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Assessing Median Nerve Regeneration in Rodent Models– A Systematic Review

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Abstract

Peripheral nerve injuries (PNI), particularly median nerve injuries, lead to significant motor and sensory impairments, affecting daily function and quality of life. Rodent models are extensively used for studying nerve regeneration due to their physiological similarity to humans. Accurate assessment of nerve regeneration is critical for evaluating therapeutic approaches, yet existing methods lack standardization and comprehensive analysis. A systematic review was conducted following PRISMA guidelines, searching databases including PubMed, Google scholar and science direct from 2013 to 2024. Inclusion criteria focused on studies using rodent models to investigate median nerve regeneration with surgical interventions and reporting functional, physiological, histomorphometry, or molecular outcomes. Out of 110 studies, 13 studies were selected and reviewed. The review identified various assessment techniques includes, Functional test evaluates motor and sensory recovery. Electrophysiological test measure nerve conduction velocity and muscle action potentials. Histological analyses examine nerve morphology, myelination, and axonal regeneration. Molecular methods assess gene expression and protein markers. A multimodal approach combining these methods provides the most comprehensive evaluation of nerve regeneration. This systematic review highlights the current state of median nerve regeneration in rodent models. The results suggest that rodent models are a valuable tool for studying nerve regeneration and evaluating potential therapeutic interventions. However, there is a need for standardization in the methods used to assess nerve regeneration, as well as the reporting of study results.

Keywords: *Electrophysiology Assessment, Functional Assessment, Histomorphometry Measure, Peripheral Nerve Injury.*

Introduction

Peripheral nerve injuries (PNI) can occur due to a variety of factors, such as traumatic incidents, complications arising from surgical procedures, and unintended consequences of medical interventions [1]. These injuries have the potential to cause significant harm to the structure and proper functioning of nerves [2]. Peripheral Nerve Injury (PNI) disrupts nerve-body communication, causing motor/sensory impairments, physical disabilities, and chronic neuropathic pain [3]. Peripheral nerve damage significantly impacts quality of life, cognitive function, social relationships, and economic stability. PNI's repercussions extend beyond physical limitations, affecting emotional well-being and overall well-being [4, 5].

The median nerve is essential for precise hand and forearm movements, facilitating both delicate motor functions and everyday tasks [6]. Nerve damage can severely impair motor skills (dexterity, grip) and sensory perception in the affected limb. This trauma often has lasting consequences, significantly impacting daily life

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and mobility [7]. These impairments substantially diminish an individual's quality of life, making everyday tasks challenging and hindering participation in previously routine activities [8].

Untreated median nerve injuries in the forearm can have severe consequences, significantly impairing hand function [9]. Approximately 8 million median nerve injuries are reported annually in the United States, emphasizing their prevalence and significance. Prompt recognition and proper management are crucial to prevent long-term disability and ensure optimal recovery outcomes [10].

Rodent models, namely rats and mice, play a vital role in advancing our knowledge of peripheral nerve regeneration within the realm of medical research [11]. Rodent models are extensively utilized among various pre-clinical models and techniques for evaluating nerve regeneration following injury [12-14]. The most significant advantage of using rodents as model organisms lies in their striking anatomical, physiological, and genetic parallels with humans [15, 16]. These models enable cost-effective, in-depth evaluations of treatments for nerve regeneration. Insights from rodent studies inform clinical trial design and guide therapeutic interventions [17].

Accurate assessment of nerve regeneration plays a crucial role in evaluating the efficacy of treatments targeting this process. In rodent models, a range of methodologies have been devised for the evaluation of median nerve regeneration, encompassing diverse approaches such as behavioural analysis(measures of motor and sensory function, such as grip strength, locomotor activity, and sensory threshold testing)[18],electrophysiological testing(measures of nerve conduction velocity, compound muscle action potential, and electromyography)[19], histological examination(measures of nerve morphology, myelination and axonal regeneration)and molecular biological techniques(measures of gene expression, protein levels, and cellular markers of regeneration)[20]. These various methods offer valuable insights into different facets of nerve regeneration, including the degree of regrowth, reinnervation patterns, and the subsequent functional recovery of the nerve [21, 22].

