The power of placebo to restore neurological function after spinal cord injury: implications for neuromodulation

Jessica McDougall[1,2], Jacquelyn J. Cragg[1,3], Robert M. Brownstone[4], John L.K. Kramer*[1,5]

[1]International Collaboration on Repair Discoveries (ICORD), Blusson Spinal Cord Centre, University of British Columbia, Vancouver, British Columbia, Canada.

[2]Department of Rehabilitation Sciences, University of British Columbia, Vancouver, British Columbia, Canada.

[3]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada.

[4] University College London, Queen Square Institute of Neurology, UCL, London, UK, WC1N 3BG.

[5]Department of Anesthesiology, Pharmacology, and Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada.

Word count: 2665

Corresponding Author:

Dr. JLK Kramer

kramer@icord.org

604-675-8810

Blusson Spinal Cord Centre, 3rd floor

818 West 10th Avenue

V5Z 1M9

Abstract

Uncontrolled, unblinded studies demonstrate that neuromodulation, especially spinal cord stimulation, improves function for those with chronic spinal cord injury, justified by the claim that placebo control conditions are unethical and impossible. Here we discuss the validity of that claim and provide potential solutions to investigate the true effectiveness of neuromodulation for spinal cord injury.

Keywords: spinal cord injury, neuromodulation, placebo, research design, clinical trials, randomized clinical trials

Neuromodulation has gained considerable attention as a potential therapeutic option for individuals with chronic spinal cord injury, with studies showcasing remarkable recovery of both motor and sensory function[1,2] Encompassing a variety of techniques, neuromodulation broadly involves "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation, to specific neurological sites in the body."[3] Particularly promising are the results of seminal applications of spinal cord stimulation, both permanently implanted and non-invasive forms.[4–7] The underlying technology of spinal cord stimulation is advancing, as evidenced in the development of novel stimulation paradigms and interfaces,[8] accompanied by patents and industry partnerships.

To date, spinal cord stimulation techniques in the field of spinal cord injury are most commonly examined in open label trials. This has been largely justified on the basis that a true sham is impossible to achieve, owing primarily to paresthesia that accompanies active stimulation. Additionally, ethical issues have been raised, including concerns around the use of sham stimulators infringing on patient autonomy, and the potential of violating the principles of beneficence, justice, and nonmaleficence.[9] Until recently, it also reflects the relative infancy of the field, with pivotal phase trials chiefly focused on proof of concept. The obvious question arising from these studies is: how much of the functional benefits of spinal cord stimulation in individuals with spinal cord injury is attributable to the placebo effect?

To aid the progress of spinal cord stimulation interventions for individuals with spinal cord injury, we aim to summarize key factors underlying the placebo effect and its putative role in modifying neurological function. Secondly, we explore potential solutions that would improve understanding of the true efficacy of spinal cord stimulation as a therapy for spinal cord injury.

What is the "placebo effect"?

A placebo is an intervention that has no biological effect (i.e., inert).[10] The "placebo effect" – the end result of administering placebo – encompasses 5 critical factors:[11]

1. **Natural fluctuations in the course of disease.** For many health conditions, disease progression varies over time, seemingly spontaneously. If a participant enrolls at their "worst" (when they are most likely to seek novel interventions), this increases the likelihood that an improvement will be seen even in the absence of intervention (i.e., after some spontaneous improvement in function, that would have occurred regardless of the intervention).
2. **Impact of co-interventions.** Because care is multi-faceted for complex conditions, including rehabilitation and treatment for secondary complications, this may lead to improvements in function unrelated to the target intervention.
3. **Regression towards the mean.** Representing a statistical phenomenon, whereby extreme values tend to approach less extreme values over time, regardless of the intervention.[12]
4. **Hawthorne effect.** There is a tendency to change behavior with knowledge that one is being observed. For example, the Hawthorne effect has been proposed as a source of increasing symptom severity at screening, aligning with examiner expectations that symptoms should be severe enough to justify inclusion in the trial, leading to improvement which is due to a participant returning to baseline at a later follow-up time-point.[11] This effect also applies to an unblinded examiner, whose behavior may also change, impacting outcome assessments.
5. **Participant expectation and conditioning.** Expectation produces similar biological effects in the central nervous system (and elsewhere) as active treatment. These biological effects have been demonstrated in Parkinson's disease, where conditioning and expectation for change increases dopamine in the brain, paralleling the effect of active pharmacological

treatment.[13] Several trial design features enhance expectation, including a history of success, the invasiveness of study procedures (e.g., surgery versus pharmacological interventions), and increased number of visits with study personnel.

