OPEN ACCESS

Review

# The brain nebula: minimally invasive brain–computer interface by endovascular neural recording and stimulation

Qiheng He ,[1,2] Yi Yang,[1,2,3,4,5,6,7] Peicong Ge,[1] Sining Li,[8] Xiaoke Chai,[2] Zhongqiu Luo,[9] Jizong Zhao[1,3,4]

For numbered affiliations see end of article.

**Correspondence to**
Professor Jizong Zhao, Department of Neurosurgery, Capital Medical University, Beijing, China; zhaojizong@bjtth.org

QH, YY and PG contributed equally.

Received 30 November 2023
Accepted 19 January 2024

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** He Q, Yang Y, Ge P, *et al*. *J NeuroIntervent Surg* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnis-2023-021296

## ABSTRACT

A brain–computer interface (BCI) serves as a direct communication channel between brain activity and external devices, typically a computer or robotic limb. Advances in technology have led to the increasing use of intracranial electrical recording or stimulation in the treatment of conditions such as epilepsy, depression, and movement disorders. This indicates that BCIs can offer clinical neurological rehabilitation for patients with disabilities and functional impairments. They also provide a means to restore consciousness and functionality for patients with sequelae from major brain diseases. Whether invasive or non-invasive, the collected cortical or deep signals can be decoded and translated for communication. This review aims to provide an overview of the advantages of endovascular BCIs compared with conventional BCIs, along with insights into the specific anatomical regions under study. Given the rapid progress, we also provide updates on ongoing clinical trials and the prospects for current research involving endovascular electrodes.

## INTRODUCTION

A brain–computer interface (BCI) serves as a direct communication channel between brain activity and external devices, typically a computer or robotic limb. The prototype of BCI can be traced back to 1929 when the first scalp electroencephalography (EEG) was collected.[1] Since then, BCIs have evolved to encompass non-invasive methods like EEG, partially invasive approaches such as electrocorticography (ECoG) and endovascular techniques, and invasive methods involving microelectrode arrays and deep brain stimulation (DBS), depending on the proximity of electrodes to brain tissue.

Currently, many patients experience prolonged bedridden periods or are unable to lead normal social lives due to sequelae of brain disease, which places a substantial burden on them. Conventional treatment methods, including manual therapy and electronic biofeedback, primarily focus on peripheral treatments. However, there are limited treatment options that directly intervene in the patient's brain.

Advances in technology have led to the increasing use of intracranial electrical recording or stimulation in the treatment of conditions such as epilepsy, depression, and movement disorders.[2–4] In the process of BCIs, changes in electrical signals originating from neural activity in the brain are captured using either invasive or non-invasive techniques. Whether invasive or non-invasive, the collected cortical or deep signals enables external devices to be controlled to achieve the intended output, and neurofeedback stimulation can enhance brain responsiveness, leading to functional improvements. Therefore, the exploration of new technologies to locate, identify, and decode the intentions behind brain electrical activity and subsequently execute them with the assistance of external devices holds great significance for the diagnosis and treatment of diseases, as well as the understanding of human consciousness.

This topic review aims to provide an overview of the advantages of endovascular BCIs compared with conventional BCIs, along with insights into the specific anatomical regions under study. Given the rapid progress in endovascular neurosurgery, we also provide updates on ongoing clinical trials and the prospects for current research involving endovascular electrodes.

## ENDOVASCULAR SIGNAL DETECTION TECHNOLOGIES

### The advantage of endovascular signal recording

Currently, cortical BCIs have demonstrated their effectiveness in primates.[5 6] In this field, language production and motor function are highly focused research directions, requiring different degrees of feedforward together with feedback processing. In addition, various cases focused on the general algorithm followed in the real-time system. However, traditional invasive electrode placement methods like ECoG and SEEG come with a range of complications, such as hematoma, infection, and blood–brain barrier disruption.[7] Moreover, these methods are not suitable for covering large areas, limiting the collection of neural signals both in terms of scope and invasiveness. Long-term electrode implantation can lead to issues such as scarring, infection, and even epilepsy.

Non-invasive scalp electrode arrays, while less invasive, are inadequate for measuring neuronal signals within deep cortex and brain structures, and their sensitivity is limited. Establishing connections between neural devices and the brain offers the potential for detailed recording and stimulation, but there is typically a trade-off between invasiveness and device resolution. Signal exchange through

J NeuroIntervent Surg: first published as 10.1136/jnis-2023-021296 on 22 February 2024. Downloaded from http://jnis.bmj.com/ on July 18, 2024 by guest. Protected by copyright.

electrodes and nerves inevitably leads to varying degrees of damage to brain tissue, which can only be mitigated by reducing the size of the implant material.

