Endovascular delivery of leads and stentrodes and their applications to deep brain stimulation and neuromodulation: a review

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Neuromodulation and deep brain stimulation (DBS) have been increasingly used in many neurological ailments, including essential tremor, Parkinson’s disease, epilepsy, and more. Yet for many patients and practitioners the desire to utilize these therapies is met with caution, given the need for craniotomy, lead insertion through brain parenchyma, and, at many times, bilateral invasive procedures. Currently endovascular therapy is a standard of care for emergency thrombectomy, aneurysm treatment, and other vascular malformation/occlusive disease of the cerebrum. Endovascular techniques and delivery catheters have advanced greatly in both their ability to safely reach remote brain locations and deliver devices. In this review the authors discuss minimally invasive endovascular delivery of devices and neural stimulating and recording from cortical and DBS targets via the neurovascular network.

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Neurostimulation has proven effective for many diseases, including Parkinson’s disease11 and essential tremor,23 and has shown promising results for newer targets, including chronic pain, obsessive-compulsive disorder,19 refractory depression,14 and, most recently, neurocognitive disorders.12,37 As advances in neuromodulation continue, its promise grows in remedying various neurological ailments. At this time, deep brain stimulation (DBS) devices consist of surgically implanted leads passed, using the assistance of neuronavigation, through the cortical surface to rest in deep brain structures. MRI, awake-craniotomy procedures, or microelectrode recordings are utilized to ensure that the lead penetrates the correct area of the neural network. The lead is then tunneled under the galea and connected to a generator implanted subcutaneously. While DBS systems have greatly advanced in electrode design and patterns of stimulation,20 common DBS systems today such as the Activa PC (Medtronic) still rely on a transcranial lead connected to a battery. Wireless systems have been proposed in theory and reported on, but they still necessitate a transcranial lead.28 Nonincisional alternatives to DBS also exist: techniques such as focused ultrasound30 and Gamma Knife radiosurgery26 provide therapeutic results via a nonsurgical lesionectomy within their targets. One drawback of these noninvasive therapies is the finality of the lesion that is created. Even these nonsurgical therapies, however, can result in unwanted neurological deficits. One study of 209 patients in whom the Gamma Knife was used to treat the ventral intermediate thalamic nucleus reported a 6.9% rate of both transient and permanent complications.58 While the complications of DBS are low in comparison to other procedures, there is risk for permanent neurological damage.13 Long-term hardware complication rates associated with DBS are reported to be 8.4% per electrode/year.39 Major surgical complication rates for DBS lead insertion include a 3.3% risk of hematoma of any type per lead implanted and a 0.6% risk of major neurological deficits. Hemorrhage rates have been shown to correlate with the number of electrode passes.2 Thus, while DBS systems
continue to advance in design, safety, and effective modulation of their chosen target, new techniques utilizing minimally invasive lead placement should be trialed. This review will discuss the progress made in endovascular lead delivery, stentrodes (stents with the ability to record or stimulate surrounding tissue), and their application to DBS, responsive neural stimulation, and neuromodulation.

Endovascular Delivery of Leads

Many intracranial pathologies are treated using catheter-based techniques utilizing the vascular network largely via a transfemoral artery or vein approach. Stents are delivered for the treatment of wide-necked aneurysms, stenosis, and repair of vessels. Similarly coils, particles, and liquid embolic agents are also delivered into the intracerebral vessels for the treatment of aneurysms, arteriovenous malformations, arteriovenous fistulas, and hypervascular tumors. There are now numerous guide catheters, intermediate catheters, and microcatheters or wires capable of safely delivering devices of many sizes in awake or anesthetized patients. Benefits of endovascular delivery of devices include avoiding craniotomy, faster recovery times, and possibly less patient anxiety. There are numerous patients listed for endovascular cranial lead insertion, and many electrodes could provide theoretical advantages over the small lead size. Wong et al. have also evaluated polymers and metal able to create capillary or venule-compatible leads is outside the scope of this review.

