

RESEARCH ARTICLE OPEN ACCESS

Thermoresponsive Soft and Self-Anchoring Cuff Electrode for Chronic Peripheral Interfaces

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Received: 22 January 2026 | **Revised:** 5 July 2026 | **Accepted:** 28 July 2026

Keywords: peripheral nervous system (PNS) | self-closing | self-holding | shape memory polymer (SMP) | thermal deformation

ABSTRACT

Cuff type neural interfaces are widely used for peripheral nerve stimulation and monitoring. The traditional cuff electrodes typically require sutures or rigid fixation; this can lead to nerve damage and unstable electrode contact, ultimately compromising long-term performance. To address these issues, we developed a thermoresponsive soft and self-anchoring (TSSA) cuff electrode that automatically wraps around nerves in response to body temperature. This functionality is made possible by a shape memory polymer (SMP) substrate designed to soften and deform near physiological temperatures, enabling the electrode to self-close and securely hold without the need for an external force. Additionally, the SMP provides gentle yet stable contact with the nerve, thereby enhancing biocompatibility. In vivo experiments using rat sciatic nerves demonstrated reliable recordings of mechanically evoked nerve responses for 16 weeks, with signal-to-noise ratios reaching approximately 10 and stable impedance profiles. Histological and immunohistochemical analyses showed no significant tissue damage or inflammatory responses caused by the implanted device. By removing the need for sutures and providing a soft, stable contact with the nerve, the cuff electrode represents a safe and durable platform for chronic neural interfacing. The proposed technology holds strong potential for use in prosthetic limbs and bioelectronic medicine.

1 | Introduction

Peripheral nerve interfaces (PNIs) represent part of a cutting-edge biomedical technology used to facilitate bidirectional communication between the peripheral nervous system and external devices [1–5]. These interfaces have been pivotal in advancing the restoration of motor function for individuals experiencing paralysis, enabling control of prosthetic limbs, and providing effective management of chronic pain due to neuropathy or spinal cord injuries [6–8]. Traditional PNIs include a variety of electrode designs, including cuff, patch, rotating, and needle electrodes, each suited to specific applications depending on the

clinical setting or research requirement [4, 9–12]. Cuff electrodes accurately record neural signals and modulate nerve activity due to their ability to completely cover peripheral nerves. Thus, they have become the predominant choice in PNIs for clinical and research applications [4, 9, 13, 14]. However, despite their widespread use, cuff electrodes have inherent limitations related to their fixation strategies. Specifically, cuff electrodes often require sutures [15] or additional mechanical fixtures for stable placement [16], which introduces surgical complexity and risks such as potential nerve compression, ischemia, and fibrosis. These factors can compromise device performance and lead to adverse outcomes, particularly during long-term implantation.

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For peripheral nerve electrodes to achieve optimal performance and long-term reliability *in vivo*, they must meet several criteria. These include mechanical properties that mimic the softness and flexibility of peripheral nerve tissues, secure and conformal adhesion to prevent migration, and biocompatibility that supports seamless integration with the surrounding environment. To reduce mechanical mismatch, prior studies have introduced soft and stretchable elastomer-based cuff electrodes, which enhance conformal contact and biocompatibility [9, 17–19]. Additional cuff designs have incorporated holdable structures such as sleeves [20], helices [21], and other mechanically adaptive geometries to assist with nerve gripping [22]. More recently, self-wrapping cuffs activated by fluid injection methods have improved controllability of grasping pressure or structural deformation, enabling the electrodes to maintain spiral shapes around peripheral nerves in small-animal models [23].

Furthermore, recent advances in cuff electrodes have incorporated microfluidic channels, thermally reformed spiral structures [24], electrochemical actuation [25], or bioresorbable materials [26] to realize self-wrapping or active wrapping mechanisms around peripheral nerves. While these innovations demonstrate promising performance, especially in small-animal models, they often rely on external activation inputs, swelling-induced deformation, elevated thermal inputs, or structurally bulky architectures. Such dependencies can limit scalability, complicate fabrication, and hinder reliable implantation on very small-diameter nerves. The peripheral nerves of rodents, which range from millimeter to submillimeter scales, require exceptionally secure fixation; yet, suturing is difficult, and even minor imprecision in electrode placement can significantly deteriorate signal fidelity.

To overcome these challenges, several studies have explored miniaturized cuff electrodes with built-in fixation functionalities such as magnetically aligned liquid-crystal polymer [27] systems, sleeve-type self-locking structures [9], and other mechanically adaptive designs for peripheral nerve applications in small animals [28, 29]. While these strategies improve handling and positional robustness, many still require auxiliary mechanical elements, preconfigured geometries, or activation mechanisms that may introduce fabrication complexity or restrict further miniaturization.

Here, we introduce a novel thermoresponsive soft and self-anchoring cuff electrode that we call the TSSA cuff electrode. The electrode enables thermoresponsive softening and bending at body temperature and provides a self-anchoring function on the peripheral nerve without requiring glues, structures, or sutures. The TSSA cuff electrode was fabricated as a two-layered structure using a thermally curable shape memory polymer (SMP). The thermoresponsive bending mechanism of the device induced by body temperature results from differences in thermal stress between layers and changes in the elastic modulus. The SMP used in the cuff electrode was engineered to transition from a glassy state at room temperature to an elastic state at body temperature. Thus, this device remains flat and easy to handle at room temperature before surgery. However, upon implantation into peripheral nerves, the cuff autonomously bends at body temperature to conform to the geometry and mechanical stiffness of the peripheral nerve tissue. The TSSA device and its functions

are implemented on a single wafer using conventional MEMS techniques, eliminating the need for an additional programming process to define the device's specific shape. We validated the mechanical and thermal properties of the TSSA cuff electrode and tested its *in vivo* performance by applying the fabricated device to the sciatic nerve. The electrode's performance and applicability in biological environments during both acute and chronic stages were demonstrated through measurements of electrophysiological signals under electrical and mechanical stimulation.

2 | Results

2.1 | Fabrication and Functioning of the TSSA Cuff Electrode

We developed a TSSA cuff electrode designed to facilitate thermoresponsive softening and bending, with self-anchoring on the sciatic nerve at body temperature (35°C–38°C) (Figure 1a–d). The thermoresponsive mechanical properties of the SMP used in the cuff electrode's substrate were engineered to be glassy at room temperature (20°C) and elastic at body temperature. The TSSA cuff electrode operates as follows: at room temperature (20°C), the device retains its original flat shape. Upon implantation and exposure to body temperature (37°C), the electrode transforms to wrap around the nerve and maintain a stable configuration (Figure 1b). The SMP is designed to increase the adhesion between the substrates at body temperature, allowing the device to stably and tightly hold the peripheral nerve (Figure 1c; Videos S1 and S2). The TSSA cuff electrode transitions from the flat state to the fully wrapped state within approximately 2–3 min. The wrapping process occurs gradually through thermoresponsive softening and bilayer-induced bending, rather than abrupt snapping, thereby minimizing the risk of acute mechanical trauma during implantation. In addition to the initial self-closing behavior, the surgical repositioning capability of the TSSA cuff electrode was evaluated during implantation. After self-closing around the sciatic nerve, the TSSA cuff could be gently reopened using fine forceps, relocated along the nerve, and released to reclose around the desired position (Figure S1). To further assess whether repeated manipulation affects the post-closing holding capability, reopening–relocation–reclosing cycles were repeated using a nerve-mimicking cylindrical model, followed by a pull test after each cycle (Figure S1b). The pulling force decreased by 6.99% during the second reopening–reclosing cycle compared with the initial cycle but was subsequently maintained at approximately 1.3 N/mm² during 10 cycles. This result indicates that the TSSA retained its holding capability after repeated repositioning.

The autonomous bending of the TSSA cuff electrode arises from the thermo-mechanical properties of the SMP combined with a thermal pre-strain in the first SMP layer (Figure 1e). This pre-strain is a result of the simultaneous thermal expansion of the first SMP and the polymerization of the second SMP layer. During the second SMP's curing, the expanding first SMP transitions to a glassy state, thereby locking in the thermal strain upon completion of the curing process.

This unique mechanical behavior, along with the device's thickness and method of fabrication, was deliberately designed to

