

The Translesional Spinal Network and Its Reorganization after Spinal Cord Injury

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Abstract

© The Author(s) 2020. Evidence from preclinical and clinical research suggest that neuromodulation technologies can facilitate the sublesional spinal networks, isolated from supraspinal commands after spinal cord injury (SCI), by reestablishing the levels of excitability and enabling descending motor signals via residual connections. Herein, we evaluate available evidence that sublesional and supralesional spinal circuits could form a translesional spinal network after SCI. We further discuss evidence of translesional network reorganization after SCI in the presence of sensory inputs during motor training. In this review, we evaluate potential mechanisms that underlie translesional circuitry reorganization during neuromodulation and rehabilitation in order to enable motor functions after SCI. We discuss the potential of neuromodulation technologies to engage various components that comprise the translesional network, their functional recovery after SCI, and the implications of the concept of translesional network in development of future neuromodulation, rehabilitation, and neuroprosthetics technologies.

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Keywords

CPG, discomplete spinal cord injury, neuromodulation, neuroplasticity, regeneration, spinal cord injury, translesional spinal network

References

- [1] Abematsu M, Tsujimura K, Yamano M, Saito M, Kohno K, Kohyama J, and others. 2010. Neurons derived from transplanted neural stem cells restore disrupted neuronal circuitry in a mouse model of spinal cord injury. *J Clin Invest* 120(9):3255-66.
- [2] Albieri G, Barnes SJ, de Celis Alonso B, Cheetham CE, Edwards CE, Lowe AS, and others. 2015. Rapid bidirectional reorganization of cortical microcircuits. *Cereb Cortex* 25(9):3025-35.
- [3] Alstermark B, Lundberg A, Pinter M, Sasaki S. 1987. Subpopulations and functions of long C3-C5 propriospinal neurones. *Brain Res* 404(1-2):395-400.
- [4] Anderson MA, O'Shea TM, Burda JE, Ao Y, Barlatey SL, Bernstein AM, and others. 2018. Required growth facilitators propel axon regeneration across complete spinal cord injury. *Nature* 561(7723):396-400.
- [5] Angeli CA, Boakye M, Morton RA, Vogt J, Benton K, Chen Y, and others. 2018. Recovery of over-ground walking after chronic motor complete spinal cord injury. *N Engl J Med* 379(13):1244-50.
- [6] Asboth L, Friedli L, Beauparlant J, Martinez-Gonzalez C, Anil S, Rey E, and others. 2018. Cortico-reticulo-spinal circuit reorganization enables functional recovery after severe spinal cord contusion. *Nat Neurosci* 21(4):576-88.

- [7] Azim E, Jiang J, Alstermark B, Jessell TM. 2014. Skilled reaching relies on a V2a propriospinal internal copy circuit. *Nature* 508(7496):357-63.
- [8] Bachmann LC, Matis A, Lindau NT, Felder P, Gullo M, Schwab ME. 2013. Deep brain stimulation of the midbrain locomotor region improves paretic hindlimb function after spinal cord injury in rats. *Sci Transl Med* 5(208):208ra146.
- [9] Baker SN. 2011. The primate reticulospinal tract, hand function and functional recovery. *J Physiol* 589(Pt 23):5603-12.
- [10] Barbeau H, Rossignol S. 1987. Recovery of locomotion after chronic spinalization in the adult cat. *Brain Res* 412(1):84-95.
- [11] Bareyre FM, Kerschensteiner M, Raineteau O, Mettenleiter TC, Weinmann O, Schwab ME. 2004. The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. *Nat Neurosci* 7(3):269-77.
- [12] Barnabe-Heider F, Goritz C, Sabelstrom H, Takebayashi H, Pfrieger FW, Meletis K, and others. 2010. Origin of new glial cells in intact and injured adult spinal cord. *Cell Stem Cell* 7(4):470-82.
- [13] Becker MI, Parker D. 2014. Changes in functional properties and 5-HT modulation above and below a spinal transection in lamprey. *Front Neural Circuits* 8:148.
- [14] Bikoff JB, Gabitto MI, Rivard AF, Drobac E, Machado TA, Miri A, and others. 2016. Spinal inhibitory interneuron diversity delineates variant motor microcircuits. *Cell* 165(1):207-19.
- [15] Blesch A, Tuszynski MH. 2009. Spinal cord injury: plasticity, regeneration and the challenge of translational drug development. *Trends Neurosci* 32(1):41-7.
- [16] Bohnert DM, Purvines S, Shapiro S, Borgens RB. 2007. Simultaneous application of two neurotrophic factors after spinal cord injury. *J Neurotrauma* 24(5):846-63.
- [17] Brown LT. 1974. Rubrospinal projections in the rat. *J Comp Neurol* 154(2):169-87.
- [18] Buckingham SC, Campbell SL, Haas BR, Montana V, Robel S, Ogunrinu T, and others. 2011. Glutamate release by primary brain tumors induces epileptic activity. *Nat Med* 17(10):1269-74.
- [19] Burda JE, Sofroniew MV. 2014. Reactive gliosis and the multicellular response to CNS damage and disease. *Neuron* 81(2):229-48.
