

Light-Controlled Battery-Integrated Nerve Conduit for Peripheral Nerve Pain Management

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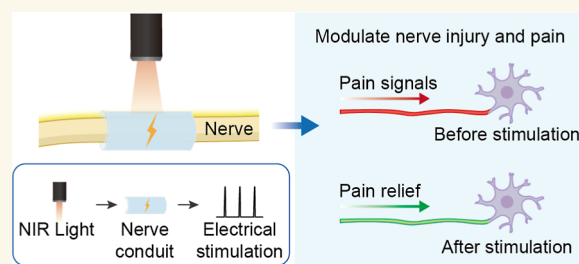
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ABSTRACT: Pain management typically relies on pharmaceutical treatments, which frequently carry a risk of dependence and exhibit limited efficacy. The utilization of implantable electroceuticals is a developing field that shows great promise as an alternative. However, current devices are incapable of providing long-term, reliable electrical stimulation in situ. Here, we present a light-controlled, battery-integrated nerve conduit with tunable output, enabled by the light-induced reversible relocation of water molecules in the electrolyte. Precise modulation of the nerve conduit's electrical output is realized through the modulation of light intensity and pulsing protocols. The design of the device eliminates the need for external control circuitry, thus minimizing the size and maximizing energy efficiency. Consequently, the nerve conduit possesses a total volume of just 26 mm³. This compact and conformal design enables direct nerve interfacing, and hence facilitates precise and programmable neuromodulation in situ. Moreover, in vivo studies demonstrate its efficacy in the inhibition of peripheral nerve pain for a period of up to 30 days.

KEYWORDS: implantable, light-controlled, batteries, nerve conduits, bioelectronics



INTRODUCTION

Pain is a major health issue affecting a large proportion of the global population.¹ Statistics indicate that over 30% of adults worldwide experience chronic pain, imposing a substantial socioeconomic burden each year.^{2–4} The current pharmacological treatments for chronic neuropathic pain are effective for fewer than 50% of patients, often accompanied by challenges such as low efficacy and dependence risks.^{5,6} This underscores the urgent need for novel interventional approaches.^{7–9} Implantable electroceuticals, which deliver targeted electrical stimulation to block pain signals, demonstrate considerable potential as an engineering-based therapy for pain.^{10–12} The ideal implantable electroceutical should have a small total implant volume, operate without percutaneous leads, and promise long-term reliability.

However, existing implantable electroceuticals are characterized by rigidity and substantial size, which exceed the dimensional compatibility required for nerve stimulation, making in situ electrical stimulation unfeasible.^{13–15} This mismatch necessitates lead extensions to bridge the stimulation site and the distant implanted device, which raises clinical risks including lead fracture and infection.^{16,17} Furthermore, the external control circuitry largely increases energy consumption, thereby limiting operational longevity.¹⁸ Consequently, regular replacement surgeries for electroceuticals increase the risk of

complications including bleeding, postoperative infection, and organ dysfunction.^{19,20}

Here, we introduce a light-controlled, battery-integrated nerve conduit with tunable output, enabled by the light-induced reversible relocation of water molecules in the electrolyte (Figure 1a). The electrical output of the nerve conduit can be precisely modulated by programming light intensity and pulsing protocols. This design eliminates the need for external control circuitry, thereby minimizing the device's size and maximizing its energy efficiency. The nerve conduit has a total volume of just 26 mm³. Its compact and conformal architecture allows direct interfacing with nerve tissue, enabling precise, programmable neuromodulation in situ. The nerve conduit inhibits peripheral nerve pain for a period of 30 days, highlighting its potential for use in next-generation programmable neuromodulation therapies.

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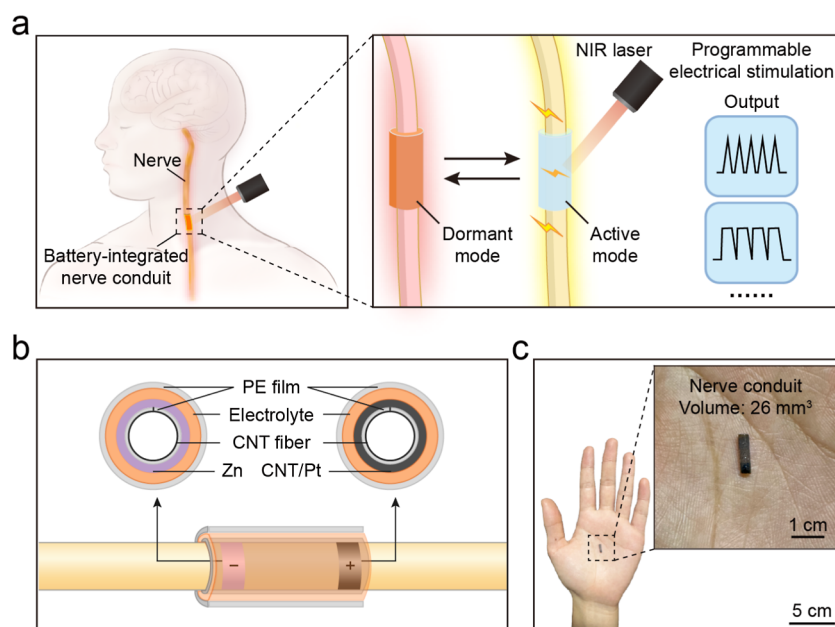


Figure 1. Design of the light-controlled battery-integrated nerve conduit. (a) Schematic illustration of a light-controlled battery-integrated nerve conduit encircling a nerve to deliver various electrical stimulation waveforms for programmable neuromodulation. (b,c) Engineering design (b) and optical images (c) of the nerve conduit.

