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Sensory nerve regeneration and reinnervation in muscle following peripheral nerve injury

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ABSTRACT

Sensory afferent fibers are an important component of motor nerves and compose the majority of axons in many nerves traditionally thought of as "pure" motor nerves.[16] These sensory afferent fibers innervate special sensory end organs in muscle including muscle spindles that respond to changes in muscle length and golgi tendons that detect muscle tension. Both play an important role in proprioception, sensorimotor extremity control feedback, and force regulation. Following peripheral nerve injury, there is histological and electrophysiologic evidence that sensory afferents can reinnervate muscle, including muscle that was not the nerve's original target. Reinnervation can occur following different nerve injury and muscle models including muscle graft, crush, and transection injuries and occurs in a nonspecific manner, allowing for cross-innervation to occur. Evidence of cross-innervation includes the following: muscle spindle and golgi tendon afferent-receptor mismatch, vagal sensory fiber reinnervation of muscle, and cutaneous afferent reinnervation of muscle spindle or golgi tendons. There are several interesting clinical applications of sensory reinnervation and cross-reinnervation of muscle including restoration of optimal motor control following peripheral nerve repair, flap sensation, sensory protection of denervated muscle, neuroma treatment and prevention, and facilitation of prosthetic sensorimotor control. This review focuses on sensory nerve regeneration and reinnervation in muscle, and the clinical applications of this phenomena. Understanding the physiology and limitations of sensory nerve regeneration and reinnervation in muscle may ultimately facilitate improvement of its clinical applications.

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INTRODUCTION

Sensory nerves and the sensory organs they innervate detect internal and external tactile, noxious, and special sensory stimuli that are critical for interactions with the environment. When the peripheral sensory nerve pathway is disrupted, such as in traumatic nerve transection or loss of sensory end organs from soft tissue injury, there is an interruption in the ability to perceive one's surroundings and to adapt in a changing environment. As a response to the damage, transected proximal axons undergo a process of regeneration and reinnervation.[1] This process is frequently incomplete, particularly when the distal sensory target is missing. Without distal sensory end organs to help direct regeneration via neurotrophic signaling and provide a target for reinnervation, regenerating axons may form neuromas or aberrantly reinnervate incorrect targets.[3]

The literature on sensory regeneration and reinnervation has been focused on cutaneous afferent nerves, which represents only a fraction of the overall sensory afferents in the peripheral nervous system. Furthermore, functional reinnervation of muscle after peripheral nerve injury has mainly focused on motor function, not sensory recovery. What is less explored is the regeneration and reinnervation of muscle sensory afferents, which provide sensory information to coordinate muscle function, regulate force and tone of muscle, modulate fine object manipulation, and facilitate the myotatic reflex. As a result, sensory afferent reinnervation of muscle is a fundamental component of rehabilitation after peripheral nerve injury. Another clinical application involves the transfer of a local sensory nerve to denervated skeletal muscle ("sensory babysitting"), which prevents muscle atrophy and preserves functional potential until motor reinnervation can occur.[9,10]

In this paper we discuss the anatomy and physiology of normal sensory innervation of muscle, the process of sensory reinnervation of muscle following peripheral nerve injury and repair, and review the potential clinical implications of these phenomenon. It is critical to have a

comprehensive understanding of the process of sensory nerve regeneration and muscle reinnervation in optimizing rehabilitation following peripheral nerve injury, neuroma treatment, development of prosthetic peripheral nerve interfaces, and sensory protection of muscle.

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METHODS

This literature review incorporated elements of the Cochrane Handbook of Systematic Reviews of Interventions standards and was written in the format provided by the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guideline.[11] A health sciences informationist developed a search strategy and tested it against a set of sentinel articles. The search included controlled subject headings (when relevant), title and abstract terms, and author supplied keywords (see Supplemental Methods). On June 3rd, 2021, we performed a comprehensive and reproducible electronic search for studies regarding sensory reinnervation of muscle in MEDLINE (via Ovid: MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions), Embase and Scopus (via Elsevier), and BIOSYS Previews (via Clarivate). No limits were applied. Duplicates were removed in EndNote X9 (Clarivate) using a modified version of the Bramer method.[12]

Eligibility assessment was performed in a standardized manner. The retrieved hits were screened and reviewed by two independent reviewers based on the title and abstract using predefined inclusion and exclusion criteria. A third reviewer adjudicated when consensus could not be reached among initial reviewers. All English-language studies including *in vitro* studies, animal studies, case reports, randomized control trials (RCT) and observational studies (cohort, case–control studies) evaluating sensory reinnervation of muscle were included. Please refer to Figure 1 for details regarding the selection process and exclusion criteria.

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The search identified 2,875 unique articles, after duplicates were removed, and screening of the references of the selected studies yielded an additional 10 hits for a total of 2,885 articles that underwent primary screening. This resulted in 270 studies that subsequently underwent a secondary screening. Ultimately, 110 original studies were included in the systematic review.

