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Review

Millimetric devices for nerve stimulation: a promising path towards miniaturization

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Abstract

Nerve stimulation is a rapidly developing field, demonstrating positive outcomes across several conditions. Despite potential benefits, current nerve stimulation devices are large, complicated, and are powered via implanted pulse generators. These factors necessitate invasive surgical implantation and limit potential applications. Reducing nerve stimulation devices to millimetric sizes would make these interventions less invasive and facilitate broader therapeutic applications. However, device miniaturization presents a serious engineering challenge. This review presents significant advancements from several groups that have overcome this challenge and developed millimetric-sized nerve stimulation devices. These are based on antennas, mini-coils, magneto-electric and opto-electronic materials, or receive ultrasound power. We highlight key design elements, findings from pilot studies, and present several considerations for future applications of these devices.

Key Words: biomedical engineering; deep brain stimulation; electrical engineering; electrical stimulation; neuromodulation; peripheral nerve stimulation

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Introduction

"Electroceutical" interventions that stimulate the nervous system are revolutionizing modern medicine (Charthad et al., 2018). Stimulation devices that target the central nervous system (deep brain stimulators, epidural electrical stimulators) have shown significant promise for several neurological conditions (Thompson et al., 2014). Similarly, nerve stimulation (NS) devices in the peripheral nervous system have demonstrated efficacy across an ever-expanding catalog of disorders, including various chronic pain conditions (Chakravarthy et al., 2016), nerve repair (Willand et al., 2016) and spinal cord injury (Dorrian et al., 2023). NS devices can also target cranial nerves, with vagal NS demonstrating efficacy for epilepsy and depression, among other conditions (Howland, 2014). Despite these successes, the rapid uptake of NS interventions has revealed several shortcomings. Current devices are relatively large and complicated, necessitating invasive surgical implantation (Singer et al., 2020; Silverå Ejneby et al., 2022). Further, devices receive power via internal pulse generators, which require periodic replacement and can be subjected to failure due to lead damage (Banks and Winfree, 2019). These factors limit their clinical applications and prompted several research groups to explore and develop smaller devices.

Although smaller devices can facilitate broader applications and less invasive implantation methods, miniaturization presents a significant engineering challenge (Joung, 2013). A smaller device can be created by removing implanted wires and power sources. However, this requires an external, wireless power source coupled to the device (Long et al., 2021). The power source must traverse various tissues to reach the target nerve while remaining within safety limits for human applications (Thimot and Shepard, 2017). Furthermore, the device must incorporate specific components to convert this power into an electrical signal that can stimulate nervous tissue (Singer et al., 2020).

Despite these drawbacks, researchers have recently developed wireless devices that remain in the millimetric size range. Whilst a clear definition of millimetric is not widely agreed on in literature, we consider devices "millimetric" if their main dimensions (length, width, and depth) are in the millimeter-size range or below. These devices are primarily based on antennas, mini coils, magneto-electric and opto-electronic materials, or are ultrasound-powered (**Figure 1**; Yitzhak-David and Rotenberg, 2023). While such devices are in their infancy and face several hurdles, they have accelerated the path towards miniaturization. This review explores fundamental developments in millimetric NS devices, highlighting design elements, findings from pilot studies, and key considerations for future development and applications.

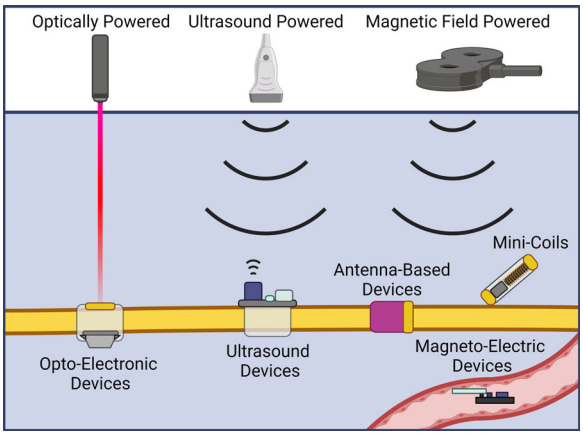

Figure 1 | **Overview of key millimetric nerve stimulation devices.**
These include devices that are powered by light (opto-electronic devices), ultrasound (ultrasound devices), or magnetically powered (Magneto-Electric devices, Mini-Coils, Antenna-based devices). Created with BioRender.com.

Data Sources

Our search strategy aimed to identify several state-of-the-art NS devices within the millimetric size range. We employed a variety of databases, including PubMed, Google Scholar, and Scopus, using keywords such as "Nerve Stimulation", "Peripheral Nerve Stimulation", "Electrical Stimulation", "Neural Stimulation", "Peripheral Nerves", "Millimetric", "Miniature" and "Wireless". The authors then screened articles for relevance and selected seminal papers that have significantly progressed the field.