On this foundation, it is reasonable to assume that common outcomes incorporated in spinal cord stimulation trials will show improvement independently of active treatment. Indeed, neurological outcomes can fluctuate spontaneously (e.g., spasticity) and stimulation is often paired with active rehabilitation (i.e., a cointervention that could, conceivably, lead to improvements in neurological function without stimulation). Additionally, spinal cord stimulation trials often include individuals that are extreme outliers. For example, spinal cord stimulation has been proposed as an intervention to manage cardiovascular deficits associated with spinal cord injury, including orthostatic hypotension – a condition characterized by low blood pressure.[14] Orthostatic hypotension tends to be most pronounced when an individual with spinal cord injury is in the upright, sitting position compared to the supine position, where blood pressure values are higher (i.e., closer to normal). Therefore, an open label study examining the effects of spinal cord stimulation on orthostatic hypotension will – by virtue of more extreme initial values and regression towards the mean – observe benefits on sitting systolic blood pressure far greater than supine systolic blood pressure. Improvements in function associated with spinal cord stimulation could also be attributable to the expectation of a benefit. Spinal cord stimulation trials are characterized by nearly all of the design features that are known to increase expectation for benefit – invasiveness (in the case of epidural stimulation), many study visits, and designed on past, well documented, and public successes.[15] Lastly, the Hawthorne effect could affect trial results: by participating in a clinical trial aimed at improving a specific function, a person with spinal cord injury engages more in that target function in daily life, which translates into gains non-specific to stimulation.[16]

Additionally, examiner blinding is a major concern in open label trials. Meta-research has demonstrated the importance of blinding in controlled trials, finding those with unblinded examiners produce larger treatment effects,[16] mirroring that reported in preclinical studies.[17] Overall, this suggests that unblinded examiners, which is often the case for open-label neuromodulation trials (see[8] as an exception), tend to overestimate the benefits of treatment (i.e., “round up”) or underestimate the benefits of placebo/sham effects (i.e., “round down”), or both.

Beyond theory, past clinical trials aiming to restore neurological function in individuals with spinal cord injury clearly demonstrate the potential for placebo effects. For example, open-label spinal cord stimulation trials demonstrate a similar improvement in 6-minute walk test distances to those reported in sham intermittent hypoxia (i.e., normoxic air)[18] – an increase of 60 m.[4] A similar magnitude of change for the 6-minute walk test has also been reported for studies addressing test-retest reliability, with a trend emerging for increased distances upon reevaluation (~+20 m)[19] – an outcome that reflects a natural tendency to “beat” the baseline.

Parallels also exist with applications of neuromodulation in other neurological conditions. Perhaps most relevant to spinal cord stimulation in individuals with spinal cord injury is deep brain stimulation in individuals with Parkinson’s disease. Based on secondary analysis of treatment effects in cross-over designed trials, upwards of 40% of improvement in motor function has been proposed as a function of placebo (more specifically, the expectation component of placebo).[13,20] This could be, at least in part, attributable to an overlap in mechanisms, with both active and sham deep brain stimulation engaging dopaminergic systems.[21] The role of dopamine after spinal cord injury has been extensively studied,[22] including with regards to locomotion[23] and, more recently, micturition reflexes.[24,25] To the extent that changes in dopamine associated with the expectation for a benefit (i.e., a "reward") are associated with improvements in function in individuals with spinal cord injury remains unknown.

What to do?

In order to address the placebo effect, there are a number of options to consider. First, to truly address its impact in spinal cord injury, trials need an "untreated" condition. Individuals in this group would neither undergo active nor sham stimulation, but rather be randomized to observe natural history, thereby accounting for spontaneous fluctuations and regression towards the mean (as well as improvements attributable to co-interventions). These individuals, by virtue of not being treated or assurances of treatment, will also have no expectation (or at least less compared to the other groups) to experience a benefit. By contrasting changes in the natural history condition to the placebo condition, one can isolate how much an outcome is impacted by expectation. While interesting from the perspective of understanding placebo, the obvious challenge with including a natural history group in a clinical trial is the burden on participants and investigators.