RESULTS AND DISCUSSION

Materials, Designs, and Mechanisms

The light-controlled battery-integrated nerve conduit is designed in a tubular form to accommodate nerves specifically (Figure 1b). The nerve conduit exploits a self-powered mechanism, where the battery electrodes consist of a carbon nanotube/platinum (CNT/Pt) cathode and zinc (Zn) anode (Figure S1). Zn is selected for its high specific capacity, biosafety, and stability in physiological environments.^{21,22} The CNT/Pt cathode is fabricated by electrodepositing Pt nanoparticles onto a porous, flexible CNT film, providing high catalytic activity for the oxygen (O_2) reduction reaction.²³ During discharge, O_2 is reduced to hydroxide ions (OH^-) at the cathode, which then migrate to the Zn anode driven by the potential difference. Simultaneously, the Zn anode undergoes oxidation to form Zn^{2+} ions. The stimuli-responsive electrolyte, composed of water, sodium laurate, polydopamine, and polyacrylamide (PAAm) (Figure S2), is designed to respond to the tissue-penetrating near-infrared (NIR) wavelengths. A CNT fiber, electrically connected to the battery electrodes, serves as the active stimulation electrode, with its distal end contacting the nerve directly. The CNT fiber electrode exhibited a low impedance of $48.4 \pm 5.2 \Omega$ at 1 kHz in PBS, indicating efficient interfacial charge transfer for neural stimulation (Figure S3a–c). In addition, the cathodic charge storage capacity was $254.6 \text{ mC}\cdot\text{cm}^{-2}$ (Figure S3d). The CNT fiber electrode also exhibited a wide electrochemical water window, with reduction and oxidation potentials of -1.2 and 1.3 V , respectively (Figure S3e). Based on voltage transient measurements at a conservative maximum cathodic potential excursion of -0.6 V , the charge injection capacity was calculated to be $1.4 \text{ mC}\cdot\text{cm}^{-2}$ (Figure S3f). Collectively, these results support the CNT fiber electrode as an effective stimulation interface for neural applications. The polyethylene (PE) layer, which is transparent, waterproof, and air-permeable,²⁴ encapsulates the remaining components. The

final device assumes a tubular shape with a total volume of 26 mm^3 (Figure 1c).

To assess the mechanical compatibility with neural tissue, the mechanical compliance of the nerve conduit was evaluated. The Young's modulus was $3.2 \pm 0.3 \text{ MPa}$ in the absence of NIR illumination and decreased to $0.6 \pm 0.3 \text{ MPa}$ upon NIR illumination, due to the softening of the stimuli-responsive electrolyte (Figure S4a,b). Both values fall within the range of soft neural tissues,^{25,26} indicating good mechanical compatibility. The bending stiffness was also reduced from $2 \times 10^{-5} \text{ N}\cdot\text{m}^2$ to $3 \times 10^{-6} \text{ N}\cdot\text{m}^2$ under NIR illumination (Figure S5c,d), several orders of magnitude lower than those of conventional PCL- and collagen-based nerve conduits.^{27,28} This softness enables the conduit to conformally wrap cylinders of various diameters without structural failure (Figure S5e). Together, these results demonstrate that the nerve conduit is soft, compliant, and mechanically stable.

The stimuli-responsive electrolyte enables precise, on-demand switching of nerve conduit operation through the relocation of water molecules (Figure 2a,b). In the initial off-state (without NIR irradiation), the electrolyte exists as a crystal/polymer composite with sodium laurate crystals embedded in the PAAm polymer matrix (Figures 2c and S6). In this state, water molecules are immobilized in the $C_{11}H_{23}COONa\cdot 5H_2O$ crystals, as confirmed by the X-ray diffraction (XRD) analysis (Figures 2e and S7). Upon NIR irradiation, polydopamine nanoparticles convert light into localized heat (Figure S8), inducing a solid-to-liquid phase transition in the sodium laurate crystals at a tunable transition temperature (Figures S9 and S10). During the phase transformation, water molecules are released and rapidly hydrate the surrounding polymer network, causing the electrolyte to shift from a crystal/polymer composite to a continuous ion-conducting hydrogel (Figures 2d, S11 and S12). Throughout the transformation process from off-state to on-state, the characteristic XRD peak of $C_{11}H_{23}COONa\cdot 5H_2O$ crystal gradually decreased and eventually disappeared (Figures

