led to a restoration of a normal pattern of habituation in the reflex activity, thus suggesting that repetitive passive stretching of the muscles in spinalized animals and the accompanying stimulation of Group I and II proprioceptive fibers has modulatory effects on spinal cord reflexes after SCI. To verify this hypothesis, pyridoxine neurotoxicity, preferentially affecting large DRG, has been induced in intact and spinalized rats who were subjected to PC exercise.²¹ Pyridoxine treatment completely eliminated the H-reflex in intact animals, while transection paired with pyridoxine treatment led to a reduction of the frequency-dependent habituation of the H-reflex that was not affected by exercise. These findings indicate that normal Group I and II afferent input is critical to achieve exercise-based reversal of hyperreflexia after SCI.

Beaumont *et al.* examined the electrophysiological properties of rat lumbar motoneurons following spinal cord transection and the effects of two interventions that are known to markedly attenuate the associated

hindlimb muscle atrophy.²² Adult rats receiving a complete thoracic spinal cord transection (T-10) were divided into three groups receiving no further treatment, PC exercise for 5 days/week, or acute transplantation of fetal spinal cord tissue. Transection resulted to in a significant change in the rhythmic firing patterns of motoneurons in response to injected currents as well as a decrease in the resting membrane potential and spike trigger level. Transplants of fetal tissue and PC each attenuated these changes, and PC had a stronger effect on maintenance of motoneuron properties. Even if the exact mechanisms of the distinct treatments are still not completely understood, these changes in motoneuron excitability are in part consistent with influences on ion conductance at or near the initial segment of the axon. These results may support a therapeutic role for passive limb manipulation and transplant of stem cells in slowing the deleterious responses of motoneurons to SCI.

Another study was carried out to determine if an intraspinal transplant (Trpl) of fetal spinal cord tissue or hind limb exercise (daily PC) affected the changes in myosin heavy chain (MyHC) composition or myofiber size that occur following a complete transection of the lower thoracic spinal cord of the adult rat.²³ Transection led to atrophy of type I myofibers to approximately 50% of normal size, whereas myofibers were significantly larger after exercise (of control) and in Trpl recipients, at 74% and 77% of control size, respectively. Although neither strategy shifted the MyHC profile to the control values, both interventions influenced the extent of atrophy observed after spinalization.

Table 1 illustrates the studies examining the effects of PC on experimental SCI.

Human experimental studies

Several human experimental studies have aimed at exploring the therapeutic effects of PC on spasticity or bone mineral density, as well as the cardiorespiratory/vascular effects, after traumatic SCI. Some studies have examined the muscle biopsy specimens in subjects with SCI.

In other studies, a comparison between the outcome of a PC program and other cycling interventions, such as functional electrical stimulation (FES) has been performed.

The effects of PC exercise on myosin heavy chain (MHC) isoform and ubiquitin (UBI) protease mRNA expression in patients with SCI have been investigated.

PC increases the expression of fast MHC isoforms and concomitantly decreases proteolytic activity

associated with muscle degradation, thus possibly helping to ameliorate muscle atrophy in patients with SCI.²⁴

In another study, the same research group aimed to determine the effects of PC exercise on UBI, heat shock protein 72 (HSP-72) mRNA, protein expression, and myofibrillar protein content in subjects with SCI. Total body mass and muscle biopsies were obtained pre- and posttraining. PC exercise in subjects with SCI increased myofibrillar protein content, possibly because of up-regulation of the expression of HSP-72 with concomitant down-regulation in the expression of UBI.²⁵

To investigate the influence of rhythmic passive movements of the legs on the reduction of spasticity after SCI, a total of 10 subjects with motor complete SCI were treated with a cycling device for 30 minutes.²⁶ Before and after PC, their spasticity was tested with an isokinetic dynamometer. The subjects were tested one week later in the same procedure with a 30-minute break instead of the PC. Although it was not possible to show an effect of PC on spasticity reduction, six out of 10 of the subjects reported a subjective reduction of their spasticity after PC. This positive effect might be attributed to a reduced spasticity in the trunk and/or to the attention the subjects perceived during the intervention.

