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Characterization of preclinical models to investigate spinal cord stimulation for neuropathic pain: a systematic review and meta-analysis

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Abstract

Despite advancements in preclinical and clinical spinal cord stimulation (SCS) research, the mechanisms of SCS action remain unclear. This may result from challenges in translatability of findings between species. Our systematic review (PROSPERO: CRD42023457443) aimed to comprehensively characterize the important translational components of preclinical SCS models, including stimulating elements and stimulation specifications. Databases (Embase, PubMed, Web of Science, and WikiStim) were searched on October 5, 2023, identifying 78 studies meeting the search criteria. We conducted a post hoc meta-analysis, including subgroup analyses and meta-regression, to assess SCS efficacy on mechanical hypersensitivity in rats subjected to neuropathic pain. Although monopolar electrodes were predominantly used as stimulating elements until 2013, quadripolar paddle and cylindrical leads gained recent popularity. Most research was conducted using 50 Hz and 200 μs stimulation. Motor threshold (MT) estimation was the predominant strategy to determine SCS intensity, which was set to 71.9% of MT on average. Our analysis revealed a large effect size for SCS (Hedge $g = 1.13$, 95% CI: [0.93, 1.32]) with similar magnitudes of effect between conventional (≤100 Hz) and nonconventional SCS paradigms while sham SCS had nonsignificant effect size. In addition, different stimulation intensity, frequency, and electrode design did not affect effect size. The risk of bias was assessed using Systematic Review Centre for Laboratory animal Experimentation criteria and was unclear, and only the frequency subgroup analysis showed publication bias. In summary, our review characterizes the critical components of preclinical SCS models and provides recommendations to improve reproducibility and translatability, thereby advancing the scientific foundation for SCS research.

Keywords: Spinal cord stimulation, Neuropathic pain, Rat, Mechanical hypersensitivity, Analgesia

1. Introduction

Spinal cord stimulation (SCS) involves the electrical stimulation of the dorsal column. It was first proposed as a therapeutic intervention for pain management following Melzack and Wall's seminal Gate Control Theory of pain processing.[45] The first SCS implants in humans were performed by Shealy et al.[68] in 1967. Since then, SCS has been successfully used for managing neuropathic pain conditions unresponsive to pharmacotherapy and other less invasive interventions.[16,34,37,42,54,76,109] However, not all individuals benefit from SCS,[37] and the therapy has recently faced some skepticism.[99] These challenges highlight the importance of further research into SCS, particularly those that can further our understanding of the underlying mechanisms of SCS action.

Preclinical models play a crucial role in understanding the physiological processes that underlie the mechanisms of action in SCS. These models use a variety of neuropathic pain models (eg, spared nerve injury[15,39]), SCS electrodes (eg, design and

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dimensions), and stimulation parameters (eg, conventional vs nonconventional stimulation frequencies).[10,25,88,89] Through these approaches, researchers have developed and refined SCS technologies (eg, electrode design and electrical stimulation specifications) that may target different mechanisms.[67] They also used different outcomes measures, including behavioral and nonbehavioral assessments, to provide valuable insights into the analgesic efficacy (eg, evident through shifts in pain behaviors) and underlying mechanisms of actions in SCS (eg, identified through physiological changes).[41,51,80,85,98] Some of these proposed mechanisms include the modulation of neurotransmitters (eg, release of intracellular inhibitory γ-aminobutyric acid [GABA])[2,11,13,32,87] or the regulation of neuroinflammatory responses (eg, glial modulation).[60,72,96]

However, despite the significant advancements achieved in preclinical SCS research, there remains a lingering ambiguity concerning the translatability of these findings to the clinic. All preclinical models, including those used in SCS research, are challenged by the translatability of findings between species; in the preclinical SCS literature, they heavily rely on studies conducted in rats. Specific factors of SCS therapy that require consideration in preclinical models are the morphometrics of the implantable stimulating elements and stimulation specifications, because of the size difference between species and that rats cannot communicate sensation. These factors have not been comprehensively synthesized in the literature, which may contribute to knowledge gaps concerning SCS mechanisms of action and to debates on the long-term efficacy of SCS in clinical settings. Building on the work of Smits et al.,[77] the aim of our systematic review was to comprehensively characterize preclinical SCS models to better understand the translatability of these models to clinical research. We also conducted a post hoc meta-analysis to assess SCS efficacy across studies, particularly as the field has evolved through technological developments and the introduction of novel SCS waveforms since the work of Smits et al.[77] Thus, our review will help identify components that, when more thoroughly investigated, may lead to the improvement and subsequent translatability of preclinical SCS models, and further advance our understanding of SCS mechanisms of action. Finally, we make recommendations for future research to improve the reproducibility of the described models and results and to progress the scientific foundation for this therapy.

2. Methods

The systematic review was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[55] The protocol is registered on the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42023457443. The meta-analysis was not predetermined but deemed feasible after initial data extraction. In addition to the protocol published on PROSPERO, we expanded our meta-regression to assess the impact of stimulation intensity, frequency, and pulse duration on SCS effects.

2.1. Search strategy

We searched the electronic databases MEDLINE, EMBASE, Web of Science, and the SCS collection of WikiStim on October 5, 2023. WikiStim is an open-access database dedicated to neuromodulation publications (https://www.wikistim.org/search-menu). The search strategy was developed with input from an expert Librarian at Newcastle University. The search string ("spinal cord stimulation" OR "dorsal column stimulation" OR "SCS" OR "DCS") AND ("animal" OR "preclinical" OR "basic science") AND ("neuropathic pain" OR "neuralgia" OR "chronic pain" OR "neuropathy" OR "pain") was used to search MEDLINE, EMBASE, and Web of Science. The individual terms "animal" and "preclinical" were used to search WikiStim. There were no restrictions on publication date or language.

2.2. Study selection

Two reviewers (D.M. and Q.V.) undertook the initial electronic database search, and D.M. manually removed duplicate records. The reviewers then independently reviewed records for study eligibility. **Table 1** illustrates the inclusion and exclusion criteria for study eligibility used by both reviewers. Each reviewer first screened the title and abstract of records for initial consideration. They then retrieved full-text articles for these records and assessed them for final inclusion. Disagreements were reviewed and resolved during a meeting between D.M., Q.V., and a third reviewer (I.O.).

2.3. Risk of bias assessment

The risk of bias was assessed with the tool developed by the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE).[29] D.M. and I.O. defined specific criteria for each included study to be graded "Yes," "No," or "Unclear" against each of the 10 SYRCLE questions related to performance bias, selection bias, attrition bias, detection bias, reporting bias, and other biases. D.M. and I.O. independently assessed the study, and any disagreements were resolved through discussion.

2.4. Data extraction

To address our aims, we created 5 categories for our primary data extraction: Model information, Stimulating elements, Stimulation specifications, Behavioral assays, and Nonbehavioral assays. **Table 2** illustrates the data types extracted for each category.

We also extracted secondary data that were not directly related to our aims and make this additional information available. D.M. created a spreadsheet based on **Table 2** and conducted the initial data extraction of all included studies. Q.V., I.O., and B.D. were randomly allocated approximately one-third of the studies to check accuracy of data extraction. Any disagreements were resolved through discussion. The full set of data extracted, including the primary and secondary data, is available as an Excel file at the Open Science Framework (osf.io/dhx38/) or upon request to the authors.

2.5. Data synthesis

If studies reported a value range for the data extracted, we calculated the midpoint of the range. For example, if a study reported animal weights between 200 and 300 g, then 250 g was the midpoint weight for the animals used in that study. We then synthesized and reported the mean, standard deviation (SD), minimum and maximum values across studies for the data extracted.

A majority of the studies used mechanical hypersensitivity measured by the von Frey test (ie, paw withdrawal thresholds) to assess the efficacy of SCS on neuropathic pain. Therefore, we focused on this behavioral assay for the meta-analysis. The thresholds were reported in the unit gram, the log transform of gram (ie, $\log_{10}$ [g × 10,000]), or Newton. If standard errors of the mean (SEMs) were reported, we converted these to SD based on sample size. In one study, there were different number of rats in

Table 1

Inclusion and exclusion criteria used for study eligibility.

Inclusion criteria	Exclusion criteria
SCS applied below vertebral level C1	Target tissue is not the spinal cord (eg, DRG or peripheral nerve)
Rat model of neuropathic pain	Only naive animals
At least one session of SCS ≥5 min	Only uses a pain model other than neuropathic pain (eg, inflammatory pain)
Published in a peer reviewed journal	Abstracts or conference proceedings
At least one of the following behavioral assays used to assess efficacy of SCS Mechanical hypersensitivity test (eg, von Frey or pressure algometry) Cold hypersensitivity test (eg, acetone or ethyl chloride application) Heat hypersensitivity test (eg, heat pad)	Studies in humans or animals other than the rat Literature reviews or secondary analysis of previously published experiments

C1, Cervical vertebrae 1; DRG, dorsal root ganglion; SCS, spinal cord stimulation.

the 2 assessment time points of interest (45 vs 30 rats), so we used the smaller number.[13]

2.6. Meta-analysis

After the initial data extraction, there was sufficient data to perform a post hoc meta-analysis to quantify the effect of SCS on the von Frey test (as a measure of pain-related behavior) in neuropathic animals across studies. Too few studies used other types of assays to include in the meta-analysis. We therefore developed the inclusion criteria below to enable selection of data from studies that presented sufficient detail to allow for meta-analysis (including subgroup analysis and meta-regression).

2.6.1. Inclusion criteria

The following criteria were used for including a study in the meta-analysis: (1) von Frey test conducted on the same rat at 2 time points (within-subjects design); (2) reported von Frey test during a period before SCS but after pain induction (pre-SCS); (3) reported von Frey test during a period of experimental or sham SCS (post-SCS); and (4) provided sufficient information for calculating effect sizes (ie, sample size, mean, and SD or SEM). When post-SCS data were reported at multiple time points, we used the time point closest to the SCS termination. When post-SCS data were reported for multiple sessions, we used data from the last session. Finally, we used data presented in text, or tables or graphs. For graphs, the mean and SD/SEM were estimated using a freely available online digitizer (WebPlotDigitizer, version 5.0; https://automeris.io).

