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Micro-structured thin-film electrode technology enables proof of concept of scalable, soft auditory brainstem implants

Authors: Nicolas Vachicouras[1†], Osama Tarabichi[2†], Vivek V. Kanumuri[†], Christina M. Tringides[1], Jennifer Macron[1], Florian Fallegger[1], Yohann Thenaisie[1], Lorenz Epprecht[2], Stephen McInturff[2], Ahad A. Qureshi[2], Valentina Paggi[1], Martin W. Kuklinski[2], M. Christian Brown[2], Daniel J. Lee[2*], Stéphanie P. Lacour[1*]

Affiliations:

[1]Bertarelli Foundation Chair in Neuroprosthetic Technology, Laboratory for Soft Bioelectronic Interfaces, Institute of Microengineering, Institute of Bioengineering, Centre for Neuroprosthetics, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

[2]Eaton-Peabody Laboratories and Department of Otolaryngology – Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, Department of Otology and Laryngology, Harvard Medical School, Boston, Massachusetts, USA

[†]These authors contributed equally to this work.

[*]Corresponding authors: stephanie.lacour@epfl.ch, daniel_lee@meei.harvard.edu

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One Sentence Summary: Engineered conformability in auditory brainstem implant electrode arrays enhances the electrode-brainstem interface both in an *in vivo* mouse model and in human cadaveric models thereby promising improved ABI outcomes.

Abstract: 150-250 words

Auditory brainstem implants (ABI) provide sound awareness to deaf individuals who are not candidates for the cochlear implant. The ABI electrode array rests on the surface of the cochlear nucleus (CN) in the brainstem and delivers multichannel electrical stimulation. The complex anatomy and physiology of the CN together with poor spatial selectivity of electrical stimulation and inherent stiffness of contemporary multichannel arrays lead to only modest auditory outcomes among ABI users. Here, we hypothesize that a soft ABI can enhance biomechanical compatibility with the curved CN surface. We developed an implantable neurotechnology to manufacture ABIs that are compatible with surgical handling, conform to the curvature of the CN following placement, and deliver efficient electrical stimulation. The soft ABI array design relies on precise micro-structuring of plastic/metal/plastic multilayers to enable mechanical compliance, patternability and electrical function. We fabricated soft ABIs to the scale of mouse and human CN and validated them *in vitro*. Experiments in mice demonstrated that these implants reliably evoke auditory neural activity over a month *in vivo*. Evaluation in human cadaveric models confirmed compatibility following insertion using an endoscopic-assisted craniotomy surgery, ease of array positioning, and robustness and reliability of the soft electrodes. This neurotechnology is an exciting opportunity for advancing the treatment of deafness in a specialized group of patients who are not candidates for the cochlear implant, and is broadly applicable to implantable soft bioelectronics throughout the central and peripheral nervous system.

Introduction

The auditory brainstem implant (ABI) provides sound sensations to deaf patients who have damaged or absent cochlear or cochlear nerve anatomy *(1, 2)*. Most ABI users have Neurofibromatosis type 2 (NF2), an autosomal dominant genetic syndrome associated with the formation of multiple brain and spinal neoplasms, including bilateral vestibular schwannomas. Growth or clinical management of these intracranial tumors results in damage to cochlear nerves and profound hearing loss. The ABI has also been studied in several clinical trials in children with congenital aplasia of the cochlea or cochlear nerve or patients with scarring of the cochlea following trauma, otosclerosis, or meningitis *(3, 4)*. The ABI bypasses the auditory periphery to evoke sound sensations using electrical stimulation of the cochlear nucleus (CN). The CN is a < 25 mm^3 structure in the brainstem *(5, 6)* that receives inputs from the cochlear nerve (Fig. 1A-C) *(7, 8)*. To stimulate the CN, the ABI uses a planar electrode array, with up to 21 contacts, that is placed during a posterior fossa craniotomy. Unlike the majority of users of the cochlear implant (CI), however, most ABI users do not achieve open-set comprehension of speech and are limited to sound awareness that assists in lip reading *(9, 10)*.