Since passive exercise is thought to enhance blood flow via mechanical pump effects or reflex activation, Ter Woerds *et al.* assessed the effects of PC on the arterial circulation in subjects with SCI.²⁷ The results of their study demonstrate that PC, as well as passive other leg movements, did not alter the arterial peripheral circulation in control or subjects with SCI. Therefore, these findings did not support the use of passive exercise for the prevention of cardiovascular disease-related secondary complications.

Children with SCI are at risk for musculoskeletal and cardiovascular complications. Stationary cycling using FES or passive motion has been suggested to address these complications. A small case series has been published to report the outcomes of a 6-month at-home cycling program for 4 children with SCI: two children cycled with FES and the other 2 cycled passively at home for 1 hour, 3 times per week.²⁸ The 2 children cycling with FES and 1 child cycling passively exhibited improved bone mineral density, muscle volume, stimulated quadriceps strength, and lowered resting heart rate. For the second child cycling passively, few changes were observed. The authors concluded that cycling with or without FES may have positive health benefits and represents a practical home exercise option for children with SCI.

Table 1 Studies on the effects of passive cycling in animals

References	Animal species and injury level	Measurement/Intervention	Outcomes/Endpoints	Effects
Houle <i>et al.</i> , 1999 ²³	Adult rats T10	Myofiber expression in the soleus muscle	Effects of Trpl of fetal spinal cord tissue or PC in MyHC or myofiber size	Typar IIa myofibers larger, myofiber size larger after both interventions
Raasch and Zajac, 1999 ¹⁵	Adult rats T3	Pressor response of colorectal distension	Effects of PC on autonomic dysreflexia	Changes in primary afferent morphology, no changes on peripheral vascularure
Beaumont <i>et al.</i> , 2004 ²²	Adult rats T10	Intracellular recording of motoneurons	Electrophysiological properties of motoneurons	Maintenance of motoneuron properties
Ollivier-Lanvin <i>et al.</i> , 2010 ²¹	Adult rats T10	Low-frequency habituation of the H-Reflex activity	Effects of H-reflex habituation	Restoration of normal pattern of inhibition
Garrison <i>et al.</i> , 2011 ²⁰	Adult rats T10	SR during ankle dorsiflexion H-Reflex	Effects of PC on spasticity	SR wind-up; restoration of H-reflex
Keeler <i>et al.</i> , 2012 ¹⁹	Adult rats T10	Gene expression, responses of motoneurons, intermediate gray and proprioceptive sensory neurons	Molecular processes involved in activity dependent plasticity	Increased levels of mRNA for BDNF, GDNF, and NT4, decreased capsase mRNA expression
Chopek <i>et al.</i> , 2014 ¹⁸	Adult rats T3	Extensor and flexor MSR	Effects of PC on spinal excitability	Attenuated excitability Extensor MSR
Dugan and Shumsky, 2014 ¹⁷	Adult rats T10	Weight-supported stepping	Effects of PC, cellular graft of NRP/GRP cells, quipazine treatment on locomotion	Combination therapy effective Individual treatments non-effective
West <i>et al.</i> , 2014 ¹⁶	Adult rats T3	Left ventricular dimension Myocardial contractility Collagene deposition TGFβ1 and Smad3 level	Cardio-protective effects of PC	Reduction of the left ventricular dimension and function. Down regulation of TGFβ1 and Smad3 Myocardial contractility and collagene deposition unchanged

MyHC = myosin heavy chain; Trpl = intraspinal transplant; SR = stretch reflex; BDNF = brain-derived neurotrophic factor; GDNF = glial cell line-derived neurotrophic factor; NT4 = neurotrophin-4; MSR = monosynaptic reflex; NRP/GRP = neural and glial restricted precursor; TGFβ1 = transforming growth factor beta-1; Smad3 = decapentaplegic homolog 3

