Small-scale robotic devices for medical interventions in the brain

Lorenzo Noseda and Mahmut Selman Sakar*

This article summarizes the recent advancements in the design, fabrication, and control of microrobotic devices for the diagnosis and treatment of brain disorders. With a focus on diverse actuation methods, we discuss how advancements in materials science and microengineering can enable minimally invasive and safe access to brain tissue. From targeted drug delivery to complex interfacing with neural circuitry, these innovative technologies offer great clinical potential. The article also underscores the importance of device mechanics for minimizing tissue damage and the growing role of advanced manufacturing techniques for maximizing functionality, offering an up-to-date multidisciplinary perspective on this rapidly evolving field.

Introduction

The rapid convergence of microengineering and neurotechnology has ushered in a new era of innovation in biomedical technology. At the heart of this revolution are miniaturized instruments designed to interface with the brain, enabling the study of neuroanatomy and facilitating the diagnosis and treatment of a spectrum of brain disorders. Brain interventions are inherently complex due to the organ's delicate and intricate structures. As an exciting advancement, robotic control systems that can safely and effectively navigate miniaturized instruments to previously inaccessible areas of the brain have started to emerge. This article aims to provide a comprehensive overview of the state-of-the-art small-scale robotic instruments for brain interventions, focusing on the advancements made possible by integrating novel materials, actuation mechanisms, and manufacturing techniques.

Brain interventions can be classified by their targets: functional and structural. Functional targets are regions with abnormal neural activity typically associated with neurological disorders, such as Parkinson's disease, epilepsy, and psychiatric disorders. Robotics could aid in the accurate placement of electrodes in target regions such as the subthalamic nucleus for Parkinson's disease or the anterior thalamic nucleus for epilepsy. On the other hand, structural targets typically involve physical abnormalities within the brain, such as tumors, aneurysms, or blood clots. In these instances, accuracy is key to ensure the complete removal or treatment of the abnormality while minimizing damage to surrounding healthy tissue. Robotic instruments could offer a high level of accuracy and speed that is otherwise challenging to attain, thus maximizing efficacy.[1–4]

There are two primary access routes to the brain: endovascular and transcranial. The endovascular route involves navigating the intricate network of blood vessels in the brain, making it ideal for treating conditions such as aneurysms or facilitating clot removal in stroke patients. The miniaturization of endovascular instruments could aid navigation inside small and tortuous arteries. The arteries supplying blood to the brain primarily originate from the internal carotid arteries and the vertebrobasilar system, which together converge to form the Circle of Willis, an arterial network branching out to cover the entire brain[5] (**Figure 1**a). The vasculature presents several successive branching points called bifurcations. Each bifurcation leads to a decrease in the dia. of the vessels deeper in the brain[6] and, combined with the varying angle and orientation, to an increase in the complexity of the system. Furthermore, the smaller arterioles and capillaries exhibit high tortuosity, often making sharp turns and

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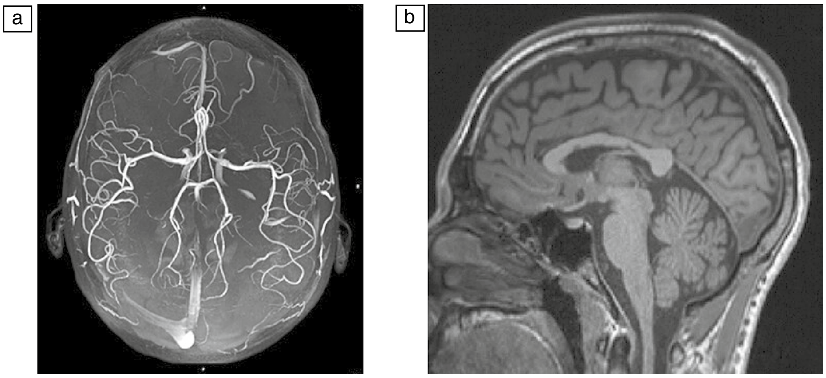

Figure 1. Human brain imaging. (a) Magnetic resonance angiography reconstruction of arterial tree in the brain shows increased tortuosity and decreased dia. in distal regions. Reprinted with permission from Reference 7. © 2014 Wiley. (b) Cerebral cross section of a human brain in 3 T magnetic resonance imaging (MRI) shows the geometrical complexity of the brain anatomy. Reprinted with permission from Reference 8. © 2023 Wiley.

three-dimensional (3D) loops. The geometry of this network is highly variable and individualized, presenting unique challenges with every patient. Therefore, to conform to the geometry and enable navigation, the instrument must be adaptable and display a certain degree of flexibility.

The transcranial route, on the other hand, involves direct access to the brain through the skull and is often used for treating conditions such as brain tumors.[9] The objective is to use small incisions and precise movements to reach the target area with minimal tissue disruption. The various tissues encountered during transcranial interventions exhibit diverse mechanical properties,[10,11] directly impacting the design and operation of robotic instruments. The human skull, composed primarily of cortical bone, has high rigidity and strength, demanding robust tools for perforation. Upon penetrating the skull, the instrument encounters the dura mater, the outermost of the three meninges that envelop the brain.[5] It is a tough, fibrous membrane composed of dense, irregular connective tissue, requiring sharp instruments for incision. Its stiffness varies significantly from the skull, making it a delicate transition point in the procedure. The tissue of the brain is composed of gray and white matter (Figure 1b), a soft, gelatinous substance with mechanical properties vastly different from any of the preceding structures. Gray matter, primarily found in the cerebral cortex and subcortical structures, is slightly stiffer than the underlying white matter due to its higher cellular density, leading to different responses to stress and strain.[12] Thus, an ideal instrument is expected to adapt to these mechanically variable conditions. Moreover, damage to these tissues can have serious neurological implications,[13] emphasizing the need for precision and minimally invasive strategies in navigation.