Magnetically-Powered Devices

These devices receive power through an externally generated magnetic field; remarkable examples are magneto-electric, mini-coil, and antenna-based devices.

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Magento-electric devices

Magneto-electric (ME) devices achieve miniaturization through the use of ME materials. ME materials possess an impressive capability: they can energize miniature neural stimulators using magnetic energy, effectively spanning low to high frequencies. These materials, somewhat akin to inductive coils, accomplish this feat by transforming a magnetic field into an electric field through a mechanical interplay between specific layers within a thin film (Alrashdan et al., 2021). The film typically consists of a magnetostrictive layer (typically Metglass) and a piezoelectric layer (typically lead zirconium titanate, PZT). In this process, the magnetic film induces a deformation in the magnetostrictive layer as it aligns with the magnetic dipole of the film. This deformation subsequently applies a mechanical strain onto the piezoelectric layer, generating an electric voltage that stimulates the nerve (Singer et al., 2020). By leveraging this mechanism, ME materials can operate with weak magnetic fields of around a few milli-Tesla without the miniaturization constraints that coils face. The Robinson group has pioneered the development of ME devices for central and peripheral stimulation (Singer et al., 2020; Chen et al., 2022).

Singer et al. (2020) demonstrated proof-of-principle for ME neural stimulation by developing a device for deep brain stimulation (DBS) in freely moving animals. The device comprised two ME films (fabricated using Metglass and PZT) of different sizes (4.3 × 2 mm and 5.4 × 2 mm) and, hence, different resonation frequencies. This principle allows for biphasic stimulation by alternating the magnetic field frequency between the resonance of the two films. This allows the device to safely operate at high frequencies (> 500 Hz) without accumulating charge, making it suitable for DBS interventions that often have a therapeutic range of 100–200 Hz. These films were connected to a circuit, wired to a stereotrode, and packed in an epoxy-coated plastic shell that facilitated implantation on a rat's skull. The device also included a small bias magnet that balanced the charge between the two stimulation phases.

Singer and colleagues demonstrated device efficacy for DBS in a hemi-Parkinsonian rat model. Rats that received DBS (200 Hz biphasic pulses for 1-minute periods) performed significantly better in an amphetamine-induced rotation test that examines functional deficits in rodent Parkinson's disease models. A subsequent place-preference experiment confirmed device efficacy, with rats spending significantly more time beneath an active coil (ON resonance) than an inactive control coil (OFF resonance) (Singer et al., 2020).

Building upon this success, Chen et al. (2022) developed the MagnetoElectric-powered Bio-ImplanT (ME-BIT), a ME device specialized for stimulating peripheral nerves (**Figure 2**). Similarly to Singer et al. (2020), the ME-BIT device comprises an ME film, which receives power from an external magnetic field transmitter. However, the transmitter also functioned as a data transfer method for this device. Alternating the applied field between three frequencies (345, 350, and 500 kHz) adjusts the voltage amplitude received by the film. A custom integrated circuit then interprets this change in voltage as digital data and programs the shape (monophasic/biphasic), amplitude, pulse width, and delay of stimulation. The size of the ME-BIT (1.75 mm × 5 mm, 0.3 mm thick) allows it to be delivered endovascularly through a minimally invasive catheter, meaning that implantation does not require an open surgical procedure.

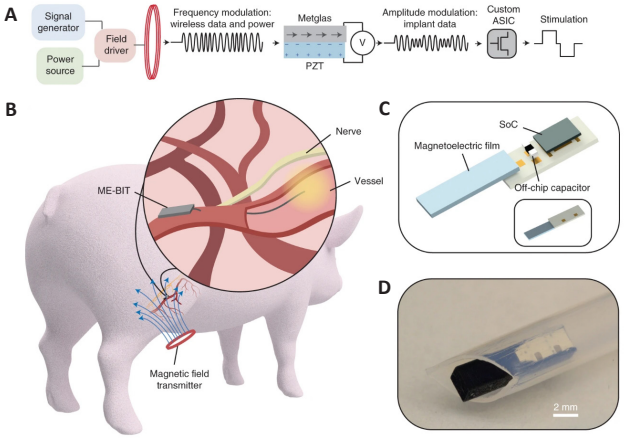

Figure 2 | **The ME-BIT device developed by Chen and colleagues.**
(A) Overview of the complete ME-BIT system, highlighting frequency modulation via the magnetic field driver, which modulates data and power received via the implant to program stimulation. (B) Rendering of endovascular implantation of the ME-BIT for NS in a pig. (C) Overview of the ME-BIT device highlighting major components, including Magneto-electric film, an off-chip capacitor for energy storage, and the integrated circuit (SoC – System On Chip). (D) Fully encapsulated device packaged within a clear sheath that facilitates endovascular deployment. Reproduced and modified (re-formatted labels) with permission from Chen et al. (2022). Custom-ASIC: Custom Application Specific Integrated Circuit; ME-BIT: MagnetoElectric-powered Bio-ImplanT; PZT: lead-zirconium titanate; SoC: System On a Chip.

