The Potential of Closed-Loop Endovascular Neurostimulation as a Viable Therapeutic Approach for Drug Resistant Epilepsy: A Critical Review

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The potential of endovascular neurostimulation

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Key Words: Endovascular, Stimulation, Recording, Neurostimulation, Neuromodulation

Abstract
Over the last few decades, biomedical implants have successfully delivered therapeutic electrical stimulation to reduce the frequency and severity of seizures in people with drug-resistant epilepsy. However, neurostimulation approaches require invasive surgery to implant stimulating electrodes, and surgical, medical and hardware complications are not uncommon. An endovascular approach provides a potentially safer and less invasive surgical alternative. This article critically evaluates the feasibility of endovascular closed-loop neuromodulation for the treatment of epilepsy.

By reviewing literature that reported the impact of direct electrical stimulation to reduce the frequency of epileptic seizures, we identified clinically validated extracranial, cortical and deep-cortical neural targets. We identified veins in close proximity to these targets, and evaluated the potential of delivering an endovascular implant to these veins based on their diameter. We then compared the risks and benefits of existing technology to describe a benchmark of clinical safety and efficacy.
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that would need to be achieved for endovascular neuromodulation to provide therapeutic benefit.

For the majority of brain regions that have been clinically demonstrated to reduce seizure occurrence in response to delivered electrical stimulation, vessels of appropriate diameter for delivery of an endovascular electrode to these regions could be achieved. This includes: delivery to the vagus nerve via the 13.2±0.9mm diameter internal jugular vein, the motor cortex via the 6.5±1.7mm diameter superior sagittal sinus, and the cerebellum via the 7.7±1.4mm diameter sigmoid sinus or 6.2±1.4mm diameter transverse sinus. Deep cerebral targets can also be accessed with an endovascular approach, with the 1.9±0.5mm diameter internal cerebral vein and 1.2mm diameter thalamostriate vein lying in close proximity to the anterior and centromedian nuclei of the thalamus, respectively.

This work identified numerous veins that are in close proximity to conventional stimulation targets that are of a diameter large enough for delivery and deployment of an endovascular electrode array, supporting future work to assess clinical efficacy and chronic safety of an endovascular approach to deliver therapeutic neurostimulation.

1. INTRODUCTION

Epilepsy affects up to 1% of the population\(^1\), with one third failing to achieve seizure control with medication alone\(^2\). Of these patients with drug resistant epilepsy (DRE), surgical resection is an effective treatment for a minority who have an identifiable epileptogenic zone that is safe to resect, leaving many patients suffering ongoing uncontrolled seizures\(^3\).

Recent advances in medical bionics have provided new therapeutic options for patients with DRE who are not suitable for epilepsy surgery, or in those who fail to achieve seizure control following surgery. By delivering electrical pulses, the generation, propagation and modulation of seizures has been shown to significantly reduce the frequency of seizures in many people. The most common open-loop
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implants are vagus nerve stimulators (VNS), with over 100,000 nerve-cuff electrodes implanted globally. Open-loop stimulation of the cortical surface with grid-electrodes has also shown clinical efficacy with a good responder rate, as has deep-brain stimulation of deep cerebral targets with penetrating electrode arrays, although gliotic inflammatory responses resulting in scar formation affects electrode impedance and stimulation focus. While the majority of commercially available technologies deliver open-loop stimulation, providing continual, albeit intermittent, stimulation to adjacent neurons, this method delivers unnecessary pulses of electrical charge when no seizure is occurring and places a significant strain on device batteries.

To overcome this, closed-loop stimulation systems acquire and interpret physiological signals and only trigger the delivery of a stimulation pulse when a predetermined parameter, precursory to an epileptic event, has been achieved. Automatic stimulation triggering using tachycardia detection algorithms have been proposed for VNS. Ictal tachycardia occurs in over 80% of partial onset-seizures, which may precede electrographic or clinical onset. Seizure prediction algorithms that record and interpret neurological signals are also being established as methods to alert users or trigger deep-brain stimulation systems. NeuroPace (CA, USA) has developed an implantable, closed-loop system that has shown clinical efficacy in preventing the occurrence of seizures. However, placement requires both recording electrode arrays placed the cortical surface and deep-brain electrodes that penetrate through delicate tissue to deep brain targets to

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The potential of endovascular neurostimulation provide stimulation. In addition, this technology requires carving out some of the skull to provide space for the hardware.