One factor that may contribute to poor outcomes is that ABI arrays are stiff compared to the underlying brainstem so they do not conform to the curvature of the CN (Fig. 1C). This situation almost certainly leads to poor electrode contact with neural structures, thus requiring higher currents to stimulate auditory neurons and consequent activation nearby non-auditory areas (Fig. 1D-E) *(11)*. Side effects observed by ABI users include transitory dizziness, tingling sensations, facial twitching, pain, and the electrodes producing them must be turned off so that the number of auditory channels is reduced *(12)*. Recent advances in soft bioelectronics have produced neural implants with greater conformability, narrowing the biomechanical mismatch between

man-made implants and soft neural tissues *(13, 14)*. The use of soft and elastic materials also opens the design path for implants that can accommodate micro- and macroscopic movements of neural tissue secondary to blood and CSF flow, respiration or head and neck movements *(15, 16)*. A critical challenge when designing soft bioelectronic implants is the patterning of robust, elastic and highly conducting wires to interface the electrodes (in contact with neural tissue) with an implantable pulse generator. Typical strategies involve designs of meandering paths *(17, 18)*, structured materials *(19)* and the use of inherently stretchable materials, such as micro and nano-composites that form percolating pathways *(20)*.

In this study, we explore how advances in thin-film bioelectronic structures combined with soft materials can help in revising the design of the clinical ABI *(21–25)*. Plastic and elastic polymers such as polyimide and silicone respectively, and thin metal films are routinely processed and machined using microfabrication technology *(26–28)*. Translational demonstrations and FDA (Food & Drug Administration) approved devices using these materials in various neuroprosthetic applications have motivated their use in this study *(29–31)*. We design, fabricate and test a soft multichannel ABI array with better biomechanical match between the array and the curved brainstem surface than existing systems (Fig. 1F). We engineer and define stretchable metallic tracks (leads) from strain relief patterns and thin-film multilayers to carry electrical pulses to soft electrode coatings with efficient charge injection properties (Fig. 1G-I). We scaled the array to the size of a human ABI and verified the feasibility of surgical implantation onto the CN of a cadaveric specimen. Our microtechnology also allows for scaling down the design to the CN of a mouse, which we used as a model to validate the function and durability of the soft ABIs *in vivo*.

Results

Electromechanical design and characterization

The soft ABI array should withstand repeatedly stretching cycles (> 100k) at low strains (< 10 %) *(32)* and endure prolonged surgical manipulation without losing electrical and mechanical integrity. Interconnects consist of long and narrow metallic tracks embedded in the bulk, elastomeric structure of the implant. Their anisotropic layout and critical role in the function of the implant require careful design to guarantee mechanical compliance, robustness and electrical continuity. The technique we used to fabricate these interconnects involved the micro-structuring of hexagonally arranged Y-shaped cuts that were previously shown to allow for isotropic stretchability in millimeter-sized plastic sheets *(33)*. We further optimized these shapes by smoothing the edges of the Y pattern and embedding them on a microscopic multi-layered stack of polyimide-platinum-polyimide (PI/Pt/PI) (~ 2.2 μm thick). These smoothed microstructures are geometrically defined by three parameters (Fig. 2A), which are the length of the branch *a*, the radius of the circle at the tips *r*, and the horizontal distance between two motifs *L*. See Supplementary Materials for the geometric descriptions. All micro-structured tracks are next embedded in silicone rubber (200 μm thick).

Finite element modeling of strain distribution and corresponding photograph of the optimized structure highlight the engineered strain relief mechanism (Fig. 2B). Calculations and samples were prepared at the macroscale for ease of manipulation. As the polyimide (PI) structure is stretched, the PI ligaments deflect out-of-plane thereby locally relieving strain *(19, 34)*. This is confirmed by the Finite Element Analysis (FEA) model, which revealed the maximum local strain is always significantly lower than the applied strain.

The Y-shaped design must also meet a mechanical and an electrical compromise. Narrow and open Y meshes are most compliant but at the expense of high electrical resistance of the

115 structured tracks. We computed the maximal local strain and relative electrical resistance of
116 patterns prepared with a range of *a* and *r* upon applied uniaxial strain of 10 % (Fig. 2C).

