Assessment of safety of a fully implanted endovascular brain-computer interface for severe paralysis in four patients: results of the Stentrode with Thought-Controlled Digital Switch (SWITCH) study

Peter Mitchell, MMed[1]*; Sarah C.M. Lee, MBBS[2]*; Peter E. Yoo, PhD[3]; Andrew Morokoff, MD[4]; Rahul P. Sharma, MBBS[5]; Daryl L. Williams, MBBS[6]; Christopher MacIsaac, PhD[7]; Mark E. Howard, MBBS, PhD[8]; Lou Irving, MBBS[9]; Ivan Vrljic, MBBS[1]; Cameron Williams, MBBS[10]; Steven Bush, MBBS[10]; Anna H. Balabanski, MBBS[10,11,12]; Katharine J. Drummond, MD[13]; Patricia Desmond, MD[1]; Douglas Weber, PhD[14]; Timothy Denison, PhD[15]; Susan Mathers, MD[2]; Terence J. O'Brien, MD[10,16,17]; J Mocco, MD[18]; David B. Grayden, PhD[19]; David S. Liebeskind, MD[20]; Nicholas L. Opie, PhD[21,22]; Thomas J. Oxley, MD, PhD[3,21]; Bruce C.V. Campbell, MBBS[10,11]

*First two authors contributed equally

Author Affiliations

[1]Department of Radiology, The University of Melbourne, The Royal Melbourne Hospital, Parkville, Victoria, Australia
[2] Neurology, Calvary Healthcare Bethlehem, Parkdale, Victoria, Australia
[3]Synchron, Inc, 63 Flushing Avenue, 303 Suite 501, Brooklyn, New York, USA
[4] Parkville Neurosurgery, The University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia
[5] Stanford Healthcare Cardiovascular Medicine, Stanford University, California, USA
[6]Department of Anaesthesia and Pain Management, The University of Melbourne, The Royal Melbourne Hospital, Parkville, Victoria, Australia
[7]Intensive Care Department, The University of Melbourne, The Royal Melbourne Hospital, Parkville, Victoria, Australia
[8]Victorian Respiratory Support Service, Austin Health, Heidelberg, Victoria, Australia
[9]Peter MacCallum Cancer Centre, The University of Melbourne, The Royal Melbourne Hospital, Melbourne, Victoria, Australia
[10]Department of Neurology, The University of Melbourne, The Royal Melbourne Hospital, Parkville, Victoria, Australia
[11]Melbourne Brain Centre, The University of Melbourne, The Royal Melbourne Hospital, Parkville, Victoria, Australia
[12]Department of Neuroscience, Alfred Brain, Alfred Health, Melbourne, Victoria, Australia
[13]Department of Neurosurgery, The University of Melbourne, The Royal Melbourne Hospital, Parkville, Victoria, Australia
[14]Department of Biomedical Engineering, College of Engineering, Carnegie Mellon University, Pittsburgh, Pennsylvania, USA
[15]Institute of Biomedical Engineering, The University of Oxford, Oxford, United Kingdom
[16]Department of Medicine, The University of Melbourne, The Royal Melbourne Hospital, Parkville, Victoria, Australia
[17]Department of Neuroscience, The Central Clinical School, Monash University & Alfred Health, Melbourne, Victoria, Australia
[18]Department of Neurosurgery, Klingenstein Clinical Center, The Mount Sinai Hospital, New York, New York, USA
[19]Department of Biomedical Engineering, Faculty of Engineering and Information Technology, The University of Melbourne, Parkville, Australia

[20]Department of Neurology and UCLA Comprehensive Stroke Center, Neuroscience Research Building, University of California Los Angeles, Los Angeles, California, USA
[21]Vascular Bionics Laboratory, Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia
[22]Synchron, 200 Lygon Street, Carlton, Victoria, Australia

Corresponding Author:

Peter Mitchell, MMed, Department of Radiology, The University of Melbourne, The Royal Melbourne Hospital, Level 1, B Building, 300 Grattan Street, Parkville, Victoria 3050, Australia
(Peter.Mitchell@mh.org.au)

Key Points

Question Is an endovascular brain-computer interface (BCI) implant safe, and can it enable paralyzed patients to control a computer with their thoughts?

Findings Final results of a first-in-human study showed the BCI device could be implanted into the superior sagittal sinus using a neurointerventional procedure. It appeared to be safe, and enabled subjects with paralysis to do hands-free texting, emailing, online banking and shopping, and communicating care needs using their thoughts.

Meaning The clinical study indicates that it is possible to record neuronal signals from a blood vessel in the brain. The favorable safety profile of this approach could promote wider and more rapid translation of BCI to people with paralysis.