Organization and function of the sensory system

The somatosensory system allows for the perception of many sensory modalities including touch, pain, temperature, and proprioception. [13] Sensory stimuli are detected by free nerve endings and by modality-specific receptors that transduce mechanical and thermal stimuli into electrical signals.[13] Different classes of sensory afferents synapse to these receptors and carry the electrical signals to the central nervous system (CNS), which interprets the electrical input into meaningful sensory perceptions.[13]

Immunohistochemical studies have revealed that sensory fibers can be found in motor nerves, even those that have been considered "pure" motor nerves.[14,15] Maki et al showed that 60% of myelinated axons in the rat motor branch to the quadriceps femoris were sensory afferents.[16] A study of the axonal components of "pure" motor nerves of the human upper extremity demonstrated that motor efferents make up only 23% of the accessory nerve axons and 15% of thoracodorsal nerve axons while other fibers in these nerves are sensory afferents.[14] Interestingly, the percentage of afferent axons is higher for muscle groups that control greater numbers of functions (axes of movement), suggesting the importance of sensory fibers in complex motor function.

Some of the afferent fibers that travel within motor nerves innervate sensory targets within muscle.[17] Afferents innervating mammalian skeletal muscle can terminate at sensory receptors

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such as muscle spindles, golgi tendons, corpuscles, or more commonly as freely ending afferents around blood vessels, fat, and connective tissue (Figure 2).[18,19] Muscle spindles are sensory receptors located in skeletal muscle that detect changes in the length of the muscle to mediate the spinal reflex and regulate muscle length.[20] Golgi tendons sense the tension in the muscle, mediate the inverse myotatic reflex, and help maintain force levels in muscle. Muscle spindles are innervated by Ia and II afferent fibers as well as motor fibers that adjust the sensitivity of the spindle, while Golgi tendons are innervated by Ib afferent fibers.[13,21]

Given the afferent fiber predominance in the upper extremity and the rich afferent innervation of skeletal muscle, it is evident that sensory input is fundamentally important in the ability to perform complex motor tasks, and sensory-motor integration is the primary mechanism for regulating human movement.[2] Muscle spindles and golgi tendons respond to mainly proprioceptive information that guides adjustments in limb movement and positioning. [2] They are also key components of reflex pathways that are activated in response to muscle or tendon stretch, which subsequently activate several targets: motor neurons that innervate the same muscle, motor neurons that innervate synergist muscles that contribute to the same movement, and interneurons that inhibit motor neurons of antagonist muscles[8]. This allows for a phenomenon called co-activation, or agonist-antagonist activation, where opposing muscles are simultaneously activated[8]. Co-activation is important for maintaining limb positions, facilitating fast movements, and optimizing movements.[8] Due to the significant afferent sensory fiber contribution to human movement, disruption of these fibers can lead to devastating functional loss. A thorough understanding of the anatomy and pathophysiology of the regeneration and reinnervation of transected muscle sensory fibers is therefore critical to improving functional recovery after peripheral nerve injury and understanding the clinical importance of peripheral nerve repair.

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Muscle afferent regeneration and reinnervation following peripheral nerve transection

Repair of transected peripheral nerves can result in afferent reinnervation of muscle, which is intimately involved in the regeneration of intrafusal muscle fibers after peripheral nerve injury.[22] Tables 1 and 2 summarize the key evidence of muscle afferent reinnervation. In animal models, after nerve division and repair, there was significant histologic evidence of sensory reinnervation up to 84% of muscle sensory end orgaans.[19,23–27] In addition, there was electrophysiologic evidence of stretch responses in sensory reinnervated muscles that were comparable to native Ia afferents.[25,28] Reinnervation occurs even after delay of repair for up to 6 weeks post-injury, but the level of reinnervation may decrease with an increasing delay prior to repair.[29–31] In humans, transfer of intercostal nerves to the musculocutaneous nerve for brachial plexus injury generated somatosensory evoked potentials in the proximal transferred intercostal nerve. The patient experienced a concomitant pressure sensation on the chest wall with tapping of the biceps.[32] In addition, tapping the biceps induced a biceps stretch reflex, indicating that muscle afferent fibers in intercostal nerves reinnervated mechanoreceptors in the biceps.[32,33]

Unfortunately, muscle afferent reinnervation can be imperfect, which can lead to functional deficits such as poor multi-joint coordination and abnormal locomotion.[34,35] There is conflicting data on how much muscle sensory function can be restored following reinnervation. Several studies have shown significantly reduced or abnormal response to stretch and/or tendon vibration after transection and repair,[25,35–37] while others show some reinnervating afferents with successful dynamic and static responses to stretch.[25,28,38–40] Additionally, several studies show return of the reflex response, with one study demonstrating restoration of up to 70% of normal reflex contraction tension in rats.[41–43] A possible explanation for incomplete sensory recovery in muscle

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is abnormal reinnervation and ultrastructural changes in a fraction of the sensory end organs and nerve endings.[24,36,44–47] This may explain why some studies have demonstrated abnormal neural response and/or reflex muscle contraction despite evidence of successful regeneration and reinnervation.[48,49] There are many variables that may influence functional recovery following peripheral nerve injury including the level of injury, type of lesion and repair, the neurotropic/trophic environment, and the rehabilitation protocol.[50–53] However, it is unclear why some sensory end organs, nerve endings, and connections are abnormal, while others are functionally and physiologically normal. Understanding why these changes occur may identify avenues for improvement for functional recovery after muscle denervation.