Krause *et al.* performed a comparison of cycling interventions to reduce spastic muscle tone increase in adult subjects with SCI.²⁹ Five patients with SCI were enrolled in a crossover study in which the lower limbs were stimulated by FES to induce leg-cycling movements and were passively moved by an ergometer machine. Patients sat in a comfortable chair fastened to the ergometer while FES was done to induce leg cycling (active session). During the PC session the ergometer moved their legs for the same period of time at the same velocity and frequency. The averaged data of the relaxation index of the Wartenberg pendulum test increased after FES by approximately 68% and only of 12% after the passive movement training; peak velocity of the pendulum test also increased after FES by approximately 50%, while it was nearly unchanged after the passive intervention. Similar results were obtained with the peak velocity and the modified Ashworth Scale.

Subsequently, the cardiorespiratory/vascular effects of cycling with and without FES were examined in

children with SCI. Thirty children ages 5 to 13 years with SCI levels from C4 to T11 were randomly assigned to 1 of 3 groups: FES leg cycling exercise, PC, or a non-cycling control group receiving electrical stimulation therapy. The FES cycling group showed a significant improvement in oxygen uptake compared with the PC group, whereas electrical stimulation alone led to improvements in cholesterol levels.³⁰

In a later study, this research group using the same experimental design aimed to determine the effect of cycling, electrical stimulation, or both, on hip and knee bone mineral density (BMD) in children with SCI.³¹ The FES group exhibited increases in hip, distal femur and proximal tibia BMD of 32.4, 6.62 and 10.3%, respectively, while the PC group exhibited significant increases at the hip, but no change at the distal femur or proximal tibia. Cycling with and without electrical stimulation may be beneficial for skeletal health in pediatric SCI, but further research with a larger sample size is needed.

Further, the same researchers determined the effect of PC, electrical stimulation, or both, on thigh muscle volume and stimulated muscle strength in this population of children with SCI. Only children receiving either electrically stimulated exercise experienced changes in muscle size, stimulated strength, or both, which may decrease their risk of cardiovascular disease, insulin resistance, glucose intolerance, and type 2 diabetes.³²

Table 2 illustrates the studies examining the effects of PC on humans with SCI.

Discussion

The non-human and human experimental studies reviewed here have demonstrated that, among the activity-based interventions, hind-limb PC could have a positive influence on the spinal circuitry leading to functional improvement following a SCI.

Passive exercise below the level of the lesion may promote cortical reorganization after SCI, uncovering a brain-body interaction connecting the affected limbs and supraspinal structures, even in absence of sensorimotor spinal connections.³³

PC may thus represent a low-cost therapeutic intervention with demonstrable motor, sensory and cardiovascular benefits. The results illustrated in this review are consistent with the findings of other experimental studies, demonstrating that passive training after spinal cord transection is sufficient to increase the neural responsiveness of the deafferented hindpaw cortex to tactile stimuli delivered to the forepaw/forelimb under deep anesthesia.³³ The authors found that the level of proteins associated with plasticity, in particular BDNF and adenylyl cyclase type 1, increased in the somatosensory cortex of adult rats with complete thoracic transection that received passive hindlimb bike exercise compared to transected rats that received sham exercise. Electrophysiological techniques revealed that neurons in the deafferented hindlimb cortex increased their responsiveness to tactile stimuli delivered to the forelimb in transected animals that received PC exercise compared to transected animals that received sham exercise. Interestingly, a similar increased responsiveness of the hindpaw cortex to tactile stimuli delivered to the forepaw/forelimb has been observed by decreasing the depth of anesthesia.³⁴ Therefore, the exercise-dependent increase of neural responsiveness might be mediated not only by axonal sprouting,^{35,36} but also by the alteration of the dynamic equilibrium of dendritic spines and axonal boutons between interneurons and pyramidal neurons,^{37,38} which likely represents a compensatory mechanism to maintain the delicate cortical balance

between excitation and inhibition,³⁹ or even by the alteration of more subtle intrinsic properties of cortical neurons. Nonetheless, because the neurophysiological reorganization we observed in the deafferented hindlimb cortex was not layer-specific, a subcortical contribution to the cortical reorganization cannot be excluded.^{40–42}