Abstract

Importance Brain-computer interface (BCI) implants have previously required craniotomy to deliver penetrating or surface electrodes to the brain. Here we present complete results of a first-in-human BCI study using a minimally invasive endovascular technique to deliver recording electrodes through the jugular vein to superior sagittal sinus (SSS).

Objective To assess safety of an endovascular BCI and feasibility of using the system to control a computer by thought.

Design The **S**tentrode **wi**th **T**hought-**C**ontrolled Digital Switc**h** (SWITCH) trial, a single-center, prospective, first-in-human study, evaluated five subjects with severe bilateral upper-limb paralysis, with a follow-up of 12 months.

Setting Surgical procedure and follow-up visits at Royal Melbourne Hospital, Victoria, Australia. Training sessions performed at subjects' homes and a university clinic.

Participants From a referred sample, four patients with amyotrophic lateral sclerosis and one with primary lateral sclerosis met inclusion criteria and were enrolled in the study.

Intervention Recording device was delivered via catheter and connected to subcutaneous electronics unit. Device communicated wirelessly to an external device for personal computer control.

Main Outcomes and Measures Primary safety endpoint was device-related serious adverse events resulting in death or permanent increased disability. Secondary endpoints were blood vessel occlusion and device migration. Exploratory endpoints were signal fidelity and stability over 12 months, number of distinct commands created by neuronal activity, and use of system for digital device control.

Results Four male subjects with age 61 (17) years, preserved motor cortex activity, and suitable venous anatomy were implanted. Each completed 12-month follow-up with no serious adverse events and no vessel occlusion or device migration. Signal bandwidth was 233 (16) Hz and was stable throughout study in all four subjects (standard deviation: 7-32 Hz). At least 5 attempted movement types were decoded offline, and each subject successfully controlled a computer with the BCI.

Conclusions and Relevance Endovascular access to the sensorimotor cortex is an alternative to placing BCI electrodes in or on the dura by open-brain surgery. These final safety and feasibility data from the first-in-human SWITCH study indicate that it is possible to record neural signals from a blood vessel. The favorable safety profile could promote wider and more rapid translation of BCI to people with paralysis.

Trial Registration Registered at clinicaltrials.gov (NCT03834857).

Introduction

Personal computing devices have transformed how people can interact with the world. In the U.S., there are 5.4 million individuals with severe paralysis resulting in limited ability to control a computer or smartphone.[1] While many people with paralysis can still generate cortical activity associated with attempted movements in the motor cortex,[2] disrupted motor signal transmission results in impaired limb function. A BCI could restore motor capability by using the cortical motor signal to bypass impaired limbs and directly control a computer. The number of people who could potentially be assisted with BCI is estimated to reach 50 million in the world's advanced economies by 2025.[3]

Case reports of investigational BCI devices have described control of exoskeletons,[4] prosthetic limbs,[2, 4, 5] and communication technologies,[6, 7] and demonstrated the ability to directly decode speech and handwriting from cortical motor activity.[8, 9] Application to wider patient populations is limited, in part by the invasiveness of craniotomy or partial skull removal to implant electrodes in or on the brain.[10-13]

The blood vessels of the brain offer a less invasive route for obtaining access to the motor cortex. Venous stenting has routinely been performed for treating intracranial idiopathic hypertension (IIH) in the transverse sinus, with a major complication rate of less than 2%.[14, 15] An endovascular device incorporating recording electrodes and implantable in the superior sagittal sinus has recently been developed (Stentrode™, Synchron, Brooklyn, NY, USA).[16-20]

The first-in-human study evaluated if the endovascular BCI could be safely implanted and used by subjects with paralysis to control a personal computer. We describe complete results of the study, including safety endpoints and feasibility of computer control using electrocorticography signals recorded from the motor cortex. Implant experience and initial findings from the first two patients in this study were reported previously.[20]

Methods

Study design and recruitment

The SWITCH study was approved by the Human Research Ethics Committees of St. Vincent's Hospital, Royal Melbourne Hospital, and Calvary Health Care Bethlehem in Australia. The study adhered to Good Clinical Practice and the Declaration of Helsinki, and all subjects provided written informed consent prior to undergoing study procedures. A detailed clinical protocol was previously published.[20]

Subjects were recruited following a selective referral process. Eligibility requirements included paralysis following a clinical diagnosis of spinal cord injury, motor neuron disease, stroke, muscular dystrophy, or loss of limbs, age 18-75 years, and a life expectancy of at least 12 months. Inclusion in the study required a caregiver willing to participate with study procedures, capacity to provide informed consent, and ability to complete study procedures. Further details on inclusion and exclusion criteria are available at clinicaltrials.gov (NCT03834857).