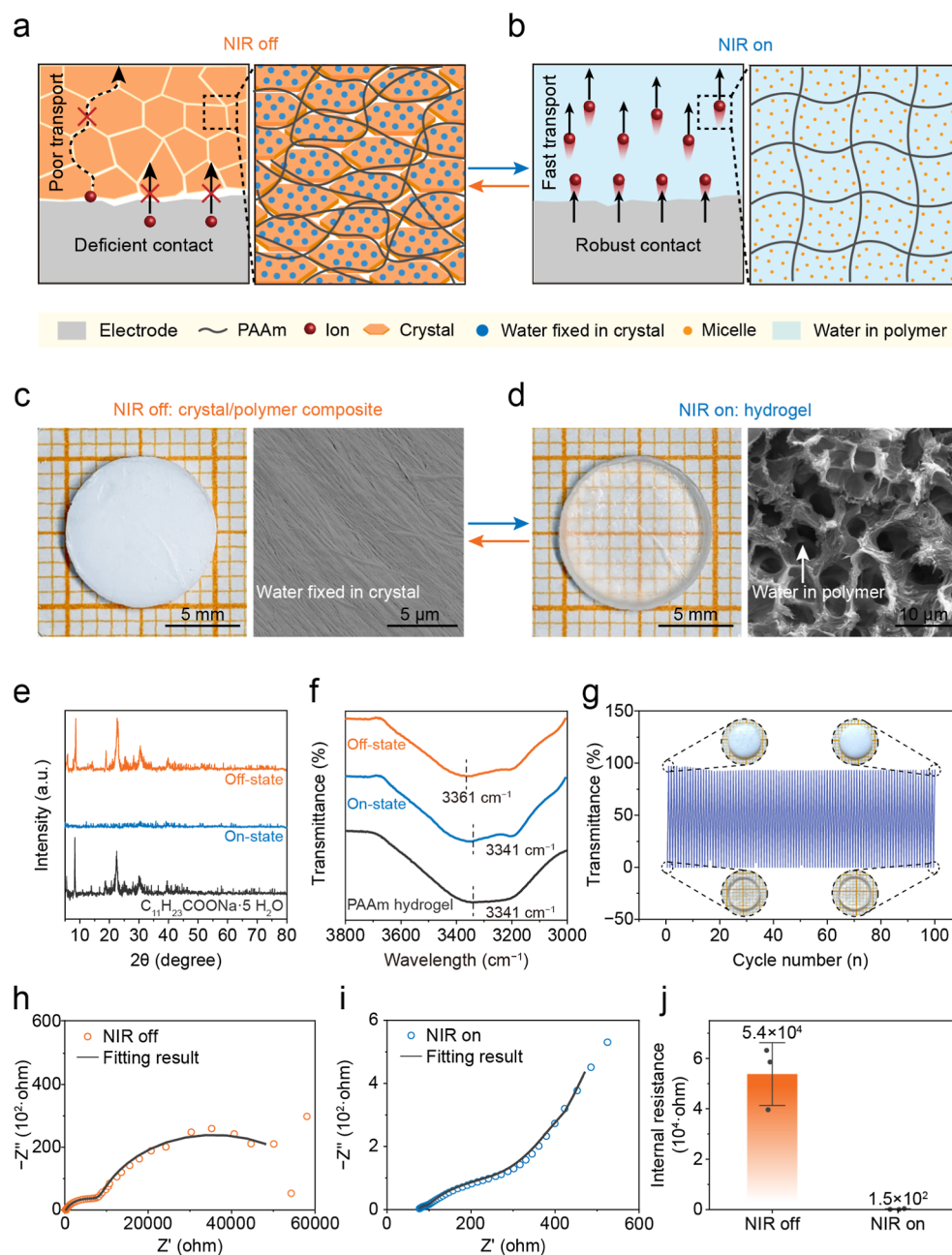


Figure 2. Working mechanism. (a,b) Schematic diagram of the light-controlled output mechanism. Illumination repositions water molecules from being intercalated in layered crystals into the polymer network, thereby altering the internal resistance of the nerve conduit and enabling switchable power output. (c,d) The scanning electron microscope images and photographs of stimuli-responsive electrolyte without (c) or with (d) illumination. (e,f) X-ray diffraction patterns (e) and Fourier-transform infrared spectroscopy curves (f) of off-state and on-state stimuli-responsive electrolytes. (g) Reversibility of transformation of a stimuli-responsive electrolyte. (h,i) Electrochemical impedance spectroscopy of light-controlled battery-integrated nerve conduit without (h) and with (i) illumination. (j) Statistics for nerve conduit internal resistance without or with illumination. Values are the mean $\pm$ SD for $n = 3$ light-controlled battery-integrated nerve conduit samples.

2e and S7). In parallel, a distinct red shift was observed in the characteristic peak associated with the amide group ($-\text{NH}-$) stretching vibration, shifting from 3361 cm^{-1} in the off-state to 3341 cm^{-1} in the on-state electrolyte (Figure 2f). This shift indicates a strengthening of hydrogen bonding interactions, confirming that the released water molecules interact with the amide groups of the PAAm network, effectively integrating into the hydrogel structure.

This structural transformation substantially enhances the ion mobility within the electrolyte and facilitates efficient ion transport at the interface between the electrode and the

electrolyte. As a result, the nerve conduit exhibited a pronounced reduction in internal resistance, decreasing from approximately $5.4 \times 10^4\ \Omega$ to $1.5 \times 10^2\ \Omega$ under NIR irradiation (Figure 2h–j).

The polymer network plays a crucial role in tuning performance. Here, six commonly used polymers, i.e., poly(ethylene oxide) (PEO), sodium alginate (SA), poly(acrylic acid) (PAA), poly(ethylene glycol) diacrylate (PEGDA), poly(vinyl alcohol) (PVA), and PAAm, were investigated (Figure S13). PEO lacks effective cross-linking points, preventing the formation of a stable network capable of immobilizing the

