Spinal cord stimulation: Harnessing the capacity of the human lumbar spinal circuitry for the recovery of motor function after spinal cord injury

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Traumatic spinal cord injury severs the descending control of spinal circuits caudal to the injury, causing paralysis or paresis as well as impairment of other vital body functions below the lesion. In severe injuries, the recovery of any meaningful motor function by standard-of-care rehabilitation regimens is limited, often leading to confined and dependent lives of those afflicted.

Neuromodulation through electrical spinal cord stimulation has currently been revisited as a potential breakthrough treatment for motor dysfunction following severe spinal cord injury. The underlying principle is to re-balance the excitability of spared spinal circuits caudal to the lesion (Holsheimer 1998) and to harness their rich intrinsic motor-output generating capacity (Dimitrijevic et al. 1998; Minassian et al. 2004; Jilge et al. 2004).

Epidural stimulation of the lumbar spinal cord through electrodes placed in the posterior epidural space (Fig. 1) activates large-to-medium diameter afferent fibers within several lumbar and upper sacral posterior roots bilaterally (Rattay et al. 2000; Minassian et al. 2004; Ladenbauer et al. 2010; Danner et al. 2011). Spinal reflex circuits as well as (pluri-) segmentally organized circuits within the spinal cord gray matter controlling stereotyped lower-limb motor patterns (Dimitrijevic et al. 1998; Jilge et al. 2004; Minassian et al. 2004; Hofstoetter, Danner, et al. 2015; Danner et al. 2015) are transsynaptically recruited through the afferent driving input.

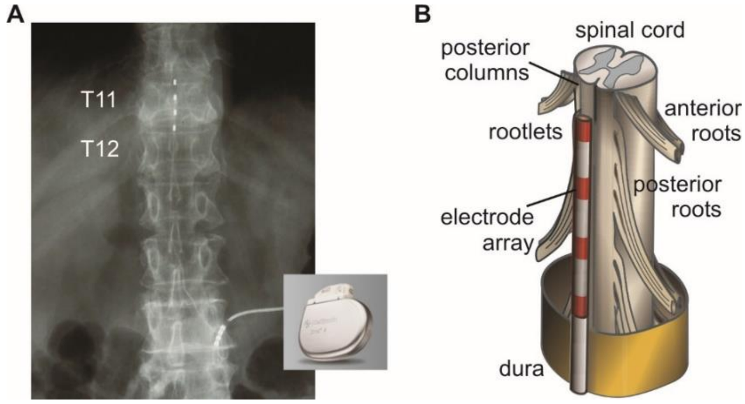

Figure 1. Epidural stimulation of the lumbar spinal cord. **A** X-ray of the low thoracic (T) spine and an epidurally placed lead with four electrodes (white rectangles). **B** Sketch showing the placement of the epidural electrode with respect to relevant anatomical and neural structures.

The therapeutic effects of epidural lumbar spinal cord stimulation in spinal cord injured individuals strongly depend on the stimulation parameters applied (Minassian & Hofstoetter 2016; Minassian, McKay, et al. 2016). When delivered at a frequency within a range of 50–100

Hz and with an intensity below the threshold for the elicitation of muscle activity in the lower extremities, the stimulation can effectively control refractory, generalized forms of lower-limb spasticity (Pinter et al. 2000). Stimulation at 25–50 Hz can generate rhythmic flexion-extension leg movements (Dimitrijevic et al. 1998; Minassian et al. 2004; Danner et al. 2015) in paralyzed individuals lying supine. When combined with assisted and body weight supported treadmill stepping, such stimulation augments the rhythmic motor activity produced by the gait-phase related proprioceptive feedback input and recruits additional, otherwise non-responding lower-limb muscle groups (Minassian et al. 2005; Harkema et al. 2011). Epidural stimulation at 5–20 Hz can induce strong bilateral leg extension in completely paralyzed individuals tested in the supine position (Jilge et al. 2004) that can translate, after intensive training, into functional, full weight-bearing upright standing with only minimum self-assistance for balance (Angeli et al. 2014; Rejc et al. 2015). Much of the current resurgence of interest in epidural lumbar spinal cord stimulation can be ascribed to the finding that it may indeed enable some rudimentary voluntary control over otherwise paralyzed muscles by enhancing the responsiveness of the lumbar spinal circuitry to otherwise insufficient descending command signals (Barolat et al. 1986; Harkema et al. 2011; Angeli et al. 2014; Minassian, McKay, et al. 2016).

