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REVIEW

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Application of oscillating field stimulation in the treatment of spinal cord injury: a systematic review and meta-analysis of preclinical studies

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Abstract

Background Oscillating Field Stimulation (OFS) is an emerging therapeutic approach for spinal cord injury (SCI) that is currently undergoing extensive investigation in preclinical in vivo studies. However, there has yet to be a comprehensive systematic review and meta-analysis of the existing literature. This systematic review and meta-analysis aims to evaluate the effectiveness of OFS technology in treating spinal cord injuries based on studies conducted with experimental animal models.

Methods A thorough search was performed across PubMed-MEDLINE, Embase, and Web of Science. Studies that were not in vivo preclinical research or were published in languages other than English were excluded. The SYRCLE tool was utilized to assess the risk of bias, and the extracted data underwent qualitative synthesis and meta-analysis.

Results Out of the 89 studies identified from the electronic databases, 8 fulfilled the inclusion criteria. Among these, 7 studies utilized a contusion model, while 1 employed a compression model. The application of OFS consistently resulted in significant enhancements in motor function scores compared to untreated SCI rats across all studies. This observed functional recovery correlated with histological improvements at the injury site. Although all studies were deemed to have a low risk of bias, some displayed incomplete reporting in specific areas.

Conclusion Our results indicate that OFS is a promising therapeutic approach for SCI, significantly enhancing functional recovery through multiple mechanisms. These include promoting nerve regeneration, aiding in myelin repair, and minimizing glial scarring. Future studies should concentrate on determining the optimal timing for OFS intervention, refining the electric field application methods, and investigating potential synergies with stem cell therapies. Thorough validation is essential before progressing to clinical applications.

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Introduction

Spinal cord injury (SCI) represents a significant trauma to the central nervous system, frequently resulting in high rates of disability and increased mortality risk. This condition not only profoundly affects patients' physical health but also induces considerable psychological stress [1]. The pathological progression of SCI initiates with a primary injury caused by direct mechanical trauma [2]. This is followed by secondary damage, characterized by inflammatory responses, oxidative stress, and apoptosis, which exacerbate the injury area and lead to more severe functional impairments, ultimately resulting in the permanent loss of motor and sensory capabilities [3–7]. Effectively addressing SCI presents challenges that require multifaceted treatment strategies, including neural repair and reconstruction, mitigation of secondary damage, and comprehensive regulation of the spinal microenvironment. Conventional clinical interventions, such as surgical decompression, steroid pulse therapy, and hyperbaric oxygen therapy, may slow the progression of secondary damage but do not fundamentally foster nerve regeneration [8]. Consequently, the investigation of effective treatment modalities to enhance neural regeneration post-SCI remains a critical area of ongoing research.

Research on Oscillating Field Stimulation (OFS) technology began with observations of changes in direct current electric fields (DC EF) during the wound healing process in animals [9]. Investigations have shown that animal cells generate a potential difference of + 30 to + 40 mV across their membranes via ion pumps, establishing a physiologically relevant DC EF [10]. When tissues are injured, ionic flow through the wound disrupts this electric field, triggering cellular responses that encourage migration and proliferation in specific directions, thereby aiding in wound healing [11]. Additionally, this electric field signal contributes to limb regeneration and embryonic development [12–14].

In vitro studies of the nervous system indicate that applied electric fields promote the growth of neuronal axon growth cones toward the cathode, while axons directed toward the anode tend to grow more slowly and may even retract [15, 16]. In vivo experiments have shown that implanting devices at both the rostral and caudal ends of a damaged spinal cord to create a unidirectional electric field can enhance axonal growth toward the cathode and improve motor function [17]. However, DC EF is limited to facilitating axonal growth in one direction; for comprehensive recovery of motor and sensory functions, axons must grow toward both ends [18]. Subsequent research has demonstrated that reversing the polarity of the electric field within a specific time frame can effectively promote bidirectional axonal growth and prevent retraction [15]. Building on this principle, OFS technology has been further refined. By applying a continuous DC EF at the injury site and periodically reversing its polarity, OFS enhances bidirectional axonal growth, resulting in improved functional recovery.

Several studies have applied OFS to dogs with SCI [19, 20], demonstrating fewer complications and significant recovery in somatosensory evoked potentials (SSEPs) and superficial sensation, indicating favorable efficacy and safety. Subsequent Phase I clinical trials have further confirmed the safety and tolerability of OFS in human SCI patients [21]. Additionally, OFS has shown promising results in the recovery of sensory and motor functions, particularly in the restoration of pain perception and light touch sensation. These studies not only support the translational potential of OFS but also highlight important safety considerations.

While progress has been made in preclinical research on OFS technology, its application in studies of SCI has not undergone systematic evaluation or meta-analysis. Therefore, this study aims to systematically assess the efficacy of OFS technology in treating SCI through experiments using animal models.

Methods

This investigation adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22]. Additionally, the research protocol was submitted for registration with PROSPERO (registration number: CRD42024593802).

PICO definition

In the current study, the Populations, Intervention, Comparison and Outcome (PICO) framework was defined as follows: P (Population): animals with experimentally induced SCI; I (Intervention): application of OFS; C (Comparator): nonfunctional oscillating field stimulator, blank, or normal saline; O (Outcome): improvement in locomotor functions, motor evoked potential (MEP) latency, and histological neural regeneration.

Research question

In animal models, does the application of OFS improved outcomes for SCI?

Data sources

A comprehensive literature search was conducted across several electronic databases, including PubMed–MEDLINE, EMBASE, and Web of Science. The search strategy involved specific terms aimed at capturing relevant studies, which are detailed in Supplementary Table 1. Only studies published in English were considered for inclusion. Additionally, the reference lists of the studies that met the inclusion criteria were screened to identify any

further eligible studies that may not have been captured in the initial search.

Inclusion and exclusion criteria

The following criteria were used to determine eligibility for inclusion in this study: (1) use of OFS; (2) in vivo studies utilizing the SCI animal model; (3) (3) manuscripts written in English. The following types of studies were excluded: (1) manuscript designs including reviews, systematic reviews, meta-analyses, case reports, guidelines, clinical studies, and conference proceedings; (2) studies without a separate control group; (3) non-available full-text.

Study selection

Two investigators (GW and JF) independently examined the titles and abstracts of all retrieved articles to assess their relevance to this review. Full-text articles were obtained if either investigator deemed the abstract potentially suitable. Following the retrieval of these articles, both investigators independently evaluated each study's eligibility based on the established inclusion and exclusion criteria. Any discrepancies in opinions regarding eligibility were resolved through consultation with a third investigator (YY).

