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Review Article

REVIEW ARTICLE

Effect of neuromodulation for chronic pain on the autonomic nervous system: a systematic review

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Abstract

Background: In recent years, there has been a growing interest in the use of neuromodulation as an alternative treatment option for chronic pain. Neuromodulation techniques, such as spinal cord stimulation (SCS), dorsal root ganglion (DRG) stimulation, deep brain stimulation (DBS), and peripheral nerve stimulation, have shown promising results in the management of various chronic pain conditions and involve targeted modulation of neural activity to alleviate pain and restore functional capacity. The autonomic nervous system (ANS) plays a crucial role in the regulation of various bodily functions including pain perception. However, the effects of neuromodulation on the ANS in the context of chronic pain remain poorly understood. This systematic review aimed to comprehensively assess the existing literature about the effects of neuromodulation on the ANS in chronic pain settings.

Methods: Searches were conducted using four electronic databases (PubMed, EMBASE, SCOPUS, and Web of Science). The study protocol was registered before initiation of the review process. The Office of Health Assessment and Translation (OHAT) Risk of Bias tool was used to evaluate risk of bias.

Results: A total of 43 studies were included, of which only one was an animal study. Several studies have reported more than one outcome parameter in the same population of chronic pain patients. Cardiovascular parameters were the most frequently used outcomes. More specifically, 18 outcome parameters were revealed to evaluate the function of the ANS, namely heart rate variability (n=17), arterial blood pressure (n=15), tissue oxygenation/perfusion (n=5), blood markers (n=6), multiunit postganglionic sympathetic nerve activity (n=4), skin temperature (n=3), skin conductance (n=3), cephalic autonomic symptoms (n=2), ventilatory frequency (n=2), vasomotor tone (n=1), baroreflex sensitivity (n=1), sympathetic innervation of the heart, neural activity of intrinsic cardiac neurons (n=1), vascular conductance (n=1), arterial diameter (n=1), blood pulse volume (n=1), and vagal efficiency (n=1). Most studies evaluated SCS (62.79%), followed by DBS (18.6%), peripheral nerve stimulation (9.3%), DRG stimulation (4.65%), and vagus nerve stimulation (4.65%).

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Overall, inconsistent results were revealed towards contribution of SCS, DBS, and peripheral nerve stimulation on ANS parameters. For DRG stimulation, included studies pointed towards a decrease in sympathetic activity.
Conclusions: There are indications that neuromodulation alters the ANS, supported by high or moderate confidence in the body of evidence, however, heterogeneity in ANS outcome measures drives towards inconclusive results. Further research is warranted to elucidate the indirect or direct mechanisms of action on the ANS, with a potential benefit for optimisation of patient selection for these interventions.
Systematic review protocol: PROSPERO (CRD42021297287).

Keywords: autonomic nervous system; chronic pain; electrical stimulation; neuromodulation; systematic review

Chronic pain is a pervasive and debilitating condition affecting millions of individuals worldwide, thereby significantly impacting their health-related quality of life and posing a substantial burden on healthcare systems.[1] Although traditional pharmacological approaches to pain management are effective for some patients, they are not successful for every patient and could be associated with important side-effects and increased risks for dependence or anxiolytic effects.[2] In this context, neuromodulation, specifically through implantable devices, has emerged as a promising therapeutic strategy for chronic pain management.[3]

Neuromodulation involves the alteration of nerve activity through targeted delivery of a stimulus, such as electrical discharges, to specific neurological sites in the body.[4] Implantable neuromodulation devices, including spinal cord stimulators, peripheral nerve stimulators, deep brain stimulators, and other devices, have shown significant promise in reducing pain in various conditions, including neuropathic pain, complex regional pain syndrome, intractable back and neck pain, different types of cephalgia, and refractory angina.[5]

The autonomic nervous system (ANS) plays a critical role in physiological responses to pain through connections between both the autonomic and pain regulating systems. Connections are established through different systems among which projections from periaqueductal grey neurones to autonomic centres in the medulla, baroreflex activity, and vagal-nociceptive interactions whereby descending nociceptive inhibitory pathways provide input to sympathetic and parasympathetic preganglionic nuclei.[6] Chronic pain conditions are often associated with dysregulation of the ANS, manifesting with reduced heart rate variability (HRV), increased sympathetic activity, and decreased parasympathetic activity.[7] Nevertheless, the relationship between chronic pain and autonomic function appears to be complex and not yet fully understood.[8,9]

Recent evidence suggests that neuromodulation devices not only alleviate pain but may also modulate ANS activity.[10] Proposed supraspinal hypothesis for spinal cord stimulation (SCS) and dorsal root ganglion (DRG) stimulation encompass modulation of the ascending medial and lateral pathway, spinal-cerebral-loop, and descending pathways, which points towards an influence of neuromodulation on the ANS through the descending pathways.[11,12] For example, SCS has been shown to influence sympathetic activity, potentially offering a dual benefit of pain relief and autonomic regulation.[13]

This review aimed to further explore the influence of the ANS on neuromodulation and to provide a systematic overview of alterations in outcome parameters of the ANS in patients undergoing neuromodulation for chronic pain management.

Methods

Protocol and registration

This systematic review was conducted according to the PRISMA statement (Preferred Reporting Items for Systematic Review and Meta-Analyses).[14] The protocol was registered *a priori* in PROSPERO (registration number CRD42021297287).

Search strategy

The searches were done in four online databases: PubMed, EMBASE, SCOPUS, and Web of Science on January 4, 2022, and updated on May 5, 2024. The search strategy was developed according to the PICO (Population-Intervention-Comparison-Outcome) framework[15] to explore ANS changes (O) with invasive neuromodulation therapies (I) in chronic pain settings (P). The component 'Comparison' was not relevant to our research question and was therefore not defined. The component 'Population' was not restricted to human studies to ensure that all studies elaborating on the mechanisms of action of neuromodulation on the ANS could be included (i.e. human, animal, and computational studies were allowed). The search strategy was built by combining free-text terms and MeSH terms. Within each part of the PICO question (i.e. within 'intervention', 'outcome', and 'population'), the search terms were combined using the Boolean operator OR. Between the components of the Boolean operator AND was used. No additional search filters were used in this study. The complete search strategy for all databases can be found in the Supplementary Material. After constructing the search string in PubMed, it was individually adapted for the other three databases. We also screened the reference lists of all relevant publications for additional papers (backward reference search).

Eligibility criteria

This review explored the effect of neuromodulation for pain on ANS parameters, whereby there were no restrictions on specific types of autonomic parameters. Studies with acute pain (<3 months) patients were not eligible, meaning only studies on chronic pain patients, animal pain models, and computational models for chronic pain were included. The types of neuromodulation therapies that were included were electrical systems among which SCS, DRG stimulation, peripheral nerve stimulation, peripheral nerve field stimulation, and deep brain stimulation (DBS), when applied for treating chronic pain. Both observational and experimental studies investigating changes in ANS parameters using neuromodulation devices were included in this systematic review. Review meta-analysis, case reports (because of a high risk for uncontrolled findings), abstracts from conference,

proceedings, expert opinions, and letters to the editor were excluded. Full eligibility criteria are presented in Table 1.

Study selection

After de-duplication, all retrieved articles were screened for their title and abstract by two reviewers independently, using Rayyan online software.[16] Subsequently, two reviewers performed the full text screening independently from each other. The percentage agreement was calculated to assess inter-rater reliability. Discrepancies were discussed after each stage of the screening in a consensus meeting with both reviewers and a third independent reviewer.

Data extraction

The data extraction form included the following items, which were determined *a priori*: author, year, country, study design, population, type of neuromodulation therapy, outcome measurements related to ANS. Data extraction was performed by the first reviewer and checked for correctness by the second reviewer. Any discrepancies were discussed in a consensus meeting with the third reviewer. Studies are reported with the metrics that were presented in the original studies, meaning no calculations were performed to obtain standardised metrics. Articles were grouped and discussed by ANS parameter and within these categories according to type of neuromodulation. In line with the PROSPERO registration, a meta-analysis would be included if possible. However, because of the heterogeneity in outcome measures, a meta-analysis could not be calculated.

Risk of bias assessment

The internal validity, meaning the degree to which the design, conduct, and analysis of a study avoids bias, and the overall risk of bias of the included studies was assessed using the approach recommended by the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT). The OHAT risk of bias reacting tool consists of a set of questions and provides detailed instructions on how to evaluate methodological rigour in both human and animal studies. As recommended by OHAT, methodological criteria are dependent on the study design. Nine criteria were applied for animal studies, eight for human-controlled trials, seven for cohort studies, case-control studies, cross-sectional studies, and five criteria for case series to evaluate selection bias, confounding bias, performance bias, attrition/exclusion bias, detection bias, selective reporting bias, and other sources of bias. Two authors (BB, LG) independently evaluated risk of bias for each article with the following ratings: definitely low risk of bias, probably low risk of bias, probably high risk of bias, and definitely high risk of bias. Afterwards, the overall risk of bias for each individual study was assessed through the OHAT approach for categorising each study into tiers. Study quality was rated according to a three-tier system (1st tier: high confidence in the reported results, 2nd tier: moderate confidence in the reported results or 3rd tier: low confidence in the reported results). Studies were not excluded based on the results of the risk of bias assessment, to avoid selective reporting of study findings.