An endovascular approach to closed-loop neurostimulation has potential to provide a safer and less surgically invasive alternative to existing electrical stimulation devices\textsuperscript{27}, while simultaneously enabling high-fidelity acquisition of desired neural and physiological signals from within the skull\textsuperscript{28}. To assess this opportunity, we have reviewed the clinical evidence reporting mean seizure frequency reduction (SFR, mean change in the average number of seizures reported using a technology when compared to baseline) and 50% seizure reduction responder rate (RR, the percentage of people obtaining an SFR$>50\%$) of existing open-loop and closed-loop technologies. We evaluate patient risks, identifying the technology-specific frequency of serious adverse events occurring during the surgical procedure and throughout the course of the trial that place the patient in immediate danger, have permanent side-effects, or are hardware-related failures that require un-planned surgical intervention or reduce the ability of the technology to perform. Clinical reports, acquired from critical and comparative literature reviews, were supplemented with additional works released after the publication date of these major reviews to obtain a complete and current clinical safety and efficacy dataset.

The reported risks of current neurostimulation devices were compared with literature evaluating safety of permanent venous implantation of cortical stents for the treatment of intracranial idiopathic hypertension, and are used to evaluate a benchmark for clinical efficacy required by an endovascular approach to supersede the risk-benefit profile of existing technologies. Finally, we evaluated the proximity of clinically proven neural targets to cortical and extracranial vessels, and through analysis of neighbouring vessel diameters, have identified epilepsy targets that are likely to provide enhanced patient benefit using an endovascular approach.

2. NEUROMODULATION

2.1. Extracranial Neuromodulation: Vagus Nerve Stimulation

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Vagus nerve stimulation (VNS) is a US Food and Drug Administration (FDA) and CE-mark approved extracranial stimulation therapy used as palliative treatment in medication resistant patients who are poor candidates for resection or those in whom resection has failed. The implantable unit, developed initially by Cyberonics (TX, USA), consists of a bipolar pair of spiral electrodes that are manually positioned around the cervical vagus nerve trunk located between the clavicle and mastoid process. Continuous electrical stimulation is delivered from a sub-clavicular implantable pulse generator (IPG) in the form of 250-500μS charge-balanced biphasic pulses, generally of 0.25-2.0mA (titrated to effect and tolerance), at a frequency of 10-30Hz, intermittently stimulating for 10-30 seconds on followed by 200-300 seconds off. While the exact mechanism of seizure inhibition from electrical stimulation is unknown, results have shown promise in reducing seizures in a significant number of patients. Across 12,332 participants an RR of 49.7% and SFR of 50.2% was achieved. However, there was a 5.5% chance (1,839/33,539) of a participant incurring a serious medical complication (including infection requiring device removal, vocal cord paralysis and permanent hoarseness), and a 2.3% chance (767/33,539) of hardware failure, predominantly caused by lead breakage.

Closed-loop VNS therapy has been evaluated in a 113 participant study conducted with an AspireSR system (Cyberonics, TX, USA). By utilising ictal tachycardia as a surrogate marker for seizure prediction, they reported an improved median SFR of 70.8% across 67/113 (59.3%) participants. There was also a marginally reduced risk, with a 2.7% occurrence (4/151) of transient vocal cord paralysis, and four cases (one lead migration and three lead revisions) of hardware failure reported.

2.2. Cortical Neuromodulation: Motor Cortex and Cerebellar Stimulation

Delivery of open-loop electrical stimulation to the cortex via implanted subdural electrodes has shown encouraging results for reducing seizures in people with DRE and well localised epileptogenic zones. While the potential mechanisms for the
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antiepileptic effect of cortical stimulation are unknown, sodium channel inactivation for high frequency stimulation, long term depression for low frequency stimulation, and glutaminergic synaptic depression for both high and low frequency stimulation have been proposed\(^6\). The two primary locations that have reported clinical benefit for epilepsy are the motor cortex (MCX) and the cerebellum (CER). Both of these sites are accessed through a craniotomy, an invasive procedure that removes a portion of the skull to access the brain, with acute medical and hardware complication rates of 22.0% (351/1,599) and 0.9% (13/1,433), respectively\(^37-39\). Once the skull is opened and the brain is exposed, flat electrode arrays are placed beneath the dura (subdural) or on top of the dura (epidural). The arrays are then connected via a tunnelled lead to the IPG, and similar to VNS stimulation, electrical energy is delivered continuously, albeit intermittently. Both low (3-5Hz) and high (50-130Hz) bipolar frequency pulses have shown therapeutic benefit, with stimulation parameters ranging from 1-7V and 90-540\(\mu\)S, with 1-3 minutes on and 4-10 minutes off\(^40-44\).