- [20] Butler JE, Godfrey S, Thomas CK. 2016. Interlimb reflexes induced by electrical stimulation of cutaneous nerves after spinal cord injury. *PLoS One* 11(4):e0153063.
- [21] Caggiano V, Leiras R, Goñi-Erro H, Masini D, Bellardita C, Bouvier J, and others. 2018. Midbrain circuits that set locomotor speed and gait selection. *Nature* 553(7689):455.
- [22] Capogrosso M, Milekovic T, Borton D, Wagner F, Moraud EM, Mignardot JB, and others. 2016. A brain-spine interface alleviating gait deficits after spinal cord injury in primates. *Nature* 539(7628):284-8.
- [23] Chen BK, Madigan NN, Hakim JS, Dadsetan M, McMahan SS, Yaszemski MJ, and others. 2018. GDNF Schwann cells in hydrogel scaffolds promote regional axon regeneration, remyelination and functional improvement after spinal cord transection in rats. *J Tissue Eng Regen Med* 12(1):e398-e407.
- [24] Chen Q, Zheng W, Chen X, Li X, Wang L, Qin W, and others. 2019. Reorganization of the somatosensory pathway after subacute incomplete cervical cord injury. *NeuroImage: Clinical* 21:101674.
- [25] Christiansen L, Perez MA. 2018. Targeted-plasticity in the corticospinal tract after human spinal cord injury. *Neurotherapeutics* 15(3):618-27.
- [26] Colangelo AM, Alberghina L, Papa M. 2014. Astroglial gliosis as a therapeutic target for neurodegenerative diseases. *Neurosci Lett* 565:59-64.
- [27] Conta AC, Stelzner DJ. 2004. Differential vulnerability of propriospinal tract neurons to spinal cord contusion injury. *J Comp Neurol* 479(4):347-59.
- [28] Courtine G, Song B, Roy RR, Zhong H, Herrmann JE, Ao Y, and others. 2008. Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. *Nat Med* 14(1):69-74.
- [29] Cuellar CA, Mendez AA, Islam R, Calvert JS, Grahn PJ, Knudsen B, and others. 2017. The role of functional neuroanatomy of the lumbar spinal cord in effect of epidural stimulation. *Front Neuroanat* 11:82.
- [30] Danilov AI, Covacu R, Moe MC, Langmoen IA, Johansson CB, Olsson T, and others. 2006. Neurogenesis in the adult spinal cord in an experimental model of multiple sclerosis. *Eur J Neurosci* 23(2):394-400.
- [31] Darrow D, Balser D, Netoff TI, Krassioukov A, Phillips A, Parr A, and others. 2019. Epidural spinal cord stimulation facilitates restoration of dormant motor and autonomic supraspinal pathways after chronic neurologically complete spinal cord injury. *J Neurotrauma* 36(15):2325-36.
- [32] Davidson AG, Schieber MH, Buford JA. 2007. Bilateral spike-triggered average effects in arm and shoulder muscles from the monkey pontomedullary reticular formation. *J Neurosci* 27(30):8053-8.
- [33] De Luca C, Colangelo AM, Virtuoso A, Alberghina L, Papa M. 2020. Neurons, glia, extracellular matrix and neurovascular unit: a systems biology approach to the complexity of synaptic plasticity in health and disease. *Int J Mol Sci* 21(4):1539.
- [34] Dietz V, Fouad K. 2014. Restoration of sensorimotor functions after spinal cord injury. *Brain* 137(Pt 3):654-67.

- [35] Dimitrijevic MR, Dimitrijevic MM, Faganel J, Sherwood AM. 1984. Suprasegmentally induced motor unit activity in paralyzed muscles of patients with established spinal cord injury. *Ann Neurol* 16(2):216-21.
- [36] Dimitrijevic MR, Gerasimenko Y, Pinter MM. 1998. Evidence for a spinal central pattern generator in humans. *Ann N Y Acad Sci* 860:360-76.
- [37] Drew T, Rossignol S. 1990. Functional organization within the medullary reticular formation of intact unanesthetized cat. II. Electromyographic activity evoked by microstimulation. *J Neurophysiol* 64(3):782-95.
- [38] Du Beau A, Shakya Shrestha S, Bannatyne BA, Jalicy SM, Linnen S, Maxwell DJ. 2012. Neurotransmitter phenotypes of descending systems in the rat lumbar spinal cord. *Neuroscience* 227:67-79.
- [39] Dulin JN, Adler AF, Kumamaru H, Poplawski GHD, Lee-Kubli C, Strobl H, and others. 2018. Injured adult motor and sensory axons regenerate into appropriate organotypic domains of neural progenitor grafts. *Nat Commun* 9(1):84.
- [40] Edgley SA. 2001. Organisation of inputs to spinal interneurone populations. *J Physiol* 533(Pt 1):51-6.
- [41] Edwards DJ, Cortes M, Thickbroom GW, Rykman A, Pascual-Leone A, Volpe BT. 2013. Preserved corticospinal conduction without voluntary movement after spinal cord injury. *Spinal Cord* 51(10):765-7.