2.6.2. Statistical analysis

For studies included in the meta-analysis, we used the sample size, mean and SD in their respective unit to calculate the (within-group) Hedge *g* as our measure of effect size, with an assumed

Table 2

Categories and the details of data extracted.

Category	Data extracted	Short description
Model information	Neuropathic pain model	Neuropathic pain model(s) used (eg, SNI)
	Pain period	Time between pain induction and intervention
	Total number of animals/number of SCS animals	Number of rats in the experiment and treated with SCS
	Stimulation level (vertebral)	Vertebral level of stimulating elements
Stimulating elements	Design	Design of implanted electrode (eg, cylindrical)
	Dimensions	Dimensions (mm) of electrodes and stimulating contacts
Stimulation specifications	Intensity	Stimulation intensity expressed as a percentage of motor threshold or in amperes (A)
	Rate	Stimulation frequency (Hz); this can include conventional stimulation frequencies (≤100 Hz) and nonconventional frequencies (high frequencies and burst)
	Pulse width	Stimulation pulse duration (μs)
Behavioral assays	List of assays	Behavioral assays used to assess hypersensitivity (eg, von Frey test for mechanical hypersensitivity) at different times points: preinduction of pain model, postinduction of pain model but pre-SCS and post-SCS
Non-behavioral assays	List of assays	Nonbehavioral assays used to assess physiological processes after pain induction and SCS (eg, proteomic analysis), including specifics of tissue tested (eg, L5 segment of the spinal cord)

SCS, spinal cord stimulation; SNI, spared nerve injury.

Table 3

Descriptions of subgroups defined for meta-analysis.

Subgroup	Group	Description
1	Conventional	Stimulation set at ≤100 Hz frequency
	Nonconventional	Stimulation >100 Hz or burst frequency
	Sham	Stimulating elements implanted but no current applied
2	HF	Stimulation frequency >100 Hz and <10 kHz (excluding Burst)
	10 kHz	Stimulation frequency of 10 kHz
	Burst	Burst stimulation frequency
3	Low	Stimulation intensity of ≤65% MT
	Mid	Stimulation intensity of 66% or 67% MT
	High	Stimulation intensity of ≥68% MT
4	Mono	Monopolar plate designed electrode implanted
	Cylindrical	Multi-polar cylindrical designed electrode implanted
	Paddle	Multi-polar paddle designed electrode implanted

HF, high frequency; MT, motor threshold.

pre–post correlation, $r = 0.5$. We used the inverse variance method with a random-effects model and Hartung–Knapp adjustment to measure the effect of SCS on paw withdrawal threshold after neuropathic pain induction. We report I^2 and τ^2 as measures of between-study heterogeneity.

For our primary analysis, we used subgroup analysis to compare the effect size for conventional SCS (≤100 Hz stimulation frequency), nonconventional SCS (>100 Hz and burst frequencies), and sham SCS. We conducted additional subgroup analyses that compared groups based on stimulation intensity, stimulation frequency, and stimulating element as indicated in **Table 3**. We conducted a meta-regression to investigate the relationship between SCS effect and stimulation parameters if all parameter values were sufficiently reported. Finally, we used the Egger regression test[21] in combination with funnel plots to assess publication bias. For the Egger test, it is recommend to use either the raw or normalized mean difference rather than the standardized mean difference (SMD).[107,121] However, the data were not on the same scale in the different studies, so we could not use raw mean difference, and we did not have all the conditions needed to calculate normalized mean difference. In this case, we correlated SMD against the sample size–based precision estimate ($1/\sqrt{n}$) rather than the standard error (SE) as recommended.[121] The meta-analysis was conducted using the meta (version 5.0-1), metasens (version 1.0-1),[27,66] and metafor (version 3.8-1)[108] packages for R Studio (version 1.4.1106). In particular, we used metagen for precalculated effect sizes.[27] The data and script for all analyses are available at the Open Science Framework (osf.io/dhx38/) or upon request to the authors.

2.7. Missing data

D.M. contacted the corresponding author of a study when details of the stimulating elements were not reported. Instances when the corresponding author provided the missing data are noted. Otherwise, the data are reported as "Not Specified." Because of the large number of data extracted, other missing data were not proactively sought and is also reported as "Not Specified."

3. Results

3.1. Study selection

Figure 1 illustrates the PRISMA flow diagram for study selection. The initial search yielded 1,617 unique records. After screening, 78 studies met the inclusion criteria (**Table 1**). Of these studies, 46 studies were included in the meta-analysis.

3.2. Study characteristics

Figure 2 illustrates characteristics of the 78 studies included in our systematic review. **Figure 2A** shows the cumulative increase in the number of publications from 1994 to October 2023. **Figure 2B** shows that the studies were conducted in 22 laboratories across 8 countries, with 5 laboratories producing 74.4% of the studies (with 6 or more publications). Fifty-one studies (65.4%) disclosed full or partial funding from a commercial partner, and 4 studies did not disclose their funding source (**Fig. 2C**). Of those that received commercial funding, Medtronic accounted for 67.3% and Boston Scientific for 23.1% of commercially funded studies (Supplementary Table 1, http://links.lww.com/PR9/A275).

3.3. Risk of bias assessment

Figure 3 summarizes the risk of bias using the SYRCLE assessment tool.[29] In terms of selection bias (Q1–Q3), most studies ensured that groups were similar at baseline (Q2) but other measures to avoid selection bias were unclear. A majority of studies were unclear regarding housing for rats and blinding procedures, leading to potential performance bias (Q4–Q5). Similarly, a majority of studies were unclear regarding how rats were selected for outcome measurements and blinding procedures, leading to potential detection bias (Q6–Q7). A majority of the studies were free of attrition and reporting bias (Q8–Q9). Finally, it was unclear if studies had other biases (Q10), predominantly driven by the involvement of commercial partners.

3.4. Model information

Table 4 provides the primary data extracted from each study. The spared nerve injury (SNI), Seltzer and chronic constriction injury (CCI) models of neuropathic pain were used in 34.6%, 29.5%, and 14.1% of the studies, respectively. These 3 models were the predominant pain model used in a majority of the studies (78.2%) (see also Supplementary Table 2, http://links.lww.com/PR9/A275). The average time between induction of the pain model and implementation of SCS (application of stimulation) was 11.6 ± 6.2 days. This average excluded 5 studies that implemented a pain model requiring ≥4 weeks.[3,19,23,89,105] An average of 54.9 ± 41.9 rats were used per study, with an average of 33.2 ± 21.8 rats receiving an SCS implant.

Supplementary materials, http://links.lww.com/PR9/A275, show additional information about the preclinical models. A majority of studies (92.3%) used Sprague-Dawley rats, which were predominantly male (89.7%) and averaged 280.1 ± 58.1 g (Supplementary Tables 3 and 4, http://links.lww.com/PR9/A275). In addition, isoflurane was the predominant method of anesthesia and used in 70.5% of the studies (Supplementary Table 5, http://links.lww.com/PR9/A275).

3.5. Stimulating elements

To address our aims, we focused on the design and dimension of the stimulating elements. Stimulating electrodes were

Table 4

A summary of spinal cord stimulation preclinical model characteristics extracted from the included studies.