Across 24 participants implanted with grid electrodes over the motor and supplementary cortices for chronic, open-loop stimulation, 20 participants (83.3%) responded with an average SFR of 89.6\%\(^40-44\). Infection was reported in one participant (4.2%) with two reports of hardware failure (8.3%) related to premature battery depletion\(^40\). Direct stimulation of the cerebellum provided a more modest benefit, with an average RR of 51.1\% (69/135) and SFR of 57.5\%\(^41\). A medical complication rate of 6.5\% and hardware failure rate of 3.3\% across 337 implantations was reported, predominately from infection and cerebrospinal fluid leak, and lead migration, respectively\(^42\).

While two closed-loop studies conducted on a total of eight participants demonstrated the ability to reduce seizures with non-implantable benchtop stimulators connected to subdural grids (RR of 87.5\% and SFR of 55.5\%)\(^43,44\), recent studies evaluating the efficacy of closed-loop stimulation through cortical grids are limited. In these studies, stimulation was delivered when periodic examination of the
The potential of endovascular neurostimulation results observed a seizure, based on pattern-recognition algorithms, energy and patient specific epileptiform activity.

2.3. Subcortical Neuromodulation: Deep Brain Stimulation of the Thalamus and Neighbouring Areas

Subcortical stimulation, or deep brain stimulation (DBS), requires the implantation of penetrating electrodes through brain tissue into deep cerebral structures following a burr-hole craniotomy. Numerous deep brain targets have been identified and evaluated as targets for open-loop neurostimulation for the treatment of DRE, with the primary locations being the anterior nucleus of the thalamus (ANT), the centromedian nucleus of the thalamus (CMT), and the hippocampus (HIP). Other, smaller clinical trials, have reported the seizure-reduction benefits of delivering electrical stimulation to the sub-thalamic nucleus (STN), nucleus accumbens (NA), hypothalamus (HYP), caudal zone incerta (CZI) and fornix (FOR).

Overall, 80 of 153 (52.3%) participants with DRE responded to open-loop ANT DBS with an average SFR of 60.1%\textsuperscript{5-8,45}. However, there was a 30.1% chance of medical complication (51/166 implantations), and a 17.5% chance of hardware-related failure. The largest, most definitive, trial of ANT DBS to reduce epileptic seizures in patients with DRE is a 110 participant, multicentre, double-blinded randomised controlled trial\textsuperscript{46}. After 13 months of stimulation (145Hz, 90μs pulse width, 5V pulses, 1 minute on, 1 minute off), an SFR of 41% and RR of 44% was reported (n=99 participants), increasing to an SFR of 56% and RR of 54% (n=81 participants) after 25 months. After five years, 68% of the 59 participants remaining in the study had an SFR of 69%\textsuperscript{47}. Safety was closely monitored, with 808 adverse events reported across 109 participants, 238 of these being device related.

Stimulation of the CMT, which is connected to the ascending reticular system, is proposed to desynchronize and inhibit electrical conduction\textsuperscript{5}. Across the 41 participants with DRE implanted with DBS electrodes in the CMT, 29 participants (70.7%) responded with a median SFR of 60.0% and average SFR of 40.3%\textsuperscript{5,6,8,45}. This article is protected by copyright. All rights reserved
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There were four medical complications (9.8%), and two hardware-related serious adverse events (4.8%). From 54 patients with DRE, treated with electrical DBS of the HIP, 37 responded (68.5%) with an average SFR of 64.9%. However, twelve participants were impacted by serious, treatment related, adverse events. Eight (14.8%) were related to intracranial haemorrhage, infection and skin erosion, with four (7.4%) hardware-related adverse events caused by electrode displacement and fracture also reported. Since 2002, eighteen participants from eight small clinical studies have been implanted with DBS electrodes directed to the STN with an average RR of 61.1%. No adverse medical or hardware complications were reported. The NA has also been identified as a target, however across nine patients from two studies, only five participants benefited (5/9, 55.6%), with a mean seizure frequency decrease of 22.5%. Additional small studies reporting preliminary feasibility of seizure reduction through direct electrical stimulation included the posterior hypothalamus (n=7, RR=100%, SFR=84.0%), the fornix (n=7, RR=100%, SFR=92.0%), and the caudal zone incerta (n=2, RR=100%, SFR=71.0%).

With respect to complications, Bullard analysed 34,089 participants implanted with DBS electrodes to treat a variety of neurological disorders, including Parkinson’s disease, tremor, dystonia, obsessive compulsive disorder, pain and epilepsy. The overall surgical and hardware risks were 8.8% (1,717/19,594) and 10.3% (551/5,340), respectively.