Data extraction

Two independent reviewers (LX and GJ) extracted data from the eligible studies after thoroughly examining their full texts, resolving any discrepancies with the help of a third investigator (XY). The data extracted from each eligible article included the following: (1) first author; (2) publication year; (3) method of applying oscillating field; (4) type of animals; (5) animal model; (6) study cohorts; (7) follow-up duration; (8) outcomes. The models for SCI induction comprised both contusion and compression methods. The animal species included Sprague-Dawley (SD) rats and Wistar rats. The interventions applied were OFS, while comparators included nonfunctional oscillating field stimulators, blank controls, or normal saline. Outcomes assessed included improvements in locomotor function (as measured by BBB scores), motor evoked potential (MEP) latency, and histological indicators of neural regeneration, which involved HE, Nissl, and Luxol Fast Blue (LFB) staining, as well as immunohistochemistry (IHC) and immunofluorescence (IF) staining. In cases where relevant studies were identified but essential information was missing from the published articles, attempts were made to contact the original authors for clarification.

Quality assessment

Using SYRCLE's Risk of Bias tool for animal research, two reviewers (WZ and GJ) independently evaluated the quality of the articles included in the analysis [23]. The assessment was based on ten criteria designed to identify potential biases in the enrolled studies: (1) sequence generation, (2) baseline characteristics, (3) allocation concealment, (4) random housing, (5) blinded animal intervention, (6) random outcome assessment, (7) blinded outcome assessment, (8) incomplete outcome data, (9) selective outcome reporting, and (10) other types of bias. In case of any disagreements regarding study quality, a third reviewer (YY) was consulted to reach a consensus. Each study was categorized as having a "low," "high," or "unclear" risk of bias.

Data synthesis

The systematic review and meta-analysis consisted of two components: data analysis and narrative synthesis. For the statistical analysis, two quantifiable indicators were assessed: Basso, Beattie, and Bresnahan (BBB) scores and motor evoked potential (MEP) latency in rats following SCI. However, due to variability in methodologies and measurement techniques, certain histological indicators of neural regeneration—such as HE, Nissl, and Luxol Fast Blue (LFB) staining, in addition to immunohistochemistry (IHC) and immunofluorescence (IF) staining, and enzyme-linked immunosorbent assay (ELISA)—could not be statistically aggregated. Instead, these aspects were systematically evaluated and presented narratively to provide a comprehensive understanding of the findings.

Statistical analysis

All statistical analyses were conducted using Revman 5.4 and Stata. The mean difference for continuous variables was calculated, along with a 95% confidence interval (CI). Statistical significance was determined at a p-value of less than 0.05. Random-effects models were utilized for the analysis, while funnel plots were employed to assess publication bias.

Result

Study selection

A total of 89 records were retrieved from the database. After deduplication, 52 records remained. Based on the objectives of this systematic review, the titles and abstracts of the identified articles were screened, leading to the inclusion of 14 articles. Following a full-text review in accordance with the inclusion and exclusion criteria, 8 articles were ultimately deemed eligible for qualitative synthesis and meta-analysis [24–31]. Six articles were excluded for the following reasons: one was an in vitro study, one lacked a separate intervention group for OFS, and four were published in non-English languages. The PRISMA flow diagram illustrating the included studies is presented in Fig. 1.