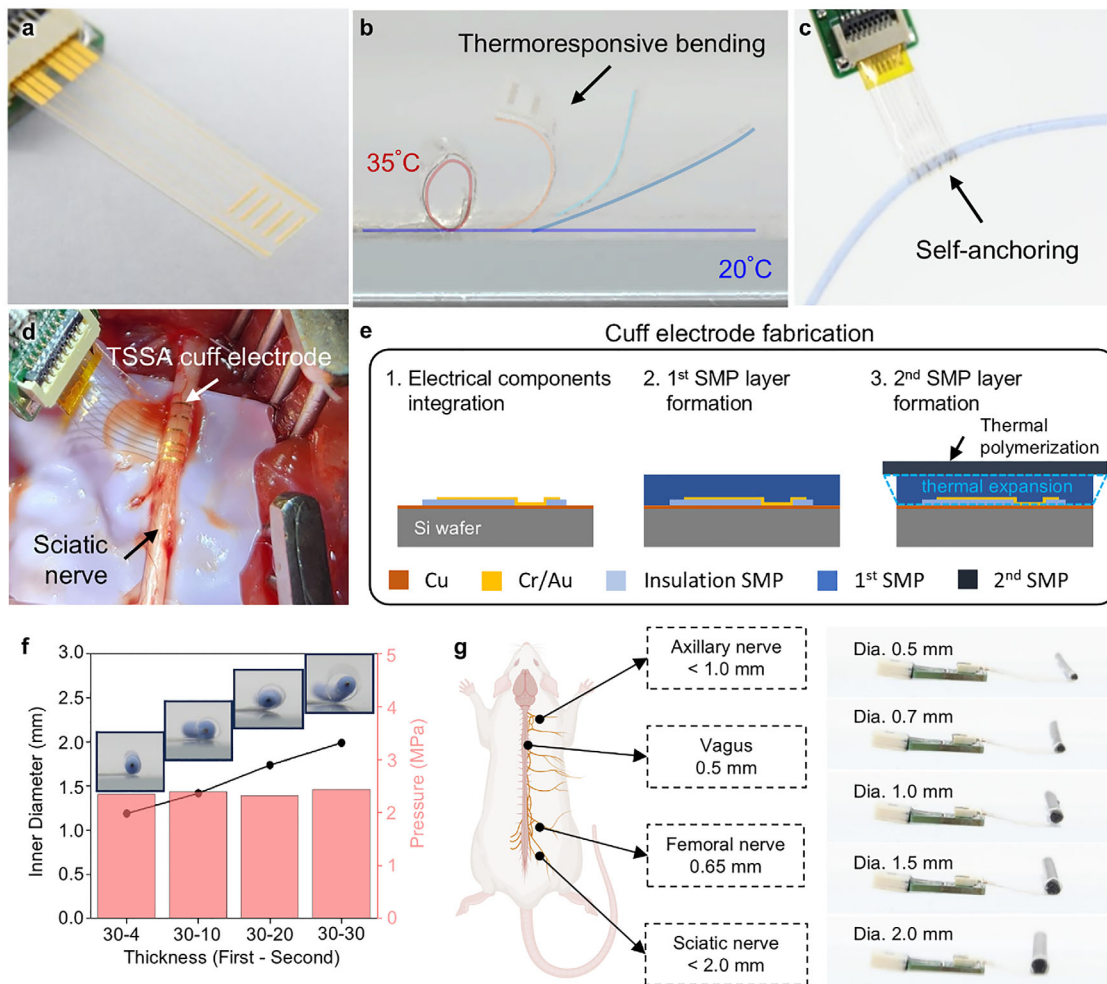


FIGURE 1 | A thermoresponsive soft and self-anchoring (TSSA) cuff electrode. A schematic illustrating the TSSA's temperature-responsive deformation that enables the device to automatically secure itself around the rat sciatic nerve. The figures show (a) the device's states at room temperature (20°C), (b) during thermoresponsive softening and bending upon exposure to body temperature (37°C), and (c) in a self-anchored state around the nerve. (d) An image showing the electrode's placement on the sciatic nerve during in vivo implantation. (e) Thermal stress differences in the double-layered SMP during the fabrication process. (f) The plot and images show the self-closed inner diameter of the bent double-layered SMP substrate and the corresponding normalized anchoring pressure for different second SMP layer thicknesses at 36°C . (g) An illustration of the electrode's closing behavior based on the size of a simulated nerve circumference. 3D-printed nerves with diameters of 0.5, 0.7, 1.0, 1.5, and 2.0 mm were used.

enable autonomous deformation via the double-layered SMP structure, operating without relying on the conventional shape-memory effect. When the device closes, its first layer faces inward, positioning the electrode pattern on its surface to ensure adhesion to the nerve. Considering this deformation direction, the device was fabricated by patterning the wafer before forming the substrate, followed by encapsulation with the double-layered SMP (Figure 1e; Figure S2).

The bending diameter of the proposed cuff electrode at body temperature is determined by the thickness of its first and second SMP layers. To optimize the bilayer geometry of the cuff electrode, we compared the self-closing inner diameter and normalized detachment pressure of SMP structures with different thickness ratios (30–4, 30–10, 30–20, and 30–30 μm) (Figure 1f). The normalized detachment pressure did not differ substantially among the tested configurations, proving sufficient for self-anchoring in all cases. Therefore, the 30–4 μm configuration (the thickness of the first and second SMP layers: 30 and 4 μm) shows that the

bending property is optimized for a diameter of approximately 1 mm, corresponding to the size of the rat sciatic nerve.

The bending capability of the TSSA cuff electrode was designed to accommodate rat sciatic nerve diameters ranging from approximately 0.5 to 2 mm; this includes nerves such as the axillary, vagus, femoral, spinal, and sciatic nerves (Figure 1g). To confirm its adaptability to various nerve sizes, 3D-printed cylindrical models with diameters between 0.5 and 2.0 mm were employed. The TSSA cuff electrode wrapped around all cylindrical nerve models within this range, indicating diameter adaptability beyond a single fixed nerve size (Figure 1g).

The TSSA cuff electrode consists of seven independent channels, each connected from an individual connecting pad to a signal recording pad through a serpentine electrode line (Figure S3). The overall device size was $15.2\text{ mm} \times 5.0\text{ mm}$, and the separation between adjacent electrode lines in the routing region and between recording pads was 400 and 450 μm , respectively. The

metal lines were designed with a serpentine pattern to reduce possible damage to the electrode during deformation. The signal recording pads are arranged horizontally to maximize the contact surface area once the electrode wraps around the nerve.

Electrochemical impedance spectroscopy (EIS) was performed in an in vitro setting to validate the recording capability of the fabricated electrode array. The EIS results closely matched values reported in previous studies (Figure S4) [20].

2.2 | Thermoresponsive Softening and Bending

The temperature at which the closing deformation is triggered depends on the *N*-glycidyl ether (NGDE) content in the polymer. The SMP substrate is designed to exhibit temperature-dependent properties: it remains in a glassy state at room temperature, transitions between room and body temperature, and becomes elastic at body temperature. To verify the deformation at body temperature, various ratios of NGDE to other components were combined, and dynamic mechanical analysis (DMA) was performed to determine the deformation temperature relative to the NGDE content (Figure 2a,b). The SMP substrate with 32.9 wt.% of NGDE showed a transition where the storage modulus fell below the loss modulus at approximately 25°C, marking the onset of deformation. However, samples containing 3.5 g of poly(bisphenol A-co-epichlorohydrin), 1.6 g of EC 301, and either 19.7 or 42.4 wt.% of NGDE showed deformation at temperatures of 0°C and above 50°C, well below and above body temperature, respectively. DMA analysis revealed a peak in the $\tan(\delta)$ value at 30°C. Differential Scanning Calorimetry (DSC) analysis was performed to confirm the thermal transition of the SMP blends with different NGDE contents. The glass transition temperature (T_g) values of the SMP blends containing 1.75, 2.50, and 3.75 g NGDE were approximately 25°C, 37°C, and 58.5°C, respectively. Among these compositions, the 2.50 g NGDE blend was selected because its T_g was close to physiological temperature, allowing the device to remain stable at room temperature while enabling full thermoresponsive activation at 35°C–38°C (Figure S5).

The dual-curing process of the first and second SMP substrates creates a thermal strain mismatch between the two layers (Figure 2c). When in the glassy state, the first layer's compressive stress induced by the thermal pre-strain of the first SMP layer is insufficient to deform the device. However, as the substrate temperature approaches body temperature and the SMP transitions to an elastic state, the device can bend due to this compressive stress. Consequently, the combination of differential thickness, thermomechanical properties, and curing conditions of the SMP generates a bending moment toward the first layer, where the electrode is located, causing the device to wrap around the peripheral nerve in the SMP's elastic state.

2.3 | Mechanical Characterization of Nerve Anchoring

Conventional cuff electrodes are typically made of polymeric materials such as polyimide, parylene, polydimethylsiloxane (PDMS), and medical-grade silicone. To assess the holding performance of these electrodes, we fabricated a sleeve-type cuff

electrode using PDMS, a common substrate material. In contrast, the TSSA cuff electrode has a flat design without extra holding features such as sleeves to secure the peripheral nerve (Figure 3a). At body temperature, the device bends to close around the nerve; during this movement, adhesive contact points form, enabling the device to lock firmly in place. PDMS, however, does not have self-securing properties. Therefore, a triangular structure was added at one end to aid in securing the device, and interlocking holes were introduced at the contact points post-bending to achieve secure fixation (Figure 3b).

To quantitatively assess the adhesive property responsible for the fixation forces between contacting substrates at body temperature, pulling force and T-peel tests were performed under both dry and wet conditions (Figure S6). The T-peel test showed that under dry conditions, the adhesion strength of the SMP was six times greater than that of PDMS (Figure 3c). In the wet environment, PDMS maintained a similar adhesion force to its dry state at 0.039 N/mm², while the adhesion force of SMP increased considerably, ranging from 0.258 to 0.453 N/mm², representing a 70% increase. Furthermore, the adhesion strength varied with the NGDE content. Specifically, under dry and wet conditions, the respective adhesion strength was 0.129 and 0.215 N/mm² at 19.7 wt.% NGDE, and 0.211 and 0.638 N/mm² at 42.4 wt.% NGDE (Figure 3d). Studies have shown that variation in the curing agent or tackifier content in adhesives influences the compounds' adhesive properties, where the increased crosslinking density in epoxy/amine systems improves both adhesion strength and durability. Infrared spectroscopy (FTIR) analysis of epoxy resin revealed that the peak at 3400 cm⁻¹ corresponds to O–H (amine group) stretching, while the peaks at 2960, 2920, and 2860 cm⁻¹ represent C–H (epoxy group) stretching [30] (Figure 3e; Figure S7). Increasing NGDE content leads to a higher presence of both O–H and C–H groups. The proportions of these groups are directly involved in adhesion performance, with a greater NGDE content enhancing fixation forces under both dry and wet conditions.

