BIOELECTRONICS

Neuron-like neural probes

Neural probes that mimic the subcellular structural features and mechanical properties of neurons assimilate across several structures of the brain to provide chronically stable neural recordings in a mouse model.

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Over the past 10–15 years, academics and companies have been attempting to redefine how we use our brains. Brain–computer interfaces (BCIs) can be used to control toys, reach a 'better' meditative state, control robotics, and as part of a system to rehabilitate paralyzed limbs[1]. Several companies and federal agencies have even promised the ability to accelerate learning, enable telepathy, expand and transfer memory, or become symbiotic with AI-enabled machines.

Arguably, higher-order tasks require more invasive BCI devices to communicate with finer populations of neurons within the brain. Neural recordings from individual or small populations of neurons within the brain come at a cost of not just invasiveness, but also self-destructive inflammatory responses that are both damaging to the implanted device and neurodegenerative, ultimately causing the BCIs to fail prematurely[2]. In fact, implanting BCI probes in the region of the brain associated with fine motor skills can actually cause a decline in the performance of fine motor tasks in healthy rats[3]. Therefore, numerous teams have attempted to develop strategies to circumvent the neuroinflammatory response to chronically implanted neural probes within the structures of the brain[4]. Writing in *Nature Materials*, the team led by Charles Lieber at Harvard University reports on neural probes that attempt to mimic the cellular structural features and mechanical properties of neurons, enabling these devices to evade the typical inflammatory process[5]. The researchers build on the often-tested hypothesis that smaller, more flexible devices will reduce the neuroinflammatory response and improve the functional recording performance of brain-dwelling electronics.

Lieber's team used photolithography to develop their 'neuron-like electronics' (NeuE) with an impressive size scale of only ~0.9 μm in total thickness, comparable to a myelinated axon (Fig. 1a). Utilizing their previously published methods for insertion[6], they were able to successfully implant ~80% of their animals across several brain