Alternatively, trials could include outcomes resistant to placebo. A placebo condition is ethically included in trials on the grounds that the outcomes measures are subject to placebo effects – for example, tend to fluctuate over time. This is, of course, not always the case. In the field of pain, brain function has been proposed as a robust surrogate of pain ratings that is resistant to placebo (at least more so than pain ratings themselves).[26] The challenge is two-fold. First, placebo-resistant outcomes are unlikely priorities for individuals with spinal cord injury and, as a result, only applicable in early stages of investigation. Second, many commonly employed outcomes, despite their proposed objectivity, may still be subject to placebo effects. For example, motor evoked potentials (MEPs) rank among the best ways to evaluate cortical excitability and continuity in the corticospinal tract after spinal cord injury and thus are ideal to serve as an objective biomarker of motor function. MEPs are, however, reportedly modified by placebo.[27] Determining the resiliency of outcomes to placebo in the context of spinal cord injury is an important area of research.

As an active comparator, peripheral nerve stimulation represents a logical condition to include in spinal cord stimulation studies. There are demonstrated benefits of pairing rehabilitation with cutaneous peripheral nerve stimulation, improving a variety of neurological outcomes in individuals with spinal cord injury,[28] much the same way that has been reported for spinal cord stimulation.[1,4,5] A comparison with peripheral nerve stimulation provides an opportunity to determine the degree that benefits associated with spinal cord stimulation are beyond what can be achieved with existing technologies (participant expectations included). A recent case report has demonstrated comparable effects of spinal and spinal adjacent stimulation, both ameliorating spasticity after transcutaneous application.[29]

The ideal solution would involve a sham condition. Shams should incorporate a stimulation paradigm that maintains blinding (i.e., evokes paresthesia to some comparable degree) but is ineffective in modulating spinal cord activity. Critically, sham stimulation does not need to be completely inert, rather it just should not act on the same substrate or mechanism as the active form of intervention. In the case of neuromodulation of the spinal cord, sham stimulation must not directly activate the dorsal roots (but it can active the same roots by way of the periphery). This, in effect, demonstrates the specificity of the approach (i.e., what is special about spinal cord stimulation?), while providing a blinded comparison group. Two inactive sham groups have been used in trials so far, both in relation to transcutaneous stimulation. The predominant method involves turning on stimulation for a short period of time, before turning it off, accompanied by instructions that participants may perceive the stimulation as turning off – an attempt to modify participant expectation.[30] A similar approach could, presumably, be programmed into epidural stimulation. This approach accepts that sham activates the dorsal roots but does not do so for a long enough period of time to yield meaningful benefits (i.e., mechanism of benefits is related to persistent activation). The main challenge with this approach, however, is that it relies on modifying the expectation of the participant (through verbal instruction) to believe that perception to stimulation may wane (or habituate) over time – expectation that may depend on a variety of factors, including previous knowledge of the intervention. Another inactive approach modifies stimulation parameters to a point of biological inertness. For example, Sayenko and colleagues incorporated biphasic stimulation on the grounds that it had no measurable effect to evoked spinal reflexes (compared to monophasic active transcutaneous spinal cord stimulation).[31] The primary challenge with this approach is that it requires an investment of time and funds to develop adequate sham and blinding procedures. Nevertheless, the importance of investing in sham devices is evidenced in other neuromodulation modalities, such as repetitive transcranial magnetic stimulation.[32]

There is also the emerging use of "paresthesia free" stimulation. The development of paresthesia free spinal cord stimulation represented a significant advance in spinal cord stimulation technology in the field of chronic pain.[33] As the name implies, the advantage of this approach, from the perspective of a user, is that, unlike conventional forms of spinal cord stimulation, there is no sensory feedback. It was principally designed to manage pain symptoms without the discomfort associated with stimulation. From a trial design perspective, paresthesia free spinal cord stimulation represents an intriguing opportunity to incorporate double blinding and a true placebo/sham control – the participant is randomized to an "on" or "off" condition and is "truly" blinded. Recent reports indicate that paresthesia free stimulation, like more conventional forms of spinal cord stimulation, may improve motor function in individuals with spastic paralysis, indicating feasibility, at least for epidural stimulation.[34]