Understanding these complexities in brain morphology — the tortuous geometry of the arteriovenous system and the variable mechanical properties of different brain tissues — is crucial in advancing the design, actuation, and control of small-scale robotic instruments for effective and safe brain interventions.

Endovascular route

Leveraging the vast and intricate network of blood vessels that irrigate the brain, endovascular procedures offer a pathway that, although challenging in its complexity, also opens the door to a range of unique therapeutic possibilities. The endovascular route provides access to areas of the brain that could be hard to reach by other means, often facilitating treatments for conditions uniquely suited to this approach. Cerebral aneurysms, arteriovenous malformations (AVMs), and certain types of strokes, particularly those involving large vessel occlusions, can be directly treated via endovascular techniques.[14] By allowing clinicians to reach and treat problematic vascular structures directly, endovascular interventions can provide a minimally invasive alternative to open neurosurgery. This is especially beneficial when the affected areas are located deep within the brain or in regions that are surgically inaccessible. Moreover, due to the minimally invasive nature of the endovascular approach, it often presents a reduced risk of causing brain damage compared to traditional open surgical procedures. Navigating through the vascular network rather than traversing brain tissue directly minimizes the chance of damaging crucial neural structures. Consequently, these procedures can result in quicker patient recovery and lower complication rates.[15]

Neurovascular interventions typically include inserting a guidewire,[16] a slender device that is manually pushed for advancement and twisted for steering through reorientation of the tip. Following this step, a catheter is pushed over the guidewire, following the charted path to reach the target. After that, the guidewire is retrieved, and the catheter cavity is employed to perform a range of interventions. Among the procedures using mechanical tools, we find coiling for aneurysms, thrombectomy for clot removal, stenting to keep vessels open, and flow diversion to redirect blood flow. Other procedures include the injection of chemical compounds for treatments such as tumor and AVM embolization, thrombolysis, or intra-arterial chemotherapy.[14] The typical dia. for neurovascular guidewires ranges from 0.007 to 0.014 in.[17] or approximately 0.18 to 0.36 mm. To enable steering, the tip is usually bent, either through the selection of a preshaped product or by manually shaping the tip prior to insertion. Most guidewires are made of stainless steel[18] or nitinol,[19] which can sometimes be coated for improved hydrophilicity.[20] They typically consist of a stiffer core and a bendable outer shell, which is usually more flexible or shapable at the tip. The bendability is generally achieved through a coiled design or laser and diamond-cutting patterning of creases. To increase the steerability of the tip region and retain structural support in the proximal regions, a stiffness gradient is included.

The steering method of traditional guidewires requires prior knowledge of the path and experience in selecting the optimal shape based on the required successive steering maneuvers.[17] One of the main limitations is that the bent shape might not be optimal for all steering maneuvers or even completely unsuitable in more tortuous regions. The ability to conform to small curvature radii in tortuous regions is in direct conflict with the ability to push the device because, in the prior case, a compliant device is required and, in the latter, a rigid one. Catheters have similar requirements to guidewires regarding flexibility and pushability. However, their design is tubular to be able to slide around the guidewire and to have a working channel for bringing treatment tools to the target. To achieve the required specifications, the device typically consists of a coiled metal wire coated in a polymer.[18,21] They also typically present a longitudinal stiffness gradient.

Actuated miniaturized endovascular devices

The main technological feature enabling advanced guidance is intraoperative tip reshaping, which greatly enhances the steerability of endovascular devices. Active steerable guidewires have recently started to appear on the market. Rapid Medical is in the process of commercializing the 0.014-in. (0.36 mm) dia. Columbus guidewire[17] after receiving FDA approval in 2020. The device is made steerable by a nitinol core wire attached to the tip that can be pushed or pulled to modify its curvature (**Figure 2**a). Another device that obtained FDA approval in 2023 is the SmartGUIDE deflectable hydrophilic guidewire by Artiria Medical,[22] which shares the actuation principle with the Columbus guidewire. The company is currently recruiting participants for their clinical trial. Another example is Bendit,[23] the 0.021-in. (0.53 mm) steerable microcatheter that was approved by the FDA in 2022. As explained earlier, the common practice is to use a guidewire prior to the insertion of a catheter. In the case of Bendit, the catheter consists of two concentric nitinol-patterned tubes that bend when one is axially shifted with respect to the other, allowing the direct steering of the catheter. These market advances show the growing interest in steerable endovascular devices.

An alternate actuation strategy with a rich developmental history is magnetics. The first endovascular devices using this technique can be found in the 1950s[24] when a catheter steel tip was steered with the use of externally applied magnetic fields (Figure 2b), and later by Stereotaxis, who commercialized a catheter with a permanent magnet tip.[25] A possible implementation of such actuation, along with the robotization of the surgical procedure, is illustrated in **Figure 3**a.