It should also be considered that passive exercise can induce the systemic effects that are typical of active exercise, such as increases in cardiovascular fitness,⁴³ improved circulation,⁴⁴ and neuroendocrine changes.⁴⁵ These effects of exercise are thought to have a great impact on brain function,⁴⁶ because they contribute to stimulation of neurogenesis and to increase the levels of growth factors such as BDNF, thus promoting brain plasticity.^{47–49} These cardiovascular and neuroendocrine systemic effects can boost or simply accelerate the cascade of plasticity-related events that are already occurring in the deafferented somatosensory cortex after SCI.³³

Furthermore, PC exercise was able to elicit sensory inputs that have beneficial effects for functional recovery after stroke.^{50,51} Cycling motion itself can activate somatosensory receptors and generate ascending inputs to the central nervous system. In healthy subjects, as well as in stroke patients, proprioceptive inflow from upper limb movements can lead to increased activation in the sensorimotor cortex (SMC), supplementary motor area (SMA), premotor cortex (PMC), primary and secondary sensory cortex, with resultant improvement in motor performance.^{50–52} In fact, supraspinal neural structures are also known to affect the control of human locomotion.^{53,54} It is therefore conceivable that PC motion could elicit sensory inputs to activate cortical structures and produce cortical changes leading to improved lower limb motor performance.

A frequency-domain near-infrared spectroscopy (FD-NIRS) system was used in stroke patients to detect the hemodynamic changes resulting from neuronal activity during the pedaling exercise from the bilateral SMCs, SMAs, and PMCs.⁵⁵ The results showed that PC had a cortical activation pattern similar to that observed during active cycling without feedback but with a smaller intensity in the SMC of the unaffected hemisphere.

On the other hand, it should be considered that FES has been known to cause symptoms of autonomic dysreflexia.⁵⁶ The effect of functional neuromuscular stimulation (FNS) on muscle strength and endurance was studied in patients with long-standing complete SCI, and the energy demand of FNS-assisted walking was measured to be more than 60% of the maximal endurance capacity of this patient, thus partly explaining the low patients acceptance of FNS by patients.⁵⁷

Table 2 Studies on the effects of passive cycling in humans

References	Subjects		Injury level	ASIA	Measurement/Intervention	Outcomes/Endpoints	Effects
	No. M/F	A					
Willoughby <i>et al.</i> , 2000 ²⁴	8 5/3	28.7 ± 11	C6–T12	A,C	Antropometric measures and muscle biopsy	MHC and UBI mRNA expression	Increased expression of MHC isoforms
Willoughby <i>et al.</i> , 2002 ²⁵	7 4/3	28.2 ± 11.7	C6–T12	A	TBM and muscle biopsy	UBI, HSP-72, protein expression, Myofibrillar protein content	Increased myofibrillar protein content
Krause <i>et al.</i> , 2004 ²⁹	5 3/2	37–66	T3–T7	A	Ergometer machine	Muscle tone by means of MAS and pendulum test	Slight increase of the relaxation index
Kakebeeke <i>et al.</i> , 2005 ²⁶	10 9/1	23–60	C6–T10	A, B	Isokinetic dynamometer	Spasticity	Subjective reduction in spasticity
Ter Woerds <i>et al.</i> , 2006 ²⁷	8 8/0	21–49	T2–L1	A,B	Echo Doppler to measure leg blood flow, blood pressure, vascular resistance	Arterial circulation	No changes in arterial peripheral circulation
Johnston <i>et al.</i> , 2008 ²⁸	2 2/0	5 and 8	C7–T4	A,B,C	Bone mineral density, muscle volume, fasting lipid profile, heart rate, oxygen consumption	Risk for musculo-skeletal and cardiovascular complication	Few changes after PC alone
Johnston <i>et al.</i> , 2009 ³⁰	10 5/5	5–12	C4–T11	A	Oxygen uptake, resting heart rate, forced vital capacity, lipid profile	Cardiorespiratory/vascular effects	Improvement with FES when compared with PC
Johnston <i>et al.</i> , 2011 ³²	9 ?	5–13	C4–T11	A,B,C	MRI, computerized dynamometer	Muscle volume and strenght	No significant changes
Lauer <i>et al.</i> , 2011 ³¹	9 5/4	5–13	C7–T8	A,B,C	DXA	Hip and knee BMD	Increases at the hip, no changes distal femur or proximal tibia