In the pulling force test, PDMS- and SMP-based cuff electrodes were attached to a mockup nerve and pulled to identify the detachment point, thereby measuring the maximum fixation strength to the peripheral nerve (Figure 3f). The SMP-based cuff electrode exhibited a maximum fixation force of 0.848 N/mm², five times greater than that of the sleeve-type PDMS cuff electrode. Under wet conditions, the SMP-based cuff showed an even higher fixation force of approximately 1.636 N/mm², a value seven times greater than that of PDMS, while maintaining its locked configuration. This trend was consistent with the adhesion results observed in the T-peel test of the SMP and PDMS layers.

The sleeve-type cuff electrode based on PDMS relies on structural features to secure it to the nerve. In contrast, the proposed SMP-based cuff electrode relies on the material's properties and thermal pre-strain to enable closing and holding, resulting in a unique pulling force profile. Comparing the slopes of pulling force versus distance for SMP and PDMS confirmed the SMP's fixation mechanism (Figure 3g). While both materials showed similar slopes in the closing state, the slope for SMP in the holding state was nearly twice that of PDMS, indicating stronger fixation. Specifically, the slope for SMP in the holding state ranged from 2.8 to 3.0, while for PDMS, this was 1.5. This considerable

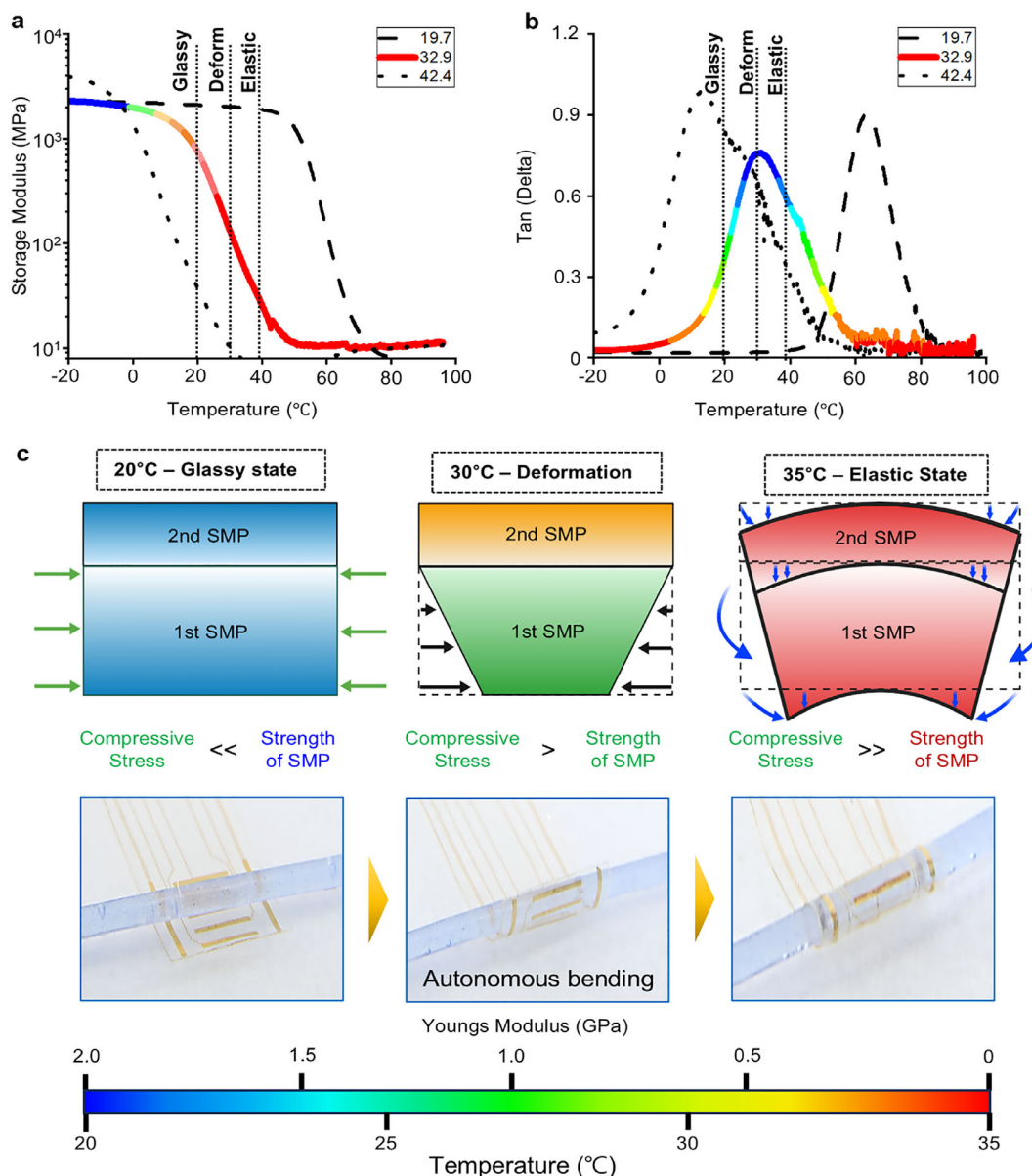


FIGURE 2 | Thermoresponsive characteristics of the TSSA cuff electrode. The results of a dynamic mechanical analysis (DMA) for the storage modulus (a) and $\tan(\delta)$ (b) of SMP substrates with 19.7, 32.9, and 42.4 wt.% of NGDE. Panel (c) illustrates the thermoresponsive softening and autonomous bending mechanism of the developed TSSA cuff electrode. The top panel displays the temperature-dependent Young's modulus and compressive stress of the double-layered SMP substrate. The middle panel presents images of the cuff electrode bending in response to temperature. The bottom panel illustrates the changes in the stiffness of the SMP with temperature.

difference highlights SMP's superior fixation strength compared to PDMS (Figure 3h,i). To validate the fixation performance in in vivo environments, the TSSA cuff electrode was attached to a rat's peripheral nerve. The device demonstrated an average maximum tensile strength of 2.7 ± 0.6 MPa (Figure S8), closely matching the in vitro results. These findings demonstrate SMP's potential for more effective and reliable nerve fixation in practical applications. The fixation stability of the TSSA cuff electrode was quantitatively supported by T-peel and mock-up nerve pulling tests. Compared with a PDMS-based cuff mock-up, the SMP-based TSSA showed higher adhesion strength and greater detachment resistance under both dry and wet conditions. In particular, the TSSA showed maximum pulling forces of 0.848 N/mm^2 under dry conditions and 1.636 N/mm^2 under wet

conditions, and the in vivo-like tensile strength measured on rat peripheral nerve was 2.7 ± 0.6 MPa. These results indicate that the TSSA can provide stable post-closing anchoring through thermoresponsive wrapping and SMP surface contact without sutures or additional locking structures.

2.4 | In Vivo Recording of Stimulation-Evoked Responses

The TSSA cuff electrode was applied to the rat sciatic nerve to evaluate its feasibility for in vivo electrophysiological recording. For electrical stimulation, a tungsten hook electrode was positioned more than 30 mm away from the center of the implanted