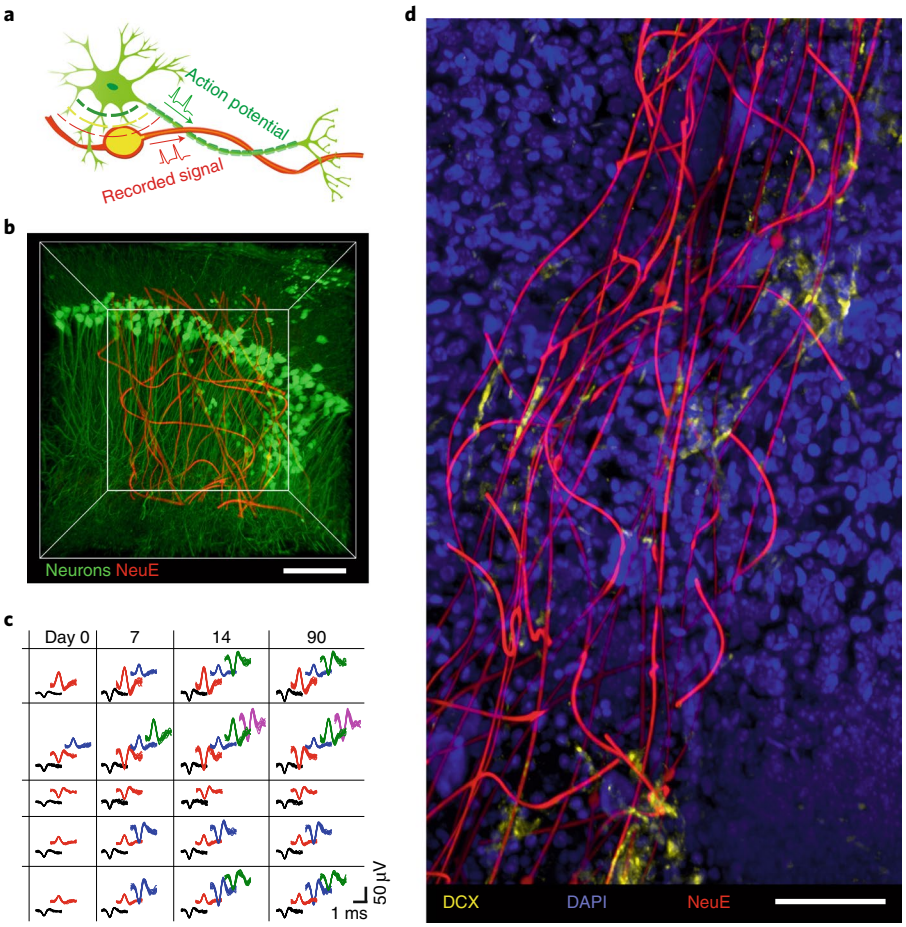

Fig. 1 | Bioinspired probes for neural recordings. a, The neuron-like electronics (NeuE) technology (electrodes and interconnects in yellow, polymer layers in red) compared to the shape of a neuron (green). **b**, 3D histology showing a network of NeuE recording probes (red) interpenetrating neurons (green) two days after implantation. Scale bar, 100 μm. **c**, Action potentials from single neurons detected by five NeuE channels (shown in the different rows) over 90 days post-injection. For each channel, each colour shows spikes from the same neuron. **d**, 3D representation of the distribution of doublecortin (DCX+) newborn neurons (yellow) along NeuE (red) after one week from implantation. Blue represents the 4′,6-diamidino-2-310 phenylindole marker used to stain nuclear DNA. Reproduced from ref. [5], Springer Nature Ltd.

structures. Full three-dimensional mapping of implanted NeuE devices displayed the intimate integration between the NeuE devices and native neurons (Fig. 1b), complete with triangulated positioning of the presumptive neuron believed responsible to the units recorded across electrode contacts.

Recently, fabrication techniques to create micro- and nanosized electronics have been

refined by several groups[7]. For example, carbon-based probes with diameters of ~8–10 μm have been used to demonstrate stable chronic neural recordings with minimally detectable inflammatory responses[8]. Neural probes fabricated on the same polymeric substrate used by Lieber's team, SU-8, and with a cross-section of just 10 μm × 1.5 μm have also enabled stable neural recordings and seamless tissue integration[9]. A remarkable aspect of the NeuE technology is the decrease by a further order of magnitude of the dimensions of the neural electronic devices (thus predictably reducing neuroinflammation), while still allowing reliable implantation in deep regions of the brain. Specialized techniques are regularly being introduced for such feats[6,10], as smaller, more flexible devices are difficult to implant without buckling.

Intriguingly, the researchers not only reported stable single unit recordings from the same neurons over the duration of the 90-day electrophysiology study, but they also measured additional units weeks after implantation that remained throughout the duration of the study (Fig. 1c). Unlike most BCI probes[4], the NeuE probes do not exhibit the initial loss of neuronal density at the probe–tissue interface. In fact, neither the sham insertion nor the implanted device revealed detectable neuroinflammation or neurodegeneration. Therefore, the increase in the number of distinct neurons detected via single unit recordings is not likely to be due to tissue remodelling or reduction in edema seen in other studies[11]. Consequently, Lieber and his team considered an alternative source, the migration of endogenous neural progenitor cells (NPCs), which they propose differentiate into doublecortin (DCX^+) 'newborn neurons'. Representative images from one week after device implantation show DCX^+ cells aligning with the NeuE structure, and the lack of DCX^+ cells away from the probes (Fig. 1d). Comparing the 0.9 μm NeuE probes to their previously reported 20 μm diameter neural mesh devices suggested that cell adhesion and migration of the endogenous NPCs is modulated by the shape of the neuron-like probes. The researchers also speculated that the NPC migration may contribute to the observed healing of the tissues and detection of neural spikes from additional units.

Further investigation will be required to elucidate the mechanisms behind the recruitment of NPCs to the implant–tissue interface. The NeuE is simply dip-coated in poly-D-lysine, allowing uniform surface adsorption of the polypeptide that is not expected to generate chemotactic gradients driving the migration of NPCs to the NeuE interface. It is worth noting that heightened levels of cell proliferation and neurogenesis have been reported in brain injury models, raising the possibility that the NPC effect may be due (at least in part) to the insertion technique rather than exclusively to the persistence of the NeuE device[12]. Additionally, transplanted neocortical neurons have been shown to migrate selectively to areas of neurodegeneration[13]. Therefore, we look forward to future studies that describe the proposed mechanisms that drive NPC activation to subdue the native neuroinflammatory response to device implantation, and result in the generation of newborn neurons. Perhaps, exploiting that mechanism can prove to be a valuable tool in the treatment of brain injuries and neurodegenerative diseases.

Clearly, the development of immune-evasive neural interfaces that can seamlessly integrate across multiple brain structures represents an exciting tool for basic neuroscience and rehabilitative neural engineering research. It will be important to follow future advances with the NeuE devices, to better understand how fabrication methods can scale to larger animal models, and potentially even human BCIs. Although the initial implantation studies in mice are a promising starting point, biocompatibility and long-term performance will have to be further assessed when these devices will be implanted at the density required to drive the restoration of human limbs, or augment able-bodied humans with enhanced memory, creating a form of a 'brain-wide-web' of integrated neural interfaces. ❐

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