M/F = male/female; A = age; ASIA = American Spinal Cord Injury Association Impairment Scale; MHC = myosin heavy chain, UBI = ubiquitin; HSP-72 = heat shock protein 72; TBM = Total bone mass; MAS = Modified Ashworth Scale; BMD = bone mineral density; FES = functional electrical stimulation; DXA = dual-energy X-ray absorptiometry.

However, so far only a few translational studies have been conducted in humans. Notably, severity and level of the injury, as well as outcome measures and endpoints are rather heterogeneous between the studies. In most of the studies PC failed to restore the sensorimotor and autonomic deficits. There is also little evidence that exercise can prevent muscle changes, bone loss and microarchitectural decay. Moreover, very few studies have addressed the question whether PC can improve leg blood flow.

It should be considered that all these studies have been conducted in rats, while experimental research in other primates is surprisingly lacking.

Overall, many experimental interventions in laboratory rodents have been shown to ameliorate the functional deficits caused by SCI, but as always, the challenge is to determine whether the interventions can be translated into useful clinical techniques in the clinical setting. There are important differences between clinical SCI in human patients and SCI in laboratory rodents related to the size of the spinal cord and

heterogeneity of injury severity. A further key issue is whether the significant difference in outcome observed in the laboratory studies will translate into a useful difference in clinical outcome. In the human studies also small sample size, lack of placebo or technical difficulties with "true" placebo, and lack of adequate control groups, might have contributed to this translational failure.

Conclusion

Strategies for rehabilitation can promote sensorimotor recovery after SCI by enhancing adaptive structural and functional plasticity while preventing maladaptive changes at multiple levels of the CNS. Experimental studies support the notion that the acquisition of motor abilities is extensively dependent on various sensory inputs generated by movement. Plastic changes induced by activity and sensory inflow occur both in the brain and spinal cord. Such plasticity inducing stimulation provides an attractive approach to promote changes in sensorimotor circuits that have

been degraded by SCI. An advantage of this neurorehabilitation treatment is that performing PC does not require any volitional motor control and can thus be initiated early after SCI. However, available evidence to support the use of PC as standard treatment in patients with SCI is still rather limited. The mechanisms by which passive exercise programs may lead to a functional improvement after SCI need to be better understood because they allow for the development of new and more effective therapeutic strategies. Understanding the mechanisms and sites of plasticity within spinal circuits is an important step to develop strategies for regaining motor function after SCI and other injuries to the CNS. In particular, a thorough investigation of the mechanisms underlying activity-dependent and sensory-inflow induced plastic changes is essential for the development of new methods that can be used to regain spinal cord function after injury.

Acknowledgements

This topic was discussed at the Spinal Cord Injury and Tissue Regeneration Summit held in Salzburg, Austria in November 2015.

ORCID

Luca Sebastianelli <http://orcid.org/0000-0001-6463-000X>

Yvonne Höller <http://orcid.org/0000-0002-1727-8557>

Disclaimer statements

Contributors None.

Funding None.

Conflict of interest None.

Ethics approval None.