Devices

The implanted devices comprise the Stentrode (Synchron, Brooklyn, NY), a 16-electrode sensing device implanted endovascularly, connected by a transvascular lead to an implantable receiver transmitter unit (IRTU) in an infraclavicular subcutaneous pocket. The recording head of the sensing device contains platinum electrodes with a surface area of 0.3 mm^2 and an intercontact spacing of 3 mm. Impedance between the recording electrodes and reference electrode on the IRTU was 37 (11) kΩ. Data are transmitted wirelessly to an external controller that translates the neural signals into switch outputs to control a laptop computer **(Figure 1A)**.[21]

Procedures

Subjects who met enrollment criteria provided informed consent prior to undergoing any study procedures. A pre-implant magnetic resonance imaging (MRI) study was performed to assess the suitability of neuroanatomy and venous pathway for implantation. Preserved motor cortex activation was assessed by blood-oxygenation-level dependent functional MRI during attempted lower limb movements.

Pre-implant computed tomography (CT) venography was also collected for baseline assessment. Dual antiplatelet therapy commenced two weeks before implant.

The implant procedure was conducted in an operating room under general anesthesia. The recording device was permanently implanted with angiography techniques used in neurovascular stenting and clot retrieval. Device delivery was guided by three-dimensional digital subtraction angiography co-registered to the target location marked on the preoperative structural MRI. After direct percutaneous access of an internal jugular vein, a 2-mm guide catheter was used to reach the target location in the SSS. The device was advanced through the guide catheter and deployed adjacent to the precentral gyrus. The 1.3-mm-diameter lead was tunneled to the IRTU implanted in a subcutaneous pocket. Left or right placement was determined for individual patients based on venous anatomy.

Safety endpoints

The primary endpoint was device-related serious adverse events resulting in death or permanently increased disability within 12 months after implantation. Adverse events were recorded by the implanting physician or other clinicians, and classified by the investigator as definitely, probably, possibly, unlikely to be related or not related to a device or procedure. Events that were classified as definitely or probably related to a device or procedure were categorized as adverse device effects. The investigator also graded adverse events as mild, moderate, or severe. An independent safety monitor skilled in neurointerventional procedures conducted an independent review of safety data.

Secondary endpoints were target vessel occlusion and device migration, evaluated by an independent expert vascular neurologist from CT venography performed before, 3 and 12 months after implantation. Target vessel occlusion was evaluated by comparing vessel size and shape on CT venograms at baseline, 3 and 12 months. Device migration was evaluated by comparing the distance of the distal electrode to a fiducial line on the 3- and 12-month venograms. The fiducial line was defined by drawing a straight line through the center of the pineal gland that was orthogonal to the recording head to bony landmark on the skull on the 3-month venogram I the sagittal view (**eFigure 1** in the **Supplement**).

The pineal gland and the bony landmark on the skull identified on the 3-month venogram were used to identify the corresponding fiducial line on the 12-month venogram.

Feasibility endpoints

The three exploratory endpoints were signal fidelity and stability over 12 months, number of decoded switches, and use of the system for digital device control. Signal fidelity and stability was evaluated by calculating effective signal bandwidth with the subject at rest in each training session. The bandwidth was calculated over multiple non-overlapping segments and defined as the highest frequency band with mean power above the noise floor.[21, 22] Number of switches refers to different types of digital commands the BCI can generate from distinct neuronal signals. A two-button mouse is an example of a device that uses cursor navigation and two switches. Number of decoded switches was evaluated by comparing balanced accuracy (mean of true positive and true negative rate) for different types of movement attempt, compared to chance-level performance with randomly assigned data.

Subjects used the device to perform routine computer tasks. The neural decoder was calibrated on periods of rest and attempted limb movement. The power in specific frequency bands, primarily targeting beta activity, was used as features to train a support vector machine or threshold classifier (see **Supplement,** ***Neural decoders***). Multiple types of click commands could be generated from the classifier's output (Figure 3). The neural decoder was initially used to generate switches in combination with eye tracking for cursor navigation to achieve computer control (BCI+ET, **Figure 1B**). Subjects completed a typing test, evaluated by correct characters per minute (CCPM), selection accuracy (percentage of correct characters), and response accuracy (percentage of correct words). No word prediction was used. Subjects were tested for the ability to perform instrumental activities of daily living using the system. The email task involved navigating to a web browser and sending email. The texting task involved sending a message with a messaging application. The finance task involved logging in to an online banking account and checking the balance. The shopping task involved navigating to an online store, adding items to the cart, and checking out. Subjects also used the system to express care needs to the caregiver. Usage of the system was evaluated by the research team and collected in a diary.

