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Review

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Novel approaches in peripheral nerve repair: a review of current and emerging therapies

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Abstract

The peripheral nervous system is a complex anatomical structure essential for the normal functioning of the human body. Defects in peripheral nerves can lead to significant morbidity and a marked decline in quality of life. These defects may arise iatrogenically, from trauma, or as a result of degeneration. Among these, head and neck surgeons most frequently encounter nerve damage or sacrifice during surgical procedures. In the treatment of head and neck cancer, nerve resection - whether complete or partial - is often necessary, compromising the nerve's anatomic and functional integrity. Despite advances in treatment, a well-defined, universally accepted paradigm for the functional rehabilitation of patients with sensory or motor deficits remains elusive. This review summarizes recent breakthroughs in peripheral nerve repair, highlights novel repair strategies, and identifies critical gaps that must be addressed to advance the field.

Keywords: Peripheral nerve regeneration, sensory reinnervation, head and neck reconstruction, free flap reconstruction

INTRODUCTION

Peripheral nerve injuries (PNIs) frequently result from trauma or ablative procedures, causing lifelong deficits and a significant reduction in patients' quality of life. The economic burden of PNI represents a

global health challenge due to the limited recovery rates[1,2]. Unlike the central nervous system, the peripheral nervous system has the capacity to regenerate, although this process occurs at a very slow rate. Following nerve injury, a cascade of molecular and cellular changes initiates to prepare the damaged nerve for repair and regeneration[3]. Recent advancements in understanding the cellular and molecular responses to nerve injury have paved the way for novel approaches to peripheral nerve repair. This review aims to explore the anatomy, physiology, and mechanisms underlying nerve injuries. It focuses on innovative methodologies currently being investigated for reconstructing and rehabilitating these injuries, with an emphasis on experimental techniques still in early development.

PERIPHERAL NERVE ANATOMY AND PHYSIOLOGY

Peripheral nerves transmit sensory, motor, and autonomic information between the brain, spinal cord, and peripheral tissues [Figure 1]. The smallest functional unit of a nerve is the axon, a cytoplasmic extension of the neuronal cell body. Axons transmit electrical signals, known as action potentials, away from the cell body. Each axon is enveloped by the neuron's cell membrane, the axolemma, which houses mechanical and ion channels essential for generating action potentials. Axons may be myelinated or unmyelinated, with Schwann cells forming the myelin sheath in the peripheral nervous system.

Groups of axons are embedded within the endoneurium, a microenvironment containing connective tissue, collagen fibrils, fibroblasts, ground substance, and endoneurial fluid[4]. These axons are further organized into fascicles, which are surrounded by the perineurium. The perineurium, composed of perineural cells lined by tight junctions and a thick basement membrane, functions as an anatomical blood-nerve barrier[5]. This structure, rich in fibronectin and connective tissue, modulates stretching forces exerted on the nerve[5]. Finally, bundles of fascicles are insulated by the epineurium, a vessel-rich layer that encloses the entire nerve. Following nerve injury, epineural tensionless end-to-end repair remains the gold standard for surgical reconstruction[6,7].

Physiology of PNI

Seddon was the first to classify nerve injuries, with his classification being modified by Sunderland to be based on nerve histopathology[8,9]. Subsequent to nerve injury, Wallerian degeneration occurs after a latent period of 24 to 72 h[10]. This is a process of axonal degeneration at the distal nerve stump. During this process, resident Schwann cells undergo molecular changes to upregulate genes involved in regeneration and repair, such as neurotrophic factors, neuregulin, and growth-associated genes, while downregulating other genes, such as those associated with myelination[11,12]. Another factor affecting regeneration is the nerve's surrounding microenvironment. A number of biochemical modulators play a role in nerve healing. These modulators can be targeted in nerve regenerative therapies[13], which will be discussed later in this chapter. Should nerves regenerate aberrantly, synkinesis can occur in which nerve inputs can activate unintended muscles. Indeed, misdirected axonal growth remains the most significant challenge in peripheral nerve repair[14]. Other factors such as atrophy of targeted muscles and chronic Schwann cell denervation limit meaningful clinical recovery[15].