At a minimum, investigators should consider blinding examiners, as well as the adoption of minimum thresholds for improvements in primary and secondary outcomes. Blinding of examiners is feasible in open label trials. For example, a trial could use an external examiner to perform assessments before and after an intervention unaware of the study purpose and intervention, independently appointed by the study team, uncompensated beyond time in completing the assessment. To this point, blinding has rarely been employed in neuromodulation trials involving individuals with spinal cord injury (with some exceptions[8]). This too will come at a cost to the study (e.g., financial burden to complete assessments) but is perhaps the most feasible solution that could be immediately implemented in open label spinal cord stimulation clinical trials. The adoption of clear cut-offs, established on historical psychometric properties of an outcomes – namely, test-retest reliability – would also greatly enhance the interpretation of improvements beyond that which is expected to occur naturally. It is important, however, to keep in mind that test-retest reliability metrics have been established in the absence of an expectation for improvement, and thus do not account for the potential bias of placebo effects.

Regardless of the approach taken to account for placebo effects, understanding the effectiveness of blinding, from both the participant and examiner perspective, is critically important. This will only be achieved if trials query the success of blinding. Moreover, masking other potential sources of unblinding would be important to consider. Substantial effort in the field of pain has been paid to ensure blinding in neuromodulation trials, including the use of magnetic cards to automatically select active or sham stimulation without the operator's knowledge.[35] Such methods should be considered in future spinal cord stimulation trials.

The inclusion of placebo controls in spinal cord stimulation trials may be challenging; the options proposed include additional equipment, effort, time, and financial support that will be burdensome. However, these are challenges that have been overcome in similar fields. For example, through understanding the neuronal response to placebo in the subthalamic nucleus (a common target for deep brain stimulation), and subsequently employing outcome measures tailored to record such changes in well-controlled studies, there is now support that deep brain stimulation is beneficial for Parkinson's Disease beyond that attributable to placebo effect.[36] The success in employing placebo controls in other challenging scenarios should be encouragement for the use of sham in spinal cord stimulation trials.

Spinal cord stimulation and other neuromodulatory therapies are promising technologies to restore neurological function in individuals with spinal cord injury. Basic science and clinical anecdotes support a profound effect on function; however, to this point studies have been designed such that they are likely prone to placebo effects, including mounting expectations from individuals with spinal cord injury. In parallel to developing more advanced technologies, pause is warranted to consider the impact of placebo and adjust trial designs accordingly. Confirmation of the potential placebo effects of spinal cord stimulation is vital in ensuring the observed recovery is truly due to the stimulation itself. And, through unraveling the mechanisms of observed functional recovery, we may be able to avoid unnecessary invasiveness and combine treatments in the future and lead to even greater improvements in those with spinal cord injury.

To this end, we have proposed options to consider in clinical trials, including the use of active and/or sham comparators, and paresthesia-free stimulation.

Declaration of Conflicting Interests: The Authors declare that there is no conflict of interest.

References

1. James ND, McMahon SB, Field-Fote EC, Bradbury EJ. Neuromodulation in the restoration of function after spinal cord injury. *Lancet Neurol*. 2018;17(10):905-917. doi:10.1016/S1474-4422(18)30287-4

2. Cajigas I, Vedantam A. Brain-computer interface, neuromodulation, and neurorehabilitation strategies for spinal cord injury. *Neurosurg Clin N Am*. 2021;32(3):407-417. doi:10.1016/j.nec.2021.03.012

3. Thomson S. Neuromodulation, or Neuromodulatory Effect. International Neuromodulation Society. November 21, 2021. Accessed December 12, 2024. https://www.neuromodulation.com/neuromodulation-defined

4. Wagner FB, Mignardot JB, Le Goff-Mignardot CG, et al. Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature*. 2018;563(7729):65-71. doi:10.1038/s41586-018-0649-2