A proof-of-concept for computer control using the BCI without eye tracking was investigated in the final subject (BCI-only; **Figure 1C**). The subject made selections using BCI from an automatic item scanner by attempted movement. The BCI-only system was evaluated using the typing test, a custom item scanner for answering yes/no questions, and ability to send text messages.

Statistical analysis

This first-in-human safety study did not involve formal hypothesis testing. Serious adverse events were recorded from time of enrollment, and non-serious adverse events from 14 days before implant, until the 12-month follow-up visit. Adverse events are presented as number of events and subjects experiencing an event. Categorical variables are presented with counts, and continuous variables as mean (standard deviation).

Results

From May 2019 to June 2021, five subjects were enrolled in the study (**Table 1**). All were identified by author SCML (Calvary Healthcare Bethlehem, Victoria, Australia) and referred to Royal Melbourne Hospital for study procedures. Four subjects satisfied all preoperative requirements and went on to receive the implant. One subject was withdrawn from the study because of isolated transverse sinus drainage observed in pre-implant MRI. Mean age at enrollment was 61 years (standard deviation 17 years). All subjects were male and had severe upper-limb paralysis, four with amyotrophic lateral sclerosis (ALS) and one with primary lateral sclerosis (PLS). Subjects had varying impairment in lung function and speech capability at enrollment.

The recording device was implanted in the SSS adjacent to the precentral gyrus and connected to the electronics unit implanted in an ipsilateral subcutaneous infraclavicular pocket for all four subjects. Post-operative imaging demonstrated that the electrode array self-expanded to conform to the curvature and diameter of the blood vessel. On average, the total procedure took 232 (52) minutes (range:155-273 minutes; **eTable 1** in the **Supplement**), including intraoperative testing of the device following implantation. Cumulative fluoroscopy exposure time was 43 (8) minutes. Three subjects were discharged within 48 hours and one subject remained in hospital for an additional day. All subjects attended their scheduled visits, and there were no unscheduled visits. Some study visits occurred later than scheduled due to COVID-19 restrictions.

Safety endpoints

In the primary endpoint evaluation, there were no device-related serious adverse events leading to death or permanent disability during the implantation and the 12-month follow-up period. No serious adverse device effects or unrelated serious adverse events occurred during the study. There were eight adverse device effects, which were classified as mild and resolved without intervention (**Table 2** and **eTable 2** in the **Supplement**). The non-serious events included headache and bruising at the incision sites. Subjects 1 and 3 died from complications of ALS unrelated to the device 12 months and 1 month after completion of the study, respectively.

For the secondary endpoints, review of the 3- and 12-month CT venograms found no target vessel occlusion or thrombosis in any of the four subjects. Mean absolute difference in the distance between the distal electrode and the fiducial line at 3 and 12-month venogram was 0.45 (0.28) millimeters, indicating no clinically meaningful change in device position (**Figure 2** and **eFigure 1** in the **Supplement**).

Feasibility endpoints

The signal bandwidth for the four subjects was 233 (16) Hz (range: 206-245 Hz). Bandwidth remained stable throughout the 12-month period, with standard deviation across all sessions ranging from 7-32 Hz for the four subjects (**Figure 3A**). Between five and seven different attempted movements (including rest) could be decoded in all subjects. Mean accuracy for 2-class decoding (e.g., rest and bilateral ankle movements) was 85.2% (7.9%), 3-class decoding was 68.3% (12.5%), and ≥5-class decoding was 41.1% (8.0%) (**Figure 3C**).

Subjects initially used click actions from BCI with eye tracking for cursor movement (BCI+ET) to achieve computer control. Study subjects all received at-home training on use of the device (**eTable 3** in the **Supplement**). Subject 1 was able to perform routine computer tasks by the ninth session; all other subjects performed routine tasks in the first session. With help of a caregiver, subjects were able to voluntarily use the system at home without any intervention from the research team after Session 12 for Subject 1 and after Session 2 for all others. Subjects controlled the system with selection accuracy of 93.9% (1.8%) at 16.6 (5.6) CCPM, where 97.2% (2.6%) of the total text produced was correct (1147 total words typed: **Figure 3D**). Subjects used the BCI+ET decoder to achieve computer control and perform everyday digital tasks, including email, text, shopping, and finance tasks for Subjects 1, 2, and 4, and the finance task for Subject 3.

In four sessions of testing, Subject 4 was able to use the BCI-only decoder without eye tracking, to make selections from five different options with a 97.4% (4.2%) accuracy (**eFigure 2** in the **Supplement**). The subject used the BCI-only system to answer all ten yes/no questions correctly in two separate sessions, and successfully used the system for sending text messages without eye tracking.