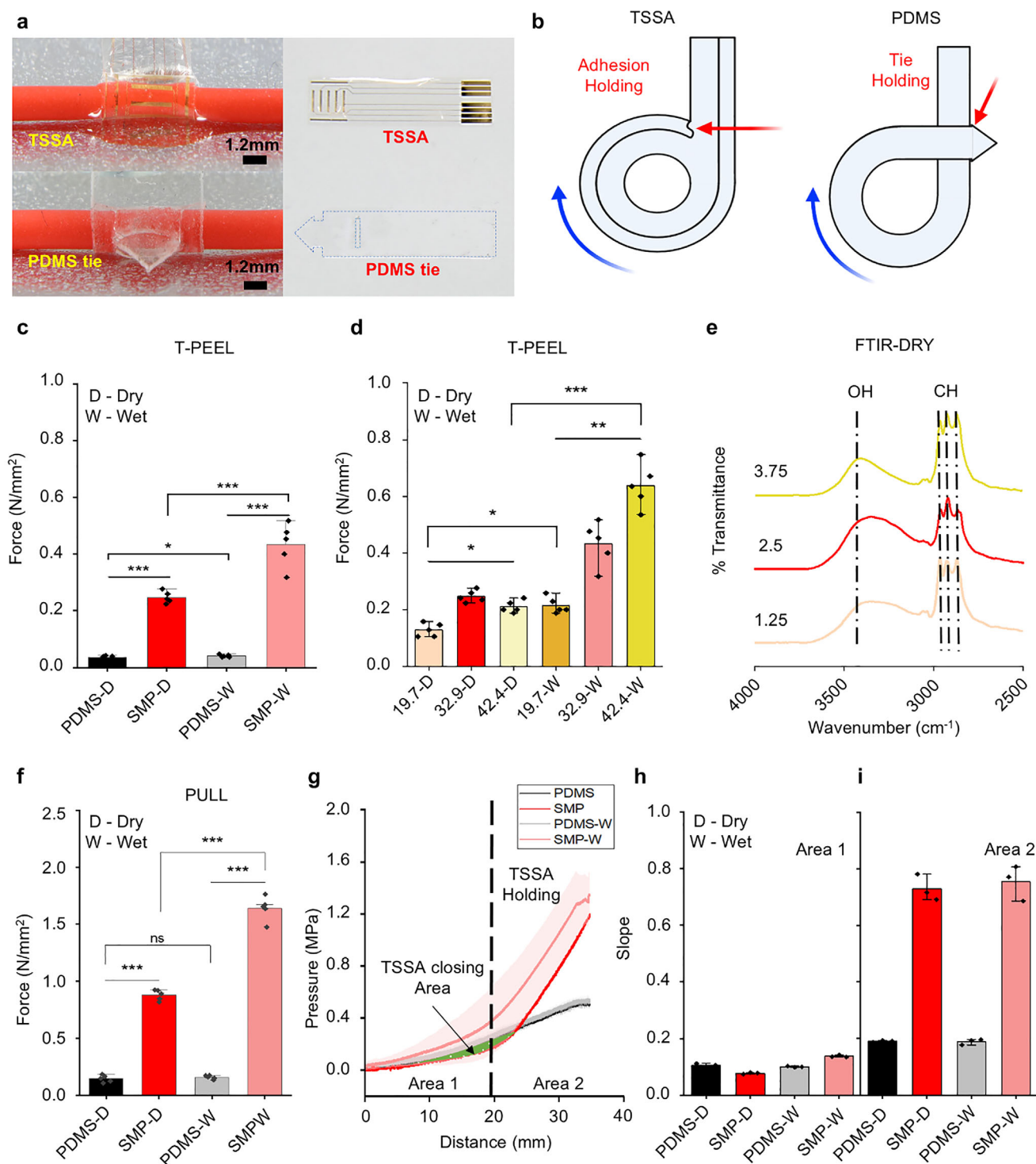


FIGURE 3 | Analysis of the nerve-holding properties via mechanical characteristic analysis. Panel (a) shows the TSSA cuff electrode (TSSA) and the PDMS-based cuff mock-up (PDMS tie) for comparing their anchoring properties. (b) A comparison of fixation structures between the TSSA and the PDMS tie. (c) The T-peel testing evaluated the adhesion of the TSSA cuff electrode and PDMS under dry (-D) and wet (-W) conditions. (d) The adhesion strength between TSSA surfaces under dry and wet conditions was measured for SMPs containing 19.7, 32.9, and 42.4 wt.% of NGDE. Panel (e) presents the FTIR results for SMPs with varying concentrations of NGDE (19.7, 32.9, and 42.4 wt.%). Panel (f) depicts the pulling force required to detach the TSSA and a PDMS device under dry and wet conditions, showing the pressure the TSSA substrates withstand during extension. (g) The pulling force behavior of the TSSA and PDMS tie, quantifying the detachment force and revealing different slope behaviors depending on the strain. The closure phase is divided into Areas 1 and 2 for the slope analysis. Panels (h, i) show a slope analysis of the closure (Area 1) and holding (Areas 2) phases, based on SMP characteristics.

TSSA cuff electrode. Biphasic pulses with a duration of 100 μ s were delivered at 1 Hz, with stimulation currents ranging from 0.1 to 1.0 mA. The resulting electrically evoked responses were recorded through the TSSA cuff electrode (Figure 4a; Figure S9).

The initial stimulation artifact was excluded from the amplitude analysis, and the peak-to-peak N1–P1 amplitude was measured from the subsequent post-artifact response window. In Figure S9a, the red dots and the red dashed line indicate the stimulus onset and the boundary of the post-artifact response region, respectively. The stimulation artifact, N1–P1 amplitude, and latency are annotated in the representative trace. Representative stimulus-triggered traces showed current-dependent increases in the evoked nerve response following the initial artifact (Figure 4c; Figure S9b). The peak-to-peak amplitude of N1–P1 increased with stimulation current and showed a nearly linear relationship with stimulation intensity ($R^2 = 0.97$; Figure 4b). For latency estimation, the first post-artifact negative deflection was defined as the N1 component. The latency from stimulus onset to the N1 component was 1.43 ± 0.17 ms, which corresponds to an estimated conduction velocity of 21.2 ± 2.7 m/s over the 30 mm stimulation-to-recording distance. These results confirm the capability of the TSSA cuff electrode to record electrically evoked compound nerve responses from the sciatic nerve [31, 32].

To further evaluate the stimulation capability of the TSSA cuff electrode, a PEDOT: PSS-coated channel was used to electrically stimulate the sciatic nerve, and distal muscle responses were recorded as compound muscle action potentials from the ipsilateral gastrocnemius muscle using needle electrodes (Figure S10).

We next examined whether the TSSA cuff electrode could detect responses associated with mechanical stimulation of the hind paw. The central plantar surface was subjected to tactile stimulation every 10 s using von Frey filaments (58.8, 147, and 588 mN) under the same recording configuration (Figure 4d). Representative nerve responses captured from two TSSA channels exhibited clear waveforms during repeated stimulation (Figure 4e; Figure S11). Notably, the peak-to-peak amplitude of these responses progressively increased with filament force (Figure 4f). However, von Frey stimulation activates cutaneous mechanoreceptors asynchronously via mechanical propagation through tissue layers. Thus, the resulting signals were not interpreted as canonical, time-locked CNAPs or fiber-specific nerve conduction waveforms. Consequently, these waveforms represent reproducible, force-dependent, and mechanically evoked nerve responses recorded directly from the sciatic nerve.

2.5 | Long-Term Recording of Mechanically Evoked Nerve Responses

To assess the long-term recording capability of the TSSA cuff electrode, the device was implanted around the rat sciatic nerve and monitored for 16 weeks. During this period, mechanically evoked nerve responses were recorded during brush stimulation of the hind paw. To evaluate whether the recorded responses were dominated by passive motion artifacts, passive limb movement was performed without direct sensory stimulation. Passive limb movement did not generate comparable stimulus-evoked nerve

responses (Figure 4g), whereas brush stimulation of the hind paw produced reproducible responses during the stimulation period (Figure 4h). Due to the uncertainty in precisely defining mechanoreceptor activation onset relative to external paw stimulation, conduction velocity was not determined. Instead, the mechanically induced signals were evaluated based on their amplitude and trial-to-trial reproducibility.

Analysis of weekly averages demonstrated that mechanically evoked nerve responses were detectable throughout the 16-week implantation period (Figure 4i). The response amplitude remained stable over time, and the signal-to-noise ratio (SNR), calculated from the averaged mechanically evoked responses, increased during the early implantation period, reaching 10.0 at week 6 and remaining 10.0 through week 16. To benchmark this performance, the SNR of the TSSA cuff electrode was compared with values from previously reported peripheral nerve cuff electrodes (Table S2). While varying calculation methods across the literature preclude a strict head-to-head comparison, the TSSA electrode maintained an SNR level highly comparable to existing designs over a long duration, clearly demonstrating its chronic stability. Furthermore, to corroborate this functional longevity, electrochemical impedance spectroscopy (EIS) was performed after 8 weeks of implantation to evaluate the electrochemical stability of the implanted TSSA electrodes (Figure S12). The impedance magnitude and phase were measured from 1 Hz to 1 MHz across five electrodes, showing that the implanted electrodes maintained electrochemical characteristics after long-term in vivo implantation. Combined with the consistent EIS, nerve response quality and high SNR, these results demonstrate the device's potential for chronic neural interface applications.

2.6 | Validation of Long-Term Biostability

Histological and immunohistochemical analyses were performed on explanted sciatic nerves to evaluate tissue responses and potential nerve damage after TSSA cuff electrode implantation. Four groups were compared based on morphological characteristics and cellular marker expression: control animals without surgery, sham-operated animals with nerve exposure but no implantation, and implanted animals assessed at 1 and 8 weeks after TSSA cuff electrode implantation (Figure 5a–d).

Hematoxylin and eosin (H&E) staining showed preserved overall fascicular morphology in the control and sham groups (Figure 5a,b). At 1 week after implantation, the implanted nerve showed evident swelling of the surrounding connective tissue, particularly around the epineurial and perineurial regions (Figure 5c, Figure S13). Quantitative analysis confirmed a marked increase in connective tissue thickness around both the tibial and peroneal nerve branches at 1 week (Figure 5e). By 8 weeks, this thickening was substantially reduced, and the connective tissue thickness was not significantly different from the control group (Figure 5d,e). These results indicate that the tissue swelling observed after implantation was most prominent during the early postoperative period and was attenuated during recovery.

Immunohistochemical staining was performed using Iba-1 to assess macrophage-associated inflammatory response, MBP to evaluate myelin integrity, NF to assess axonal structure, and DAPI