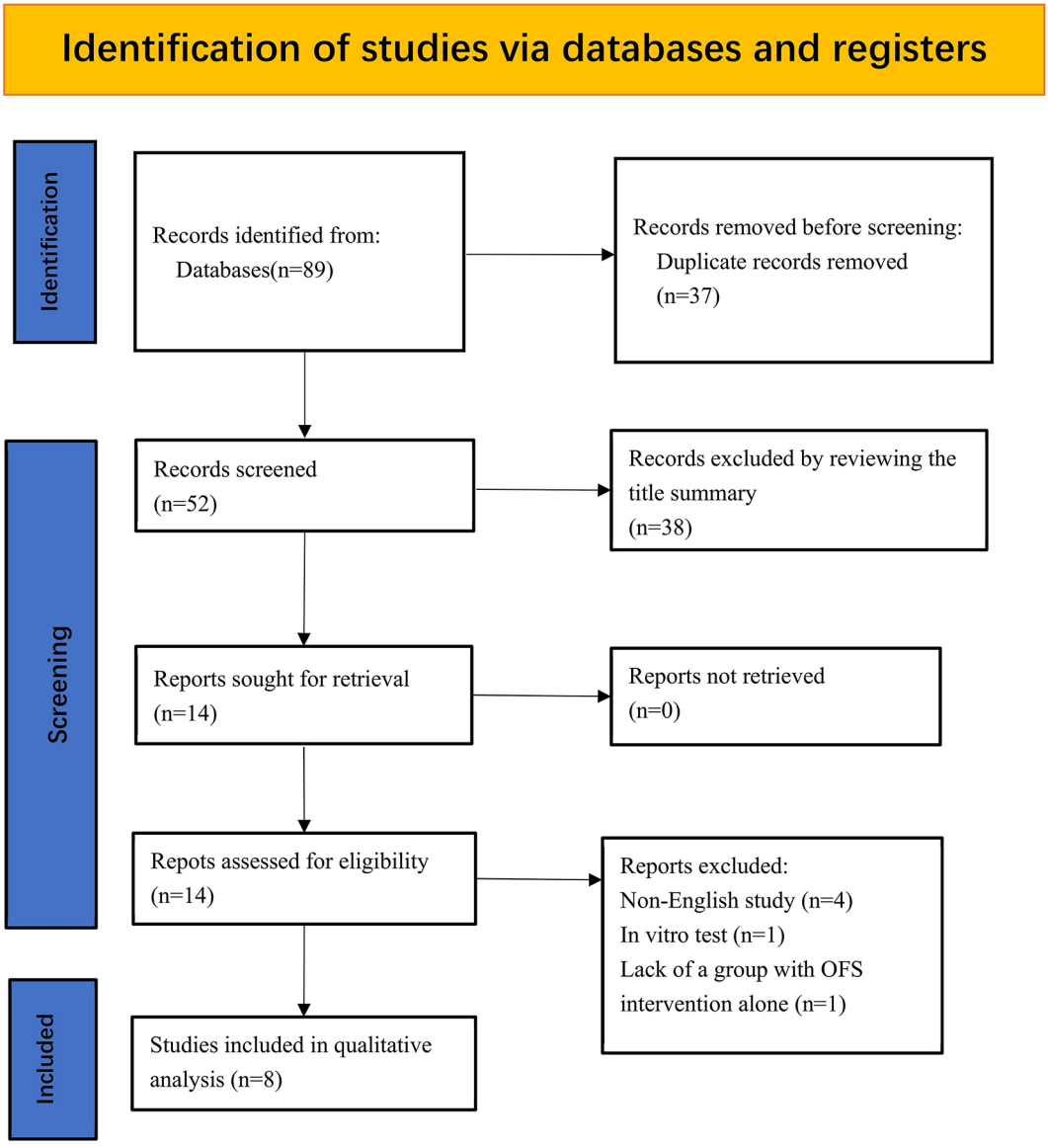

Fig. 1 PRISMA flow diagram for identifying eligible studies

Study quality assessment

We employed the SYRCLE Risk of Bias (RoB) tool to evaluate the risk of bias for each study. The results of this assessment are summarized in Table 1; Fig. 2. While all studies demonstrated low-risk bias items, several did not adequately report on certain aspects. Utilizing SYRCLE's RoB tool, we identified 80 entries across 10 relevant criteria. Of these, 34 items indicated low RoB, 46 items were classified as unclear RoB, and none were rated as high RoB. Notably, none of the 8 studies provided clear evidence of randomization; although they mentioned random sequence generation, the specific method used was not reported.

All studies indicated that baseline characteristics, including age, sex, and weight, were matched. For item 3, all studies were marked as having unclear RoB due to the lack of reported allocation concealment. In item 4, two studies did not specify whether random housing was utilized, resulting in unclear RoB, while the others were rated as low. Items 5 and 6 regarding the intervention received by each animal, researcher blinding, and random outcome assessment were also rated as unclear. For item 7, no study described the method of blinding outcome assessors, leading to unclear RoB for outcome assessment blinding. Three studies did not clarify whether there was data loss, resulting in uncertain RoB for item 8; however, the remaining studies were rated as low RoB for this criterion. The risks of selective reporting and other biases were assessed as low for all studies.

Table 1 Risk of bias summary: review authors' judgments about each risk of bias item for each included study according to SYRCLE's risk of bias tool

Research	SYRCLE Item									
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10
Wang et al., 2022 [24]	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
Bacova et al. [25]	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Low
Tian et al. [26]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Bacova et al. [27]	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
Zhang et al. [28]	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Low
Fang et al., 2021 [29]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Moriarty et al. [30]	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Low
Jing et al. [31]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low

SYRCLE Items: 1, sequence generation; 2, baseline characteristics; 3, allocation concealment; 4, random housing; 5, blinded animal; 6, random outcome assessment; 7, blinding outcome assessors; 8, incomplete outcome data; 9, selective outcome reporting; 10, other types of bias

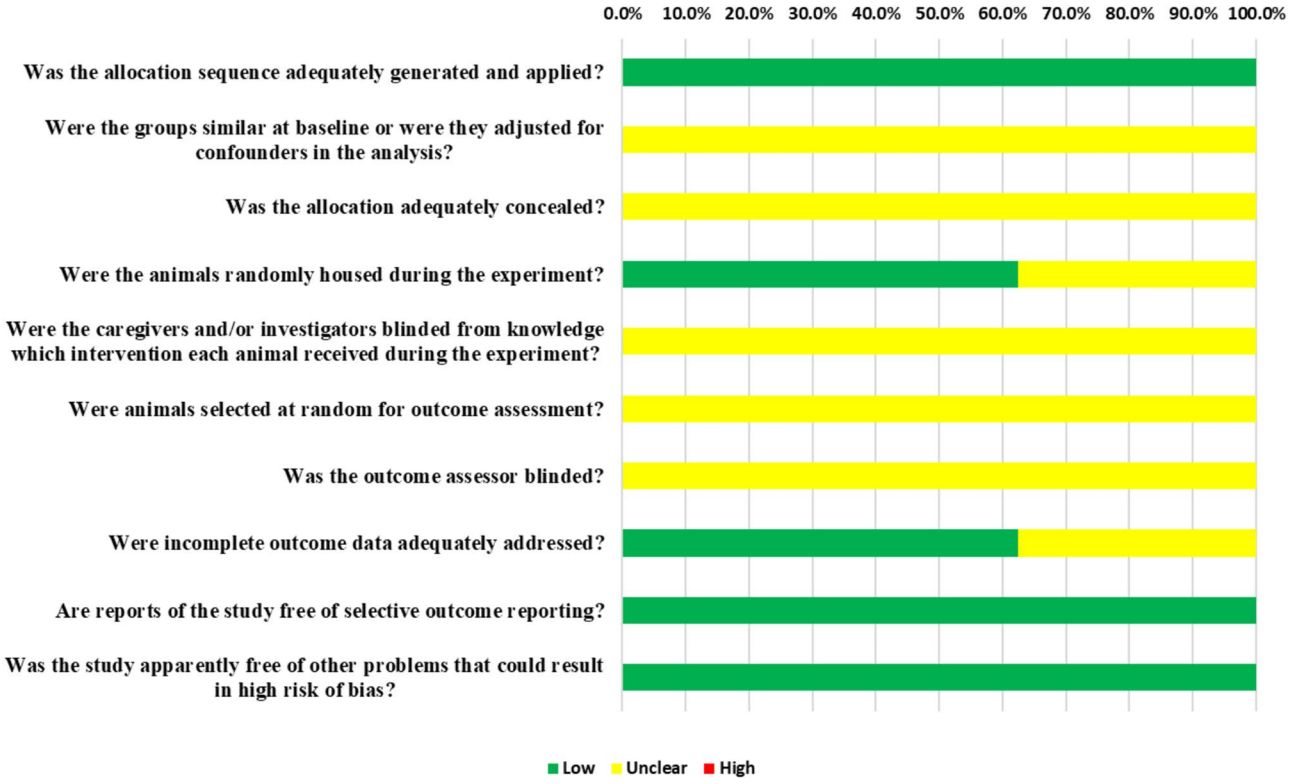

Fig. 2 The results of the risk of bias assessment

Characteristics of included studies

The main characteristics of all included studies are summarized in Table 2. Seven studies utilized Sprague-Dawley (SD) rats, while one study employed Wistar rats. The modeling methods used comprised contusion (in seven studies) and compression (in one study). The SCI segments were located at T10 in four studies and T9 in the remaining four studies. Sample sizes across the included studies ranged from 14 to 180 animals. Follow-up durations varied, with three studies having an 8-week follow-up, two studies at 12 weeks, two studies at 4 weeks, and one study at 5 weeks. The oscillating electric field was generated using devices positioned at both the rostral and caudal ends of the injury site, with polarity switched every 15 min, although the strength of the electric field varied among studies.