Results

Study selection

The search yielded 5041 articles. After deduplication, 4296 articles were retained for title and abstract screening. Subsequently, 85 articles were selected for full-text screening, of which 43 were included in the systematic review. The percentage of agreement on title and abstract screening between reviewers was 96.9% (129 conflicts). The reasons for exclusion were wrong intervention/drug (n=2196), wrong population (n=916), wrong study design (n=1067), and wrong outcome (n=728). It is noteworthy that some articles had more than one reason for their exclusion. To a lesser extent, incorrect publication type, language, and study duration. Five articles were excluded because no full text was available. Citation screening did not result in additional articles eligible for full-text screening. After full-text screening of 85 articles, 43 were included in this systematic review. Percentage of agreement during full-text screening was 90%. The PRISMA flow diagram (Fig 1) provides an overview of the study selection process.

Study characteristics

In total, 43 studies were included, of which 42 were human-based studies and one an animal study (Table 2). Most studies (n=27) investigated SCS, followed by DBS (n=8),

Table 1 Eligibility criteria.

Inclusion criteria	Exclusion criteria
Animals/humans treated with implantable neuromodulation or transcutaneous devices for chronic pain. Computational studies on implantable neuromodulation devices were also allowed.	Other neuromodulation devices including, but not limited to, non-implantable devices.
Autonomic outcome measurements, including, but not limited to, tissue perfusion and oxygenation, HRV, skin temperature, blood pressure, photoplethysmography.	No measurements of autonomic nervous system outcomes.
RCT, cross-sectional, clinical trial, controlled clinical trial, cohort studies, case series.	(Systematic) reviews, meta-analyses, abstract only from conference, proceedings, case reports, expert opinion, letters to editor.
English, French, German, Dutch.	Other languages.

HRV, heart rate variability; RCT, randomised controlled trial.

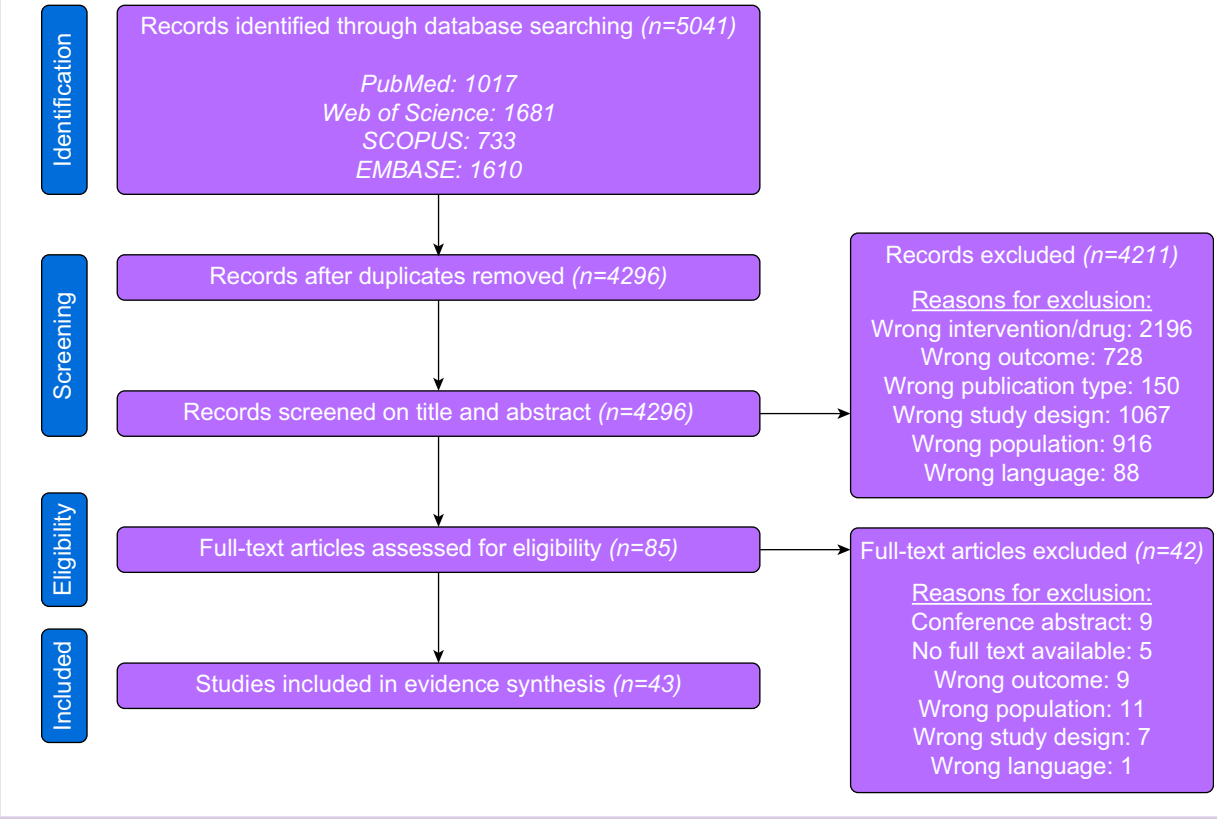

Fig. 1. Flowchart of the systematic review.
This figure shows the complete flowchart of the search and screening of articles for this systematic review. Under records excluded, some articles are double, or triple accounted for if there were multiple reasons for exclusion. *n*, number of studies.

peripheral nerve stimulation (*n*=4), DRG stimulation (*n*=2), and vagus nerve stimulation (*n*=2).

The most reported outcomes related to the ANS were HRV (*n*=17), arterial blood pressure (ABP) (*n*=15), and skin temperature (*n*=12). Other outcomes included tissue oxygenation and perfusion (n=10), skin conductance (n=8), blood marker levels (*n*=6), multiunit postganglionic sympathetic nerve activity (*n*=6), cephalic autonomic symptoms (*n*=5), arterial diameter (*n*=4), baroreflex sensitivity (*n*=3), sympathetic innervation of the heart (*n*=2), neural activity of the intrinsic cardiac neurones (*n*=2), vascular conductance (*n*=2), blood pulse volume (*n*=2), vagal efficiency (VE) (*n*=1), vasomotor tone (*n*=1), and ventilatory frequency (*n*=1).

Risk of bias

The results of the risk of bias assessment for each study can be found in Table 3. Seventeen studies were placed in the '1st tier', 17 in the '2nd tier' and the remaining nine studies were assigned to the '3rd tier'. Only three studies (7%) did not adequately address confidence in outcome assessment. In total, 97.67% of the studies properly took into account confidence in exposure characterisation. For the third key component (i.e. confounding and modifying conditions), low risk of bias was revealed in all studies for which this criterion was relevant (*n*=12). The items on which the included studies often revealed a high risk of bias were randomisation of exposure level and allocation concealment.

Autonomic nervous system parameters

Arterial blood pressure

One study evaluated ABP for limb ischemia. In patients with arteriosclerosis and diabetes treated with SCS for severe limb ischemia, ABP was measured at the first toe using the strain-gauge technique. The same method was used for patients with vasospastic disorders and severe upper limb ischemia of the thumb. SCS therapy showed an average increase of 8 (3) mm Hg in the toe and 19 (2) mm Hg in the thumb.[17] Only one study has evaluated ABP and vascular conductance in the femoral artery with SCS therapy in the ON and OFF states. The leads were placed for lower limb chronic neuropathic pain in 11 patients. Vascular conductance and resistance are directly related to ABP.[18] The results showed a significant increase in vascular conductance during 60 min of SCS therapy compared with that at 15 min post-SCS therapy (P=0.02). However, no changes in the systolic or diastolic ABP were observed. The mean ABP significantly increased by a small amount; baseline: 87 (10) mm Hg; 60 min: 91 (12) mm Hg.[19]

In a retrospective study, both low-frequency (LF-SCS) and high-frequency (HF-SCS) SCS significantly reduced systolic blood pressure (SBP) in hypertensive patients with chronic pain,

Table 2 Summary table of included studies.