Following peripheral nerve injury and repair, the capacity of sensory afferents to specifically reinnervate their original sensory organ appears to be limited. Cross-innervation occurs when one sensory afferent reinnervates a sensory end organ that is different than its original sensory end organ. The majority of studies that examined cross-innervation appear to suggest that sensory axons undergo non-specific reinnervation during the regeneration process. Studies have shown evidence of various end organ and sensory afferent axon mismatches such as muscle spindle afferents reinnervating cutaneous mechanoreceptors,[56–59] vagal sensory fibers innervating skeletal muscle (although the authors weren't specific as to whether or not the sensory fibers innervated muscle fibers or distinct sensory organs within the skeletal muscle),[60] and cutaneous afferents reinnervating muscle spindles or golgi tendons.[19,58,61] In a study of the regeneration of transected and repaired cat tibial nerve, inappropriate reinnervation of end organs by modality-different afferent fibers was found 51% of the time.[58] Cross-innervation of sensory afferents is not only limited to mismatching of muscle sensory afferents with end organs in other tissue types, but can occur between muscle afferents and different end organs within same muscle. In a different cat

model, transfer of the interosseous nerve to the flexor digitorum longus resulted in Ib afferents (normally innervating golgi tendon organs) reinnervating muscle spindles (normally innervated by Ia and II afferents).[19,23] It is important to note that despite the origin of the sensory nerve that reinnervates the end organ, the final neurophysiologic response characteristics were similar to that of the end organ, the muscle afferents [19,23] Interestingly, the histochemical properties of afferents also change with reinnervation of the new sensory end organs.[61] Only one primary study suggested specificity of sensory muscle afferents for its muscle end organs[15], but this study did not examine the cross-innervation possibility between muscle afferents axons and end organs (i.e. Ib to spindle or Ia/II to golgi tendon organs) to prove true specificity. Given the complex interplay between the nerve and surrounding microenvironment needed to support peripheral nerve regeneration and reinnervation, it is not surprising that sensory afferents can reinnervate sensory targets other than their own and may disrupt proprioceptive and reflex recovery.

Sensory reinnervation of muscle entails complex processes that are imperfect, but nevertheless possible after peripheral nerve injury. It remains unclear as to why misdirected reinnervation occurs so frequently with afferents and may contribute to functional motor and reflex impairment. If the process is better understood, we may be able to improve functional impairment after peripheral nerve injury and repair, regaining optimal motor control with improved proprioception and co-activation of agonist and antagonist muscles as described above. Interestingly, the ability of both cutaneous and motor sensory afferents to cross-innervate muscle sensory targets is likely the underlying mechanism that allows for its exciting clinical application in sensory babysitting, sensory neurotization of free flaps, and the surgical management of neuromas.

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Sensory neurotization of denervated muscle

The phenomenon of sensory cross-innervation has led to its clinical application in "sensory protection" of denervated muscle.[9] Skeletal muscle will atrophy within 3 weeks of denervation, which progresses to irreversible fibrosis by 2 years if not promptly reinnervated.[1] Due to progressive fibrosis, collagenization of the distal nerve stump, and motor endplate loss, prolonged denervation leads to both decreased reinnervation potential and poor functional recovery after nerve repair.[62–66] With the slow regeneration rate of peripheral neurons in humans (~1mm/day), there is a high risk of permanent damage to denervated muscles while awaiting reinnervation, particularly following proximal nerve injuries.[1,67] Prevention of irreversible muscle fibrosis and loss of function can be achieved with muscle reinnervation.[68] When motor nerves are not available or expendable, sensory nerves can serve as a substitute and be transferred to the denervated muscle (direct muscle neurotization) or its motor neuron stump (either by end-to-end [ETE] or end-to-side [ETS] neurorrhaphy), a concept termed sensory protection or sensory "babysitting" (Figure 3). This temporary sensory protection may prevent atrophy until definitive motor reinnervation is achieved via nerve graft, nerve transfer, or ETE nerve repair.[9,10]

Sensory protection has shown promising results. Although a few animal studies demonstrated limited success of muscle preservation with sensory protection,[69,70] most studies showed that compared to denervated control muscle, sensory protection resulted in preservation of muscle structure and mass,[62,63,71–79] as well as improved functional recovery of denervated skeletal muscle, following definitive motor reinnervation.[62,63,72,73] Histological studies show evidence of muscle architecture preservation, reduction of distal nerve stump collagenization allowing for improved regeneration of axons into the muscle, and maintenance of motor end plates.[62,64,80] Although one study has shown thickening of sensory fibers as they come in close