Interestingly, the blood vessels in the brain provide a preexisting pathway, and modern medical interventions often involve minimally invasive procedures through these vessels. Endovascular methods are substantially less invasive than open surgical approaches, resulting in minimal recovery time and greatly reduced concerns regarding site infections. Furthermore, many valuable targets within the central and peripheral nervous systems are situated near vascular structures. Delivering electroceutical devices to these targets through arterial or venous routes might offer a safer and more broadly applicable approach to neuromodulation. Moreover, for endovascular electrodes like Stentrode, its team reported that the electrical signal will be more stable after the electrode fuses with the vascular endothelium, while most invasive electrodes into the cortex may suffer from signal loss as a result of gliosis.

## Large-scale endovascular signal recording

In 1973, Penn *et al* pioneered the use of a platinum cobalt magnet EEG electrode for endovascular recording in humans during arteriography and embolization surgery.[8] They also conducted endovascular intracranial electrical signal recordings in the carotid artery at the siphon in baboons, establishing the feasibility of endovascular intracranial electrical signal recordings from structures not accessible through routine method.

Over 20 years later, Nakase *et al* utilized a Seeker Lite-10 guide wire to collect intracranial EEG signals in 14 patients, revealing signals 2–5 times stronger than those obtained from scalp EEG.[9] They also compared frequent interictal spike discharges between subdural strip electrodes and endovascular electrodes placed in the middle carotid artery, yielding similar results. Simultaneously, in the same year, Stoeter *et al* employed Seeker-10 guide wires covered with polytetrafluoroethylene (Polytef) to record endovascular EEG and evoked potential signals for diagnostic purposes in 23 patients.[10] They carried out the procedure superselectively in the middle meningeal artery, basilar artery, and anterior and middle cerebral arteries, discovering signals two to four times larger than those obtained from simultaneous extracranial recordings.

Subsequently, researchers recognized that recording epilepsy may be an excellent indication for intravascular neural recording. Patients with epilepsy require EEG to identify abnormal discharge areas, but scalp EEG can only record very shallow positions, leading to a high false-negative rate. Endovascular EEG proved to be a feasible technique, revealing clear epileptiform abnormalities at corresponding sites even when no abnormalities were recorded on scalp EEG.[11–15] Table 1 summarizes the different sites. Despite these benefits of endovascular EEG, it has certain limitations. Existing research suggests that electrodes used for endovascular signal recording do require anticoagulant treatment like traditional stent implantation procedures. In some studies, dual anticoagulation preparation was performed before the electrode placement. Therefore, endovascular electrodes still need to improve their structure as much as possible to achieve as little foreign body implantation as possible. In this way, blood flow disturbance may be reduced, thereby reducing the patient's risk of stent thrombosis.

At this stage, the only preclinical animal study was conducted by Bower *et al* to assess the applicability of endovascular EEG recording for high-frequency monitoring.[16] They used multiple electrodes in the superior sagittal sinus of pigs and observed similar magnitudes and waveforms of epileptiform spikes. Furthermore, they determined that endovascular EEG was adequate for localizing epilepsy ictal foci, even with acceptable pulse artifacts in some leads, paving the way for the clinical implementation of endovascular neural recordings. In 2022, Duan *et al* collected endovascular EEG from the superior sagittal sinus in sheep and classified the state of movement using interventional BCI. Then in 2023, they established the world's first interventional BCI system in cynomolgus macaques, which connected the brain and manipulator directly and allowed the monkey to grab food by controlling the manipulator.[17]

## Stentrode

However, these studies lacked reliable preliminary animal experiments and utilized existing interventional catheter consumables, presenting challenges for further research on endovascular recording. In 2018, Oxley *et al* established a sheep model for intravascular neural recording and conducted a preliminary feasibility analysis of this technology.[18] The study indicated a higher success rate when using a 4 French (4F) catheter instead of a 5F or 6F when placing the endovascular recording device into the superior sagittal sinus. Additionally, the ovine model for cerebral catheter venography demonstrated generalizability to the human cerebral venous system in relation to the motor cortex location.