Author, year	Pain model	Pain period (d)*	No. of Animals/ with SCS†	Stim level (vertebral)	Design	Dimensions (length × width × height; mm)	Stim intensity (%MT)	Rate (Hz)	Pulse width (μs)	Beh assays	Nonbeh assays	Meta
Mayerson, 1994[51]	CCI Seltzer	≤3	NSP	T13	Monopolar	NSP	67	NSP	NSP	VF		ND
Mayerson, 1995[52]	CCI Seltzer	10–18	66/26	T10–12	Monopolar	2 × 2 ∅ × NSP	40–90	50	200	VF		NE
Cui, 1996[11]	CCI	5–10	130/26	T11	Monopolar	3 × 2 oval × 0.25	67	50	200	VF		ND
Stiller, 1996[90]	Seltzer	7–14	153/30	T11	Monopolar	NSP × 2 oval × 0.25	67	50	200	VF	MD	NE
Cui, 1997[14]	CCI	5–10	29/6	T11	Monopolar	3 × 2 × 0.2	67	50	200	VF		NE
Cui, 1997[13]	Seltzer	5–10	220/40	T11	Monopolar	3 × 2 × 0.2	67	50	200	VF	MD	Y
Cui, 1998[12]	SNLp	3	43/17	T11	Monopolar	3 × 2 × 0.2	67	50	200	VF	MD	Y
Wallin, 2002[111]	SNLp CCI	NSP	66/36	T12	Monopolar	3 × 1.5 × 0.25	67	50	200	VF	DHR	NN
Schechtmann, 2004[65]	Seltzer	4–10	NSP	T12	Monopolar	3 × 1.5 × 0.25	67	50	200	VF		Y
Li, 2006[39]	SNI mSNI	7–11	153/57	T11	Monopolar	NSP × 2 oval × 0.25	90	50	200	VF		Y
Smits, 2006[80]	Seltzer	16	45/30	T13	Monopolar	3 × 1 × 0.1	67	50	200	VF		Y
Maeda, 2008[41]	SNI	14	58/46	T10–12	Paddle	NSP × 2 × 0.6‡, (1 mm spacing)	85–90 85–90 85–90 85–90	4 60 100 250	250 250 250 250	VF PPT	IHC	Y
Schechtmann, 2008[64]	Seltzer	7–14	139/38	T11	Monopolar	3 × 1.5 × 0.25	67	50	200	VF	MD	Y
Song, 2008[84]	Seltzer	14	46/32	T11	Monopolar	3 × 1.5 × 0.25	67	50	200	VF CH HH		Y
Smits, 2009[79]	Seltzer	16	25/17	T13	Monopolar	3 × 1 × 0.1	67	50	200	VF	IHC	Y
Song, 2009[87]	Seltzer	≥9	96/62	T11	Monopolar	3 × 1.5 × 0.25	80	50	200	VF CH HH	IHC ELISA	Y
Song, 2011[85]	Seltzer	14	NSP	T11	Monopolar	3 × 1.5 × 0.25	80	50	200	VF		ND
Song, 2011[86]	Seltzer	14	40/20	T11	Monopolar	3 × 1.5 × 0.25	80	50	200	VF		ND
Truin, 2011[101]	Seltzer	1 or 16	53/42	T13	Monopolar	3 × 1 × 0.1	67	50	200	VF		Y
Truin, 2011[100]	Seltzer	16	22/15	T13	Monopolar	3 × 1 × 0.1	67	50	200	VF		Y
Yang, 2011[85]	mChung	12	32/26	T10–12	Paddle	NSP§	80–90	50	200	VF	ECAP	Y
Barchini, 2012[2]	SNI	14	38/38	T11–12	Monopolar	NSP × 1 × 0.5	70	50	200	VF CH HH		ND
Janssen, 2012[32]	Seltzer	16	59/42	T13	Monopolar	3 × 1 × 0.1	67	50	200	VF	IHC WB	Y
Smits, 2012[78]	Seltzer	16	42/33	T11 or T13	Monopolar	3 × 1 × 0.1	67	50	200	VF		Y
Pluijms, 2013[58]	STZ	28	76/26	T13	Monopolar	3 × 1 × 0.1	67 67 67	4–10 35–55 150–375	200 200 200	VF		NE
Sato, 2013[62]	SNI	14	120/120	NSP	Paddle	NSP§‖	90	4 or 60	250	VF		Y
Shechter, 2013[69]	mChung	12–14	110/93	T10–12	Paddle	NSP§	20, 40, 80 20, 40, 80 20, 40, 80	50 1k 10k	24 24 24	VF	DHR ECAP	Y
Song, 2013[82]	SNI	14	34/30	T11	Monopolar	3 × 1.5 × 0.25	80	50	200	VF	DBR	Y
Song, 2013[81]	SNI	21	59/52	T11	Monopolar	3 × 1.5 × 0.25	80	50	200	VF	DBR	Y

(*continued on next page*)

Table 4 (*continued*)

A summary of spinal cord stimulation preclinical model characteristics extracted from the included studies.

Author, year	Pain model	Pain period (d)*	No. of Animals/ with SCS†	Stim level (vertebral)	Design	Dimensions (length × width × height; mm)	Stim intensity (%MT)	Rate (Hz)	Pulse width (μs)	Beh assays	Nonbeh assays	Meta
Ultenius, 2013[102]	Seltzer	14	44/26	T11–12	Monopolar	3 × 1.5 × NSP	80	50	200	VF	IHC	Y
Sato, 2014[60]	SNI	14	123/108	T10–12	Paddle	NSP§‖	50 70 90	4 or 60 4 or 60 4 or 60	NSP NSP NSP	VF	IHC	ND
Sato, 2014[61]	SNI	14	37/32	NSP	Paddle	NSP§‖	90	4 or 60	250	VF ACT		Y
Song, 2014[88]	SNI AP IP	NSP	34/30	T10–12	Paddle	NSP (contact 0.9–1 ∅—pitch of 1.8–2 mm)	80 PT ∼ 40–50 PT ∼ 40–50 PT ∼ 40–50	50 500 1k 10k	200 24 24 24	VF CH HH PPT	DBR	Y
Yuan, 2014[118]	CCI	12–14	48/24	T11	Monopolar	3 × 1.5 × 0.25	67	50	200	VF	IHC ELISA WB PCR	Y
Crosby, 2015[10]	CNRC	4	30/12	C3–4	Paddle	NSP (contacts 3 mm^2, 1 mm spacing)	80 80	Burst[a] 50	1k 250	VF	ELISA	ND
Saadé, 2015[59]	SNI	19–28	30–36/ 30–36	T11–12	Monopolar	1 × 0.5 × NSP	70	50	200	VF CH HH	IHC	ND
Song, 2015[83]	SNI	14	25/22	T10–12	Paddle	NSP (contact 0.9–1 ∅—pitch of 1.8–2 mm)	80 50	50 1k	200 24 monophasic, 12 + 12 bi phasic or 24 + 24 biphasic	VF CH HH		Y
Tazawa, 2015[95]	mChung	≥5	>24/NSP	T10–11 and L4–5	Paddle	NSP (contact 0.2 mm ∅)	70–80	50	200	VF ACT	IHC WB	NN
Tilley, 2015[98]	SNI	4	80/40–52	L1	Cylindrical	NSP × 0.72 ∅	70	50	20	VF CH		NN
Gong, 2016[25]	SNI	14	64/57	L1–4	Paddle	NSP§‖	90 90 90 90 90 90 90	16 60 160 Burst[b] Burst[c] Burst[d] Burst[e]	500 500 500 500 200 200 1k	VF ACT		OT
Tilley, 2016[96]	SNI	4	36/30	L1	Cylindrical	NSP × 0.72 ∅	70	50	20	VF	PCR	Y
Yang, 2016[117]	mChung	14–21	21/11	T10–12	Paddle	NSP§	80	50	200	VF	IHC PC DHR ECAP	ND
Inoue, 2017[31]	SNI	14	40/38	T11–12	Paddle	NSP§‖	90	4 or 60	250	VF ACT		Y
Sun, 2017[93]	Seltzer	3	25–35/ 17–25	T13	Monopolar	3 × 0.5 × 0.1	60 60	25 10	50 50	VF	IHC	Y
Tilley, 2017[97]	SNI	4	36/24	L1	Cylindrical	NSP × 0.72 ∅	70	50	20	VF	PCR	Y
van Beek, 2017[105]	STZ	140	44/39	T10–12	Paddle	NSP§‖	67 67 67	5 50 500	200 200 200	VF		Y
Koyama, 2018[36]	CCI	8	9/9	L2–3	Cylindrical	NSP × 0.72 ∅	NSP (PT < 0.1 mA)	50	200	HH	EEG	ND
Meuwissen, 2018[48]	Seltzer	18	12/11	NSP	Cylindrical	NSP × 0.72 ∅	66, 50, 33 66, 50, 33	50 Burst[f]	200 1k	VF		Y

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Meuwissen, 2018[47]	Seltzer	17	52/43	L1–2	Cylindrical	NSP × 0.72 ⌀	66 66	50 Burst[f]	200 1k	VF		Y
Stephens, 2018[89]	CCI	36	12/8	T13–L1	Paddle	NSP§	80	50	200	VF	PCR	Y
van Beek, 2018[3]	STZ	42	60/24	L2–5	Paddle	NSP§‖	67	50	200	VF	LD	Y
Chen, 2019[9]	mChung	14	45/32	T10–12	Paddle	NSP§	40 40 40 40 40	10k 1.2k 500 200 50	24 200 500 1k 200	VF		Y
Sivanesan, 2019[75]	CIPN	0	34/17	T10–12	Paddle	NSP§	80	50	200	VF CH ACT	PCR	OT
Edhi, 2020[20]	CCI	9	8/8	T10–11	Cylindrical	NSP × 0.72 ⌀	NSP (90% of PT)	25–150	150–250	VF	EEG	Y
Liao, 2020[40]	SNI	3	50/40	T10–12	NSP	NSP	30	10k	30	VF CH	WB	Y
Liao, 2020[40]	SNI	3	50/40	T10–12	NSP	NSP	30	10k	30	VF CH ACT	MD WB PC	Y
Meuwissen, 2020[46]	Seltzer	18	38/27	L1–2	Cylindrical	NSP × 0.72 ⌀	66 50	50 Burst[f]	200 1k	VF CPP		Y
Meuwissen, 2020[50]	Seltzer	16	36/36	L1–2	Cylindrical	NSP × 0.72 ⌀	66 50	50 Burst[f]	200 1k	VF	IHC	Y
Meuwissen, 2020[49]	Seltzer	16	19/17	T13	Cylindrical	NSP × 0.72 ⌀	66 66	50 Burst[f]	200 1k	VF	MRI	Y
Sato, 2020[63]	SNI	14	54/6	NSP	Paddle	NSP§‖	90	60	250	VF PPT		ND
Shinoda, 2020[71]	SNI	3	81/NSP	L1–4	Cylindrical	NSP	80	60	240	VF	WB OPT	NE
Shu, 2020[72]	CCI	18	33/25	T10–12	Paddle	NSP (contact 0.9–1.0 mm, 2 mm spacing)	80	50	200	VF	ICC WB PCR	Y
Sun, 2020[92]	SCI	4	96/54	T12	Monopolar	3 × 0.5 × 0.1	60 60	25 10	50 50	VF ACT	IHC	ND
Vallejo, 2020[104]	SNI	NSP	55/34	L1	Cylindrical	NSP × 0.62 ⌀ (contact 1 mm)	70 70 70	50 1.2k DTM[a]	150 50 150	VF CH HH	PCR	ND
Vallejo, 2020[103]	SNI	4	84/70	L1	Cylindrical	NSP × 0.62 ⌀	66	50	50	VF CH	PCR	ND
Duan, 2021[19]	SCI	40–42	16/10	T10–12	Paddle	NSP§	80 40	50 1.2k	200 200	VF ACT	DHR ECAP	ND
Tao, 2021[94]	SNI	21–28	13/12	T12	NSP	NSP	40 or 80	1k	100	VF CH	ELISA	Y
Sun, 2022[91]	CCI	13	160/NSP	T10–12	Cylindrical	NSP × 0.75 ⌀	80	60	240	VF	WB IF	ND
Wang, 2022[112]	STZ	21	29/12	L5–6 spinal	Cylindrical	NSP × 0.42 ⌀ (contact 1 mm, 1 mm spacing)	30	10k	30	VF	SDH	NE
Wang, 2022[113]	Chung	2	126/48	T13	Monopolar	2.8 × 1 × 0.1	50	10k	24	VF	WB IF	Y
Yun, 2022[119]	SNI	10	5/5	T13–L1	Paddle	0.442^2 ⌀ × 0.1	NSP	38.8	120	VF		ND

(*continued on next page*)

Table 4 (*continued*)

A summary of spinal cord stimulation preclinical model characteristics extracted from the included studies.