Recent advances have enabled miniaturization and increased the flexibility of such devices. Kim et al. have introduced a 400-μm dia. magnetically steerable soft continuum guidewire for neurovascular applications.[26] The device consists of a nitinol wire coated with thermoplastic polyurethane (TPU) with embedded neodymium iron boron microparticles.[27] To allow injection molding and stability of the TPU-NdFeB mix, it is turned into a thixotropic paste by applying a magnetic field that generates strong interactions between the embedded particles. This prevents phase separation of the mixture and enables extrusion through its shear-thinning properties. The magnetized mixture is then injection-molded into a microtube where the nitinol wire is inserted concentrically. The molding is completed through heating for solvent evaporation of the TPU composite. It is then axially magnetized to maximize the torque applied to the instrument. The presence of the stiff nitinol core allows for the device to be fed through a microcatheter. The device's tip lacks the core to decrease stiffness and increase steerability. The device is telerobotically guided by external permanent magnets, which allow steering through the alignment of the tip with the magnetic field and attraction caused by the magnetic field gradient. The guidewire was successfully used to navigate cerebrovascular phantoms *in vitro* (Figure 3b) and to guide catheters for aneurysm coil embolization and clot retrieval thrombectomy. The device was also validated *in vivo* in a porcine brachial artery. Finally, its performance was compared by an experienced neuro-interventionalist to a traditional guidewire. The use of magnetic steering resulted in lower numbers of undesirable maneuvers and lower intervention time after less than 1 h of training with the telerobotic system.

To overcome the limitations of the tradeoff between steerability and pushability, magnetically steerable catheters with variable stiffness have been developed.[29] Part of the catheter tip is composed of encapsulated low-melting-point alloy, which can be melted with the embedded resistance heating wire, lowering the stiffness of the device and increasing its steerability. Steering of a 1-mm dia. device is achieved by an external magnetic field acting upon

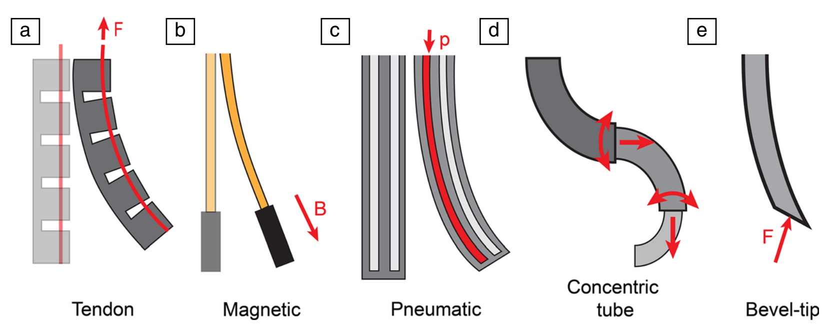

Figure 2. Schematic illustration of main actuation and steering mechanisms of small-scale robotic devices developed for brain interventions. Robotic devices can be navigated using (a) tendon-driven mechanisms, (b) magnetic forces and torques, (c) pneumatic systems, (d) concentric tubes, and (e) slender features with beveled tips.