- [42] Esposito MS, Capelli P, Arber S. 2014. Brainstem nucleus MdV mediates skilled forelimb motor tasks. *Nature* 508(7496):351.
- [43] Fan J, Xiao Z, Zhang H, Chen B, Tang G, Hou X, and others. 2010. Linear ordered collagen scaffolds loaded with collagen-binding neurotrophin-3 promote axonal regeneration and partial functional recovery after complete spinal cord transection. *J Neurotrauma* 27(9):1671-83.
- [44] Flynn JR, Graham BA, Galea MP, Callister RJ. 2011. The role of propriospinal interneurons in recovery from spinal cord injury. *Neuropharmacology* 60(5):809-22.
- [45] Freund P, Wheeler-Kingshott CA, Nagy Z, Gorgoraptis N, Weiskopf N, Friston K, and others. 2012. Axonal integrity predicts cortical reorganisation following cervical injury. *J Neurol Neurosurg Psychiatry* 83(6):629-37.
- [46] Frigon A, Thompson CK, Johnson MD, Manuel M, Hornby TG, Heckman CJ. 2011. Extra forces evoked during electrical stimulation of the muscle or its nerve are generated and modulated by a length-dependent intrinsic property of muscle in humans and cats. *J Neurosci* 31(15):5579-88.
- [47] Ganzer PD, Moxon KA, Knudsen EB, Shumsky JS. 2013. Serotonergic pharmacotherapy promotes cortical reorganization after spinal cord injury. *Exp Neurol* 241:84-94.
- [48] Gerasimenko YP, Avelev VD, Nikitin OA, Lavrov IA. 2001. Initiation of locomotor activity in spinalized cats by epidural stimulation of the spinal cord. *Russ Fiziol Zh Im I M Sechenova* 87(9):1161-70.
- [49] Gerasimenko YP, Ichiyama RM, Lavrov IA, Courtine G, Cai L, Zhong H, and others. 2007. Epidural spinal cord stimulation plus quipazine administration enable stepping in complete spinal adult rats. *J Neurophysiol* 98(5):2525-36.
- [50] Gerasimenko YP, Lu DC, Modaber M, Zdunowski S, Gad P, Sayenko DG, and others. 2015. Noninvasive reactivation of motor descending control after paralysis. *J Neurotrauma* 32(24):1968-80.
- [51] Gerasimenko YP, Makarovskii A, Nikitin O. 2002. Control of locomotor activity in humans and animals in the absence of supraspinal influences. *Neurosci Behav Physiol* 32(4):417-23.
- [52] Ghosh A, Haiss F, Sydekum E, Schneider R, Gulló M, Wyss MT, and others. 2010. Rewiring of hindlimb corticospinal neurons after spinal cord injury. *Nat Neurosci* 13(1):97.
- [53] Ghosh A, Sydekum E, Haiss F, Peduzzi S, Zorner B, Schneider R, and others. 2009. Functional and anatomical reorganization of the sensory-motor cortex after incomplete spinal cord injury in adult rats. *J Neurosci* 29(39):12210-9.
- [54] Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, and others. 2018. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nat Med* 24(11):1677-82.
- [55] Goldshmit Y, Lythgo N, Galea MP, Turnley AM. 2008. Treadmill training after spinal cord hemisection in mice promotes axonal sprouting and synapse formation and improves motor recovery. *J Neurotrauma* 25(5):449-65.
- [56] Grahn PJ, Lavrov IA, Sayenko DG, Van Straaten MG, Gill ML, Strommen JA, and others. 2017. Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. *Elsevier*. P. 544-54.
- [57] Grillner S. 1996. Neural networks for vertebrate locomotion. *Sci Am* 274(1):64-9.
- [58] Grillner S, Wallén P, Saitoh K, Kozlov A, Robertson B. 2008. Neural bases of goal-directed locomotion in vertebrates—an overview. *Brain Res Rev* 57(1):2-12.
- [59] Guest JD, Herrera L, Margitich I, Oliveria M, Marcillo A, Casas CE. 2008. Xenografts of expanded primate olfactory ensheathing glia support transient behavioral recovery that is independent of serotonergic or corticospinal axonal regeneration in nude rats following spinal cord transection. *Exp Neurol* 212(2):261-74.

- [60] Guevremont L, Renzi CG, Norton JA, Kowalczewski J, Saigal R, Mushahwar VK. 2006. Locomotor-related networks in the lumbosacral enlargement of the adult spinal cat: activation through intraspinal microstimulation. *IEEE Trans Neural Syst Rehabil Eng* 14(3):266-72.
- [61] Hakim JS, Rodysill BR, Chen BK, Schmeichel AM, Yaszemski MJ, Windebank AJ, and others. 2019. Combinatorial tissue engineering partially restores function after spinal cord injury. *J Tissue Eng Regen Med* 13(5):857-73.
- [62] Harkema S, Gerasimenko Y, Hodes J, Burdick J, Angeli C, Chen Y, and others. 2011. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *Lancet* 377(9781):1938-47.