Author, year	Pain model	Pain period (d)*	No. of Animals/ with SCS†	Stim level (vertebral)	Design	Dimensions (length × width × height; mm)	Stim intensity (%MT)	Rate (Hz)	Pulse width (μs)	Beh assays	Nonbeh assays	Meta
Zhai, 2022[120]	SNI	7	142/61	T12–L1	Cylindrical	NSP × 0.6 ⌀ (contact 1 mm, 2 mm spaced)	20, 40, 60, 80 20, 40, 60, 80 20, 40, 60, 80 20, 40, 60, 80 20, 40, 60, 80 20, 40, 60, 80	2 15 50 100 10k 2/100 (3 sec at 2 Hz then 3 sec at 100 Hz)	200 200 200 200 30 200	VF	ELISA	Y
Cedeño, 2023[8]	SNI	5	40/34	L1–2	Cylindrical	NSP × 0.62 ⌀ (contact 1 mm)	40 or 70	DTM[b]	DTM[b]	VF	PCR	ND
de Geus, 2023[23]	STZ	49	64/28	T13–L1	Cylindrical	NSP‖—NSP × 0.62 ⌀ (contact 1 mm pitch)	50	50 1.2k DTM[c]	150 50 DTM[c]	VF CPP	PCR	Y
Kang, 2023[33]	SCI	21	5/5	T11	Paddle	1.1 × 0.4 × 0.07 (3 mm pitch)	40 or 80 40 or 80	50 1k	200 200	VF		OT
Ni, 2023[53]	STZ	21	30/24	T13	NSP	NSP	80	50	200	VF HH	ELISA WB PCR	Y
Sivanesan, 2023[74]	CIPN	0 or 14	88/40	T10–12	Paddle	NSP × NSP × <0.25 (1 mm spacing)	80	50	200	VF CH HH ACT	IHC WB MA	OT
Yang, 2023[115]	SNI	7	90/56	T9–11	Paddle	NSP × 1.5 ⌀ (2 mm spacing)	NSP	Burst[g]	25k	VF CH ACT	DBR ECAP	ND

* Time between induction of pain model and activation of SCS.
† Includes animals implanted with an SCS electrode.
‡ Assessed from Figures 1 and 2C in Maeda 2008 (see Supplementary Figure 1, http://links.lww.com/PR9/A275
§ Same device as described by Maeda 2008.
‖ Confirmation from the corresponding author.
Burst[a], 500 Hz bursts of 5 pulses at 40 Hz; Burst[b], 60 Hz bursts of 4 pulses at 4 Hz; Burst[c], 1 kHz bursts of 4 pulses at 4 Hz; Burst[d], 1 kHz bursts of 4 pulses at 40 Hz; Burst[e], 500 Hz bursts of 4 pulses at 40 Hz; Burst[f], 449 Hz bursts of 5 pulses at 40 Hz; Burst[g], 500 kHz bursts at 2 Hz.
DTM[a], 50 Hz and 1.2 kHz combined; DTM[b], combined—×3 300 Hz at 50 μs and ×1 50 Hz at 150 μs; DTM[c], combined—50 Hz at 150 μs and 1.2 kHz at 50 μs.
ACT, activity assessment; AP, acute pain; Beh, behavioral; CCI, chronic constriction injury; CH, cold hypersensitivity; CIPN, chemotherapy-induced peripheral neuropathy; CNRC, cervical nerve root compression; DBR, direct brain recording; DHR, dorsal horn recording; DTM, differential target multiplexed; ECAP, evoked compound action potential recording; EEG, electroencephalogram recording; ELISA, enzyme-linked immunosorbent assay; HH, heat hypersensitivity; HF, high frequency; Hz, Hertz; ICC, immunocytochemistry; IF, immunofluorescence; IHC, immunohistochemistry; IP, inflammatory pain; LD, laser Doppler imaging; LF, low frequency; μs, microseconds; mA, milliampere; MA, multiplexed assay; mChung, modified Chung model; Meta, meta-analysis; MD, microdialysis; MF, medium frequency; MRI, magnetic resonance imaging; MT, motor threshold; NSP, not specified; OPT, in vivo optical imaging; PC, patch clamp recordings; PCR, polymerase chain reaction analysis; PPT, pain pressure threshold; PT, perception threshold; SCI, spinal cord injury; SCS, spinal cord stimulation; mSNI, modified spared nerve injury; SNI, spared nerve injury; SNLp, sciatic nerve lesion (photochemical); Stim, stimulation; STZ, streptozotocin-induced diabetic neuropathy; VF, von Frey; WB, Western blot.
Meta-analysis abbreviations: ND, no data—absolute value for paw withdrawal thresholds on VF testing is not presented or is not discernible from text or charts; NE, no error—SEM or SDs are not presented or are unclear; NN, no N—sample sizes are not presented or are ambiguous; OT, other—includes Gong 2016; not possible to discern the response of different groups from text or charts, Kang 2023; unclear what % of MT was tested, Sivanesan 2019 and 2023; different experimental design in which stimulation was delivered before/concurrent with the induction of pain.

implanted epidurally in all 78 studies, predominantly in the lower thoracic spine (65 of 78 studies); 83.3% of the studies implanted electrodes spanning T10 to T13 (Supplementary Table 6, http://links.lww.com/PR9/A275). **Table 5** provides descriptive statistics for the electrode dimensions for the monopolar, cylindrical, and paddle lead designs. The 3 design

Table 5

Average dimensions (mm) of the different designs of epidural electrodes used.

	Monopolar			Cylindrical		Paddle*			
	Length	Width	Height	Diameter	Spacing	Diameter	Width	Height	Spacing
Mean	2.8	1.4	0.2	0.7	1.3	0.9	1.8	0.5	1.9
SD	0.6	0.5	0.1	0.1	0.6	0.2	0.5	0.2	0.4
Max	3.0	2.0	0.3	0.8	2.0	1.5	2.0	0.6	3.0
Min	1.0	0.5	0.1	0.4	1.0	0.2	0.4	0.1	1.0
N	31	30	26	20	3	23	15	16	21

* Diameter relates to the stimulating electrodes embedded in the paddle lead, width and height relate to the dimensions of the lead itself, spacing describes the space between electrodes on the lead.

Table 6

Stimulation intensity defined as percentage of motor threshold stratified by stimulation frequency (Hz).

	50	≤100	>100 ≤ 1K	>1K < 10K	10K	Burst
Mean	69.8	71.9	60.2	47.5	39.3	64.5
SD	9.9	10.6	13.6	12.3	9.3	16.0
Max	90.0	90.0	87.5	70.0	50.0	90.0
Min	40.0	40.0	45.0	30.0	30.0	49.5
N	58	69	8	10	7	7

types were used in 39.7%, 23.1%, and 32.1% of the studies, respectively. There was an insufficient number of studies reporting length for paddle or cylindrical leads to calculate descriptive statistics for this dimension.

Supplementary materials, http://links.lww.com/PR9/A275, show additional characteristics of the stimulating electrodes. Both paddle and cylindrical lead designs can house different numbers of stimulating contacts on the lead. Nearly half of the studies (48.7%) used 4-contact leads. However, monopolar electrodes were used in 20 of 22 studies (90.9%) published before or during 2012, whereas quadripolar leads were used in 36 of 56 studies (64.3%) published after 2012 (Supplementary Table 7, http://links.lww.com/PR9/A275). Preparations that use monopolar stimulation also require an anodal contact, which is implanted subcutaneously and averaged 5.7 mm in diameter and 0.2 mm in height. Eight studies (10.3%)[3,10,31,33,53,61,63,119] used a fully implanted pulse generator. Medtronic supplied monopolar electrodes and paddle leads for 80.6% and 80% of the studies, respectively. Boston Scientific supplied cylindrical electrodes for 55.6% of the studies (Supplementary Table 8, http://links.lww.com/PR9/A275).

3.6. Stimulation specifications

Studies use different SCS paradigms, which include combinations of stimulation intensity, frequency (rate), and pulse width (duration). A majority of studies (94.9%) defined intensity as a percentage of motor threshold (MT) (**Table 4**). This threshold is determined after lead implantation by increasing stimulation current until muscle responses are observed in the back and/or leg muscles, typically presenting as twitching or cramping depending on the stimulation frequency used. Regarding stimulation frequency, 71 studies (90.0%) tested conventional frequencies (≤100 Hz), 58 (74.4%) of these studies tested 50 Hz specifically. Seven studies (9.0%) investigated 10 kHz and 8 (10.3%) tested burst frequencies (Supplementary Tables 9 and 10, http://links.lww.com/PR9/A275).

Table 6 presents descriptive statistics for the intensity based on MT as a function of frequency. There was a large range across all frequencies from 30% to 90% of MT. The mean intensity was similar across all frequency ranges ≤1 kHz (60.2 ± 13.6% to 71.9 ± 10.6% of MT). For frequencies between 1 and 10 kHz (>1 kHz and <10 kHz), 10 kHz, and burst frequencies, the mean intensity was 47.5 ± 12.3%, 39.3 ± 9.3%, and 64.5 ± 16.0% of MT, respectively. Four studies did not report the intensity in terms of MT.[20,36,115,119] Two of these[20,36] reported intensity based on perception threshold defined by careful observation of the rat's behavior to detect a change believed to reflect the onset of stimulation induced sensations. Forty-five studies (57.7%) had a sham stimulation group as part of their experimental design.

