Your brain on mesh: Injectable flexible probe melds with neurons, causes little or no chronic immune response

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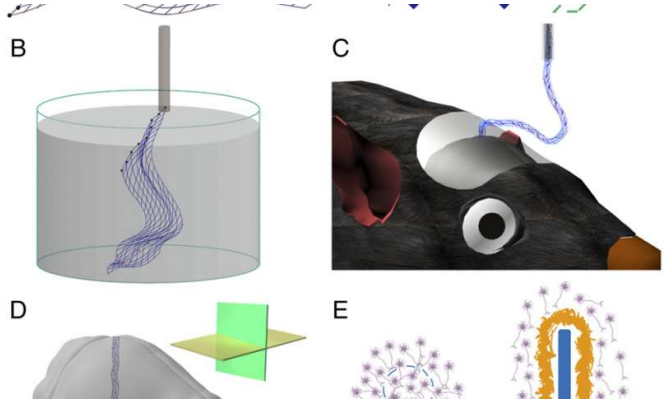

Fig. 1. Schematics of mesh electronics. (*A*) Schematics of the mesh electronics structure in 2D. (*I*) Overall design of mesh electronics structure, where the blue lines highlight the overall mesh structure, the black filled circles at left indicate I/O pads, and the red filled circles indicate recording electrodes. (*II*) A single unit cell of mesh electronics, where the orange lines, which are shown without top polymer layer, highlight the metal interconnects and blue lines correspond to polymer passivation layer; w_1, w_2, and w_m indicate the widths of the longitudinal polymer, transverse polymer, and metal lines, respectively. The schematic in the green dashed box highlights the cross-section view, which shows the polymer encapsulated metal structure, at the position indicated by the green dashed line. (*B*) Schematic of free-standing mesh electronics floating in aqueous solution and ready to be loaded into a glass needle. (*C*) Schematic of mesh electronics injected into mouse brain, with part of the mesh sagging between the brain and the needle. (*D*) Schematic of mesh electronics implanted in brain tissue with horizontal (yellow plane) and sagittal (green plane) sectioning directions highlighted in the inset. (*E*) Schematics of the interface between mesh electronics and the brain tissue (*Left*, cross-section view) and that between flexible thin-film and the brain tissue (*Right*, cross-section view). Mesh elements and the flexible thin-film are highlighted in blue, neurons are in purple, and glial scar is in yellow. Credit: Zhou T, Hong G, Fu T-M, Yang X, Schuhmann TG, Robert D. Viveros, RD, Lieber CM (2017) Syringe-injectable mesh electronics integrate seamlessly with minimal chronic immune response in the brain. *Proc Natl Acad Sci USA* 114(23):5894-5899.

(Phys.org)—Neuroprostheses, neural probes and other intraneural tissue implants have offered remarkable benefits to recipients in a number of areas in neuroscience research and biomedical applications, therapeutic examples being not only Alzheimer's Disease, Parkinson's Disease, epilepsy, traumatic brain injury, and other neurological/neurologically-related conditions, as well as cognition, memory, and sensorimotor disorders. However, current neural implants have several drawbacks, including neural tissue inflammation or scarring due to device micromotion, as well as longevity and the potential need for removal, and high power requirements. Devising electrical probes that seamlessly integrate within neural tissue has therefore been a coveted goal. To that end, scientists at Harvard University have reported the successful implantation of a neuromorphic (that is, having a structure similar to brain tissue) ultraflexible open mesh electronics neural probe that is delivered to specific brain regions via syringe injection (a protocol they published in 2015 in *Nature Nanotechnology*)[1].

The probe—which does not require a power supply—directly records neural voltage changes by being able to interface with all regions of the brain from the level of single neuron through circuits and networks, in which the mesh recording electrode is connected by passivated metal lines (that is, having a protective coating applied to its surface) to input/output pads located at the opposite end of the mesh structure. These I/O pads, in turn, are then connected to Flat Flexible Cables (FFC) and plugged in external system for recording. The researchers also conducted systematic post-implantation studies, finding minimal or absent

neural immune responses, and moreover that brain tissue had penetrated and merged with the mesh probe. The scientists note that the mesh implant may never require removal—but if it does, doing so would be a straightforward if not issue-free procedure. They conclude that most areas of fundamental neuroscience research could benefit from mesh electronics providing long-term stability and single-neuron resolution—unique capabilities not found in conventional neuroprosthetics—and state in their paper that ultraflexible open mesh electronics probes could in the future enable a wide range of opportunities for *in vivo* chronic recording and modulation of brain activity.

