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Review

# Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain

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ABSTRACT

Spinal cord stimulation (SCS) is an established and cost-effective therapy for treating severe chronic pain. However, despite over 40 years of clinical practice and the development of novel electrode designs and treatment protocols, increases in clinical success, defined as the proportion of patients that experience 50% or greater self-reported pain relief, have stalled. An incomplete knowledge of the neural circuits and systems underlying chronic pain and the interaction of SCS with these circuits may underlie this plateau in clinical efficacy. This review summarizes prior work and identifies gaps in our knowledge regarding the neural circuits related to pain and SCS in the dorsal horn, supraspinal structures, and the Pain Matrix. In addition, this review discusses and critiques current experimental and computational models used to investigate and optimize SCS. Further research into the interactions between SCS and pain pathways in the nervous system using animal and computational models is a fruitful approach to improve this promising therapy.



## Contents



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## 1. Introduction

Spinal cord stimulation is a treatment option for patients with refractory chronic pain including failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), and idiopathic conditions such as fibromyalgia and irritable bowel syndrome. (Wall and Melzack, 1996; Kumar et al., 2007; Guan, 2012) Over 30,000 individuals receive SCS devices annually for chronic pain, and SCS is a growing industry with global annual sales exceeding $1.8 billion. In conventional SCS, short duration current or voltage pulses are delivered at a constant frequency through an epidural electrode to excite the axons in the dorsal columns that carry sensory non-nociceptive information from the source of pain (Shealy et al., 1972; Oakley and Prager, 2002). Stimulation parameters such as amplitude, pulse duration, pulse repetition frequency, and the configuration of active electrode contacts are selected based on a combination of paresthesia location, pain relief, and comfort and can have a significant impact on clinical outcomes (Table 1) (Aló and Holsheimer, 2002; Cameron, 2004; Turner et al., 2004). Patients undergoing SCS report higher quality of life, greater pain relief, and more frequent resumption of normal activities and employment relative to individuals undergoing pharmacological treatment alone (Cameron, 2004; Kumar et al., 2007). For some indications, SCS along with conventional therapies (drugs, physical therapy) is both more efficacious and cost-effective than conventional therapies alone (Kumar et al., 2002; Kumar and Rizvi, 2013)

Despite the success of SCS, there remain significant opportunities to improve the clinical efficacy of SCS. Notably, SCS has a relatively low mean "success rate" for treatment and significant variation in efficacy (Fig. 1): only 58% of patients experienced successful outcomes – defined as a 50% or greater improvement in self-reported pain – based on data from two reviews of clinical studies and case series encompassing 1972 through 2013 (North et al., 1993; Taylor et al., 2013). Furthermore, success rate does not correlate with study year ($R=0.09$, $p=0.4$ $t$-test), indicating that the therapy is not improving with innovation and experience. As well, an analysis of 74 studies originally intended to reveal prognostic factors for SCS efficacy identified only one statistically significant trend: a *negative* correlation between study quality as assessed by Jadad score and reported clinical success (Taylor et al., 2005, 2013).

The lack in improvement in SCS efficacy over the years, the high variability of clinical success rates, and the apparent dependence of efficacy on pain etiology (Kumar et al., 1998)

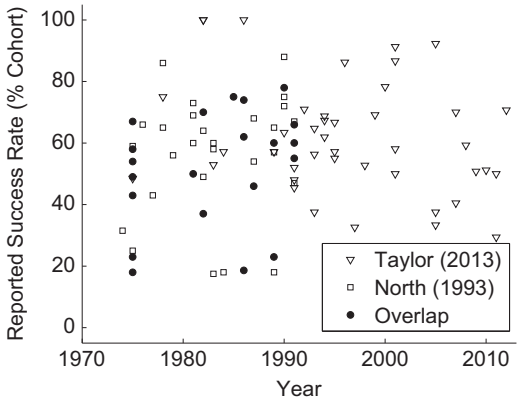


**Fig. 1 – A scatter plot showing reported mean success rates from clinical studies on SCS over the period of 1973–2013 where "success" is defined as 50% or greater subjective pain relief reported by the patient. Studies mentioned solely in one review and studies mentioned in both reviews are delineated by different markers. Adapted from North et al. (1993), Taylor et al. (2013).**

**Table 1 – Critical stimulation parameters and sample ranges reported from clinical studies.**

| Parameter | Representative ranges |
|---|---|
| Stimulation frequency | 50–150 Hz;[1] 15–750 Hz;[2] 80±29 Hz[b3]; 2–200 Hz[4]; 49±16.4 Hz[b5] |
| Stimulation amplitude[a] | 2–5 V;[2] 2.8–5.4 V;[1] 3±1.5 V;[b3] 3.7±2.0 V[†5] |
| Waveform pulse width | 150–500 μs[1]; 80–500 μsb[2]; 270±79 μs[b3]; 350±95.5 μs[b5] |
| Electrode geometry[1,2,3,6] | Bipolar, "guarded" tripolar, quadrupolar, other multipolar |

[a] Constant voltage stimulation.
[b] Denotes mean±standard deviation instead of full range, as the latter was not reported in source.
[1] Abejon et al. (2005).
[2] Alo et al. (2002).
[3] Butyen (2003).
[4] North et al. (1993).
[5] Kumar et al. (2007).
[6] Aló and Holsheimer (2002).