PRIMARY NERVE REPAIR

Primary nerve repair refers to direct suturing (neurorrhaphy) of an injured nerve. This technique, although simple to perform, hinges on a tension-free repair with minimal gap in addition to debridement of injured nerve ends and removal of any surrounding scar[16]. Tensions as low as 25 g of force have been shown to decrease the success of the repair[17]. Neurons can regenerate over gaps up to 4 mm in length[18]. If done properly, primary neurorrhaphy represents the highest likelihood of return to function for the nerve[19]. The number of viable axons decreases with each anastomosis; thus, cable grafting (two anastomoses) will lead to

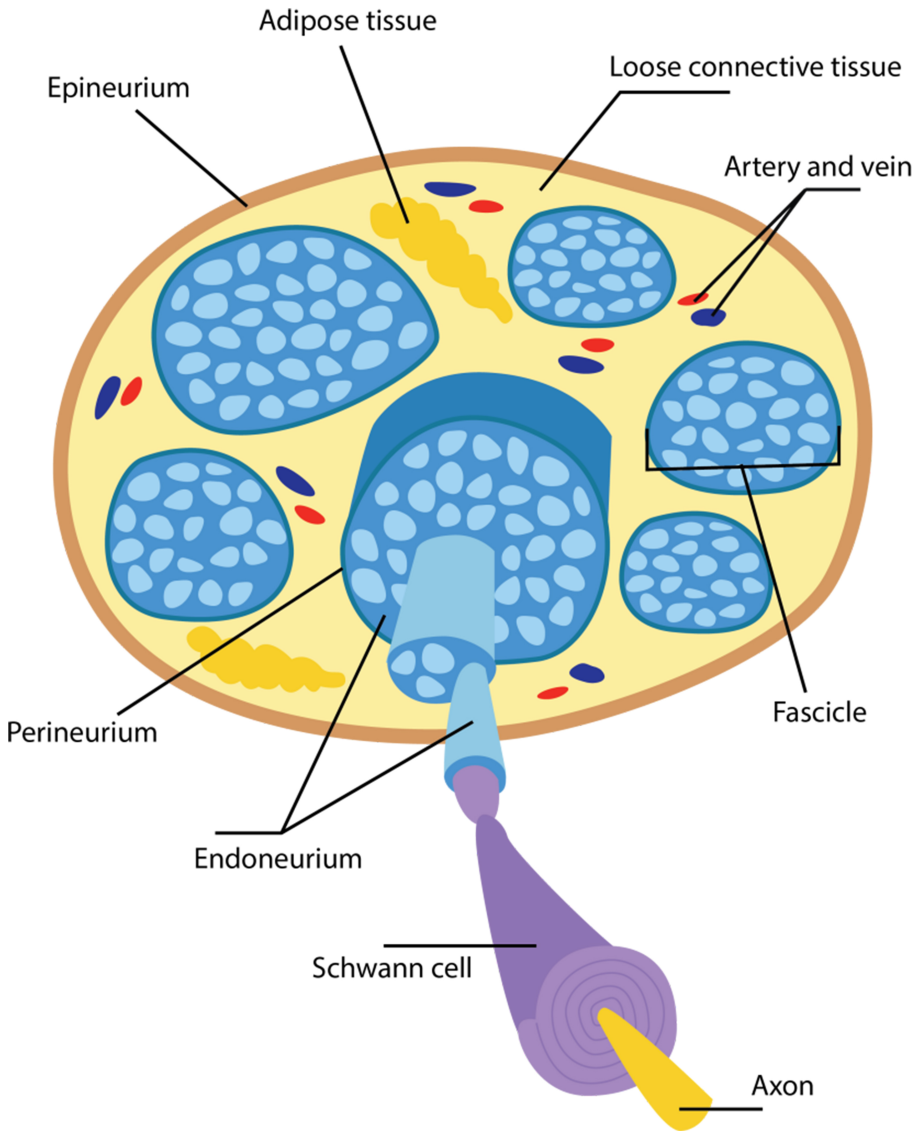

Figure 1. Detailed anatomy of the peripheral nerve.

fewer viable axons compared to primary repair[19]. However, emphasis should remain on a tensionless repair as this is the single most important prognostic factor in the success of the repair[20,21].