Author and year	Animal/human study	Study design	Design specifications	Number of participants	Chronic pain type	Type of stimulation	Relevant autonomic outcomes
Andersen (1998)	Human	Cohort		21	Angina pectoris	SCS	HRV
Ather (2003)	Human	Non-randomised experimental study		12	Neuropathic pain (mixed aetiology)	SCS	Tissue oxygenation/ perfusion
Augustinson (1995)	Human	Cohort		34	Peripheral vascular disease	SCS	ABP, ST
Barloese (2018)	Human	RCT	Double blind, crossover trial	16	Cluster headache	Sphenopalatinum stimulation	HRV, ABP
Bocchi (2010)	Human	Non-randomised experimental study		10	Diabetic type 2 with suggestion of polyneuropathy	Frequency Rhythmic Electrical Modulation System (FREMS)	Tissue oxygenation/ perfusion, SC, ST
Black (2022)	Human	Cohort		10	PSPS II	SCS	HRV, MSNA, VF
Da Silva (2017)	Human	RCT	Double blind, crossover trial	18	Spinal cord injury	Transcranial direct current	HRV
Foreman (2000)	Animal	Experimental		9	Myocardial ischemia	SCS	Neural activity intrinsic cardiac neurons
Fricke (2008)	Human	Cohort		23	Angina pectoris	SCS	Sympathetic innervation of the heart + myocardial perfusion
Garzon (2020)	Human	Cross-sectional		16	CRPS type 1	SCS	Tissue oxygenation/ perfusion
Ghajar (1998)	Human	Non-randomised experimental study		10	PVD	SCS	Tissue oxygenation/ perfusion, ST
Goudman (2019)	Human	Non-randomised experimental study		22	PSPS II	SCS	HRV
Goudman (2021)	Human	Non-randomised experimental study		22	PSPS II	SCS	HRV
Goudman (2022)	Human	Non-randomised experimental study		28	PSPS II	SCS	SC, HR, VF, blood pulse volume
Goudman (2021)	Human	Non-randomised experimental study		23	PSPS II + HC	SCS	SC
Gravius (2019)	Human	Cohort		24	CRPS + HC	DRGS	Blood markers
Green (2010)	Human	Non-randomised experimental study		6	Chronic neuropathic pain (mixed aetiology)	DBS	ABP, HRV
Green (2006)	Human	RCT	Double blind, parallel groups	11	Chronic neuropathic pain (mixed aetiology)	DBS	ABP, HRV, baroreflex

Continued

Table 2 Continued

Author and year	Animal/human study	Study design	Design specifications	Number of participants	Chronic pain type	Type of stimulation	Relevant autonomic outcomes
Green (2006)	Human	RCT	Double blind, parallel groups	16	Chronic neuropathic pain (mixed aetiology)	DBS	ABP
Green (2005)	Human	Non-randomised experimental study		15	Chronic neuropathic pain (mixed aetiology)	DBS	ABP, HRV
Guo (2020)	Human	RCT	Double blind, crossover trial	12	Migraine	Sphenopalatinum stimulation	CAS, ABP
Guo (2018)	Human	RCT	Double blind, crossover trial	20	Cluster headache	Sphenopalatinum stimulation	CAS, arterial diameter, blood marker, ABP
Hassenbusch (1996)	Human	CaS		32	Reflex sympathetic dystrophy	Peripheral nerve stimulation	Vasomotor tone (minimal - mild - moderate)
Hautvast (1998)	Human	Cohort		19	Angina pectoris class III or IV	SCS	HRV
Holwerda (2018)	Human	Non-randomised experimental study		12	Neuropathic pain in lower back, limbs, or both	SCS	Vascular conductance (femoral) with Doppler, MSNA, ABP
Jessurun (1999)	Human	RCT	Parallel groups with crossover for one group, open label	24	Angina pectoris class III or IV	SCS	HRV, ABP, blood markers epinephrine and norepinephrine
Kalmar (2013)	Human	Non-randomised experimental study		7	FBBS and CRPS type II	SCS	HRV
Kemler (2000)	Human	Non-randomised experimental study		22	CRPS type I	SCS	Tissue oxygenation/ perfusion
Kovacic (2020)	Human	RCT	Double blind, parallel groups	92	Visceral pain	Transcutaneous auricular stimulation	Vagal efficiency
Kriek (2018)	Human	RCT	Double blind, crossover trial	10	CRPS	SCS	Blood markers
Memar (2023)	Human	Retrospective cohort		132	PSPS II/CRPS	SCS	ABP
Norrsell (1997)	Human	Non-randomised experimental study		10	Angina pectoris class III or IV	SCS	Blood marker norepinephrine, ABP
Paccione (2022)	Human	RCT	Double blind trial	116	Fibromyalgia	tVNS (transcutaneous vagus nerve stimulation)	HRV
Parker (2021)	Human	RCT	Single blind, crossover trial	18	Chronic neuropathic pain (mixed aetiology)	DRGS	HRV, ABP
Patterson (2023)	Human	Cohort		20	PSPS II, PSPS I and CRPS	SCS	HRV

Continued

Table 2 Continued

Author and year	Animal/human study	Study design	Design specifications	Number of participants	Chronic pain type	Type of stimulation	Relevant autonomic outcomes
Pereira (2010)	Human	RCT	Double blind trial	16	Chronic neuropathic pain (mixed aetiology)	DBS	HRV
Petrakis (2000)	Human	Cohort		60	Diabetic type 1	SCS	Tissue oxygenation/ perfusion
Prim (2019)	Human	RCT	Double blind, crossover trial	21	Chronic low back pain	Transcranial alternating current	HRV
Robaina (1989)	Human	Cohort		11	CRPS (N=8) + idiopathic Raynaud's disease (N=3)	SCS	ST
Sverrisdóttir (2014)	Human	RCT	Single blind trial	7	Neuropathic pain	DBS	MSNA, ABP, VF
Sverrisdottir (2020)	Human	Cohort		14	Mixed aetiology	DRGS	MSNA, ABP
Velasco (2009)	Human	RCT	Double blind trial	5	CRPS	Motor cortex stimulation	Trophic sympathetic changes
Yang (2024)	Human	RCT	Single blind trial	27	Chemo-induced painful peripheral neuropathy	tVNS	Blood markers

ABP, arterial blood pressure; CaS, case series; CAS, cephalic autonomic symptoms; CRPS, complex regional pain syndrome; DBS, deep brain stimulation; DRGS, dorsal root ganglion stimulation; FBBS, failed back surgery syndrome; HC, human controls; HRV, heart rate variability; MSNA, multiunit postganglionic sympathetic nerve activity; PSPS II, persistent spinal pain syndrome type II; PVD, peripheral vascular disease; RCT, randomised controlled trial; SCS, spinal cord stimulation; ST, skin temperature; SC, skin conductance; VF, ventilatory frequency.

Table 3 Risk of bias in individual studies.

Author/Year	Design	Randomization Exposure level	Allocation Concealment	Appropriate Comparison Groups	Confounding and Modifying Variables	Identical Experimental Conditions	Blinding of Research Personnel and Subjects	Attrition or Exclusion of Outcome Data	Confidence Exposure Characterization	Confidence Outcome Assessment	All Measured Outcomes Reported	Other Potential Threats	Quality Category (TIER-System)
Andersen (1998)	Cohort	NA	NA	++	+	NA	NA	++	++	+	++	--	2nd tier
Ather (2003)	N-RES	--	--	NA	NA	NA	NR	++	++	+	++	-	2nd tier
Augustinson (1985)	Cohort	NA	NA	++	+	NA	NA	++	++	+	++	++	2nd tier
Barloese (2018)	RCT	++	++	NA	NA	NA	++	++	++	++	--	++	1st tier
Bocchi (2007)	N-RES	--	--	NA	NA	NA	NR	+	++	+	--	++	3rd tier
Black (2022)	Cohort	NA	NA	++	+	NA	NA	++	++	+	--	++	3rd tier
Da Silva (2017)	RCT	-	-	NA	NA	NA	-	++	++	++	++	+	1st tier
Foreman (2000)	EA	++	+	NA	NA	+	NR	++	++	+	++	++	2nd tier
Fricke (2008)	Cohort	NA	NA	++	+	NA	NA	++	-	+	++	+	3rd tier
Garzon (2020)	Cross Sectional	NA	NA	++	+	NA	NA	++	+	+	++	++	2nd tier
Ghajar (1998)	N-RES	--	--	NA	NA	NA	NR	-	++	+	++	++	2nd tier
Goudman (2019)	N-RES	--	--	NA	NA	NA	NR	++	++	+	++	++	1st tier
Goudman (2021)	N-RES	--	--	NA	NA	NA	NR	++	++	+	++	++	1st tier
Goudman (2022)	N-RES	--	--	NA	NA	NA	NR	++	++	+	++	++	1st tier
Goudman (2021)*	N-RES	--	--	NA	NA	NA	NR	++	++	+	++	+	2nd tier
Gravius (2019)	Cohort	NA	NA	++	++	NA	NA	++	++	+	++	++	1st tier
Green (2010)	N-RES	--	--	NA	NA	NA	NR	+	++	+	++	-	3rd tier
Green (2006)	RCT	+	NR	NA	NA	NA	+	++	++	++	++	++	1st tier
Green (2006)*	RCT	+	NR	NA	NA	NA	+	++	++	++	++	+	2nd tier
Green (2005)	N-RES	--	--	NA	NA	NA	NR	++	++	+	++	++	1st tier
Guo (2020)	RCT	++	++	NA	NA	NA	++	++	++	++	++	++	1st tier