Subjects in the study who were under regular care of the referring investigator expressed satisfaction and fulfillment from regaining the ability to perform everyday tasks on the computer. The perceived benefit was subject-specific: increased communication speed for one subject who previously used eye tracking alone, communication with friends and family overseas for another subject, and the ability to organize a music collection for another subject. The system operates with a commercial software on a laptop computer. Use of familiar applications on a laptop computer, as opposed to specialized equipment requiring additional training, could have contributed to the positive experience in feeling connected.

Discussion

This prospective first-in-human clinical trial of an endovascular BCI was completed with no device-related serious adverse events or persistent neurological deficits. There was no vascular occlusion, thrombosis, or device migration observed at 3 and 12 months. There was stable signal bandwidth, and subjects were able to use the implant for routine digital activities such as texting, emailing, personal finance, online shopping, and communication of care needs. By the end of the trial, the final subject used the BCI system alone without an eye tracker to type, hold a simple conversation, and send text messages.

The safety profile was consistent with previous literature on dural venous sinus stenting. In a systematic review reporting on long-term safety data for 473 patients from 24 studies who were implanted with a intracranial venous stent for treatment of IIH, major neurological complications including thrombosis were found to be less than 2%.[15] Mean follow-up for 368 subjects was 18.3 months. Results of the present study are consistent with these findings, showing no evidence of development of thrombosis on the intravascular component of the device for the four subjects in the 12-month study. No stenosis was observed. Use of dual antiplatelet therapy for 3 months with aspirin continued for at least one year, in a regimen consistent with literature on venous stenting, appeared to be effective. Due to location of the recording device in the venous system, there is a theoretical risk of proximal migration. In an assessment with CT venography at 3 and 12 months, there was no evidence of clinically significant movement. Hemostasis at the point of jugular puncture was achieved with manual compression. Local bruising was observed at the incision site, and one subject experienced hematoma without mass effect or requirement for surgical drainage.

Manual compression is typically used for venous access hemostasis; however, jugular access is not routinely performed for neurointerventional procedures. The lack of serious adverse events in a cohort of ALS patients is unusual and reflects the effective selection of subjects who had adequate pulmonary function, received respiratory support if necessary, and had no comorbidities at enrollment. Study subjects experienced progression of ALS, as was expected.

One subject did not undergo implant due to unilateral venous drainage, detected during screening procedures. In a representative sample of 600 patients, stenosis or hypoplasia that may potentially impede flow was detected by CT in one transverse sinus in 33% of patients. However, stenosis with contralateral hypoplasia occurred in just 1% of patients.[23] This fraction is a reasonable approximation of the number of patients who would be at risk if thrombus occurred. In this first-in-human study, we adopted a conservative approach by excluding the subject. As further safety data accumulate, it may be possible for such patients to undergo the implant.

The endovascular electrode array records electrocorticographic (ECoG) signals resulting from sensorimotor cortex activity. Signal quality of subdural and endovascular arrays has been found to be comparable.[19] Intracortical microelectrode arrays achieve greater spatial resolution but may be susceptible to diminished effectiveness over time.[25-27] ECoG signals from implanted subdural arrays have been used to decode motor activity in severely impaired patients,[7, 8] however, long-term clinical data are limited. For example, subdural ECoG BCI implanted in one patient with locked-in syndrome was reported to remain functional for over three years.[24] A subdural electrode array in a patient with anarthria recorded speech-related cortical activity for over one and a half years.[8] A subdural ECoG system for seizure detection recorded high-frequency activity for up to 2.1 years in 15 patients.[22] Data from the present feasibility study suggest that endovascular ECoG may provide a stable signal suitable for long-term recordings from a permanently implanted device.

The use of a pre-implant target marker to guide neurointerventional device delivery is novel. Co-registering a motor cortex marked pre-implant structural MRI with an intra-operative three-dimensional digital subtraction angiography enabled live visualization of the target location by the interventionalist during the procedure. The target markers were positioned at the anterior and posterior margins of the precentral gyrus at the level of the SSS. fMRI was not required for co-registration of the target location. There was a small margin of error in device deployment posteriorly resulting in greater than expected overlap of postcentral gyrus. Future work may assess the utility of positioning distal electrodes at the

supplementary motor area given prior work demonstrating the value of decoding signal from this brain region.[28]

System uptake and training appeared to compare favorably with other experiences with BCI.[29] Although subjects in the present study could adequately use an eye tracker, not all paralyzed individuals have this ability. All subjects in the study initially used an eye tracker to perform two-dimensional cursor navigation and demonstrate instrumental activities of daily living, such as online shopping and texting. Over the course of the study, the system was refined to create an BCI-only method of digital device control.