Educated guess on device-related effects can be gleaned from Pipeline embolization device (PED; Medtronic) data on flow diversion for the treatment of aneurysms. Meta-analysis data on the PED identified a 5% procedure-related morbidity and mortality rate among 1451 patients. Perforator infarction occurred in 3% of patients, and subarachnoid hemorrhage and intraparenchymal hemorrhage in 3% each. The ischemic stroke rate was 6% (lower in the anterior circulation and higher in the posterior circulation). One caveat to the aforementioned data is that the amount of metal coverage is 33%–35% for PEDs, which is very high, likely indicating the uppermost level of risk for stroke or occlusion. Since the stentrode would not be placed for an aneurysm, the risk of aneurysm rupture would be absent. Neuroform stents used for stent-assisted coiling of aneurysms have 6% metal coverage (much less than the PED). One study examining thromboembolic risks in these stents reported a 0.5% thromboembolism risk (13/237 patients), with 2 patients having late in-stent stenosis. LVIS (low profile visualized intraluminal support) and LVIS Jr. devices have 18%–22% metal coverage, and Iosif et al. reported a 2.2% event rate of sequelae related to the stent. Antiplatelets remain an option, such as aspirin or dual antiplatelet therapy, as currently prescribed for patients receiving intravascular stents. Trials involving stentrodes, as discussed in a later section, have shown similar coagulation profiles to modern stents, further reinforcing the possibility of similar management. New stent coatings are also on the horizon, credited with decreasing the amount of thrombogenicity. One such coating is the SHIELD technology, a phosphorylcholine coating for PEDs. Similar coating technology may prove useful for neurovascular lead design. The stents of today may look nothing like the stents of the future, especially as stentrodes will not have to support coils, hold open plaques, or test electrodes may be utilized to determine if the desired physiological response is present prior to permanent stent placement. While not optimal, currently stents can be placed over one another when necessary, as in the case with recurrent stent-coiled aneurysms treated with PED flow diversion. Last, anatomical vessel variation may preclude some stentrode placements. Awake physiological testing during angiography will help identify these patients in whom a stentrode should not be placed.

Feasibility of Neurovascular Array Efficacy for Target Disease

Studies of intravascular neuromodulation for both recording and stimulation have described a variety of potential targets for therapeutic management (Table 1). Teplitzky et al. identified 17 potential DBS targets utilizing a computational model that assessed targets ideal
Responsive technology was only recently applied to the brain with the advent of NeuroPace’s RNS System, a responsive neural pacing system that consists of a battery generator to supply leads in the vascular space, and wirelessly stimulates a receiver on the stentrode, which is then able to convert the radiofrequency into an electrical pulse. Thus, in theory, different stentrodes can be controlled by different radiofrequencies. Integral to this minimally invasive approach would be a stentrode and a transcutaneous/transcalvarial wireless method of exciting such a device. Similar studies utilizing an ultrasound generator and transvenously placed receiver electrode (on a catheter) capable of converting ultrasound energy to electrical energy was demonstrated, in 24 people, to be a safe and feasible way of “wireless” cardiac pacing. Thus, one can explore the concept of placing an electrode on a stent rather than a catheter. The wireless nature of the electrode allows for less thrombogenicity, given the smaller surface area of a foreign body in vasculature and easier, less disturbing placement.

Minimally invasive implantation of cortical recording stents (stentrodes) were reported in 2016 by Oxley et al. The small stentrode was endovascularly placed in the cortical vein of sheep, with demonstrated recording of cortical activity over 190 days. Venous patency was maintained, and vascular corticography data were comparable to those obtained by epidural arrays. A stentrode.

TABLE 1. Potential vascular targets for recording or stimulating neural targets

<table>
<thead>
<tr>
<th>Target Location</th>
<th>Vessel</th>
<th>Previously Described</th>
<th>Vessel or Device Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor or sensory strip; other cortical convexity area depending on MRV or angiography findings</td>
<td>Cortical vein or petrososmal branch of the middle meningeal artery</td>
<td>Oxley et al., 2016; Stoeter et al., 1995: EEG recording</td>
<td>1–5 mm*</td>
</tr>
<tr>
<td>Mesial temporal structures</td>
<td>Cavernous sinus &amp; petrosal sinus</td>
<td>Kunieda et al., 2000, EEG recording</td>
<td>Utilized a Seeker Lite-10 guidewire electrode</td>
</tr>
<tr>
<td>Lateral temporal structures</td>
<td>Middle meningeal artery</td>
<td>Ishida et al., 1998, EEG recording</td>
<td>Microwire utilized</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Basilar artery</td>
<td>Stoeter et al., 1995, EEG recording</td>
<td>Microguidewire, poly-teflon insulated</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>Middle cerebral artery branch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal lobe (medial)</td>
<td>Callasomarginal artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem auditory evoked potentials, waves 4 &amp; 5</td>
<td>Peduncular posterior cerebral artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior nucleus (thalamus)</td>
<td>Internal cerebral vein</td>
<td>Nowinski et al., 2010; Teplitzky et al., 2014; computational modeling</td>
<td>0.4–1.4 mm</td>
</tr>
<tr>
<td>Fornix</td>
<td>Internal cerebral vein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>A1 segment of the anterior cerebral artery</td>
<td></td>
<td>2.2–2.6 mm</td>
</tr>
<tr>
<td>Subgenual cingulate white matter</td>
<td>A2 segment of the anterior cerebral artery</td>
<td></td>
<td>1.9–2.2 mm</td>
</tr>
<tr>
<td>Ventricle capsule</td>
<td>A2 segment of the anterior cerebral artery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MRV = MR venography.

consisted of platinum discs mounted 2.5 mm apart on a stent-like device, delivered through a 4-Fr catheter via the jugular vein, with the leads anchored at the jugular access site. A cortical vein near the motor area was used, given its relatively constant colocalization with the motor area. Somatosensory evoked potentials were detectable in 98% of channels. Micro-CT and histological evaluation have shown vessel patency and stent strut incorporation into the vessel wall with neointima coverage of 78% at 2–4 weeks. Intravascular electrode recording has also been verified in a swine model to record high-bandwidth, high-fidelity electrical correlates of physiological activity.35