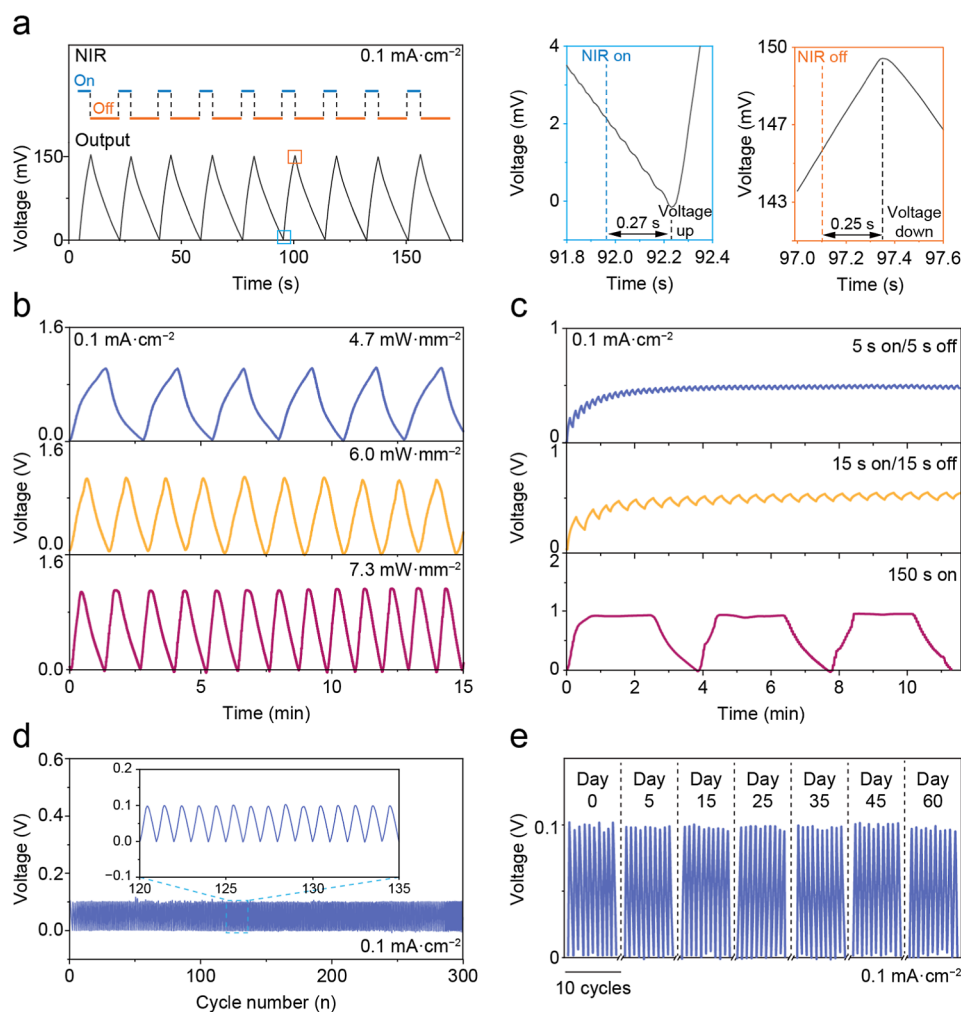


Figure 3. Tunable electrical output. (a) Temporal response of the light-controlled battery-integrated nerve conduit under pulsed light illumination (current density: $0.1 \text{ mA}\cdot\text{cm}^{-2}$; light intensity: $4.7 \text{ mW}\cdot\text{mm}^{-2}$; voltage change amplitude: 0.15 V). (b) Output voltage of the nerve conduit under different light intensities (current density: $0.1 \text{ mA}\cdot\text{cm}^{-2}$; voltage change amplitude: 1 V). (c) Output voltage of the nerve conduit under different pulsing protocols (current density: $0.1 \text{ mA}\cdot\text{cm}^{-2}$; light intensity: $6.0 \text{ mW}\cdot\text{mm}^{-2}$; voltage change amplitude: 1 V). (d) Output voltage of the nerve conduit (current density: $0.1 \text{ mA}\cdot\text{cm}^{-2}$; light intensity: $4.7 \text{ mW}\cdot\text{mm}^{-2}$; voltage change amplitude: 0.1 V). (e) Output voltage of the nerve conduit over days (current density: $0.1 \text{ mA}\cdot\text{cm}^{-2}$; light intensity: $4.7 \text{ mW}\cdot\text{mm}^{-2}$; voltage change amplitude: 0.1 V).

released water, which leads to leakage. For SA and PAA, the cross-linking conditions (e.g., high valence ion, acidic condition) induce adverse reactions (e.g., precipitation) with sodium laurate, disrupting the intended phase transition. PEGDA-based systems exhibit severe phase separation from sodium laurate, likely due to hydrophobicity mismatch, hindering homogeneous hydrogel formation. The high inherent crystallinity of PVA combined with significant steric hindrance severely impedes the phase transformation dynamics and leads to a $> 20 \text{ min}$ transition time. Only PAAm forms a chemically cross-linked stable network with sufficient affinity for water molecules to generate hydrogels, thereby enabling the desired transformation. Rheological analysis shows that the storage modulus consistently exceeds the loss modulus throughout the transition process, underscoring the structural integrity of the PAAm network (Figure S14). The PAAm electrolyte demonstrated highly reversible transitions even after 100 transition cycles (Figure 2g). After cycling, the characteristic XRD peaks of $\text{C}_{11}\text{H}_{23}\text{COONa}\cdot 5\text{H}_2\text{O}$ reappeared in the off-state and disappeared in the on-state, and Fourier-transform infrared (FTIR) spectra showed a reversible red shift

of the amide stretching vibration, consistent with water redistribution (Figure S15). The PAAm electrolyte showed a weight loss of approximately 1% after 25 days, indicating excellent stability (Figure S16). These results confirm robust structural reversibility and long-term stability of the PAAm electrolyte.

Tunable Electrical Output

The electrical output of the nerve conduit is regulated by an external light source. In the absence of light, no detectable output occurs. The nerve conduit demonstrated stable storage characteristics, with only a 4% decay in open-circuit voltage over 60 days (Figure S17). Upon illumination, the nerve conduit discharged normally, delivering a specific capacity exceeding $625 \text{ mAh}\cdot\text{g}^{-1}$ at a current density of $2 \text{ mA}\cdot\text{cm}^{-2}$ (Figure S18). Critically, the nerve conduit output responded rapidly and precisely to light modulation (Figure S19 and Video S1). The rise and fall times of the output voltage closely followed the light modulation within approximately 0.25 s at a current density of $0.1 \text{ mA}\cdot\text{cm}^{-2}$ (Figure 3a), enabling accurate dynamic control of the output waveform. These results