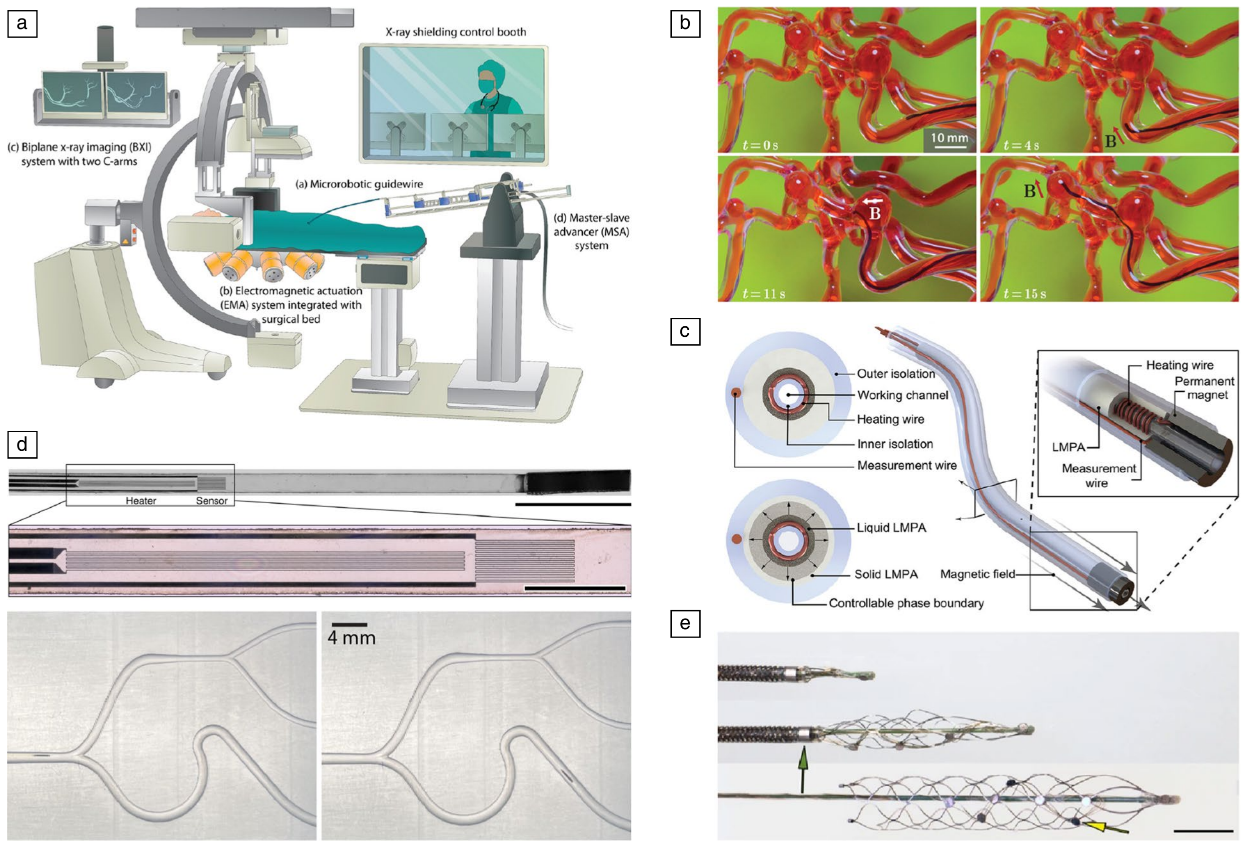

Figure 3. Small-scale actuated endovascular instruments. (a) Magnetic steering system with real-time fluoroscopy imaging. Reprinted with permission from Reference 28. © 2022 Wiley. (b) Ferromagnetic soft continuum robot navigating a cerebrovascular phantom. Reprinted with permission from Reference 27. © 2019 Science. (c) The design of a magnetically steered variable stiffness catheter. Reprinted with permission from Reference 29. © 2021 Wiley. (d) Flow-driven endovascular device. Top: Magnified device tip showing microfabricated flow sensor and magnetic elastomer tip. Scale bars = 1 mm in the overview and 0.5 mm in the detail view. Reprinted with permission from Reference 30. © 2020 Springer Nature. Bottom: Navigation of the device in a brain artery phantom. (e) The compacted and expanded configurations of the Stentrode device. The green arrow shows the delivery catheter, and the yellow arrow shows an electrode. Scale bar = 3 mm. Reprinted with permission from Reference 31. © 2016 Springer Nature. LMPA, low-melting-point alloy.

a permanent magnet attached at the tip of the device (Figure 3c). The inner tube is made of silicone, onto which a copper wire is coiled, which is then inserted coaxially in an outer tube, over which a low-melting-point alloy is poured and molded. The magnetic tip is attached at the end of the structure. Details on the manufacturing of further-generation devices with improved biocompatibility and stiffness control can be found in follow-up articles.[32,33] The project is part of a more significant effort to build a minimally invasive surgical platform by the startup Nanoflex, currently targeting neurovascular applications.

Toward extreme miniaturization, Pancaldi et al. introduced a magnetically steerable ultraflexible device that consists of a 4-µm-thick, 0.2-mm-wide polyimide ribbon with a magnetic elastomer tip.[30] Instead of requiring pushing for insertion, as with traditional guidewires, the device is transported by arterial flow. By applying a uniform external magnetic field, the magnetic tip can be reoriented, allowing steering at bifurcations. Using a polyimide ribbon enables the deposition of conductive elements and the patterning of electrical circuits. A flow sensor was implemented by depositing two platinum serpentines, allowing the measure of the time of flight between the local heating of blood and its detection downstream (Figure 3d). Furthermore, the authors proposed a device variant using 0.12-mm outer dia. catheters, enabling targeted injection. For manufacturing, polyimide is spin-coated on a Si wafer, gold electrical circuits are patterned, and the ribbons are laser cut. The catheters are manufactured by dipping a 40-µm tungsten wire in PDMS. The wire is then heated to enable rapid local curing of the PDMS. As a follow-up to this work, the authors developed a magnetic tip that complements flow-driven advancement with crawling.[34] Crawling is achieved in vessels with little-to-no flow by magnetizing the tip of the device in an inhomogeneous profile and applying a rotating magnetic field. Flow-driven and crawling advancements were performed together in *ex vivo* pig coronary arteries with the same device. Magnetic actuation becomes more challenging as the devices are miniaturized toward the microscale because both magnetic force and torque scale with volume. Notably, the magnetic force decreases sharply with distance, following a cubic relationship, necessitating the application of stronger external magnetic field gradients for navigation inside deeper brain regions. Not surprisingly, most magnetic actuation schemes are based on the application of torque where the required magnetic field strength is dictated by a square relationship with distance.

As an alternative to magnetic steering, hydraulic actuation has been explored[35] (Figure 2c). The catheter tip consists of a 0.9-mm outer dia. (OD), 0.4-mm inner dia. (ID) tube with 4×50-µm saline-filled channels disposed at 90° from each other. The device was manufactured by molding a platinum-cure hyperelastic silicone rubber. The tip radius and orientation can be modified by individually modulating the pressure of the fluid in the channels. In other words, the channels can be considered as tendons of the guidewires from Columbus and Artiria. Steering was tested *in vitro* in a human neurovascular model at the ICA and *in vivo* in a porcine pharyngeal artery. A potential challenge in the pursuit of miniaturization of hydraulically actuated devices is that prohibitively high pressure could be required to inflate microscopic channels presenting extremely high resistance.