Building on this model, John *et al* compared the signal quality of the Stentrode with conventional subdural and epidural electrodes and found comparable decoding accuracy between the electrode arrays.[19] They further observed that blood vessels exhibit higher conductivity values, leading to a reduction in impedance magnitude, which can reduce the voltage required to stimulate neural tissue.[20] To assess feasibility, Forsyth *et al* trained two sheep to perform an automated forced-choice task designed to elicit left and right head movements following an external stimulus through the placement of a Stentrode in the superior sagittal sinus adjacent to the motor cortex.[21]

John *et al* also examined vascular remodeling after the implantation of endovascular recording devices and noted the accumulation of macrophages, foreign body giant cells, and new vascular channels lined with endothelium around the implant. Importantly, this foreign body reaction did not obstruct blood flow and enabled the recording of epileptic spike activity with various spike shapes, helping to minimize detrimental vascular remodeling. They also observed the impact of long-term endovascular device implantation on blood vessels and found that the combination of electrodes with the vessel wall improved signal recording quality.[22] Although the diameter of the blood vessels decreased in the ninth month, they remained unobstructed for 100 to 190 days with acceptable tolerance.[23 24]

Simultaneously, Mitchell *et al* conducted a single-center, prospective first human study known as the SWITCH study on the Stentrode.[25] This study evaluated five patients with severe bilateral upper limb paralysis and followed them for 12 months. Four of the patients had amyotrophic lateral sclerosis, and one had primary lateral sclerosis. The study commenced on May 27, 2019, and the follow-up was completed on January 9, 2022. The primary safety endpoint of the study was device-related serious adverse events leading to increased mortality or permanent disability, while secondary endpoints included vascular occlusion and device migration. The four male patients included in the analysis had an average age of 61 years. Notably, there were no serious adverse events, vascular occlusions, or device displacements. The SWITCH study represents early proof of the safety of clinical subjects using BCI technology.

J NeuroIntervent Surg: first published as 10.1136/jnis-2023-021296 on 22 February 2024. Downloaded from http://jnis.bmj.com/ on July 18, 2024 by guest. Protected by copyright.

**Table 1** Endovascular neural recording in human or animals

| Study, year | Country | Type | Method | Species | Position | Scale | Conclusion |
|---|---|---|---|---|---|---|---|
| Large-scale endovascular signal recording | | | | | | | |
| Penn *et al*, 1973[8] | USA | Conceptual validation | Recording | Human | MCA | 0.6 mm | Established a method that intravascular EEG recordings from localized intracerebral structures not accessible to routine EEG techniques |
| Nakase *et al*, 1995[9] | Japan | Conceptual validation | Recording | Human | MCA | 0.31 mm | Endovascular EEG signals are 2–5 times higher signal than scalp EEG, while evaluation of corroborative of endovascular EEG and ECoG recordings in similar locations is required |
| Stoeter *et al*, 1995[10] | Germany | Conceptual validation | Recording | Human | Middle meningeal artery, basilar artery, ACA, and MCA | 0.31 mm | Intra-arterial recording technique is an additional method to register the electric phenomena of deep cerebral structures otherwise only accessible by direct puncture |
| Boniface and Antoun, 1997[11] | UK | Conceptual validation | Recording | Human | MCA | Standard 14 steerable guide wire | Endovascular EEG is a feasible technique that can identify intracranial epileptiform abnormalities, and has the potential to achieve more in a bipolar format |
| Mikuni *et al*, 1997[12] | Japan | Conceptual validation | Recording | Human | Cavernous sinus | 0.31 mm | The cavernous sinus EEG demonstrated clear epileptiform discharges, sometimes even when they were absent on the simultaneously recorded scalp EEG |
| Thömke *et al*, 1997[14] | Germany | Conceptual validation | Recording | Human | NA (seems to be MCA) | NA | Endovascular EEG shows acceptable pulse artefacts in some leads and simultaneous recordings from different contacts may be helpful in the preoperative evaluation for seizure patients |
| García-Asensio *et al*, 1999[15] | Spain | Prospective study | Recording | Human | Middle meningeal artery | 0.31 mm | Intra-arterial electroencephalography is able to perform dynamic electroencephalographic recording and patient tolerance is excellent |
| Kunieda *et al*, 2000[13] | Japan | Conceptual validation | Recording | Human | Cavernous sinus, superior petrosal sinus | 0.31 mm | Endovascular EEG is clinically useful to determine ictal foci and its spreading pattern and thus for the selection of surgical candidate among patients with intractable TLE |
| Bower *et al*, 2013[16] | USA | Conceptual validation | Recording | Pigs | Superior sagittal sinus | 2–5 mm | Sinusoidal electrical stimulation showed that intravascular electrodes provide sufficient broadband fidelity to record high-frequency, physiological events that may also prove useful in localizing seizure onset zones |
| Oxley *et al*, 2018[18] | Australia | Conceptual validation | Recording | Sheep | Superior sagittal sinus | 1.2 mm | The ovine model for cerebral catheter venography has generalizability to the human cerebral venous system in relation to motor cortex location |

Continued

J NeuroIntervent Surg: first published as 10.1136/jnis-2023-021296 on 22 February 2024. Downloaded from http://jnis.bmj.com/ on July 18, 2024 by guest. Protected by copyright.