5. Jackson A, Zimmermann JB. Neural interfaces for the brain and spinal cord: Restoring motor function. *Nat Rev Neurol*. 2012;8(12):690-699. doi:10.1038/nrneurol.2012.219

6. Herrity AN, Williams CS, Angeli CA, Harkema SJ, Hubscher CH. Lumbosacral spinal cord epidural stimulation improves voiding function after human spinal cord injury. *Sci Rep*. 2018;8(1):8688. doi:10.1038/s41598-018-26602-2

7. Hachmann JT, Yousak A, Wallner JJ, Gad PN, Edgerton VR, Gorgey AS. Epidural spinal cord stimulation as an intervention for motor recovery after motor complete spinal cord injury. *J Neurophysiol*. 2021;126(6):1843-1859. doi:10.1152/jn.00020.2021

8. Lorach H, Galvez A, Spagnolo V, et al. Walking naturally after spinal cord injury using a brain-spine interface. *Nature*. 2023;618(7963):126-133. doi:10.1038/s41586-023-06094-5

9. Mollica A, Greben R, Cyr M, Olson JA, Burke MJ. Placebo effects and neuromodulation: Ethical considerations and recommendations. *Can J Neurol Sci J Can Sci Neurol*. 2023;50(s1):s34-s41. doi:10.1017/cjn.2023.24

10. Stewart-Williams S, Podd J. The placebo effect: Dissolving the expectancy versus conditioning debate. *Psychol Bull*. 2004;130(2):324-340. doi:10.1037/0033-2909.130.2.324

11. Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: The role of placebo, nocebo, and Hawthorne effects. *Lancet Neurol*. 2016;15(7):736-747. doi:10.1016/S1474-4422(16)00066-1

12. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: What it is and how to deal with it. *Int J Epidemiol*. 2005;34(1):215-220. doi:10.1093/ije/dyh299

13. de la Fuente-Fernández R, Stoessl AJ. The placebo effect in Parkinson's disease. *Trends Neurosci*. 2002;25(6):302-306. doi:10.1016/S0166-2236(02)02181-1

14. Harkema SJ, Legg Ditterline B, Wang S, et al. Epidural spinal cord stimulation training and sustained recovery of cardiovascular function in individuals with chronic cervical spinal cord injury. *JAMA Neurol*. 2018;75(12):1569-1571. doi:10.1001/jamaneurol.2018.2617

15. Howard J. Experimental spinal cord implant helps Parkinson's patient walk in new study. CNN Health. May 9, 2024. Accessed December 5, 2024. https://www.cnn.com/2023/11/06/health/parkinsons-spinal-cord-implant-study/index.html

16. Hróbjartsson A, Thomsen ASS, Emanuelsson F, et al. Observer bias in randomized clinical trials with measurement scale outcomes: A systematic review of trials with both blinded and nonblinded assessors. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2013;185(4):E201-211. doi:10.1503/cmaj.120744

17. Watzlawick R, Antonic A, Sena ES, et al. Outcome heterogeneity and bias in acute experimental spinal cord injury: A meta-analysis. *Neurology*. 2019;93(1):e40-e51. doi:10.1212/WNL.0000000000007718

18. Hayes HB, Jayaraman A, Herrmann M, Mitchell GS, Rymer WZ, Trumbower RD. Daily intermittent hypoxia enhances walking after chronic spinal cord injury: A randomized trial. *Neurology*. 2014;82(2):104-113. doi:10.1212/01.WNL.0000437416.34298.43

19. van Hedel HJ, Wirz M, Dietz V. Assessing walking ability in subjects with spinal cord injury: Validity and reliability of 3 walking tests. *Arch Phys Med Rehabil*. 2005;86(2):190-196. doi:10.1016/j.apmr.2004.02.010

20. de la Fuente-Fernández R. Uncovering the hidden placebo effect in deep-brain stimulation for Parkinson's disease. *Parkinsonism Relat Disord*. 2004;10(3):125-127. doi:10.1016/j.parkreldis.2003.10.003

21. de la Fuente-Fernández R. The placebo-reward hypothesis: Dopamine and the placebo effect. *Parkinsonism Relat Disord*. 2009;15 Suppl 3:S72-74. doi:10.1016/S1353-8020(09)70785-0