Recent developments do not only concern increasing the reachable workspace and reducing the invasiveness of the intervention, but also enabling novel interventions. A prime example is the recording of brain activity from the vasculature, which has gained traction in recent years. Stentrode,[31] a stent-based implant decorated with electrodes, is currently one of the leading technologies capable of this. It is released from a catheter of 1-mm inner dia. and, when deployed, it expands and can maintain contact with the vascular wall of vessels up to 8- or 10 mm in dia. (Figure 3e). Recently, Zhang et al. described an implantable probe for recording brain activity in blood vessels of sub-100-µm dia.[36] The probe is a prime example of a new class of devices called injectable mesh electronics.[37] The device is a guidewire with a 0.9-mm-wide ribbon mesh, which curls and maintains contact with the vascular wall upon release when the vessel dia. is significantly smaller than the mesh width. *In vivo* brain activity was recorded in rodents with up to 16 electrodes on a single mesh. With the electrodes, the authors were able to analyze penicillin-induced seizure activity and identify and isolate single-unit spikes corresponding to single-neuron activity. The devices were fabricated on a 4-in. wafer using conventional cleanroom techniques. The electrodes are made through platinum deposition, the interconnect out of gold, and the guidewire backbone is made from SU-8, an epoxy-based photoresist known for its stable mechanical properties and high-aspect ratio in microfabrication processes.

Untethered endovascular devices and capsules

Aside from the classic guidewire and catheter interventions, there is significant research thrust in the development of untethered devices. One application that has gained the most traction is targeted drug delivery.[38] The exact nature of these devices can be quite unconventional; stimuli-responsive polymers, gels, and vesicles, as well as engineered cells, have been considered viable options. Nevertheless, the common understanding is that one of the most critical factors is the retrieval or neutralization of the device right after the completion of the intended task.

As a seminal example, Ozdas et al. have described a method for aggregating microbubbles to deliver small drug molecules and cross the blood–brain barrier with focused ultrasound.[39] The device consists of lipid-encapsulated perfluorobutane, a safe contrast agent that has also been commercialized under the name Sonazoid, with liposomes containing the drug molecules attached to it. Once released into the bloodstream, the application of focused ultrasound at a specific location agglomerates the microbubbles and bursts the liposome shell via the modulation of the sound intensity. Another actuation method proposed for positioning devices in vessels with flow is magnetics, such as the device presented by Wang et al., which consists of a magnetic elastomer mesh that conforms to the vessel walls and can move through crawling locomotion.[40] Rolling magnetic microbeads on the vessel walls using rotating uniform magnetic fields have also been proposed as an effective strategy for targeted cargo delivery in physiological blood flow.[41–43] The microrollers are composed of 10-µm-sized silica microparticles, half-sputtered with Ni and Au layers.

Untethered devices present several critical challenges, such as the monitoring and control of the journey of such free devices through the body's complex vascular network. Their design faces a fundamental tradeoff; the devices must be small enough to navigate narrow passages without causing occlusions yet large enough to perform their intended mechanical functions. Additionally, in the case of nonbiodegradable devices, retrieval poses a significant challenge, considering the presence of flow and interactions with the vessel walls.

Transcranial route

The transcranial route provides direct access to the brain through the skull. Unlike the endovascular route, which relies on the predefined architecture of the brain's vascular system, the transcranial approach is not bound by these constraints. Instead, it provides the possibility to adapt the entry point according to the clinical necessity, offering a versatile access strategy to virtually any part of the brain. Historically, transcranial surgery has been characterized by open procedures, where a section of the skull is removed or opened to gain direct access to the brain. This approach, known as craniotomy, allows surgeons to treat neurological conditions such as brain tumors, aneurysms, and epilepsy.[9] Traditional craniotomies require extensive exposure of the brain, often involving longer recovery times and potential risks to healthy brain tissue. The inherent flexibility of the transcranial approach proves especially beneficial for disorders that demand interventions in areas not readily accessible via the vascular network. It's worth mentioning, however, that although the transcranial approach provides a higher degree of flexibility, it also comes with its own set of challenges. Direct access to the brain necessitates drilling a hole in the skull, a procedure that could carry a risk of infection and other complications. Moreover, from a surgical perspective, the cranial cavity presents a markedly confined space compared to other traditional surgical specialties. This constraint demands exceptionally precise navigation and meticulous movements to avoid inadvertent damage to the delicate brain tissues.

With the advancement of technology and surgical techniques, transcranial surgery has undergone a significant transformation toward minimally invasive approaches. These techniques aim to reduce the impact on the patient and offer several benefits, including less pain, lower risk of infection, and quicker recovery.[44] A common method to reach the target more accurately is stereotactic insertion, a minimally invasive robot-assisted intervention.[45–47] This method combines the use of imaging techniques, such as magnetic resonance imaging (MRI) or computed tomography (CT) scans, with a fixed frame or frameless system to provide precise spatial localization for insertion of the device. By offering surgeons the ability to target specific neural structures with high precision, stereotactic surgery enables procedures such as biopsies, ablations, deep brain stimulation electrode placements, and the delivery of therapeutic agents with minimized disruption to surrounding brain tissue. This accuracy not only optimizes the therapeutic effect, but also reduces the risk of collateral damage, making stereotactic surgery a cornerstone of modern, minimally invasive neurosurgical practices.