Thus, two types of stentrodes are reported. One utilizes connecting wires, which must be anchored and tunneled as in standard DBS leads. This type of stentrode is more easily seen as working via a jugular vein puncture, as described by Oxley et al.,42 which can decrease the amount of intravascular lead necessary and likely will not be suitable for arterial use. The second wireless stentrode would require microchip circuitry with a transmitting and receiving antenna, similar to that as described by Howard.22 Similar devices have been described and implanted in cardiac swine models. One such device is a battery-less, wireless, 4 x 1-mm device with a microchip and radiofrequency “on chip” antenna capable of harvesting an external radiofrequency signal at 2-cm tissue thickness. Furthermore, it generates a stimulation pulse signal of 1.3 V.47 Implantable microchip technology has been trialed in humans previously in the form of a parathyroid drug dispenser that responded wirelessly over medical device frequency.14 An external generator or receiver would be necessary. In either case, recording and stimulating capabilities would be present. Such adaptive stimulation has been performed with current DBS leads and brain-computer interfacing, leading to a 56% reduction in DBS stimulation time in Parkinson’s disease patients.31

**Future Applications of Vascular Stent–Based Technologies**

Brancato et al. have described an intravascular pressure-sensing device utilizing piezoelectric technology. They tested the device in carotid arteries of sheep successfully.6 Thus, the ability to develop multimodality stentrodes is feasible, with devices able to sample electrographic, hematological, and pneumatic stresses. One can imagine the application of a pressure-sensing device implanted into the middle meningeal artery as a viable alternative to intracranial pressure monitors, with little risk of symptomatic morbidity if the artery were occluded. Such a device would aid in trauma patients and shunt-treated patients with the possibility of responsive shunting via programmable valve communication.

Similarly, stents can be made to transmit other signals of physiological relevance. RFID STENTag is a stentrode of sorts described by Occhiusu et al. as a radiofrequency-tagged stent that can monitor the in-stent stenosis of the carotid artery in correlation with the signal strength emitted.38

Yanagisawa et al.57 utilized surgically implanted subdural electrodes in a poststroke patient and were able to demonstrate real-time control of a prosthetic hand. The authors reported that the onset of the hand movement was detected within 0.37 seconds of the actual movement. After electrocorticography decoding, the brain-machine interface used power modulations of the patient’s electrocorticography during hand movement. In a free-run period, the patient’s hand movements were faithfully mimicked by the prosthesis.57 Stentrodes would allow a craniotomy-free placement of the leads, and one could conceptualize a type of device in which the patient’s own arm could be “innervated” with electrodes, allowing for brain-machine-body interfacing.33 This type of limb reinnervation could one day help patients with stroke, demyelinating conditions, spinal cord injury.

Alternating electrical field treatment of tumors, most notably Optune (formerly known as NovoTTF-100A, Novocure Ltd.), has been shown to be efficacious in the treatment of glioblastoma.56 The alternating fields are antimitotic. The device is large and cumbersome, and it requires the head to be shaved and numerous electrodes to be connected to the head. This may be yet another field where stentrode-like devices may aid current technology.

Stentrodes have briefly been discussed as above for epilepsy treatment, but there may also one day be a better way of long-term recording allowing the patient to be free of wires, glue, and so on.

The use of stentrodes may also have possible applications in the realm of neurocognitive disorders. Previous studies have explored the use of DBS in hippocampal and medial-temporal regions using open-loop stimulation with stimulation leading to improvements in memory.15,35,48,51 Recently, researchers reported the use of closed-loop stimulation of lateral temporal cortex for sensing and stimulating the brain during a memory task in 25 neurosurgical patients undergoing intracranial EEG monitoring for refractory epilepsy, demonstrating improved recall.12 The lateral temporal cortex would be available to stentrode placement via the middle meningeal artery, as shown in Table 1.

**Conclusions**

Endovascular delivery of neuromodulating devices appears to be a feasible, minimally invasive technique with therapeutic applications in many fields. The catheter-based techniques utilized today are able to reach most desired locations for therapeutic action. Limitations at this time lie in the development of durable and safe endovascular leads and stentrodes with the capability of wireless transmission.

**References**


Disclosures
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Author Contributions
Conception and design: Rajah, Saber. Acquisition of data: Rajah, Saber, Singh. Analysis and interpretation of data: Rajah, Saber, Singh. Drafting the article: Rajah. Critically revising the article: Rajah, Saber, Singh. Reviewed submitted version of manuscript: Rajah, Saber, Singh. Approved the final version of the manuscript on behalf of all authors: Rangel-Castilla. Administrative/technical/material support: Rangel-Castilla. Study supervision: Rangel-Castilla.

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