- [63] Heald E, Hart R, Kilgore K, Peckham PH. 2017. Characterization of volitional electromyographic signals in the lower extremity after motor complete spinal cord injury. *Neurorehabil Neural Repair* 31(6):583-91.
- [64] Hoffman LR, Field-Fote EC. 2010. Functional and corticomotor changes in individuals with tetraplegia following unimanual or bimanual massed practice training with somatosensory stimulation: a pilot study. *J Neurol Phys Ther* 34(4):193-201.
- [65] Hofstoetter US, Danner SM, Freundl B, Binder H, Mayr W, Rattay F, and others. 2015. Periodic modulation of repetitively elicited monosynaptic reflexes of the human lumbosacral spinal cord. *J Neurophysiol* 114(1):400-10.
- [66] Holstege G, Kuypers HG. 1982. The anatomy of brain stem pathways to the spinal cord in cat. A labeled amino acid tracing study. *Prog Brain Res* 57:145-75.
- [67] Honeycutt CF, Kharouta M, Perreault EJ. 2013. Evidence for reticulospinal contributions to coordinated finger movements in humans. *J Neurophysiol* 110(7):1476-83.
- [68] Houle JD, Côté MP. 2013. Axon regeneration and exercise-dependent plasticity after spinal cord injury. *Ann N Y Acad Sci* 1279(1):154.
- [69] Humanes-Valera D, Foffani G, Alonso-Calvino E, Fernandez-Lopez E, Aguilar J. 2017. Dual cortical plasticity after spinal cord injury. *Cereb Cortex* 27(5):2926-40.
- [70] Ichiyama R, Gerasimenko YP, Zhong H, Roy R, Edgerton VR. 2005a. Hindlimb stepping movements in complete spinal rats induced by epidural spinal cord stimulation. *Neurosci Lett* 383(3):339-44.
- [71] Ichiyama RM, Courtine G, Gerasimenko YP, Yang GJ, van den Brand R, Lavrov IA, and others. 2008. Step training reinforces specific spinal locomotor circuitry in adult spinal rats. *J Neurosci* 28(29):7370-5.
- [72] Ichiyama RM, Gerasimenko YP, Zhong H, Roy RR, Edgerton VR. 2005b. Hindlimb stepping movements in complete spinal rats induced by epidural spinal cord stimulation. *Neurosci Lett* 383(3):339-44.
- [73] Inman DM, Steward O. 2003. Ascending sensory, but not other long-tract axons, regenerate into the connective tissue matrix that forms at the site of a spinal cord injury in mice. *J Comp Neurol* 462(4):431-49.
- [74] Islam R, Siddiqui AM, Cuellar CA, Silvernail JL, Knudsen B, Curley DE, and others. 2019a. Sparse re-connection across complete spinal cord injury influences sub-lesional spinal network excitability during epidural electrical stimulation enabled locomotor activity in rats. *Neuroscience Meeting Planner*. Chicago, IL: Society for Neuroscience; 2019. Online Poster: 136—Spinal Cord Injury: Responses and Repair.
- [75] Islam R, Cuellar CA, Felmlee B, Riccelli T, Silvernail J, Boschen SL, and others. 2019b. Multifactorial motor behavior assessment for real-time evaluation of emerging therapeutics to treat neurologic impairments. *Sci Rep* 9(1):16503.
- [76] Islamov RR, Sokolov ME, Bashirov FV, Fadeev FO, Shmarov MM, Naroditskiy BS, and others. 2017. A pilot study of cell-mediated gene therapy for spinal cord injury in mini pigs. *Neurosci Lett* 644:67-75.
- [77] Izmailov AA, Povysheva TV, Bashirov FV, Sokolov ME, Fadeev FO, Garifulin RR, and others. 2017. Spinal cord molecular and cellular changes induced by adenoviral vector- and cell-mediated triple gene therapy after severe contusion. *Front Pharmacol* 8:813.
- [78] Jain N, Qi HX, Collins CE, Kaas JH. 2008. Large-scale reorganization in the somatosensory cortex and thalamus after sensory loss in macaque monkeys. *J Neurosci* 28(43):11042-60.
- [79] Jeffery N, Fitzgerald M. 2001. Effects of red nucleus ablation and exogenous neurotrophin-3 on corticospinal axon terminal distribution in the adult rat. *Neuroscience* 104(2):513-21.
- [80] Jurkiewicz MT, Mikulis DJ, McIlroy WE, Fehlings MG, Verrier MC. 2007. Sensorimotor cortical plasticity during recovery following spinal cord injury: a longitudinal fMRI study. *Neurorehabil Neural Repair* 21(6):527-38.
- [81] Jutzeler CR, Freund P, Huber E, Curt A, Kramer JLK. 2015. Neuropathic pain and functional reorganization in the primary sensorimotor cortex after spinal cord injury. *J Pain* 16(12):1256-67.
- [82] Kadoya K, Lu P, Nguyen K, Lee-Kubli C, Kumamaru H, Yao L, and others. 2016. Spinal cord reconstitution with homologous neural grafts enables robust corticospinal regeneration. *Nat Med* 22(5):479-87.