Locomotor function recovery

A meta-analysis was performed on studies that utilized the BBB score to assess motor function at various time points (2 weeks, 4 weeks, 6 weeks, and 8 weeks post-SCI). At the 2-week post-SCI point, six studies were included in the analysis, employing a random effects model. The mean difference (MD) was 0.03 (95% CI [-0.42, 0.48], $P = 0.89$), indicating no statistically significant difference. However, the heterogeneity was high (I^2 = 60%), which

Table 2 Summary of articles included in the systematic review

Study	Types of electrodes and implantation methods	Method of applying oscillating field	Type of animals	Animal model	Study cohorts	Follow-up	Outcomes
Wang et al., 2022 [24]	Platinum/iridium wires Intraspinal Each side of the SCI site	500 V/mm, polarity alternated every 15 min	SD rats, 220 ± 10 g, male/female, 6months	T10, Contusion	1) OFS + SCI group, *n* = 60 2) SCI group, *n* = 60	12 weeks	Locomotor functions (BBB) + MEP latency + axonal regeneration (HE staining) + astrocyte proliferation (IHC + IF staining).
Bacova et al., 2019 [25]	Platinum/iridium wires Intraspinal Each side of the SCI site	50 μA, polarity alternated every 15 min	Wistar rats, 280 ± 30 g, femlale, Wistar rats	T9, Contusion	1) Sham group *n* = 6 2) SCI group, *n* = 8 3) SCI + OFS group, *n* = 8	4 weeks	Locomotor function (BBB) + axonal regeneration (IF staining) + relative area of myelin (LFB/CV staining).
Tian et al., 2016 [26]	Intraspinal Each side of the SCI site	40 μA, 400 μV, polarity alternated every 15 min	SD rats, 230 ± 10 g, female, adult rats	T10, Contusion	1) Sham group *n* = 12 2) SCI group, *n* = 84 3) SCI + OFS group, *n* = 84	12 weeks	Locomotor functions (BBB + MEP latency) + relative area of myelin (LFB/CV staining).
Bacova et al., 2022 [27]	Platinum/iridium wires Intraspinal Each side of the SCI site	50 μA, polarity alternated every 15 min	Wistar rats, 275 ± 25 g, female, 3-4months	T9 Compression	1) Sham group *n* = 6 2) SCI group, *n* = 10 3) SCI + OFS group, *n* = 10 4) SCI + nOFS group, *n* = 10	8 weeks	Locomotor functions (BBB) + histological morphology (HE staining) + relative area of myelin (LFB/CV staining) + axonal regeneration (IHC staining).
Zhang et al., 2015 [28]	Platinum/iridium wires Intraspinal Each side of the SCI site	600 μV/mm, polarity alternated every 15 min	SD rats 225 ± 25 g, female, adult rats	T10 Contusion	1) SCI + OFS group, *n* = 30 2) SCI + nOFS group, *n* = 30	8 weeks	MEP latency + axonal regeneration (IF staining).
Fang et al., 2021 [29]	Intraspinal Each side of the SCI site	400 μv/mm, polarity alternated every 15 min	SD rats 220 ± 10 g, female, adult rats	T9 Contusion	1) Sham group, *n* = 24 2) SCI group, *n* = 24 3) SCI + OFS group, *n* = 24	5 weeks	Locomotor functions (BBB) + differentiation of NSCs (IF staining) + histological morphology (HE and Nissl staining) + myelin sheath morphology (TEM).
Moriarty et al., 2001 [30]	Platinum/iridium wires Intraspinal Each side of the SCI site	350 ± 50 μV/min, polarity alternated every 15 min	SD rats, 275 ± 25 g, male/female, adult rats	T10 Contusion	1) SCI + OFS group, *n* = 7 2) SCI + nOFS group, *n* = 7	4 weeks	histological morphology (HE staining) + the accumulation and orientation of astrocytes (IHC staining).
Jing et al., 2015 [31]	Platinum/iridium wires Intraspinal Each side of the SCI site	400 μv/mm, polarity alternated every 15 min	SD rats, 230 ± 10 g, female, 8weeks	T9 Contusion	1) Sham group, *n* = 20 2) SCI + OFS group, *n* = 20 3) SCI + nOFS group, *n* = 20	8 weeks	Locomotor function (BBB) + MEP latency + differentiation of oligodendrocyte precursor cells (IF staining).

