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Soft devices in neurological surgery

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The translation of soft biomedical devices from academia to commercialization remains limited despite the substantial growth of the field over the past decade. To drive the next stage of innovation, it is crucial to identify applications that can be uniquely addressed by soft devices. Neurological surgery presents numerous opportunities for harnessing the potential of soft devices in medical applications.

Neural tissue is delicate and prone to damage when interfaced or manipulated with devices made of stiff, unyielding materials[1]. Soft medical devices have a low mechanical mismatch with biological tissues but can still be durable. They may therefore offer unique solutions to a range of clinical problems that cannot be fully addressed using 'hard' devices. New classes of soft devices for neurosurgery can have a major impact in three areas in particular: minimally invasive surgery, targeted drug delivery and implantable neural electrodes. Although there are currently no regulated soft neurosurgical devices used clinically, this young field has already produced a wide range of technologies at various technology readiness levels (TRLs), including early laboratory prototypes (TRL 1–3) and devices nearing clinical use (TRL 5+). Some of these technologies are highlighted in Fig. 1.

Soft surgical tools

Endoscopic cranial surgery uses rigid, straight endoscopes, which require a straight path to the area of interest. Soft endoscopic actuators can facilitate the development of endoscopes[2] and tissue retractors[3] that eliminate the requirement of line-of-sight style operation.

Many neurological diseases, such as brain tumours, are located within small, deep openings in the subarachnoid space called cisterns. Traditional endoscopic approaches often struggle to access these subarachnoid cisterns. Soft continuum robots controlled by the external application of a telerobotic magnetic force offer a smoother, safer and faster navigation than traditional manual and magnet-tipped wires[2], with the added advantage of remote access. These devices have been tested in porcine models (TRL 5) but are expected to reach a much higher TRL soon (TRL 7–8) due to intense activity, interest and a clear regulatory pathway in the subfield of neurovascular surgery[2]. Research into soft, endoscopic tools, however, has so far mostly been limited to abdominal surgery, with only a few examples in neurosurgery.

Another type of tool that can be improved using soft materials are brain retractors (Fig. 1a). Brain retraction is frequently required during surgery for diseases such as brain tumours. The limited space within the brain and skull makes tissue retraction difficult. Neural tissue dies after a short period (~4 min) of reduced blood supply, which can happen when using hard tools. Soft retractors can accommodate the naturally pulsating, dynamic neural tissue, resulting in reduced tissue damage. For example, an origami actuator deployable via a burr hole (TRL 4 with limited in vitro testing) that can be guided more easily and to deeper locations than rigid tools, and can be pneumatically inflated during surgery, has been developed[3]. As the tool is only inflated once it reaches the site of the lesion, the tissue is retracted for a short period, thus reducing the overall pressure applied to the cranial tissue.

Soft devices for drug delivery

For the most part, the blood–brain barrier only allows transport of lipophilic or small molecules into the central nervous system, thus making targeted, efficient drug delivery a challenge. Soft actuators made from silicones enable targeted delivery of a wide range of drugs to hard-to-reach locations in the nervous system at a controlled rate (Fig. 1b). Soft robotics for drug delivery is an area that has developed recently, in part thanks to new fabrication strategies such as multi-step molding and self-folding combined with photolithography. One such soft implantable device delivered epilepsy medication within 70 seconds of the command for drug ejection and successfully suppressed seizures in mice (TRL 5)[4]. This type of drug delivery system could potentially treat status epilepticus, a medical emergency. The current version of the device, however, was designed for one-time insertion under the skin and long-term use, requiring that the drug supply be replenished after use, a feature not currently offered. Once this is achieved, soft robots could enable unique pharmaceutical intervention, such as in situ treatment of fatal seizures[4]. This direction should be the focus of the field, as many cost-effective, efficient drug delivery methods already exist (such as oral, subcutaneous and intravenous). Soft devices, with their durability and ease of manipulation, could allow rapid delivery and administration of drugs to regions of the body with complex anatomy with high spatial selectivity and minimal invasiveness.

Soft implantable neural electrodes

Implanted neural electrodes enable communication between the central nervous system and an external computer or device. Implanted electrodes directly interface with neural tissue to record neural signals and/or provide electrical stimulation for neuromodulation[5] or neuroprostheses[1]. Implanted hard electrodes for deep brain stimulation, one common clinical application, are typically made of platinum–iridium alloy[1] and polyurethane through sputtering and photolithography-based microfabrication. The performance of hard electrodes drops over time, producing poorer quality recordings and less effective stimulation. The main reason is the formation of a fibrotic capsule around the device, due in part to the inability of hard electrodes to adapt to complex neural geometries and pulsating blood flows, which causes damage to the tissue. Hard metallic electrodes are also not compatible with MRI measurements. Soft electrodes offer a lower mechanical contrast and higher degree of biomimicry[1] and can adapt to complex geometries.

For example, E-dura (TRL 5) is a long-term, implantable neural electrode with the same elasticity as the brain's dura mater[5].