Guo (2018)	RCT	++	++	NA	NA	NA	++	++	++	++	++	++	1st tier
Hassenbusch (1996)	Case series	NA	NA	++	+	NA	NA	++	++	-	++	+	3rd tier
Hautvast (1998)	Cohort	NA	NA	++	+	NA	NA	++	++	+	++	++	2nd tier
Holwerda (2018)	N-RES	--	--	NA	NA	NA	NR	++	++	+	++	++	2nd tier
Jessurun (1999)	RCT	+	NR	NA	NA	NA	NR	++	++	+	++	+	2nd tier
Kalmar (2013)	N-RES	NR	NR	NA	NA	NA	--	++	++	+	++	--	3rd tier
Kemler (2000)	N-RES	--	--	NA	NA	NA	NR	++	++	+	++	++	2nd tier
Kovacic (2020)	RCT	+	NR	NA	NA	NA	+	++	++	++	++	+	1st tier
Kriek (2018)	RCT	+	NR	NA	NA	NA	+	+	++	++	++	++	1st tier
Memar (2023)	Retrospective cohort	NA	NA	NR	+	NA	NA	+	++	-	+	+	3rd tier
Norrsell (1997)	N-RES	--	--	NA	NA	NA	--	++	++	+	++	++	2nd tier
Paccione (2022)	RCT	++	++	NA	NA	NA	NR	++	+	+	++	++	1st tier
Parker (2021)	RCT	+	NR	NA	NA	NA	--	++	++	+	++	+	2nd tier
Patterson (2023)	Cohort	NA	NA	++	+	NA	NA	+	++	+	++	++	1st tier
Pereira (2010)	RCT	+	NR	NA	NA	NA	+	++	++	++	++	+	1st tier
Petrakis (2000)	Cohort	NA	NA	++	+	NA	NA	++	++	+	++	++	2nd tier
Prim (2019)	RCT	+	NR	NA	NA	NA	++	++	++	++	++	++	1st tier
Robaina (1989)	Cohort	NA	NA	++	+	NA	NA	++	++	+	+	-	3rd tier
Sverrisdottir (2014)	RCT	+	NR	NA	NA	NA	NR	++	++	++	++	+	2nd tier
Sverrisdottir (2020)	Cohort	+	NR	NA	NA	NA	+	++	++	++	++	+	2nd tier
Velasco (2009)	RCT	++	NR	NA	NA	NA	+	+	++	++	+	-	3rd tier
Yang (2024)	RCT	++	NR	NA	NA	NA	-	-	++	-	++	+	1st tier

Key risk-of-bias criteria are indicated with a black frame. Definitely low risk of bias is indicated as '++' and coloured dark green, probably low risk of bias as '+' and light green, probably high risk of bias as '-' and orange and definitely high risk of bias as '- -' and coloured red. EA, experimental animal; N-RES, non-randomised experimental study; NA, not applicable in this specific study; NR, not reported in this specific study; RCT, randomised controlled trial. * different manuscirpts.

showing decreases of 8 mm Hg ($P<0.01$) with LF-SCS and 7 mm Hg ($P<0.01$) with HF-SCS. These reductions were specific to patients with stage 2 hypertension and occurred independently of changes in pain intensity. The findings indicate that SCS may directly modulate autonomic function to lower blood pressure.[20]

Patients ($n=24$) treated with SCS for refractory angina participated in an RCT in which they monitored ABP when SCS treatment was stopped for 4 weeks. However, no alterations in ABP have been detected.[21] Another study involving patients ($n=10$) with SCS for refractory angina demonstrated a significant decrease in ABP during atrial pacing under SCS therapy compared with atrial pacing with SCS therapy OFF ($P=0.02$).[22]

Five studies described the effects of DBS on ABP. Each study involved stimulation of the periventricular/periaqueductal grey (PVG/PAG) area. A study of 15 patients with refractory neuropathic pain treated with DBS showed a significant difference in ABP alterations depending on the area of stimulation in the PVG/PAG. SBP was decreased stimulating the ventral part of the PVG/PAG (14.2 [3.6] mm Hg, $n=7$), this in contrast to stimulating the dorsal PVG/PAG. Stimulating the dorsal part led to an increase in SBP (16.7 [5.9] mm Hg, $n=6$). A significant difference was observed between the ventral and dorsal electrodes ($P<0.05$). These changes are accompanied by analogous changes in diastolic blood pressure.[23] The relationship between pain and ABP was investigated in 16 patients who participated in this prospective study. All patients had DBS electrodes positioned in the PAG. Similarly, ventral placement and stimulation resulted in a significant decrease in ABP, which correlated significantly with short-term VAS score changes. Furthermore, they found a significant correlation between ventral and dorsal PAG stimulations and VAS score changes ($r^2=0.62$, $P<0.01$, $n=16$). There was a 56.6% reduction in the VAS score in the ventral group and 33.6 in the dorsal group ($P=0.04$, Wilcoxon, $n=16$). Linear regression analysis was performed on the absolute values of pain and

blood pressure in each patient but showed no significant relationship. This indicates that a reduction in ABP is more important than absolute blood pressure.[24] One study showed a significant reduction in blood pressure drop while standing upright in patients with orthostatic hypotension treated with DBS for neuropathic pain syndrome. One patient had orthostatic hypotension, five patients had mild orthostatic hypotension, and five patients did not have orthostatic intolerance. Patients with orthostatic hypotension and mild symptoms showed significantly less drop in ABP with ON stimulation ($P<0.001$). DBS electrodes were placed over the PAG, but the exact ventral or posterior positioning was not mentioned in the study description.[25] The same group performed a study with a small number of patients ($n=5$), which showed a significant correlation between changes in ABP and the low-frequency (LF) domain in HRV ($P=0.02$). The DBS electrodes were also placed at the PAG and showed the same alternating ABP variation as in previous studies when placed ventral or dorsal.[26] A subset of seven patients with chronic neuropathic pain was examined, and the patients showed a small but significant decrease in diastolic blood pressure when DBS stimulated the ventral part of the PAG.[27]

Two studies on DRG stimulation examined ABP. One study was conducted over a period of 2 yr ($n=16$). Interestingly, only DRG leads placed on the left side led to a significant decrease in all three blood pressure parameters (systolic, diastolic, and mean). There was no difference between the 6 months follow-up and 2 yr follow-up, suggesting a long-term effect on ABP.[28] The second study ($n=18$) also showed a significant reduction in ABP but did not correlate with the left- or right-sided placement of the electrodes ($P=0.061$) with a mean MAP reduction of -8.9, SD=12.1.[29]

Two studies by Guo and colleagues[30,31] on LF stimulation of the sphenopalatine ganglion (SPG) compared with sham stimulation did not show a significant change in ABP during LF or sham stimulation.

Heart rate variability

Kalmár and colleagues[32] investigated a small number of patients ($n=7$) receiving SCS therapy for chronic neuropathic pain (complex regional pain syndrome [CRPS] and persistent spinal pain syndrome type II [PSPS II]). A 5-min HRV evaluation in the switch-on state showed a significant decrease in the high-frequency (HF) domain ($P=0.043$) but not in the LF domain, standard deviation of the NN interval (SDNN), root mean square of successive RR interval differences (RMSSD), or LF/HF ratio. In contrast, two studies by Goudman and colleagues[33,34] included only patients with PSPS II ($n=22$) treated with SCS. LF power was significantly lower when SCS was activated ($P=0.02$). Furthermore, absolute ($P=0.01$) and normalised HF power ($P=0.001$) significantly increased during SCS compared with those without SCS. The LF/HF ratio was also significantly lower ($P=0.04$) in the time-frequency domain.[33,34] A feasibility study with a very small number of patients ($n=10$) failed to find a significant change in HRV parameters in PSPS II patients treated with SCS.[35]

In a recent study,[36] HRV was used as a key predictor in a machine learning model to forecast pain levels in individuals with SCS systems. The model, which incorporated HRV along with other physiological and activity data from wearable devices, demonstrated that higher HRV correlates with lower pain intensity. This predictive capability underscores the potential of HRV as a significant biomarker in understanding and managing chronic pain.

In one study involving seven patients treated with DBS for neuropathic pain, intraoperative stimulation showed a significant correlation between SBP percentage change and LF power (Pearson's $r=0.82$, $P=0.02$). For HF power (Pearson's $r=0.69$) and LF/HF ratio (Pearson's $r=0.667$), the correlation was lower.[26] They demonstrated a significant increase in LF power compared with baseline, with stimulation ON ($n=11$) in a different study. No changes were observed in the HF power analysis.[25]

A different study by the same research group did not find an alteration in the LF power with DBS (ventral PAG) ON stimulation. However, there was a significant increase in HF power ($P=0.02$) and a decrease in the LF/HF ratio ($P=0.01$). Moreover, there was a correlation between HF power changes ($y^2=0.27$, $P=0.04$, $n=16$), LF/HF ratio ($y^2=0.36$, $P=0.01$, $n=16$), and analgesic efficacy of the therapy. This correlation was not observed for LF power changes.[37]

A final study that examined RR interval changes in patients ($n=15$) with DBS for the treatment of chronic pain did not find a significant change.[23]

Two prospective studies examining the effect of SCS as a treatment for refractory angina did not demonstrate an alteration in HRV parameters between the baseline assessment and assessments at 6 weeks ($n=19$) and 1 yr ($n=21$).[38,39] Patients ($n=24$) treated with SCS for refractory angina participated in an RCT in which they monitored HRV when SCS treatment was stopped for 4 weeks. However, no alterations in HRV (assessed by HF power, SDNN, and RMSSD) have been detected.[21]

A double-blind RCT examining the effect of LF stimulation on the SPG showed an initial increase in sympathetic drive after 10 min of stimulation (increase in LF power and decrease in HF power [$P<0.05$]). When a cluster-like attack was induced, typically after 30 min, the HF power increased significantly ($P<0.05$) and the LF power decreased significantly ($P<0.05$), which was the case in the sham group (four attacks) and LF stimulation group (six attacks).[40]