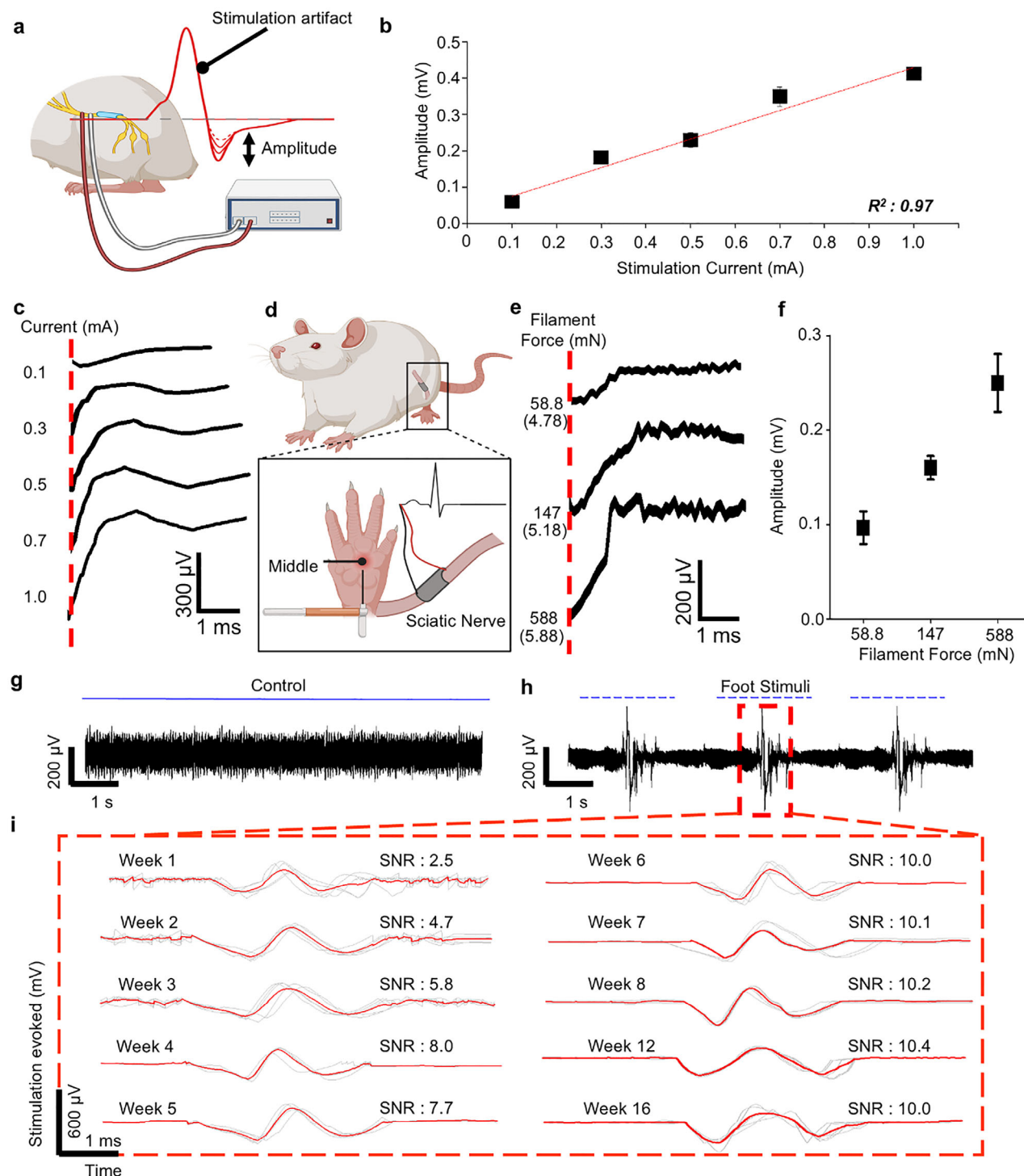


FIGURE 4 | In vivo acute and chronic recording of stimulation-evoked responses using the TSSA cuff electrode. (a) Schematic of in vivo electrical stimulation and recording. Electrical stimulation was delivered to the sciatic nerve using a tungsten hook electrode, and electrically evoked nerve responses were recorded with the TSSA cuff electrode. (b) Peak-to-peak amplitude of electrically evoked responses measured after excluding the initial stimulation artifact as a function of stimulation current from 0.1 to 1.0 mA. The response amplitude increased nearly linearly with stimulation current ($R^2 = 0.97$; $n = 5$). (c) Representative stimulus-triggered traces showing current-dependent electrically evoked responses recorded by the TSSA cuff electrode. (d) Schematic of hind paw mechanical stimulation using von Frey filaments. (e) Representative force-triggered traces showing mechanically evoked nerve responses recorded during von Frey filament stimulation. Red dashed line indicates start line of the mechanically evoked response. (f) Peak-to-peak amplitude of mechanically evoked nerve responses as a function of filament force. (g) Representative raw recording during passive limb movement without direct sensory stimulation. (h) Representative raw recording during hind paw brush stimulation. Blue dashed lines indicate periods without brush stimulation, and the red dashed box indicates the foot-stimulation period used for response analysis. (i) Weekly averaged mechanically evoked nerve responses and corresponding SNRs recorded over 16 weeks after implantation. Gray traces indicate individual stimulus-triggered responses, and red traces indicate average responses.

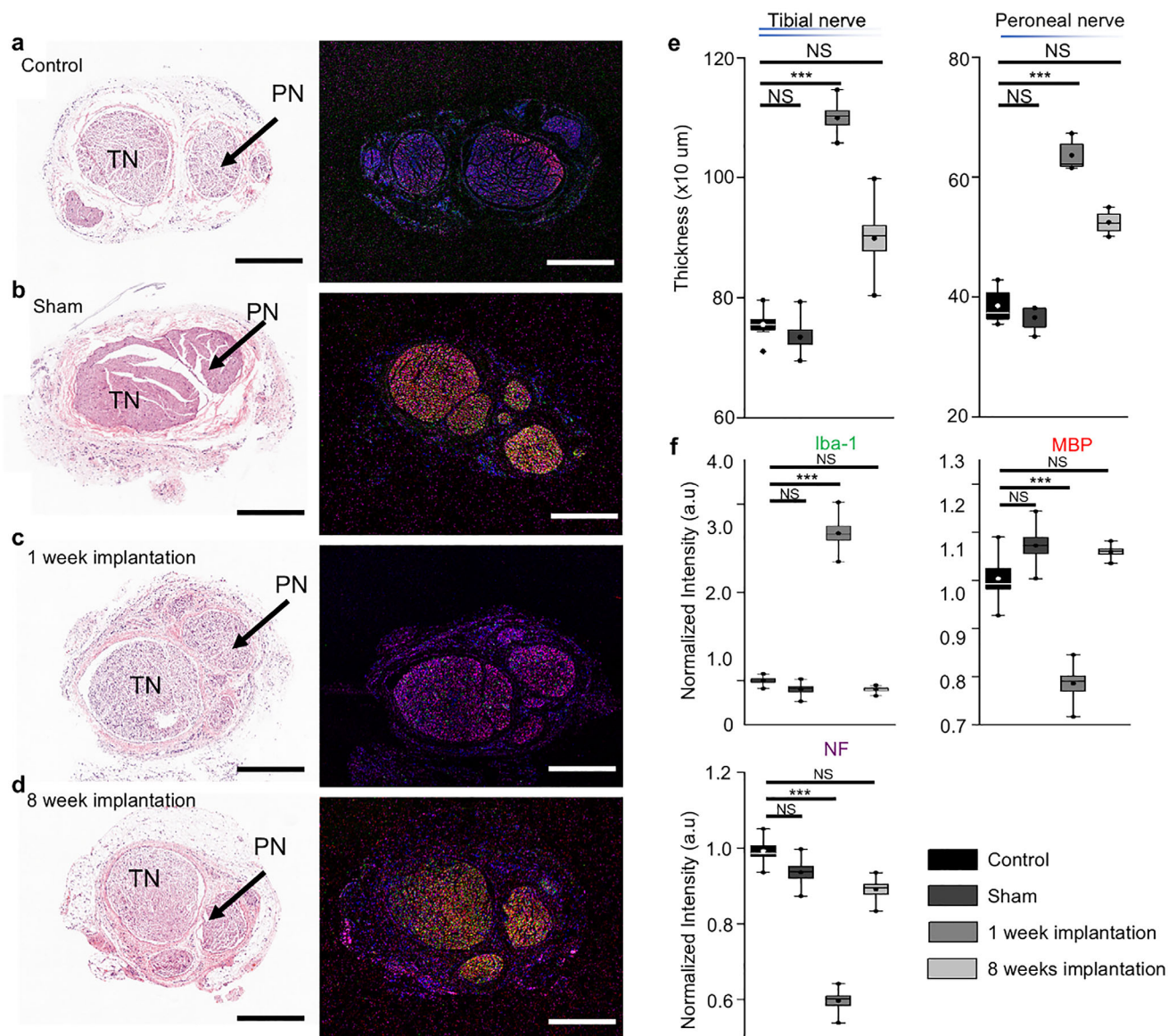


FIGURE 5 | Histological and immunohistochemical evaluation of sciatic nerve biostability after TSSA cuff electrode implantation. (a–d) Representative H&E-stained transverse sections of sciatic nerves from a control, (b) sham-operated, (c) 1-week implantation, and (d) 8-weeks implantation groups. The tibial nerve (TN) and peroneal nerve (PN) branches are indicated. A representative merged confocal immunohistochemical image of the 8-week implantation group is shown next to the H&E image in (d). (e) Quantitative analysis of connective tissue thickness surrounding the tibial and peroneal nerve branches. (f) Quantification of normalized fluorescence intensity for Iba-1, MBP, and NF in sciatic nerve sections. Iba-1 was used to assess macrophage-associated inflammatory response, MBP to evaluate myelin integrity, and NF to assess axonal structure. Statistical analysis was performed using two-way ANOVA; $n = 8$. NS: not significant, $***p < 0.001$. Scale bars: 500 μ m.

to label nuclei. Consistent with the H&E results, the 1-week implantation group showed increased Iba-1 signal, indicating an acute inflammatory response after implantation (Figure 5f). In parallel, MBP and NF signals were reduced at 1 week, suggesting temporary alterations in myelin- and axon-associated markers during the acute postoperative phase. By 8 weeks, Iba-1 signal decreased toward the control level, while MBP and NF signals recovered compared with the 1-week implantation group (Figure 5f). The representative merged confocal image at 8 weeks further showed relatively preserved nerve structure, consistent with recovery of the tissue environment after the early inflammatory phase (Figure 5d). Together, these results indicate that TSSA cuff electrode implantation induced an acute postoperative tissue

response at 1 week, characterized by connective tissue thickening, increased Iba-1 expression, and transient reduction of MBP and NF signals. However, these changes were largely reduced by 8 weeks, supporting the long-term biostability of the TSSA cuff electrode without evidence of persistent severe structural nerve damage (Figure S14). This favorable chronic tissue response is highly consistent with the non-constrictive, optimized geometry of the proposed device.