Another technique that has been enabled by stereotactic insertion is convection-enhanced delivery (CED),[48–50] whose aim is to deliver therapeutic agents directly to the brain tissue. Unlike traditional systemic delivery, which often faces the challenge of crossing the blood–brain barrier, CED uses continuous, low-pressure infusion to drive therapeutic substances into the targeted brain region. One of the most exciting uses of stereotactic surgery is deep brain stimulation[51–53] (DBS), which involves the implantation of electrodes within certain areas of the brain. These electrodes produce electrical signals that regulate abnormal neural activity or, in some cases, stimulate specific brain regions to produce necessary neurotransmitters. Initially developed to manage the tremors associated with Parkinson's disease, the applications of DBS have expanded to treat other neurological conditions such as epilepsy, dystonia, obsessive–compulsive disorder, and even major depressive disorder.[54] By directly modulating the neural circuitry, DBS offers symptom relief for patients who are unresponsive to conventional treatments.

Most devices used in minimally invasive transcranial surgery consist of needles, catheters, and probes with electrodes, which are inserted through a small hole in the skull either manually or stereotactically by the surgeon.[9,15,55–58] A common theme in the reduction of invasiveness is a reduction in the size of the inserted devices. Although this can greatly help in reducing the risks of transcranial surgery, the devices are usually rigid and rectilinear, which limits the access path to the target region. This ultimately makes it difficult or impossible to avoid penetration of specific areas. Furthermore, the mismatch in compliance tends to damage brain tissues further.[59]

In order to overcome these issues, robotics research has been focused on the development of concentric tube robots[60–63] (CTRs) and steerable flexible needles. CTRs consist of prebent segments that are inserted concentrically in other tubes (Figure 2d). They are typically made of nitinol[64] because of its superelastic properties and biocompatibility.[65] When deployed, each concentric tube bends to the programmed shape, generating a curvilinear path. The advantage of this technique is that the segments maintain sufficient rigidity to penetrate the brain tissue. However, the prebent shapes ultimately require careful advanced planning of the path to be followed and limit the path the device can take. Recently, a miniaturized CTR, Caturo, was developed,[65] which consists of glass tubes as small as 90 µm in dia. (**Figure 4**a).

Another conventional robotics approach to navigation in soft tissues such as the brain is the use of bevel-tip flexible needles.[66–70] The bevel in needle tips leads to an offset in the application point of the forces, which, when combined with a more flexible needle, can be used for steering (Figure 2e). The amount of steering can be adapted by modifying the bevel angle and choosing a different needle rigidity. Typically, the needles are made of steel, nitinol, or polymer, which can be used in combination with geometric parameters to achieve the targeted curvature.[68,69] Change in the steering direction is achieved through the axial rotation of the needle.[72] Furthermore, the steering radius can be modulated by selectively rotating the needle similarly to duty cycle control of a motor. Continuous rotation leads to a straight path line and no rotation to a curved path with maximal curvature radius. A significant limitation of bevel-tip needles is their limited ability to execute more than a single turn, constraining their maneuverability and application range.

As a further control over steering, tendon-driven actuation, where wires routed along the flexible needle's body can be used to reorient the tip of the needle.[70,71] This strategy is particularly suited for omnidirectional steering, removing the planning requirements of the CTR and the rotating motion of the bevel tip. An example of such a device for neuroendoscopic applications is given by Kato et al., who present a 3.4-mm OD tendon-driven robot made of nitinol and poly(ether ether ketone) (PEEK).[73] The primary challenge in the development of tendon-driven devices lies in the difficulty of scaling down the multiple mobile, sliding components that constitute the system. Moreover, as the tendons are responsible for load bearing, their miniaturization makes them increasingly susceptible to deformation and breakage.