A double-blind RCT examining the effect of transcranial alternating current stimulation (tACS) found only an overall effect on HRV in patients with chronic low back pain. The SDNN changed with 10 Hz tACS, but not in the sham group, thereby showing an effect on sympathetic and parasympathetic inputs to the heart.[41] A second double-blind RCT evaluating the effect of transcranial direct current stimulation (tDCS) in patients with spinal cord injury demonstrated a significant increase in the LF/HF ratio ($P=0.003$) compared with sham stimulation.The observed changes suggest a trend towards the normalisation of autonomic nervous system parameters..[42]

A study on DRG stimulation found significantly decreased normalised LF power ($P=0.02$) and increased normalised HF power ($P=0.02$) with acute DRG stimulation. These changes were also reflected in the statistically significant reduction in the LF/HF ratio ($P=0.005$). No correlation was found between the LF/HF ratio and changes in the reported pain score (two-tailed Pearson's correlation, $r=-0.02$, $P=0.95$).[29]

In the study by Paccione and colleagues,[43] no significant changes were observed in HRV outcomes after 2 weeks of treatment with either meditative-based diaphragmatic breathing or transcutaneous vagus nerve stimulation in individuals with fibromyalgia.

Skin temperature

Patients with atherosclerotic disease and diabetes with severe limb ischemia treated with SCS, showed a faster increase in

skin temperature after local cooling (14 of 20 patients) compared with the situation without SCS.[17] A study with patients suffering from severe vasospastic disease included eight patients with CRPS I and three patients with Raynaud's disease of the upper limbs treated with SCS. The investigators reported an increase in skin temperature of up to 4°C compared with baseline measurements before SCS therapy. Statistical analyses were not performed.[44] In a small study of four patients implanted with a motor cortex stimulation device for CRPS I, a decrease in skin temperature was reported. This has only been reported as a clinical feature and has not yet been quantified.[45]

Skin conductance

Goudman and colleagues[46,47] investigated the effect of SCS in patients with chronic low back pain in two studies on skin conductance. Skin conductance levels were not altered between the ON and OFF states of SCS in either study. A study of patients with dysautonomic diabetic (type 2) neuropathy treated with a frequency rhythmic electrical modulation system (FREMS) did not show a change in skin conductance either.[48]

Blood markers

Kriek and colleagues[49] obtained inflammatory panels from patients (n=20) treated with SCS for CRPS before and after implantation of the neuromodulation device. Samples were collected from artificial skin blisters on the affected side. Concentrations of the pro-inflammatory cytokine interleukin-15 (IL-15) were significantly reduced over time (P=0.001). For all the other pro- and anti-inflammatory panels, there was only a trend of decreasing concentrations. The chemokine IP-10 (CXCL10) was significantly decreased (P=0.012), as were vascular endothelial growth factor (VEGF) (P=0.032) and platelet-derived growth factor-BB (PDGF-BB) (P=0.034).[49] Another study on the effect of selective L4 stimulation on CRPS compared inflammatory panels with those of healthy controls. IL-1, IL-6, and tumour necrosis factor-alfa (TNF-alfa) concentrations were significantly higher at baseline than in healthy individuals (P=0.02, P=0.001, and P<0.001, respectively), but did not change after 3 months of DRG stimulation. All three parameters remained significantly higher after 3 months of therapy compared with healthy controls but did not significantly change compared with baseline. The same was reported for leptin and high-mobility group box 1 protein (HMGB1). The baseline values were significantly higher than those of the healthy control group (P=0.02) and (P<0.001, respectively). These values did not change significantly after 3 months of DRG stimulation therapy.[50]

Norepinephrine spillover secondary to pacing-induced myocardial stress was calculated with and without SCS therapy. Total body norepinephrine spillover decreased by 18% (P=0.02) with SCS therapy ON compared with SCS therapy OFF. SCS therapy did not affect cardiac norepinephrine spillover. This finding suggests that the anti-ischemic effect of SCS is not attributable to reduced cardiac sympathetic activity.[22] Catecholamine concentrations recorded after cessation of SCS therapy for refractory angina for 4 weeks did not significantly change in the blood plasma.[21]

Parasympathetic markers, such as vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide-38 (PACAP38), were monitored in the blood plasma during LF stimulation and sham of the SPG. No significant differences were observed between the groups.[30]

In a randomised controlled trial, Yang *et al.*[51] evaluated the efficacy of transauricular vagus nerve stimulation (taVNS) in patients with chemotherapy-induced painful peripheral neuropathy. There were no significant changes in inflammatory cytokines or quantitative sensory testing, suggesting the absence of physiological changes in nerve function or systemic inflammation.[51]

Tissue oxygenation and perfusion

Several studies have investigated the effects of SCS and peripheral nerve stimulation on tissue oxygenation tension ($tcpO_2$), vasomotor tone, tissue oxygen saturation (StO_2) and blood pulse in patients with neuropathic pain and CRPS. Only one study revealed a baseline difference in $tcpO_2$ between the healthy limb and the affected CRPS limb.[52] However, stimulation with or without ischemia did not significantly change $tcpO_2$.[46,53] However StO_2, during SCS treatment, in the affected limbs was significantly higher than in the contralateral unaffected limbs (mean difference: 4.7%, 95% CI: 1.41, 6.7; p = 0.005). Vasoreactivity seemed unaffected as no StO_2 changes occured during an ischemia-reperfusion test between affected and unaffected limbs.[88] Vasomotor tone was evaluated during physical examination as minimal, mild or moderate in one study, although an improvement in vasomotor tone was reported, it was not quantitavely measured.[89]

SCS for severe limb ischemia, trophic lesions <3 cm^2 or >3 cm^2, and rest pain showed a significant improvement in the $tcpO_2$ (P=0.03). If definite autonomic neuropathy was present in patients with diabetes, the $tcpO_2$ did not increase significantly.[54] A case series on patients with peripheral vascular disease (PVD) showed that four out of five patients with SCS under T10 showed an increase in $tcpO_2$, but no statistical analysis was performed because of the small sample size.[55]

Multiunit muscle sympathetic nerve activity

Only individual cases have been described in DBS for patients with chronic pain, measuring the effect on multiunit muscle sympathetic nerve activity. The different effects on burst frequency depend on the area of PAG stimulation. No statistically relevant data were available owing to the small sample size (n=7).[27]

Data from patients treated with DRG stimulation for neuropathic pain syndromes (n=14) were obtained during the DRG stimulation ON and OFF states. During the DRG stimulation ON state, the multiunit postganglionic sympathetic nerve activity (MSNA) burst frequency was reduced by 13.3%. The MSNA burst incidence was reduced by 11.8% (P=0.01). No correlation was found between MSNA changes and VAS scores.[28]

In another study, MSNA during SCS for neuropathic pain gradually declined and became significantly reduced at 45 and 60 min of SCS compared with baseline and 15 min (P=0.02). Similar results were observed for changes in the MSNA burst frequency and absolute values of MSNA burst incidence in these patients.[19]

The final study examining the effect of SCS in patients with PSPS II on MSNA did not observe a significant difference, likely due to the limited sample size, which lacked sufficient power to detect potential effects (n=6).[35]

Miscellaneous parameters

SCS for refractory angina in 23 patients (10 diabetics and 13 non-diabetics) did not change the sympathetic innervation of the myocardium at 1 yr of follow-up. This was confirmed by segmental C-hydroxyephedrine PET retention measurements at baseline and 1 yr in both diabetic and non-diabetic patients.[56]

Modulation of intrinsic cardiac neurones by SCS was examined in an animal study of nine anesthetised dogs. SCS suppressed the activity generated by intrinsic cardiac neurones during transient ventricular ischemia, and during the early reperfusion period. This was confirmed using three protocols. 1) Occlusion of the coronary artery in the middle of the SCS, 2) occlusion overlapped by SCS, and 3) occlusion followed by stimulation for all three protocols; the suppression of intrinsic cardiac neurones was significant ($P<0.01$).[57]

Cephalic autonomic symptoms, HR, and ABP were assessed in two studies that evaluated the effect of LF stimulation on the SPG in a double-blind RCT. However, no significant differences were observed.[30,31]

A study by Goudman and colleagues[46] evaluated RR and HR changes in patients treated with SCS for PSPS II. HR significantly increased ($P<0.001$) and RR significantly decreased ($P=0.04$).