The same input structures to the lumbar spinal cord as with the epidural technique, i.e., afferent fibers within the posterior roots, can also be selectively stimulated from the body surface using self-adhesive electrodes placed on the back and the lower abdomen (Fig. 2; Minassian et al. 2007; Minassian et al. 2011), mainly due to tissue heterogeneities in the stimulation area (Ladenbauer et al. 2010; Danner et al. 2011; Ursula S. Hofstoetter et al. 2014). Consequently, when used to apply a tonic driving input to the lumbar circuitry, this transcutaneous version of spinal cord stimulation can also induce similar neuromodulative effects. Proof-of-concept studies demonstrated that a 30-minute session of transcutaneous spinal cord stimulation at 50 Hz and with an intensity below the threshold to generate muscle activity in the legs temporarily ameliorates various clinical manifestations of spasticity in spinal cord injured individuals (Ursula S Hofstoetter et al. 2014) and that these effects outlast the stimulation application for at least two hours (US Hofstoetter et al. 2014). In one patient, it was shown that the effects progressively increased and persisted for even prolonged periods of time (up to ten days) when the stimulation was repetitively applied during a period of six weeks (US Hofstoetter et al. 2014). The subject was later implanted with an epidural system that similarly controlled his spasticity, suggesting that the transcutaneous technique may also develop into a non-invasive trial procedure to identify in advance responders to epidural stimulation. Transcutaneous spinal cord stimulation at around 30 Hz was further demonstrated to facilitate the locomotor capacity of ambulatory, motor-incomplete spinal cord injured individuals (Hofstoetter et al. 2013; Hofstoetter, Krenn, et al. 2015) and to considerably enhance the motor output produced by step-related proprioceptive feedback input and to recruit otherwise non-responding muscle groups in patients with (motor) complete lesions passively stepping on a treadmill (Minassian, Hofstoetter, et al. 2016). When applied at 15 Hz, transcutaneous spinal cord stimulation induced upright standing in four individuals with (motor) complete spinal cord injury studied (Hofstoetter & Minassian 2016).

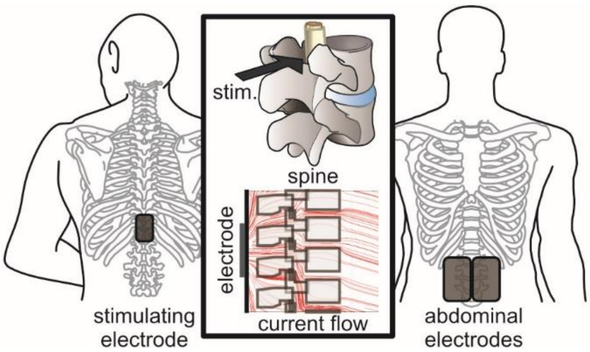

Figure 2. Transcutaneous stimulation of the lumbar spinal cord. Schematic drawing depicts the placement of the paraspinal stimulating electrode on the back at the level of the lumbar spinal cord corresponding on average to T11 and T12 vertebral levels and of the indifferent abdominal electrodes. Sketch in the middle illustrates stimulation (stim.) through the better conductive ligaments and discs in-between the vertebral bones, along with a computer simulation of the current flow produced in a mid-sagittal plane.

In summary, electrical stimulation of the lumbar spinal cord appears as a promising neuromodulation intervention to considerably shift the limits of standard-of-care modalities in spinal cord injury rehabilitation. Recent observations further strongly suggest that its effects are not confined to the alleviation of symptoms, but that its chronic application may indeed trigger beneficial structural and physiological plasticity at various levels of the central nervous system leading to long-term, unprecedented therapeutic outcomes.

References

Angeli, C.A. et al., 2014. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain : a journal of neurology*, 137, pp.1394–409.

Barolat, G., Myklebust, J.B. & Wenninger, W., 1986. Enhancement of voluntary motor function following spinal cord stimulation--case study. *Applied neurophysiology*, 49, pp.307–14.

Danner, S.M. et al., 2011. Can the human lumbar posterior columns be stimulated by transcutaneous spinal cord stimulation? A modeling study. *Artificial organs*, 35, pp.257–62.

Danner, S.M. et al., 2015. Human spinal locomotor control is based on flexibly organized burst generators. *Brain : a journal of neurology*, 138, pp.577–88.

Dimitrijevic, M.R., Gerasimenko, Y. & Pinter, M.M., 1998. Evidence for a spinal central pattern generator in humans. *Annals of the New York Academy of Sciences*, 860, pp.360–76.