NERVE GRAFTING

When a tensionless repair is not feasible, bridging the gap between nerves may be necessary either with an autograft, allograft, or nerve conduit[22]. Nerve grafting is also called cable grafting or interposition grafting and requires two sutured anastomoses. Autografts refer to nerve grafts harvested from patients themselves. These donor nerves typically include the great auricular nerve, medial antebrachial cutaneous nerve, or sural nerve[23]. Harvesting autograft results in some form of donor site morbidity, which must be taken into consideration when deciding on which technique of nerve grafting to pursue. Allografts, on the other hand, are typically processed cadaveric nerve grafts. They were originally developed by Axogen (Alachua, FL)[24]. These nerve grafts are prepared and ready "off-the-shelf" in a variety of sizes and diameters. Allograft outcomes have been found to be equivalent to autografts in both the peripheral nerve literature as well as

the head and neck[11,25].

NERVE GUIDANCE CONDUITS

Currently, tensionless repair using microsurgical anastomosis, with or without autologous nerve grafts, stands as the gold standard for treating PNI. However, surgical repair still faces limitations, such as incomplete sensory and motor recovery and donor site morbidity. An international survey of 324 patients with PNI revealed that many continue to suffer functional deficits and a reduced quality of life[26]. Consequently, significant clinical interest has shifted toward novel approaches in peripheral nerve repair, particularly those involving tissue engineering [Figure 2].

A major advancement in this field is the development and approval of nerve guidance conduits (NGCs) made from natural or synthetic materials[27]. NGCs aim to create an optimal regenerative environment that supports axonal regrowth, prevents fibrosis and scarring, and retains neurotrophic factors for axonal targeting[27]. Typically, NGCs consist of semi-permeable, permanent, or biodegradable materials such as chitosan, type I collagen, or copolyester[27]. These materials form hollow tubes or three-dimensional scaffolds. Various NGCs are now available on the market, including NeuraGen[28], AxoGuard[29], Neuroflex[30], Reaxon[31], Neurolac[32], and Nerbridge[33], among others.

Research on clinical outcomes after nerve repairs using NGCs is mostly found in extremity and digital nerve repair literature. In a randomized prospective study of 98 patients undergoing digital nerve repair, Weber *et al.* found that NGC repair for nerve gaps less than 4 mm led to superior sensory recovery compared to autologous grafts or end-to-end repair[34]. Interim data from the RANGER Registry, the largest nerve allograft study to date, revealed that 82% of 385 patients achieved meaningful sensory, motor, or mixed recovery after repairing nerve gaps up to 70 mm[35]. Notably, the study reported that small nerve gaps (< 15 mm) achieved 91% functional recovery. In clinical practice, NGCs are generally used for small-diameter nerves with gaps less than 30 mm. Repair of larger nerve defects with NGCs often yields suboptimal results[25]. Consequently, innovations in multimodal therapy, that is, combining NGCs with pharmacology, cell-based therapy, gene therapy, and/or electrical stimulation to enhance functional recovery, are being investigated. These approaches will be discussed in the following sections.

Pharmacologic agent for peripheral nerve regeneration

Several pharmacologic agents have been investigated to enhance peripheral nerve regeneration. These agents aim to boost neuroprotection, reduce neurodegeneration, promote regenerative effects, or prevent neuro-excitotoxicity. One of the most extensively studied agents is brain-derived neurotrophic factor (BDNF). BDNF is crucial for nerve development and neuronal survival[36]. After PNI, Schwann cells significantly increase BDNF mRNA expression, presumably to promote nerve regeneration and repair by activating the JAK/STAT pathway[37,38]. In a rat sciatic nerve injury model, sustained delivery of BDNF to the injury site has enhanced functional recovery and improved nerve regeneration[39]. Similarly, administering endogenous BDNF to spinal cord and sciatic nerve lesions has promoted neurite outgrowth and locomotion recovery, an effect that can be blocked by BDNF antiserum[40].