Chen et al. (2019, 2022) tested device functionality by implanting the ME-BIT mote directly on the rat sciatic nerve. Wireless powering of the ME-BIT evoked compound muscle action potentials (CMAPs) in the plantar muscles and produced observable leg kicks, indicating successful nerve stimulation via the device. Further, a modified version of the device could stimulate the femoral nerve of a pig after implantation in the femoral artery. While this required an invasive surgical procedure, this finding provides proof-of-principle for endovascular deployment and stimulation.

Considerations for ME devices

The properties of ME materials facilitate the fabrication of millimetric devices capable of delivering electric pulses to nervous tissue. Advantageously, these devices have a high tolerance for misalignment. Indeed, simulations of Chen et al. (2022)'s ME-BIT suggest that the device can tolerate ~3 cm of translational misalignment at a 3 cm implantation depth and maintain > 40% of maximal voltage at a 90° angular rotation. Further, the relatively low magnetic field strength (< 1 mT) required for device function makes wearable transmitters a possibility (Alrashdan et al., 2021). Such advantages make ME devices a possible option for clinical and in-home use. The potential for endovascular implantation is also a considerable strength. While alternative millimetric devices are minimally invasive compared to current practices, at this stage, they still necessitate an open surgical procedure with inherent risks. Endovascular implantation would facilitate low-risk device deployment with minimal recovery time and would be particularly beneficial to stimulate nerves that are anatomically challenging to target without invasive surgery (Fan et al., 2020).

Despite these advantages, endovascular implantation requires further investigation before it can be considered viable. Notably, the safety of long-term implantation within the vasculature requires thorough investigation, given the risk of thrombosis development (Fan et al., 2020). While adjunct blood-thinning intervention may overcome this issue, this may not be possible for all clinical scenarios, limiting device applications. Further safety concerns are associated with device failure and whether retrieval could be achieved through minimally invasive methods or require invasive surgical procedures, diminishing the benefits of endovascular implantation. Hence, future studies should explore minimally invasive methods for device removal.

A further limitation of ME devices is that they typically use PZT as the piezoelectric layer. While PZT can generate a high power output compared to other piezoelectric materials, the materials make these devices potentially hazardous and unsuitable for long-term implantation (Chen et al., 2019). Chen et al. (2022) acknowledged this concern, highlighting that future studies could investigate a hermetically-sealed capsule for the ME-BIT. Indeed, Singer et al. (2020) encapsulated their ME films with Parylene-C and packaged the device in an epoxy-coated plastic shell. While the primary purpose of encapsulation was to protect the ME films and circuits from the biological environment, it may also protect the body from these toxic components and improve biocompatibility (Singer et al., 2020).

Nonetheless, alternative piezoelectric materials would be worthwhile investigating. For example, Chen et al. (2019) recently developed a biocompatible, lead-free piezoelectric film (Group III-Nitride) with comparable performance to lead zirconium nitrate. Natural piezoelectric materials are also a significant research area and would vastly improve the biocompatibility and biodegradability of implantable devices (Deng et al., 2022). Despite these considerations, the promising advantages of ME devices are apparent and warrant intensive investigation.

Mini-coils

Like magneto-electric devices, mini-coils use an external magnetic field to deliver NS or wireless power. Mini-coils work on the principle that a time-variable electric current flowing through a coil of wires will generate a time-variable magnetic field that can cause neural stimulation (Yitzhak-David and Rotenberg, 2023). This principle has allowed for the development of transcranial magnetic stimulation (TMS), which uses large external coils for brain stimulation. However, the size of these coils limits applications, and they are not effective for stimulating deep tissue. Further, TMS coils lack spatial resolution, limiting their applications for targeting specific nerves or superficial brain regions (Bonmassar et al., 2012). Mini-coils of sub-millimetric size would improve spatial resolution and allow for direct, targeted stimulation of deeper structures.

In 2012, Bonmassar et al. provided proof-of-principle experiments for mini-coils, demonstrating through computer modeling that they can produce an electric field capable of stimulating nervous tissue. Electrophysiological experiments confirmed their modeling and showed that neural activity could be evoked in retinal ganglion cells via a mini-coil, highlighting device efficacy. Later, in 2019, Colella et al. utilized flex circuit technology to devise a figure-of-eight micro coil (30 mm) suitable for use on humans. Tests carried out on the peripheral nervous system of healthy participants demonstrated that the mini-coil could generate an electrical field (~0.6 V/m) in the radial nerve direction and trigger somatosensory nerve action potentials when positioned over the nerve (Colella et al., 2021).

While Colella's external mini-coil can directly stimulate nerves, Freeman et al. (2017) developed an implanted mini-coil device powered via an external magnetic field transmitter for indirect stimulation. The device consisted of a 150-turn coil of wire wrapped around a nickel-zinc ferrite core to receive power, a tuning capacitor, and a diode and shunt capacitor for rectification.

