



Editorial

Scientific Achievements of Our Era: “Making the Lame Walk”



Martin N. Stienen¹, Yoon Ha²

¹Department of Neurosurgery & Spine Center of Eastern Switzerland, Kantonsspital St.Gallen, St.Gallen, Switzerland

²Department of Neurosurgery, Spine and Spinal Cord Institute, Severance Hospital, College of Medicine, Yonsei University, Seoul, Korea

Corresponding Author

Martin N. Stienen

<https://orcid.org/0000-0002-6417-1787>

Department of Neurosurgery, Spine
Center of Eastern Switzerland,
Kantonsspital St.Gallen Rorschacher Str.
95, CH-9000 St.Gallen, Switzerland
Email: mnstienen@gmail.com

It has long been the goal of mankind to restore mobility to patients with spinal cord injury (SCI), although the results of studies that attempt to implement therapeutic measures immediately after the injury has occurred have so far not been of overwhelming benefit. Hence, it was with pleasure and admiration that we read the article of our colleagues from the Romandy in the journal *Nature Medicine* at the beginning of February this year,¹ in which they report groundbreaking progress in research on functional rehabilitation in the chronic phase after severe SCI. Their extensive work over the past years, with various pre-clinical and clinical successes, culminates for the time being in the currently reported study. The group of authors, consisting of (clinical) neuroscientists, IT-, electrical and biomechanical engineers, and physicists, among others, put some essential development steps in a logical order and aligned them to develop and apply novel technology in 3 patients within the setting of a clinical trial (www.clinicaltrials.gov identifier NCT02936453). In the following 2 paragraphs we briefly summarize the key steps of their work:

In the preclinical phase of this project, spinal cord topology and its variability was studied with the intention to identify an arrangement of electrodes that would be suitable to target all 16 dorsal roots between the lower thoracic (Th12) and upper sacral spinal segments (S1, S2) selectively, considering anatomical differences across the human population. From here, the optimal arrangement of the 16 electrodes contained in an epidural electrical stimulation (EES) paddle was determined based on 15 personalized computational anatomical and biophysical models, and a corresponding atlas was generated. Electrode positioning was optimized by analyzing rostral-caudal distribution, lateral position (to maximize left-right selectivity), use of a midline electrode to minimize undesired contralateral recruitment at high EES amplitudes, as well as selective recruitment of sacral dorsal rootlets by transverse arrangement of electrodes. Paddles were fabricated and their selectivity was again tested on the 15 computational models, which revealed expected performance variability, resulting from inter-individual differences in spinal cord topology.

For the clinical phase of this project, personalized models of the spine were hence generated for each of the so far included 3 participants with complete sensorimotor SCI. These models outline the projectome of afferents by determining the blood oxygenation level-dependent response in the spinal cord with activation of those proprioceptors that typically lead to the predominant activation of homonymous motor neurons.² The optimal position of the paddle lead was determined based on an algorithm derived from these measurements,



This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2022 by the Korean Spinal Neurosurgery Society

and implants were precisely advanced to the desired position by a neurosurgeon and with the assistance of intraoperative 3-dimensional computed tomography image guidance. Intraoperative stimulations with single pulses were monitored with electromyographic recordings to quantify the selectivity of electrodes and to verify, whether lead position could be optimized. The authors modified the commercially available implantable pulse generator to build a neurostimulation platform, which enables the delivery of concurrent stimulation waveforms that can be turned on or off with precise timing, as well as allows for the adjustment of stimulation parameters in closed-loop fashion via wireless communication modules. Using a new software to rapidly configurate the activity-dependent stimulation programs in individual patients, fine-tuning of EES parameters was possible and enabled all 3 participants to take steps and walk within 1 hour after activation of the system. As all the patients had exhibited complete sensorimotor SCI with resulting chronic (extensor) muscle atrophy of the lower limbs, substantial amounts of body-weight support were required in the first period to support ambulation, but the EES system enabled participants to perform up to 300 independent steps on the first day. Parallel to fine-tuning the walking ability by adjusting parameters and a simultaneous 5-month rehabilitation period, walking function of the participants improved and the system was extended to allow subsequent further motor activities including, e.g., climbing staircases, riding a recumbent trike, boxing, paddling a canoe or enjoying a drink at a bar while standing.¹

Besides this article constituting an innovative milestone in clinical neuroscience, it provides long awaited hope for many SCI patients who desire to regain more independence and daily function. Although the authors emphasize that—despite the restoration of independent walking ability—the patients' movements did not appear perfectly natural, patients were able to perform various activities for a long time, which was previously impossible. Extrapolating from these results, it appears even conceivable that with ongoing research such a therapeutic concept might address further neurological functions that are often impaired and likewise prioritized by patients with SCI, e.g., the regulation of bladder and bowel function, hemodynamics, or upper limb function.³ Moreover, the authors reported that 2 out of 3 included patients were able to modulate the leg movements during EES, and recovered activation of proximal motor groups of the leg even without the EES being active.¹ This raises the hope that, in addition to the positive effects of the EES itself, reactivation of residual descending pathway systems will be pos-

sible, which would not take place without external stimuli.⁴

Without wanting to diminish these outstanding and inspiring results, we should still be aware that for now, the level of evidence for this new application corresponds to the one of a case-series ($n=3$). Whether the coordinated generation of harmonized muscle contraction required for complex movements as in walking, swimming, etc. will be possible in a reasonable fraction of SCI patients, some of which suffer from extreme hypertonic and spastic muscles, remains to be proven. We are hence very much looking forward to the final results of the ongoing study (according to the clinicaltrials.gov protocol a total of 10 patients will be examined), which will—besides the beautifully illustrated photos and videos of individual patient vignettes—also report summative data with objectively measurable changes on standardized outcome measures like the 10-meter or the 6-minute walk test.⁵ These, besides other more subjective scales measuring functional impairment, functional capacity, neurological function, pain and quality of life, will eventually be used to evaluate the net value of this innovative technique for our patients and to request official approval. If the current, extremely promising results are confirmed in the larger cohort, and no major issues (e.g., adverse effects of long-term spinal cord stimulation, poor battery life for complex stimulation patterns, joint pain or even fracture when stimulating patients with severe stiffness/spasm, etc.) are encountered and hamper the application of this new device in the “real-life setting,” the door is wide open for further clinical trials that ideally also include cost-benefit analyses. It seems that we have come a great deal closer to a long-desired goal of mankind.

Conflict of Interest: The authors have nothing to disclose.

REFERENCES

1. Rowald A, Komi S, Demesmaeker R, et al. Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. *Nat Med* 2022;28:260-71.
2. Kinany N, Pirondini E, Micera S, et al. Dynamic functional connectivity of resting-state spinal cord fMRI reveals fine-grained intrinsic architecture. *Neuron* 2020;108:424-35.e4.
3. Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma* 2004;21:1371-83.
4. van den Brand R, Heutschi J, Barraud Q, et al. Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science* 2012;336:1182-5.

5. Stienen MN, Ho AL, Staartjes VE, et al. Objective measures of functional impairment for degenerative diseases of the

lumbar spine: a systematic review of the literature. *Spine J* 2019;19:1276-93.



Title: The Dream (Le Rêve)
Artist: Pablo Picasso
Year: 1932
© 2022 - Succession Pablo Picasso - SACK (Korea)