- [83] Kambi N, Halder P, Rajan R, Arora V, Chand P, Arora M, and others. 2014. Large-scale reorganization of the somatosensory cortex following spinal cord injuries is due to brainstem plasticity. *Nat Commun* 5:3602.
- [84] Kambi N, Tandon S, Mohammed H, Lazar L, Jain N. 2011. Reorganization of the primary motor cortex of adult macaque monkeys after sensory loss resulting from partial spinal cord injuries. *J Neurosci* 31(10):3696-707.

- [85] Karni A, Meyer G, Rey-Hipolito C, Jezard P, Adams MM, Turner R, and others. 1998. The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proc Natl Acad Sci U S A* 95(3):861-8.
- [86] Kleim JA, Hogg TM, VandenBerg PM, Cooper NR, Bruneau R, Remple M. 2004. Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. *J Neurosci* 24(3):628-33.
- [87] Kramer JL, Minhas NK, Jutzeler CR, Erskine EL, Liu LJ, Ramer MS. 2017. Neuropathic pain following traumatic spinal cord injury: Models, measurement, and mechanisms. *J Neurosci Res* 95(6):1295-306.
- [88] Krupa P, Svobodova B, Dubisova J, Kubinova S, Jendelova P, Machova Urdzikova L. 2019. Nano-formulated curcumin (Lipodisq) modulates the local inflammatory response, reduces glial scar and preserves the white matter after spinal cord injury in rats. *Neuropharmacology* 155:54-64.
- [89] Krupa P, Vackova I, Ruzicka J, Zaviskova K, Dubisova J, Koci Z, and others. 2018. The effect of human mesenchymal stem cells derived from Wharton's jelly in spinal cord injury treatment is dose-dependent and can be facilitated by repeated application. *Int J Mol Sci* 19(5):1503.
- [90] Kuchler M, Fouad K, Weinmann O, Schwab ME, Raineteau O. 2002. Red nucleus projections to distinct motor neuron pools in the rat spinal cord. *J Comp Neurol* 448(4):349-59.
- [91] Kumamaru H, Kadoya K, Adler AF, Takashima Y, Graham L, Coppola G, and others. 2018. Generation and post-injury integration of human spinal cord neural stem cells. *Nat Methods* 15(9):723-31.
- [92] Langlet C, Leblond H, Rossignol S. 2005. Mid-lumbar segments are needed for the expression of locomotion in chronic spinal cats. *J Neurophysiol* 93(5):2474-88.
- [93] Lapointe NP, Rouleau P, Ung RV, Guertin PA. 2009. Specific role of dopamine D1 receptors in spinal network activation and rhythmic movement induction in vertebrates. *J Physiol* 587(Pt 7):1499-511.
- [94] Lavrov I, Dy CJ, Fong AJ, Gerasimenko Y, Courtine G, Zhong H, and others. 2008. Epidural stimulation induced modulation of spinal locomotor networks in adult spinal rats. *J Neurosci* 28(23):6022-9.
- [95] Lavrov I, Musienko PE, Selionov VA, Zdurowski S, Roy RR, Edgerton VR, and others. 2015. Activation of spinal locomotor circuits in the decerebrated cat by spinal epidural and/or intraspinal electrical stimulation. *Brain Res* 1600:84-92.
- [96] Li X, Dai J. 2018. Bridging the gap with functional collagen scaffolds: tuning endogenous neural stem cells for severe spinal cord injury repair. *Biomater Sci* 6(2):265-71.
- [97] Liang H, Watson C, Paxinos G. 2016. Terminations of reticulospinal fibers originating from the gigantocellular reticular formation in the mouse spinal cord. *Brain Struct Funct* 221(3):1623-33.
- [98] Liu K, Lu Y, Lee JK, Samara R, Willenberg R, Sears-Kraxberger I, and others. 2010. PTEN deletion enhances the regenerative ability of adult corticospinal neurons. *Nat Neurosci* 13(9):1075-81.
- [99] Liu S, Sandner B, Schackel T, Nicholson L, Chtarto A, Tenenbaum L, and others. 2017. Regulated viral BDNF delivery in combination with Schwann cells promotes axonal regeneration through capillary alginate hydrogels after spinal cord injury. *Acta Biomater* 60:167-80.
- [100] Lu P, Wang Y, Graham L, McHale K, Gao M, Wu D, and others. 2012a. Long-distance growth and connectivity of neural stem cells after severe spinal cord injury. *Cell* 150(6):1264-73.
- [101] Machova Urdzikova L, Karova K, Ruzicka J, Kloudova A, Shannon C, Dubisova J, and others. 2015. The anti-inflammatory compound curcumin enhances locomotor and sensory recovery after spinal cord injury in rats by immunomodulation. *Int J Mol Sci* 17(1):49.
- [102] Manohar A, Foffani G, Ganzer PD, Bethea JR, Moxon KA. 2017. Cortex-dependent recovery of unassisted hindlimb locomotion after complete spinal cord injury in adult rats. *Elife* 6:e23532.