**Table 1** Continued

| Study, year | Country | Type | Method | Species | Position | Scale | Conclusion |
|---|---|---|---|---|---|---|---|
| John *et al*, 2018[19] | Australia | Conceptual validation | Recording | Sheep | Superior sagittal sinus | 1.3–2 mm | The spatial resolution depends on the array location and the frequency of recording. There is a direct correlation between the signal-noise ratio and classification accuracy, and that decoding accuracy is comparable between electrode arrays |
| Forsyth *et al*, 2019[21] | Australia | Feasibility validation | Recording | Sheep | Superior sagittal sinus | 1.3–2 mm | Stentrode can be used to acquire motor-related brain signals to detect movement of the sheep in a forced-choice task |
| John *et al*, 2019[20] | Australia | Feasibility validation | Recording | Sheep | Superior sagittal sinus | 1.2 mm | The distinctive effects of the blood vessel location are limited to the lower frequency ranges, and the effect of the blood vessel was a combination of the highly conductive blood vessel wall and the CSF, with higher conductivity values leading to a reduction in the impedance magnitude |
| John *et al*, 2022[19] | Australia | Conceptual validation | Recording | Sheep | Superior sagittal sinus | 250 µm | The study demonstrated an uneven narrowing of the SSS lumen proportional to the stent material within the blood vessel. However, the foreign body response did not occlude blood flow |
| SWITCH study, 2023[25] | USA | Clinical trial | Recording | Human | Superior sagittal sinus | 1.3–2 mm | Endovascular access to the sensorimotor cortex indicates it may be possible to record neural signals from a blood vessel |
| Microelectrode endovascular recordings | | | | | | | |
| Llinás *et al*, 2005[26] | USA | Microelectrode material | Recording (also capable for stimulation) | In vitro | Capillaries | Nanoscale | Microelectrodes made using conductive polymers can be made smaller while achieving the same conductivity |
| Watanabe *et al*, 2009[27] | USA | Microelectrode material | Recording | Ex vivo | Anterior spinal artery | Submicron scale | Using Wollaston platinum wire, it is able to address any brain area to detect EEG signal through the vascular system |
| Wong *et al*, 2016[28] | Australia | Microelectrode material | Recording (also capable for stimulation) | Sheep | Surface of the cortex | 4 mm | Nitinol has the potential to be used as material in the manufacture of shape-conforming electrodes |
| Zhang *et al*, 2023[29] | USA | Microelectrode material | Recording | Rodents | ACA | Micrometer scale | By the ultrasmall and flexible sub-100 micrometer scale electrode, the electrophysiology recording of local field potentials and single-unit spikes in the cortex and olfactory bulb can be achieved with minimal immune response and long-term stability |

ACA, anterior cerebral artery; CSF, cerebrospinal fluid; ECoG, electrocorticography; EEG, electroencephalogram; MCA, middle cerebral artery; SSS, superior sagittal sinus; TLE, temporal lobe epilepsy.

Before the publication of this study, Synchron announced the initiation of patient recruitment for the COMMAND trial (NCT05035823) to evaluate safety and explore quantitative efficacy measures for the Stentrode. The study planned to enroll six patients with severe quadriplegia. On September 5, 2023, Synchron reported that the COMMAND trial had completed patient enrollment.

## Microelectrode endovascular recordings

While intravascular nerve signal acquisition offers solutions to many limitations of other methods, such as its lower invasiveness and the ability to reach deep brain regions, most prior experiments were primarily proof-of-concept endeavors, and the electrodes used were not purpose-designed. Existing collection strategies have proven inadequate for detecting small epileptic

J NeuroIntervent Surg: first published as 10.1136/jnis-2023-021296 on 22 February 2024. Downloaded from http://jnis.bmj.com/ on July 18, 2024 by guest. Protected by copyright.

foci or conducting research on specific localized neuronal discharges. Consequently, researchers have delved deeper into optimizing electrode size, materials, and signal decoding.

In 2005, Llinás *et al* developed nanowires utilizing conductive polymers and demonstrated their capacity to be miniaturized while maintaining comparable conductivity, even within capillaries.[26] Watanabe *et al* proposed a plan employing non-metallic materials for electrical conduction to reduce electrode size.[27] They utilized Wollaston platinum wire and, in ex vivo experiments, showed that the prototype electrode could measure neuronal activity in the spinal cord from the anterior spinal artery.

Wong *et al* pursued the development of a neural prosthesis that would be well tolerated by both the brain and the body.[28] Traditionally, Nitinol allowed electrodes to conform well to vessel walls, making it suitable for electrode recording. Notably, they demonstrated that such materials could effectively measure neural signals. Their research indicated that the electrode's diameter was relatively large in comparison to prior studies, suggesting potential drawbacks of alloy materials in terms of conductivity.