To verify whether the device provides conformal contact without causing excessive nerve compression, the inner diameter of the self-closed TSSA cuff electrode was evaluated. The average diameter of the rat sciatic nerve was 1.56 ± 0.09 mm, whereas the

optimized 30–4 μm bilayer configuration exhibited a self-closed inner diameter of 1.63 ± 0.10 mm at 37°C (Figure S15). Given that this inner diameter is slightly larger than that of the sciatic nerve and that the SMP substrate softens at body temperature, the TSSA cuff ensures conformal circumferential contact rather than rigid constriction.

To further assess whether this cuff interface prevents functional degeneration distal to the implantation site, semithin resin-embedded sections of the distal sciatic nerve were stained with toluidine blue (Figure S16). Representative images showed preserved overall fascicular morphology in the 1-week implantation group compared with the control and sham groups. Quantitative analysis of myelinated fiber number, fiber density, mean fiber diameter, median fiber diameter, and degenerated fiber count showed no apparent reduction in myelinated fiber number or fiber size after implantation, supporting the absence of substantial distal axonal loss during the early postoperative period.

Beyond validating these tissue-level biological responses, the long-term structural stability of the implanted TSSA cuff electrode was investigated. FTIR, SEM, and EDS analyses were performed on non-implanted control electrodes and explanted TSSA electrodes after chronic implantation and washing (Figures S17 and S18). FTIR analysis after 8 weeks of implantation showed minor reductions in O–H and C–H stretching peaks around 3400 and 2960–2860 cm^{-1} , indicating subtle changes in surface-exposed functional groups post-implantation. However, the overall FTIR spectral profile was retained. In addition, the 16-week explanted electrode maintained its overall morphology without obvious cracking, fragmentation, severe erosion, collapse, or delamination. EDS elemental mapping did not show abnormal elemental accumulation, extensive metal exposure, or corrosion-related changes, supporting the structural stability of the SMP substrate during long-term implantation.

2.7 | Assessment of Long-Term Anchoring and Minimal Limb Dysfunction

To verify the long-term placement of the implanted electrode around the sciatic nerve, micro-computed tomography (micro-CT) imaging was conducted on both control and implanted rat models (Figure S19). In the control group, the electrodes were implanted immediately before imaging; in the implanted group, the devices had been in place for eight weeks (Figure S19). The micro-CT images, including dorsal and lateral views, showed the electrode positioned approximately 2 cm from the upper femoral shaft toward the pelvis, targeting the sciatic nerve. Comparative analysis demonstrated that the electrode's morphology and placement relative to the sciatic nerve remained consistent immediately post-implantation and after eight weeks, confirming stable *in vivo* fixation over time (Figure 6a,b).

The functional integrity and biocompatibility of the implanted electrodes were further evaluated using the sciatic functional index (SFI) (Figure 6c), a quantitative measure ranging from 0 to –100 that reflects sciatic nerve function, with –100 indicating complete loss of function. SFI was assessed weekly over eight weeks via footprint analysis (Figure 6d,e; Figure S20).

The implanted group showed a transient SFI decrease to –26 at week 1, whereas the sham group showed a milder decline to –9. SFI values in the implanted group recovered after 4 weeks and nearly returned to baseline by week 6, indicating no apparent long-term behavioral impairment associated with electrode implantation (Figure 6f, Figure S20). This functional improvement was accompanied by an increase in SNR during the same period, indicating restoration of nerve conduction and stable electrode performance. Collectively, these results indicate that although implantation may cause a temporary functional impairment, the nerve spontaneously recovers, and the electrode remains securely positioned and functionally stable throughout long-term implantation.

3 | Discussion

In this study, we introduced a thermoresponsive soft and self-anchoring (TSSA) cuff electrode that wraps around peripheral nerves through thermally induced deformation. While various actuation methods, such as pneumatically driven devices [23] based on the structure induced by hydrogel swelling [33] and thermally responsive [12] systems, have been explored to improve nerve interfacing, achieving a stable yet gentle fit, especially for small-diameter nerves, remains challenging. The TSSA cuff electrode overcomes this by using an SMP bilayer design that allows the electrode to self-close at physiological temperatures. This feature ensures consistent nerve contact, reduces mechanical stress, and eliminates the need for external actuators or sutures.

To evaluate its anchoring performance, the fixation capability of the TSSA cuff electrode was compared against traditional sutured silicone cuffs and other advanced designs in Table S1. Unlike conventional cuffs that rely on tight sutures or rigid mechanical clamps, which often introduce risks of nerve displacement, misalignment, or excessive compression, the TSSA achieves stable, sutureless self-anchoring via tissue adhesion without compromising neural integrity. This soft and adaptive interface is driven by a thermomechanical transition at body temperature, where the substrate's elastic modulus decreases by nearly two orders of magnitude to ensure conformal circumferential contact with minimal force. Long-term recordings with minimal tissue damage indicate that the applied pressure remains well within safe physiological limits for normal nerves. Furthermore, even under pathological conditions such as post-injury chronic swelling (edema) where the nerve expands abruptly, the softened SMP matrix provides a vital mechanical buffer that significantly alleviates constrictive pressure compared to traditional rigid stabilization methods. Nevertheless, the anchoring might limit free expansion under severe edema. Therefore, evaluating chronic swelling safety remains a subject for future work.

The 16-week *in vivo* trial confirmed the proposed cuff electrode's ability to accurately record mechanically evoked nerve responses elicited by gentle stimuli (plantar). The signal amplitude and SNR steadily improved, the latter reaching 10.4, significantly above the typical SNR of 3–10 reported for conventional cuff electrodes. This performance reflects the cuff electrode's self-conforming, SMP-based electrode–nerve interface. In addition, eight-week histological and immunohistochemical analyses revealed that the TSSA cuff electrode preserved the morphology and cellular

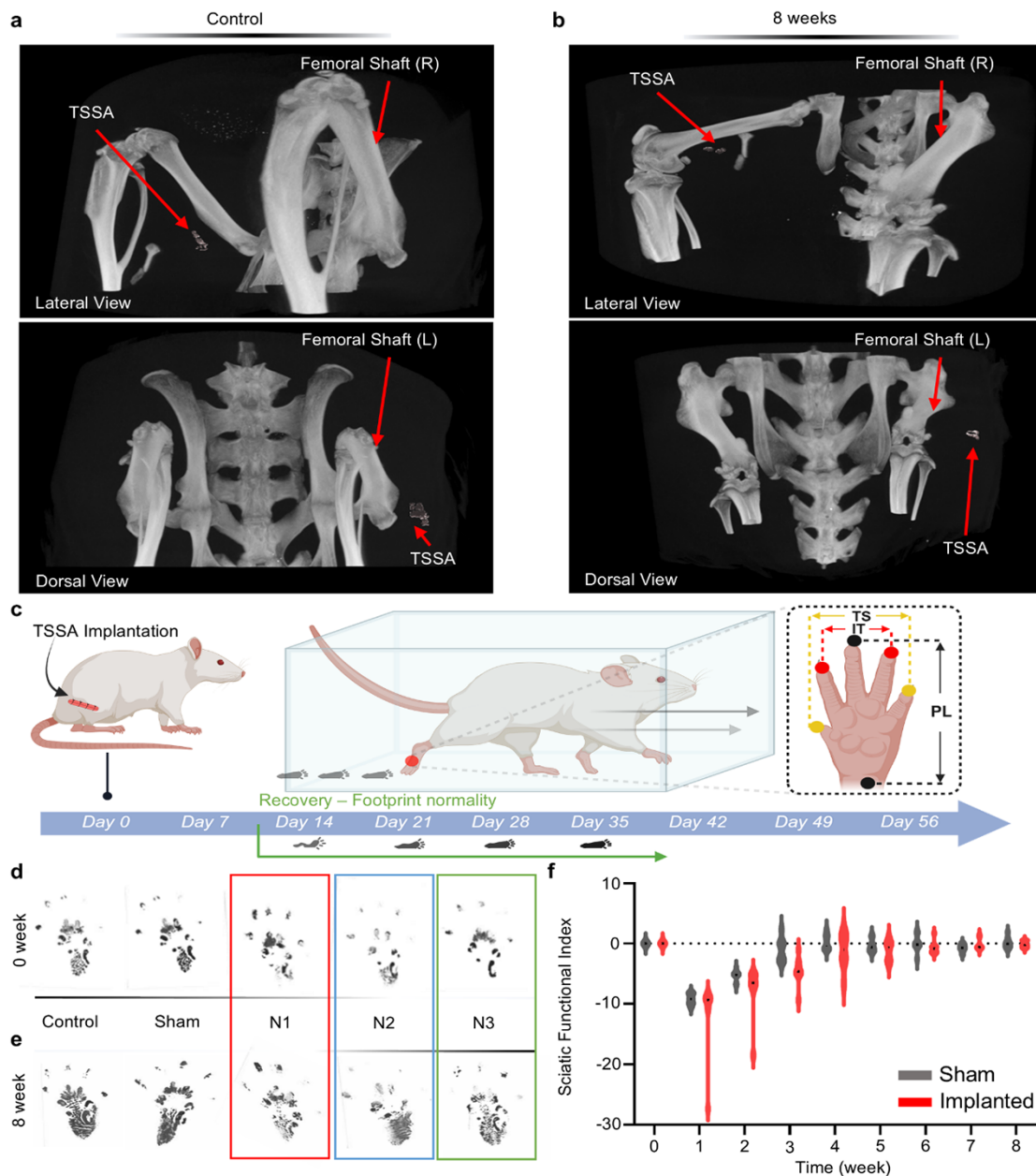


FIGURE 6 | Long-term Anchoring and Nerve Damage After Implantation of the TSSA Cuff Electrode. Micro-computed tomography (micro-CT) images show (a) a pre-implanted and (b) an eight-week post-implanted TSSA cuff electrode at the sciatic nerve near the pelvis, adjacent to the proximal femoral shaft. (c) A schematic depicting the assessment of the sciatic functional index (SFI), which is calculated using three gait parameters: toe spread (TS; distance between the first and fifth toes), intermediate toe spread (IT; distance between the second and fourth toes), and print length (PL; longitudinal length of the hind paw footprint). (d) and (e) show the footprint analysis at baseline (week 0) and week 8 for the control, sham, and cuff electrode groups ($n = 8$). (f) A graph showing the SFI values derived from footprint longitudinal analysis for each group over eight weeks.

architecture of the nerve, showing no evidence of fibrosis or macrophage infiltration at the implant site. Furthermore, blood flow to the nerve remained comparable to the level of the controls, demonstrating the device's vascular compatibility and minimal invasiveness, a critical, often overlooked feature of long-term neural implants. While transient inflammation and nerve swelling were observed over the acute phase, these eventually resolved, further confirming the TSSA's biocompatibility.