Nonetheless, an essential gap exists in the current literature concerning a thorough examination and comparison of these assessment methodologies specifically in the context of median nerve regeneration in rodent models. This systematic review aims to synthesize and critically evaluate existing research, highlighting the benefits and drawbacks of various methodological approaches. By undertaking this comprehensive review, we aim to deliver a valuable resource that will aid researchers working in the domain of peripheral nerve regeneration. Ultimately, this review intends to catalyse advancements in the field by enhancing our understanding of effective assessment techniques and promoting the development of more impactful treatments for injuries affecting the median nerve.

Methodology

A systematic literature search was conducted following PRISMA guidelines. Electronic databases, including Google Scholar, PubMed, and Science direct, were searched. The search spanned from 2013 to 2024 using a combination of keywords and MeSH terms such as Median Nerve Regeneration, Rodents, Functional, Histomorphometry, Electrophysiological Assessment. A comprehensive search strategy was employed to identify relevant studies. Various permutations and combinations of these keywords ensured a thorough search.

Data Collection Criteria

Studies using rodent models (rats or mice) for median nerve regeneration research, Studies employing surgical interventions (e.g., nerve transection, crush injury) to induce nerve

damage. Studies using various treatments or interventions (e.g., nerve grafts, stem cells, growth factors) to enhance nerve regeneration. Studies reporting outcomes measures such as: Functional assessments (e.g., grip strength, locomotor activity), Physiological evaluation (e.g., nerve conduction velocity, electromyography, Histomorphometry evaluation (e.g., nerve fibre density, myelination) and Molecular assessment were included. Studies published in English language are considered. Only experimental studies are included. Recent studies (2013-2024) were selected to capture the most up-to-date findings to guarantee contemporary relevance.

Study Selection Process

The study selection process (Figure 1), details the step-by-step process of identifying and selecting studies for inclusion. Initially, 110 records were identified through database searching (from 2013-2024). 55 duplicates were removed, leaving 45 records. After screening, 13 records were excluded.32 records were selected for retrieval. However, 11 records couldn't be retrieved.

This resulted in 21 records being assessed for eligibility. The remaining records underwent further evaluation. Out of these 21 reports, 8 were excluded for specific reasons: 3 due to being narrative/expert reviews, 1 for having a small population size, and 4 for poor methodology. Finally, 13 studies were included in the review (Table 1). The flow chart (Figure 1) visually represents the filtering process from initial identification to the final inclusion of studies.

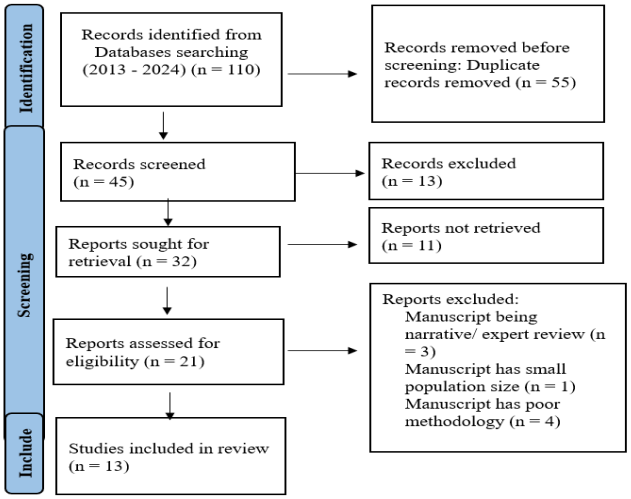

Figure 1. Prisma Flow Chart for Literature Published between 2013 to 2024

Methodological Quality

The SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) risk of bias tool [23], is designed for assessing bias in animal studies using Revman software. It includes ten items addressing six types of bias: selection, performance, detection, attrition, reporting, and other biases. Each item is evaluated using a signalling question, with responses categorized as “yes” (low risk of bias), “no” (high risk of bias), or “unclear” (unclear risk of bias). A response of “no” indicates a high risk of bias for that particular item. Reviewers independently assessed key elements such as the adequacy of randomization and allocation concealment, baseline characteristics, blinding of participants and outcomes, randomization of housing and outcome assessment, completeness of data, and selective reporting. Each aspect of bias was classified as low (green), high(red), or unclear (yellow).