In efforts to transport bioelectronics to brain regions characterized by narrower and less accessible blood vessels, Zhang *et al* devised a network-like recording device that is smaller and more flexible than previously used technologies.[29] This device comprises 16 distinct recording elements inserted into an intravascular catheter. Utilizing a rat model, they made an incision in the neck and guided the catheter to the internal carotid artery. Thanks to its flexibility, this device can be deployed to previously inaccessible internal carotid artery branches with a diameter $<100\,\mu m$. This capability allowed Zhang *et al* to record discharge patterns in different brain regions from the middle cerebral artery and anterior cerebral artery, covering the cortex and olfactory bulb, respectively.

Despite the fragility of these small blood vessels, the implanted device did not induce substantial changes in cerebral blood flow, rat behavior, or blood–brain barrier structure, nor did it provoke an immune response. Owing to its compact size, this device not only proved capable of recording local field potentials, as observed by the scaffold electrode recording array, but also demonstrated the ability to record single neuron activity. This capacity for non-invasive single-neuron recording is of paramount importance for the study of deep brain regions, such as the medial temporal lobe, where activity does not spatially aggregate and can only be discerned at the single-neuron level.

## ENDOVASCULAR STIMULATIONS

### Evolution

Conventionally, DBS stands as a primary therapy for drug-resistant seizures and movement disorders, including the motor symptoms of conditions such as Parkinson's disease and essential tremor.[2] On the other hand, transcranial magnetic stimulation (TMS) serves as a non-invasive tool capable of delivering repetitive bursts of high-frequency waves to the brain cortex through the intact scalp. TMS finds applications in the treatment of conditions such as depression, migraine, and movement disorders.[3 4] While both techniques are used for neural stimulation, DBS necessitates invasive implantation, which can lead to complications like hematoma or electrode drifting. Conversely, TMS exhibits variable efficacy, and standardized treatment regimens are lacking. As a result, researchers have turned their attention to finding a less invasive approach for DBS, with a focus on the endovascular method (table 2).

Tellitzky *et al* employed computational models to reconstruct 17 established and hypothesized anatomical targets for DBS.[30] Their subsequent performance studies on the fornix and subgenetic circular white matter tracts revealed that a ring-electrode conforming to the vessel wall proved more efficient at neural activation. Increasing the length of a ring-electrode had minimal impact on neural activation thresholds, and suboptimal placement resulted in considerable variability. Gerboni *et al* discovered differences in the neural activation centers for visual and electrical stimulation by placing the Stentrode into the superior sagittal sinus of sheep, as previously reported, indicating that the scaffold electrode possesses the capacity for local activation of neural tissue.[31] Opie *et al* reported the application of a platinum electrode array mounted on a nitinol endovascular stent for the localized stimulation of cortical tissue from within a blood vessel.[32] The proximity of the electrode to the motor cortex, rather than its orientation, proved essential for eliciting reliable responses from discrete neuronal populations. These studies have demonstrated the feasibility of intravascular electrodes for stimulation, yet new challenges arise concerning how to power such devices. Chen *et al* sought to minimize the bulkiness of devices and designed a battery-free millimetric implant for specific peripheral nerves that are typically challenging to reach through traditional surgical methods.[33]

Transvascular vagus nerve stimulation is another treatment method that has recently garnered increased attention. Liu *et al* utilized a computational model to simulate vagus nerve stimulation endovascularly.[34] Although no further experimentation was performed for validation, they observed that the stimulation thresholds were comparable to those of ring electrodes and depended on the inter-electrode distance and the orientation of the device. Nicolai *et al* designed an animal study using pigs and discovered efficient stimulation within the electrode.[35] However, they found that the thresholds for vagus nerve activation were several times higher than those for direct stimulation. This could be attributed to suboptimal electrode design, with the electrode contact area not being sufficiently large, and the lantern-like cages limiting its use during the acute phase. These mentioned shortcomings render this study unable to fully represent real-world scenarios, and there remains a need for more specific stimulation of vagal nerve A fibers and a long-term electrode placement more akin to the shape of a stent.

### Closed-loop stimulation systems

In 2020, Neudorfer *et al* conducted a study investigating the neuroanatomical relationships between DBS targets and the vascular system using Stentrodes.[36] Utilizing a preliminary volume of tissue activated analysis, they identified six out of 10 DBS targets suitable for endovascular stimulation. These included the medial forebrain bundle (corresponding to the posterior cerebral artery), nucleus accumbens (corresponding to the anterior cerebral artery), dentatorubrothalamic tract (corresponding to the superior cerebellar artery), fornix (corresponding to the internal cerebral vein), pedunculopontine nucleus (corresponding to the lateral mesencephalic vein), and subcallosal cingulate cortex (corresponding to the anterior cerebral artery).