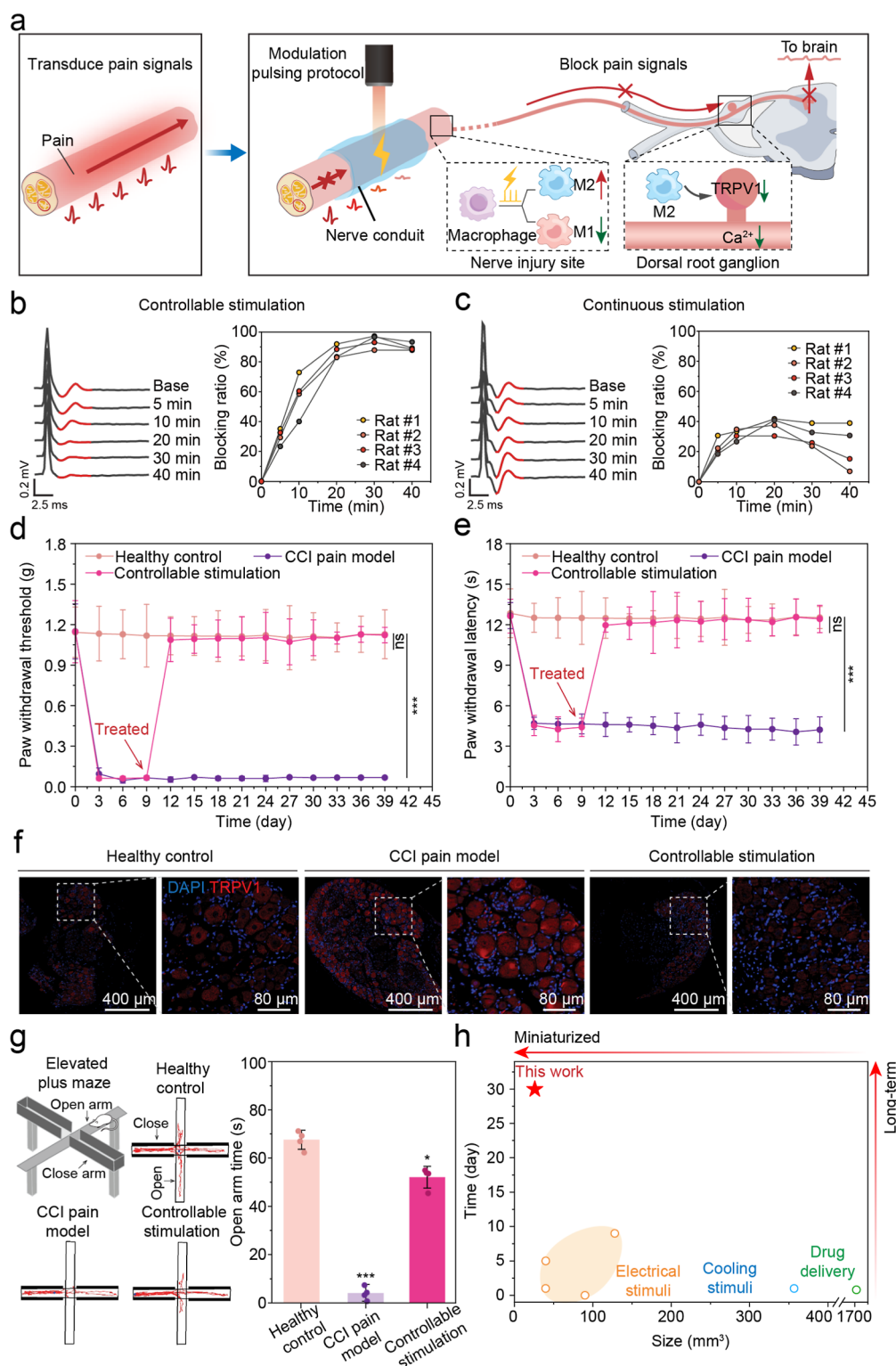


Figure 4. Light-controlled battery-integrated nerve conduit for programmable neuromodulation in pain management. (a) Schematic illustration of the effect of the nerve conduit for pain management. (b,c) Compound nerve action potentials recorded under controllable stimulation (b) and continuous stimulation (c), and the related quantitative analysis of blocking ratio over time. (d,e) Evaluation of the therapeutic effect for pain using mechanical (d) and thermal (e) pain thresholds. Values are the mean $\pm$ SD for $n = 4$ rats. (f) The immunofluorescence images of TRPV1 in the dorsal root ganglion from three groups: the healthy control group, chronic constriction injury (CCI) pain model group, and controllable stimulation group. (g) Illustration of the elevated plus maze setup. Statistics for the retention time in the open arm. Values are the mean $\pm$ SD for $n = 4$ rats. (h) Ashby-style plot comparing the device size and effect time of the light-controlled battery-integrated nerve conduit to other neural stimulators. References and data are provided in Table S2. P values are calculated using one-way ANOVA. ns $P > 0.05$; not significant, $*P \leq 0.05$, $**P \leq 0.01$, and $***P \leq 0.001$.

demonstrate precise and rapid light-controlled modulation of the device output.

The voltage transient characteristics are directly governed by light intensity. The voltage rise rate increases significantly with increasing light intensity. The rise rates were $13.0 \pm 0.7 \text{ mV} \cdot \text{s}^{-1}$, $24.9 \pm 0.9 \text{ mV} \cdot \text{s}^{-1}$, and $46.6 \pm 5.2 \text{ mV} \cdot \text{s}^{-1}$ under light intensities of $4.7 \text{ mW} \cdot \text{mm}^{-2}$, $6.0 \text{ mW} \cdot \text{mm}^{-2}$, and $7.3 \text{ mW} \cdot \text{mm}^{-2}$, respectively (Figures 3b and S20). This dependence is attributed to enhanced photothermal heating rates at higher light intensities (Figure S21), which accelerate the reduction in internal resistance.

Consequently, the output voltage waveform can be precisely programmed via light pulsing protocols. Figure 3c illustrates the temporal voltage evolution under three pulsing protocols. The voltage exhibited rapid periodic oscillations under a 5 s on/5 s off protocol. Extending both phases to 15 s maintained periodicity but reduced the frequency, resulting in prolonged plateaus at high and low voltage levels. Further extending the duration to 150 s led to a stable and constant voltage output, maintaining a level of approximately 1 V after the initial transient. The nerve conduit exhibited excellent stability and could be reliably cycled over 300 times (Figure 3d). The output profiles demonstrated the nerve conduit's ability to operate continuously for 60 days (Figure 3e), highlighting its suitability for long-term applications.

To evaluate the tissue penetration capability of light control, we characterized the light-controlled battery-integrated nerve conduit embedded in porcine tissue at different depths. For a nerve conduit implanted at tissue depths of 5 mm, 10 mm, 15 mm, and 20 mm, an output power density above $1000 \text{ mW} \cdot \text{cm}^{-3}$ was achieved with light intensities of approximately $3.4 \text{ mW} \cdot \text{mm}^{-2}$, $4.7 \text{ mW} \cdot \text{mm}^{-2}$, $7.3 \text{ mW} \cdot \text{mm}^{-2}$, and $7.9 \text{ mW} \cdot \text{mm}^{-2}$, respectively (Figure S22). These results confirm that illumination can penetrate biological tissues to activate the nerve conduit, ensuring reliable operation postimplantation. When discharged at $7.3 \text{ mW} \cdot \text{mm}^{-2}$ light intensity and $0.1 \text{ mA} \cdot \text{cm}^{-2}$ current density, the nerve conduit exhibited output voltage rise rates of $24.3 \pm 4.0 \text{ mV} \cdot \text{s}^{-1}$, $16.9 \pm 3.6 \text{ mV} \cdot \text{s}^{-1}$, $15.9 \pm 1.4 \text{ mV} \cdot \text{s}^{-1}$, and $10.0 \pm 1.1 \text{ mV} \cdot \text{s}^{-1}$ at 5 mm, 10 mm, 15 mm, and 20 mm depths, respectively (Figure S23). The decrease in voltage rise rates is attributed to light attenuation caused by reflection and absorption within tissue layers (e.g., skin and fat). Despite this limitation, the optical responsiveness under tissue penetration demonstrates the feasibility of in vivo nerve conduit modulation via external light stimuli. For deeper targets where NIR penetration is insufficient, alternative activation modalities, including magnetothermal or sonothermal approaches, may offer promising routes for future deep-tissue applications.

This intrinsic tunability of electrical output via light establishes a paradigm for optically programmable systems, advancing the design of next-generation implantable devices. Current state-of-the-art implantable bioelectronics require external control circuits to adjust output. However, integrating these external circuits necessitates an additional implantable module, resulting in an $80\text{--}1000 \text{ mm}^3$ volume overhead from auxiliary modules and continuous power consumption in the microwatt range accelerating energy depletion (Table S1). These limitations fundamentally conflict with the minimal volume-power paradigm of implantable bioelectronics aimed at mitigating clinical risks and prolonging device lifespan. While energy harvesting devices, including radio frequency transmitters,²⁹ optoelectronic capacitors,^{30,31} and ultrasonic con-

verters,^{32,33} bypass control circuits, their unstable energy output and low conversion efficiency remain prohibitive. In contrast, the light-controlled battery-integrated nerve conduit enables controller-free output tuning via rapid and highly reversible transitions, zero continuous auxiliary power consumption, and stable on-demand output governed solely by light. This innovation not only addresses the limitations of existing technologies but also opens new avenues in developing autonomous, miniaturized implantable medical devices.