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proximity to motor end plates, no study to date has shown direct visualization of sensory fibers innervating the neuromuscular junction.[81] However, studies have shown regeneration beyond the coaptation site and that transferred sensory cutaneous afferents reinnervate muscle spindles, protecting those spindles from degeneration.[71,80,82,83] Furthermore, neurophysiologic recordings indicate that the reinnervated spindles respond to stretch, providing evidence of functional reinnervation and again demonstrating that the end organ provides similar neurophysiologic response despite the origin of the sensory nerve[80,82] There is no significant difference between a sensory protected muscle and a muscle reinnervated with its native nerve in the number of muscle spindles and action potentials generated in response to muscle stretch.[82] Importantly, when compared to motor reinnervation of chronically denervated control muscle, sensory protection resulted in better functional recovery following native motor reinnervation.[63] Muscle mass and functional recovery were further improved when augmented with electrical stimulation, which is thought to increase the number of regenerating sensory afferents to the muscle through altered gene expression.[84,85] Sensory protection is thought to be due to modulation of the neurotrophic environment within the muscle and in the distal nerve stump, though the specific mechanism has yet to be elucidated.[86–88] These animal studies collectively support the application of sensory protection in preservation of form and function of denervated muscle.

Though sensory protection has largely been studied in experimental models, it may have significant clinical applications, such as enhancing functional recovery following proximal peripheral nerve injuries. In a sentinel clinical case report, a patient underwent sensory nerve neurotization three months after sustaining complete sciatic nerve palsy from total hip arthroplasty.[89] The authors performed sensory neurotization of the gastrocnemius and tibialis anterior muscle with the saphenous nerve, and decompression and internal neurolysis of the sciatic

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neuroma-in-continuity. One year after surgery, the patient recovered some motor activity. He was able to perform ankle dorsiflexion through the tibialis anterior with supporting electromyography of the tibialis anterior showing an increase in the number of motor unit potentials on needle electromyograph from zero to six and an increase in the amplitude of the compound muscle action potential from 0 mV to 0.03 mV by 16 months postoperatively. The patient also had recovering proprioception of the ankle. Unfortunately, this is the only clinical example in the literature to date of sensory neurotization after a proximal peripheral nerve injury. The findings are promising and can set the stage for future clinical studies. This could have clinical application in proximal peripheral injuries such as those to the brachial plexus, in which there are long delays in motor neuron reinnervation of distal forearm and hand muscles. Prior to further clinical study, it would be helpful to optimize the sensory neurotization procedure. The optimal timing, duration and method (ETE, ETS, etc) of sensory protection are difficult to identify given the wide variability in study design and outcomes in previously published animal studies.

Sensory neurotization can also potentially be used to provide sensation to muscle flaps. Animal studies have shown that when compared to non-neurotized muscle island flaps, coaptation of a donor sensory nerve to the motor nerve of a muscle flap resulted in both improved muscle weight preservation and somatosensory evoked potentials, suggesting afferent reinnervation of both the muscle flap and skin overlying the muscle.[90] Histologic evidence of regenerating sensory nerve fibers could be traced from the coaptation to the free muscle flap and to the overlying skin graft.[71,91,92] In a series of patients who underwent microsurgical free flap reconstruction of their lower extremity, sensory neurotization of the lower extremity resulted in return of sensation that was comparable to the contralateral normal foot.[93] In a case series by Chang et al, several patients underwent either direct neurotization or sensory-to-motor neurorrhaphy of the free flap muscle

using the sural nerve, which resulted in some return of sensation to pressure, light touch, and pinprick stimuli.[94] Neurotization of the latissimus dorsi thoracodorsal nerve with a sensory nerve resulted in return of sensation in the free flap that was not reported in control patients.[95] In head and neck reconstruction, sensory neurotization of muscle flaps has also resulted in multimodal sensory return.[96] It is speculated that sensation may provide a protective function in free flap reconstruction, though the evidence is largely observational and still controversial, with some studies showing flap reinnervation without deliberate surgical neurotization.[97] Flap sensation in weight bearing areas may alert the patient when there is too much pressure or trauma to the flap, which may prevent flap breakdown and ulceration.[98–100] In oropharynx reconstruction, sensation may improve swallowing and smooth articulation.[101] Furthermore, sensory reinnervation in rats has been shown to preserve muscle flap mass.[71,102] In patients in whom flap bulk preservation is desired, such as reconstruction of pressure ulcers, sensory neurotization can help prevent free muscle flap atrophy over bony prominences.

Implications in neuroma surgery and prosthetic sensory interfaces

Sensory nerve regeneration and end organ reinnervation are influenced by many factors, including the presence or absence of a distal nerve stump and/or sensory end organs. Without a distal target to help guide regeneration, transected peripheral nerves will regenerate in a disorderly fashion into disorganized, painful, hyper-excitable masses of tissue called neuromas.[2] Definitive treatment for neuroma involves resection of the distal neuroma bulb. To prevent neuroma reformation, a multitude of interventions have been proposed including implantation into surrounding tissue (i.e. muscle or bone), nerve capping, nerve ligation, and neurorrhaphy.[103] However, these techniques have been hampered by neuroma recurrence and varying success in

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symptom improvement, which is not surprising given the continued lack of targets for the regenerating nerve fibers in the aforementioned techniques. Contemporary neuroma surgical strategies, such as the regenerative peripheral nerve interface (RPNI) and targeted muscle reinnervation (TMR), harness normal physiologic mechanisms of peripheral nerve regeneration and reinnervation by providing dennervated end organ targets within muscle for the regenerating nerve. This differs from implantation into already-innervated muscle, which does not have available end targets and therefore does not result in muscle reinnervation.[104] Additionally, unlike other neuroma procedures, RPNI and TMR have been used as neural interfaces that amplify neural signal, which is ideal for high fidelity prosthetic control.