117 We aimed for design parameters compatible with a maximum increase in electrical
118 resistance of magnitude 10, critical dimensions compatible with standard UV lithography on
119 plastic foil, i.e. CD < 5 μm, and the lowest local strain possible. Three examples (designs 1, 2, 3)
120 are displayed in Fig. 2C-D with arbitrarily set pattern pitch of L = 26 μm. We found design #3 (*a*
121 = 16 μm and *r* = 5.5 μm) offered the best design trade-off (Fig. 2C) and displayed the lowest
122 increase in resistance after 1000 strain cycles (Fig. 2D). The lithographic patterning of the Y-shape
123 structures provides a versatile method to pattern conductive tracks down to a width of 20 μm (Fig.
124 S14), which is the smallest track width geometrically allowed by the selected Y-shaped motifs
125 parameters (analytical equations in the supplementary materials).

126 We next compared the compliance and electromechanical response of bulk PDMS, plain
127 and Y-shaped PI/Pt/PI tracks embedded in PDMS upon tensile deformation. Tracks prepared with
128 Y-shaped microstructure display surprising deformability and stability compared to plain ones.
129 200 μm wide, 17 mm long, Y-shaped metallic tracks mechanically failed at 80% tensile strain
130 albeit did not fail electrically while plain tracks of identical geometry failed both mechanically and
131 electrically at only 3% applied strain (Fig. 2E, Fig. S10). Moreover, Fig. 2F demonstrates that the
132 micro-structured tracks impact minimally the mechanical properties of the PDMS carrier in terms
133 of apparent elastic modulus and fracture strain (Fig. S11). During fatigue testing (1 million cycles,
134 10 % applied strain), the micro-structured tracks embedded in PDMS did not fail and showed an
135 increase in resistance from 8 to 45% across 8 tracks (average 18 ± 12 %) (Fig. 2G). We next
136 evaluated the ability of the micro-structured tracks embedded in PDMS to conform to curvilinear

surfaces. We found the overall conformability of the soft membrane only depends on the PDMS, the thin tracks being "mechanically transparent" (Fig. 2H).

Electrochemical characterization

To enable efficient delivery of electrical pulses to neighboring neural tissue, electrodes (interfaced to the micro-structured tracks) were coated with a soft composite *(13)*. We characterized the impedance of the combined interconnect and composite coating using electrochemical impedance spectroscopy (EIS). In a medium of phosphate buffered saline (PBS), the average impedance at 1 kHz was 5.78 ± 0.62 kΩ (n = 18, 0.385 mm^2 surface area, Fig. 2I), and the flat impedance spectrum in the 100 Hz to 100 kHz frequency range suggests that the coating roughness decreases successfully the interfacial impedance.

A typical voltage transient (VT) response to a biphasic current pulse (1 mA, 300 µs pulse, a typical ABI stimulation current), recorded in PBS, is presented in Fig. 2J and further demonstrates the suitability of soft and microfabricated neural leads to deliver safe and efficient current stimulation (Fig. 1G).

Cadaveric evaluation of the soft ABI

Next, we implemented soft neurotechnology to design and fabricate a soft ABI array and assessed its ability to conform to the curvature of the human CN. The soft ABI array had identical dimensions to current clinical devices used in humans (Fig. S16) and initially tested on agarose models of the human brainstem and CN based on three-dimensional magnetic resonance imaging (MRI) reconstructions (Fig. 1F). The CN had a radius of curvature of 2.85 ± 0.5 mm (n = 3 CN, histological reconstructions of the human dorsal cochlear nucleus (DCN), Fig. S17). The 200µm

thick soft array conformed well to anatomic curvatures down to 2.8 mm (See calculations and data in Supplementary Methods).