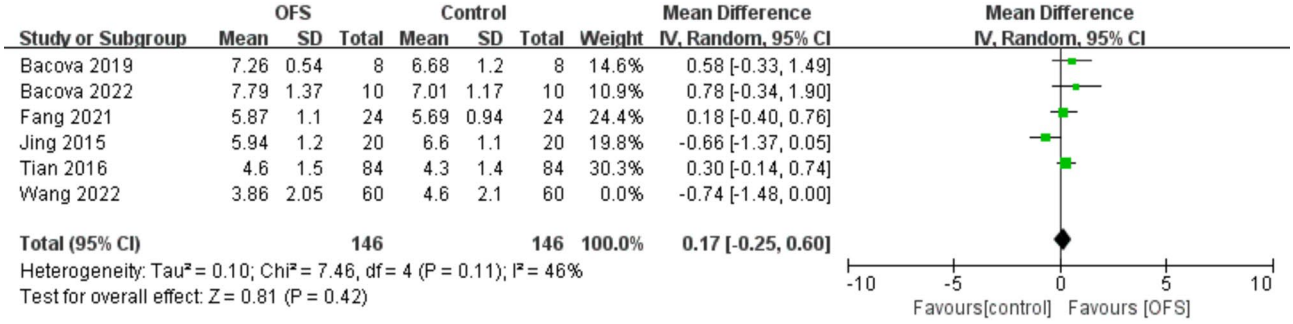

Fig. 3 2-week post-SCI BBB score meta-analysis

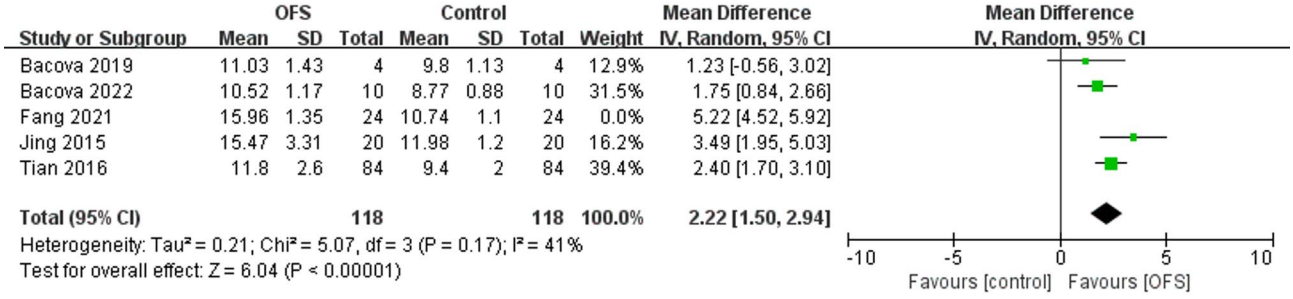

Fig. 4 4-week post-SCI BBB score meta-analysis

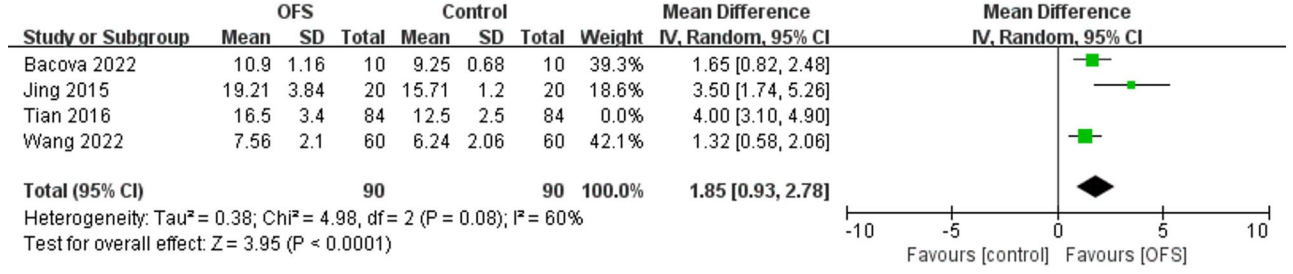

Fig. 5 6-week post-SCI BBB score meta-analysis

may limit the reliability of the results. To address this, we conducted a sensitivity analysis by sequentially excluding each study to assess their individual impact on the overall results. This analysis revealed that the heterogeneity was primarily driven by Study Wang 2022 [24], which employed a different intervention protocol. After excluding Study Wang 2022, the heterogeneity decreased to I^2 = 46%, and the MD remained non-significant (MD = 0.17, 95% CI [-0.25, 0.60], $P = 0.11$), suggesting that the overall conclusion was robust despite the initial heterogeneity (Fig. 3).

At the 4-week post-SCI time point, five studies were analyzed using the same random effects model. The MD was 2.87 (95% CI [1.30, 4.44], $P < 0.05$), demonstrating a statistically significant difference. However, the heterogeneity was very high (I^2 = 92%). To explore this further, we performed a sensitivity analysis by excluding Study Fang 2015 [29], which had divergent results. After exclusion, the heterogeneity decreased to I^2 = 41%, and the MD remained significant (MD = 2.22, 95% CI [1.50, 2.94], $P < 0.05$), indicating that the overall effect was consistent despite the methodological variations among studies (Figs. 1 and 4).

For the 6-week post-SCI time point, four studies were included, again using a random effects model. The MD was 2.54 (95% CI [1.17, 3.92], $P < 0.05$), indicating a statistically significant difference. However, the heterogeneity among studies was high (I^2 = 88%), which may limit the reliability of the pooled results. To explore the potential sources of heterogeneity and assess the robustness of the findings, we conducted a sensitivity analysis by sequentially excluding each study. This analysis revealed that the exclusion of Study Tian 2016 [26] significantly altered the results, with the MD decreasing to 1.85 (95% CI [0.93, 2.78], $P = 0.08$) and the heterogeneity reducing to I^2 = 60% (Fig. 5). In contrast, the exclusion of other studies did not result in significant changes to the MD or heterogeneity. These findings indicate that Study Tian 2016 [26]

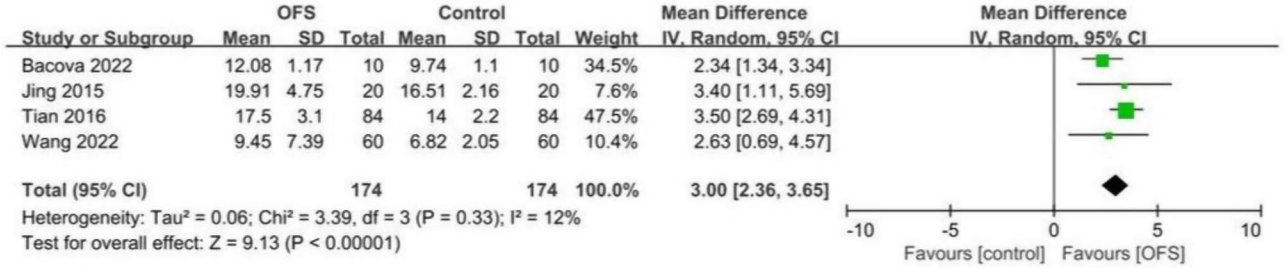

Fig. 6 8-week post-SCI BBB score meta-analysis

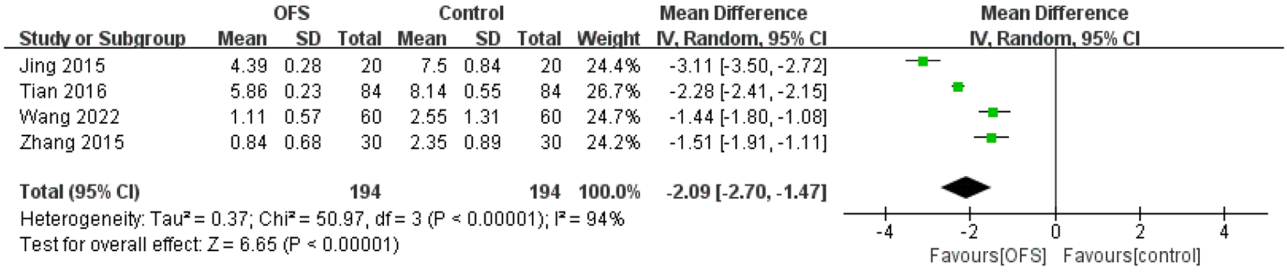

Fig. 7 MEP latency meta-analysis. Note: In contrast to previous figures where higher values indicate improvement, the 'Favors' direction is reversed in this figure as reduced MEP latency corresponds to better functional recovery. And MEP latency assessment time points were synchronized at 8 weeks post-SCI across studies, with the exception of Study [24] (12-week measurement)

has a substantial impact on the overall results. While the inclusion of Study Tian 2016 [26] supports a statistically significant improvement in motor function, its exclusion renders the results non-significant. This highlights the fragility of the findings at the 6-week time point, which is likely attributable to the small number of studies and high heterogeneity.