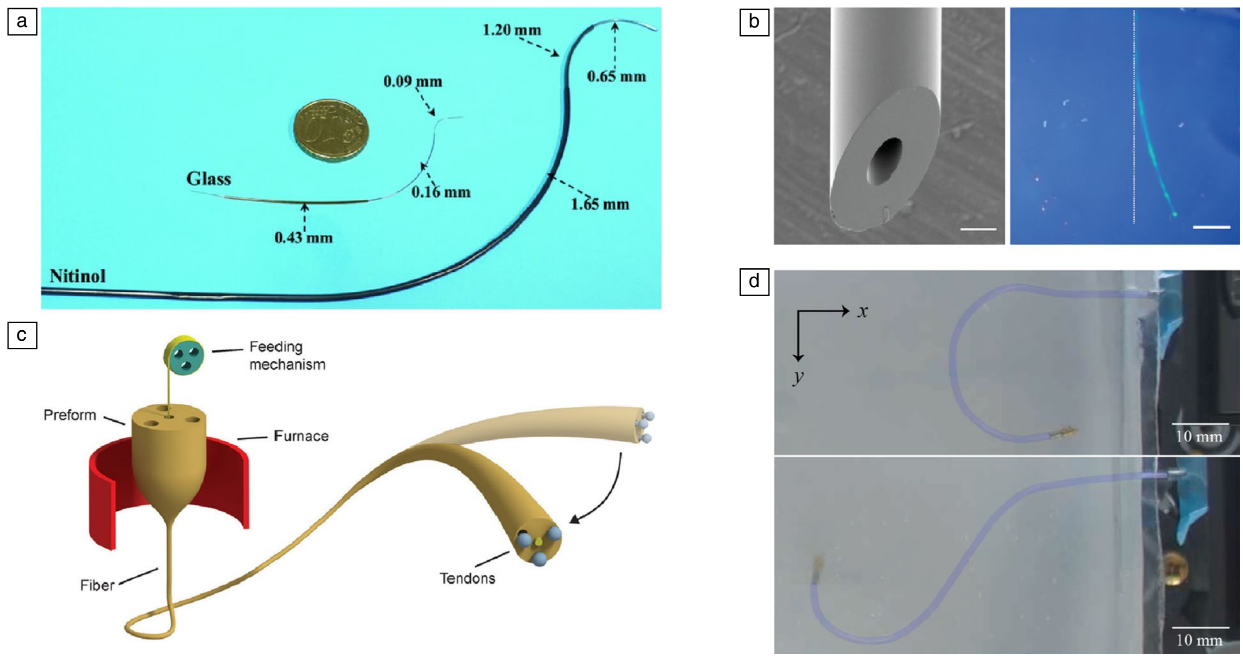

Figure 4. Small-scale actuated transcranial devices. (a) A miniaturized concentric tube robot with various segments. Reprinted with permission from Reference 65. © 2022 Wiley. (b) A microengineered steerable borosilicate needle. Left: Close-up view of the beveled tip. Scale bar = 20 μm. Right: Steering capabilities in 0.6% agarose phantom. Scale bar = 10 mm. Reprinted with permission from Reference 74. © 2019 Wiley. (c) Manufacturing scheme for fiber-drawn tendon-driven instruments. Reprinted with permission from Reference 78. © 2022 Wiley. (d) Navigation of a screw-tip magnetic device in a 0.5% agarose phantom. Reprinted with permission from Reference 79. © 2023 IEEE.

Actuated miniaturized transcranial devices

Recent developments in devices for neural interventions mainly focus on two topics: miniaturization of steerable surgical devices and long-term interfacing with the brain. The latter has stemmed from research tied to the study of the function of the brain and the treatment of functional neurological conditions, such as DBS for Parkinson's disease.

Cotler et al. have recently introduced 60-μm dia. microneedles made of borosilicate that are polished at the tip to achieve a bevel angle for steering[74] (Figure 4b). The steerability of the device was shown in agarose phantoms and *ex vivo* porcine brains, along with the *in vivo* chronic implantation and infusion in rats. In addition to infusion, the authors envision implanting electrodes through the needle or through integration with the needle itself. A similar device was successively used for chronic sampling of the brain interstitial fluid of a rat.[75] Other potential applications for this miniaturized device include drug delivery for chemical modulation of brain activity[76] and simultaneous neural activity recording, achieved with a three-channel borosilicate needle tip.[77]

Multifunctional devices can be extremely valuable for the treatment of neurological conditions, where integrated sensing and actuation reduce the invasiveness of the implants and allow for real-time supervision and control of the treatment. A manufacturing technique that has driven the development of such devices is the thermal drawing of multimaterial and multichannel thin fibers. A seminal example is a 0.4-mm dia. fiber device with integrated channels for optical, electrical, and chemical interfacing with the rat brain.[80] Recent work has shown that light sources, electrodes, and thermal sensors can be incorporated into this device.[81] The same drawing technique has also been used for manufacturing a 0.7-mm dia. polymer fiber with up to three channels for tendon actuation (Figure 4c) and other functional channels to act as fluidic, optical, or electrical guides.[78] Toward further miniaturization, the same research group reported a method to produce 0.3-mm dia. steerable magnetic fibers.[82]

An interesting application that merges bevel tip steering for actuation and fiber drawing for manufacturing is a small-scale steerable catheter for neurosurgery.[83] It consists of four interlocking modules that can slide with respect to one another. Each module is beveled with respect to a plane, allowing for steering at desired trajectories by arranging the modules at different longitudinal offsets. This removes the requirement of rotation of traditional beveled needles along their axis to change the course and improves the modulation of curvature radius. Two device variants are proposed, one of 2.5-mm OD and one of 1.3 mm. Steering of the device was tested *in vitro* in gelatin phantoms and, in another study,[84] in a sheep brain, where the needle was successfully implanted at 12-mm depth for five days without abnormal parameters. The 2.5-mm dia. device was manufactured by extruding poly(vinyl chloride), which was then nano-coated with biocompatible and low-friction poly para-xylylene. The 1.3-mm dia. devices were made through thermal drawing of a polycarbonate 3D printed 40-mm dia. preform. Another commonly used method for steering, tendon actuation, is used in the device presented by Chitalia et al. It is a steerable endoscope tool targeting pediatric applications composed of a nitinol tube with an outer dia. of 1.9 mm, which is laser-patterned to achieve bending using tendons.[85]

As with endovascular devices, magnetics has also been widely used in recent advances for transcranial robots. Specifically, steering in the brain tissues is described by Petruska et al. Their device consists of a thin nitinol wire encapsulated in a 0.7-mm dia. silicone tube with a 1.3-mm dia. permanent magnet tip attached with a ball joint to increase the steerability of the device by partially decoupling the orientation of the wire from the magnet.[86] The external magnetic field is used for steering, and the external linear actuation of the nitinol wire controls the insertion depth. The device was successfully guided and steered both *in vitro* agarose gel and *ex vivo* porcine brain in a later article.[87]