The circuit is attached to two platinum disk electrodes that deliver stimulation. The device was encapsulated in epoxy to allow implantation, ensuring the electrodes remained exposed. An external transmitter was positioned 7.5 cm above the device to provide wireless power. Successful NS was demonstrated by implanting the device on the rat sciatic nerve, placing the cathode on the epineurium and anode adjacent to the muscle. Stimulation (1 ms pulses, 50 Hz, 250 ms) produced a visible hindlimb movement with a displacement of > 10 mm, highlighting device efficacy.

Considerations for mini-coils

Although mini-coils may have significant therapeutic applications for NS and DBS, they require further before they are viable alternative to current practices. Freeman et al. highlighted that their implanted device must be incorporated with a nerve cuff to facilitate long-term use for NS. However, this would be associated with an increased device volume and greater distance from the stimulator to the nerve (Freeman et al., 2017). Increasing this distance would necessitate a higher threshold for NS, which may require increased device dimension. Further, Freeman and colleagues have yet to investigate device excision strategies and suggested that difficulties in device removal would limit clinical applications for DBS. A further limitation to clinical applications is device biocompatibility, which still requires further evaluation. External mini-coils that provide direct NS may overcome these challenges by delivering less invasive stimulation. However, Colella's device remains a prototype, with current studies focused mainly on computational modeling. Further studies that have a greater *in-vivo* focus are needed before it can be considered a viable alternative. Future comparisons to other direct NS techniques (for example, Focused ultrasound) are also necessary to determine the strengths and limitations of each technique. Despite these challenges, mini-coils present a viable option for targeted NS and may facilitate tether-free evaluation of DBS within animals to improve the translational relevance of these studies.

Antenna-based devices

Implanted antennas can harness external magnetic fields to deliver wireless NS. Examples of antenna-based millimetric NS devices include Koo et al. (2018)'s wireless NS and Sliow et al. (2019)'s graft-antenna.

Koo et al. (2018) developed a biocompatible, antenna-based NS device to stimulate and repair peripheral nerves. The device is formed on a poly-lactic-co-glycolic acid substrate and comprises two key elements: a radio frequency power harvester and an electrical interface. The radio frequency power harvester consists of a dual-coil configured loop antenna created from Magnesium and a radio frequency diode. This converts the magnetic field into an electrical signal that passes through magnesium wires to electrodes that encapsulate the nerve in a cuff. Hence, providing radio frequency power to the antenna can deliver nerve stimulation. The device is highly bioresorbable, with constituent material dissolving within three weeks after immersion in PBS at 37°C. Koo et al. (2018) implanted the device onto the rodent sciatic nerve and inserted the harvester into a subcutaneous pocket over the hind limb. Successful NS was confirmed via electromyograms from the tibialis anterior muscles. In a subsequent experiment, the device improved the recovery rate following sciatic nerve transection (Koo et al., 2018).

Another antenna-based stimulation and nerve repair device is the graft-antenna, developed by Lauto and colleagues (**Figure 3**). The devices comprise only two components: a bioadhesive and a gold strip (Sliow et al., 2019). The bioadhesive (5 × 5 mm^2, ~15 µm thick) is a chitosan-based film that contains rose Bengal dye. When irradiated by a laser (532 nm, power 180 mW), the rose Bengal dye is activated, allowing sutureless implantation onto the target nerve via photochemical tissue bonding. This serves as a method for device implantation but also acts as a scaffold to facilitate nerve repair in peripheral nerve transections. When wrapped around a nerve, the gold strip (70 nm thick) forms a loop antenna that is wirelessly stimulated via an external TMS coil. This is advantageous compared to direct magnetic NS, which produces diffuse stimulation that is difficult to focus on a specific target (Babbs, 2014). The graft-antenna combines, in a single device, the ability to concurrently perform functions that have, until now, been carried out by two distinctive implants, namely a wireless stimulator and a biocompatible conduit to graft nerves.

While existing stimulators are bulky and fabricated with complex electronics involving several pairs of electrodes to create and deliver a voltage to tissue, the graft-antenna stimulates nerves without circuitry components and electrodes as it relies on a different stimulation mechanism. Initially, the hypothesis was that the TMS coil induces a current within the loop antenna, which creates a tangential electric field that produces the voltage necessary for NS. A new study has challenged this hypothesis by demonstrating an "edge effect" around the gold strip with the appearance of an electrical field gradient in the axon direction (Smith et al., 2022). This gradient is assumed to trigger nerve action potentials and not secondary tangential electrical fields, as previously assumed.