Table 1. Review Of Literature

Author name and Year of Publication	**Study title**	**Type of Study**	**Rodents Model**	**Sample Size**	**Interventional surgery**	**Treatment Duration**	**Outcome Measure**	**Reflection**
Barton, M., et al 2013	Laser-activated adhesive films for suture less median nerve anastomosis	Experimental study	Long Evans rat	80	Nerve transection	12 weeks	Nerve tensile test Histomorphometry evaluation Electrophysiology assessment	**Nerve tensile test:** Tensiometer (Instron, MA, USA) was used to measure the repair strength and recorded using Merlin IX software. **Histomorphometry evaluation:** Transverse and longitudinal sections (5-10 mm thickness) were made at specific locations relative to the repair site for further analysis. Longitudinal haematoxylin and eosin(H&E), Transverse H&E, Transverse Luxol Fast Blue LFB. **Median Nerve Morphometric :** Nerve Area (mm^2), Diameter (mm), Myelinated fibres Number, Fibre diameter (mm), Fibre Area (mm^2), Axon diameter (mm),

								Axon Area (mm^2), Myelin density (mm^2). **Electrophysiology:** Flexor Digitorum superficialis and flexor carpi radialis were measured using EMG Nerve conduction (Compound action potential – CAP).
Beck-Broichsitter, B. E., et al (2014).	Sensoric Protection after Median Nerve Injury: Babysitter-Procedure Prevents Muscular Atrophy and Improves Neuronal Recovery	Experimental study	Wistar rat	20	Nerve transection	15 weeks	Functional assessment Histomorphometry evaluation	**Functional assessment:** **Grasping test** Rats are lifted by tail, allowing them to grasp an 8x14cm wire grid attached to an electronic balance. **Histomorphometry analysis:** Axon and nerve fibre diameter were measured Nerve fiber metrics were calculated.
Casal, D., et al., 2018	Reconstruction of a 10-mm-long median nerve gap in an ischemic environment using autologous	Experimental study	Wistar rat	120	Nerve Defect Model with Silicone Conduit and Ischemic Simulation	100 days	Functional assessment Electroneuromyography assesement Histomorphometric evaluation	**Functional** **Grasping test** **Pin prick test:** von Frey filament used **Ladder run test:** forelimb strength, coordination, stepping and placement were measured.

	conduits with different patterns of blood supply: A comparative study in the rat							**Walking track analysis:** FIJI free software used. **Infrared thermography:**Digital thermometer used **Electroneuromyography Assessment** Muscle Weight Neurological stimulation threshold, Motor stimulation threshold, Latency, Neuromuscular transduction velocity, CMAPS amplitude and duration were measured. **Histomorphometry Evaluation** Nerve fibre diameter, Myelination, Conduction velocity was measured.
Colonna, M. R., et al 2019	The Use of a Hypoallergenic Dermal Matrix for Wrapping in Peripheral Nerve Lesions Regeneration:	Experimental study	Wistar rat	16	Nerve transection	7 months	Functional assessment Histomorphometry assessment	**Functional assessment** Graspingtest: (BS-GRIP Grip Meter) was used to quantitatively measure muscle function. **Histomorphometry assessment:**

	Functional and Quantitative Morphological Analysis in an Experimental Animal Model							Nerve fibre metrics were measured.
Coradinia J. G., et al., 2015	Evaluation of grip strength in normal and obese Wistar rats submitted to swimming with overload after median nerve compression	Experimental study	Wistar rat	48	Nerve compression: Four chromed Catgut 4.0 sutures are placed around the median nerve, approximately 1 mm apart.	3 weeks	Muscle strength - grip strength meter	**Muscle strength** flexor digitorum muscle function measured using grip strength meter.
Daeschler, S. C., et al 2018	Clinically Available Low Intensity Ultrasound Devices do not Promote Axonal Regeneration After Peripheral Nerve Surgery—A Preclinical Investigation of	Experimental study	Sprague Dawley	60	Nerve transection	8 weeks	Functional muscle testing Electrodiagnostic evaluation Histological analysis	**Functional muscle testing** Grasping test, **Muscle wet weight** The FDS muscle was harvested and weighed on an Ohaus microscale. **Electrodiagnostic evaluation** CMAP and distal latencies were measured using EMG device **Histological analysis**