Surgical insertion of the soft ABI array was then assessed in cadaveric models following standard clinical procedures. A posterior fossa craniotomy was performed using either a retrosigmoid and/or translabyrinthine approach to visualize the cerebellum, brainstem, lower cranial nerves and choroid plexus. The human CN is not directly visualized during surgery and accurate placement relies on the identification of indirect landmarks and electrophysiology. We compared surgical insertion of a clinical ABI and a soft ABI array in terms of ease of handling and positioning and removal from the lateral recess of the IVth ventricle (key landmark for the CN) (Fig. 3A-B). We found the soft ABI array was difficult to insert though the lateral recess of the IVth ventricle although the target was reached in all specimens (Suppl. Movie S1). We next modified the soft ABI design to account for repeated positioning of the array that is often required during surgery to optimise the electrophysiological responses. We implemented a temporary guide affixed to the back (non-electrode side) of the array. The guide is prepared with a hydro-soluble polymer, i.e. PVA - poly(vinyl alcohol) - that temporarily stiffens the tip of the implant (Fig. 3C) and helps with handling and positioning of the soft ABI (Fig. 3D). The implant can then be manipulated for about 35 min (in and out of the brainstem region) before the PVA (1 mm thick) softens and eventually dissolves to allow the soft ABI to match the curvature of the underlying CN (Fig. 3E).

We next assessed the electrochemical stability of the microfabricated electrodes before, during and after implantation. We found both the clinical array and soft ABI electrodes display higher electrode impedance following surgical insertion (Fig. 3F-G); this reflects the usual

electrode-tissue interface. After explantation, impedances recovered to their pre-implantation values indicating minimal damage to the electrodes from the procedure.

While the impedance of the soft ABI electrodes is higher than that of the clinical device ($Z_{@1kHZ}$ = 5.78 ± 0.62 *k*Ω | n = 18 soft electrodes, GSA = 0.385 mm^2; $Z_{@1kHZ}$ = 2.11 ± 0.07 *k*Ω | n = 8 clinical electrodes, GSA = 0.385 mm^2, Fig. 3H-I), the electrochemical properties of the soft coating at the interface are superior. The double layer voltage at the electrode-electrolyte interface was 0.80 ± 0.22 *V* (n = 18) for the soft ABI vs. 0.32 ± 0.05 *V* (n = 9) for the clinical ABI (Figure 3H), indicating that the charge injection capacity of the soft ABI is larger than that of the clinical ABI. Furthermore, the charge storage capacity (CSC) was measured using cyclic voltammetry *in vitro* of the soft ABI (21.23 ± 4.19 mC/cm^2, n = 5) and was 13 times larger than that of the clinical ABI (1.60 ± 0.37 mC/cm^2, n = 5) (Fig. 3I), thereby confirming that the electrochemical surface area of the soft coating is larger than that of the flat platinum-iridium electrode used in the clinical ABI. These results indicate the soft ABI electrodes display potentially larger dynamic range compared to the clinical ABIs, and the electrode contact may be miniaturized and deliver safely the same amount of charges to the underlying cochlear nucleus.

The soft ABI array also had superior resolution on computed tomography (CT) and MRI (magnetic resonance imaging); this is mainly enabled by the thinness of the micro-structured metallization. A CT scan performed on one of the cadaveric head specimens implanted with the soft ABI showed the array was clearly visible without artifacts or distortions in the surrounding brain (Fig. 3J). For comparison, a CT scan image from a pediatric patient implanted with a clinical ABI (Cochlear Ltd.) shows significant distortions and artifacts around the array (Fig. 3K). MRI also showed an artifact-free soft ABI while the clinical ABI induced substantial artifacts (Fig. S18). Endoscopic visualization of the ABI following imaging confirmed that neither array had

migrated as a result of these scans.

Chronic evaluation of the soft ABI in a mouse model

Functionality of the soft ABI was tested in chronic conditions in a mouse model. The small size of the mouse DCN surface (~ 500 x 500 μm^2) required miniaturization of our micro-structured interconnects and electrodes to host three electrode sites in the array (detailed layout Fig. S20). Fig. 4A-D display a schematic view of the mouse auditory pathways and location of the stimulation and recording electrode arrays. We developed a novel surgical approach suitable for chronic implantation, and based on a double craniotomy through which the array was looped (Figs. 4B-C, Fig. S21). Access to the DCN required partial removal of the cerebellum. Ten mice were implanted with identical soft ABIs for 4 weeks (experimental timeline shown in Fig. 4E).