The most frequently used frequency and pulse width combination was 50 Hz and 200 μs, which was used in 49 studies (66.2%). The average pulse duration was 185.1 ± 56.3 μs for ≤100 Hz, 27.0 ± 3.2 μs for 10 kHz, and 942.9 ± 151.2 μs for burst frequencies (excluding[115] which used an outlier pulse duration of 25,000 μs) (Supplementary Table 10, http://links.lww.com/PR9/A275). The average duration of stimulation for a given session of SCS was 303.6 ± 490.3 minutes, and most studies applied multiple SCS sessions (60.3%), although 19.2% of selected studies did not report the number of sessions in which SCS was applied. The high degree of variability in session duration is because of the use of continuous (24 hours) stimulation in some studies. If the 11 studies that used continuous stimulation are excluded, the average duration of an SCS session was 117.0 ± 173.1 minutes. Despite this, most studies reported SCS sessions ≤60 minutes (62%) (Supplementary Tables 11, 12 and 13, http://links.lww.com/PR9/A275).

The supplementary materials, http://links.lww.com/PR9/A275, provide additional information about stimulation specifications. Studies varied in the extent to which they reported how MT was established. Thirty-four studies (43.6%) did not specify the frequency settings used to establish MT. Of the remaining 44 studies that specified the frequency used to determine MT, 33 studies (75.0%) used frequencies of ≤4 Hz, 4 studies (9.1%) used the same settings used in the SCS experiments and the remaining 7 studies (15.9%) used a different frequency to establish MT. Thirty-eight studies (48.7%) did not report pulse duration used to

Table 7

Publication bias and adjusted Hedges *g* for the 4 subgroup analyses.

Subgroup analysis	Groups	Publication bias		Hedges *g*, 95% CI	
		t	*Df*	Nonadjusted	Adjusted
1	Conventional Nonconventional Sham	0.21	119	1.13 [0.93, 1.32]	NA
2	HF 10 kHz Burst	2.18	31*	1.51 [1.06, 1.96]	1.07 [0.62, 1.53]
3	Low Mid High	0.55	98	1.35 [1.14, 1.56]	NA
4	Mono Cylindrical Paddle	0.46	94	1.32 [1.13, 1.51]	NA

All nonadjusted and adjusted Hedge *g* significant at $P < 0.0001$.

* Only subgroup analysis 2 (frequency) showed publication bias, $P = 0.037$.

95% CI, lower and upper bounds of the 95% confidence interval; *df*, degrees of freedom; HF, high frequency; NA, no adjustment; *t*, *t*-value.

Table 8

Predictor coefficient from the meta-regression model.

Regressor	Coefficient, 95% CI	*T*	*df*	*P*
Percentage of MT	1.21 [−0.34, 2.77]	1.55	82	0.12
$\log_{10}$ frequency	0.16 [−0.21, 0.52]	0.86	82	0.39
Pulse duration	-4.0×10^{-4} [$-2/3 \times 10^{-3}$, 1.5×10^{-3}]	−0.45	82	0.65
Intercept	0.32 [−1.33, 1.97]	0.38	82	0.70

95% CI, lower and upper bounds of the 95% confidence interval; *df*, degrees of freedom; MT, motor threshold; *t*, *t*-value.

determine MT. Of the remaining 40 studies that reported pulse duration, 31 studies (77.5%) used a duration of ≤250 μs, and the remaining 9 studies used either the same duration used during the SCS experiments or different durations (see also Supplementary Table 14, http://links.lww.com/PR9/A275).

Twenty-seven studies reported the experimentally applied stimulation intensity in amperes and with respect to MT (one study only reported intensity in amperes[119]), and 2 studies reported intensity as voltages.[25,115] For frequencies ≤100 Hz, the average intensity was 462.1 ± 329.3 μA; for frequencies between 100 Hz and 1 kHz, the average intensity was 188.2 ± 150.2 μA; and for 10 kHz frequencies, the average intensity was 232.8 ± 152.8 μA. No studies using burst waveforms reported intensity in amperes. The intensity range for conventional low-frequency stimulation experiments (≤100 Hz) was from 50 to 980 μA (Supplementary Table 15, http://links.lww.com/PR9/A275).

3.7. Behavioral assays

Different behavioral measures were used to investigate the analgesic effect of SCS on neuropathic pain. All but one of the 78 studies used the von Frey test to assess mechanical hypersensitivity. Fifteen studies (19.2%) assessed cold hypersensitivity using acetone, ethyl chloride, or a cold plate. Ten studies (12.8%) used a (modified)

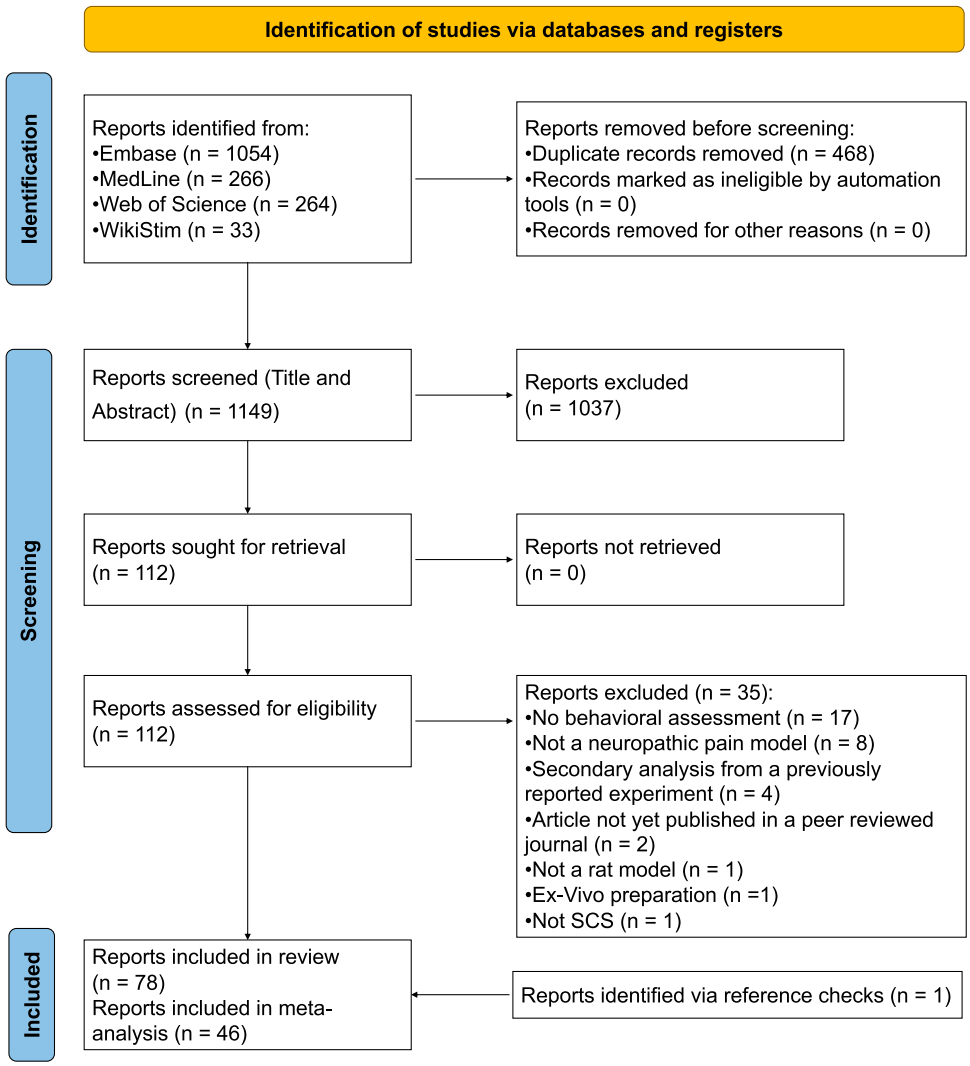

Figure 1. The PRISMA flow diagram of the search strategy and study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