In TMR, after end neuroma resection, the freshly resected nerve is coapted to a newly divided donor motor nerve, which provides a conduit for regenerating nerves to reinnervate the newly denervated muscle, whereas in RPNI, the distal end of a transected peripheral nerve is implanted into a free skeletal muscle graft[8]. Studies have demonstrated that both RPNI[4-7] and TMR[105-107] treat neuroma pain, even for neuromas resulting from sensory nerve injuries. RPNI's can also be used to prophylactically prevent the formation of neuromas at the time of peripheral nerve transection and/or amputation.[4]

Interestingly, TMR studies have suggested that residual donor afferents can travel through donor muscle and reinnervate the skin overlying the donor muscle, which led to the development of targeted sensory reinnervation (TSR).[10-8–110] In TSR, mixed nerves are surgically rerouted to the chest or transhumeral residual limb and can be coapted to a donor muscle nerve with subsequent reinnervation of the overlying skin.[108–111] Clinical studies have demonstrated that mechanical stimulation of the reinnervated skin evokes the perception of sensation from the missing limb in patients.[108,111,112] However, the evoked sensation lacks selectivity and stability, is unnatural

(tingling sensation instead of touch/pressure felt) and has variable somatotopic representation.[108,113–115]

Compared to TSR, the fate of regenerating afferents in RPNI is currently unknown and under investigation. As previously discussed, sensory afferents within "pure" motor and mixed motor/sensory nerves have been shown to reinnervate muscle sensory end organs that are not their natural target muscle. This would explain how electrical stimulation of median and ulnar nerve RPNI in humans can result in anatomically appropriate proprioceptive sensation in the phantom hand.[116] Collectively, this suggests that the afferents in transected motor nerves can reinnervate golgi tendon and muscle spindles in the RPNI. Afferents in transected cutaneous sensory nerves (i.e. sural and saphenous nerves) may also innervate dennervated sensory targets within RPNI as evident in our success in pure sensory nerve neuroma prevention with transected cutaneous nerve RPNI surgery in both rodent models and humans (Figure 4).[4] This conclusion is appropriate given the aforementioned cross-innervation studies, which demonstrate the ability of cutaneous sensory afferents to successfully reinnervate sensory targets within muscle. Furthermore, electrical stimulation of RPNI in two patients resulted in elicitation of rudimentary cutaneous sensations in their phantom limbs corresponding to the dermatomes of the stimulated nerves.[116] These results demonstrate the immense potential for RPNI surgery to restore meaningful prosthetic sensory feedback, and future directions will focus on developing the RPNI as the first bidirectional interface, one that can utilize sensory feedback to modulate and transmit motor commands to the prosthetic.

Conclusion

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Afferents can regenerate and reinnervate sensory end organs within muscle after peripheral nerve injury, and this reinnervation can be non-specific. When presented with sensory targets within muscle, regenerating cutaneous and muscle afferents make functional connections with sensory targets within muscle including muscle spindle, golgi tendon, and Pacinian corpuscles, which has many exciting clinical applications. A better understanding of sensory reinnervation of muscle will lead to better clinical outcomes in terms of function and motor control for peripheral nerve injury repairs and further advance the field of neuroma surgery, prosthetic development, sensory protection, and restoration of free flap when direct repair is not possible.

FIGURE LEGEND

Figure 1: Study Selection Process. Flow diagram depicting the number of manuscripts identified, retrieved, screened, and included in the final review.

Figure 2: Organization of the Muscle Sensory System. Sensory end organs of muscle fibers (free nerve endings and Pacinian corpuscles), muscle spindles (Ia and II fibers endings), and tendons (Ib fiber endings) are depicted here with a typical neuron structure.

Figure 3: Sensory Babysitting. Following muscle denervation, sensory babysitting can help prevent muscle atrophy by transferring a transected sensory nerve directly to muscle or the transected motor nerve end.

Figure 4: Sensory Nerve RPNI. A. The sural nerve is dissected and implanted into the extensor digitorum longus (EDL) muscle, creating the sensory nerve RPNI. **B.** Immuno-enabled three-dimensional imaging (iDISCO) of a sensory nerve RPNI. Neurofilament (NF200) staining reveals extensive sensory axonal branching throughout the RPNI. **C.** 3-dimensional analysis showing sensory nerve distribution through the RPNI in space.