Limitations

There are several limitations to the first-in-human study, including small sample size. Although there was a follow-up period of 12 months, it is desirable to evaluate usage of the system over multiple years. The patient group was homogeneous, with all subjects being male, of European ancestry, and their motor impairment caused by either ALS or PLS. The declining health status of subjects introduced variables such as respiratory artifact and decreased mobility. Varying decoding strategies were used during the study. A challenge for future BCI studies will be establishing a fixed decoding algorithm, or one that adapts to the patient without requiring manual changes and frequent regulatory updates. Such an algorithm will reduce the variability in the training protocols experienced by the subjects. The endovascular approach included a requirement for dual antiplatelet therapy for 3 months and aspirin for 12 months.

Conclusions

In this prospective, open-label, first-in-human study conducted in Australia, an endovascular motor neuroprosthesis BCI implanted in the SSS of four patients with severe paralysis was associated with no serious adverse events and no occlusion of target vessels or device migration during the 12-month follow-up period. The BCI maintained a stable signal throughout the study and all subjects successfully controlled a computer with the BCI. Endovascular access to the sensorimotor cortex offers an alternative to BCI technologies where electrodes are placed in or on the dura by open-brain surgery. Safety and feasibility data from the first-in-human study indicate that it is possible to record neural signals from a blood vessel, and the favorable safety profile could promote wider and more rapid translation of BCI to people with paralysis.

Author Contributions

Drs. Mitchell and Lee had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Mitchell and Lee served as co–first authors, with equal contribution to the manuscript.

Clinical trial screening and recruitment: Lee, Mathers, Campbell, Mitchell.

Neurointerventional procedure: Mitchell, Morokoff, D.L. Williams, Balabanski, C. Williams, Vrljic, Bush.

Peri-procedural care: Campbell, Mitchell, Morokoff, Lee, Balabanski, D.L. Williams, Howard, Irving, Drummond, Desmond.

Experimental design: Oxley, Opie, Yoo, Mocco, Morokoff, Mitchell, D.L. Williams, Denison, O'Brien, Grayden, Balabanski, MacIsaac, Sharma.

Data collection: Yoo, Mitchell, Morokoff, Balanski, Campbell, Lee, Weber, Vrljic.

Data analysis: Yoo, Opie, Oxley, Denison, Grayden, Liebeskind, Mocco.

Manuscript drafting: Yoo, Oxley, Opie, Mocco.

Critical revision of the manuscript for important intellectual content: Oxley, Yoo, Opie, Mitchell, Campbell, Grayden, Lee, Weber.

All authors reviewed and edited the manuscript. Oxley and Mitchell verified the data.

Data Sharing

Data from this study will not be made available to others because of sponsor data ownership and limited consent provided by study subjects.

Declaration of Interests

The study sponsor, Synchron, was involved in collection, analysis, and interpretation of the data, patient recruitment, writing of the manuscript, and decision to submit the manuscript for publication. The

corresponding author had full access to data in the study and all authors reviewed the manuscript and made the decision to submit for publication. Drs. Oxley, Opie, and Yoo are employees of Synchron. Drs. Oxley, Opie, Yoo, and Sharma report stock options and Drs. Denison and Mocco report consulting fees from Synchron during conduct of the study. Drs. Oxley, Opie, and Yoo report issued and pending patents for sensing or stimulating activity of tissue.

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References

1. Armour BS, Courtney-Long EA, Fox MH, Fredine H, Cahill A. Prevalence and Causes of Paralysis-United States, 2013. *Am J Public Health*. Oct 2016;106(10):1855-7. doi:10.2105/AJPH.2016.303270

2. Hochberg LR, Bacher D, Jarosiewicz B, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature*. May 17 2012;485(7398):372-U121. doi:10.1038/nature11076

3. McKinsey & Company. Disruptive technologies: Advances that will transform life, business, and the global economy. https://www.mckinsey.com/~/media/mckinsey/business%20functions/mckinsey%20digital/our%20insights/disruptive%20technologies/mgi_disruptive_technologies_full_report_may2013.pdf. Accessed September 6, 2022

4. Benabid AL, Costecalde T, Eliseyev A, et al. An exoskeleton controlled by an epidural wireless brain–machine interface in a tetraplegic patient: a proof-of-concept demonstration. *The Lancet Neurology*. 2019;18(12):1112-1122.