- [103] Matsuyama K, Mori F, Nakajima K, Drew T, Aoki M, Mori S. 2004. Locomotor role of the corticoreticular-reticulospinal-spinal interneuronal system. *Prog Brain Res* 143:239-49.
- [104] May Z, Fenrich KK, Dahlby J, Batty NJ, Torres-Espin A, Fouad K. 2017a. Following spinal cord injury transected reticulospinal tract axons develop new collateral inputs to spinal interneurons in parallel with locomotor recovery. *Neural Plast* 2017:1932875.
- [105] McCrea DA, Rybak IA. 2008. Organization of mammalian locomotor rhythm and pattern generation. *Brain Res Rev* 57(1):134-46.
- [106] Mendez A, Islam R, Latypov T, Basa P, Joseph O, Knudsen B, and others. 2020. Segment-specific orientation of the dorsal and ventral roots for precise therapeutic targeting of human spinal cord. *bioRxiv*. <https://doi.org/10.1101/2020.01.31.928804>
- [107] Mikhaylov A, Pimashkin A, Pigareva Y, Gerasimova S, Gryaznov E, Shchanikov S, and others. 2020. Neurohybrid memristive CMOS-integrated systems for biosensors and neuroprosthetics. *Front Neurosci* 14:358.
- [108] Militskova A, Mukhametova E, Fatykhova E, Sharifullin S, Cuellar CA, Calvert JS, and others. 2020. Supraspinal and afferent signaling facilitate spinal sensorimotor network excitability after incomplete spinal cord injury: a case report. *Front Neurosci* 14:552.

- [109] Minassian K, Hofstoetter US, Dzeladini F, Guertin PA, Ijspeert A. 2017. The human central pattern generator for locomotion: does it exist and contribute to walking? *Neuroscientist* 23(6):649-63.
- [110] Mitchell EJ, McCallum S, Dewar D, Maxwell DJ. 2016. Corticospinal and reticulospinal contacts on cervical commissural and long descending propriospinal neurons in the adult rat spinal cord; evidence for powerful reticulospinal connections. *PLoS One* 11(3):e0152094.
- [111] Muir GD, Webb AA, Kanagal S, Taylor L. 2007. Dorsolateral cervical spinal injury differentially affects forelimb and hindlimb action in rats. *Eur J Neurosci* 25(5):1501-10.
- [112] Mukhamedshina Y, Shulman I, Ogurcov S, Kostennikov A, Zakirova E, Akhmetzyanova E, and others. 2019. Mesenchymal stem cell therapy for spinal cord contusion: a comparative study on small and large animal models. *Biomolecules* 9(12):811.
- [113] Paino CL, Fernandez-Valle C, Bates ML, Bunge MB. 1994. Regrowth of axons in lesioned adult rat spinal cord: promotion by implants of cultured Schwann cells. *J Neurocytol* 23(7):433-52.
- [114] Panek I, Bui T, Wright AT, Brownstone RM. 2014. Cutaneous afferent regulation of motor function. *Acta Neurobiol Exp (Wars)* 74(2):158-71.
- [115] Parker D. 2017. The lesioned spinal cord is a "new" spinal cord: evidence from functional changes after spinal injury in lamprey. *Front Neural Circuits* 11:84.
- [116] Parker D. 2018. Functional changes after spinal lesions: implications for interventions. *Neural Regen Res* 13(5):811-2.
- [117] Peña Pino I, Hoover C, Venkatesh S, Ahmadi A, Sturtevant D, Patrick N, and others. 2020. Long-term spinal cord stimulation after chronic complete spinal cord injury enables volitional movement in the absence of stimulation. *Front Syst Neurosci* 14:35.
- [118] Raineteau O, Fouad K, Noth P, Thallmair M, Schwab ME. 2001. Functional switch between motor tracts in the presence of the mAb IN-1 in the adult rat. *Proc Natl Acad Sci U S A* 98(12):6929-34.
- [119] Raineteau O, Schwab ME. 2001. Plasticity of motor systems after incomplete spinal cord injury. *Nat Rev Neurosci* 2(4):263-73.
- [120] Raivich G, Makwana M. 2007. The making of successful axonal regeneration: genes, molecules and signal transduction pathways. *Brain Res Rev* 53(2):287-311.
- [121] Rao JS, Zhao C, Zhang A, Duan H, Hao P, Wei RH, and others. 2018. NT3-chitosan enables de novo regeneration and functional recovery in monkeys after spinal cord injury. *Proc Natl Acad Sci U S A* 115(24):E5595-E5604.
- [122] Riddle CN, Baker SN. 2010. Convergence of pyramidal and medial brain stem descending pathways onto macaque cervical spinal interneurons. *J Neurophysiol* 103(5):2821-32.
- [123] Riddle CN, Edgley SA, Baker SN. 2009. Direct and indirect connections with upper limb motoneurons from the primate reticulospinal tract. *J Neurosci* 29(15):4993-9.
- [124] Roseberry TK, Lee AM, Lalive AL, Wilbrecht L, Bonci A, Kreitzer AC. 2016. Cell-type-specific control of brainstem locomotor circuits by basal ganglia. *Cell* 164(3):526-37.