Upon implantation, electrode impedances displayed expected increase in modulus (Fig. 4F). Over the course of 4 weeks, little further change in impedance was observed on average (Fig.4G), suggesting both electrodes and interconnects remained stable. High impedance values (>150 kΩ) were measured intermittently on some electrodes and are mostly artifacts due to a noisy and sensitive measurement setup.

In response to electrical stimulation of the array, we recorded electrically evoked auditory brainstem responses (eABR) at weekly intervals (Fig. 4H). Although there was some variability in waveform, the ABI array elicited robust responses up to the conclusion of the experiment (4 weeks). Recordings from the inferior colliculus (IC) were performed using a commercially available silicon shank that was inserted inside the midbrain on week 0, removed during the

implantation period, and re-inserted in the IC at week 4. The spike rate computed from IC recordings collected at week 4 was approximately the same as at week 1 (Fig. 4I-J) although differences in temporal patterns are observed. This difference may have resulted re-insertion and recording at a slightly different position at week 4, or perhaps from scaring of the brain tissue as a result of the week 0 recording *(35)*. The fact that both eABR and IC neural activity showed robust responses confirmed the functionality of the soft ABI over 4 weeks in chronic conditions *in vivo* (Fig. 4K).

Discussion

In this study we propose a soft ABI technology that has a design and materials that allow for ease of surgical insertion and conformability to the curvature of the brainstem. We successfully engineered the critical components, namely elastic micro-structured multilayers, soft electrode coating, and transient surgical features that allowed for fabrication of a scalable ABI from miniaturized mouse implants to human-size arrays. In a human cadaveric model, we demonstrated that the soft ABI is robust to surgical manipulation and insertion into the lateral recess of the IVth ventricle, and displays improved electrochemical performance compared to current clinical devices. In a mouse model, we showed that soft neurotechnology could be implemented to reliably recruit central auditory neurons *in vivo* for up to 4 weeks.

The technology used to fabricate our soft ABI is novel in a number of distinct ways that are essential for the ABI patient population and may help inform implant design for other applications. First, in order to better withstand implant manipulation during the ABI surgical procedure as well as the dynamic microenvironment of the brain, we fabricated stretchable interconnects that conferred elasticity to the electrode tracks. We showed that micro-structuring

interconnects made of PI/Pt/PI with hexagonal arrays of optimized Y-shaped motifs could achieve reversible elasticity for a million cycles at 10% elongation, as well as remain electrically and mechanically functional for applied strains up to 70%. This is a significant improvement compared to non-patterned tracks that would fail at strains as low as 2-3%.

Second, for surgical insertion into the lateral recess, it is important that the array remains stiff for some time to ease insertion and enable repositioning of the array if the initial placement is unsatisfactory. To tackle this issue, we developed a novel hydro-soluble mechanical guide to temporarily stiffen the array. Third, we also incorporated stretchable coatings with high electrochemical area, which allowed us to improve the electro-mechanical performance of the arrays at the electrode-tissue interface, compared to conventional platinum contacts currently used in ABIs. This technology can potentially allow the use of larger currents for CN stimulation without generating electrolysis around the tissue. Finally, the reduced amount of metal in the novel electrodes makes the soft ABI ~~more~~ compatible with conventional clinical imaging techniques (MRI and CT scans) thereby minimizing artifacts that can obscure details about device position as well as surrounding neural anatomy *(36, 37) (38, 39)*. This is critical as NF2 patients (the most common patient cohort to receive the ABI) require routine MRI surveillance to detect new tumor growth. As both monitoring and therapeutical neural implants are deployed in clinical care, their compatibility with high resolution imaging techniques is now a prerequisite.