	an FDA-Approved Device							Myelinated axon number and axon distribution density were measured
Ferreira, M. C., et al 2019	Effects of two intensities of treadmill exercise on neuromuscular recovery after median nerve crush injury in Wistar rats	Experimental study	Wistar rat	24	Crush injury	21 days	Functional evaluation Histomorphometry analysis	**Functional evaluation** **Grasping test** **Histomorphometry analysis** Number of myelinated fibres Fibre diameter Axon diameter Thickness of myelin sheath Ratio of axon diameter to fibre diameter were measured.
Heinzel J.C., et al., 2021	Evaluation of Functional Recovery in Rats After Median Nerve Resection and Autograft Repair Using Computerized Gait Analysis	Experimental study	Lewis's rat	10	Median nerve resection with autograft repair	12 weeks	Functional analysis Electrophysiological analysis	**Functional analysis** **Catwalk XT:** Automated gait analysis system was used. 14 parameters were measured **Reflex based grasping :** A grip strength Meter (Ugo Basile, Italy) measured forelimb grip strength in rats. **Electrophysiological analysis:** Neuromax Emg Used, CMAP amplitude and latency were measured.

Ho, C. Y., et al., (2013)	Electroacupuncture and Acupuncture Promote the Rat's Transected Median Nerve Regeneration	Experimental study	Sprague-Dawley rats	21	Silicone Rubber Tube Entubulation	5 weeks	Histomorphometry analysis Electrophysiological analysis Functional assessment	**Histomorphometry analysis**: axon number, Endo neural area, total nerve area, blood vessel number, blood vessel area were measured. **Electrophysiological analysis:** latency, amplitude, MAP area, NCV were measured. **Grasping analysis: S**quare grids were used.
Lamia,A et al 2014	Does Pulsed Magnetic Field Therapy Influence Nerve Regeneration in the Median Nerve Model of the Rat?	Experimental study	Wistar rat	24	microsurgical coaptation	12 weeks	Functional assessment Histomorphometry evaluation	**Functional assessment** Grasping test: wire grid (8 x 14cm) used. **Histomorphometry assessment:** Total number of nerve fibers, density, surface area, axon diameter, nerve fiber diameter, myelin thickness were measured.
Machado et al., 2013	Stretch-induced nerve injury: a proposed technique for the study of nerve regeneration and evaluation of the influence	Experimental study	Wistar	36	Stretch and crush injury	30 days	functional analysis histomorphometry analysis measurement of neurotrophic factor in the median nerve	**functional analysis** Grasping test Grid (1.5 mm diameter, 86.14 cm long) was used. Response to mechanical stimulation: Using von Frey filament method.

	of gabapentin on this model							Response to electrical stimulation: Assessed by neurostimulator **histomorphometry analysis** Four nerve regeneration parameters were quantified: Degeneration debris (%) Connective tissue area (%) Myelinated fibre area (%) Myelinated fibre density (per mm^2) **measurement of neurotrophic factor in the median nerve:** BDNF and NGF levels were then measured using ELISA kits from R&D Systems.
Marcioli, M. A. R., et al 2018	Neurotrophin expression and histomorphometric evaluation in Wistar rats subjected to neural mobilization after compression of the median nerve	Experimental study	Wistar rat	18	Nerve compression: Four chromed Catgut 4.0 sutures are placed around the median nerve, approximately 1 mm apart.	6 days	Histomorphometric Analysis	**Histomorphometric Analysis,** Axon count expression of neurotrophins, nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) by RT-PCR.

Stößel, M., et al 2017	Reflex-based grasping, skilled forelimb reaching, and electrodiagnostic evaluation for comprehensive analysis of functional recovery—The 7-mm rat median nerve gap repair model revisited	Experimental study	Lewis's rat	16	Nerve transection	12 weeks	Functional test Electrophysiological test Histomorphometry evaluation	**Functional test** Grasping test (reflex based): Grip strength meter used. Staircase test: Staircase apparatuses, each consisting of 7 steps with 3 sugar pellets were used to assess motor function **Electrophysiological studies** CMAP Amplitude area, amplitude height, nerve conduction velocity was measured **Histomorphometric** Cross sectional area of distal nerve segment, number of myelinated axons, nerve fibre density, axon diameter, fibre diameter, myelin thickness, fibre diameter distribution was measured.

Study-Specific Risk of Bias (Figure 2) provides a study-by-study breakdown of the risk of bias across various domains. Each row represents an individual study, and each column represents a specific bias domain. Studies such as Casal, D et al and Colonna, M.R et al exhibit high-risk domains, especially in "Allocation Concealment" and "Blinding," raising concerns about potential selection and performance bias. These studies may have methodological flaws that weaken their credibility. All other Studies exhibit consistently low risk, making their findings highly reliable.