- [125] Rosenzweig ES, Brock JH, Lu P, Kumamaru H, Salegio EA, Kadoya K, and others. 2018. Restorative effects of human neural stem cell grafts on the primate spinal cord. *Nat Med* 24(4):484-90.
- [126] Rossignol S, Dubuc R, Gossard JP. 2006. Dynamic sensorimotor interactions in locomotion. *Physiol Rev* 86(1):89-154.
- [127] Roy RR, Edgerton VR. 2012. Neurobiological perspective of spasticity as occurs after a spinal cord injury. *Exp Neurol* 235(1):116-22.
- [128] Roy RR, Harkema SJ, Edgerton VR. 2012. Basic concepts of activity-based interventions for improved recovery of motor function after spinal cord injury. *Arch Phys Med Rehabil* 93(9):1487-97.
- [129] Ruigrok TJ, Pijpers A, Goedknegt-Sabel E, Coulon P. 2008. Multiple cerebellar zones are involved in the control of individual muscles: a retrograde transneuronal tracing study with rabies virus in the rat. *Eur J Neurosci* 28(1):181-200.
- [130] Ruzicka J, Machova-Urdzikova L, Gillick J, Amemori T, Romanyuk N, Karova K, and others. 2017. A comparative study of three different types of stem cells for treatment of rat spinal cord injury. *Cell Transplant* 26(4):585-603.
- [131] Ryczko D, Auclair F, Cabelguen JM, Dubuc R. 2016. The mesencephalic locomotor region sends a bilateral glutamatergic drive to hindbrain reticulospinal neurons in a tetrapod. *J Comp Neurol* 524(7):1361-83.
- [132] Ryczko D, Gratsch S, Auclair F, Dube C, Bergeron S, Alpert MH, and others. 2013. Forebrain dopamine neurons project down to a brainstem region controlling locomotion. *Proc Natl Acad Sci U S A* 110(34):E3235-E3242.
- [133] Ryczko D, Grätsch S, Schläger L, Keuyalian A, Boukhatem Z, Garcia C, and others. 2017. Nigral glutamatergic neurons control the speed of locomotion. *J Neurosci* 37(40):9759-70.
- [134] Shah PK, Lavrov I. 2017. Spinal epidural stimulation strategies: clinical implications of locomotor studies in spinal rats. *Neuroscientist* 23(6):664-80.

- [135] Shah PK, Sureddi S, Alam M, Zhong H, Roy RR, Edgerton VR, and others. 2016. Unique spatiotemporal neuromodulation of the lumbosacral circuitry shapes locomotor success after spinal cord injury. *J Neurotrauma* 33(18):1709-23.
- [136] Sharma S, Kim LH, Mayr KA, Elliott DA, Whelan PJ. 2018. Parallel descending dopaminergic connectivity of A13 cells to the brainstem locomotor centers. *Sci Rep* 8(1):7972.
- [137] Shechter R, Ziv Y, Schwartz M. 2007. New GABAergic interneurons supported by myelin-specific T cells are formed in intact adult spinal cord. *Stem Cells* 25(9):2277-82.
- [138] Shik ML, Severin FV, Orlovskii GN. 1966. Control of walking and running by means of electric stimulation of the midbrain. *Biofizika* 11(4):659-66.
- [139] Siddiqui AM, Islam R, Cuellar CA, Silvernail JL, Knudsen B, Curley DE, and others. 2020. Newly regenerated axons through a cell-containing biomaterial scaffold promote reorganization of spinal circuitry and restoration of motor functions with epidural electrical stimulation. *bioRxiv*. <https://doi.org/10.1101/2020.09.09.288100>
- [140] Siebert JR, Middleton FA, Stelzner DJ. 2010. Long descending cervical propriospinal neurons differ from thoracic propriospinal neurons in response to low thoracic spinal injury. *BMC Neurosci* 11:148.
- [141] Sivertsen MS, Perreault MC, Glover JC. 2016. Pontine reticulospinal projections in the neonatal mouse: Internal organization and axon trajectories. *J Comp Neurol* 524(6):1270-91.
- [142] Skinner RD, Garcia-Rill E. 1984. The mesencephalic locomotor region (MLR) in the rat. *Brain Res* 323(2):385-9.
- [143] Song P, Cuellar CA, Tang S, Islam R, Wen H, Huang C, and others. 2019. Functional ultrasound imaging of spinal cord hemodynamic responses to epidural electrical stimulation: a feasibility study. *Front Neurol* 10:279.
- [144] Soteropoulos DS, Williams ER, Baker SN. 2012. Cells in the monkey ponto-medullary reticular formation modulate their activity with slow finger movements. *J Physiol* 590(16):4011-27.
- [145] Stecina K. 2017. Midbrain stimulation-evoked lumbar spinal activity in the adult decerebrate mouse. *J Neurosci Methods* 288:99-105.
- [146] Suzuki Y, Kitaoura M, Wu S, Kataoka K, Suzuki K, Endo K, and others. 2002. Electrophysiological and horseradish peroxidase-tracing studies of nerve regeneration through alginate-filled gap in adult rat spinal cord. *Neurosci Lett* 318(3):121-4.
