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Opinion

Innovating innervation: how non-biological targets can revolutionize amputation care

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Abstract

Amputation is a historically well-grounded procedure, but such a traumatic operation invites a litany of postoperative complications, such as the formation of agonizing neuromas. Developments in mitigating these complications include the clinically successful targeted muscle reinnervation (TMR) and regenerative peripheral nerve interface (RPNI), which showcased the potential for utilizing peripheral nerves' regenerative capabilities to circumvent neuroma formation and isolate neural activity for control of a sophisticated prosthetic device. Nevertheless, these techniques only record the aforementioned neural activity from the reinnervated muscle, not the nerve itself, which may ultimately limit the degree of functionality they can restore to amputees. Alternatively, regenerative sieve electrodes are non-biological end targets for reinnervation that utilize their porous structure to isolate regenerating axons into discrete transient zones lined with stimulating and recording electrodes. Albeit more invasive, such direct contact with the once-damaged nerve opens the door for highly selective, bi-directional neural interfaces with the capacity to restore higher degrees of sensorimotor functionality to patients for enhanced rehabilitation outcomes. By expanding the definition of innervation to include non-biological targets, clinicians can make room for these advancements in neural interfacing to revolutionize patient care.

INTRODUCTION

The amputation of a limb represents one of the oldest surgical procedures in medical history. In recent years, rapid advances in biomechanics and prosthetic technology have ushered in a new era of innovation for amputation procedures[1]. We have seen a paradigm shift from a focus on limb salvage to limb reconstruction that prioritizes the care of peripheral nerves, residual bone, and muscle to reduce post-amputation pain and improve prosthetic control[2-4]. From a reconstructive surgery perspective, the focal point of innovation for amputation has been the prevention and treatment of terminal neuromas. Terminal neuromas are non-tumorigenic, bulbous masses that form at the distal end of amputated nerves in a vain attempt to reinnervate the now absent distal target. As one of the most common sequelae accompanying amputation, the prevention and treatment of terminal neuromas have historically been described as unsatisfactory[5,6]. To address these complications, surgeons have sought to identify new targets for transected nerves. Their search produced novel techniques such as targeted muscle reinnervation (TMR) and regenerative peripheral nerve interface (RPNI), which resolve the problems of nerve transection by embedding the transected nerve end into muscle. This coupling of biologically compatible tissues provides the damaged nerve somewhere to go and something to do[3,4]. In addition to circumventing painful neuroma formation, the newly innervated muscle amplifies neural signals, providing an opportunity to record efferent motor activity via electromyography (EMG) and translate it into commands for a coupled prosthetic device. Both TMR and RPNI rely on the innate regenerative capacity of nerves to innervate new biological targets. The term innervation generally means to supply an organ or tissue with nerves, but do terminal targets need to be biological in order to form functional units? In the digital age, we have the technology to provide advanced robotic limb substitutes and the neural interfaces to control them, and so the philosophical question becomes: what constitutes innervation in the 21st century? In this opinion piece, we explore the concept of innervation as it relates to the field of neuroprosthetics, and the integral roles plastic surgeons may play in innovating innervation.

DISCUSSION

One class of devices capable of redefining innervation is the regenerative sieve electrode Figure 1. Like TMR and RPNI, sieve electrodes rely on axonal regeneration; however, rather than form functional neuromuscular junctions or cutaneous sensory receptors, sieve electrodes allow axonal regeneration through porous electrodes Table 1. These porous electrode structures enable greater isolation of axons into separate channels for highly selective recording and stimulation Figure 2[7,8]. Maximization of axonal contact cements this class as the most selective electrodes available, with improvements such as double layering allowing for upwards of 64 recording channels for even greater specificity[9]. Implementing guidance materials with cuff electrode functionality bolsters interface stability and selectivity[10]. Additionally, contemporary sieve electrodes boast substantial chronic viability; their thin polyimide build is highly flexible, reducing the risk of axonopathy commonly seen in their silicon variants[11]. Incorporating polyimide significantly reduced the immune response to the electrode with no signs of inflammation at 12 months of implantation in a rat model[12]. Once supplied with nerves, these electrodes can chronically interface with the user's nervous system to actuate a sophisticated prosthesis[10]. This formation of long-term functional neural connections with a synthetic target contends with the current definition of innervation, which holds the distal site of reinnervation to be exclusively biological.

Regenerative sieve electrodes have demonstrated a trajectory of increasing selectivity and stability, but implantation’s predication on the transection of an intact nerve categorizes these electrodes as the most invasive. This categorization is symptomatic of experimental methodology, which evaluates invasivity via traditional neurorrhaphy models, comparing repair methods restoration of function to an intact limb[13]. While nerve transection is a prerequisite to regenerative electrode application, in an amputation and neuroma repair model, neurotmesis would have already occurred, significantly reducing the invasivity of electrode implantation. Srinivasan *et al.*[14]. validated the chronic viability of regenerative electrodes in a rat amputation model, exhibiting spontaneous, sensory-evoked, and electrically evoked action potentials in the sciatic nerve at five months. However, electrode implantation is not without risk, and despite the improved

Table 1. Summary of neural interfaces for prosthetic control that rely on nerve regeneration for prosthetic actuation