It is important to note that DBS stimulation targets are often associated with a range of advanced motor, cognitive, and emotional functions, and the effects of stimulation can vary between different diseases and individuals. Consequently, when employing DBS therapy, medical professionals must conduct comprehensive assessments and devise personalized treatment plans based on each patient's specific condition. In neurological diseases, brain networks exhibit dynamic, non-static, and highly individualized characteristics.

J NeuroIntervent Surg: first published as 10.1136/jnis-2023-021296 on 22 February 2024. Downloaded from http://jnis.bmj.com/ on July 18, 2024 by guest. Protected by copyright.

**Table 2** Endovascular neural stimulation studies

| Study, year | Country | Type | Method | Species | Position | Scale | Conclusion |
|---|---|---|---|---|---|---|---|
| Teplitzky *et al*, 2014[30] | USA | Conceptual validation | Stimulation | Computational model | Internal cerebral vein, ACA | 1.3 mm | Ring electrodes that conform to the shape of the blood vessel wall are more efficient at electrical stimulation, and the increase in length has minimal impact on neural activation thresholds. Large variability in neural activation occurred with suboptimal placement of a ring-electrode along the targeted vessel |
| Gerboni *et al*, 2018[31] | Australia | Conceptual validation | Stimulation | Sheep | Superior sagittal sinus | 1.3 mm | Stentrode to provide localized activation of neural tissue |
| Opie *et al*, 2018[32] | Australia | Conceptual validation | Stimulation | Sheep | Superior sagittal sinus | 1.3 mm | Proximity of the electrode to the motor cortex, yet not its orientation, was integral to achieving reliable responses from discrete neuronal populations |
| Chen *et al*, 2022 | USA | Conceptual validation | Stimulation | Pigs | Femoral artery | $3\times2.15\times14.8\,\text{mm}^3$ | Minimally invasive magnetoelectric implants may allow for the stimulation of nerves without the need for open surgery or the implantation of battery-powered pulse generators |
| Liu *et al*, 2023[34] | Australia | Conceptual validation | Stimulation | Computational model | Pudendal and vagal neurovascular bundles | 0.75 mm | This study predicts that the endovascular stent-electrode array is a feasible stimulation option for peripheral nerves, and the electrode array can be flexibly optimized to achieve the lowest stimulation threshold |
| Nicolai *et al*, 2023[35] | USA | Conceptual validation | Stimulation | Pigs | IJV | 2.81–4 mm | The stimulation electrode position within the IJV is critical for efficient activation of the vagus nerve, and the thresholds for vagus nerve activation were several times higher than direct stimulation of the nerve using a cuff electrode |

ACA, anterior cerebral artery; IJV, internal jugular vein.

Fixed mechanical electrical stimulation may not produce therapeutic effects and could potentially increase the occurrence of complications or side effects. Furthermore, the unstable internal environment in the early stages of neurological diseases amplifies the dynamic changes in the brain network, making it risky to use a single fixed parameter for electrical stimulation, as this may impact treatment effectiveness. The timing of stimulation and real-time adjustment of stimulation parameters may hold the key to enhancing therapeutic outcomes. Hence, the development of a reactive closed-loop electrical stimulation system to cater for dynamic, individualized needs is crucial. EEG signals collected by the electrode array are transmitted to a cloud server for processing and analysis through wireless communication. The intention is determined from the collected signals using artificial intelligence algorithms and subsequently fed back to internal devices to enable the required closed-loop signal control. The application of a platinum electrode for stimulation as reported by Opie *et al* represents the only example of closed-loop stimulation possibilities for patients with seizures.[32]

## LIMITATIONS AND PROSPECTS

Endovascular neural recording and stimulation have experienced a surge in applications in the treatment of clinical disorders. Neuromodulatory techniques have now become an essential component of care for conditions such as essential tremor and Parkinson's disease, and their utilization is rapidly expanding to encompass a broad spectrum of other neurological and psychiatric disorders.

J NeuroIntervent Surg: first published as 10.1136/jnis-2023-021296 on 22 February 2024. Downloaded from http://jnis.bmj.com/ on July 18, 2024 by guest. Protected by copyright.

Nevertheless, endovascular recording still grapples with specific challenges that hinder its clinical implementation.[37]

Concerning endovascular stimulation, several safety considerations must be addressed before its clinical adoption. These include the imperative need to minimize the risks of thromboembolic events, hemorrhage, and infection.[38]

Notwithstanding these challenges, the progress in endovascular approaches to cerebrovascular diseases has led to the development of minimally invasive techniques that enable the delivery of devices to neural tissue in both the central and peripheral nervous systems. Importantly, these advances have resulted in significantly enhanced safety and efficacy.