Patients with functional abdominal pain were treated using auricular neurostimulation. VE is measured by the slope of the linear regression between short epoch estimates of HR and respiratory sinus arrhythmia (RSA), representing the magnitude of HR change per unit increase/decrease in RSA. In this double-blind, sham-controlled RCT, only patients with a low VE had significantly lower pain scores at 3 weeks. No effect was observed in patients with high VE.[58]

Discussion

This study systematically evaluated the effect of different neuromodulation interventions on ANS output parameters. A broad variety of outcome parameters were revealed, namely ABP, HRV, tissue oxygenation and perfusion, oedema, skin temperature, skin conductance, blood markers, multiunit postganglionic sympathetic nerve activity, cephalic autonomic symptoms, arterial diameter, baroreflex sensitivity, sympathetic innervation of the heart, neural activity of intrinsic cardiac neurones, vascular conductance, blood pulse volume, VE, vasomotor tone, and ventilatory frequency. This heterogeneity in parameters clearly denotes the complexity of the ANS, responsible for regulation and integration of the physiology of organ systems and to control blood vessels, pupils, transpiration, and salivary glands.[59]

Within chronic pain settings, dysregulation of ANS is often observed with blunted autonomic reactivity.[60,61] For HRV, increased sympathetic and decreased parasympathetic modulation is observed in adults with musculoskeletal pain compared with controls.[62,63] Similarly, skin conductance measurements in patients with fibromyalgia compared with healthy women revealed reduced tonic and reactivity sympathetic influences in patients with chronic pain,[64] as was previously already revealed in patients with irritable bowel syndrome.[65] Decreased respiratory strength is observed in chronic pain patients with specifically a decrease in maximum voluntary ventilation in both patients with chronic low back and neck pain.[66] Based on the vagal-nociceptive interactions in the form of projections from the PAG to brainstem autonomic centres, baroreflex activity and the input from the descending pathways to preganglionic autonomic nuclei on the one hand[67] and modulation of the descending nociceptive inhibitory pathways by neuromodulation on the other hand,[68] it was expected that neuromodulation,[69] as effective pain management therapy, would alter the functioning of ANS output mechanisms. Nevertheless, based on this systematic review, it became clear that a uniform modulation of ANS output parameters cannot be obtained with currently used neuromodulation interventions. It may be possible that despite the direct connections between the nociceptive and autonomic systems, neuromodulation interventions are not directly modulating autonomic activity but rather indirectly by modifying physical activity patterns and lifestyle habits. Previous research has indicated that sport activities and smoking behaviour induce a decrease in HR and increase in RSA, supporting the effect of lifestyle on parasympathetic activity.[70] Moreover, chronic stress in combination with unhealthy lifestyles contributes to ANS dysfunction, while physical activity is known for its beneficial effects.[71] As neuromodulation techniques alter a broad spectrum of characteristics not only limited to pain,[72] but extended towards functionality, psychological measures and quality of life among others,[73] an indirect influence on the autonomic disbalance could be induced by the modulation of these characteristics. Naturally, this is only a hypothesis, whereby the direct and indirect modulatory effects of different types of neuromodulation should still be examined.

One remarkable finding across the different neuromodulation techniques is that for DRG stimulation, results consistently point towards a similar result, namely a decrease in sympathetic activity as revealed by a significant decrease in ABP during stimulation,[28] a decrease in normalised LF power as marker for orthosympathetic and vagal activity, a reduction of LF/HF ratio as an indicator for sympathovagal balance,[29] and a significant decrease in firing frequency of sympathetic nerves during stimulation.[28] DRGs, located within the dural sheath, are bilateral structures found at every vertebral level within the neuroforamen.[74] Based on anatomic assessments, the centre of the DRG can be found bilaterally in the medial zone of the foramen of L1–4 and the lateral zone at L5.[75] The DRG is an enlargement of the dorsal root that contains cell bodies of primary sensory neurones and glial cells.[74] DRGs are intimately connected with the sympathetic chain via rami communicantes nerves.[76] Alongside the vertebral column, elongated chains of sympathetic nerve fibres can be found with a number of sympathetic ganglia along its length.[77] The axon from the intermediate horn of the spinal cord migrates toward the sympathetic ganglia by passing through the ventral root of the spinal nerve to reach the sympathetic ganglia via white rami communicantes (i.e. myelinated preganglionic fibres).[77] These axons can make connections with the neurones in the same sympathetic ganglia or the ganglia above or beneath.[77] The axons of the neurones in the sympathetic ganglion pass back through grey rami communicantes to reach the spinal nerves.[77] Based on the presence of rami communicantes, DRG stimulation could directly alter functioning of the sympathetic ganglia, consistently pointing towards a decrease in sympathetic activity (Fig 2). The other neuromodulation techniques do not seem to have this direct connection between the target region and the ANS, wherefore a more indirect and widespread result may be observed.

In the field of chronic pain, and consequently also in the field of neuromodulation, the search towards biomarkers is

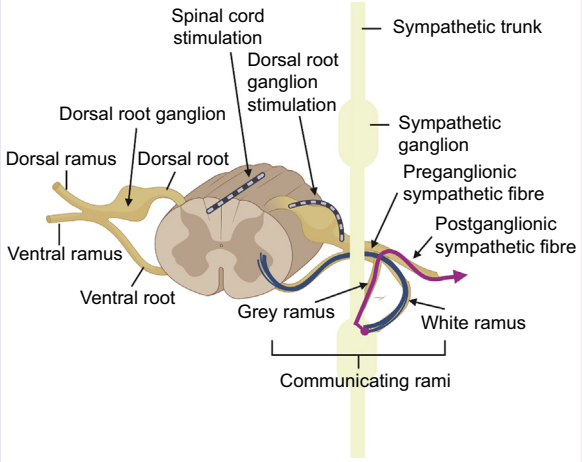

Fig. 2. Schematic representation of the involvement of the sympathetic chain ganglia in relation to the dorsal root ganglion.

still ongoing.[78] Up until now, no satisfactory results have yet been obtained, wherefore the US Food and Drug Administration (FDA) and the European Medicines Agency for use in clinical trials stated that there are no valid and psychometrically sound biomarkers qualified for pain assessment.[79] Among the potential candidate markers are autonomic output parameters such as HRV,[80] pupil reflexes, or electrodermal activity.[81] Both for HRV and electrodermal activity, the current review could not consistently point out a standalone biomarker for the effect of neuromodulation. Presumably, these markers could be incorporated into a composite measure, to answer to the recent call to combine self-reported and more objective markers into composite or multicomponent markers to evaluate the efficacy of neuromodulation.[82]

As a limitation to the results from this systematic review, more than two-thirds of the papers were included before the introduction of DRG stimulation[83] and the introduction of paraesthesia-free stimulation.[84] The waveforms and paradigms applied nowadays might influence the ANS differently compared with the standard tonic stimulation from the 1990s and early 2000. An advantage of the paraesthesia-free or independent waveforms over standard stimulation is that the noise attributable to the influence of psychological stress on the ANS can be reduced in a proper head-to-head comparison.[85] This might lead to more robust results and more homogeneity among the conclusions. Finally, animal, human, and computation studies were eligible for this systematic review. No computational studies were found and only one animal study was included, wherefore the results cannot be generalised towards animal settings and are mainly derived from human studies.

Conclusion

This systematic review revealed that different neuromodulation interventions result in heterogeneous effects on autonomic output parameters, presumably because of the broad variety in conditions and patient groups. Further research is warranted to elucidate the indirect or direct mechanisms of action on the ANS, with a potential benefit for optimisation of patient selection for these interventions.

Authors' contributions

Conceptualisation: BB, MM, LG.
Methodology: BB, LG, MM.
Formal analysis: BB, LG, MM.
Writing—original draft preparation: BB, LG, MM.
Writing—review and editing: BB, LG, MM, SV, MB, PR, MR, WN.
Have read and agreed to the published version of the manuscript: all authors.
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Supplementary Material

Search strings

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("pain" OR "chronic pain patients" OR "chronic pain" OR "persistent pain" OR "intractable pain" OR "causalgia" OR "reflex sympathetic dystrophy" OR "failed back surgery syndrome" OR "persistent spinal pain syndrome" OR "post laminectomy syndrome" OR "failed neck surgery syndrome" OR "CRPS" OR "complex regional pain syndrome" OR "FBSS" OR "FNSS" OR "peripheral neuropathy" OR "neuropathic pain" OR "angina pectoris" OR "peripheral vascular disease" OR "peripheral nervous system disease" OR "diabetic neuropathy") AND ("autonomic nervous system" OR "autonomic neuroanatomy" OR "enteric nervous system" OR "parasympathetic nervous system" OR "sympathetic nervous system" OR "autonomic function testing" OR "autonomic innervation" OR "autonomic neurons" OR "autonomic dysfunction" OR "autonomic function" OR "vegetative nervous system" OR "autonomic pathways") AND ("spinal cord stimulation" OR "neurostimulation" OR "neuromodulation" OR "dorsal column stimulation" OR "neurostimulator" OR "spinal cord stimulator" OR "electrical stimulation" OR "pain stimulator" OR "pain stimulation" OR "transcutaneous electric nerve stimulation" OR "implantable neurostimulator")