At 8 weeks post-SCI, four studies were analyzed using a random effects model. The MD was 3.00 (95% CI [2.36, 3.65], $P<0.05$), showing a statistically significant difference (Fig. 6). These findings suggest that the application of OFS technology can significantly enhance motor function in rats, with notable improvements observed as early as the 4-week mark.

Motor evoked potential latency recovery

MEP latency serves as a crucial objective indicator for evaluating the recovery of motor function following SCI, effectively reflecting the loss or alteration of spinal motor capabilities. A meta-analysis was performed on the results from all included studies that utilized MEP latency as an evaluation metric. Four studies were incorporated into the meta-analysis, employing a random effects model. The mean difference (MD) was – 2.09 (95% CI [-2.70, -1.47], $P<0.05$, Fig. 7), indicating a statistically significant difference. However, it is important to note that the time points for MEP measurements varied across studies. Three studies reported data at a common time point of 8 weeks post-injury, while one study only [24] provided data at 12 weeks. This variability in measurement timing may have contributed to the observed heterogeneity (I^2 = 94%), potentially influencing the comparability and interpretation of the results. To explore the potential sources of heterogeneity, we conducted a sensitivity analysis by sequentially excluding each study. This analysis revealed that the exclusion of any single study did not significantly alter the heterogeneity (I^2 remained consistently high, ranging from 88 to 96%). These findings suggest that the high heterogeneity in the MEP latency analysis is not driven by any single study but rather reflects broader methodological or clinical differences among the included studies. Future studies should aim to standardize assessment time points to enhance the consistency and reliability of MEP latency as an outcome measure.

Narrative synthesis of neural regeneration

In addition to the quantitative assessments, we conducted a descriptive synthesis of the histological indicators of neural regeneration reported in the included studies. Various methods were employed to evaluate neural regeneration, including histological staining, transmission electron microscopy (TEM), immunohistochemistry (IHC), immunofluorescence (IF) staining, and enzyme-linked immunosorbent assay (ELISA). Detailed characteristics of the outcomes from the included studies are summarized in Table 3.Immunofluorescence and immunohistochemistry results demonstrate that OFS effectively promotes neural regeneration. In the included studies, SCI rats that received the OFS intervention

Table 3 Summary of main outcomes and conclusions of the included studies

Study	Intervention and control groups	Histological analysis
Wang et al., 2022 [24]	1) OFS + SCI group 2) SCI group	Higher density of NF200-positive fibers and a greater axon count were observed in the OFS + SCI group. The processes of astrocytes were smaller, with less proliferation of astrocytes and a more linear arrangement.
Bacova et al., 2019 [25]	1) Sham group 2) SCI group 3) SCI + OFS group	OFS + SCI has a larger residual tissue area and a higher percentage of white matter area; the number of activated astrocytes in OFS + SCI is lower.
Tian et al., 2016 [26]	1)Sham group 2) SCI group 3) SCI + OFS group	The relative area of myelin was significantly higher in OFS + SCI (65.2 ± 9.0) compared with SCI (50.1 ± 6.5).
Bacova et al., 2022 [27]	1) Sham group 2) SCI group 3) SCI + OFS group 4) SCI + nOFS group	Compared with SCI and SCI + nOFS, OFS + SCI retained the largest amount of spinal cord tissue and significantly promoted the preservation of myelin. The number and density of APC + cells in the OFS + SCI group were higher than those in the SCI and SCI + nOFS groups. The number of NF-l + filaments was the highest in the OFS + SCI group, and it also had the highest density of GAP43 + axons. Compared to the OFS + SCI group, the MBP/NF-l + signals were decreased in the SCI and nOFS + SCI groups.
Zhang et al., 2015 [28]	1) SCI + OFS group 2) SCI + nOFS group	The axon count and the number of myelinated axons in OFS + SCI are both higher than those in nOFS + SCI.
Fang et al., 2021 [29]	1)Sham group 2) SCI group 3) SCI + OFS group	In SCI + OFS, the number of Nestin and β-tubulin III positive cells was the greatest and peaked on the 7th day. Compared with SCI, SCI + OFS had less inflammatory cell infiltration. The number of Nestin and NG2 positive cells at each measurement point in the SCI + OFS group was significantly higher than that in the SCI group. The number and thickness of myelin sheaths after SCI surgery were higher than those in SCI.
Moriarty et al., 2001 [30]	1) SCI + OFS group 2) SCI + nOFS group	The number of non-isodiametric astrocytes and stellate astrocytes in the SCI + OFS group was both lower than that in the SCI group.
Jing et al. 2015 [31]	1) Sham group 2) SCI + OFS group 3) SCI + nOFS group	The number of SCI + OFS MBP-positive cells and Galc-positive cells was significantly higher than that of SCI + nOFS.

showed a significantly higher number of nerve fibers labeled with specific markers such as NF200, NF-L, and NF-H [24, 27, 29], indicating successful regeneration of nerves and axons at the injury site. Additionally, the study by Fang et al. revealed that during the postoperative period, the number of Nestin and β-tubulin III positive cells in the OFS group significantly increased, suggesting that OFS facilitates the differentiation of neural stem cells into neurons [29]. Through electron microscopy observations, Fang et al. reported that both the quantity and thickness of myelin in the OFS group were greater than those in the control group at 14 days post-surgery [29]. Jing et al. employed immunofluorescence to label myelin basic protein (MBP) for detecting mature oligodendrocytes and used Galactocerebrosidase (Galc) to label immature oligodendrocytes. Their results indicated a significant increase in the number of MBP-positive and Galc-positive cells in the OFS group between 4 and 14 days post-SCI [30]. This suggests that OFS promotes the formation of oligodendrocytes and facilitates myelin regeneration. In studies assessing glial scar formation, staining with glial fibrillary acidic protein (GFAP) demonstrated that the number of GFAP-positive cells in the OFS group was consistently significantly lower than in the control group, with the GFAP-positive cells exhibiting a more linear arrangement [24, 25, 30]. This indicates that OFS can inhibit astrocyte proliferation and reduce scar formation.

The results consistently indicate that the application of OFS technology can promote neural regeneration and myelin formation, reduce glial scar formation, and enhance the overall histological appearance of the injured spinal cord. This suggests that OFS has a beneficial effect on neuroprotection and regeneration following SCI. However, due to the heterogeneity in study designs and methodologies, a quantitative synthesis of these histological results is not feasible. Consequently, we adopted a descriptive approach to summarize the findings from the studies.