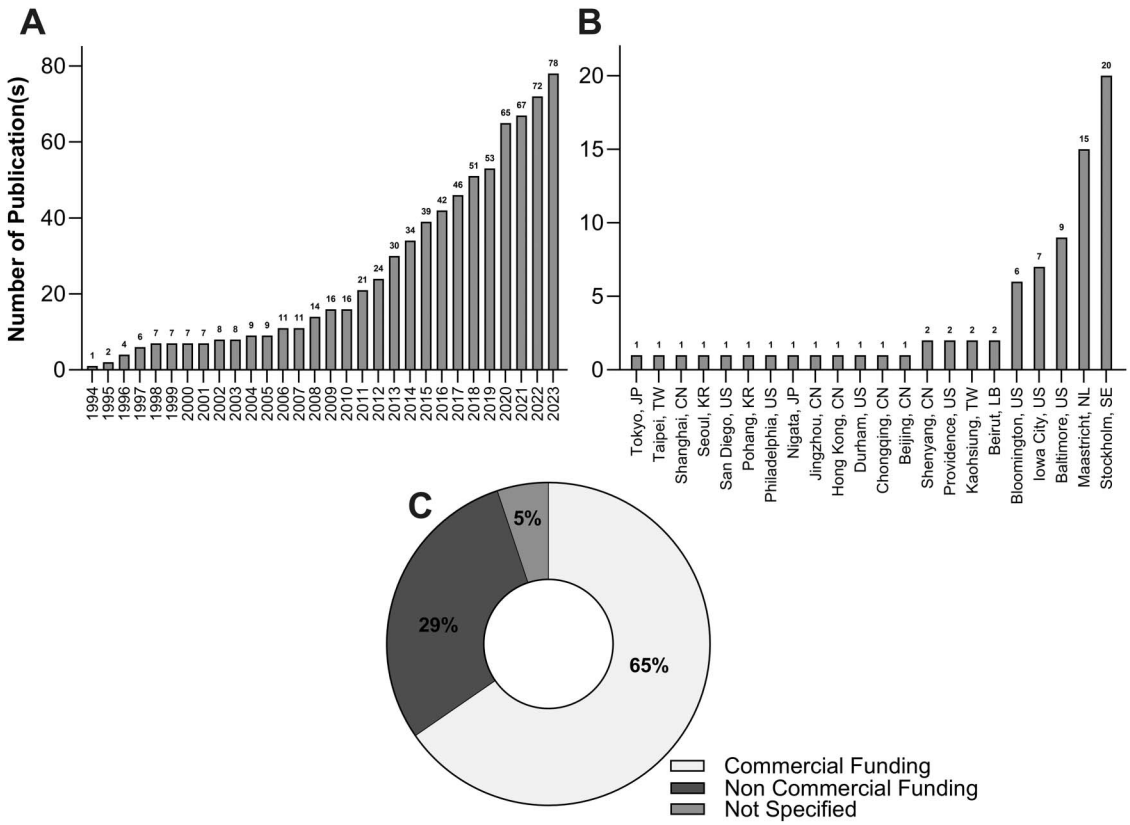

Figure 2. (A) Cumulative number of selected studies over the years. (B) Number of selected studies per laboratory (indicated by city and country). (C) Percentage of selected studies reporting specifics of funding source.

Hargreaves test to assess hypersensitivity to heat. Nine studies (11.5%) assessed animal activity as a proxy for pain behavior using a treadmill, raised beam, rotarod, or videography. Three studies[41,63,88] conducted pressure pain threshold testing, and 2 studies used conditioned place preference[23,46] (Supplementary Table 16, http://links.lww.com/PR9/A275).

3.8. Nonbehavioral assays

Different nonbehavioral assays were used to investigate different physiological aspects of the SCS mechanisms of action. Proteomic (and nonprotein amino acids) analysis was used in 28 studies (35.9%), electrophysiological assessments were used in 13 studies (16.7%), DNA/RNA transcriptomics were analyzed in 11 studies (14.1%), and 4 studies used imaging methods (eg, Laser Doppler Imaging, Magnetic Resonance Imaging or In Vivo Optical Imaging)[3,49,71,74] (Supplementary Table 16, http://links.lww.com/PR9/A275).

3.9. Meta-analysis

3.9.1. Subgroup analysis

Figure 4 presents the results of the primary subgroup analysis in a forest plot. Forty (of 78) unique studies were included in the meta-analysis, with 121 effect sizes for Conventional, Nonconventional,

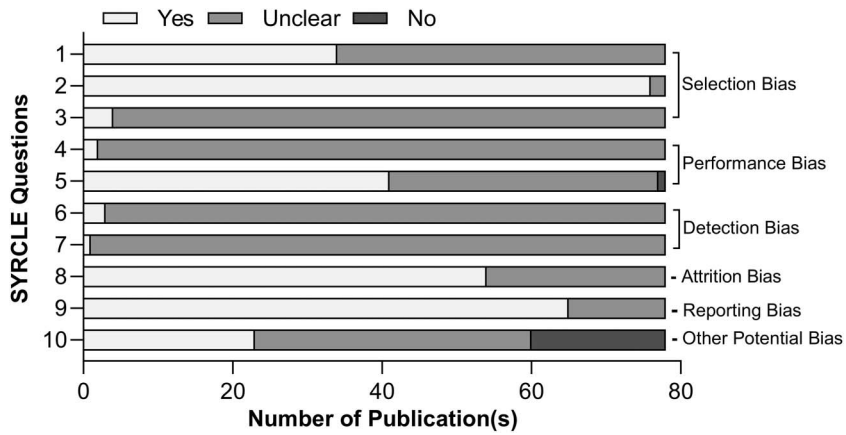

Figure 3. Summary of SYRCLE risk of bias assessment. SYRCLE, Systematic Review Centre for Laboratory animal Experimentation.

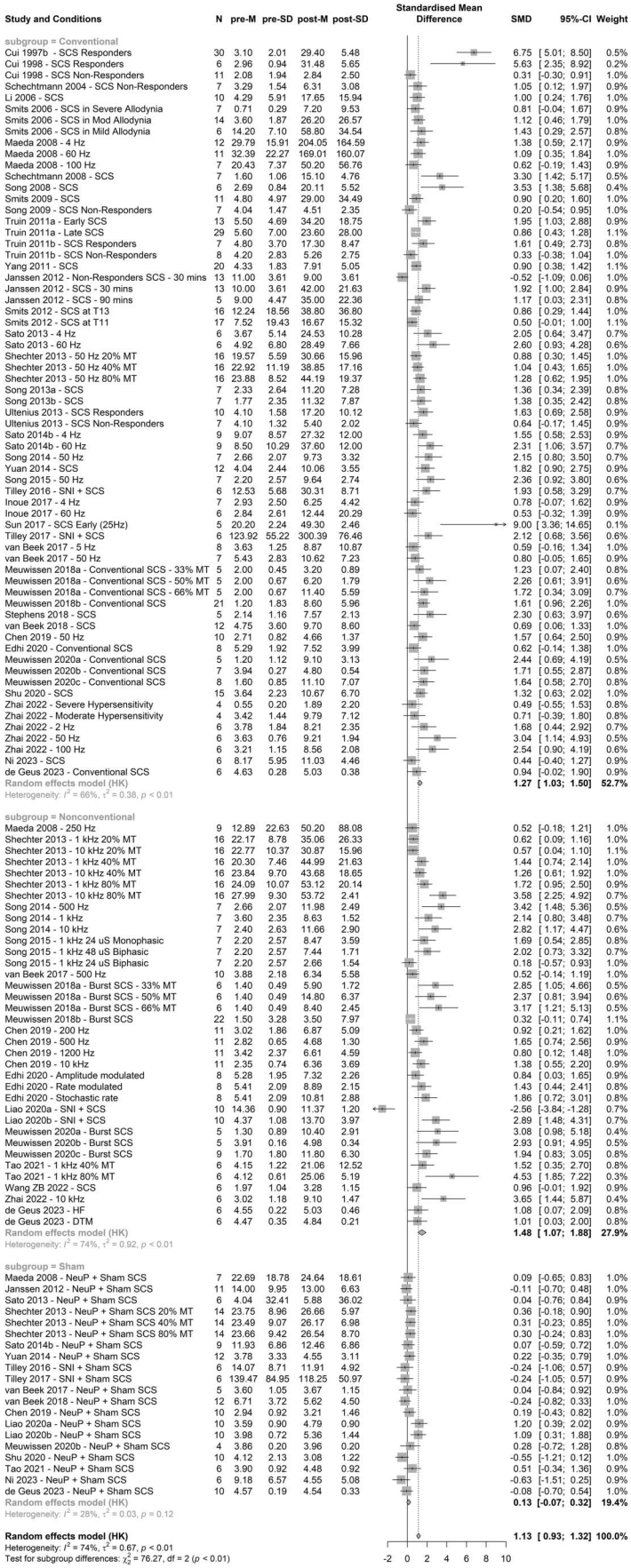

Figure 4. Forest plot from the primary subgroup analysis of the analgesic effect of SCS on neuropathic pain assessed using the von Frey test after conventional, nonconventional, and sham stimulation conditions. 95% CI, 95% confidence interval; N, sample size; post-M, post-SCS mean; post-SD, post-SCS SD; pre-M, pre-SCS mean; pre-SD, pre-SCS SD; SMD, standardized mean difference with small sample size correction (Hedge *g*).