Erythropoietin (EPO) also demonstrates neuroprotective effects following PNI. After axonal injury, dorsal root ganglion (DRG) and Schwann cells significantly express EPO, which acts on the axon to prevent degeneration and apoptosis[41]. Lee *et al.* found that combining EPO with dexamethasone increased nerve myelination and reduced muscle atrophy in treated groups compared to untreated ones, resulting in improved motor function[42]. Another study reported that sustained EPO delivery, both *in vitro* and *in vivo*, correlated with reduced axonal scarring and enhanced myelination of regenerated nerves[43].

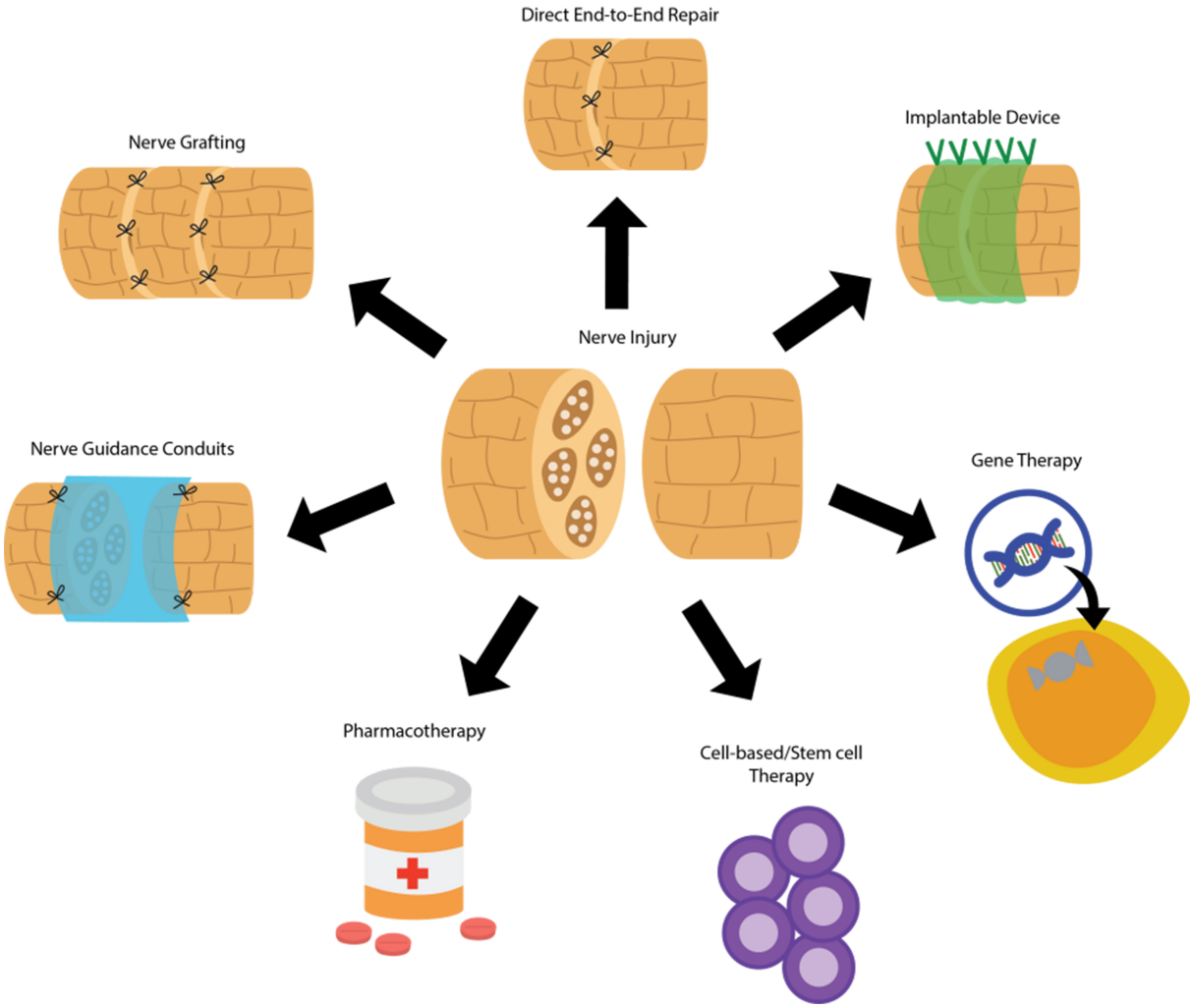

Figure 2. Current strategies for peripheral nerve repair.

N-acetyl cysteine (NAC) serves as a potent antioxidant and anti-inflammatory agent with known neuroprotective properties[44]. In rat models, NAC treatment has improved neuronal survival following sciatic axotomy[45]. Combining NAC with nerve grafting further enhances neuronal survival. In another animal model of facial nerve crush injury, daily NAC infusion led to a significant recovery in electromyography and overall functional scores compared to untreated controls[46].

Numerous other agents have shown benefits[47]. It is important to note, however, that no single pharmacologic agent has been approved for nerve repair and remains experimental at this time.

Advancement in cell-based and gene therapy for peripheral nerve regeneration

As previously mentioned, peripheral Schwann cells play a critical role in repair by locally secreting neurotrophic factors[48]. For example, mutant mice with inactivating mutations in Schwann cells exhibited dysregulated and poor axonal regeneration following nerve injury compared to controls[49]. One theoretical approach to cell-based or stem cell therapy involves adding Schwann cells to NGCs or grafts to promote regeneration. Hadlock *et al.* demonstrated that nerve grafts coated with Schwann cells achieved superior functional outcomes after sciatic nerve injury in rats[50]. Similarly, Takeya *et al.* developed a Schwann cell-

encapsulated hydrogel nerve conduit that improved motor function and histologic recovery following grafting[51]. However, isolating and purifying autologous Schwann cells remains challenging and time-consuming, which limits their practical use in clinical settings.