The bar chart (Figure 3) shows the proportion of studies classified under Low Risk of Bias (Green), Unclear Risk of Bias (Yellow), and High Risk of Bias (Red) for each bias domain. Low Risk (Green) dominates in most categories, such as baseline characteristic, random housing, Incomplete Outcome Data, selective outcome reporting indicating that many studies followed rigorous methodology in these areas. Unclear Risk (Yellow) is prevalent in categories like sequence generation, allocation concealment, blinding and random outcome assessment suggesting that some studies lacked sufficient information to make a clear judgment. High Risk (Red) is most noticeable in Allocation Concealment, Blinding, and Random Outcome Assessment, highlighting potential methodological flaws in these areas.

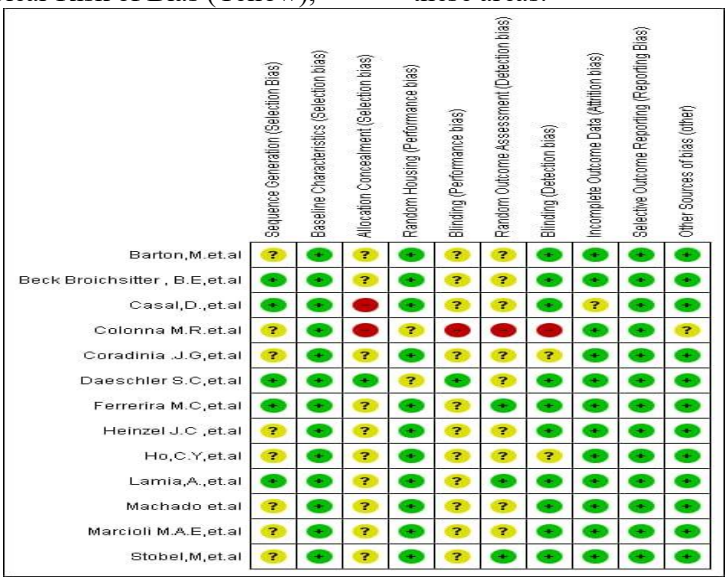

Figure 2. Study-Specific Risk of Bias

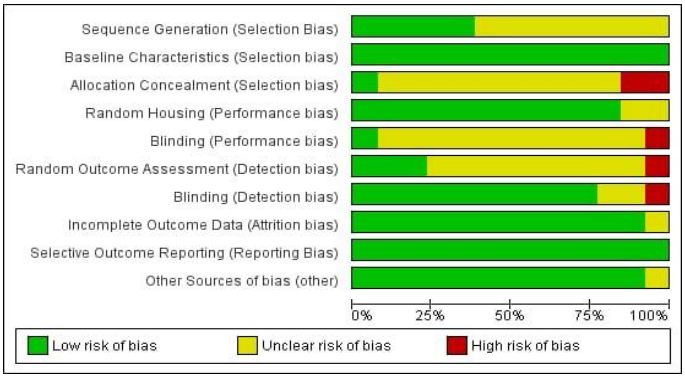

Figure 3. Summary of Risk of Bias of all Studies

Result

This systematic review analysed 13 studies on median nerve regeneration in rodent models, highlighting the diverse methodologies employed to assess nerve repair and recovery. The results are categorized into four main

assessment types - Functional Assessments, Electrophysiological Testing, histology and molecular analysis.

Functional Assessments

Functional assessment includes, techniques such as grasping tests, ladder test, staircase test, and gait analysis were commonly used to evaluate motor and sensory recovery in rodents. Out of 13 studies, 10 studies used grasping test to evaluate motor function particularly grip strength and fore limb function. The test involves placing a rodent on a grasping apparatus consisting of a horizontal bar or grid, allowing it to grasp the bar with its forelimbs. The grasping time, or the duration the rodent can maintain its grip, is measured, and some apparatuses also record the grasping force exerted by the rodent. Sensory assessment is done using von Frey filament is used in 2 studies, while gait analysis (e.g., Catwalk XT system) and walking track analysis were used to analyse the variables of gait in rodent. Ladder run test and stair case test were widely used to measure forelimb strength, coordination, stepping and placement and to assess motor function.