Publication bias

To assess potential publication bias, funnel plots and Egger's tests were performed for the effect sizes of BBB scores at both 2 weeks and 8 weeks post-SCI.

For the 2-week time point, the funnel plot included five studies (Study Wang 2022 [24] was excluded due to its high heterogeneity). The scatter points were symmetrically distributed within the inverted funnel shape, suggesting a low risk of publication bias (Fig. 8). This finding was further supported by Egger's test, which showed no significant evidence of publication bias ($P > 0.05$).

Similarly, for the 8-week time point, the funnel plot included four studies. The scatter points exhibited a

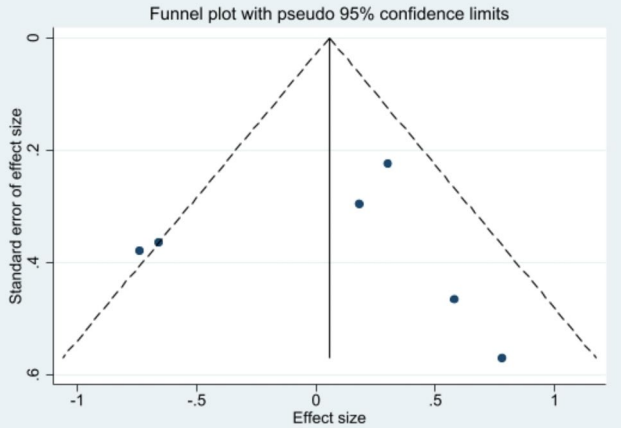

Fig. 8 2-week post-SCI BBB score funnel plot

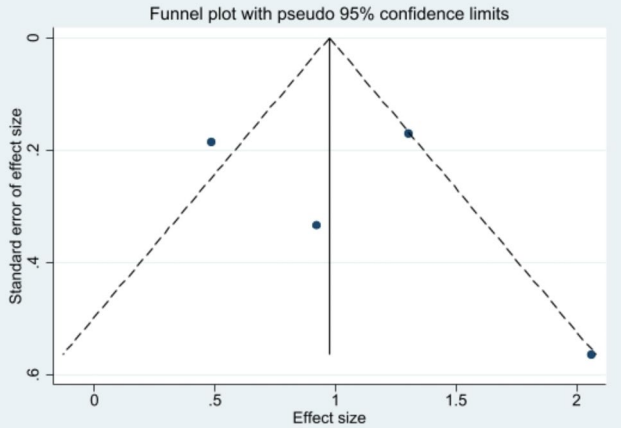

Fig. 9 8-week post-SCI BBB score funnel plot

symmetrical distribution within the inverted funnel shape, indicating a low risk of publication bias (Fig. 9). Egger's test also confirmed this result, demonstrating no significant evidence of publication bias ($P > 0.05$).

These findings suggest that the meta-analysis results are robust and unlikely to be influenced by publication bias at both time points. However, it is important to note that the limited number of studies included in the analysis may reduce the statistical power of these tests. Future research with larger sample sizes is needed to further validate these findings.

Discussion

This is the first systematic review and meta-analysis to investigate the effects of OFS on neural regeneration and functional recovery in animal models of SCI. The findings from the included studies indicate that OFS can significantly enhance motor function recovery, promote axonal regeneration, improve myelin repair, and reduce glial scar formation, thereby facilitating the restoration of motor function. Additionally, OFS stimulates the differentiation of neural stem cells and increases the number of regenerating nerve fibers at the injury site, creating a microenvironment conducive to neuronal regeneration and functional recovery. The potential of OFS technology in treating SCI is primarily reflected in its ability to promote axonal regeneration and motor function recovery.

OFS simulates the natural electric field environment in vivo by applying a DC EF at the site of SCI and periodically reversing the polarity [32, 33], guiding axons to grow bidirectionally. This mechanism relies on the regulation of intracellular and extracellular ion concentrations, particularly the flow of sodium and calcium ions. Changes in these ionic flows can activate various signaling pathways, such as the phosphoinositide 3-kinase (PI3K)/Akt pathway and the phosphatase and tensin homolog (PTEN) pathway [11], promoting the extension and regeneration of neuronal growth cones.

Furthermore, OFS enhances axonal growth and neural repair by influencing the levels of neurotrophic factors in the microenvironment, such as brain-derived neurotrophic factor (BDNF) [34]. Existing studies have demonstrated that neuronal growth cones actively extend toward the cathode of the electric field [35]. Reversing the polarity of the electric field effectively prevents axonal retraction and promotes bidirectional growth, which is beneficial for the restoration of motor function [1].

Stem cell transplantation has emerged as a promising approach for supplementing lost neural cells following SCI [36]. However, a significant challenge lies in maintaining the viability and migratory and differentiative abilities of transplanted stem cells [37]. OFS has been shown to significantly accelerate neural regeneration by influencing the migration and differentiation of neural stem cells. In vitro studies have demonstrated that, under electric field stimulation, oligodendrocyte precursor cells derived from neural stem cells isolated from fetal rats migrate toward the cathode, with this migration bias being proportional to the field strength [38]. Another study indicated that electric fields as small as 16 mV/mm can also guide the migration of embryonic human neural stem cells [39].

OFS not only increases the survival rate of transplanted neural stem cells in the injury area but also promotes their directed differentiation into neurons, further enhancing the recovery of neural function [34]. Moreover, OFS creates more favorable conditions for neural regeneration by regulating the local microenvironment and reducing glial scar formation. Although the aforementioned study [34] was excluded from this meta-analysis due to the lack of a separate OFS intervention group, it suggests that the combined application of OFS and neural stem cell transplantation holds significant promise for the treatment of SCI.

Furthermore, OFS demonstrates positive effects in promoting myelin regeneration. SCI is often accompanied

by damage and loss of myelin, making myelin regeneration crucial for restoring nerve conduction velocity. OFS can enhance the formation of oligodendrocytes, thereby accelerating myelin regeneration. Immunofluorescence results indicate that the expression of myelin protein markers, such as MBP, was significantly increased in the OFS group, with myelin thickness notably greater than that in the control group [27, 29, 31]. This suggests that OFS has potential advantages in promoting myelin regeneration.

However, the relationship between the quality of myelin regeneration and functional recovery still requires further investigation, particularly concerning the long-term effects of OFS on myelin regeneration, which remain unclear.

Another significant advantage of OFS is its ability to reduce the formation of glial scars. Following SCI, astrocytes accumulate at the injury site to form glial scars. While this process initially acts as a barrier to limit the spread of inflammation, it later obstructs axonal regeneration and the recovery of nerve function [40]. OFS effectively mitigates glial scar formation by inhibiting the proliferation of astrocytes and the expression of GFAP. This effect has been validated in multiple animal studies [24, 25, 30], which demonstrated that the number of GFAP-positive cells in the OFS group was significantly lower than in the control group, with a more organized arrangement of glial cells [24, 30].