We tested the soft ABIs in human cadavers and a mouse model. It is important to note that the evaluation for the mouse ABI was centered on whether the array was durable enough to continue to stimulate the CN for a 4-week period. Further experiments will be necessary to evaluate the influence of device connector fixation and torque of the cable on long term ABI position as well as the effects of chronic stimulation on the electrode array, since it was only tested here for 4

weeks. The small number of pulses tested in our experiments compared to the billions of pulses that would be required for daily stimulation across decades of use. Finally, evaluation of human-sized soft array requires the more appropriate model of non-human primates (NHPs) that have similar anatomy as humans. NHPs have been successfully implanted with an ABI using the same surgical approach used clinically, even though the paddle was slightly reduced in size *(40)*. Nevertheless, our mouse ABI model has proven to be valuable for initial *in vivo* evaluation of novel electrode materials and also represents a good tool to pursue more fundamental research to better understand the mechanisms of CN electrical stimulation.

Our studies with the soft ABI in human cadavers provided important insights on feasibility for the clinic and showed how using a temporary guide could ease surgical insertion of the array. However, the technique used for the cadaveric specimens does have a few notable differences from live human surgery, including the absence of brain pulsations, cerebrospinal fluid and bleeding as well as a more flattened cerebellum that enables a more direct approach with less retraction. In addition, candidates for ABI surgery often have tumors (e.g. vestibular schwannomas), which can deform brainstem anatomy and further complicate surgery. This consideration was not evaluated in this work, though the conformability of our implants might compensate for patient-to-patient anatomic variability. Again, a larger animal model, such as NHPs, would aid in better determining the clinical feasibility of using a soft ABI and provide the necessary pre-clinical validation for a human clinical trial to assess safety and the impact of the soft ABI on sound and speech perception outcomes.

Finally, auditory prostheses such as the cochlear implant and ABI (which were some of the earliest and remain among the few FDA approved implantable neural interfaces for the brain

surface) have a long history of paving the way for subsequent implants in other systems. The developments showed in this work could help advance neural interfaces used in epilepsy, Parkinson's disease, motor paralysis, and blindness among others. Softer materials, stretchable interconnects, temporary rigidification, and reduced metallic artifact represent potential advances for all of these existing implants and may also ultimately enable novel applications in regions of the brain which are otherwise inaccessible with existing rigid implants. Our soft neurotechnology is versatile enough to be optimized and tailored to modulate responses of the auditory cortex *(41)* or auditory midbrain *(42)* for restoring hearing or the caudate nucleus to suppress tinnitus *(43)*.

Materials and Methods

See Supplementary Materials

Supplementary Materials

Materials and Methods

Fig. S1. Agarose mold of the human brainstem.

Fig. S2. Simulation of CN electrical stimulation.

Fig. S3. Geometrical construction of the Y-shape pattern.

Fig. S4. Critical dimension of the Y-shape pattern.

Fig. S5. Process-flow for micro-structured PI/Pt/PI multilayer.

Fig. S6. Electron microscopy of micro-structured multi-layers of PI/Pt/PI.

Fig. S7. Equivalent electrical circuit of micro-structured electrical tracks.

Fig. S8. Resistance of micro-structured platinum tracks.

Fig. S9. Electrical redundancy of tracks with Y-shaped micro-structures.

Fig. S10. Failure mechanisms of non-structured tracks compared to micro-structured tracks.

Fig. S11. Apparent elastic modulus of micro-structured tracks embedded in PDMS.

Fig. S12. Electro-mechanical properties of micro-structured tracks of varying width.

Fig. S13. Smallest practical track width of a micro-structured interconnect.

Fig. S14. Smallest theoretical track width of a micro-structured interconnect.

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Figure legends:

