Self-rectifying magnetoelectric device for remote neural regeneration and function restoration

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Recently, Joshua C. Chen, Gauri Bhave, and Jacob T. Robinson from Rice University reported a magnetoelectric nonlinear metamaterial (MNM) for neural signal transmission and nerve function restoration.[1] Nonlinear charge transport between the semiconductor layers enabled this magnetoelectric (ME) metamaterial to have a nonlinear ME coupling coefficient, which allowed for self-rectification (**Figure 1**). This material could generate a steady bias voltage with time-averaged voltage biases larger than 2 V, enabling the generation of arbitrary pulse sequences when subjected to an alternating magnetic field. Researchers demonstrated that MNM could effectively cover the sciatic nerve gap and allow nerve impulses to travel in less than 5 ms to target distal muscle groups. This resulted in a rapid sensorimotor response in rats under anaesthesia. It is widely accepted that electrical stimulation is vital for nerve regeneration. Thus, this type of device can shed light on novel therapies for nerve injuries.

Peripheral nerve injury is a common and refractory disease in clinical practice with approximately 1 million new cases each year.[2] Peripheral nerve injuries often cause sensory and motor dysfunction, which significantly decreases quality of life and results in huge economic costs.[2] Currently, surgical repair is the primary treatment. However, satisfactory functional restoration cannot be achieved because of various factors. Other physical therapies have been studied, such as electrical stimulation, magnetic stimulation, low-intensity ultrasound, phototherapy, and photobiomodulation therapy.[3] It has been demonstrated that electrical stimulation increases the number of regenerated axons and encourages the regeneration of motor and sensory nerves.[3] Low-frequency (20 Hz or less) electrical stimulation paradigms are now widely acknowledged to be beneficial in improving functional recovery following peripheral nerve injury in humans and animal models.[4] However, only short-range stimulation is currently available, which inevitably results in an invasive injury. More in-depth researches on non-invasive electrical stimulation are required.

ME nanoparticles are thought to be able to transform magnetic field into electric field.[5] In this way, they have been used for remote neuromodulation and activating ion channels.[6] However, the latency of ME nanoparticles is relatively long, which may be attributed to the driving frequency being far from the resonance frequency. ME coupling coefficient (α) is relatively small when the magnetic field is not resonant with the material, and the electric field is consequently smaller. However, owing to the intrinsic low-pass filtering of the cell, the resonance frequency of existing materials is usually too high to directly stimulate neural activity. A rectifying electron transport (RET) layer was added to ME laminates by researchers to change the symmetry of the voltage. RET is made up of a trilayer structure with the piezoelectric lead zirconate titanate sandwiched between two magnetostrictive layers. MNM presented nonlinear property when researchers characterised the ME coupling coefficient, in contrast to unmodified ME laminates featuring a linear relationship. The MNM demonstrated self-rectification when an alternating current magnetic field was delivered at the mechanical resonance frequency, which was essential for precisely timed neural stimulation.

Researchers have also studied the biocompatibility of MNM as long-term implants. They cultured human embryonic kidney cells using insulated MNM for 5 days and tested them using a live–dead assay. MNM-cultured cells had 89% viability compared to 85% viability of the positive control.[1] Furthermore, the MNM and a control group