However, despite the promising potential of OFS in promoting neural regeneration and functional recovery, several technical and biological challenges remain. First, the long-term efficacy of OFS has not been fully validated. Most current studies focus on the acute phase of SCI, lacking systematic research on the application of OFS in chronic SCO. Chronic SCI often features more severe glial scar formation and the accumulation of extracellular matrix [41], which may hinder neural regeneration. Future research should explore the application of OFS in chronic SCI and assess its role in inhibiting glial scars and remodeling the extracellular matrix. Second, the optimal application intensity and timing of OFS remain unclear. Existing studies show considerable variability in electric field strength and application frequency, which may not reflect the actual in vivo electric field strength and distribution [42, 43], leading to high heterogeneity in results. Future research needs to optimize the application parameters of OFS, adjusting intensity and frequency according to different stages of SCI to achieve the best therapeutic outcomes. Third, the devices used to generate oscillating fields may trigger immune rejection reactions and have a limited lifespan [19], posing challenges for long-term patient management. Lastly, the mechanisms of action of OFS have not been fully elucidated, particularly regarding the signaling pathways involved in regulating neuronal differentiation and growth by the electric field. Future studies could utilize multi-omics techniques, such as transcriptomics and proteomics, to systematically analyze the molecular mechanisms underlying OFS, providing a theoretical foundation for its clinical applications.

Despite these limitations, current results support that OFS can significantly improve functional recovery after SCI through various mechanisms, including promoting neural regeneration, enhancing myelin regeneration, and reducing glial scars. These findings provide strong evidence for the further application of OFS, particularly in the treatment of SCI.

Across all the included studies, the majority used platinum/iridium wires as electrode materials [24, 25, 27, 28, 30, 31], with electrodes placed within the intraspinal space, at segments adjacent to the injury site, without contacting the dura mater (non-epidural). Platinum/iridium electrodes are widely utilized in neural stimulation due to their excellent biocompatibility, chemical stability, and conductivity, ensuring both safety and efficacy for long-term implantation. The intraspinal placement avoids mechanical damage to surrounding tissues while effectively delivering OFS to the target area.

Notably, a Phase 1 clinical trial applied OFS in human SCI patients, with electrodes placed at segments adjacent to the injury site, similar to preclinical animal studies [19]. Importantly, the electric field strength used in the clinical trial was not significantly different from that in animal studies, suggesting that the optimized parameters from preclinical research may be directly applicable to humans. This finding is highly significant, as it indicates that the translation of OFS technology from animal models to clinical applications may be more straightforward than anticipated.

However, despite the consistency in electrode placement and electric field strength between animal studies and the Phase 1 clinical trial, several key issues warrant further investigation. First, the long-term biocompatibility and safety of platinum/iridium electrodes in humans require more comprehensive evaluation. While platinum/iridium electrodes have demonstrated excellent biocompatibility in animal models and short-term clinical use, their performance over extended periods in the human spinal cord remains to be fully characterized. Long-term studies are needed to assess potential issues such as electrode degradation, inflammatory responses, and fibrosis, which could impact the efficacy and safety of OFS in chronic applications. Additionally, differences in spinal cord size and anatomical complexity between rodents and humans must be considered. For instance, the larger size of the human spinal cord may require adjustments in electrode spacing to ensure uniform electric field distribution. Furthermore, the design of electrodes and implantation techniques may need to be optimized to

accommodate the anatomical differences in humans. For example, the development of flexible or customizable electrodes could improve compatibility with the human spinal cord's unique geometry. Finally, while the Phase 1 trial provides promising preliminary results, its small sample size necessitates larger-scale clinical studies to validate the efficacy and safety of OFS in humans. Future research should also explore the impact of individual variability, such as differences in spinal cord anatomy and injury severity, on the outcomes of OFS therapy.

The findings of meta-analysis should also be interpreted with caution due to several limitations. First, the results exhibited high heterogeneity, which may be attributed to the following factors: (1) Although the OFS devices were generally implanted in the epidural space adjacent to the injured spinal cord segment, there were variations in the types of electrodes used and the stimulation frequencies across studies. These differences in device specifications and stimulation parameters could significantly influence the outcomes. (2) The included studies employed diverse stimulation protocols, sample sizes, and experimental designs, and the limited number of studies available for analysis further restricted the generalizability of the results. (3) While the BBB scale is widely used as a standardized measure of locomotor recovery, inter-rater variability and the need for consistent training to maintain scoring reliability may have introduced additional heterogeneity. These limitations highlight the need for standardized protocols in future preclinical studies, including consistent electrode types, stimulation parameters, and outcome assessment methods, to reduce variability and enhance the comparability of results.

In conclusion, while OFS shows therapeutic potential, addressing the heterogeneity and methodological limitations identified in this meta-analysis is critical for advancing the technology toward clinical application. Standardized protocols and further translational research will be key to improving outcomes for SCI patients.

Conclusion

As a promising therapeutic approach for SCI, OFS can significantly enhance functional recovery following spinal cord damage through various mechanisms, including promoting neural regeneration, facilitating myelin regeneration, and reducing glial scar formation. However, its long-term efficacy, optimal application parameters, and potential side effects still necessitate further research and validation. With ongoing technological advancements and deeper investigations into its mechanisms of action, OFS is expected to become an effective complement in the field of SCI treatment, offering new ideas and solutions for functional improvement.

Abbreviations

OFS	Oscillating field stimulation
SCI	Spinal cord injury
DC EF	Direct current electric fields
BBB	Basso, Beattie, and Bresnahan
MEP	Motor evoked potential
HE	Hematoxylin and Eosin
LFB	Luxol Fast Blue
IHC	Immunohistochemistry
IF	Immunofluorescence
CI	Confidence interval
ROB	Risk of Bias
SD	Sprague-Dawley
MBP	Myelin basic protein
Galc	Galactocerebrosidase
GFAP	Glial fibrillary acidic protein

Supplementary Information

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Supplementary Material 1

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None.

Author contributions

GW conceived the study. LX, JF, GJ, YG, JS, YM, XY, and YY contributed to the study design. GW and LX drafted the manuscript. XY and YY edited the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

Not applicable. Since this paper is a systematic review and does not involve human researchers or animal experiments, ethical approval is not required.

Consent for publication

All authors contributed to the article and approved the submitted version.

Competing interests

The authors declare no competing interests.

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