References

1. Institute of Medicine Committee on Advancing Pain Research C, Education. *Relieving pain in America: a blueprint for transforming prevention, care, education, and research*. National Academies Press (US); 2011
2. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 2015; **162**: 276–86
3. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. *Neuromodulation* 2014; **17**: 515–50
4. Krames ES. The role of the dorsal root ganglion in the development of neuropathic pain. *Pain Med* 2014; **15**: 1669–85
5. Kemler MA, Barendse GA, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000; **343**: 618–24
6. Millan MJ. Descending control of pain. *Prog Neurobiol* 2002; **66**: 355–474
7. Tracey I. Nociceptive processing in the human brain. *Curr Opin Neurobiol* 2005; **15**: 478–87
8. Moens M, Billet B, Molenberghs G, et al. Heart rate variability is not suitable as a surrogate marker for pain intensity in patients with chronic pain. *Pain* 2023; **164**: 1741–9
9. Bandeira PM, Reis FJJ, Sequeira VCC, Chaves ACS, Fernandes O, Arruda-Sanchez T. Heart rate variability in patients with low back pain: a systematic review. *Scand J Pain* 2021; **21**: 426–33
10. Deuchars SA, Lall VK, Clancy J, et al. Mechanisms underpinning sympathetic nervous activity and its modulation using transcutaneous vagus nerve stimulation. *Exp Physiol* 2018; **103**: 326–31
11. Bentley LD, Duarte RV, Furlong PL, Ashford RL, Raphael JH. Brain activity modifications following spinal cord

stimulation for chronic neuropathic pain: a systematic review. *Eur J Pain* 2016; **20**: 499–511
12. Goudman L, De Groote S, Linderoth B, et al. Exploration of the supraspinal hypotheses about spinal cord stimulation and dorsal root ganglion stimulation: a systematic review. *J Clin Med* 2021; **10**: 2766
13. Sdrulla AD, Guan Y, Raja SN. Spinal cord stimulation: clinical efficacy and potential mechanisms. *Pain Pract* 2018; **18**: 1048–67
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021; **10**: 89
15. O'Sullivan D, Wilk S, Michalowski W, Farion K. Using PICO to align medical evidence with MDs decision making models. *Stud Health Technol Inform* 2013; **192**: 1057
16. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016; **5**: 210
17. Augustinsson LE, Carlsson CA, Holm J, Jivegard L. Epidural electrical stimulation in severe limb ischemia. Pain relief, increased blood flow, and a possible limb-saving effect. *Ann Surg* 1985; **202**: 104–10
18. Joyner MJ, Casey DP. Regulation of increased blood flow (hyperemia) to muscles during exercise: a hierarchy of competing physiological needs. *Physiol Rev* 2015; **95**: 549–601
19. Holwerda SW, Holland MT, Reddy CG, Pierce GL. Femoral vascular conductance and peroneal muscle sympathetic nerve activity responses to acute epidural spinal cord stimulation in humans. *Exp Physiol* 2018; **103**: 905–15
20. Memar K, Varghese SN, Morrison AG, Clonch DA, Lam CM, Holwerda SW. Low- and high-frequency spinal cord stimulation and arterial blood pressure in patients with chronic pain and hypertension: a retrospective study. *Clin Auton Res* 2023; **33**: 443–9
21. Jessurun GA, DeJongste MJ, Hautvast RW, et al. Clinical follow-up after cessation of chronic electrical neuromodulation in patients with severe coronary artery disease: a prospective randomized controlled study on putative involvement of sympathetic activity. *Pacing Clin Electrophysiol* 1999; **22**: 1432–9
22. Norrsell H, Eliasson T, Mannheimer C, et al. Effects of pacing-induced myocardial stress and spinal cord stimulation on whole body and cardiac norepinephrine spillover. *Eur Heart J* 1997; **18**: 1890–6
23. Green AL, Wang SY, Owen SLF, et al. Deep brain stimulation can regulate arterial blood pressure in awake humans. *Neuroreport* 2005; **16**: 1741–5
24. Green AL, Wang S, Owen SLF, et al. Stimulating the human midbrain to reveal the link between pain and blood pressure. *Pain* 2006; **124**: 349–59
25. Green AL, Wang S, Owen SL, Paterson DJ, Stein JF, Aziz TZ. Controlling the heart via the brain: a potential new therapy for orthostatic hypotension. *Neurosurgery* 2006; **58**: 1176–83. ; discussion 1176–83
26. Green AL, Hyam JA, Williams C, et al. Intra-operative deep brain stimulation of the periaqueductal grey matter modulates blood pressure and heart rate variability in humans. *Neuromodulation* 2010; **13**: 174–81
27. Sverrisdóttir YB, Green AL, Aziz TZ, et al. Differentiated baroreflex modulation of sympathetic nerve activity during deep brain stimulation in humans. *Hypertension* 2014; **63**: 1000–10
28. Sverrisdottir YB, Martin SC, Hadjipavlou G, et al. Human dorsal root ganglion stimulation reduces sympathetic outflow and long-term blood pressure. *JACC Basic Transl Sci* 2020; **5**: 973–85
29. Parker T, Divanbeighi AP, Huang Y, Aziz TZ, Sverrisdottir YB, Green AL. Dorsal root ganglion stimulation: a new target for autonomic neuromodulation? *Clin Auton Res* 2021; **31**: 135–7
30. Guo S, Petersen AS, Schytz HW, et al. Cranial parasympathetic activation induces autonomic symptoms but no cluster headache attacks. *Cephalalgia* 2018; **38**: 1418–28
31. Guo S, Falkenberg K, Schytz HW, Caparso A, Jensen RH, Ashina M. Low frequency activation of the sphenopalatine ganglion does not induce migraine-like attacks in migraine patients. *Cephalalgia* 2020; **40**: 966–77
32. Kalmár Z, Kovács N, Balás I, et al. Effects of spinal cord stimulation on heart rate variability in patients with chronic pain. *Ideggyogy Sz* 2013; **66**: 102–6
33. Goudman L, Brouns R, Linderoth B, Moens M. Effects of spinal cord stimulation on heart rate variability in patients with Failed Back Surgery Syndrome. *PLoS One* 2019; **14**, e0219076
34. Goudman L, Brouns R, Linderoth B, Moens M. Effects of spinal cord stimulation on heart rate variability in patients with failed back surgery syndrome: comparison between a 2-lead ECG and a wearable device. *Neuromodulation* 2021 Apr; **24**(3): 512–9. https://doi.org/10.1111/ner.13091. Epub 2019 Dec 25. PMID: 31876094
35. Black S, Bretherton B, Baranidharan G, et al. A feasibility study exploring measures of autonomic function in patients with failed back surgery syndrome undergoing spinal cord stimulation. *Neuromodulation* 2022; **26**: 192–205
36. Patterson DG, Wilson D, Fishman MA, et al. Objective wearable measures correlate with self-reported chronic pain levels in people with spinal cord stimulation systems. *NPJ Digit Med* 2023; **6**: 146
37. Pereira EA, Lu G, Wang S, et al. Ventral periaqueductal grey stimulation alters heart rate variability in humans with chronic pain. *Exp Neurol* 2010; **223**: 574–81
38. Hautvast RW, Brouwer J, DeJongste MJ, Lie KI. Effect of spinal cord stimulation on heart rate variability and myocardial ischemia in patients with chronic intractable angina pectoris–a prospective ambulatory electrocardiographic study. *Clin Cardiol* 1998; **21**: 33–8
39. Andersen C. Does heart rate variability change in angina pectoris patients treated with spinal cord stimulation? *Cardiology* 1998; **89**: 14–8
40. Barloese M, Petersen AS, Guo S, Ashina M, Mehlsen J, Jensen RH. Sphenopalatine ganglion stimulation induces changes in cardiac autonomic regulation in cluster headache. *Clin Physiol Funct Imaging* 2018; **38**: 808–15
41. Prim JH, Ahn S, Davila MI, Alexander ML, McCulloch KL, Fröhlich F. Targeting the autonomic nervous system balance in patients with chronic low back pain using transcranial alternating current stimulation: a randomized, crossover, double-blind, placebo-controlled pilot study. *J Pain Res* 2019; **12**: 3265–77
42. da Silva FT, Browne RA, Pinto CB, et al. Transcranial direct current stimulation in individuals with spinal cord injury: assessment of autonomic nervous system activity. *Restor Neurol Neurosci* 2017; **35**: 159–69