Stem cells and other precursor cell therapies offer a viable alternative due to their relative ease of isolation. A range of cell types, including bone marrow stromal stem cells[52], bone marrow mesenchymal stem cells[53], adipose-derived stem cells[54], neural stem cells[55], induced pluripotent stem cells[56], amniotic mesenchymal stem cells[57], and skin-derived precursor cells[58] are also being studied. However, stem cell therapy may be limited by the low rate of graft cell survival or even tumorigenesis, highlighting the need for carefully designed and scrutinized trials[59].

Another promising approach to enhance nerve regeneration is gene therapy. Investigators have specifically targeted different components of the peripheral nervous system to deliver exogenous genetic material using viral vectors. For instance, Haastert *et al.* employed nerve conduits coated with genetically modified Schwann cells that overexpressed fibroblast growth factor-2 in a rodent sciatic nerve injury model. They found that this method significantly improved sensory reinnervation and promoted more robust axonal growth compared to controls[60]. In another study, Hoyng *et al.* overexpressed various neurotrophic factors specifically in the DRG of rats, resulting in substantial improvements in axonal regeneration, as well as sensory and functional recovery[61].

Clinical trials on gene therapy using viral vectors have surged[62]. Major challenges remain: the host immune response can severely limit the duration of transfection, often requiring the concurrent use of immunosuppressants, in addition to treatment-related toxicities[62]. Nevertheless, optimism abounds as numerous gene therapies using viral vectors have gained approval for clinical use, including Lyfgenia for sickle cell disease[63], Elevidys for muscular dystrophy[64], and Roctavian for hemophilia A[65]. It may soon be a reality that gene therapy becomes available for sensory and motor reinnervation.

Implantable devices

Electrical stimulation of the proximal nerve stump may offer a promising therapeutic approach following PNI. Animal models have well-documented the beneficial effects of brief electrical stimulation. For instance, after a facial nerve crush injury in a rodent model, a single 30-minute session of electrical stimulation accelerated the recovery of eye blink and normal whisker orientation compared to controls without stimulation[66]. Others have observed similar enhancements in recovery after electrical stimulation for sciatic nerve injury[67,68] and femoral nerve repair[69].