Closed-loop deep brain stimulation (Responsive Neurostimulation, RNS) has been developed for the clinical treatment of DRE by NeuroPace (CA, USA). Their technology uses a surgically implanted grid electrode to record neural signals near the epileptogenic zone, and on a predetermined physiological signal, delivers electrical stimulation via penetrating electrodes implanted within the epileptogenic zone. By detecting spikes and rhythmic activity in specific frequency ranges, absolute sample-to-sample amplitude difference within a predetermined time window or by measuring changes in signal energy, RNS can be configured to detect electrographic events. While this method enables delivery of electric current...
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only when deemed necessary, this method requires surgical intervention with a craniotomy that possesses the risks of both DBS electrodes and grid electrodes. However, a strong level of success has been reported with this FDA approved technology, with a 65.9\% RR (122/185) and an SFR of 72.0\% after seven years\textsuperscript{4,65}. Across 256 participants, there were twelve (4.7\%) intracranial haemorrhages and 24 infections (9.4\%, 24/256). Hardware failures occurred on 56 occasions (21.9\%), including premature battery depletion (4.3\%, 11/256), device lead damage (3.5\%, 9/256), and device lead revision (3.1\%, 8/256). In total, 14 units (5.5\%, 14/256) were removed.

3. TECHNOLOGICAL COMPARISON

There currently does not exist in the literature a single metric that combines therapeutic benefit with efficacy to enable comparison of the different treatment modalities. We therefore propose the following equation to enable a direct comparison, defined as the benefit of each technology as percentage of people who are anticipated to benefit from device implantation (responder rate) without medical or hardware complication:

\[
\text{Overall benefit} = \text{Responder Rate} \times (1 - (\text{medical risk} + \text{hardware risk}))
\]

Although this formulation has not been validated, it serves as a useful starting point to facilitate the comparison of different device-based approaches. Table 1 compares the RR for each of the different, clinically demonstrated, epilepsy neuromodulation systems, along with the associated medical and hardware risks. An overall benefit of 45.8\% was calculated for open-loop VNS therapy using nerve cuff electrodes, increasing to 56.1\% when complemented with tachycardia-based stimulation triggering. Cortical stimulation using cortical grid-electrodes had an open-loop benefit of 72.4\% and 46.1\% (for motor cortex and cerebellar stimulation, respectively), and closed-loop benefit of 46.5\%. Benefits of 27.4\%, 60.4\% and 53.3\%
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were determined for open-loop DBS of the ANT, CMT and HIP, respectively, with RNS having an overall benefit of 42.2%. Smaller targets (STN, NA, HYP and FOR) have been excluded as these small-studies did not reporte complication rates (Figure 1).

4. ENDOVASCULAR NEUROMODULATION

4.1. Endovascular Recording and Stimulation

While no clinical trials have taken advantage of an endovascular approach to deliver therapeutic neurostimulation to suppress epileptic seizures, acute recording of epileptic events using guide wires has been demonstrated in animals and humans\(^{66}\), and the potential of endovascular deep brain stimulation has been theoretically predicted\(^{67}\). In 1995, Stoeter used intracranial electroencephalographic recordings acquired with a guide wire inserted into the middle meningeal artery to record seizures from 30 participants\(^{68}\). Intracranial epileptiform abnormalities, recorded using Teflon-coated guide-wires with exposed tips, were observed in two men in 1997\(^{69}\) and transvenous EEG has been recorded in five participants with intractable temporal lobe epilepsy using wire electrodes implanted in the intracranial sinus or superior petrosal sinus\(^{70}\). Other cortical recordings acquired with non-permanent endovascular electrodes include: baboons\(^{71}\), rodents\(^{72}\), and of penicillin-induced epileptiform spikes via the superior sagittal sinus in swine\(^{73}\).

To date, the only technology designed for chronic endovascular recording and stimulation has been reported by our group\(^{27}\). We utilised a self-expanding stent as the scaffold on which to mount platinum recording or stimulating electrodes, and have shown that minimally-invasive angiographic delivery of the stent-electrode array (Stentrode) inserted into the superior sagittal sinus via the jugular vein, is possible in sheep\(^{28,74,75}\) and humans\(^{76}\). We have reported that chronic neural information can be obtained without vascular occlusion\(^{77,78}\) and with a bandwidth comparable to invasive electrode arrays\(^{79,80}\). A maximum bandwidth of 226Hz recorded from endovascular electrodes implanted in sheep, compared to 216Hz and 234Hz measured in the same animals using epidural and subdural electrodes,
respectively. We have recorded the occurrence of a seizure with a Stentrode containing 16 endovascular electrodes spaced 0.5-1mm apart, implanted within a 3-4mm vessel and have demonstrated that electrical stimulation can be delivered to focal regions of the sheep cortex. However, additional work is required to validate that platinum electrodes mounted on an endovascular scaffold can deliver safe and efficacious electrical stimulation from within a blood vessel without inducing deleterious electrochemical reactions. Recently, we reported preliminary, twelve month, safety and efficacy of the Stentrode to enable two men paralysed by motor neuron disease to control a computer with signals acquired by Stentrodes permanently implanted over their motor cortex. Signals from the Stentrode were delivered via a flexible cable that exited at the jugular vein before being wirelessly transmitted from a percutaneous telemetry unit implanted in the pectoral region. Participants able to control communication software and enhance their performance of instrumental activities of daily living.