Regardless of the mechanism, the graft-antenna successfully stimulated rat sciatic nerves, demonstrating that it does not migrate and can reliably produce CMAPs over 12 weeks post-implantation (Sliow et al., 2019). The graft-antenna successfully repaired transected sciatic nerves, with observed muscle twitches at 6–8 weeks following weekly nerve stimulation (1 hour, repetition rate = 1 Hz, B ≈ 0.72 T, pulse duration ≈ 350 µs). Further, graft-antenna-repaired nerves elicited stronger CMAPs and compound nerve action potentials than nerves repaired only with the adhesive. These findings demonstrate the feasibility of nerve stimulation via the graft-antenna and its successful application for sutureless nerve repair.

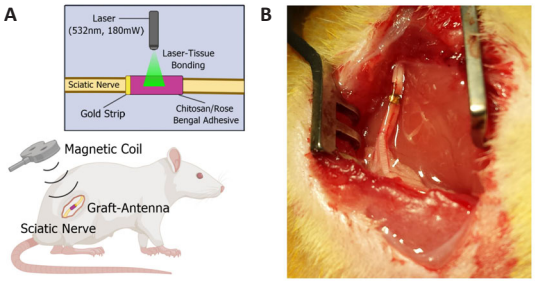

Figure 3 | The graft-antenna for stimulation and repair of peripheral nerves, developed by Sliow et al (2019).

(A) Schematic overview of nerve stimulation (NS) via the graft-antenna and implantation via laser tissue bonding (insert). Created using BioRender.com. (B) Image of the exposed sciatic nerve in a rat, where a biocompatible graft-antenna has been bonded to the nerve by a green laser (λ = 532 nm) without any visible tissue damage. The pink chitosan scaffold (~5 mm long) is visible in the central part of the nerve, and the gold ribbon (width ~0.8 mm, thickness ~80 nm) in the top part of the scaffold. An action potential is triggered upon delivery of radio frequency pulses from a magnetic stimulator. No circuitry or active electrodes are required for NS. Unpublished data.

Considerations for the antenna-based devices

The dual functionality of these antenna-based devices makes them highly advantageous for peripheral nerve repair. Indeed, both Koo et al. (2018) and Sliow et al. (2019) demonstrated an improved recovery rate following a nerve transection when delivering electrical NS via these devices. A notable difference between the two devices is that the graft-antenna comprises fewer elements, which presents fewer points of failure and may improve its stability for long-term use. Further, these components are easily scalable, meaning the device can be made larger or smaller depending on the desired application. This may allow the graft-antenna to be applied to nerves of various sizes, although this is yet to be demonstrated. Notably, both devices exhibit good biocompatibility and are biodegradable after implantation. While this may lead to device degradation over time, it also means that device excision may not be necessary after stimulation is no longer required (Sliow et al., 2019). Hence, these antenna-based devices may be particularly advantageous for therapeutic applications of NS where long-term implantation is not required.

A potential limitation for both devices is that they are powered by large external transmitter coils that may not permit long-term, continuous use. Currently, these coils are not wearable, which restricts stimulation to clinical or therapeutic purposes. For example, they may not be ideal for functional electrical stimulation where continuous coupling with the device is necessary throughout the participant's motion. However, this would not restrict therapeutic applications that use short NS protocols, such as peripheral nerve repair (Ni et al., 2023). Indeed, both Koo et al. and Sliow et al. (2019) used short-duration NS protocols, suggesting that both devices are ideal for this purpose.

Opto-Electronic Devices

Opto-electronic NS devices overcome the challenge of wireless power transfer through an external light source. The light source is typically a laser within the deep-red light spectrum (620–800 nm), as this provides sufficient penetration depth within various tissues (Jacques, 2013). In optogenetic applications, this light source can activate light-sensitive ion channels and induce neuronal activation. However, the need for genetic modification impedes the clinical translatability of this technology and has led to the development of implanted opto-electronic NS devices (Huang et al., 2023). In these applications, the light source is positioned over an implanted device that incorporates a photodiode that converts light into an electrical signal that drives stimulation. Głowacki and colleagues have made significant progress in developing opto-electronic NS devices (Donahue et al., 2022; Silverå Ejneby et al., 2022).

Silverå Ejneby et al. (2022) fabricated an organic electrolytic photo capacitor (OEPC) that transduces deep-red light into electrical signals to trigger action potentials in rat sciatic nerves (**Figure 4**). The device comprises three key elements: a P-N photoelectrode, a gold/Indium Tin Oxide (Au/ITO) return electrode and a Parylene C ribbon. The photoelectrode includes phthalocyanine and N, N'd-methyl perylene-tetracarboxylic bisimide (PTCDI). The phthalocyanine layer acts as the light-absorbing and p-type electron donor layer, whereas the PTCDI layer acts as the n-type electron acceptor layer. The second component, the Au/ITO return electrode, completes the circuit. These components were integrated on a parylene-C substrate that forms a mechanical locking cuff when inserted around the sciatic nerve. The implantable OEPC charged ~300–320 mV when illuminated with a pulsed 638-nm laser diode or a 660-nm LED.