Magnetics are also used in the device proposed by Sperry et al., which combines magnetics for steering and rotation of a screw tip for insertion.[79] The device comprises a flexible 0.76-mm Tygon tube, stacked cylindrical permanent magnets, and a screw tip. Various screw-tip designs are proposed and made of either brass or resin, with 1–2 mm dia. The authors acknowledge a possible increase in local damage due to the screw-led advancing mechanism. The devices were successfully tested both *in vitro* in agarose (Figure 4d) and *ex vivo* in ovine brain. A similar actuation method was presented in 2001 with a magnetically rotated untethered screw-like device for advancement in soft tissues[88] and expanded upon by Mahoney et al.[89]

Another method of using magnetics for steering is presented by Gao et al. Their device is a flexible electrode array built for neural activity recording.[90] The electrodes are decorated with FeNi regions, which allow steering and pulling by application of magnetic fields and gradients. The main difference with respect to other devices is its shape. Instead of having a circular section, they are ribbon-like because of the use of classical microfabrication techniques for manufacturing. The electrode stack is composed of two outer 10-µm-wide, 2-µm-thick layers of polyimide, a 10-µm-wide, 2-µm-thick layer of FeNi alloy, and a 100-µm-wide, 10-nm-thick gold layer.

Whereas most devices aimed at navigating brain tissues are tethered, Son et al. describe an untethered magnetically controlled device meant to navigate brain tissue.[91] It comprises a permanent cylindrical magnet with an outer resin capsule with a conical-shaped tip. Using an array of external permanent magnets allows for steering and displacement of the device *ex vivo* in the brain. The amount of damage to the tissues was not quantified. However, the authors suggest miniaturization as a possible solution to reduce the potential harm of the device. The device was successfully tested for steering and navigation both *in vitro* in gelatin and *ex vivo* in porcine brain.

Robotic control systems for actuated devices

In addition to miniaturization and functionalization of medical instruments, the development of robotic control systems has become a pivotal asset in the realm of modern neurosurgery and medical interventions. These systems are engineered to actuate surgical instruments with an unparalleled degree of accuracy and stability. Given the intricate nature of the human anatomy, especially the brain, a slight error or tremor during a procedure can have grave consequences. Robotic control can filter out hand tremors and enable micro-movements that could be challenging, if not impossible, for even the steadiest human hands after decades of surgical training. Furthermore, robotic control systems are often combined with advanced imaging modalities, allowing real-time feedback and adjustments during a procedure.

Another crucial advantage is the ability to perform surgeries in a minimally invasive manner. Robotic systems can be programmed to actuate instruments through much smaller incisions or access points than traditionally required. This often results in quicker patient recovery, reduced risk of infection, and minimized scarring. Techniques that have particularly benefited from robotization are stereotactic surgery,[92–94] magnetic actuation,[26,95–98] and neuroendoscopy.[99–101] These methods, when combined with robotic precision and automation, have seen significant enhancements in their execution and outcomes. The integration with real-time imaging provides an immediate feedback loop, enabling adjustments in real time and ensuring alignment with target regions or pathways. The importance of robotic control systems is multifaceted. Beyond the obvious surgical precision, they pave the way for remote surgeries, democratize access to expert care regardless of geographical boundaries, and enable the execution of complex procedures that are beyond the limits of manual manipulation. In essence, they augment human capability, pushing the boundaries of what is medically achievable and setting a new standard for care in the process.

The task of adapting robotic control systems for the manipulation of miniaturized devices in the brain is not straightforward. Although the control systems are robust and capable at larger scales, they must be refined to accommodate the precise and subtle movements necessary for the brain interventions. This entails a careful rethinking of the interface between the macroscale stiff robotic system and microscale highly flexible neurological devices. The overarching goal is to achieve a level of control that is both finely tuned and reliably consistent, ensuring that the scale of operation does not compromise the integrity of the delicate tissue. Another important issue associated with the use of miniaturized devices for brain interventions is imaging. In recent years, researchers have focused on finding novel strategies to image increasingly small devices, ensuring that such devices can be accurately placed and monitored within the brain's complex structure.[102–105] Adaptations to current imaging methodologies are also underway to accommodate the unique properties of miniaturized devices. These advancements are critical in realizing the full potential of miniaturized devices in brain interventions.

Conclusion

The evolution of small-scale devices for medical interventions in the brain represents a major step forward in neurosurgery. This article has illuminated the profound developments in the design, fabrication, and control of small-scale instruments and their significant clinical potential for the diagnosis and treatment of brain disorders. We have dissected the two primary access routes to the brain: the endovascular and the transcranial routes. The endovascular route, notable for its reduced risk of causing brain damage, has greatly benefited from recent advancements in compliant and untethered devices. These advancements are granting interventionalists increasingly sophisticated access to deep-seated brain regions via smaller and more tortuous vessels. The transcranial route, with its unconstrained access points, offers its advantages. We highlighted the historic reliance on rigid tools and the shift toward softer, smaller, and more adaptable instruments. The development of flexible and steerable needles exemplifies the convergence of engineering innovation and clinical need.

Despite the remarkable progress challenges remain. The intricate and sensitive nature of brain tissue calls for an exceptional level of precision, which these tools are increasingly capable of delivering. However, ongoing work is necessary to address key issues such as device biocompatibility, safety in retrieval or dissolution of untethered devices, and optimizing tool flexibility and steerability.[59,106–109] As these small-scale robotic instruments continue to evolve, so does our ability to navigate and intervene within the complex landscape of the human brain. This evolution is reshaping neurosurgical practice, offering new hope for patients, and setting a compelling trajectory for the future of neurosurgical interventions.

Author contributions

All authors contributed equally to the manuscript.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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