The exact mechanism underpinning the neuronal regenerative effects of electrical stimulation remains unclear, but it is likely multifactorial. English *et al.* showed that brief electrical stimulation during surgical repair in mice significantly increased neurotrophin production in DRG neurons[70]. They also found that knocking out neurotrophins negated the regenerative effects of electrical stimulation[69]. In another study, Yan *et al.* found that electrical stimulation triggered an influx of Ca^{2+}, which enhanced the phosphorylation of cAMP response element-binding protein, leading to increased neurite outgrowth[71].

In clinical settings, researchers have attempted to integrate electrical stimulation to treat PNI. Gordon *et al.* applied brief electrical stimulation to patients undergoing surgical decompression of carpal tunnel syndrome on the median nerve and observed accelerated axonal regeneration and reinnervation in the treated group[72]. In a randomized, double-blinded study, Wong *et al.* found that brief electrical stimulation in patients with complete digital nerve transection and primary repair improved sensory discrimination in

all modalities by 6 months in the treatment group[73]. Portable external devices that provide functional electrical stimulation, such as the Bioness L300[74] and Empi 300PV[75], have also shown benefits for patients with neuromuscular weakness.

However, these treatment paradigms require either an intact nerve or primary surgical repair at the time of injury. Direct stimulation with an implantable electrical stimulator also raises concerns about infection. A recent breakthrough in the field of PNI involves using graphene-based nanomaterials. Graphene, a crystalline form of carbon known for its excellent thermal and electrical conductivity, can be engineered into a 3D scaffold for nerve reconstruction[76]. Graphene-based nerve conduits have piezoelectric properties that provide electrical currents and serve as scaffolds for axonal guidance following PNI[77]. For example, Lu *et al.* synthesized a graphene-based nerve conduit for sciatic nerve crush injury in rats and found it enhanced Schwann cell migration, adhesion, and neural regeneration, resulting in improved motor function[78]. The biosafety of graphene-based nanomaterials is still under investigation in human subjects but holds promise as a novel therapeutic option in the future[79].

Current strategies and challenges in facial nerve repair

Facial nerve injury significantly impacts patients by causing disfigurement and reducing quality of life[80,81]. Common causes include iatrogenic factors, infections, trauma, neoplasms, strokes, and other conditions. The gold standard for treatment remains primary coaptation with tensionless closure[82]. However, even under optimal conditions, the best achievable outcome with end-to-end suturing is typically a House-Brackmann score of III out of VI[83].

When tensionless primary closure is not feasible, autologous nerve grafting using the sural nerve, great auricular nerve, or saphenous nerve provides viable alternatives[82]. Among these options, sural nerve grafting is often preferred due to its fascicular topography, which closely resembles that of the facial nerve[84]. A retrospective observational study of 28 patients who underwent facial nerve repair with autologous grafting following facial nerve lesion resection reported significant improvement after 21 months, with an average gain of one grade on the House-Brackmann scale. A key area of debate in autologous nerve selection involves the use of motor and mixed nerve types versus sensory nerve types. In a rat model of tibial nerve transection, motor and mixed nerve grafts demonstrated superior nerve density and regeneration compared to sensory nerve grafts[85]. However, in a rat model of facial nerve injury, sensory and motor nerve grafts yielded comparable outcomes in nerve density and functional recovery[86]. These findings highlight the need for clinical studies comparing nerve graft types in human patients, which may provide valuable insights for optimizing facial nerve repair strategies.

Current strategies and challenges in recurrent laryngeal nerve repair

Recurrent laryngeal nerve injury frequently results from iatrogenic causes, either intentional or inadvertent, during thyroid, parathyroid, or cardiothoracic surgeries. When nerve transection occurs, many surgeons advocate for immediate primary repair[87,88]. If primary end-to-end coaptation is not feasible, alternative approaches include free nerve grafting, ansa cervicalis anastomosis[89], or vagus nerve anastomosis[90].