22. Sharples SA, Koblinger K, Humphreys JM, Whelan PJ. Dopamine: A parallel pathway for the modulation of spinal locomotor networks. *Front Neural Circuits*. 2014;8:55. doi:10.3389/fncir.2014.00055

23. Rossignol S, Chau C, Brustein E, et al. Pharmacological activation and modulation of the central pattern generator for locomotion in the cat. *Ann N Y Acad Sci*. 1998;860:346-359. doi:10.1111/j.1749-6632.1998.tb09061.x

24. Hou S, Carson DM, Wu D, Klaw MC, Houlé JD, Tom VJ. Dopamine is produced in the rat spinal cord and regulates micturition reflex after spinal cord injury. *Exp Neurol*. 2016;285(Pt B):136-146. doi:10.1016/j.expneurol.2015.12.001

25. Qiao Y, Brodnik ZD, Zhao S, et al. Spinal dopaminergic mechanisms regulating the micturition reflex in male rats with complete spinal cord injury. *J Neurotrauma*. 2021;38(6):803-817. doi:10.1089/neu.2020.7284

26. Zunhammer M, Bingel U, Wager TD, Placebo Imaging Consortium. Placebo Effects on the neurologic pain signature: A meta-analysis of individual participant functional magnetic resonance imaging data. *JAMA Neurol*. 2018;75(11):1321-1330. doi:10.1001/jamaneurol.2018.2017

27. Fiorio M, Emadi Andani M, Marotta A, Classen J, Tinazzi M. Placebo-induced changes in excitatory and inhibitory corticospinal circuits during motor performance. *J Neurosci Off J Soc Neurosci*. 2014;34(11):3993-4005. doi:10.1523/JNEUROSCI.3931-13.2014

28. Field-Fote EC. Spinal cord control of movement: Implications for locomotor rehabilitation following spinal cord injury. *Phys Ther*. 2000;80(5):477-484.

29. Lieu B, Everaert DG, Ho C, Gorassini MA. Skin and not dorsal root stimulation reduces hypertonus in thoracic motor complete spinal cord injury: A single case report. *J Neurophysiol*. 2024;131(5):815-821. doi:10.1152/jn.00436.2023

30. Estes SP, Iddings JA, Field-Fote EC. Priming neural circuits to modulate spinal reflex excitability. *Front Neurol*. 2017;8:17. doi:10.3389/fneur.2017.00017

31. Sayenko DG, Rath M, Ferguson AR, et al. Self-assisted standing enabled by non-invasive spinal stimulation after spinal cord injury. *J Neurotrauma*. 2019;36(9):1435-1450. doi:10.1089/neu.2018.5956

32. Duecker F, Sack AT. Rethinking the role of sham TMS. *Front Psychol*. 2015;6:210. doi:10.3389/fpsyg.2015.00210

33. Chakravarthy K, Richter H, Christo PJ, Williams K, Guan Y. Spinal cord stimulation for treating chronic pain: Reviewing preclinical and clinical data on paresthesia-free high-frequency therapy. *Neuromodulation J Int Neuromodulation Soc*. 2018;21(1):10-18. doi:10.1111/ner.12721

34. Gazzeri R, Galarza M, Occhigrossi F. Motor improvement and spasms recovery with high-frequency 10 kHz spinal cord stimulation in a patient with spastic tetraparesis: beyond pain relief. *Eur Spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc*. 2024;33(12):4750-4756. doi:10.1007/s00586-024-08505-1

35. Bouhassira D, Jazat-Poindessous F, Farnes N, et al. Comparison of the analgesic effects of “superficial” and “deep” repetitive transcranial magnetic stimulation in patients with central neuropathic pain: A randomized sham-controlled multicenter international crossover study. *Pain*. 2024;165(4):884-892. doi:10.1097/j.pain.0000000000003082

36. Mestre TA, Lang AE, Okun MS. Factors influencing the outcome of deep brain stimulation: Placebo, nocebo, lessebo, and lesion effects. *Mov Disord Off J Mov Disord Soc*. 2016;31(3):290-296. doi:10.1002/mds.26500