Peripheral Nerve Pain Management

The light-controlled battery-integrated nerve conduit enables targeted in situ stimulation, offering a potential breakthrough for pain treatment (Figure 4a). The nerve conduit is implanted in situ on the nerve and controlled by an NIR light source to deliver electrical stimulation (controllable stimulation group, Figure S24). The stimulation is achieved via localized current injection at the CNT fiber–nerve interface, with the current flowing from the nerve conduit through the CNT fiber electrode and into the nerve tissue (Figure S25). The optimal parameters of the controllable stimulation group ($7.3 \text{ mW} \cdot \text{mm}^{-2}$, 30 s on/30 s off, 20 min duration) were identified through electrophysiology experiments (Figures S26–28). In vivo recordings showed that the nerve conduit delivered a low-frequency pulsed current with distinct relaxation intervals (Figure S29). The charge density per pulse was $15\text{--}20 \mu\text{C} \cdot \text{cm}^{-2}$, below the widely accepted safety threshold of $30 \mu\text{C} \cdot \text{cm}^{-2}$,^{34–36} indicating operation within a safe stimulation regime. Moreover, the gradually ramped stimulation waveform reduces the rate of membrane depolarization and avoids abrupt neural recruitment. This may suppress onset responses that are typically responsible for involuntary muscle contractions during stimulation.^{37,38} Video S2 showed no obvious muscle twitching under the stimulation conditions.

Studies of nerve conduction block have demonstrated the ability to reversibly suppress evoked neural signals (Figure S30). Remarkably, prolonging the total stimulation duration from 5 to 20 min progressively increased the blocking ratio from 3% to 97%, stabilizing thereafter (Figure 4b). This effect arises from a depolarization block induced by current injection at the electrode–nerve interface. Specifically, the applied current induces sustained depolarization of the neuronal membrane, leading to inactivation of voltage-gated sodium channels and suppression of action potential propagation.^{39,40} Notably, compound nerve action potentials (CNAP) returned to baseline after stimulation ceased (Figure S31), confirming the reversibility of the blockade without detectable functional impairment. In contrast, the continuous stimulation group (employing a Zn–O₂ battery-integrated nerve conduit with PAAm/sodium chloride (NaCl) hydrogel) showed no significant analgesic effect and achieved a maximum blocking ratio of only 42% after stimulation (Figure 4c). These results underscore the critical importance of waveform precision and adjustable stimulation duration for achieving effective neural conduction block.

It is critical to ensure that stimulation does not compromise cellular integrity or induce unintended tissue damage. To assess cellular responses to electrical stimulation, cells were cultured in custom Petri dishes for stimulation delivery (Figure S32). Three-day controllable stimulation maintained cell viability comparable to the control group, while the continuous stimulation group exhibited a 30–40% reduction in metabolic activity (Figure S33). Neurofilament protein 200 (NF200), a

key neuronal cytoskeleton marker, serves as an indicator of neuronal health and structural integrity. Following seven-day implantation of the nerve conduit in the sciatic nerve, NF200 immunofluorescent staining revealed that the controllable stimulation group exhibited a comparable NF200 positive area percentage to the control group, indicating well-maintained axonal integrity under controllable stimulation (Figure S34). In contrast, continuous stimulation resulted in marked degradation of neurofilament structure. These results demonstrate that the optimized pulsing parameters of the nerve conduit prevent overstimulation-induced axonal damage while maintaining blocking efficacy.

Our findings demonstrate that electrical stimulation modality critically modulates nociceptive signaling pathways, with controllable stimulation eliciting distinct neurobiological effects compared to continuous stimulation. Transient receptor potential vanilloid 1 (TRPV1) is a key mediator of pain perception in sensory neurons.^{41–43} Immunofluorescence quantification revealed that controllable stimulation (Figure S35), but not continuous stimulation (Figure S36), induced a rapid and significant reduction in TRPV1 membrane expression, consistent with acute electrophysiological outcomes. Since TRPV1 mediates nociception through cation influx-induced depolarization, its modulation consequently alters intracellular calcium dynamics. This reduction in TRPV1 expression underlies the observed normalization of capsaicin-evoked calcium ion (Ca^{2+}) influx to baseline levels in sensory neurons by controllable stimulation (Figure S37). Furthermore, the antinociceptive potential of controllable stimulation extends to neuroinflammatory modulation.^{43–45} It significantly promotes an anti-inflammatory milieu, as evidenced by enhanced M2 macrophage polarization (Figure S38), elevated anti-inflammatory cytokine IL-10 (Figure S39a), and reduced pro-inflammatory cytokine TNF- α levels (Figure S39b). By contrast, continuous stimulation exerted negligible effects on both TRPV1 dynamics and neuroinflammatory markers. Together, these results suggest that controllable electrical stimulation of the light-controlled battery-integrated nerve conduit alleviates nociception through coordinated suppression of TRPV1-mediated signaling and promotes anti-inflammatory responses.

Building on the observed cellular mechanisms, we evaluated the *in vivo* analgesic efficacy of the light-controlled battery-integrated nerve conduit implanted in the sciatic nerve. Crucially, the controllable stimulation of the nerve conduit effectively blocked capsaicin-induced acute nociception. Behavioral assessments (mechanical allodynia and thermal hyperalgesia) revealed that although the acute pain model exhibited significantly enhanced sensitivity, controllable stimulation of the nerve conduit postcapsaicin abolished these aberrant pain responses, restoring sensitivity to levels indistinguishable from healthy controls (Figure S40). This demonstrates that the controllable stimulation of the nerve conduit suppresses pathological pain without impairing baseline nociceptive function. We next evaluated the therapeutic potential for peripheral nerve pain using a sciatic nerve chronic constriction injury (CCI) model (Figure S41). Crucially, a single session of controllable stimulation, initiated at the established pain phase, produced a significant and rapid reversal of both mechanical allodynia and thermal hyperalgesia, with analgesic effects persisting for at least 4 h (Figure S42). Moreover, long-term daily controllable stimulation of the nerve conduit from post-CCI promoted progressive neurological

recovery (Figure S43). Whereas untreated CCI rats (CCI pain model group) maintained severe pain hypersensitivity, the controllable stimulation group exhibited sustained improvement, ultimately restoring mechanical thresholds and thermal latencies to levels comparable to those of healthy controls (Figure 4d,e, Videos S3 and S4). This complete functional restoration underscores the robust therapeutic efficacy and neurorestorative potential of the light-controlled battery-integrated nerve conduit in mitigating peripheral nerve pain.