Electrophysiological Testing

Electrophysiological Testing such as muscle function of flexor digitorum superficialis and flexor carpi radialis were measured using EMG device. Measurements such as nerve conduction velocity, compound muscle action potentials (CMAPs), amplitude, duration and distal latency assessments are assessed in 6 studies. This electro physiological testing provides quantitative data on nerve functionality and recovery.

Histological Evaluations

Histomorphometry methods analysed myelination, axonal density, and nerve fibre morphology. Techniques such as H&E and Luxol Fast Blue staining assessed nerve structure and integrity post-regeneration. Our review highlighted studies where these parameters significantly correlated with histological findings, such as Density of fibre, axon diameter, fibre diameter, myelin thickness, myelin thickness/axon diameter (M/d), fibre diameter /axon diameter (D/d), axon diameter / fibre diameter (d/D), reinforcing the reliability of electrophysiological evaluations in determining the success of regeneration.

Molecular Analysis

Molecular markers like neurotrophic factors (e.g., NGF, BDNF) and gene expression levels were studied to understand the biological processes underlying nerve regeneration.

The findings indicate that a multimodal approach integrating functional, electrophysiological, histological, and molecular assessments provides a comprehensive evaluation of nerve regeneration. However, standardization of methodologies across studies is lacking, limiting comparability and translation to clinical applications. These results underscore the importance of combining diverse techniques to better understand and evaluate nerve regeneration while addressing gaps in consistency and relevance for human applications.

Discussion

The assessment methods for median nerve regeneration in rodent models are varied, each with its advantages and limitations. In our systematic review, we identified several commonly used techniques, including electrophysiological measurements, histological analysis, and functional recovery assessments. Electrophysiological assessment, particularly sensory nerve action potentials (SNAPs) and motor nerve action potentials (MNAPs), remains a gold standard for evaluating nerve regeneration [24]. These methods provide quantitative data on conduction velocity and amplitude, offering a direct measure of nerve function [25].

On the other hand, histological analysis is a key quality control method for assessing nerve tissue regeneration. It requires a solid understanding of nerve histology and regeneration, along with technical proficiency [26]. Histological methods, including myelin staining and axonal density assessments, allow for a detailed analysis of the morphological changes in the nerve and surrounding tissue [27]. While histology provides crucial insights into the structural integrity of the regenerated nerve, it is important to note that these methods are invasive and often require terminal procedures, limiting their longitudinal applicability [28].

The tests used in functional assessment in rodents help researchers to evaluate the animal's motor function, sensory function, and overall behaviour [18]. Several functional tests described in this paper rely heavily on the rat's motivation and cooperation, driven by the expectation of receiving a food reward [29]. Developing sensitive behavioural tests is vital for accelerating the development of translational therapies that can effectively address functional deficit in rodent model [30].

The selection of assessment method should be tailored to the specific research question and the stage of nerve regeneration under study. The lack of correlation between evaluation methods highlights the importance of incorporating multiple outcome measures in therapeutic studies to capture the full spectrum of recovery after nerve damage [20]. A multimodal approach is often recommended, integrating electrophysiological, histological, and functional measures to provide a comprehensive overview of nerve regeneration [21]. In addition to conventional assessment tools, emerging biomaterials like carbon nanotubes (CNTs) are being explored for their role in supporting nerve regeneration [31].

One major limitation of this systematic review is that it only focuses on rodent models, which may not accurately translate to human nerve regeneration. Additionally, this review may oversimplify the intricate process of human nerve regeneration, which can be impacted by factors like age, comorbidities, and individual differences. Further research is needed to standardize these assessment methods to improve comparability across studies and ensure that findings can be effectively translated to clinical settings. Future investigations might also explore innovative imaging techniques and non-invasive assessments to monitor nerve regeneration, thus advancing the field towards more ethical and efficient research practices in rodent models of nerve injury.

Conclusion

This systematic review of 13 articles provides a comprehensive analysis of median nerve regeneration in rodent models, emphasizing the importance of a multi-modal assessment approach. The review reveals the complexity of nerve regeneration, involving significant changes in functional, behavioral, histological, and electrophysiological outcomes. This review underscores crucial factors affecting regeneration outcomes, such as injury timing and repair techniques. It provides a valuable summary of current knowledge, emphasizing the need for further research to improve understanding of nerve regeneration and develop more effective treatments.

Conflict Of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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