While the device is yet to be used therapeutically, it has shown long-term stability after implantation around the sciatic nerve. Indeed, external light stimulation (638 nm diode laser) elicited robust and repeatable CMAPs in the bicep femoris that were stable for over 100 days post-implantation. Notably, implantation did not result in motor deficits when evaluated via horizontal ladder task, and there was no significant difference in paw withdrawal following a von Frey test, suggesting that the device does not cause

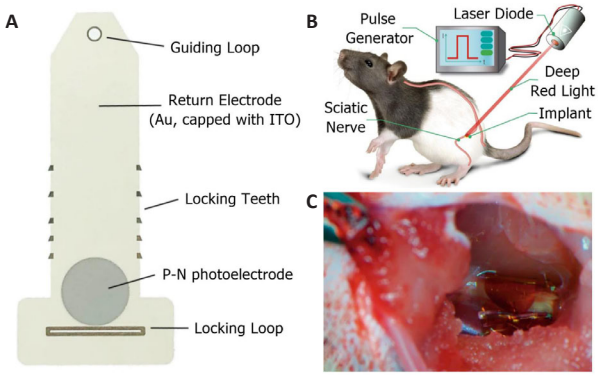

Figure 4 | **Silverå Ejnerby and colleagues' opto-electronic NS device.**
(A) Rendering of the device, highlighting major components. (B) Schematic depicting laser diode emitting deep-red light for wireless stimulation of the photo-electrode in-vivo. (C) In-vivo implantation of the device on the rat sciatic nerve. Reprinted with permission from Silverå Ejneby et al. (2022). Au: Gold; ITO: Indium Tin Oxide.

neuropathy. This was confirmed via histological analysis of the sciatic nerve, which found no difference in neurofilament or glial fibrillary acidic protein (astrocyte marker) immunoreactivity between sham and implanted animals.

The Głowacki laboratory also developed a smaller device for mouse vagal NS (Donahue et al., 2022). The small size of the mouse vagal nerve presents a complex engineering challenge and has limited vagal nerve stimulation studies such that they are mainly conducted at acute time points. To address this, Donahue et al. (2022) developed an OEPC device similar to Ejnerby et al. but with a photovoltaic "flag" design. The latter separates the photo-electrode from the previous OEPC device into two components: the stimulation electrodes, and the photovoltaic cells. This has a key advantage for the application on a smaller nerve. In the OEPC design, increasing photoelectrode size would mean that parts of the electrode are not directly contacting the nerve, thus decreasing stimulation efficacy. Separating these components permits a larger photovoltaic cell size, generating more charge when absorbing light while ensuring sufficient contact with the nerve to maintain effectiveness. The photovoltaic flag design was capable of stimulating the vagal nerve (5 Hz, light pulse duration = 266 µs, 20 s duration for a total of 100 pulses), subsequently reducing heart rate at a much lower light intensity (2–4 mW/mm^2) than the OEPC device (18.7 mW/mm^2).

An alternative opto-electronic NS method is to utilize a silicon-based semiconductor junction. These are potentially advantageous, as they do not require large photovoltaic contact panels with metal components. Further, they can operate within the near-infrared spectrum (800–1000 nm) where light has a maximum penetration depth within the tissue (Huang et al., 2023). Prominski et al. (2022) developed a silicon porosity-based heterojunction with photo-electronic capabilities for *in vivo* sciatic nerve stimulation. The device was created via a stain-etching technique to produce a nanoporous/non-porous heterojunction directly in p-type crystalline silicon. The photochemical properties of this film were enhanced via an oxygen plasma treatment. This material was then fabricated into a flexible membrane and implanted on the rat sciatic nerve, where it effectively produced action potentials and limb movement in response to both visible light (532 nm) and near-infrared (808 nm) light sources (Prominski et al., 2022).

Huang et al. (2023) developed a similar device to excite and inhibit neural activity. Implanting boron ions onto silicon-on-insulator wafers created a p+n layer, while implanting phosphorus ions created an n+p junction. When implanted in the mouse sciatic nerve, the p+n layer device stimulated the nerve and increased CMAP amplitude. Alternatively, implantation of an n+p layer device did not elicit hindlimb activity and could reduce CMAP intensity. Further, Huang and colleagues demonstrated that their device was biodegradable and biocompatible, with the device showing minimal immune responses when implanted and completely disappearing after five months (Huang et al., 2023).