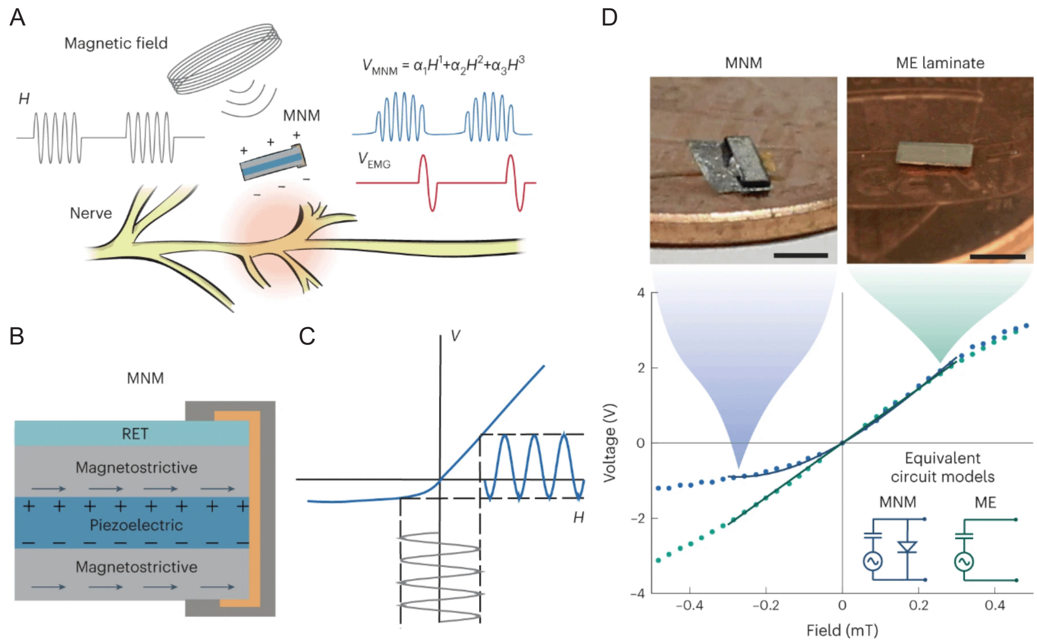

Figure 1. Magnetic field-based wireless neuromodulation is made possible by MNMs. (A) Illustration of how MNM facilitates distant neural stimulation. A biassed nonlinear electric field is created within the MNM by applying a time-varying magnetic field, and this in turn activates the neural tissue. (B) The multilayer design of the MNM shown in cross-section. An electrical circuit is made possible by the RET layer on top of a piezoelectric layer that is layered between two magnetostrictive layers in the core. The H-V curve graphic makes clear the nonlinear ME impact that this RET layer introduces. (C) Conceptual diagram showing the voltage across the MNM at its mechanical resonance in the presence of an alternating magnetic field. Voltage self-rectification is caused by the intrinsic nonlinearity in the H-V relationship. (D). The B (magnetic)-V (voltage) curves of the experimental data for certain MNMs (left) and ME laminates (right), together with the corresponding polynomial and linear fits. The corresponding circuit models are compared in the inset, along with magnified images of the materials. B denotes μ_0H; μ_0 denotes the permeability of free space. Scale bar: 2 mm. Reprinted from Chen et al.[1] under exclusive licence to Springer Nature Limited. H: magnetic field; ME: magnetoelectric; MNM: magnetoelectric nonlinear metamaterial; RET: rectifying electron transport ; V: induced electric potential.

using polydimethylsiloxane were implanted subcutaneously in rats for more than 3 weeks, and histological examination was carried out. Every week, the healing phase of the wound was evaluated, and the incision site showed little scarring and an unbroken layer of skin without any dehiscence. Staining results showed increased vascular and cellular infiltration.[1] Hence, by exploring superior encapsulating techniques, it is possible to ascertain that the material is both non-toxic and retains its functional properties under physiological conditions.

Additionally, the researchers showed that in rats under anaesthesia, MNM could recover a quick sensorimotor response. An external field generator was utilised to create a magnetic field on the skin's surface depending on the activation of a force sensor on the rat's paw, and the MNM was positioned on the exposed sciatic nerve. When the rat's foot was fully anaesthetised, there were no leg kicks or electromyography signals seen. However, they saw leg kicks and electromyography signals recovered after appling a remote magnetic on the MNM, proving that MNMs could function as a component of a neuroprosthetic system.[1] MNM has also been used by researchers in a rat sciatic nerve dissection model. The sciatic nerve gap was effectively bridged by MNM, allowing nerve impulses to activate distal muscle units with latencies of less than 5 ms. Moreover, there was very little latency—approximately 175 μs—across the nerve gap.[1]

Despite the innovative design of the structure, the performance of MNM can still be improved in the future. Encapsulating the MNM to keep the ME coefficient stable is necessary for long-term applications. Certain materials, such as a lead zirconate titanate layer, could be changed out for inert piezoelectric materials, including aluminium nitride or polyvinylidene fluoride. In addition, the RET composition can be changed to improve its performance. RET made of p-n diode which was fabricated by forming a heterojunction between p-Si and n-ZnO showed 80% yield with a larger direct current bias of > 2 V, compared with ZnO showing 10% yield and 1.7 V bias voltage. In electronic circuits, bias means applying an appropriate operating voltage to an active device, so that it is in a normal operating state. We look forward to the application of MNM in clinical treatment in the future.

Author contributions
All authors contributed to conceptualizing, writing, reviewing, editing and proofing the manuscript, and approved the final version of the manuscript.
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Conflicts of interest statement
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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