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ABBREVIATIONS

CNS	-	Central Nervous System
ETE	-	End-to-end
ETS	-	End-to-side
PRISMA	-	Preferred Reporting Items of Systematic Reviews and Analysis
RCT	-	Randomized clinical trial
RPNI	-	Regenerative Peripheral Nerve Interface
TMR	-	Targeted Muscle Reinnervation
TSR	-	Targeted Sensory Reinnervation

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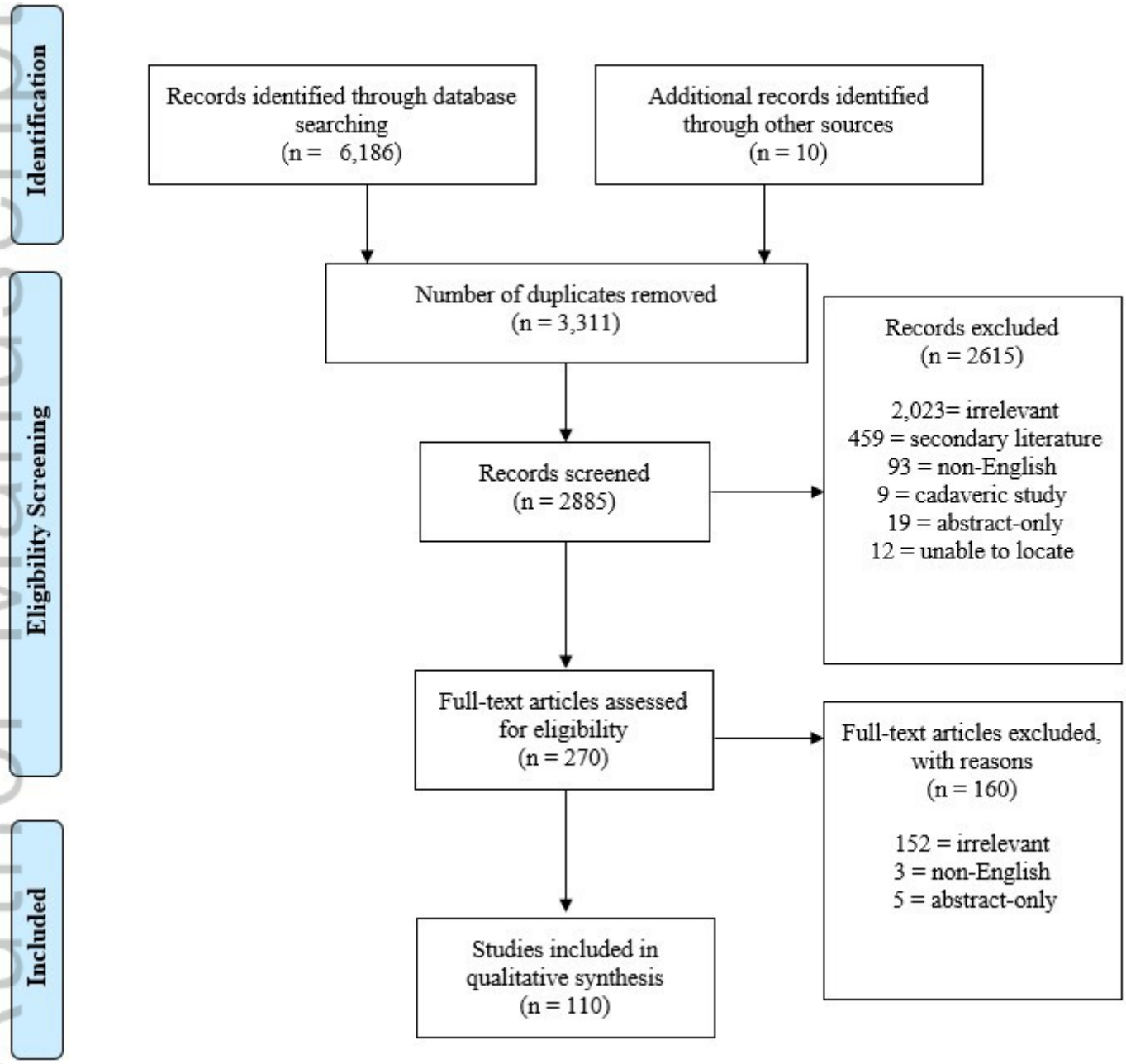
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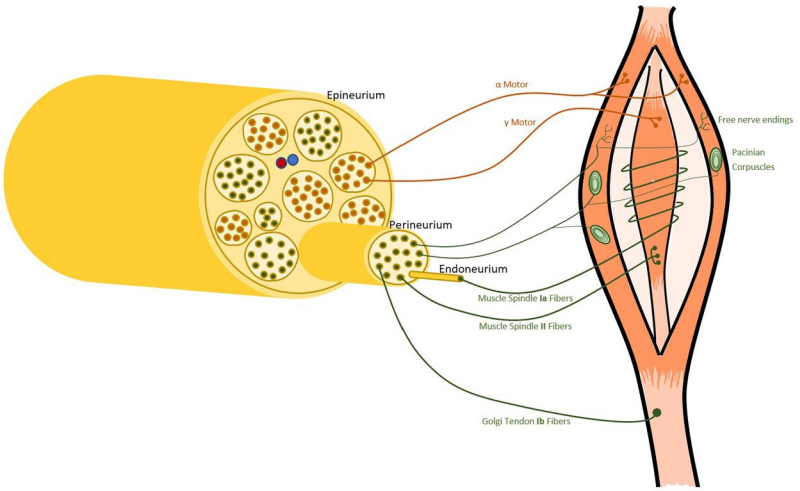
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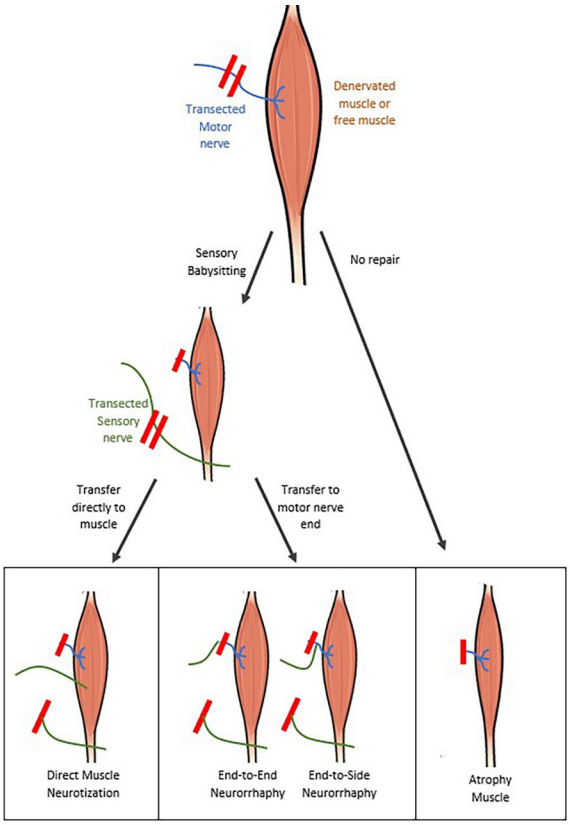
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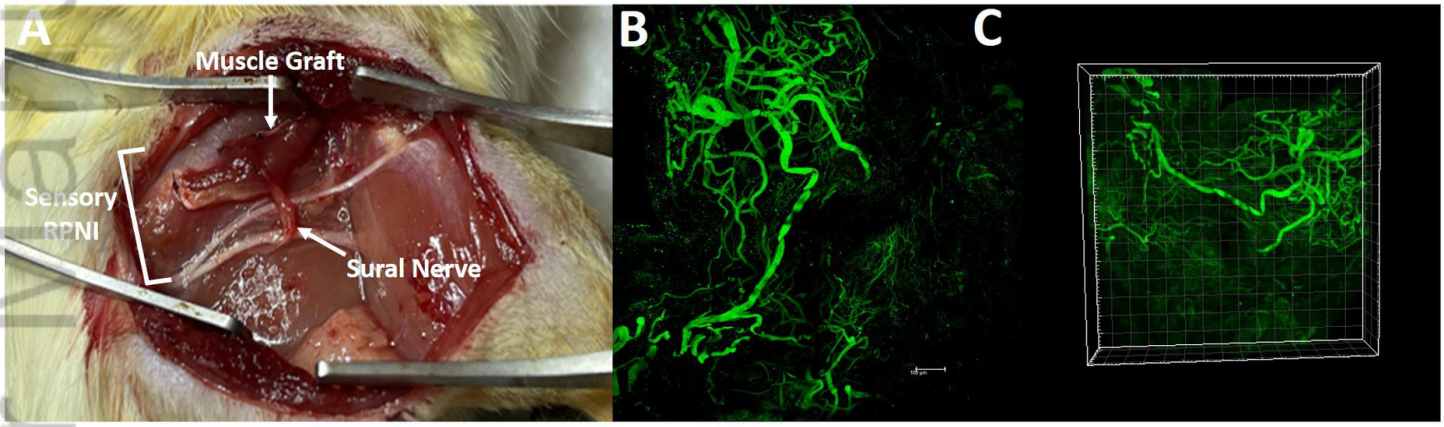
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Table 1. Histological and electrophysiologic evidence of sensory reinnervation of muscle following animal crush and transection nerve injury