- [147] Swieck K, Conta-Steencken A, Middleton FA, Siebert JR, Osterhout DJ, Stelzner DJ. 2019. Effect of lesion proximity on the regenerative response of long descending propriospinal neurons after spinal transection injury. *BMC Neurosci* 20(1):10.
- [148] Takeoka A, Arber S. 2019. Functional local proprioceptive feedback circuits initiate and maintain locomotor recovery after spinal cord injury. *Cell Rep* 27(1):71-85.e3.
- [149] Tang S, Cuellar CA, Song P, Islam R, Huang C, Wen H, and others. 2020. Changes in spinal cord hemodynamics reflect modulation of spinal network with different parameters of epidural stimulation. *Neuroimage* 221:117183.
- [150] Taylor JA. 2018. Autonomic consequences of spinal cord injury. *Autonom Neurosci* 209:1-3.
- [151] Tohyama T, Kinoshita M, Kobayashi K, Isa K, Watanabe D, Kobayashi K, and others. 2017. Contribution of propriospinal neurons to recovery of hand dexterity after corticospinal tract lesions in monkeys. *Proc Natl Acad Sci U S A* 114(3):604-9.
- [152] Ueno M, Nakamura Y, Li J, Gu Z, Niehaus J, Maezawa M, and others. 2018. Corticospinal circuits from the sensory and motor cortices differentially regulate skilled movements through distinct spinal interneurons. *Cell Rep* 23(5):1286-1300.e7.
- [153] van den Brand R, Heutschi J, Barraud Q, DiGiovanna J, Bartholdi K, Huerlimann M, and others. 2012. Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science* 336(6085):1182-5.
- [154] Vavrek R, Girgis J, Tetzlaff W, Hiebert GW, Fouad K. 2006. BDNF promotes connections of corticospinal neurons onto spared descending interneurons in spinal cord injured rats. *Brain* 129(Pt 6):1534-45.
- [155] Wagner FB, Mignardot JB, Le Goff-Mignardot CG, Demesmaeker R, Komi S, Capogrosso M, and others. 2018. Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature* 563(7729):65-71.
- [156] Wang Y, Wu W, Wu X, Sun Y, Zhang YP, Deng LX, and others. 2018. Remodeling of lumbar motor circuitry remote to a thoracic spinal cord injury promotes locomotor recovery. *Elife* 7:e39016.
- [157] Weidner N, Ner A, Salimi N, Tuszynski MH. 2001. Spontaneous corticospinal axonal plasticity and functional recovery after adult central nervous system injury. *Proc Natl Acad Sci U S A* 98(6):3513-8.
- [158] Wen TC, Lall S, Pagnotta C, Markward J, Gupta D, Ratnadurai-Giridharan S, and others. 2018. Plasticity in one hemisphere, control from two: adaptation in descending motor pathways after unilateral corticospinal injury in neonatal rats. *Front Neural Circuits* 12:28.
- [159] Whishaw IQ, Gorny B, Sarna J. 1998. Paw and limb use in skilled and spontaneous reaching after pyramidal tract, red nucleus and combined lesions in the rat: behavioral and anatomical dissociations. *Behav Brain Res* 93(1-2):167-83.

- [160] Williams RR, Henao M, Pearse DD, Bunge MB. 2015. Permissive Schwann cell graft/spinal cord interfaces for axon regeneration. *Cell Transplant* 24(1):115-31.
- [161] Xu XM, Zhang SX, Li H, Aebischer P, Bunge MB. 1999. Regrowth of axons into the distal spinal cord through a Schwann-cell-seeded mini-channel implanted into hemisectioned adult rat spinal cord. *Eur J Neurosci* 11(5):1723-40.
- [162] Yang Z, Zhang A, Duan H, Zhang S, Hao P, Ye K, and others. 2015. NT3-chitosan elicits robust endogenous neurogenesis to enable functional recovery after spinal cord injury. *Proc Natl Acad Sci U S A* 112(43):13354-9.
- [163] Yin W, Li X, Zhao Y, Tan J, Wu S, Cao Y, and others. 2018. Taxol-modified collagen scaffold implantation promotes functional recovery after long-distance spinal cord complete transection in canines. *Biomater Sci* 6(5):1099-108.
- [164] Yokota K, Kubota K, Kobayakawa K, Saito T, Hara M, Kijima K, and others. 2019. Pathological changes of distal motor neurons after complete spinal cord injury. *Mol Brain* 12(1):4.
- [165] Zhang H, Wu F, Kong X, Yang J, Chen H, Deng L, and others. 2014. Nerve growth factor improves functional recovery by inhibiting endoplasmic reticulum stress-induced neuronal apoptosis in rats with spinal cord injury. *J Transl Med* 12(1):130.
- [166] Zörner B, Bachmann LC, Filli L, Kapitza S, Gullo M, Bolliger M, and others. 2014. Chasing central nervous system plasticity: the brainstem's contribution to locomotor recovery in rats with spinal cord injury. *Brain* 137(6):1716-32.