Considerations for opto-electronic devices

A notable advantage of these devices is their small size, even compared to other millimetric stimulators. This facilitated implantation on the mouse vagus nerve – a significant engineering achievement (Donahue et al., 2022). However, applications may be limited due to the dispersion of light in tissue. Indeed, many current applications are restricted to shallow nerves, as greater light intensity is required to penetrate deeper into the tissue (Freeman et al., 2017). This effect was observed by Donahue and colleagues, who found that placing the device under the salivary gland and skin necessitated a much higher light intensity (≥ 8.5 mW/mm^2) to achieve similar effects (Donahue et al., 2022). Light intensity and several stimulation factors, including pulse duration and frequency, can contribute to photothermal tissue heating (Cardozo Pinto and Lammel, 2019). This is potentially problematic, as photothermal tissue heating could cause damage. Donahue and colleagues simulated tissue heating from their light source and found a maximum temperature increase of 0.45°C from 20 seconds of stimulation (10 Hz, 1 ms pulse duration). Tissue temperature returned to normal values after a 40-second cooldown period of no stimulation (Donahue et al., 2022). This indicates that opto-electronic NS devices can be used with minimal tissue heating. However, stimulation parameters for optoelectronic NS may need to be modified to minimize photothermal heating.

The depth of light penetration within the tissue may inhibit the translation of devices to human applications with greater tissue density. As a potential solution to this issue, Silverå Ejnerby et al. (2022) suggested that future devices could be developed to respond at a wavelength of 700 nm, which may increase transmission depth. Indeed, recent silicon-based opto-electronic devices developed by Prominski et al. (2022) and Huang et al. (2023) are operational in the near-infrared spectrum and will likely improve penetration depth. However, these devices need further examination to demonstrate NS at equivalent depths to what is required for human applications. Future studies may benefit from employing large animal models with a similar nerve depth to humans to establish whether these devices can stimulate deeper nerves. Despite these limitations, optoelectronic devices remain in their infancy, and future studies will likely improve efficacy and operational capabilities.

Ultrasound Devices

Several ultrasound systems for wireless power transfer have been adopted for device miniaturization. In 2018, Charthad et al. developed a wireless NS device incorporating a piezoelectric receiver, a custom integrated circuit, a capacitor for energy storage, two stimulation electrodes, and an LED. The piezoelectric material receives ultrasonic power and downlink data, allowing modulation of stimulation parameters via the external transmitter. The electrodes were two platinum wires (2 mm length, 0.5 mm diameter). An LED was incorporated for optical stimulation applications. While the device was not applied *in vivo*, several *in vitro* experiments demonstrated the efficacy of this system. Firstly, Charthad et al. (2018) showed that the device was operational when placed at a depth of 10.5 cm in a tissue surrogate (castor oil). A subsequent experiment confirmed that the device was operational at a depth of 6 cm in porcine tissue. Finally, the device was implanted on frog sciatic nerves, producing twitching responses that correlated with stimulation parameters.

Piech et al. (2020) created the "StimDust", a similar, ultrasonically-powered device consisting of an external ultrasonic transceiver that provides power to a mote implanted on the target nerve (**Figure 5**). The mote is comprised of several elements, including a lead zirconate titanate (750 × 750 × 750 µm) piezoceramic material that received the ultrasonic power, a custom integrated circuit for power rectification, communication and stimulation, a capacitor, and bipolar electrodes for stimulation. These components were integrated onto a thin poly-imide printed circuit board, with the stimulation electrodes on the underside of the board to maintain contact with the nerve. Together, the device volume was 1.7 ± 0.2 mm^3, plus 3.2 ± 0.4 mm^3 of volume added by a nerve cuff that facilitated *in-vivo* implantation. Piech et al. (2020) successfully used the device to stimulate the rat sciatic nerve. After implantation of the mote around the nerve, the external ultrasound source was positioned over the skin and coupled to the device using ultrasound gel. Stimulation produced repeatable compound action potentials within the sciatic nerve, CMAPs, and muscular twitches. Similarly to Charthard et al. (2018), the device remained operational at a depth of 5.5 cm in porcine tissue, suggesting functionality at depths similar to human tissue.

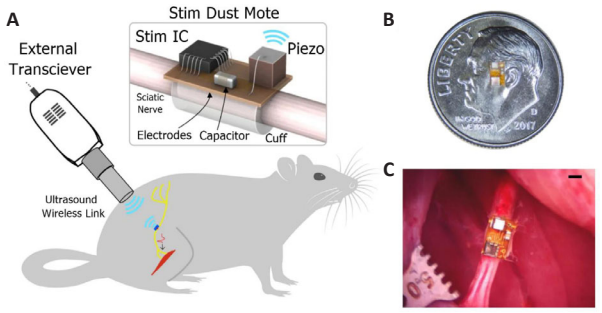

Figure 5 | **The "StimDust" NS device developed by Piech and colleagues.**
(A) Overview of the system for rodent NS. Insert depicts the Stim Dust Mote, consisting of the Piezo material, Integrated Circuit (IC), electrodes, and capacitor. (B) Size comparison between the StimDust and a United States Dime. (C) *In vivo* implantation of the Stim Dust Mote on a rat sciatic nerve. Reprinted with permission from Piech et al. (2020).