Figure 1. **Soft ABI electrode arrays conform to the curvature of the CN unlike the rigid electrode array of the clinical ABI.** (**A**) Lateral view of the human brain with the brainstem shaded (blue). (**B**) Expanded view showing the position of the ABI electrode array between the cerebellum and the brainstem, in the lateral recess of the IV^{th} ventricle. (**C**) Axial histological section of the brainstem with the dorsal and ventral subdivisions of the cochlear nucleus (DCN, VCN). The blue curve represents the soft electrode array conforming to the curved surface of the CN. The radius of curvature of the DCN (R) for this particular histological section was measured as 3 mm. (**D**) Photograph of one of the ABI electrode arrays currently in clinical use (Cochlear Ltd.). (**E**) Simulation results showing current density (black arrows) spreading in the CSF and neural tissue upon stimulation with 100 μA for an electrode (from a clinical ABI) not completely in contact with the CN (left) and for an electrode (from a soft ABI) in contact with the CN (right). The colored surface shows an estimate of the tissue activation in both cases. Methodology is detailed in the Supplementary Material. (**F**) Picture showing the soft ABI conforming and the rigid clinical array not conforming to the curved surfaces of the right and left model DCNs, respectively. The agarose gel model is based on a 3D MRI reconstruction of the human brainstem. (**G**) Above: schematic representation of the soft ABI, a micro-structured multilayer of polyimide and platinum forming the interconnects that are encapsulated between two layers of stretchable silicone. The electrodes sites are coated with a Pt-PDMS composite to decrease their impedance. Below: the actual device with its connector. (**H**) SEM picture of the Pt-PDMS composite on the ABI electrode. (**I**) SEM picture of the micro-structured multi-layer in the interconnects. S: superior, I: inferior, A: anterior, P: posterior, L: left, R: right.

Figure 2. Electromechanical characteristics of stretchable materials used in the construction of soft ABI implants. (**A**) Micrograph of the Y-shaped motifs in a micro-structured track, with the red insets indicating the 3 independent geometrical parameters: *a*, *r* and *L* as well as the critical dimension (CD). (**B**) Mechanical simulation showing the local strain resulting from an applied strain of 20% on a sheet of structured PI (left), and a picture of a real sample stretched at 20% strain (right). (**C**) Graphical representation of the optimization study, where each dot represents a Y-shape pattern with a different combination of parameters *a* and *r* (right). Three different designs are illustrated. (**D**) Change in electrical resistance as a function of stretching (10% applied strain) for 1,000 cycles on micro-fabricated samples with all three designs. The study used PI/Pt/PI interconnects embedded in PDMS. The cross indicates elongation at break. (**E**) A micro-fabricated sample with (blue) and without (purple) micro-structured Y-shaped cuts was stretched up to failure (indicated by a cross). The resistance is shown as a function of the applied strain (N=2 samples, each with 8 tracks 200 μm wide). (**F**) Measured force as a function of applied strain for the same samples as in E. The red curve shows a free-standing sample of PDMS (no interconnects were embedded in the sample) for comparison (N=2 samples) (**G**) A sample was reversibly stretched to 10% for 1 Million (1M) cycles. The graph shows the relative change in resistance as a function of the number of cycles. (**H**) The graph shows the theoretical thicknesses for which a rectangular sample of plain PDMS can conform to a specific wet cylinder of radius R. The left graph contains experimental dots with samples of plain PDMS. The right graph contains experimental dots with samples of 2 μm thick micro-structured multilayers of PI and platinum encapsulated between two layers of PDMS. The inset on the right shows an example of an experimental sample conforming to an agarose cylinder of 4 mm in radius. (**I**) Electrical impedance norm (top) and phase (bottom) of the soft ABI electrodes measured in PBS as a function of frequency. (**J**) Voltage measured on

500 the soft ABI upon stimulation in PBS with a 1 mA biphasic current pulse (300μms in width) at
501 100 Hz (N=2 samples, with 9 electrodes per device) using an external stimulator (Isolated Pulse
502 Stimulator Model 2100, AM Systems). Shaded areas denote standard deviation.