Harkema, S. et al., 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, pp.1938–47.

Hofstoetter, U. et al., 2014. Short- and long-term effects of intermittent transcutaneous spinal cord stimulation on spinal spasticity and residual motor control. *Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience. Online.*, 630.04.

Hofstoetter, U. & Minassian, K., 2016. Transcutaneous spinal cord stimulation to induce standing in individuals with motor complete spinal cord injury. In *Proceedings of the 12th Vienna International Workshop on Functional Electrical Stimulation*. Vienna.

Hofstoetter, U.S., Krenn, M., et al., 2015. Augmentation of Voluntary Locomotor Activity by Transcutaneous Spinal Cord Stimulation in Motor-Incomplete Spinal Cord-Injured Individuals.

Artificial Organs, 39, pp.E176–86.

Hofstoetter, U.S. et al., 2013. Effects of transcutaneous spinal cord stimulation on voluntary locomotor activity in an incomplete spinal cord injured individual. *Biomedizinische Technik. Biomedical engineering*.

Hofstoetter, U.S. et al., 2014. Modification of spasticity by transcutaneous spinal cord stimulation in individuals with incomplete spinal cord injury. *The journal of spinal cord medicine*, 37, pp.202–11.

Hofstoetter, U.S., Danner, S.M., et al., 2015. Periodic modulation of repetitively elicited monosynaptic reflexes of the human lumbosacral spinal cord. *Journal of Neurophysiology*, 114, pp.400–10.

Hofstoetter, U.S., Danner, S.M. & Minassian, K., 2014. Paraspinal Magnetic and Transcutaneous Electrical Stimulation. In D. Jaeger & R. Jung, eds. *Encyclopedia of Computational Neuroscience*. New York, NY: Springer New York, pp. 1–21.

Holsheimer, J., 1998. Concepts and methods in neuromodulation and functional electrical stimulation: an introduction. *Neuromodulation : journal of the International Neuromodulation Society*, 1, pp.57–61.

Jilge, B. et al., 2004. Initiating extension of the lower limbs in subjects with complete spinal cord injury by epidural lumbar cord stimulation. *Experimental brain research*, 154, pp.308–26.

Ladenbauer, J. et al., 2010. Stimulation of the human lumbar spinal cord with implanted and surface electrodes: a computer simulation study. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 18, pp.637–45.

Minassian, K. et al., 2005. Effect of peripheral afferent and central afferent input to the human lumbar spinal cord isolated from brain control. *Biocybern Biomed Eng*, 25, pp.11–29.

Minassian, K. et al., 2007. Posterior root-muscle reflexes elicited by transcutaneous stimulation of the human lumbosacral cord. *Muscle & nerve*, 35, pp.327–36.

Minassian, K., Hofstoetter, U.S., et al., 2016. Spinal Rhythm Generation by Step-Induced Feedback and Transcutaneous Posterior Root Stimulation in Complete Spinal Cord-Injured Individuals. *Neurorehabilitation and neural repair*, 30, pp.233–43.

Minassian, K. et al., 2004. Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound muscle action potentials. *Spinal cord*, 42, pp.401–16.

Minassian, K., McKay, W.B., et al., 2016. Targeting Lumbar Spinal Neural Circuitry by Epidural Stimulation to Restore Motor Function After Spinal Cord Injury. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*, 13, pp.284–94.

Minassian, K. & Hofstoetter, U.S., 2016. Spinal Cord Stimulation and Augmentative Control Strategies for Leg Movement after Spinal Paralysis in Humans. *CNS neuroscience & therapeutics*, 22, pp.262–70.

Minassian, K., Hofstoetter, U.S. & Rattay, F., 2011. Transcutaneous lumbar posterior root stimulation for motor control studies and modification of motor activity after spinal cord injury. In M. Dimitrijevic et al., eds. *Restorative neurology of spinal cord injury*. New York: Oxford University Press, pp. 226–255.

Pinter, M.M., Gerstenbrand, F. & Dimitrijevic, M.R., 2000. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 3. Control Of spasticity. *Spinal cord*, 38, pp.524–31.

Rattay, F., Minassian, K. & Dimitrijevic, M.R., 2000. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 2. quantitative analysis by computer modeling. *Spinal cord*, 38, pp.473–89.

Rejc, E., Angeli, C. & Harkema, S., 2015. Effects of Lumbosacral Spinal Cord Epidural Stimulation for Standing after Chronic Complete Paralysis in Humans. *PloS one*, 10, p.e0133998.