Considerations for ultrasound-powered devices

There are several advantages to using ultrasound-powered devices. Notably, these devices are functional at significant depths within the tissue (Piech et al., 2020). This was highlighted by both Charthad and Piech, with both devices being operational through a considerable thickness of porcine tissue. Further, ultrasound can be focused on a millimetre-sized spot, allowing for a highly efficient power transfer (Charthad et al., 2018). A notable consideration is that, similarly to magnetic coils, ultrasound alone can directly stimulate peripheral nerves in the absence of an implanted device. Indeed, Downs et al. demonstrated stimulation of the mouse sciatic nerve using focused ultrasound

delivered via a HIFU transducer (3.57 MHz center frequency) (Downs et al., 2018). Direct energy transduction for NS would be advantageous in several settings, as it negates the need for surgical implantation and prevents potential device failure at any of the various components. Further, this technique is advantageous to non-invasive magnetic NS, as it does not cause diffuse activation and can be focused on smaller targets. However, implanted ultrasound devices for indirect NS still have several key strengths. For example, Piech et al. (2020) highlighted that the "StimDust" uses lower ultrasound thresholds to achieve stimulation than direct stimulation approaches. Furthermore, the "StimDust" system has bidirectional communication abilities that would facilitate closed-loop neuromodulation strategies that may not be possible without implanted technology (Piech et al., 2020). Nonetheless, future studies may benefit from exploring non-invasive, direct ultrasound NS or invasive, indirect ultrasound devices, depending on the desired application.

A notable limitation with ultrasound NS devices is that the transmitter must remain in close contact with the skin to penetrate the tissue. Hence, these devices may lose power due to a loss of contact with the transmitter. Additionally, ultrasound gels or foams are required for energy transfer from the transmitter (Chen et al., 2022), making long-term applications of these devices challenging. A further consideration is that, similarly to the magneto-electronic devices, the "Stimdust" uses a lead zirconium titanite piezomaterial which is toxic within the body. Piech and colleagues suggested that a barium titanate piezoceramic could improve biocompatibility but slightly reduce electromechanical coupling (Piech et al., 2020). Indeed, Barium titanate was used successfully by Charthad and colleagues' device, suggesting it is a viable alternative (Charthad et al., 2018). Nonetheless, exploring alternative materials that improve biocompatibility may be necessary to aid the clinical translation of these devices.

Comparisons and Applications of Millimetric Nerve Stimulation Devices

The devices featured in this review have incorporated diverse mechanisms to achieve a millimetric design. **Additional Table 1** highlights the key characteristics of these devices for comparison. Briefly, magneto-electric devices have reached a low total volume and are operational at reasonable depths (3–5 cm). However, they are currently limited in biocompatibility, as they use PZT in their construction. Freeman et al. (2017)'s implanted mini-coil device achieves a very low total volume (0.45 mm^3) and can be powered at considerable depth, but it requires further investigation to clarify biocompatibility. Conversely, Colella's mini-coil is entirely external and does not experience biocompatibility issues, but it remains in the early stages of development. Antenna-based devices exhibit good biocompatibility and operational depths (6–8 cm). Similarly, opto-electronic devices exhibit good biocompatibility but are restricted in operation depth, although recently developed near-infrared devices may improve this limitation. Finally, ultrasound-powered devices exhibit the greatest operational depth (7–10.5 cm) but require improvements to biocompatibility.

These unique characteristics may make certain NS devices suitable for specific applications. For instance, opto-electronic devices may not effectively target deep nerves within the body due to light scattering. However, their ability to stimulate small nerves makes them suitable for targeting small, superficial targets. Conversely, ultrasound or magnetic-powered devices may be ideal for targeting deeper nerves. In cases where surgery is not feasible due to patient-related risks, endovascularly implanted magneto-electric devices or external mini-coils would be ideal. Additionally, antenna-based devices have demonstrated their suitability for stimulating and repairing peripheral nerve injuries.

Different NS devices may also lend themselves to specific therapeutic strategies. Magneto-electric devices may be well-suited for functional electrical stimulation as they can tolerate angular misalignment that would occur during movement. Conversely, ultrasound-powered devices are not ideal for this purpose as they require contact with the transmitter, but may be more beneficial for therapeutic applications in bedridden patients. As millimetric devices continue to develop, clinicians may have various options, enabling them to select the most appropriate NS device for their desired application.

Conclusion

Nerve stimulation is a rapidly progressing field, with ongoing development and testing of devices for various applications. While current devices are limited due to complexity, size, and invasiveness, significant research efforts have led to the creation of innovative millimetric devices that address many of these issues. Promising devices include mini-coils, magneto-electric, antenna-based, and optically or ultrasound-powered devices. Although these devices are still experimental and face several challenges, they offer clear advantages, such as more targeted and less invasive stimulation. Miniaturization emerges as the future direction for nerve stimulation, reflecting the evident progress in the field.

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Additional file:
Additional Table 1: *Key characteristics of millimetric devices highlighted in this review.*

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