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Case study of an amputee regaining sensation and muscle function in a residual limb after peripheral nerve stimulation by intense focused ultrasound

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Standard amputation surgery places the distal transected nerve ending in soft tissue to minimize pain from external pressure. Despite this, nerve-related pain often occurs due to a variety of peripheral and central sources [1]. Targeted muscle reinnervation (TMR) connects the distal transected nerve to a neuromuscular junction in the residual limb during amputation surgery in order to facilitate myoelectric prosthesis use and to reduce the incidence and severity of neuroma-related pain [2]. During a study to determine the relative sensitivity to external stimulation of transected nerves after standard amputation versus TMR, we encountered a single participant who recovered motor and sensory function of their tibial nerve after TMR surgery during ultrasound stimulation of the nerve.

We used intense focused ultrasound (iFU), delivered under real-time ultrasound image guidance, to stimulate at or near the distal tip of major transected nerves in amputated limbs

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Author contributions

Ezeokeke CK [validation, formal analysis, investigation, visualization, data curation, writing], Bobola MS [validation, formal analysis, investigation, resources], Selby M [validation, formal analysis, investigation, data curation], Ko JH [methodology, investigation], Friedly JL [investigation, methodology, writing, funding acquisition], Mourad PD [conceptualization, methodology, validation, investigation, writing, supervision, project administration, funding acquisition].

Declaration of competing interest

All authors declare that they have no financial interests or any other conflict of interest with other people or organizations that could inappropriately influence this work.

following a previously described protocol [3,4]. In this way we determined the minimum iFU intensity capable of generating a first discernable sensation through use of a ramp-up paradigm that started at low intensity values and increased until we achieved that aim or reached the maximum intensity value of our device.

We obtained University of Washington Institutional Review Board (IRB) and military Human Research Protection Office (HRPO) approvals for our study. All participants in the study provided informed consent. The participant in question had a below-knee amputation in March of 2003 due to posttraumatic arthritis, then a surgical revision in February of 2016 using TMR to address three painful neuromas in his residual limb, one for each of the peroneal, tibial and sural nerves. Prior to his participation in our study in February of 2017, our participant reported his inability to contract his lateral gastrocnemius muscle to which the tibial nerve was connected via the lateral motor branch of the gastrocnemius nerve using the TMR procedure (Fig. 1a). He also could not detect sensations from the posterior portion of his leg — that associated with the site of tibial nerve implantation. This lack of motor and sensory function of the tibial nerve persisted for the entire twelve months after TMR surgery until the day of our study. Together, this impaired his ability to effectively use his standard, below-knee prosthesis. The participant reported normal motor and sensory function associated with the other transected nerves. We verified these self-reports through palpation of muscle during voluntary movement by the patient and our formal, single-blinded cutaneous stimulation of the residual limb.

iFU stimulation of his non-functioning tibial nerve under ultrasound image guidance (Fig. 1b) with sufficient spatial peak temporal average intensity (71.5 W/cm^2, 2.0 MHz, for each of five individual pulses of 0.1 second in duration, spaced 1—2 seconds apart) produced corresponding transient pulses of phantom limb sensations, the first time the participant had felt sensations of any sort associated with his tibial nerve since his TMR surgery. We continued the study but, because of his surprise, we used a lower iFU intensity value (66.5 W/cm^2), doing so within 1 min of the previous stimulation that generated phantom limb sensations. By the third of five iFU pulses at that intensity, we directly observed with ultrasound imaging involuntary movement of the lateral gastrocnemius muscle. Within approximately 10 s and without additional stimulation, there followed voluntary movement of that muscle by the participant that we directly observed along with his reported ability to detect cutaneous stimulation which we verified as above. During the next 45 minutes we continued the study, for example successfully stimulating his transected peroneal nerve at a comparable intensity value as for the tibial nerve (66.5 W/cm^2). Up to and including the time the participant left our facility, he reported voluntary control of and sensations associated with his lateral gastrocnemius muscle. Regrettably we have lost the participant to follow up, so do not know the long-term outcome of this apparent reanimation of his tibial nerve.

Several published reports document the ability of ultrasound to stimulate already functioning peripheral nerves [3–7] and activate (as well as inhibit) brain with ultrasound [8]. One case study [9] reported substantial activation of a patient’s brain associated with ultrasound application after prolonged minimal consciousness. Specifically, Monti et al. [9] directed transcranial ultrasound to the thalamus of a patient whose traumatic brain injury led to 19

days of prolonged loss of consciousness. At the time of ultrasound delivery the patient had attained a minimally conscious state [10]. Three days after ultrasound delivery, the patient demonstrated significantly increased voluntary behavior consistent with emergence from a minimally conscious state; by five days post-ultrasound the patient tried to walk. In our case and theirs, at most minimally functional but structurally connected nervous system tissue started to function after delivery of ultrasound. In our case, this occurred moments after delivery of sufficient ultrasound to a major peripheral nerve, which feeds via the thalamus into the motor and sensory cortices. In their case, this occurred days after delivery of sufficient ultrasound directly to the thalamus. Monti et al. [9] may have derived inspiration for their effort by Yoo et al. [11], who observed acceleration out of an anesthetized state by rodents caused by ultrasound delivered to the rodent's thalamus. Yoo et al. [11] and Monti et al. [9] directly stimulated thalamus using non-invasively delivered ultrasound with results analogous to those achievable by deep brain stimulation of the thalamus of patients with disordered consciousness, as discussed in Yoo et al. [11]. Referring to the mesocircuit hypothesis of Schiff [10] and the discussion of Yoo et al. [11], we hypothesize that we activated a previously dormant thalamus/cortex circuit via our stimulation with iFU of the mixed motor/sensory tibial nerve.