5. Vilela M, Hochberg LR. Applications of brain-computer interfaces to the control of robotic and prosthetic arms. *Handb Clin Neurol*. 2020;168:87-99. doi:10.1016/B978-0-444-63934-9.00008-1

6. Collinger JL, Wodlinger B, Downey JE, et al. High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet*. Feb 16 2013;381(9866):557-64. doi:10.1016/S0140-6736(12)61816-9

7. Vansteensel MJ, Pels EG, Bleichner MG, et al. Fully implanted brain–computer interface in a locked-in patient with ALS. *New England Journal of Medicine*. 2016;375(21):2060-2066.

8. Moses DA, Metzger SL, Liu JR, et al. Neuroprosthesis for Decoding Speech in a Paralyzed Person with Anarthria. *N Engl J Med*. Jul 15 2021;385(3):217-227. doi:10.1056/NEJMoa2027540

9. Willett FR, Avansino DT, Hochberg LR, Henderson JM, Shenoy KV. High-performance brain-to-text communication via handwriting. *Nature*. May 2021;593(7858):249-254. doi:10.1038/s41586-021-03506-2

10. Arya R, Mangano FT, Horn PS, Holland KD, Rose DF, Glauser TA. Adverse events related to extraoperative invasive EEG monitoring with subdural grid electrodes: a systematic review and meta-analysis. *Epilepsia*. 2013;54(5):828-839.

11. Hedegärd E, Bjellvi J, Edelvik A, Rydenhag B, Flink R, Malmgren K. Complications to invasive epilepsy surgery workup with subdural and depth electrodes: a prospective population-based observational study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2014;85(7):716-720.

12. Rolston JD, Ouyang D, Englot DJ, Wang DD, Chang EF. National trends and complication rates for invasive extraoperative electrocorticography in the USA. *J Clin Neurosci*. May 2015;22(5):823-7. doi:10.1016/j.jocn.2014.12.002

13. Schmidt RF, Wu C, Lang MJ, et al. Complications of subdural and depth electrodes in 269 patients undergoing 317 procedures for invasive monitoring in epilepsy. *Epilepsia*. 2016;57(10):1697-1708.

14. Leishangthem L, SirDeshpande P, Dua D, Satti SR. Dural venous sinus stenting for idiopathic intracranial hypertension: An updated review. *Journal of Neuroradiology*. 2019;46(2):148-154.

15.Saber H, Lewis W, Sadeghi M, Rajah G, Narayanan S. Stent Survival and Stent-Adjacent Stenosis Rates following Venous Sinus Stenting for Idiopathic Intracranial Hypertension: A Systematic Review and Meta-Analysis. *Interv Neurol*. Oct 2018;7(6):490-500. doi:10.1159/000490578

16.Opie NL, John SE, Rind GS, et al. Chronic impedance spectroscopy of an endovascular stent-electrode array. *Journal of neural engineering*. 2016;13(4):046020.

17.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. *Nature biomedical engineering*. 2018;2(12):907-914.

18.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*. Mar 2016;34(3):320-7. doi:10.1038/nbt.3428

19.Oxley TJ, Opie NL, Rind GS, et al. An ovine model of cerebral catheter venography for implantation of an endovascular neural interface. *J Neurosurg*. Apr 2018;128(4):1020-1027. doi:10.3171/2016.11.JNS161754

20.Oxley TJ, Yoo PE, Rind GS, et al. Motor neuroprosthesis implanted with neurointerventional surgery improves capacity for activities of daily living tasks in severe paralysis: first in-human experience. *J Neurointerv Surg*. Feb 2021;13(2):102-108. doi:10.1136/neurintsurg-2020-016862

21.Bundy DT, Zellmer E, Gaona CM, et al. Characterization of the effects of the human dura on macro- and micro-electrocorticographic recordings. *J Neural Eng*. Feb 2014;11(1):016006. doi:10.1088/1741-2560/11/1/016006

22.Nurse ES, John SE, Freestone DR, et al. Consistency of Long-Term Subdural Electrocorticography in Humans. *IEEE Trans Biomed Eng*. Feb 2018;65(2):344-352. doi:10.1109/TBME.2017.2768442

23.Durst CR, Ornan DA, Reardon MA, et al. Prevalence of dural venous sinus stenosis and hypoplasia in a generalized population. *J Neurointerv Surg*. Nov 2016;8(11):1173-1177. doi:10.1136/neurintsurg-2015-012147

24.Pels EGM, Aarnoutse EJ, Leinders S, et al. Stability of a chronic implanted brain-computer interface in late-stage amyotrophic lateral sclerosis. *Clin Neurophysiol*. Oct 2019;130(10):1798-1803. doi:10.1016/j.clinph.2019.07.020

25.Fernandez E, Greger B, House PA, et al. Acute human brain responses to intracortical microelectrode arrays: challenges and future prospects. *Front Neuroeng*. 2014;7:24. doi:10.3389/fneng.2014.00024