Study Grouping	Histological findings	Electrophysiologic findings
Crush Injury		
Single Crush Injury	- Regeneration of nerve into muscle spindles seen first at day 25-33 after injury[45] - Normal proportion of I and II endings in spindle following reinnervation[45] - Mostly normal structure of nerve endings with abnormalities occasionally noted[44,45]	- Reduced number of afferent fibers responding to stretch than expected[43] - Improved regeneration with longer recovery time[39] - Lower compound nerve action potential (CNAP) amplitude compared to control[42] - Slower conduction velocity (CV) compared to control[42,43] **Mixed findings:** Normal[39] versus abnormal[43] response to stretch
Prolonged Crush Injury	- More abnormalities with longer denervation period[31] - Decreasing afferent innervation of receptors with longer denervation[31]	- Faster functional recovery compared to longer denervation[39] - Decreasing CV with longer denervation[31] - Decreasing proportion of normal afferent response with longer denervation[31]
Crush + Transection of Ventral roots (de-efferentation)	- More abnormalities noted at nerve ending compared to crush only[47]	- More abnormal response to stretch compared to crush only[47] - Slower CV compared to crush only[47]
Transection Injury		
Transection injury + Immediate Direct Repair	- Reduced afferent innervation of receptors than expected[24,55] - Reduced number of muscle afferent DRG cells compared to control[50] - Spindles more frequently innervated than tendon organs[23] - Frequent abnormalities noted at nerve endings[19,44,55]	- Improved regeneration with longer recovery time[19,23,28,36] - Altered proportion of I and II fibers following reinnervation[36] - Reduced number of functional afferent fibers than expected [19,23,28,55] - Lower CNAP amplitude compared to control[28,42] - Abnormal EP response to stretch[19,23,28,35,37,55] and vibration[26,36, 37] - Abnormal EP response to chemical and fatigue[36] - No functional differences between partial and complete section[19] - Reduced/abnormal[35,37] or no[25] recovery of stretch reflex than expected **Mixed findings:** Slower[19,23,28, 37, 42,55] vs. similar[36] CV compared to control
Transection + Immediate Graft Repair (silicone tube; vein and auto-graft)	- Autograft had reduced afferent innervation of receptors than expected[55] - Vein Graft had no differences in nerve ending morphology compared to direct repair[24] - Reduced number of muscle afferent DRG cells in cable and muscle graft compared to control, but similar to direct repair[50]	- Reduced number of functional afferent fibers seen in autograft compared to control[55] - Autografts[55] and silicone tube[42] had slower CV compared to control and direct repair (silicone tube had lower CNAP amplitude[42] as well) - Vein graft had lower CNAP amplitude compared to control[24] - Autograft had similar response to stretch compared to direct repair[55]
Transection + Delayed Direct Repair	- % Afferent innervation of receptor not affected by delayed repair[29]	**Mixed findings:** - % Afferent fibers that respond normally to stretch not affected by delayed repair[29] - Best afferent axon regeneration obtained after delay of 10 days[30]
Injury Comparison		