Method	Interfacing tissue	Functionality	Versatility for neural interfacing	Summary
TMR	Skin	Motor	Upper Limb	The terminal end of a transected nerve reinnervates the intact proximal muscles. High-density surface EMG electrode grids enable the recording of motor unit activity across 64 channels
RPNI	Skin Or Muscle	Motor and Sensation	Upper and Lower Limb	The transected nerve is divided into several subunits, each reinnervating a muscle graft harvested from a proximal donor site. This biological PNI can be recorded or stimulated using transcutaneous or percutaneous electrodes. The number of available recording and stimulating channels is defined by the number of nerve subunits and the interface method
Sieve electrode	Fascicles	Motor and Sensation	Upper and Lower Limb	The flat, porous structure of sieve electrodes presents discrete microchannels to isolate regenerating axons of the transected nerve. Double-layering allows for 64 channels capable of recording and stimulating specific fascicles

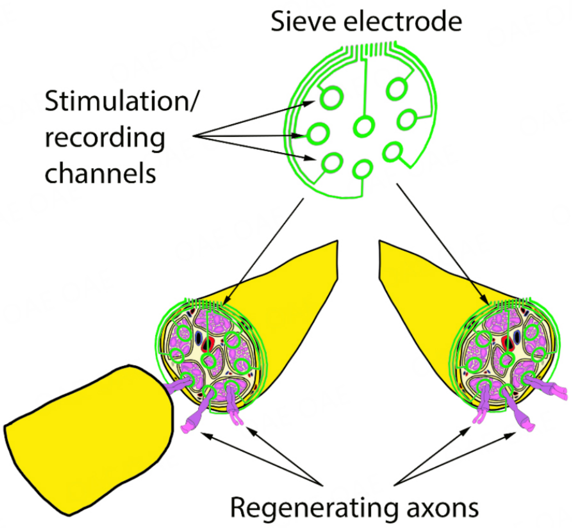

Figure 1. Sieve electrodes contain multiple stimulation/recording channels with sufficient transit zones to allow axonal regeneration through, in both nerve coaptation (left) and amputation (right) models.

flexibility of polyimide electrodes, micromotion can still erode signal fidelity and damage native tissue[15,16]. Additionally, any chronic implant can incite a harmful immune response[16]. Millevolte *et al.*[17]. utilized surgical techniques to circumvent these mechanical limitations, housing sieve electrodes in the medullary canals of rabbits. Their Osseointegrated Neural Interface (ONI) generated somatosensory cortical responses at 12 weeks and improvements in recorded signal amplitude between weeks 3 and 5[17]. Overall, sieve electrodes present an exciting avenue for peripheral nerve interfaces, but their clinical implementation will require refined surgical methodology.

The formation of functional connections between regenerative electrodes and damaged nerves to actuate robotic prostheses with high selectivity exemplifies the potential for nerves to innervate non-biological targets. If neural interfacing technology maintains this trajectory, these increasingly sophisticated devices will become progressively more relevant to plastic and reconstructive surgeons, who work with patients near the incidence of injury and often before any of these hypothetical devices would see implementation. While the technology for such devices is available, a defined surgical approach would facilitate their clinical application. To accommodate this forthcoming innovation, we posit expanding the definition of

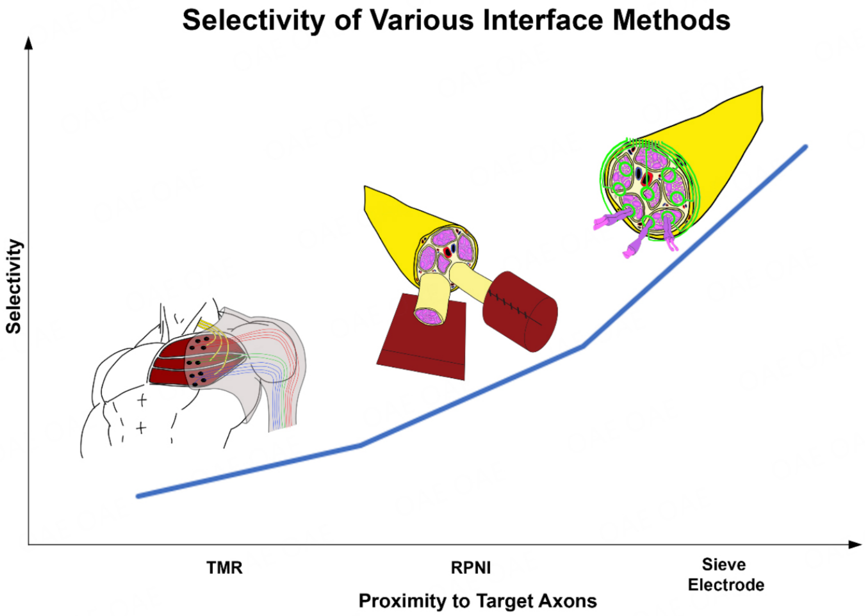

Figure 2. Graphical representation of how a neural interface's proximity to the relevant neural tissue impacts the selectivity of that neural interface. Selectivity is improved from complete nerve transfer in TMR to the fascicular level in RPNI up to the axonal level in sieve electrodes.

innervation to reach outside the boundaries of biology.

DECLARATIONS

Authors' contributions

Manuscript drafting: Sears LA, Donnelly DAT, Zeng WF, Dingle AM
Concept and figure creation: Dingle AM

Availability of data and materials

Not applicable.

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Conflicts of interest

Dr. Aaron M. Dingle and Dr. Weifeng Zeng are Junior Editor Board members of the *PAR* Journal. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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