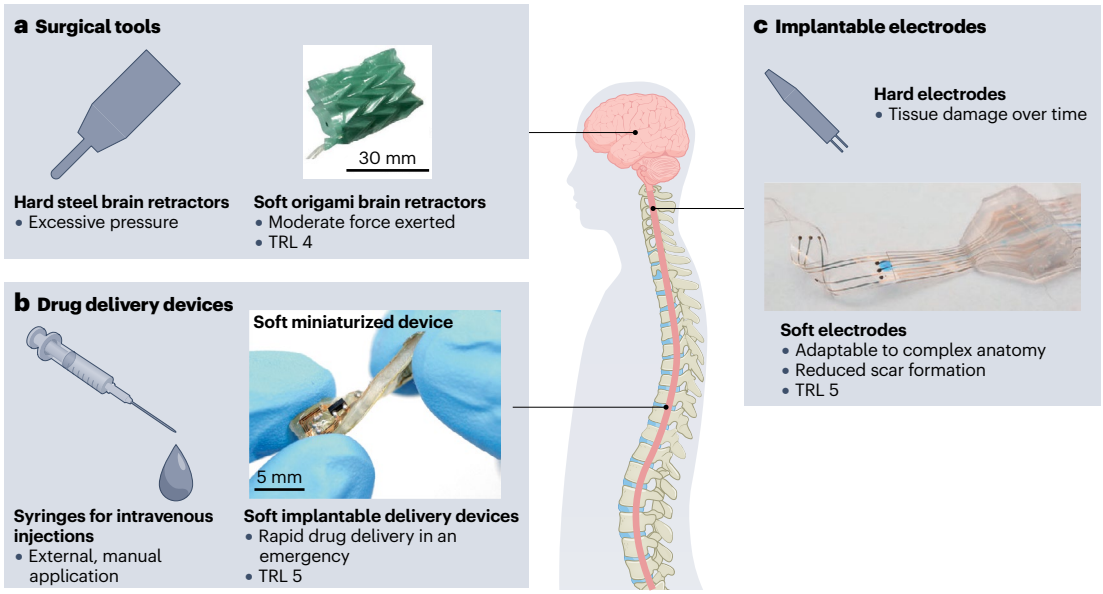

Fig. 1 | Soft devices for neurosurgery. a, Traditional brain retractors are made of stainless steel and can cause excessive pressure on tissues, whereas silicone origami actuators[3] exert less force while still resulting in the same displacement of tissue. **b**, Soft drug delivery devices[4] can deliver to hard-to-reach regions in the body in emergency situations better than syringes. **c**, Hard neural electrodes[9] may impede physiological function and form scar tissue, whereas soft neural electrodes[1] can adapt to a pulsating blood flow. TRL, technology readiness level. Panel **a**, picture of soft surgical tool, reprinted from ref. 3, CC BY 4.0. Panel **b**, picture of a soft drug delivery device, adapted with permission from ref. 4, AAAS. Panel **c**, picture of soft implantable electrode, adapted with permission from ref. 5, AAAS.

E-Dura has three functions: passively monitoring brain activity, actively providing electrical stimulation and delivering drugs through its microfluidic system. The manufacturing of E-dura integrates multiple techniques, namely soft lithography (for the silicone substrate), thermal evaporation (for the gold interconnects) and screen printing (for the platinum–silicone coating). In rats, no significant difference in inflammatory response or motor performance was observed between a control group[5] and animals implanted with E-dura for up to 6 weeks after implantation. This technology is also MRI-compatible. Currently, Neurosoft Bioelectronics, the company that commercializes E-dura, is seeking its clinical approval as a treatment for tinnitus. Because soft implantable electrodes address some of the key problems associated with hard electrodes, we envision that research in this field and eventual clinical adoption will proceed in an accelerated fashion.

Barriers to clinical translation

The development of medical devices from idea to clinical availability is long (3–7 years until clinical demonstration and regulatory compliance), complex and costly (on average US$94 million for premarket approval alone). Because soft devices are a new technology, there are no standardized processes for their industrial production at scale. This causes higher manufacturing costs and further complicates regulatory compliance. To be competitive, a new medical technology must be either substantially cheaper or substantially more effective than existing solutions, or it needs to address a currently unsolved problem. Funding the development of a new medical device is incentivized if the device also has a commercial application: for example, Neuralink's brain–computer interface implant[6] has clinical applications in restoring sensory and motor function but can also communicate with mobile phones and computer games for a faster response and reaction time. The existence and dynamic nature of start-ups within this field, such as Neurosoft Bioelectronics, accelerates the process of making new, patient-oriented technologies available in the clinic.

Soft devices face significant regulatory and ethical obstacles that slow down their clinical implementation. To accelerate the approval and improve the quality of these devices, the IDEAL-D (idea, development, exploration, assessment, long-term follow-up for device innovation) recommendations[7] offer a systematic approach to evaluating new surgical devices while considering input from various stakeholders. The application of soft devices to the brain is high risk, and the devices must usually undergo testing on animal models (such as rats and non-human primates), then first-in-human studies to ensure their safety and viability. To gauge the acceptability of these devices from the patient's perspective, focus groups or surveys must be conducted. Clinicians must consider the usability of the devices, including ergonomic and human factors, and the need for additional training. Additionally, from a systems perspective, economic modelling must be conducted to evaluate the wider health-economic implications.

Future perspectives

Soft robotics as a field has experienced a decade of rapid development during which much research has been "soft for soft's sake"[8]. To ensure sustainability, the focus should be on finding applications that can only be solved by soft medical devices[8]. For example, traditional hard electrodes were recently used to restore trunk and leg motor function after spinal cord injury[9]. Soft electrodes could facilitate long-term viability and personalization of this treatment. Soft, especially stretchable, electrodes also have potential applications in adaptive paediatric spinal implants that can change with the anatomy of the child. In a recent study, enzymatic polymerization of injectable gels was used to produce organic, substrate-free, conductive electrodes in zebrafish[10]. These electrodes are flexible and suitable for neuromodulation and thus could be implanted in a minimally invasive way for deep brain stimulation while accommodating the brain's complex morphology. Soft materials will ultimately improve the biocompatibility, longevity and versatility of implanted neural devices.

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Competing interests

The authors declare no competing interests.