Chemical Biology Mark Hyman Jr. Professor of Chemistry Charles Lieber discussed the paper that he, Lead author Graduate Student Tao Zhou, Postdoctoral Fellow Guosong Hong, and their colleagues published in *Proceedings of the National Academy of Sciences*. "The main challenge of designing and implanting an injectable ultraflexible open mesh probe is ensuring the design has four key features," Lieber tells *Phys.org*. These factors are mesh openings larger than cell bodies to facilitate neuron penetration; mesh element features that are the same size or smaller than neurons; flexibility that in this study was many orders of magnitude greater than that of neurons; and mesh electronics that can be easily injected through very high-gauge needles to precisely control the mesh position. "By designing the mesh electronics such that all key properties are neuromorphically similar to neural tissue, we eliminate chronic immune response that is found with all other probes and medical implants, which are more like thorns in your tissue."

As mentioned earlier, the scientists' 2015 paper initiated the concept of syringe injectable electronics, which Lieber notes opens up a new field with many opportunities awaiting further studies—an example being co-injection of electronics and cells where mesh electronics also functions as a tissue growth scaffold relevant to regenerative medicine. "In the paper being discussed herein we report systematic time-dependent chronic histology studies of the tissue-mesh interface after the mesh probes were implanted into rodent brains. Both horizontal (which contains cross-sections of implanted mesh probes) and sagittal (which contains nearly the entire implanted mesh probes) brain slices were used for immunohistochemistry and were stained with antibodies that can target neuron somata, axons, astrocytes and microglia. The results in this paper reveal the uniqueness of mesh probes in terms of minimal or absence of tissue response and neuron penetration when chronically implanted in the brain.

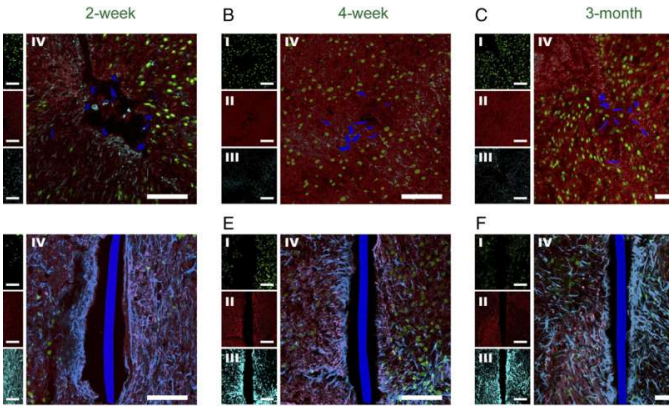

Fig. 2. Time-dependent histology of horizontal tissue slices containing implanted mesh electronics and flexible thin-film probes. Confocal fluorescence microscopy images of horizontal tissue slices containing mesh electronics/flexible thin-film probes at 2 wk (*A* and *D*), 4 wk (*B* and *E*), and 3 mo (*C* and *F*) postimplantation. In all of the panels the image labels were NeuN (*I*, green), NF (*II*, red), GFAP (*III*, cyan), and NeuN, NF, GFAP composite (*IV*). The mesh electronics and flexible thin-film cross-sections are pseudocolored blue. (Scale bars in all images, 100 ?m.) Credit: Zhou T, Hong G, Fu T-M, Yang X, Schuhmann TG, Robert D. Viveros, RD, Lieber CM (2017) Syringe-injectable mesh electronics integrate seamlessly with minimal chronic immune response in the brain. *Proc Natl Acad Sci USA* 114(23):5894-5899.

The researchers used standard photolithography to fabricate the mesh electronics probes using a polyimide-based photoresist (polyimides are biocompatible) in a three-layer structure;

1. the bottom mesh structure (typically ~400 nm thick) is defined per the specific design

2. the metal interconnects, input/output pads, and

brain electrodes are defined, these being ~100 nm thick

3. the top layer of polyimide resist is defined such that all metal is encapsulated except for the I/O pads and electrodes, where the approach and subsequent polymer processing leads to a robust near-monolithic structure

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