The observed functional recovery involves TRPV1-dependent immunomodulation, as supported by histological evidence. Immunofluorescence analysis revealed that controllable stimulation of the nerve conduit significantly downregulated TRPV1 expression in the dorsal root ganglion (DRG) and spinal cord to levels comparable to those of healthy controls (Figures 4f and S44). This TRPV1 suppression correlates with a marked attenuation of local neuroinflammation, demonstrated by reduced CD11b (a marker of innate immune cells) protein expression (Figure S45) and a significantly reduced systemic pro-inflammatory burden, as evidenced by decreased serum levels of IL-6 and IL-1 β (Figure S46). Furthermore, TUNEL and NF200 staining showed no detectable tissue damage relative to healthy controls, providing direct evidence of the strategy's safety (Figure S47). The CNAP amplitude in the controllable stimulation group was comparable to the healthy control group, indicating improved nerve conduction function (Figure S48). Collectively, these findings strongly support the hypothesis that controllable stimulation of the nerve conduit exerts its therapeutic effects, at least in part, through coordinated modulation of TRPV1 signaling and inflammatory pathways, thereby achieving both analgesia and restoration of neural homeostasis in peripheral nerve pain.

In addition to alleviating core somatosensory deficits, the controllable stimulation of the nerve conduit effectively mitigates significant comorbidities associated with neuropathic pain. The treatment significantly ameliorates affective dysregulation, as demonstrated by an improved performance in the elevated plus maze (Figure 4g). Furthermore, it rescues motor dysfunction, as indicated by reduced traversal time on the balance beam compared to the untreated CCI pain model group (Figure S49). Critically, controllable stimulation attenuates gastrocnemius atrophy induced by sciatic neuropathy, as demonstrated by a higher wet weight ratio and preserved muscle fiber cross-sectional area, reaching levels comparable to those of healthy controls (Figure S50). These collective improvements in affective behavior, motor coordination, and muscle integrity highlight the broad therapeutic impact of the light-controlled battery-integrated nerve conduit in restoring both functional and structural homeostasis disrupted by peripheral nerve damage.

The biosafety of the light-controlled battery-integrated nerve conduit, which is a critical factor for its translational potential, was evaluated *in vitro* and *in vivo*. First, cytotoxicity assays demonstrated no significant difference in cell proliferation between the controllable stimulation group and the healthy control group, indicating no cytotoxicity (Figures S51 and S52). Furthermore, *in vivo* implantation of the nerve conduit on the sciatic nerve of healthy rats induced no observable alterations in cell morphology, hematological parameters, structural integrity at the implantation site, or major organs (heart, liver, spleen, lungs, and kidneys), confirming its biocompatibility *in vivo* (Figure S53). Additionally, thermal monitoring revealed a minimal temperature increase of only

0.7 °C in directly illuminated regions during stimulation, confirming its thermal safety for cutaneous applications (Figure S54).

The light-controlled battery-integrated nerve conduit enables fully implantable and wireless stimulation via its NIR-triggered on-demand activation mechanism. The bio-compatible and compact device requires no external control circuits, conforms to neural anatomy, and delivers precisely controllable stimulation. Consequently, elimination of percutaneous wiring significantly reduces clinical risks, including lead-associated complications (e.g., migration, fracture) and infection.^{16,17} Moreover, its dynamic tunability enables wireless, real-time parameter adjustment. This capability accommodates disease progression or therapeutic tolerance while preventing axonal damage associated with overstimulation. Furthermore, the device minimizes power consumption to ensure stable long-term operation. Notably, the device size is ≈ 13.7 , 65.6, and 1.5 times smaller than that of the implantable cooling stimuli devices, drug delivery devices, and other electrical stimuli devices, respectively. Meanwhile, the treatment time surpasses by a factor of at least 3.3 (Figure 4h and Table S2).

CONCLUSIONS

In this study, we report a light-controlled battery-integrated nerve conduit featuring a tunable electrical output driven by the light-induced relocation of water molecules within the electrolyte. The nerve conduit exhibits rapid response times with its output waveform directly modulated by the intensity and pulsing protocol of incident light, eliminating the need for external controllers. This light-induced tunability of the electrical output establishes a paradigm for advancing smart, implantable bioelectronics.

The compact, light-controlled battery-integrated nerve conduit enables conformal wrapping around nerves, facilitating in situ personalized electrical stimulation. In vivo evaluations confirm its efficacy in peripheral nerve pain management and highlight its promise for minimally invasive programmable neuromodulatory therapies. It provides a universal solution for wireless, compact, and convenient electrical stimulation. The light-controlled battery-integrated nerve conduit may also be adapted for a broad spectrum of electrotherapeutic applications including nerve and bone regeneration, wound healing, and skeletal muscle stimulation.

EXPERIMENTAL METHODS

Preparation of the Stimuli-Responsive Electrolyte

First, polydopamine ($2 \text{ mg}\cdot\text{mL}^{-1}$) was dispersed in deionized water (Unique-LC R10 water purification system) via sonication for 15 min to ensure a uniform suspension. Subsequently, sodium laurate (98.0%, 25 wt %) was added to the dispersion, and the mixture was stirred at 60 °C for 10 min to obtain a homogeneous solution. Afterward, acrylamide ($213.3 \text{ mg}\cdot\text{mL}^{-1}$, as the monomer), methylene-bis-acrylamide (1.41 wt %, mass ratio relative to acrylamide, as the cross-linker), and ammonium persulfate (0.28 wt %, mass ratio relative to AAm, as the initiator) were added and fully dissolved under continuous stirring. Once homogenized, N,N,N',N' -tetramethylethylenediamine (1%, v/v ratio relative to the total solution, as the accelerator) was introduced to initiate free-radical polymerization. The resulting precursor solution was poured into a Polytetrafluoroethylene (PTFE) culture dish and polymerized in a sealed environment at 60 °C for 5 min to form the stimuli-responsive electrolyte. Finally, the electrolyte was covered with a PE (80.0%) film

and placed in a constant temperature and humidity chamber (25 °C, 20% RH) for 5 h.