We utilized wafer-scale MEMS fabrication to achieve a high-throughput, precisely dimensioned electrode suitable for sub-

millimeter nerves, such as those employed in rodent models. This scalable platform can be adapted to various biomedical applications by adjusting the thickness and modulus of the SMP layer to accommodate nerves of varying sizes. Additionally, reliable fabrication techniques allow for the integration of various electrical components, such as thermistors, chemical sensors, and micro-LEDs, with the peripheral interface for sophisticated neuroscience studies.

In conclusion, the TSSA cuff electrode comprises a unique combination of minimal invasiveness, stable and long-term interfacing,

and ease of implantation. Its thermally responsive, self-actuating mechanism ensures gentle, secure nerve contact without the use of external forces or rigid components, while maintaining high signal fidelity and biocompatibility. This represents a significant advance in soft, chronic neural interfaces for bidirectional neuroprosthetics.

4 | Methods

4.1 | Synthesis of the SMP-Based Substrate

The TSSA electrode array comprises a three-component SMP polymer: poly(bisphenol A-co-epichlorohydrin) (Sigma-Aldrich), neopentyl glycol diglycidyl ether (NGDE) (Sigma-Aldrich), and EC 301 (BASF), with a 5:11:7 molar ratio. Poly(bisphenol A-co-epichlorohydrin) was pre-melted at 70°C before mixing with NGDE and EC 301. The mixture was degassed for 30 min to remove air bubbles. Finally, spin coating was used to deposit the polymer to the desired thickness, followed by thermal curing in a convection oven.

4.2 | Fabrication of the TSSA Cuff Electrode

A 300-nm-thick sacrificial copper layer was deposited on a silicon wafer via e-beam evaporation (EI-5, ULVAC, Chigasaki, Japan) to facilitate post-fabrication release (Figure S2a). A 3 µm thick SMP polymer layer was then spin-coated onto the copper (Figure S2b). Photolithography was used to define the electrode pattern (Figure S2c), followed by reactive ion etching (RIE) (VITA, Femtoscience, Hwaseong, Korea) using argon/oxygen gas (20 sccm Ar, 100 sccm O₂). The RIE parameters were a 200 W RF power and a 40 min etching time. A photoresist pattern was prepared for metal lift-off, after which a 10/100 nm Ti/Au layer was deposited via E-beam evaporation to form the electrode, conductive lines, and connection pads. Lift-off removed excess metal, followed by RIE removal of the remaining SMP layer (Figure S2d). Finally, a 30 µm thick insulating SMP layer was deposited and cured at 100°C for 90 min and then at 130°C for 60 min to create the TSSA substrate structure (Figure S2e). A 4 µm thick second SMP layer was then applied and cured using the same parameters (Figure S2f). The device was cut to its final shape using a sharp blade. Subsequent immersion of the silicon wafer in a copper etchant dissolved the sacrificial layer (Figure S2g), thereby releasing the completed TSSA (Figure S2h).

4.3 | Thermal and Mechanical Characterization

The TSSA cuff electrode utilizes a temperature-responsive SMP polymer featuring shape transformation for closure and securement. This transformation temperature varies with the concentration of NGDE. The thermal properties of the electrode were analyzed via dynamic mechanical analysis (DMA) (DMA 850, TA Instruments, New Castle, DE, USA). Standard DMA tests were employed to assess the effect of the NGDE content (19.7, 32.9, and 42.4 wt.% – 1.25, 2.5, and 3.75 g) on SMP stiffness. For each sample, pre-melted poly(bisphenol A-co-epichlorohydrin) was combined with the specified NGDE amount and EC 301. A 30 min degassing

step preceded the pouring of 5–6 mL of the mixture into 4 cm (length) × 1 cm (width) × 0.2 cm (height) molds. Thermal curing consisted of two stages: 90 min at 100°C, followed by 60 min at 130°C. This yielded three polymer samples exhibiting varied stiffness and shape transition temperatures suitable for DMA analysis. The TSSA and PDMS substrates measured 5 mm (W, width), 15 mm (L, length), and 0.034 mm (T, thickness). In the pulling force and T-peel analyses, pressure (calculated using the force (N) and the cross-sectional area (m²)) was determined as follows:

$$\text{Cross Sectional Area} = 2(W \times L) + (W \times T) + (L \times T)$$

$$\text{Pressure (Pa)} = \text{Force (N)} \div \text{Cross Sectional Area (m}^2\text{)}.$$

4.4 | Analysis of Fixation and Tensile Strength

Tensile strength and fixation force were evaluated using pulling force and T-peel tests [34–36]. For the T-peel test, two 150 × 5000 µm PDMS samples were bonded after heating to 35°C. One end of the bonded samples was peeled apart, with one side clamped to a fixed base; the other side was clamped to a pull test machine (DST-1A, IMADA, Northbrook, IL, USA). The samples were then peeled apart at 10 mm/s to measure the fixation force. This procedure was repeated for the SMP samples.

Tensile strength was measured using a nerve-mimicking cylindrical structure. As the PDMS samples were unable to self-fix, they were modified with triangular ends and holes for secure attachment. The SMP samples, capable of self-fixing, required no modification. Both materials were fixed to the base-secured structure, then tested on a pull test machine at 10 mm/s to determine the tensile strength.

4.5 | Fixation Analysis via Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR)

SMP samples were analyzed using ATR-FTIR spectroscopy (SPECTRUM GX, PerkinElmer, Waltham, MA, USA) with a ZnSe crystal. Three sample groups, containing 19.7, 32.9, and 42.4 wt.% of NGDE, were analyzed. The spectra were recorded from 650 to 4000 cm⁻¹ at 4 cm⁻¹ resolution and room temperature.

4.6 | Characterization of the Electrode–Electrolyte Interface

Electrochemical impedance spectroscopy (EIS) measurements were performed on the fabricated electrode using an Autolab (IMP, Autolab Methrohm, Woudwetering, Utrecht, Netherlands). A standard three-electrode configuration—comprising a custom-fabricated working electrode, a Pt counter electrode, and an Ag/AgCl reference electrode was immersed in pH 7.4 phosphate-buffered saline (PBS) within a Faraday cage to minimize external interference. EIS data were acquired from 1 Hz to 1 MHz using a 10 mV_{rms} sinusoidal AC signal.

4.7 | Sciatic Nerve Surgery

All surgical procedures involving Sprague Dawley (SD) male rats (eight weeks old, weighing approximately 360 g) adhered to the guidelines approved by the KBRI Institutional Animal Care and Use Committee (IACUC; Approval No. KBRI-IACUC-24-0018-M1). All instruments, including the TSSA, were sterilized before use. The TSSA electrode served as a reference and ground electrode, while hook electrodes used for stimulation were sterilized with 70% ethanol. Anesthesia was induced and maintained using 2.5–4% isoflurane in oxygen (0.4–0.8 L/min). The surgical site was shaved and sterilized with 70% ethanol. After exposing the skin and muscle, the sciatic nerve was exposed by retracting the biceps femoris. A latex sheet was placed beneath the nerve to minimize electrical noise from surrounding muscles.

4.8 | In Vivo Experiments for Electrical Stimulation and Signal Recording

The TSSA was positioned to encircle the sciatic nerve, where the device closed in response to the rat's body temperature. A hook electrode, positioned approximately 30 mm from the TSSA, and a ground needle electrode inserted into a remote muscle were used for stimulation and grounding. A signal recording system (RHS2000, Intan Technologies, LLC, California, CA, USA) captured electrically evoked CNAPs generated by a stimulator (Model 2100, A-M Systems, Sequim, WA, USA) connected to the hook electrode. Stimulation consisted of 100- μ s pulses at 0.1 to 1.0 mA (0.2 mA increments), and CNAPs were measured from stimulus onset to peak amplitude.

4.9 | Mechanical Paw Stimulation

Using a von Frey filament (Sensory Evaluator, Exacta Precision & Performance, Scarborough, ON, Canada), three distinct forces (58.8, 147, and 588 mN, representing approximately a 5 to 10 fold difference) were applied to the central plantar surface, and mechanically evoked nerve responses were recorded from the sciatic nerve region using the TSSA cuff electrode. The resulting changes in the neural signal were recorded using the same equipment employed for electrical stimulation, with each stimulus delivered at 10 s intervals. The TSSA electrode recorded the corresponding variation in sciatic nerve activity.