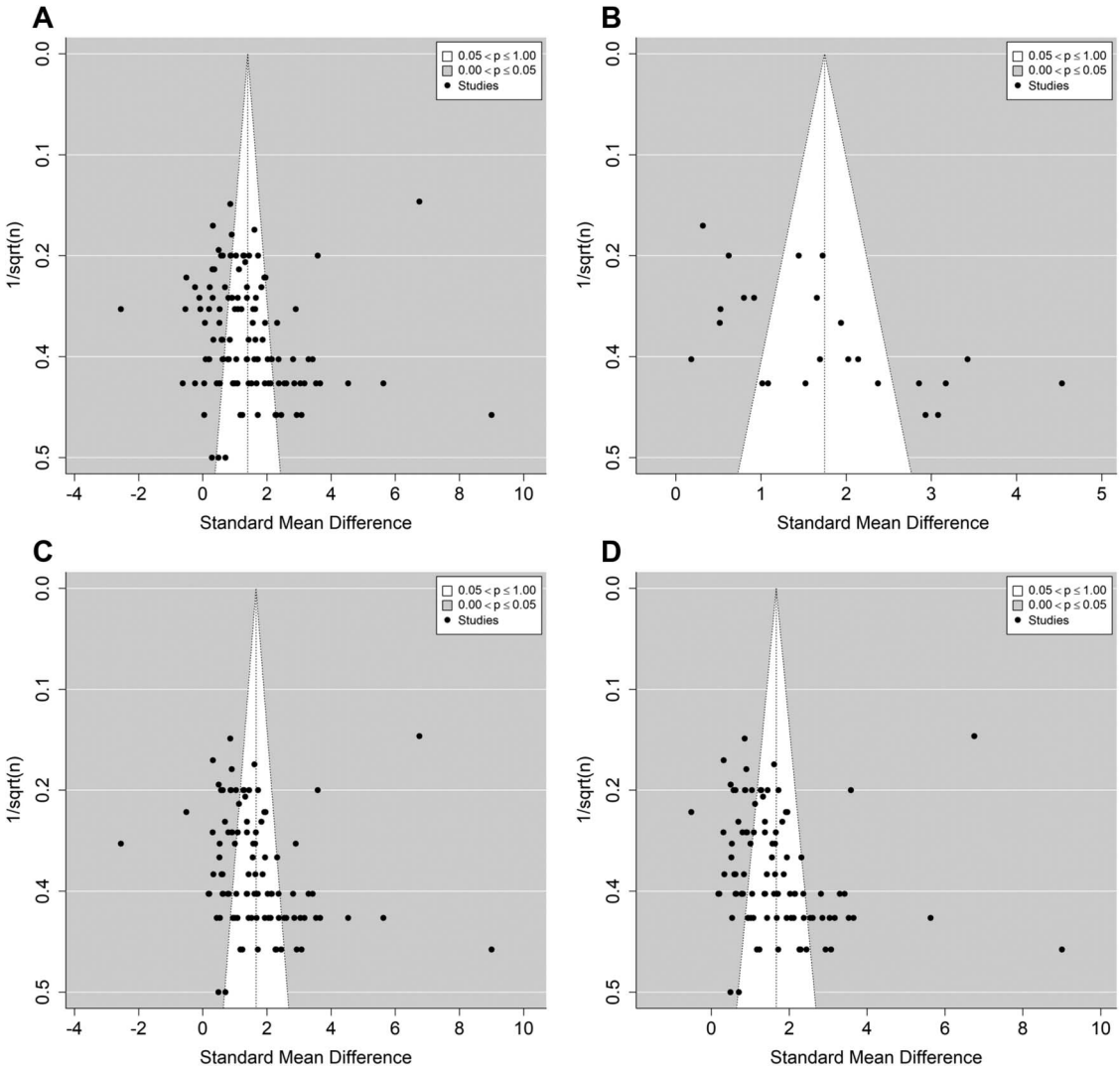

Figure 5. Funnel plots for the different subgroup analysis, using a sample size-based precision estimate ($1/\sqrt{n}$). Black dots represent effect sizes (Hedge *g*) from studies. The white triangle area represents the 95% confidence interval centered on the estimated standardized mean difference (vertical dashed line). (A) Conventional, nonconventional, and sham comparison. (B) HF, 10 kHz, and burst frequency comparison. There is an asymmetry in the plot, suggesting a publication bias. (C) Low, mid, and high percentage of motor threshold (MT) comparison. (D) Mono, cylindrical, and paddle stimulating element comparison. HF, high frequency.

and Sham SCS conditions. The effect sizes are listed separately by stimulation type for each study by first author name and year, and by different stimulation conditions within the same study (if present). The subgroup analysis showed an overall effect favoring SCS (Hedge $g = 1.13$, 95% confidence interval [0.93, 1.32]) with a significant group difference ($\chi^2_2 = 76.27$, $df = 2$, $P < 0.01$). There was a large effect favoring SCS for the Conventional (Hedge $g = 1.27$, [1.03, 1.50]) and Nonconventional (Hedge $g = 1.48$, [1.07, 1.88]) groups, but not for the Sham group (Hedge $g = 0.13$, [−0.07, 0.32]). Additional pairwise comparisons indicated that the effect size for the 2 non-Sham groups did not differ from each other ($P = 0.37$), but they were both different from the Sham group (Ps < 0.01; **Fig. 4**). Although there are SCS effects for the non-Sham groups, the heterogeneity was large. This is the case across all studies ($I^2 = 74\%$ and $\tau^2 = 0.67$, $P < 0.01$), and for the conventional ($I^2 = 66\%$ and $\tau^2 = 0.38$, $P < 0.01$) and nonconventional ($I^2 = 74\%$ and $\tau^2 = 0.92$, $P < 0.01$) groups but not for the Sham group ($I^2 = 28\%$ and $\tau^2 = 0.03$, $P = 0.12$).

The additional subgroup analyses showed that there were no group differences for stimulation frequency ($\chi^2_2 = 4.33$, $df = 2$, $P = 0.11$), stimulation intensity ($\chi^2_2 = 0.0$, $df = 2$, $P = 1.0$), and stimulating element ($\chi^2_2 = 3.36$, $df = 2$, $P = 0.19$). Stimulation frequency was restricted to nonconventional stimulation paradigms (Supplementary Figures 2, 3, and 4, http://links.lww.com/PR9/A275).

3.9.2. Publication bias

Figure 5 illustrates the publication bias as a funnel plot for each analysis, and **Table 7** presents the results of the Egger test[21] and Hedge *g* for these analyses. There was evidence of publication bias only for the frequency subgroup analysis ($P = 0.037$). To adjust for this bias, we used the trim-and-fill method[70] with the original data.

3.9.3. Meta-regression

We further investigated the relationship between SCS effect size and stimulation parameters by conducting a post hoc meta-regression. This analysis allowed us to examine these parameters

in a continuous fashion, rather than subdividing them into discrete categories (as done with the subgroup analyses). It also allowed us to examine the relative contribution of the stimulation parameters to any SCS effects. For the meta-regression model, the standardized mean difference (ie, Hedge *g*) was the response variable, and the stimulation intensity (measured by percentage of MT), $\log_{10}$ frequency, and pulse duration (μs) were the predictor variables (ie, regressors). We used $\log_{10}$ frequency to linearize the frequency range, which varied from 2 Hz up to 10 kHz but excluded burst frequencies. Eighty-three of the 96 effect sizes with SCS stimulation included values for all 3 parameters to allow for the meta-regression. We conducted the meta-regression on the data set with $r = 0.5$.

Consistent with the subgroup analyses, the meta-regression model was not significant ($F(3, 82) = 0.90$, $P = 0.45$). That is, the predictors did not account for the heterogeneity in SCS effect size. Thus, the results from the meta-analysis may not be solely explained by how we created the different groups for the subgroup analyses (eg, how we specified low, mid, and high intensity). **Table 8** presents the estimated coefficient and 95% confidence interval for the 3 predictors.

3.9.4. Sensitivity analysis

For the results reported for the subgroup analysis and meta-regression, we assumed $r = 0.5$. However, the SE of the standardized mean difference in a pre–post (within-group) design depends on the correlation (*r*) between the 2 time points. We were not able to estimate this correlation from the studies included in the meta-analysis. Therefore, we conducted a sensitivity analysis in which the Pearson correlation systematically varied from $r = 0.0$ to $r = 1.0$ in 0.1 steps. Overall, the sensitivity analyses showed the same results across all tested correlation values (Supplementary Tables 17, 18, 19, 20 and 21, http://links.lww.com/PR9/A275).

4. Discussion

This is the first systematic review and meta-analysis to comprehensively characterize preclinical SCS models, identified in 78 studies, according to their model of neuropathic pain, stimulating elements, stimulation specifications, and assessment of SCS analgesic efficacy. Our meta-analyses showed robust SCS efficacy across 46 of these studies. Although our review builds on the earlier work of Smits et al.,[77] it critically extends their review by inclusion of studies that used recent technological innovations and novel SCS waveforms, and proposed novel mechanisms of action of SCS. This increase is directly reflected in our analysis of study characteristics, which showed that since the work of Smits et al.,[77] there have been an additional 54 studies on preclinical models published (compared with their 24 studies), and an increase in the number of laboratories conducting research in this area. Thus, our systematic review provides an important step toward understanding how preclinical models can better inform clinical practice. However, although such models remain essential for bridging the gap between basic science and clinical applications in SCS research, these models will always be challenged by the translatability of findings between species. Below we discuss how preclinical models currently align with clinical practices along with their critical components to address the translational challenges of these models. We further discuss risks of bias identified in our systematic review and conclude with recommendations to improve the reproducibility and translatability of preclinical SCS research.

4.1. Components of preclinical spinal cord stimulation models affecting translatability between species

4.1.1. Pain models

The majority of studies in our review relied primarily on surgically induced peripheral nerve injury models, particularly SNI, Seltzer, and CCI models. Direct nerve injury models serve as valuable proxies for conditions like Complex Regional Pain Syndrome type II or Persistent Spinal Pain Syndrome type II.[1] Recently, there has been a growing interest in clinical settings to use SCS for nontraumatic peripheral neuropathies, particularly those associated with diabetes.[56,76,109,110] Encouragingly, several laboratories have adopted a painful diabetic neuropathy model induced by intraperitoneal injection of streptozotocin,[23,53,58,112] and one group investigated the efficacy of SCS in a preclinical model of chemotherapy-induced peripheral neuropathy.[74,75] This expansion of preclinical models using SCS will not only enhance our understanding of SCS mechanisms of actions but may also broaden applications to manage diverse neuropathic pain conditions.

It is worth noting that the rat species of choice used in almost all studies was the male Sprague-Dawley rat. Although this choice facilitates comparison between studies, such an experimental approach does not account for sex-dependent variabilities within the same species and compromises the translatability of findings between species, particularly to female humans. There has been a shift in animal research to promote the inclusion of female subjects to reduce sex biases,[4] and therefore, future preclinical SCS research should consider using gender-balanced cohorts.

4.1.2. Stimulating elements

Monopolar electrodes were predominantly used until 2013, with a shift toward the use of quadripolar cylindrical and paddle leads after 2013. The 4-contact configuration used in recent designs more closely aligns with the stimulating elements used clinically, although these can have up to 32 contacts from 2 to 4 implanted epidural leads.[6] However, they do occupy more space in the spinal canal. The average diameter of implanted cylindrical leads was 0.7 mm as compared with the average thickness of a monopolar electrode which was 0.2 mm. Although the cylindrical and paddle leads are larger than monopolar electrodes, the stimulating contacts are smaller. The average widths of the stimulating contacts on both cylindrical and paddle leads were 0.7 mm and 0.9 mm, respectively, as compared with the monopolar electrodes that have an average width of 1.4 mm.