Preparation of the Light-Controlled Battery-Integrated Nerve Conduit

The nerve conduit was constructed using a Zn–O₂ battery system. First, a Zn foil anode ($2 \times 5 \text{ mm}^2$) and a CNT/Pt film cathode ($2 \times 5 \text{ mm}^2$) were horizontally positioned at opposite ends on the same surface of the stimuli-responsive electrolyte layer ($10 \times 5 \text{ mm}^2$). Conductive CNT fibers were connected to the electrodes and extended outward to allow electrical interfacing. Finally, a flexible PE film ($11 \times 6 \text{ mm}^2$) was thermally sealed around the entire assembly, forming a waterproof encapsulation while maintaining mechanical flexibility.

Acute In Vivo Electrophysiology Trial

Rats were anesthetized, and a nerve conduit was implanted at the midsegment of the sciatic nerve. A pair of bipolar stainless-steel electrodes was placed at the proximal nerve segment for electrical stimulation, with an interelectrode distance of 0.5 mm. Another identical electrode pair was positioned at the distal nerve segment for signal acquisition, also with a 0.5 mm spacing. The distance between the stimulation and recording sites was maintained at 14 mm to ensure optimal signal fidelity. Both electrode pairs were connected to a multichannel stimulator (PowerLab 15T, ADInstruments), and a ground electrode was inserted subcutaneously at the base of the tail. Different pulsing protocols and durations of NIR irradiation (808 nm, $7.3 \text{ mW}\cdot\text{mm}^{-2}$) were applied by modulating an external laser emitter (LWIRPD-SF-808). After stimulation, electrical pulses (1 mA pulse amplitude, 1.0 Hz frequency, 0.05 ms pulse width) were delivered to evoke CNAP, which was recorded and amplified using LabChart software with a sampling rate of 4 kHz and a total acquisition time of 5 s. The blocking ratio of CNAP was calculated as follows:

$$\text{the blocking ratio } R_{\text{block}} = \left(\frac{A_0 - A}{A_0} \right) \times 100\% \quad (1)$$

where R_{block} is the blocking ratio of CNAP, A_0 is the initial CNAP amplitude, and A is the post-treatment CNAP amplitude.

Ethical Approval

All animal experiments were conducted following the Guidelines for the Care and Use of Laboratory Animals issued by the National Institutes of Health (NIH, USA) and approved by the Institutional Animal Care and Use Committee (IACUC) of Nanjing University (approval number: IACUC-2405010, Nanjing, P.R. China).

von Frey Test

The mechanical paw withdrawal threshold was assessed using the von Frey filament test. Before testing, rats were individually placed in a transparent test cage with a metal mesh floor, allowing access to the plantar surface of the hind paws from below. Animals were acclimated to the environment for 30 min to minimize stress and movement. All tests were conducted in a quiet room to avoid any external disturbances. During testing, calibrated von Frey filaments were applied perpendicularly to the midplantar surface of the hind paw through the mesh floor. Each filament was gently pressed until it bent slightly and was maintained in place for 2 s. A brisk paw withdrawal, flinching, or licking was considered a positive response. The 50% paw withdrawal threshold was determined by using the up–down method. Testing began with a filament of intermediate force. If no withdrawal response was observed, then a filament with greater force was applied; if a response occurred, then a filament with lower force was used. To prevent sensitization or fatigue, each stimulus was applied with an interval of no less than 30 s. No more than 10 stimulations per animal were performed daily to avoid stress-induced interference with the behavioral responses.

Hot-Plate Test

Thermal paw withdrawal latency was evaluated by using a hot plate analgesia meter. Before testing, each rat was placed individually in the testing room for a 30 min habituation period to minimize stress-

induced variability. The hot plate was maintained at a constant temperature of 52 °C throughout the experiment. The surface of the hot plate was cleaned with 75% ethanol before each trial to ensure consistency and eliminate olfactory interference. At the start of the test, the rat was gently placed at the center of the heated surface, and a stopwatch was immediately activated. The latency to exhibit a nociceptive response (hind paw licking, paw withdrawal, or jumping) was recorded as the paw withdrawal latency. Once these behaviors were observed, the animal was promptly removed from the plate. Rats were also removed if no response occurred within 30 s to prevent thermal injury. Repeated measurements in the same animal were conducted at intervals of no less than 15 min to avoid sensitization or carryover effects.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsnano.6c06247>.

Fabrication, characterization, cell and animal experiments, biocompatibility studies of the light-controlled battery-integrated nerve conduit; external control volume and energy consumption comparison with other externally integrated components for bioelectronics output regulation; and comparison with other pain treatment devices (PDF)

Rapid and precise response of nerve conduit output voltage to light modulation (MP4)

Controllable stimulation of the nerve conduit for pain management under light modulation (MP4)

von Frey test evaluating mechanical allodynia in treated rats (MP4)

Hot plate test evaluating thermal hyperalgesia in treated rats (MP4)

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Author Contributions

Y.Z. directed all aspects of the project. E.H., H.W., F.L., Y.J., and J.S. performed experiments on the fabrication of light-controlled battery-integrated nerve conduits and characterizations of structure. E.H. and H.W. performed experiments on the electrochemical properties. E.H., H.W., T.Y., and L.L. performed the cell and animal experiments. E.H. and H.W. performed and analyzed the biosafety of light-controlled battery-integrated nerve conduits. All authors discussed the data. E.H., H.W., and Y.Z. wrote the paper. All authors discussed and commented on the paper.

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Notes

The authors declare no competing financial interest.

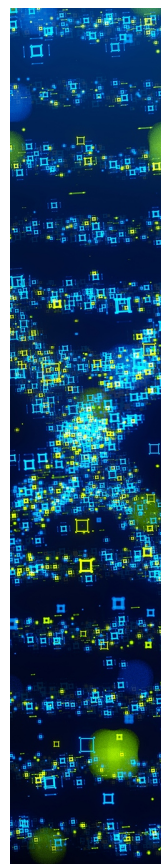
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He, E. and Wang, H. contributed equally to this work as co-first authors. We thank the Centre for Shared Scientific Research Facilities of Nanjing University.

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