We report here the first observation known to us of ultrasound stimulation causing a non-functioning peripheral nerve to recover its function. Through direct activation of a major peripheral nerve with iFU we hypothesize that we stimulated the thalamic/cortical circuit thereby entraining central function that supported tibial nerve function. Our observation may therefore have conceptual overlap with that of Monti et al. [9] and of Yoo et al. [11] in that all three studies demonstrated activation of a previously non-functioning nervous system circuit, through direct (as in Monti et al. [9] and Yoo et al. [11]) or indirect (our case) stimulation of the thalamus.

Our case report joins a burgeoning field demonstrating that ultrasound can activate the peripheral as well as the central nervous systems, with clinical applications of this phenomena in the early stages of exploration.

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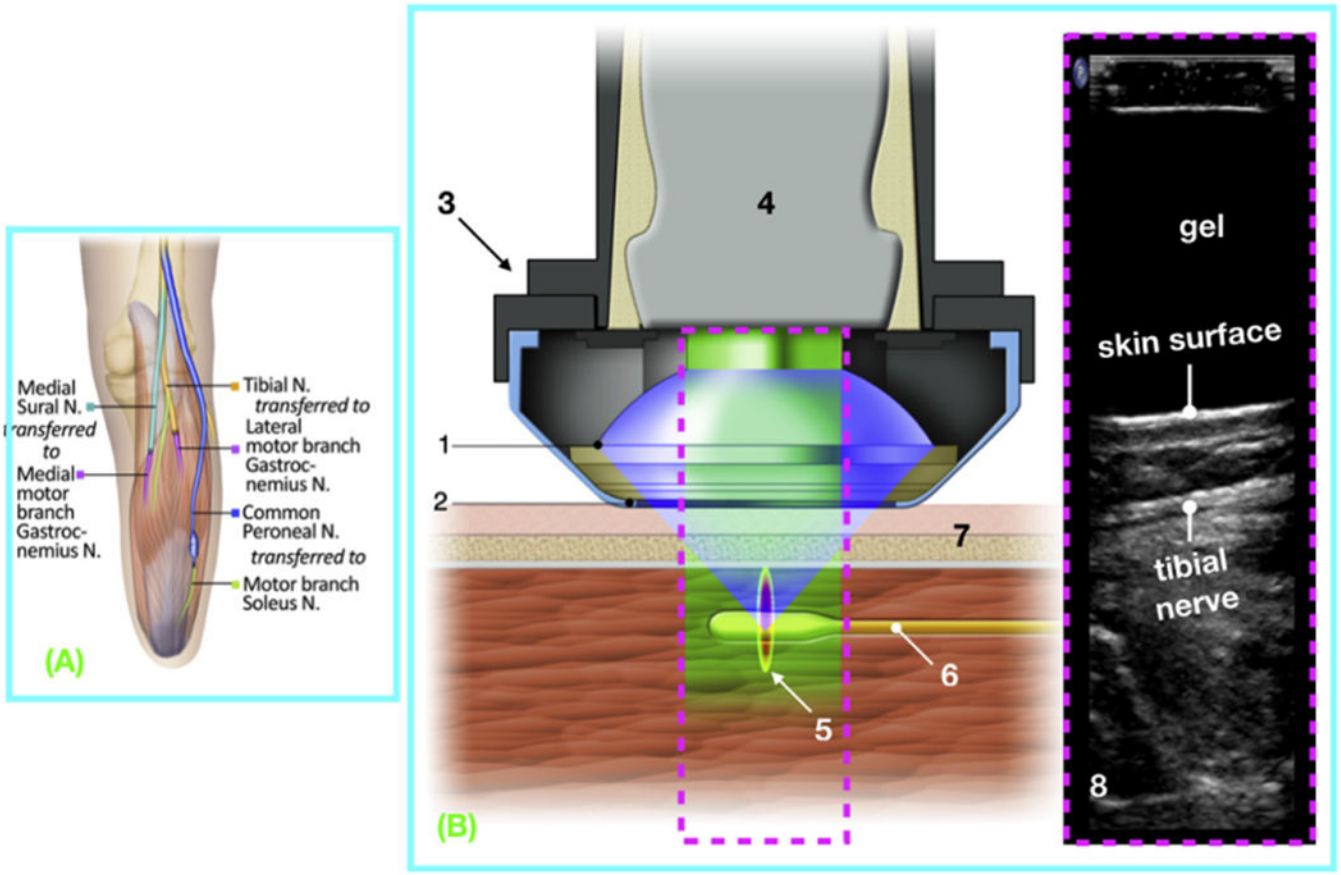

Fig. 1. Experimental target and setup.

(A) Schematic of the test subject's major peripheral nerves in his residual limb. We targeted the distal aspect of the tibial nerve for stimulation by intense focused ultrasound. This schematic also shows the other nerves that had undergone the TMR procedure, with a neuroma at the distal end of the common peroneal nerve. **(B)** Schematic of the experimental procedure using an ultrasound system (#1 {iFU transducer}, 2 {gel pad, which couples the transducer to skin}, 3 {mounting system}, 4 {diagnostic ultrasound scan head}) that puts the ultrasound focus (#5) on the tibial nerve (#6) below the skin (#7) using ultrasound image guidance (#8).