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Comparison of Crush and Transection with Immediate Direct Repair in Same Study	- Spindles reinnervation occurs after crush and transection+repair[44] - More structural abnormalities of nerve endings and slower recovery seen in transection compared to crush[44]	- Slower recovery with transection compared to crush[28, 42] Better pain sensibility recovery with crush compared to transection[42]
Specificity of nerve and end organ innervation		
Transection with Immediate Direct Repair + Field Potential for Classifying Afferent Fibers	- Regenerating afferents can regenerate into inappropriate receptors[58]	- Regenerating muscle afferent can regenerate into inappropriate receptors[23] - Random reinnervation of spindles by all muscle afferent types[23] - Specific reinnervation of muscle sensory afferent to muscle as opposed to cutaneous afferents from skin[15] - Afferent fibers that innervate inappropriate receptors don't recover normal CV[23]
Transection with Cross-Union Repair of Different Nerves (motor-motor, sensory-motor, motor-autonomic)	- Regenerating afferents can regenerate into inappropriate receptors[19] and inappropriate tissue types[61] - No difference between degree of receptor abnormality between self and cross-innervated muscle[46] - Cross-innervated muscles had less visible afferent endings compared to control[46]	- Regenerating afferents can regenerate into inappropriate receptors[19] and inappropriate tissue types[56,59,60] - Random reinnervation of spindle by different muscle afferent types[19] - Regenerated afferents can respond to inappropriate receptor[19] and tissue[56,59,60] stimulation - Regenerated afferents retain their native CV and firing characteristics despite inappropriate tissue/receptor innervation[56] with response abnormalities[19,37]

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Table 2. Histological, electrophysiologic, and behavioral evidence of sensory reinnervation of muscle following animal nerve injury, human nerve injury, and muscle graft models

Study Grouping	Histological findings	Electrophysiologic findings
Animal Muscle Graft Models (vascular supply to muscle completely disrupted and tendons severed with either nerve-intact, standard nerve-severed with reinnervation, or nonreinnervated grafts)	- Spindle death with surviving capsule seen initially after muscle injury[22, 27] - Spindle regeneration occurs w/o nerve innervation[22, 27] - Morphologic and histochemical abnormalities in regenerated spindles after muscle injury[22] - Reduced innervation of spindles than expected after muscle and nerve injury[22,38]	- Decreased number of normal stretch receptors compared to contralateral control[38] - Nerve-intact graft had more active stretch receptors compared to standard graft[38] - Abnormal stretch response in regenerated spindle after muscle and nerve injury[38]
Human Studies (musculocutaneous nerve sutured to intercostal nerve)		- Evidence of muscle sensory reflex preservation (and thus reinnervation of mechanoreceptors by afferent fibers) through EMG[32,33,89] and EEG[32,33] evaluation after tapping reinnervated muscle
Behavioral testing findings		
Animal Nerve Injury Models	- Full functional recovery after crush injury[41, 51] assessed by number of slips while traversing balance beam[51] and knee-jerk response via testing contraption[41] - No or minimal functional recovery after transection and repair injury[34,41] assessed by level and ramp walking[34] and knee-jerk response via testing contraption[41]	