References

- Dietz V, Curt A. Neurological aspects of spinal-cord repair: promises and challenges. *Lancet Neurol* 2006;5(8):688–94.
- Nardone R, Höller Y, Brigo F, Seidl M, Christova M, Bergmann J, et al. Functional brain reorganization after spinal cord injury: systematic review of animal and human studies. *Brain Res* 2013;1504:58–73.
- Moxon KA, Oliviero A, Aguilar J, Foffani G. Cortical reorganization after spinal cord injury: always for good? *Neuroscience* 2014;283:78–94.
- Schwab ME. Bridging the gap in spinal cord regeneration. *Nat Med* 1996;2(9):976–77.
- Thuret S, Moon LD, Gage FH. Therapeutic interventions after spinal cord injury. *Nat Rev Neurosci* 2006;7(8):628–43.
- Feldman DE, Brecht M. Map plasticity in somatosensory cortex. *Science* 2005;310(5749):810–5.
- Hutchinson KJ, Gomez-Pinilla F, Crowe MJ, Ying Z, Basso DM. Three exercise paradigms differentially improve sensory recovery after spinal cord contusion in rats. *Brain* 2004;127(Pt6):1403–14.
- Kao T, Shumsky JS, Knudsen EB, Murray M, Moxon KA. Functional role of exercise-induced cortical organization of sensorimotor cortex after spinal transection. *J Neurophysiol* 2011;106(5):2662–74.
- Thomas SL, Gorassini MA. Increases in corticospinal tract function by treadmill training after incomplete spinal cord injury. *J Neurophysiol* 2005;94(4):2844–55.
- Winchester P, McColl R, Querry R, Foreman N, Mosby J, Tansey K, et al. Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury. *Neurorehabil Neural Repair* 2005;19(4):313–24.
- Knikou M. Plasticity of corticospinal neural control after locomotor training in human spinal cord injury. *Neural Plast* 2012;2012:254948.
- West CR, Crawford MA, Laher I, Ramer MS, Krassioukov AV. Passive hind-limb cycling reduces the severity of autonomic dysreflexia after experimental spinal cord injury. *Neurorehabil Neural Repair* 2016;30(4):317–27.
- Lynskey JV, Belanger A, Jung R. Activity-dependent plasticity in spinal cord injury. *J Rehabil Res Dev* 2008;45(2):229–40.
- Tahayori B, Koceja DM. Activity-dependent plasticity of spinal circuits in the developing and mature spinal cord. *Neural Plast* 2012;2012:964843.
- Raasch CC, Zajac FE. Locomotor strategy for pedaling: muscle groups and biomechanical functions. *J Neurophysiol* 1999;82(2):515–25.
- West CR, Crawford MA, Poormasjedi-Meibod MS, Currie KD, Fallavollita A, Yuen V, et al. Passive hind-limb cycling improves cardiac function and reduces cardiovascular disease risk in experimental spinal cord injury. *J Physiol* 2014;592(Pt 8):1771–83.
- Dugan EA, Shumsky JS. A combination therapy of neural and glial restricted precursor cells and chronic quipazine treatment paired with passive cycling promotes quipazine-induced stepping in adult spinalized rats. *J Spinal Cord Med* 2015;38(6):792–804.
- Chopek JW, MacDonell CW, Gardiner K, Gardiner PF. Daily passive cycling attenuates the hyperexcitability and restores the responsiveness of the extensor monosynaptic reflex to quipazine in the chronic spinally transected rat. *J Neurotrauma* 2014;31(12):1083–7.
- Keeler BE, Liu G, Siegfried RN, Zhukareva V, Murray M, Houle JD. Acute and prolonged hindlimb exercise elicits different gene expression in motoneurons than sensory neurons after spinal cord injury. *Brain Res* 2012;1438:8–21.
- Garrison MK, Yates CC, Reese NB, Skinner RD, Garcia-Rill E. Wind-up of stretch reflexes as a measure of spasticity in chronic spinalized rats: the effects of passive exercise and modafinil. *Exp Neurol* 2011;227(1):104–9.
- Ollivier-Lanvin K, Keeler BE, Siegfried R, Houle JD, Lemay MA. Proprioceptive neuropathy affects normalization of the H-reflex by exercise after spinal cord injury. *Exp Neurol* 2010;221(1):198–205.
- Beaumont E, Houle JD, Peterson CA, Gardiner PF. Passive exercise and fetal spinal cord transplant both help to restore motoneuronal properties after spinal cord transection in rats. *Muscle Nerve* 2004;29(2):234–42.
- Houle JD, Morris K, Skinner RD, Garcia-Rill E, Peterson CA. Effects of fetal spinal cord tissue transplants and cycling exercise on the soleus muscle in spinalized rats. *Muscle Nerve* 1999;22(7):846–56.
- Willoughby DS, Priest JW, Jennings RA. Myosin heavy chain isoform and ubiquitin protease mRNA expression after passive leg cycling in persons with spinal cord injury. *Arch Phys Med Rehabil* 2000;81(2):157–63.
- Willoughby DS, Priest JW, Nelson M. Expression of the stress proteins, ubiquitin, heat shock protein 72, and myofibrillar protein content after 12 weeks of leg cycling in persons with spinal cord injury. *Arch Phys Med Rehabil* 2002;83(5):649–54.
- Takebeke TH, Lechner HE, Knapp PA. The effect of passive cycling movements on spasticity after spinal cord injury: preliminary results. *Spinal Cord* 2005;43(8):483–8.
- Ter Woerds W, De Groot PC, van Kuppevelt DH, Hopman MT. Passive leg movements and passive cycling do not alter arterial leg blood flow in subjects with spinal cord injury. *Phys Ther* 2006;86(5):636–45.
- Johnston TE, Smith BT, Oladeji O, Betz RR, Lauer RT. Outcomes of a home cycling program using functional electrical stimulation