To facilitate translatability, it is important to align the morphometrics and epidural placement of the stimulating contacts with clinical practice. The average diameter of cylindrical leads used clinically is 1.3 mm.[5] The average width of human dorsal column, bounded by the dorsal root entry zones, at T10 is 4.0 to 5.0 mm,[22] and the average distance of the dura mater from the spinal cord at T11 is 3.6 mm.[28] Thus, the contacts used in clinical studies are much smaller than the dorsal column and sit some distance from the spinal cord. In rats, the average diameter of cylindrical leads used is 0.7 mm. The estimated width of rat dorsal column at T10 is approximately 1.0 mm.[114] There is little research regarding the thickness of the cerebrospinal fluid layer in rats. Based on spinal cord cross sections, Idlett et al.[30] estimated a scaling factor of 1:2.5 between rat and human dorsal column

size. This factor suggests that contacts used in rats should have a width or diameter ≤0.5 mm. Only 6 studies in our systematic review used contacts this small: 4 studies used monopolar leads,[2,59,92,93] 1 study used a paddle lead,[95] and 1 study used a cylindrical lead.[112] Thus, the relatively larger electrodes used in preclinical SCS models may activate tracts in the rat spinal cord that remain unaffected in patients (eg, the dorsolateral funiculus).[114] Further research is needed to fully understand the implications of the size of epidural electrodes, as this aspect may pose a significant risk to translation of identified SCS mechanisms of action between species.

4.1.3. Stimulation specifications

Determination of the appropriate stimulation intensity is perhaps the principal challenge for preclinical SCS models. In clinical settings, current intensity is often set in relation to perception threshold, ie, the intensity at which patients report stimulation-induced sensations.[28,38,73] Clearly, this is not possible with nonverbal animals. Thus, a majority of the studies reviewed set the intensity to a percentage of MT (current intensity required to elicit muscle twitching) ranging from 30% to 90%. Although MTs are determined routinely in preclinical studies, there is no corollary in humans. The values determined as appropriate in preclinical research were determined by the pioneers in this field over 25 years ago using monopolar electrodes.[51]

One clinical development that may align intensity levels more objectively between species relates to evoked compound action potential (ECAP) measurements. The ECAP threshold is the current leading to an observable ECAP response, which, when recorded from the spinal cord, approximates to perception threshold in humans.[24,57] This correlation suggests that the ECAP threshold can be used as a proxy for perception threshold also in preclinical SCS models.[18,106] The ECAP thresholds recorded in awake rats are approximately 33% of MT.[18] Interestingly, 2 previous observational studies in rats suggested perception threshold at approximately 40% to 50% of MT.[20,36] Our review shows that the average intensity used was 71.9% of MT for low frequencies (≤100 Hz), which is significantly higher than the ECAP threshold and, potentially, perception threshold in awake rats. Thus, the relative intensity used in preclinical SCS models may be much stronger than the intensity used in patients. This is particularly relevant for studies that use 10 kHz and burst frequencies in which researchers attempt to set intensities below perception threshold in animals to mimic the clinical application. Even these intensities average at 39.3% and 64.5% of MT, respectively, in preclinical preparations, so they are probably not below perception threshold in the animal models used. It should be noted, however, that some studies in our review used 30% of MT across different stimulation frequencies. Future preclinical studies must address the potential implications of current intensity on the outcomes related to SCS mechanisms. The use of objective methods to determine current intensity, like ECAP recordings, may be a way of improving such investigations.

The most used pulse duration of 200 μs, in combination with 50 Hz, was selected to mimic clinical settings used historically.[35] However, 2 recent randomized controlled trials using ≤50 Hz reported average pulse durations of 350 μs[37] and 298 or 288 μs,[42] suggesting that longer pulse durations may be more appropriate to better reflect clinical practice. The average pulse duration of 27 μs during 10 kHz SCS is close to that used clinically,[34] as is the average of 943 μs used in combination with burst stimulation paradigms.[16] Alternatively, in vivo electrophysiological recordings can be used to determine the most efficient pulse duration, ie, by determining the chronaxie value by performing multiple input–output analyses with varying pulse durations.

Most SCS sessions were ≤60 minutes. However, this does not reflect clinical practice in the application of SCS. For example, in a recent study, patients used their SCS device more than 85% of the time even after 2 years.[43] Eleven studies in our review used continuous SCS, and 8 studies used implanted generators.[3,10,31,33,53,61,63,119] Thus, the use of longer stimulation sessions in preclinical SCS models, including continuous stimulation, is an encouraging development highlighted by our review.

4.2. Assessment of spinal cord stimulation analgesic efficacy

Another challenge for preclinical SCS models is assessing the analgesic efficacy of SCS for different pain models, stimulating elements and stimulation specifications. There is a notable lack of variety in behavioral assessments used by the majority of studies in our review, which used classic nociceptive withdrawal reflex assays to determine hypersensitivity to touch or temperature. Indeed, our meta-analyses was limited to pre- and post-SCS paw withdrawal thresholds of neuropathic animals as there was insufficient information to make comparisons using any of the other behavioral tests employed. The analyses showed robust SCS analgesic efficacy across these studies. The subgroup meta-analyses further showed no difference in effect size between studies that used conventional vs nonconventional stimulation paradigms. In fact, we found no significant effects between any of our subgroup comparisons nor did the meta-regression reveal any significant influence of stimulation intensity, frequency, or pulse duration. Such factors have no significant contributions to mechanical hypersensitivity in the studies we reviewed. This result contrasts with clinical data that demonstrates significant differences in patient outcomes for both 10 kHz and burst SCS compared with conventional SCS.[16,34] The reason for this disparity and for the lack of influence of the various stimulation paradigms on behavioral assays is unclear. It is likely that the sample sizes used in preclinical experiments are insufficient to detect changes between active treatments. Comparative clinical SCS studies typically recruit >100 study participants to detect such changes.[16,17,34,42] Comparative investigations in preclinical models are further challenged by the application of an appropriate intensity of stimulation which we discussed above. Although 10 kHz and burst frequency stimulation is delivered in preclinical models at an intensity that could induce evoked potentials in the dorsal columns, it could be that these frequencies are in fact using a common mechanism of action to conventional SCS in the animal preparations that differs from those assumed to be important in humans. Furthermore, although the von Frey test is widely used in preclinical models to assess mechanical hypersensitivity, it may not be robust enough to detect differences between conventional and nonconventional stimulation paradigms. There has been much interest in the field of SCS on the use of different stimulation patterns (eg, burst) and frequencies (eg, 10 kHz); however, a recent comparative study demonstrated that even when frequency, pulse duration, and therapy utilization are equivalent, automated stimulation intensity adjustments to maintain a consistent evoked response were also able to convey long-term benefits to patients as compared with a fixed stimulation output.[44] As such, frequency and pattern alone may not be the only important variables in the application of SCS as, ultimately, the therapy is activating neural elements within the spinal cord. Neurophysiological recordings during SCS in both

clinical and preclinical research could help to further elucidate the importance of activation of differing neural elements in the spinal cord. Caution is needed when interpreting these results, however, because there was high between-study heterogeneity.

Our review identified a few studies that assessed animal activity or conditioned place preference tests to determine the effect of SCS.[23,46] Thus, future preclinical research should transition away from solely relying on stimulus-evoked responses and incorporate operant methods of pain testing with rodents. Such an approach may lead to a more comprehensive understanding of pain perception and behavior, considering not only the reflexive responses but also the cognitive and motivational aspects, thus better representing the complexity of pain experience in patients.[7]

4.3. Limitations

In our systematic review, several limitations were identified. First, we identified risks of bias concerning randomization and blinding, which improved after 2015. Second, a large proportion of studies in our review reported funding from SCS manufacturers, which have a stake in positive outcomes. Third, the subjective nature of rodent behavior assessment introduces observer bias and interrater variability, which we detected in our SYRCLE analysis. Fourth, the meta-analysis was post hoc and was not defined a priori in the initial protocol as we did not anticipate that sufficient data would be available to conduct such an analysis. Lastly, our restriction to studies with behavioral assessments excluded those focusing on intraoperative testing, potentially skewing the proportional prevalence of nonbehavioral assessments, particularly neurophysiological assessments (eg, Yang et al.[116] and Guan et al.[26]). This exclusion, along with the omission of nonpain pathologies, may appear to reduce the contribution to the field made by some research groups.

4.4. Conclusions and recommendations

In summary, we provide a comprehensive characterization of the critical components of preclinical SCS models and identified approaches that may improve their reproducibility and translatability. Experimental methods for determining translatable stimulation intensities needs particular attention and a deeper exploration on the appropriateness of the morphometrics of the implantable stimulating elements would be useful.

To aid reproducibility, methodological descriptions should offer detailed information regarding the stimulation parameters used to determine MT, including when and how often MTs are determined, and the absolute current intensities in μA, rather than solely as a ratio of MT (eg, as demonstrated in Ref. 9). The implementation of objective methods to determine SCS intensity (eg, ECAP thresholds) should be considered whenever possible. Clearer reporting of behavioral data from experimental groups could facilitate future data extraction, providing a more accurate effect size of therapy. In addition, inclusion of a study flowchart to improve understanding of the experimental design and allocation of animals in each experimental group/analysis, including instances and reasons for animals dropping out of the study, would be beneficial (eg, as illustrated in Ref. 89).

To aid translatability, future preclinical research should consider a variety of pain models and behavioral assessments and ensure gender-balanced cohorts. When designing stimulating elements, consideration of factors such as the relative size of the epidural space and anatomical differences between species should be taken into account. This information should be clearly outlined in any publication within the SCS field, and any relevant in situ imaging, if not previously published, should be included (eg, as demonstrated in Ref. 41).

Overall, these recommendations will help enhance preclinical SCS models, leading to better translation into clinical practice and a better understanding of the mechanisms underlying SCS action.

Disclosures

The authors have no conflict of interest to declare.

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