4.10 | SNR Calculation

The signal-to-noise ratio (SNR) was calculated as a dimensionless amplitude ratio from stimulus-triggered averaged recordings. For each recording session, eight repeated stimulus-evoked traces were aligned to the stimulus marker and averaged. The stimulation artifact was excluded from the analysis. The baseline noise window was defined as –10 to –2 ms before the stimulus marker, where no evoked response was present. The post-artifact response window was defined as 0.5 to 5 ms after the stimulus marker, thereby excluding the initial stimulation artifact while including the N1–P1 response component.

The signal amplitude was calculated as the peak-to-peak amplitude of the post-artifact evoked response component within the response window. The noise amplitude was calculated by applying a peak-to-peak scaling factor (2 x RMS) to the noise amplitude of the pre-stimulation baseline window. For conservative comparison with previous cuff-electrode studies, SNR was calculated using the following equation:

$$SNR = \frac{A_{\text{signal}}}{2\sigma_{\text{noise}}} = \frac{(V_{\text{max}} - V_{\text{min}})_{\text{response window}}}{2 \times RMS_{\text{baseline}}}$$

where A_{signal} is the peak-to-peak amplitude of the evoked response component and σ_{noise} is represented by the peak-to-peak scaling factor (2 x RMS) to the noise amplitude of the pre-stimulation baseline window. The reported SNR values are dimensionless ratios and are not expressed in decibels. Individual traces were aligned to the stimulus marker and averaged across $N = 8$ repeated stimuli.

4.11 | H&E Staining

Harvested sciatic nerve tissues were fixed in 4% paraformaldehyde (PFA; Sigma-Aldrich) overnight. After fixation, the tissues were dehydrated through a graded ethanol series, cleared in xylene, and embedded in paraffin. Transverse paraffin sections with a thickness of 5 μ m were prepared using a microtome and mounted onto glass slides. The sections were then deparaffinized, rehydrated, and stained using an H&E staining kit (ab245880, Abcam) according to the manufacturer's protocol. Hematoxylin was used to visualize nuclei, and eosin was used to counterstain cytoplasmic and extracellular matrix structures. After dehydration and coverslip mounting, brightfield images were acquired using a slide scanner. (Pannoramic scan, 3DHISTECH, Budapest, Hungary).

4.12 | Immunohistochemistry

Immunohistochemical (IHC) staining was performed on harvested sciatic nerve tissue to assess the biocompatibility of the implanted TSSA. The nerves were fixed in 4% paraformaldehyde (PFA; Sigma-Aldrich) overnight, cryoprotected in 30% sucrose for 36 h, and embedded in optimal cutting temperature (OCT) compound (Sigma-Aldrich). Following freezing at –80°C, 20 μ m thick transverse cryosections were prepared using a cryomicrotome (CM3050s, Leica Microsystems, Wetzlar, Germany) and mounted onto glass slides.

Immunohistochemical (IHC) staining was performed on the sections after washing in PBS and permeabilization with blocking buffer (0.3% Triton X-100, 5% normal donkey serum) for 1 h at room temperature. The sections were then incubated overnight at 4°C with primary antibodies: anti-NF200 (1:1000, Sigma-Aldrich; for the axonal structure), anti-MBP (1:1000, Abcam; for myelin sheaths), and anti-Iba1 (1:1000, Abcam; for macrophage infiltration). After further washing, the sections were incubated with secondary antibodies for 2 h at room temperature: Alexa Fluor 488 anti-chicken, Cy3 anti-goat, and Alexa Fluor 647

anti-mouse (all 1:1000, Jackson ImmunoResearch). Finally, the nuclei were counterstained with DAPI (1 µg/mL in PBS; Sigma-Aldrich) for 5 min.

Fluorescent signals were visualized using a confocal microscope (STELLARIS 8, Leica Microsystems, Wetzlar, Germany), and the signal intensities of NF200, MBP, and Iba1 were quantified using ImageJ (NIH).

4.13 | Micro-CT

Micro-CT imaging (Quantum GX2, PerkinElmer, Waltham, MA, USA) was used to assess the position of the TSSA electrode implanted in the left sciatic nerve of the rats, both immediately post-implantation and after an eight-week period. The imaging parameters were: a 50 kV X-ray tube voltage, a 160 µA current, a 72 mm field of view (FOV), a 72 µm voxel size, and a 2 min scan time (with adjustments as needed). This micro-CT analysis was conducted using the KMEDI (Korea Medical Development Innovation).

Image quality was enhanced using a 3D filter and X-ray filters (0.06 mm Cu, 0.5 mm Al). 3D visualization of the electrode's position was achieved by processing the micro-CT images using Imaris software (Oxford Instruments, Abingdon, UK). 3D reconstruction of the electrode was accomplished by defining regions of interest (ROIs) at the electrode location and adjusting the thresholds within the software's surface module.

4.14 | Sciatic Functional Index

The recovery of motor function and nerve integrity were assessed using the SFI following implantation. Three groups were evaluated: an untreated control group (n = 8), a sham group (sciatic nerve exposure only, n = 8), and a TSSA-implanted group (n = 8), all involving the left sciatic nerve. Footprints from the left hind paw, inked with non-toxic paint, were collected as the animals walked naturally through a 7 cm wide × 70 cm long corridor lined with white paper, ensuring the acquisition of natural footprints. Post-operative gait analysis using the SFI was performed weekly for eight weeks. The SFI was calculated from standard measurements of print length (PL), toe spread (TS), and intermediary toe spread (IT), using established formulas. SFI values range from 0 (normal gait) to −100 (complete sciatic function loss), providing a quantitative measure of functional recovery across groups. The SFI values were calculated using the following equations:

$$\text{SFI} = -38.3 * \frac{\text{EPL} - \text{NPL}}{\text{H2}} + 109.5 * \frac{\text{ETS} - \text{NTS}}{\text{H4}} + 13.3 * \frac{\text{EIT} - \text{NIT}}{\text{H3}} - 8.8$$

E: Experimental

N: Normal

4.15 | Data Analysis and Statistical Comparisons

Quantitative data were processed and analyzed using OriginLab and MATLAB. For electrically evoked recordings, stimulus-triggered traces were analyzed after excluding the initial stimulation artifact. The electrically evoked compound nerve action potential (CNAP) component was defined as the short-latency biphasic response following the stimulation artifact, and the CNAP amplitude was quantified as the N1–P1 peak-to-peak amplitude. For mechanically evoked recordings induced by von Frey or brush stimulation, the traces were analyzed as mechanically evoked nerve responses rather than canonical CNAP waveforms. The recorded response amplitude was quantified from stimulus-associated response windows and compared across stimulation intensities or implantation time points.

The signal-to-noise ratio (SNR) was calculated as a dimensionless amplitude ratio from stimulus-triggered averaged recordings. The signal amplitude was defined as the peak-to-peak amplitude of the evoked response after excluding stimulation artifacts, and the baseline noise was calculated by applying a peak-to-peak scaling factor (2 × RMS) to the noise amplitude of the pre-stimulation baseline window. For conservative comparison with previous cuff-electrode studies, SNR was calculated by dividing the evoked response amplitude by twice the RMS baseline noise.

Electrochemical impedance spectroscopy (EIS) data were analyzed by comparing impedance magnitude and phase over the measured frequency range. For post-implantation impedance analysis, explanted electrodes were measured under the same frequency range as the pre-implantation electrodes.

Sciatic functional index (SFI) was calculated from footprint parameters, including toe spread, intermediate toe spread, and print length. Weekly SFI values were analyzed over the 8 weeks monitoring period, and individual animal trajectories were plotted to visualize longitudinal changes and inter-animal variability.

For histological analysis, H&E-stained transverse sciatic nerve sections were used to quantify connective tissue thickness surrounding the tibial and peroneal nerve branches. Immuno-histochemical images were analyzed by quantifying normalized fluorescence intensities of Iba-1, MBP, and NF within the sciatic nerve region of interest. Iba-1 was used to assess macrophage-associated inflammatory response, MBP to evaluate myelin integrity, and NF to assess axonal structure.

For toluidine blue analysis, semithin resin-embedded distal sciatic nerve sections were imaged by light microscopy. Myelinated fiber number, fiber density, average fiber diameter, median fiber diameter, and degenerated fiber count were quantified from selected regions of interest.

Data are presented as mean ± standard error of the mean (SEM) unless otherwise stated. Statistical comparisons between two groups were performed using unpaired two-tailed Student's t-tests. For comparisons involving multiple groups or repeated time points, one-way or two-way analysis of variance (ANOVA) followed by appropriate post hoc tests was used. A value of

$p < 0.05$ was considered statistically significant. Significance levels are indicated in the figures as follows: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$; NS indicates not significant.

Author Contributions

S.L., N.C. conceived of the main idea. S.L., S.K. and N.C. designed experiments. S.L., B.P., and J.E. conducted experiments. S.L., S.K. and N.C. analyzed the data. All the authors discussed the results and commented on the manuscript. S.L. and N.C. wrote the manuscript. S.K. and N.C. supervised the project.

Acknowledgements

This work was supported by grants of the National Research Foundation (Grant Nos. NRF-RS-2021-NR062074, RS-2024-00357432, RS-2025-02243041) and Korea Brain Research Institute (Grant Nos 26-BR-02-02, 26-BR-04-01, 26-BR-07-01) funded by the Ministry of Science and ICT of Korea.

Conflicts of Interest

The authors declare conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: adfm77781-sup-0001-SuppMat.docx.

Supporting File: adfm77781-sup-0002-SuppMat.docx.