- or passive motion for children with spinal cord injury: a case series. *J Spinal Cord Med* 2008;31(2):215–22.
- 29 Krause P, Edrich T, Straube A. Lumbar repetitive magnetic stimulation reduces spastic tone increase of the lower limbs. *Spinal Cord* 2004;42(2):67–72.
- 30 Johnston TE, Smith BT, Mulcahey MJ, Betz RR, Lauer RT. A randomized controlled trial on the effects of cycling with and without electrical stimulation on cardiorespiratory and vascular health in children with spinal cord injury. *Arch Phys Med Rehabil* 2009;90(8):1379–88.
- 31 Lauer RT, Smith BT, Mulcahey MJ, Betz RR, Johnston TE. Effects of cycling and/or electrical stimulation on bone mineral density in children with spinal cord injury. *Spinal Cord* 2011;49(8):917–23.
- 32 Johnston TE, Modlesky CM, Betz RR, Lauer RT. Muscle changes following cycling and/or electrical stimulation in pediatric spinal cord injury. *Arch Phys Med Rehabil* 2011;92(12):1937–43.
- 33 Graziano A, Foffani G, Knudsen EB, Shumsky J, Moxon KA. Passive exercise of the hind limbs after complete thoracic transection of the spinal cord promotes cortical reorganization. *PLoS One* 2013;8(1):e54350.
- 34 Moxon KA, Hale LL, Aguilar J, Foffani G. Responses of infragranular neurons in the rat primary somatosensory cortex to forepaw and hindpaw tactile stimuli. *Neuroscience* 2008;156(4):1083–92.
- 35 Darian-Smith C, Gilbert CD. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature* 1994;368(6473):737–40.
- 36 Yamahachi H, Marik SA, McManus JN, Denk W, Gilbert CD. Rapid axonal sprouting and pruning accompany functional reorganization in primary visual cortex. *Neuron* 2009;64(5):719–29.
- 37 Ghosh A, Peduzzi S, Snyder M, Schneider R, Starkey M, Schwab ME. Heterogeneous spine loss in layer 5 cortical neurons after spinal cord injury. *Cereb Cortex* 2011;22(6):1309–17.
- 38 Keck T, Scheuss V, Jacobsen RI, Wierenga CJ, Eysel UT, Bonhoeffer T, et al. Loss of sensory input causes rapid structural changes of inhibitory neurons in adult mouse visual cortex. *Neuron* 2011;71(5):869–82.
- 39 House DR, Elstrott J, Koh E, Chung J, Feldman DE. Parallel regulation of feedforward inhibition and excitation during whisker map plasticity. *Neuron* 2011;72(5):819–31.
- 40 Faggini BM, Nguyen KT, Nicoletis MA. Immediate and simultaneous sensory reorganization at cortical and subcortical levels of the somatosensory system. *Proc Natl Acad Sci U S A* 1997;94(17):9428–33.
- 41 Jones EG, Pons TP. Thalamic and brainstem contributions to large-scale plasticity of primate somatosensory cortex. *Science* 1998;282(5391):1121–5.
- 42 Jain N, Qi HX, Collins CE, Kaas JH. Large-scale reorganization in the somatosensory cortex and thalamus after sensory loss in macaque monkeys. *J Neurosci* 2008;28(43):11042–60.