Our technology was designed to replicate the surgical procedure currently performed to insert FDA-approved stents into the transverse sinus for the treatment of intracranial idiopathic hypertension (IIH), which has an overall complication rate of 0.05% (20/419). There were no cases of infection observed and only six complications (0.01%) considered major. These included three subdural hematomas (0.007%), two subarachnoid haemorrhages (0.005%), and one intracerebral haemorrhage (0.002%). While endovascular surgery is inherently safer than medical procedures requiring a craniotomy (Table 1), whether this statement holds for implantation of endovascular electrodes designed for closed-loop epilepsy management which contain additional components such as IPGs and lead wires, is unknown and requires substantial clinical evidence and an understanding of the vascular pathway to reach current stimulation target areas.

4.2. Vessels neighbouring therapeutic targets
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Vessels considered suitable for deployment of an endovascular electrode array for neurostimulation as a treatment for DRE are those vessels neighbouring previously mentioned and clinically validated epilepsy therapeutic targets (Table 2). Utilising Nowinski’s anatomical atlas “The Human Brain, Head and Neck in 2953 Pieces”, vessel proximity to clinically relevant targets, including extracranial (VN), intracranial (MCX and CER), and deep-brain (ANT, CMT, HIP, CTN, NA, FOR, HYP) targets were identified (Figure 2). The distance from the target to a vessel was categorised into four groups: those that were in direct apposition (0-2mm), those in close proximity (2-5mm), those within a medium vicinity (5-10mm) and those considered to be distant (10-15mm) to vessels. While electrical stimulation may only be suitable for targets within 5mm, targets within 15mm have been listed as possible future neuromodulation candidates as technologies and techniques, including those of focused ultrasound, improve. Vessels greater than 15mm away, and vessels that did not appear to have a section at least 1mm in diameter were excluded.

Measurements from 219 scans acquired using ultrasound reported the internal jugular vein (IJV) was in direct apposition with the vagus nerve, and had an average diameter of 13.2±0.9 mm (range 6.5-26.5mm, n=219). Past the jugular foramen into the skull, the IJV becomes the sigmoid sinus (SS), a 7.7±1.4mm diameter (range 4.1-13.9mm, n=562) vessel in apposition with the CER. The transverse sinus (TS) is a 6.2±1.4mm diameter (range 4.3-11.5mm, n=2,632) extension of the SS that is also in direct apposition to the CER. Deeper vessels, including the 5-10mm distant straight sinus (StS, 3.5±0.5mm diameter, range 2.9-4.0mm, n=903) and 10-15mm distant Basal Vein of Rosenthal (BVR, 1.7±0.4mm diameter, range 1.0-2.1mm, n=1,213) are also potential candidates for implantation of electrode arrays designed to stimulate the CER, although the small vessel diameters and increased vessel-target distances reduces the clinical and therapeutic potential.

MCX stimulation could be delivered by electrodes placed in superficial vessels, including: the superior sagittal sinus (SSS, 6.5±1.7mm diameter, range 1.0-10.9mm,
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n=2,578), post-central sulcal vein (post-CSV, range 1.8-6.1mm, n=50), central sulcal vein (CSV, range 1.6-8.5mm, n=50), pre-central sulcal veins (pre-CSV, 1.7-7.5mm, n=50), and the more distally located inferior sagittal sinus (ISS, 1.3±0.3mm diameter, range 0.5-1.4, n=221).

For DBS, the 1.2mm diameter (range 1.1-1.5mm, n=45) thalamostriate vein (TSV) lies in direct apposition to the ANT. The 5-10mm distant internal cerebral vein (ICV, 1.9±0.5mm diameter, range 0.9-3.9, n=1,416) could also be a potential deployment location for ANT stimulation, as could the 10-15mm distant BVR. These vessels would be suitable for stimulation of the CMT, with both the TSV and ICV lying in direct apposition (0-2mm) to the CMT, and the BVR 10-15mm away. The HIP, STN and CZI are all 5-10mm from the BVR, with the CZI within 15mm of the ICV. The FOR is in apposition to the TSV, close to the ICV and within 15mm of the ISS. The NA does not appear to have a suitable vein within 15mm, and the Great Cerebral Vein of Galen (GSV), while of suitable size (3.7±1.0mm diameter, range 2.3-4.6mm, n=1,013), is not in close proximity to conventional, clinically validated, therapeutic targets.