43. Paccione CE, Stubhaug A, Diep LM, Rosseland LA, Jacobsen HB. Meditative-based diaphragmatic breathing vs. vagus nerve stimulation in the treatment of fibromyalgia-A randomized controlled trial: body vs. machine. *Front Neurol* 2022; **13**, 1030927
44. Robaina FJ, Dominguez M, Díaz M, Rodriguez JL, de Vera JA. Spinal cord stimulation for relief of chronic pain in vasospastic disorders of the upper limbs. *Neurosurgery* 1989; **24**: 63–7
45. Velasco F, Carrillo-Ruiz JD, Castro G, et al. Motor cortex electrical stimulation applied to patients with complex regional pain syndrome. *Pain* 2009; **147**: 91–8
46. Goudman L, De Smedt A, Louis F, et al. The link between spinal cord stimulation and the parasympathetic nervous system in patients with failed back surgery syndrome. *Neuromodulation* 2022; **25**: 128–36
47. Goudman L, Vets N, Jansen J, et al. Electrochemical skin conductance alterations during spinal cord stimulation: an experimental study. *J Clin Med* 2021; **10**: 3565
48. Bocchi L, Evangelisti A, Barrella M, Scatizzi L, Bevilacqua M. Recovery of 0.1Hz microvascular skin blood flow in dysautonomic diabetic (type 2) neuropathy by using Frequency Rhythmic Electrical Modulation System (FREMS). *Med Eng Phys* 2010; **32**: 407–13
49. Kriek N, Schreurs MWJ, Groeneweg JG, et al. Spinal cord stimulation in patients with complex regional pain syndrome: a possible target for immunomodulation? *Neuromodulation* 2018; **21**: 77–86
50. Gravius N, Chaudhry SR, Muhammad S, et al. Selective L4 dorsal root ganglion stimulation evokes pain relief and changes of inflammatory markers: part i profiling of saliva and serum molecular patterns. *Neuromodulation* 2019; **22**: 44–52
51. Yang Y, Zhang R, Zhong Z, Li J, Feng Y. Efficacy of transauricular vagus nerve stimulation for the treatment of chemotherapy-induced painful peripheral neuropathy: a randomized controlled exploratory study. *Neurol Sci* 2024; **45**: 2289–300
52. Kemler MA, Barendse GA, van Kleef M, Egbrink MGO. Pain relief in complex regional pain syndromes due to spinal cord stimulation does not depend on vasodilation. *Anesthesiology* 2000; **92**: 1653–60
53. Ather M, Di Vadi P, Light D, Wedley JR, Hamann WC. Spinal cord stimulation does not change peripheral skin blood flow in patients with neuropathic pain. *Eur J Anaesthesiol* 2003; **20**: 736–9
54. Petrakis IE, Sciacca V. Does autonomic neuropathy influence spinal cord stimulation therapy success in diabetic patients with critical lower limb ischemia? *Surg Neurol* 2000; **53**: 182–9
55. Ghajar AW, Miles JB. The differential effect of the level of spinal cord stimulation on patients with advanced peripheral vascular disease in the lower limbs. *Br J Neurosurg* 1998; **12**: 402–8
56. Fricke E, Eckert S, Dongas A, et al. Myocardial sympathetic innervation in patients with symptomatic coronary artery disease: follow-up after 1 year with neurostimulation. *J Nucl Med* 2008; **49**: 1458–64
57. Foreman RD, Linderoth B, Ardell JL, et al. Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. *Cardiovasc Res* 2000; **47**: 367–75
58. Kovacic K, Kolacz J, Lewis GF, Porges SW. Impaired vagal efficiency predicts auricular neurostimulation response in adolescent functional abdominal pain disorders. *Am J Gastroenterol* 2020; **115**: 1534–8
59. Debnath S, Levy TJ, Bellehsen M, et al. A method to quantify autonomic nervous system function in healthy, able-bodied individuals. *Bioelectron Med* 2021; **7**: 13
60. Yeater TD, Clark DJ, Hoyos L, et al. Chronic pain is associated with reduced sympathetic nervous system reactivity during simple and complex walking tasks: potential cerebral mechanisms. *Chronic Stress (Thousand Oaks)* 2021; **5**, 24705470211030273
61. Barakat A, Vogelzangs N, Licht CM, et al. Dysregulation of the autonomic nervous system and its association with the presence and intensity of chronic widespread pain. *Arthritis Care Res (Hoboken)* 2012; **64**: 1209–16
62. Rampazo ÉP, Rehder-Santos P, Catai AM, Liebano RE. Heart rate variability in adults with chronic musculoskeletal pain: a systematic review. *Pain Pract* 2024; **24**: 211–30
63. Tracy LM, Ioannou L, Baker KS, Gibson SJ, Georgiou-Karistianis N, Giummarra MJ. Meta-analytic evidence for decreased heart rate variability in chronic pain implicating parasympathetic nervous system dysregulation. *Pain* 2016; **157**: 7–29
64. Reyes Del Paso GA, de la Coba P. Reduced activity, reactivity and functionality of the sympathetic nervous system in fibromyalgia: an electrodermal study. *PLoS One* 2020; **15**, e0241154
65. Tousignant-Laflamme Y, Goffaux P, Bourgault P, Marchand S. Different autonomic responses to experimental pain in IBS patients and healthy controls. *J Clin Gastroenterol* 2006; **40**: 814–20
66. Cuenca-Martínez F, Sempere-Rubio N, Muñoz-Gómez E, Mollà-Casanova S, Carrasco-González E, Martínez-Arnau FM. Respiratory function analysis in patients with chronic pain: an umbrella review and meta-analysis of pooled findings. *Healthcare (Basel)* 2023; **11**: 1358
67. van Weperen VYH, Vaseghi M. Cardiac vagal afferent neurotransmission in health and disease: review and knowledge gaps. *Front Neurosci* 2023; **17**, 1192188
68. De Groote S, Goudman L, Peeters R, et al. The influence of high dose spinal cord stimulation on the descending pain modulatory system in patients with failed back surgery syndrome. *Neuroimage Clin* 2019; **24**, 102087
69. Knotkova H, Hamani C, Sivanesan E, et al. Neuromodulation for chronic pain. *Lancet* 2021; **397**: 2111–24
70. Hu MX, Lamers F, de Geus EJ, Penninx BW. Influences of lifestyle factors on cardiac autonomic nervous system activity over time. *Prev Med* 2017; **94**: 12–9
71. Daniela M, Catalina L, Ilie O, Paula M, Daniel-Andrei I, Ioana B. Effects of exercise training on the autonomic nervous system with a focus on anti-inflammatory and antioxidants effects. *Antioxidants (Basel)* 2022; **11**: 350
72. Zheng Y, Liu CW, Hui Chan DX, et al. Neurostimulation for chronic pain: a systematic review of high-quality randomized controlled trials with long-term follow-up. *Neuromodulation* 2023; **26**: 1276–94
73. Goudman L, Vets N, Jansen J, De Smedt A, Moens M. The association between bodily functions and cognitive/emotional factors in patients with chronic pain treated with neuromodulation: a systematic review and meta-analyses. *Neuromodulation* 2023; **26**: 3–24
74. Ahimsadasan N, Reddy V, Khan Suheb MZ, Kumar A. Neuroanatomy, dorsal root ganglion. In: *StatPearls. Treasure Island (FL)*. StatPearls Publishing; 2022

75. Silverstein MP, Romrell LJ, Benzel EC, Thompson N, Griffith S, Lieberman IH. Lumbar dorsal root Ganglia location: an anatomic and MRI assessment. *Int J Spine Surg* 2015; **9**(3)
76. Hunter CW, Sayed D, Lubenow T, et al. DRG FOCUS: a multicenter study evaluating dorsal root ganglion stimulation and predictors for trial success. *Neuromodulation* 2019; **22**: 61–79
77. Singh GP. Chapter 2 - neuroembryology. In: Prabhakar H, editor. *Essentials of neuroanesthesia*. London: Academic Press, Elsevier; 2017. p. 41–50
78. Eldabe S, Obara I, Panwar C, Caraway D. Biomarkers for chronic pain: significance and summary of recent advances. *Pain Res Manag* 2022; **2022**, 1940906
79. United States Food and Drug Administration. *Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims*. Available from: 2009. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf
80. Gary CS, Horowitz ME, Giladi AM. Diagnostic biomarkers for upper extremity chronic pain conditions. *J Hand Surg Glob Online* 2023; **5**: 116–20
81. Cowen R, Stasiowska MK, Laycock H, Bantel C. Assessing pain objectively: the use of physiological markers. *Anaesthesia* 2015; **70**: 828–47
82. Goudman L, Pilitsis JG, Russo M, et al. From pain intensity to a holistic composite measure for spinal cord stimulation outcomes. *Br J Anaesth* 2023; **131**: e43–8
83. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation* 2013; **16**: 67–71. ; discussion 71–2
84. De Ridder D, Vanneste S, Plazier M, van der Loo E, Menovsky T. Burst spinal cord stimulation: toward paresthesia-free pain suppression. *Neurosurgery* 2010; **66**: 986–90
85. de Morree HM, Szabo BM, Rutten GJ, Kop WJ. Central nervous system involvement in the autonomic responses to psychological distress. *Neth Heart J* 2013; **21**: 64–9
86. Fujiu K, Manabe I. Nerve-macrophage interactions in cardiovascular disease. *Int Immunol* 2022; **34**: 81–95
87. Grundner E, Klinger M, Sturma A, Hassler M, Godaj E, Hager A. Physiotherapeutic interventions and functional diagnostic monitoring in patients with cardiovascular autonomic dysregulation after a SARS-CoV-2 infection. *Neurorehabil Neural Repair* 2023; **37**: NP113
88. Garzón SJC, Poveda DS, Guardo LA, Garzón SA, Zaballos FH, Montero FJS, Santos LJ, Calvo 5th JM. Evaluation through transcutaneous tissue oximetry (near infrared spectroscopy) of spinal cord stimulation in patients with complex regional pain syndrome type I. *Neuromodulation* 2020 Jul; **23**(5): 698–703. https://doi.org/10.1111/ner.12931. Epub 2019 Feb 20. PMID: 30786089
89. Hassenbusch SJ, Stanton-Hicks M, Schoppa D, Walsh JG, Covington EC. Long-term results of peripheral nerve stimulation for reflex sympathetic dystrophy. *J Neurosurg* 1996 Mar; **84**(3): 415–23. https://doi.org/10.3171/jns.1996.84.3.0415. PMID: 8609552

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