**Author affiliations**
[1]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]Brain Computer Interface Transitional Research Center, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[3]China National Center for Neurological Disorders, Beijing, China
[4]China National Clinical Research Center for Neurological Diseases, Beijing, China
[5]National Research Center for Rehabilitation Technical Aids, Beijing, China
[6]Chinese Institute for Brain Research, Beijing, People's Republic of China
[7]Beijing Institute of Brain Disorders, Beijing, People's Republic of China
[8]Tianjin Key Laboratory of Brain Science and Intelligent Rehabilitation, College of Artificial Intelligence, Nankai University, Tianjin, China
[9]Department of Neurosurgery, Shenzhen Qianhai Shekou Free Trade Zone Hospital, Shenzhen, China

**Twitter** Yi Yang @Yi Yang

**Acknowledgements** The authors thank Ziyi Wang for her assistance in computer science.

**Contributors** QH wrote the original manuscript. QH, YY, PG, ZL and JZ edited the revised manuscript. QH, SL, XC and ZL searched the literature and summarized.

**Funding** The study is funded by Science and Technology Innovation 2030-Young Scientists Project of Brain Science and Brain-like Research (2022ZD0205300), International (Hong Kong, Macao, and Taiwan) Science and Technology Cooperation Project (Z221100002722014), 2022 Open Project of Key Laboratory and Engineering Technology Research Center in the Rehabilitation Field of the Ministry of Civil Affairs (2022GKZS0003), Chinese Institute for Brain Research Youth Scholar Program (2022-NKX-XM-02), and Beijing Natural Science Foundation (7232049).

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iD**
Qiheng He http://orcid.org/0000-0001-6715-298X