5. DISCUSSION

Closed-loop neurostimulation delivered via an endovascular electrode for the treatment of epilepsy is a promising approach.

There are numerous extracranial, superficial and deep vessels that are both suitably sized for deployment of an endovascular electrode array (>2mm), and are within close proximity to conventional stimulation targets (<5mm). This work supports the hypothesis that electrical stimulation could be delivered from within a blood vessel to influence neuronal behaviour and suppress the occurrence of epileptic events. We have previously demonstrated the ability of a fully implanted endovascular Stentrode system to record and transmit neural signals related to movement intent, and physiological signals related to heart rate, through the skin to an external receiver. By combining focused electrical stimulation with the Stentrode...
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system, a closed loop system becomes achievable with a safety profile that mitigates the risks associated with open brain surgery (Figure 2).

It is acknowledged that the risk of implanting a permanent, FDA-approved, stent into the transverse sinus for treatment of IIH does not provide clinical evidence of the medical or hardware risks associated with Stentrode implantation or function. However, the significantly reduced endovascular complication rate, compared with performing a craniotomy, justifies the motive to strive towards more minimally invasive electrode deployment methodologies.

Currently, the safest clinically approved neurostimulation therapy for DRE is vagus nerve stimulation. The combined medical and hardware risk is 7.8% for open-loop simulation across 33,539 participants. However, the efficacy of this treatment is relatively low (RR of 49.7% and SFR of 50.2%), with continual stimulation of the entire nerve bundle also of concern. Increased benefit (RR of 59.3% and SFR of 70.8%) was observed utilising heart rate increase as a physiological stimulation trigger, with a lower risk (5.4%) observed across 113 participants. This target is suitable for endovascular access, with the 13.2mm diameter jugular vein in direct apposition with the vagus nerve. While it is unknown whether safe and efficacious electrical stimulation of the vagus nerve can be delivered from within the jugular vein or whether intracranial stimulation of the vagus nerve would reduce currently-observed side effects, there is potential to provide closed-loop or responsive VNS with an endovascular array.

While riskier than VNS, motor cortex stimulation provides the most effective treatment, with a RR of 83.3% and SFR of 89.6%. However, only a small number of patients have been treated with this approach (n=24), and consequently, larger trials are required to provide a more statistically robust technological comparison. While closed-loop stimulation showed a slightly improved responder rate (87.5%), a lower SFR (55.5%) was observed, again only in a small population (n=8). Superficial veins including the superior sagittal sinus and branching cortical veins provide a suitably
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sized conduit for deployment of directly apposing endovascular electrical stimulator to the motor cortex using a surgical procedure that mitigates open brain surgery.

Stimulation of deep brain regions has also shown effectiveness in reducing the occurrence of seizures. While stimulation of the anterior nucleus of thalamus has a moderate RR (52.3%) and SFR (60.1%), due to the large surgical risk (30.1%), even a moderate benefit with a safer technology such as an endovascular device deployed in the thalamostriate vein could improve overall patient benefit. A hardware risk of 17.5% was observed for epilepsy-specific implantations, with a hardware risk of 0.9% observed across 1,433 DBS implantation for other therapeutic applications. This reiterates the importance of obtaining directly relevant clinical evidence to support safety and efficacy. Closed-loop stimulation, which combines cortical-grid electrodes for recording with stimulating penetrating electrode arrays to achieve responsive neurostimulation, had a relatively high patient benefit (RR of 65.9% and SFR of 72.0%). However, due to the invasiveness of the dual procedure, the risk of adverse medical (14.1%) and hardware (21.9%) events is high. It should be noted that the method by which a comparison was made was based on overall percentage of patients, and did not take into direct account the duration the participant had been implanted. Consequently, evaluating and comparing the different technologies using ‘patient years’ could be performed.