Despite these interventions, functional restoration of vocal cord motion remains unattainable, even with primary repair at the time of surgery[88]. Instead, reinnervation primarily preserves vocal cord tone and prevents atrophy[87]. Advances in tissue engineering are opening new possibilities for repairing and regenerating transected recurrent laryngeal nerves. For example, Wang *et al.* demonstrated the return of vocal cord motion in a rat model of recurrent laryngeal nerve injury using collagen tubes coated with neurotrophic factors, outperforming autologous grafting[91].

Sensory reinnervation in free tissue transfer

Sensory and motor recovery in complex tissue reconstruction also holds significant clinical importance. For example, in the head and neck region, restoring sensation to the neo-tongue or oropharynx can significantly affect speaking and swallowing[92]. Sensory restoration in lower extremity reconstruction can enhance mobility[93]. In phalloplasty, sensory restoration may enable erogenous stimulation[94]. Similarly, restoring tactile and thermal sensation in breast reconstruction after mastectomy can improve overall quality of life[95].

The debate continues on whether innervated free flaps yield superior outcomes, partly due to spontaneous reinnervation. Shindo *et al.* studied 18 non-innervated free flaps used in head and neck reconstruction and observed a high rate of spontaneous sensory recovery within 6 to 24 months[96]. They particularly noted significant spontaneous cutaneous reinnervation in their series. In another study, Lvoff *et al.* evaluated 40 patients with non-innervated radial forearm free flaps for head and neck reconstruction[97]. They found spontaneous recovery in 80% of the patients, though complete recovery of all sensory modalities was both unpredictable and rare. In a separate study comparing innervated and non-innervated flaps for total lower lip reconstruction, the authors found no significant difference in sensory recovery between the two groups[98]. Additionally, a systematic review of sensate flaps in head and neck reconstruction, which included 29 studies, found inconclusive evidence regarding the superiority of sensate flaps in terms of swallowing and speech outcomes[99]. However, non-innervated flaps showed a wider range of sensory recovery outcomes. Despite these findings, sensate flaps are gaining popularity in reconstructive procedures beyond the head and neck regions and are showing promising results[94,95]. The limited success of sensate flaps in the head and neck region may partly be due to the complex coordination required for speech and swallowing, which involves multiple motor and sensory inputs within the upper aerodigestive tract. Further randomized controlled trials are necessary to better understand the role of reinnervation in free tissue transfer.

Nevertheless, surgeons have several popular options for sensate flaps, including: (1) the radial forearm free flap using the medial or lateral antebrachial cutaneous nerve; (2) the anterolateral thigh flap using the lateral femoral cutaneous nerve; (3) the fibular free flap using the lateral sural cutaneous nerve or the recurrent superficial peroneal nerve; and (4) the lateral arm free flap using the posterior antebrachial cutaneous nerve, among others.

CONCLUSION

In conclusion, the field of peripheral nerve repair has evolved significantly, driven by a deeper understanding of nerve anatomy, injury mechanisms, and repair strategies. While primary nerve repair and grafting remain cornerstone techniques, emerging innovations such as NGCs, pharmacologic agents, and advanced cell-based therapies offer promising avenues for improving outcomes. Despite these advancements, challenges such as incomplete sensory and motor recovery persist, underscoring the need for continued research and development. Future directions in this field will likely focus on integrating multimodal approaches to optimize nerve repair and enhance functional recovery.

DECLARATIONS

Authors' contributions

Conceptualized and wrote the manuscript: Lee JC, Trott S, Wax MK
Created figures and tables: Lee JC
Supervised and performed the final review of the manuscript: Wax MK

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Not applicable.

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Conflicts of interest
Wax MK is an Editor-in-Chief of *Plastic and Aesthetic Research*. He is also a Guest Editor for the Special Issue *Tissue Engineering and Regenerative Medicine in Head and Neck Reconstruction*. Wax MK was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. The other authors declared that there are no conflicts of interest.

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Not applicable.

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