- 43 Phillips AA, Cote AT, Warburton DE. A systematic review of exercise as a therapeutic intervention to improve arterial function in persons living with spinal cord injury. *Spinal Cord* 2011;49(6):702–14.
- 44 Faghri PD, Van Meerdervort HF, Glaser RM, Figoni SF. Electrical stimulation-induced contraction to reduce blood stasis during arthroplasty. *IEEE Trans Rehabil Eng* 1997;5(1):62–9.
- 45 Twist DJ, Culpepper-Morgan JA, Ragnarsson KT, Petrillo CR, Kreek MJ. Neuroendocrine changes during functional electrical stimulation. *Am J Phys Med Rehabil* 1992;71(3):156–63.
- 46 Seifert T, Secher NH. Sympathetic influence on cerebral blood flow and metabolism during exercise in humans. *Prog Neurobiol* 2011;95(3):406–26.
- 47 van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A* 1999;96(23):13427–31.
- 48 Ang ET, Gomez-Pinilla F. Potential therapeutic effects of exercise to the brain. *Curr Med Chem* 2007;14(24):2564–71.
- 49 Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci* 2007;30(9):464–72.
- 50 Lindberg P, Schmitz C, Forssberg H, Engardt M, Borg J. Effects of passive-active movement training on upper limb motor function and cortical activation in chronic patients with stroke: a pilot study. *J Rehabil Med* 2004;36(3):117–23.
- 51 Dechaumont-Palacin S, Marque P, De Boissezon X, Castellan E, Carel C, Berry I, et al. Neural correlates of proprioceptive integration in the contralesional hemisphere of very impaired patients shortly after a subcortical stroke: an fMRI study. *Neurorehabil Neural Repair* 2008;22(2):154–65.
- 52 Carel C, Loubinoux I, Boulanouar K, Manelfe C, Rascol O, Celsis P, et al. Neural substrate for the effects of passive training on sensorimotor cortical representation: a study with functional magnetic resonance imaging in healthy subjects. *J Cereb Blood Flow Metab* 2000;20(3):478–84.
- 53 Miyai I, Tanabe HC, Sase I, Eda H, Oda I, Konishi I, et al. Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *Neuroimage* 2001;14(5):1186–92.
- 54 Suzuki M, Miyai I, Ono T, Oda I, Konishi I, Kochiyama T, et al. Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study. *Neuroimage* 2004;23(3):1020–6.
- 55 Lin PY, Chen JJ, Lin SI. The cortical control of cycling exercise in stroke patients: an fNIRS study. *Hum Brain Mapp* 2013;34(10):2381–90.
- 56 Ashley EA, Laskin JJ, Olenik LM, Burnham R, Steadward RD, Cumming DC, et al. Evidence of autonomic dysreflexia during functional electrical stimulation in individuals with spinal cord injuries. *Paraplegia* 1993;31(9):593–605.
- 57 Cybulski GR, Penn RD, Jaeger RJ. Lower extremity functional neuromuscular stimulation in cases of spinal cord injury. *Neurosurgery* 1984;15(1):132–46.