Endovascular electrodes can be delivered to extracranial, cortical and subcortical targets via an existing vascular pathway, without open brain surgery and without placing electrodes in direct contact with sensitive neural tissue. Consequently, an endovascular approach provides a potential solution for overcoming the surgical risks associated with existing electrode arrays, while taking advantage of the therapeutic benefits that can be achieved from directly recording and stimulating the brain. However, and while it is possible to stimulate focused regions of the brain from within a cortical vein, future work will have to validate the safety, efficacy and technical reliability of a device designed for chronic endovascular stimulation from within a blood vessel, and validate the ability of the Stentrode to
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simultaneously record neural activity and deliver effective, physiological trigger-based, stimulation. Patients receiving a permanent endovascular implant will need dual-antiplatelet therapy, which usually ranges from three to six months after venous sinus stenting for IIH\(^97\). This may pose an additional risk of intracranial haemorrhage to patients with generalized seizures should they fall and injure their head. Research is being conducted to enhance closed loop paradigms and to reduce noise and stimulation artefacts during simultaneous recording and stimulation, and it is likely that this knowledge will also enhance the performance of an endovascular array. DBS electrodes and vagus nerve cuff electrodes are placed in contact with the target tissue to deliver therapeutic electrical charge directly to the desired location without causing current-generated adverse events. Endovascular electrodes can also be placed close to cortical targets, although whether stimulation can be efficaciously delivered without causing thermal damage to neighbouring tissue and of a magnitude that does not deleteriously impact the stimulating electrodes is to be determined\(^98,99\).

While preliminary safety evidence supports the chronic deployment of Stentrodes in large cortical veins has been shown\(^76\), whether it is safe to implant a permanent stimulating array in deeper, smaller veins is unknown, and strategies to evaluate and mitigate thrombosis, infection, rupture and bleeding within these small vessel are required. Evaluation of the efficacy of stimulation from a blood vessel to a neighbouring or distant target must be addressed, taking into consideration thresholds for current injection, current spreading to non-desired cortical locations, and current induced thermal heating. However, if delivery of an endovascular electrode can be achieved with a medical complication rate similar to the existing clinical practice of implanting stents within the transverse sinus for idiopathic intracranial hypertension, and stimulation can be delivered safely with respect to both electrodes and tissue, endovascular stimulation may present as a potential alternative treatment for medically refractory epilepsy in patients who are unable or unfit for open brain surgery.
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Table 1. Clinically reported efficacy of therapeutic electrical stimulation to reduce seizures in people with epilepsy and safety of electrodes implanted for non-epilepsy specific applications. The efficacy is calculated for open-loop and closed-loop (CL) as the number of people with a seizure frequency reduction greater than 50% (responder rate, RR), with the seizure frequency reduction (SFR) calculated as the average of the acquired data. Serious adverse complications (risks) are categorised as medical risks or hardware risks. Participant numbers (No.) are also provided.

CL=closed-loop.

<table>
<thead>
<tr>
<th>Target</th>
<th>Efficacy (%)</th>
<th>Risk (%)</th>
<th>Overall Benefit</th>
<th>Ref.</th>
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<tbody>
<tr>
<td></td>
<td>RR (No.)</td>
<td>SFR (No.)</td>
<td>Medical (No.)</td>
<td>Hardware (No.)</td>
</tr>
<tr>
<td>Vagal Nerve</td>
<td>49.7% (6,129/12,332)</td>
<td>50.2% (1,839/33,539)</td>
<td>5.5% (767/33,539)</td>
<td>2.3% (1,839/33,539)</td>
</tr>
<tr>
<td>Vagal Nerve (CL)</td>
<td>59.3% (67/113)</td>
<td>70.8%</td>
<td>2.7% (4/151)</td>
<td>2.7% (4/151)</td>
</tr>
<tr>
<td>Motor Cortex</td>
<td>83.3% (20/24)</td>
<td>89.6%</td>
<td>4.2% (1/24)</td>
<td>8.3% (2/24)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>51.1% (69/135)</td>
<td>57.5%</td>
<td>6.5% (22/337)</td>
<td>3.3% (11/337)</td>
</tr>
<tr>
<td>Cortical (CL)</td>
<td>87.5% (7/8)</td>
<td>55.5%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anterior Nucleus of Thalamus</td>
<td>52.3% (80/153)</td>
<td>60.1%</td>
<td>30.1% (51)</td>
<td>17.5% (29)</td>
</tr>
<tr>
<td>Centromedian</td>
<td>70.7% (29/41)</td>
<td>60.0%</td>
<td>9.8% (4/41)</td>
<td>4.8% (2/41)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>68.5% (37/54)</td>
<td>64.9%</td>
<td>14.8% (8/54)</td>
<td>7.4% (4/54)</td>
</tr>
<tr>
<td>Subthalamic Nucleus</td>
<td>61.1% (11/18)</td>
<td>62.2%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Location</td>
<td>Success Rate</td>
<td>Response Rate</td>
<td>Adverse Events</td>
<td>N/A</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>----------------</td>
<td>-----</td>
</tr>
<tr>
<td>Nucleus Accumbens</td>
<td>55.6% (5/9)</td>
<td>22.5%</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>100% (7/7)</td>
<td>84.0%</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Fornix</td>
<td>100% (7/7)</td>
<td>92.0%</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Caudal Zone Incerta</td>
<td>100% (2/2)</td>
<td>71.0%</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Responsive Neurostimulation (CL)</td>
<td>65.9% (122/185)</td>
<td>72.0%</td>
<td>14.1% (36/256)</td>
<td>21.9% (56/256)</td>
</tr>
</tbody>
</table>