## REFERENCES

1. İnce R, Adanır SS, Sevmez F. The inventor of electroencephalography (EEG): Hans Berger (1873-1941). *Childs Nerv Syst* 2021;37:2723–4.
2. Kocabicak E, Temel Y, Höllig A, *et al*. Current perspectives on deep brain stimulation for severe neurological and psychiatric disorders. *Neuropsychiatr Dis Treat* 2015;11:1051–66.
3. Daskalakis ZJ. Theta-burst transcranial magnetic stimulation in depression: when less may be more. *Brain* 2014;137(Pt 7):1860–2.
4. Suppa A, Huang Y-Z, Funke K, *et al*. Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects. *Brain Stimul* 2016;9:323–35.
5. Wang R, Chen X, Khalilian-Gourtani A, *et al*. Distributed feedforward and feedback cortical processing supports human speech production. *Proc Natl Acad Sci USA* 2023;120:42.
6. Rouzitalab A, Boulay CB, Park J, *et al*. Intracortical brain-computer interfaces in primates: a review and outlook. *Biomed Eng Lett* 2023;13:375–90.
7. Thielen B, Xu H, Fujii T, *et al*. Making a case for endovascular approaches for neural recording and stimulation. *J Neural Eng* 2023;20:011001.
8. Penn RD, Hilal SK, Michelsen WJ, *et al*. Intravascular intracranial EEG recording. *J Neurosurg* 1973;38:239–43.
9. Nakase H, Ohnishi H, Touho H, *et al*. An intra-arterial electrode for intracranial electro-encephalogram recordings. *Acta Neurochir (Wien)* 1995;136:103–5.
10. Stoeter P, Dieterle L, Meyer A, *et al*. Intracranial electroencephalographic and evoked-potential recording from intravascular guide wires. *AJNR Am J Neuroradiol* 1995;16:1214–7.
11. Boniface SJ, Antoun N. Endovascular electroencephalography: the technique and its application during carotid amytal assessment. *J Neurol Neurosurg Psychiatry* 1997;62:193–5.
12. Mikuni N, Ikeda A, Murao K, *et al*. Cavernous sinus EEG: a new method for the preoperative evaluation of temporal lobe epilepsy. *Epilepsia* 1997;38:472–82.
13. Kunieda T, Ikeda A, Mikuni N, *et al*. Use of cavernous sinus EEG in the detection of seizure onset and spread in mesial temporal lobe epilepsy. *Epilepsia* 2000;41:1411–9.
14. Thömke F, Stoeter P, Stader D. Endovascular electroencephalography during an intracarotid amobarbital test with simultaneous recordings from 16 electrodes. *J Neurol Neurosurg Psychiatry* 1998;64:565.
15. García-Asensio S, Guelbenzu S, Barrena R, *et al*. Technical aspects of intra-arterial electroencephalogram recording. *Interv Neuroradiol* 1999;5:289–300.
16. Bower MR, Stead M, Van Gompel JJ, *et al*. Intravenous recording of intracranial, broadband EEG. *J Neurosci Methods* 2013;214:21–6.
17. China National Radio. Monkey brain active brain control robotic arm! Can the mind really control everything? China National Radio; 2023. Available: http://china.cnr.cn/xwclj/20230521/t20230521_526259398.shtml
18. Oxley TJ, Opie NL, Rind GS, *et al*. An ovine model of cerebral catheter venography for implantation of an endovascular neural interface. *J Neurosurg* 2018;128:1020–7.
19. John SE, Opie NL, Wong YT, *et al*. Signal quality of simultaneously recorded endovascular, subdural and epidural signals are comparable. *Sci Rep* 2018;8:8427.
20. John SE, Apollo NV, Opie NL, *et al*. In vivo impedance characterization of cortical recording electrodes shows dependence on electrode location and size. *IEEE Trans Biomed Eng* 2019;66:675–81.
21. Forsyth IA, Dunston M, Lombardi G, *et al*. Evaluation of a minimally invasive endovascular neural interface for decoding motor activity. 2019 9th International IEEE/EMBS Conference on Neural Engineering (NER); :750–3
22. Oxley TJ, Opie NL, John SE, *et al*. Minimally invasive endovascular stent-electrode array for high-fidelity, chronic recordings of cortical neural activity. *Nat Biotechnol* 2016;34:320–7.
23. Opie NL, Rind GS, John SE, *et al*. Feasibility of a chronic, minimally invasive endovascular neural interface. *Annu Int Conf IEEE Eng Med Biol Soc* 2016;2016:4455–8.
24. Opie NL, John SE, Rind GS, *et al*. Chronic impedance spectroscopy of an endovascular stent-electrode array. *J Neural Eng* 2016;13:046020.
25. Mitchell P, Lee SCM, Yoo PE, *et al*. Assessment of safety of a fully implanted endovascular brain-computer interface for severe paralysis in 4 patients: the Stentrode with thought-controlled digital switch (SWITCH) study. *JAMA Neurol* 2023;80:270–8.
26. Llinás RR, Walton KD, Nakao M, *et al*. Neuro-vascular central nervous recording/stimulating system: using nanotechnology probes. *J Nanopart Res* 2005;7:111–27.
27. Watanabe H, Takahashi H, Nakao M, *et al*. Intravascular neural interface with nanowire electrode. *Electron Commun Jpn* 2009;92:29–37.
28. Wong YT, Opie NL, John SE, *et al*. Suitability of nitinol electrodes in neural prostheses such as endovascular neural interfaces. *Annu Int Conf IEEE Eng Med Biol Soc* 2016;2016:4463–6.
29. Zhang A, Mandeville ET, Xu L, *et al*. Ultraflexible endovascular probes for brain recording through micrometer-scale vasculature. *Science* 2023;381:306–12.
30. Teplitzky BA, Connolly AT, Bajwa JA, *et al*. Computational modeling of an endovascular approach to deep brain stimulation. *J Neural Eng* 2014;11:026011.
31. Gerboni G, John SE, Ronayne SM, *et al*. Cortical brain stimulation with endovascular electrodes. *Annu Int Conf IEEE Eng Med Biol Soc* 2018;2018:3088–91.
32. Opie NL, John SE, Rind GS, *et al*. Focal stimulation of the sheep motor cortex with a chronically implanted minimally invasive electrode array mounted on an endovascular stent. *Nat Biomed Eng* 2018;2:907–14.
33. Chen JC, Kan P, Yu Z, *et al*. A Wireless Millimetric Magnetoelectric implant for the Endovascular stimulation of peripheral nerves. *Nat Biomed Eng* 2022:706–16.
34. Liu JY, Grayden DB, Keast JR, *et al*. Computational modeling of endovascular peripheral nerve stimulation using a stent-mounted electrode array. *J Neural Eng* 2023;20.
35. Nicolai EN, Larco JA, Madhani SI, *et al*. Vagus nerve stimulation using an endovascular electrode array. *J Neural Eng* 2023;20.
36. Neudorfer C, Bhatia K, Boutet A, *et al*. Endovascular deep brain stimulation: investigating the relationship between vascular structures and deep brain stimulation targets. *Brain Stimul* 2020;13:1668–77.
37. Fan JZ, Lopez-Rivera V, Sheth SA. Over the horizon: the present and future of endovascular neural recording and stimulation. *Front Neurosci* 2020;14:432.
38. Raza SA, Opie NL, Morokoff A, *et al*. Endovascular neuromodulation: safety profile and future directions. *Front Neurol* 2020;11:351.

J NeuroIntervent Surg: first published as 10.1136/jnis-2023-021296 on 22 February 2024. Downloaded from http://jnis.bmj.com/ on July 18, 2024 by guest. Protected by copyright.