Figure 3. Comparison of clinical and soft ABI electrode arrays in human cadavers. (**A, B**) Endoscopic view of a clinical ABI and soft ABI being inserted in the lateral recess of the IVth ventricle in a human cadaver. (**C**) Schematic and picture of the soft ABI to which a hydrogel guide is glued on the back side of the electrode paddle. To adjust position of the ABI, the guide can be grasped by tweezers (right). (**D**) Endoscopic view of the insertion of the soft ABI with the guide being held by the tweezers. (**E**) Figure showing the water mass intake of a dummy soft ABI with the guide as a function of time. The red dotted line denotes the moment at which the device is too soft to be inserted in a model of the lateral recess in agarose. (**F, G**) Impedance at 1 kHz for the clinical (green, N=1 sample with 9 electrodes) and soft (purple, N=2 samples with 9 electrodes each) ABIs measured in *in vitro* phosphate-buffered saline (PBS) before insertion, after insertion in the cadaver, and again *in vitro* after removal. (**H**) The voltage drop at the electrode interface upon electrical stimulation was extracted from the voltage transients, measured during stimulation, by removing the voltage drop in the interconnects (access resistance). Stimulation was performed with a biphasic symmetrical current pulse of 1 mA for the clinical ABI (green, N=1 sample with 9 electrodes) and soft ABI (purple, N=2 sample with 9 electrodes each). (**I**) The charge storage capacity extracted from the cyclic voltammogram of the clinical ABI (green) and soft ABI (purple). N=1 sample with 5 electrodes each in both cases. (**J**) CT scan of the cadaver implanted with a soft ABI, showing almost no artifact. (**K**) CT scan of a pediatric patient with a clinical ABI, showing substantial "windmill" artifact. All bars denote standard deviation (STD). A: anterior, P: posterior, L: left, R: right.

Figure 4. Chronic functional tests of soft ABI electrode arrays in the mouse. (**A**) Picture of the mouse ABI and images showing the micro-structured tracks. The connector had pins for each of the three electrodes and a fourth pin to allow for control due to artifact stimulation. (**B**) 3D schematic of the ABI, showing the connector on the top of the head and the cable looping through a small posterior craniotomy to access the surface of the DCN as viewed through a second larger craniotomy. (**C**) Right: surgical image of the ABI and its three electrodes (each of diam. 150 μm) on the surface of the DCN. Left: illustration of the electrode array on a 3D reconstructed CN (courtesy of Muniak *et al. (44)*). (**D**) Electrophysiological setup showing how stimulation of the CN was performed with biphasic current pulses (blue) applied to the electrodes of soft ABI. Responses recorded were: 1) auditory brainstem responses (ABRs) recorded using surface electrodes on the vertex and left ear (top left), and 2) neural responses recorded by a 16-channel penetrating probe in the inferior colliculus (IC), which receives crossing projections from the CN (diagram at right). Acoustic tones were used to calibrate the position of the probe. (**E**) Timeline of experiments. (**F**) Electrochemical impedance spectra (EIS) of electrodes *in vitro* (in blue, n=11), on week 0 (in black, n=11) and on week 4 (in red, n=12). Error bars denote standard error of the mean. Measurements were sometimes inconsistent, due to subcutaneous counter electrode positioning in the mouse. Thus, some data points were discarded on some days. Overall, most electrodes remained under 80 kΩ, which is the theoretical impedance limit for stimulation at 150 μA with a voltage compliance of 12 V. Further plots of impedance at 10 kHz (instead of the typical 1 kHz) were used because the impedance at this frequency is much closer to the resistance of the system (the double layer capacitance being short-circuited at higher frequency) and thus more representative of how much current can be injected before reaching the voltage compliance of the

stimulator (12 V), which in this case is the limiting factor for electrical stimulation and not charge injection capacity. (**G**) Impedance at 10 kHz (indicating the access resistance) at different timepoints for all electrodes. Error bars denote standard deviation. Data extracted from 4 mice (4 implants, 3 electrodes each). (**H**) Example waveforms of electrically evoked ABRs (eABRs) evoked by monopolar electrical stimulation of one electrode in a single mouse. The beginning of the traces (first millisecond) contains electrical stimulation artifacts and thus have been blanked out. (**I**) Example post-stimulus time histogram (PSTH) elicited by monopolar stimulation on week 0. (**J**) PSTH of the same mouse and same stimulation electrode on week 4. (**K**) Level curves of IC activity for all stimulation electrodes across all mice. The bold curves show the average for weeks 0 (in black) and 4 (in red). n = 3x4 = 12. Bars denote standard error. L: lateral, M: medial, A: anterior, P: posterior.