**Safety**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Adverse Event Rate</th>
<th>N/A</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grid Electrodes</td>
<td>22.0% (351/1,599)</td>
<td>N/A</td>
<td>37-39</td>
</tr>
<tr>
<td>Deep-Brain Stimulation Electrodes</td>
<td>8.8% (1,717/19,594)</td>
<td>N/A</td>
<td>60</td>
</tr>
<tr>
<td>Idiopathic Intracranial Hypertension Stents</td>
<td>0.05% (6/429)</td>
<td>N/A</td>
<td>83, 84</td>
</tr>
</tbody>
</table>
Table 2. Extracranial, superficial and deep cortical vessels average diameter, range, number (N) of scans and their proximity to conventional therapeutic targets.

VN=vagal nerve, CER=cerebellum, MCX=Motor cortex, FOR=fornix, ANT=anterior nucleus of thalamus, CMT=centromedian nucleus of thalamus, HIP=hippocampus, STN=subthalamic nuclei, CZI=caudal zone incerta. Proximity: A=Adjacent, 0-2mm; C=Close, 2-5mm; M=Medium, 5-10mm; D=Distant, 10-15mm.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Target (Proximity)</th>
<th>Diameter (mean±SD, mm)</th>
<th>Range (mm)</th>
<th>Scans (N)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Jugular Vein</td>
<td>VN (A)</td>
<td>13.2±0.9</td>
<td>6.5-26.5</td>
<td>219</td>
<td>88-90</td>
</tr>
<tr>
<td>Sigmoid Sinus</td>
<td>CER (A)</td>
<td>7.7±1.4</td>
<td>4.1-13.9</td>
<td>562</td>
<td>91, 92</td>
</tr>
<tr>
<td>Transverse Sinus</td>
<td>CER (A)</td>
<td>6.2±1.4</td>
<td>4.3-11.5</td>
<td>2,632</td>
<td>91-93</td>
</tr>
<tr>
<td>Superior Sagittal Sinus</td>
<td>MCX (A)</td>
<td>6.5±1.7</td>
<td>1.0-10.9</td>
<td>2,578</td>
<td>28,91-94</td>
</tr>
<tr>
<td>Post-Central Sulcal Vein</td>
<td>MCX (A)</td>
<td>-</td>
<td>1.8-6.1</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>Central Sulcal Vein</td>
<td>MCX (A)</td>
<td>-</td>
<td>1.6-8.5</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>Pre-Central Sulcal Vein</td>
<td>MCX (A)</td>
<td>-</td>
<td>1.7-7.5</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>Straight Sinus</td>
<td>CER (M)</td>
<td>3.5±0.5</td>
<td>2.9-4.0</td>
<td>903</td>
<td>92,94-96</td>
</tr>
<tr>
<td>Inferior Sagittal Sinus</td>
<td>MCX (M), FOR (D)</td>
<td>1.3±0.3</td>
<td></td>
<td>221</td>
<td>28</td>
</tr>
<tr>
<td>Great Cerebral Vein (of Galen)</td>
<td>-</td>
<td>3.7±1.0</td>
<td>2.3-4.6</td>
<td>1,013</td>
<td>92,94</td>
</tr>
<tr>
<td>Basal Vein of Rosenthal</td>
<td>CER (D), ANT (D), CMT (D), HIP (M), STN (M), CZI (M)</td>
<td>1.7±0.4</td>
<td>1.0–2.1</td>
<td>1,213</td>
<td>92,94-96</td>
</tr>
<tr>
<td>Internal Cerebral Vein</td>
<td>ANT (M), CMT (A), HYP (D), FOR (C), CZI (D)</td>
<td>1.9±0.5</td>
<td>0.9–3.9</td>
<td>1,416</td>
<td>92,94-96</td>
</tr>
<tr>
<td>Thalamostriate Vein</td>
<td>ANT (A), CMT (A), FOR (A)</td>
<td>1.2</td>
<td>1.1-1.5</td>
<td>45</td>
<td>95</td>
</tr>
</tbody>
</table>