26.Gunasekera B, Saxena T, Bellamkonda R, Karumbaiah L. Intracortical recording interfaces: current challenges to chronic recording function. *ACS Chem Neurosci*. Jan 21 2015;6(1):68-83. doi:10.1021/cn5002864

27.Obidin N, Tasnim F, Dagdeviren C. The Future of Neuroimplantable Devices: A Materials Science and Regulatory Perspective. *Adv Mater*. Apr 2020;32(15):e1901482. doi:10.1002/adma.201901482

28.Yoo PE, Hagan MA, John SE, et al. Spatially dynamic recurrent information flow across long-range dorsal motor network encodes selective motor goals. *Hum Brain Mapp*. Jun 2018;39(6):2635-2650. doi:10.1002/hbm.24029

29.Nuyujukian P, Albites Sanabria J, Saab J, et al. Cortical control of a tablet computer by people with paralysis. *PLoS One*. 2018;13(11):e0204566. doi:10.1371/journal.pone.0204566

List of Tables

Table 1. Baseline characteristics of study subjects

Table 2. Safety endpoints

Table 1. Baseline characteristics of study subjects

Number of subjects	**5**
Age at enrollment	61 (17) years
Sex	5 males
	0 females
Diagnosis	4 amyotrophic lateral sclerosis
	1 primary lateral sclerosis
Forced vital capacity	71% (20%)
Speech capacity	3 normal,
	1 dysarthric
	1 very limited
Medical Research Council muscle strength assessment	
Finger	3.0 (1.6)
Wrist	3.2 (0.8)
Elbow	3.6 (0.9)
Shoulder	3.4 (1.3)
Hip	4.2 (0.4)
Knee	4.4 (0.5)
Foot plantar flexion	4.2 (1.0)
Foot dorsiflexion	3.2 (2.4)

Values reported are mean (standard deviation).

Table 2. Safety endpoints

Primary endpoint	**Events**	**Subjects with event**
Device-related serious adverse events resulting in death or permanently increased disability in 12-month follow-up	**0**	**0**
Secondary endpoints	**Events**	**Subjects with event**
Migration at 3 months	**0**	**0**
Migration at 12 months	**0**	**0**
Target vessel occlusion at 3 months	**0**	**0**
Target vessel occlusion at 12 months	**0**	**0**
Adverse events	**Events**	**Subjects with event**
Serious adverse device effects [a]	**0**	**0**
Serious adverse events	**0**	**0**
Adverse device effects [a]	**8**	**4**
Severe	0	0
Moderate	0	0
Mild	8	4
Bruising at incision sites	4	4
Hematoma near jugular vein insertion site	1	1
Anemia	2	2
Post-operative fatigue	1	1

[a] Definitely or probably related to device or procedure.

List of Figures

Figure 1. Motor neuroprosthesis system overview

Figure 2. Endovascular electrode array placement and migration across a 12-month period

Figure 3. Feasibility evaluations of an endovascular brain-computer interface

Figure Legends

Figure 1. **Motor neuroprosthesis system overview**

Panel A shows a schematic of the fully implanted BCI. Device with electrodes is implanted in blood vessel of brain (top and inset) and connected to IRTU electronics unit in subcutaneous pocket (lower middle). IRTU communicates with external ERTU, which relays signal to signal control unit for controlling a laptop computer or tablet. **Panel B** shows BCI used with an eye tracker for computer control. ET is used to move the cursor, and BCI is used to click. **Panel C** shows the BCI used without eye tracking for computer control. An item scanner highlights items in sequence, and the BCI is used to click an item when it is highlighted. BCI=brain computer interface. IRTU=internal receiver telemetry unit. ERTU=external receiver telemetry unit.

Figure 2. Endovascular electrode array placement and migration across a 12-month period

Panel A shows the location of the recording device in the superior sagittal sinus adjacent to motor cortex. The precentral gyrus can be identified immediately anterior to the central sulcus (curved cyan line). Image at left shows a 3D rendering of the pre-implantation MRI with regions of significant activation during attempted movement and the implanted electrodes (green crosses). Image at right shows a 3D rendering of CT taken 3 months after implantation. **Panel B** shows stable device position at 3 and 12 months after implantation. Bars represent distance of the anterior-most electrode from a fiducial point measured from CT at 3 months (cyan) and 12 months (magenta) after implantation, depicting sub-millimeter differences between time points for all patients (mean 0.45 mm, standard deviation 0.28 mm). Middle image shows magnified CT taken before, 3 and 12 months after the implantation. Right image

shows whole-head CT at 12 months after implantation. 3D=three-dimensional. CT=computed tomography.

Figure 3. Feasibility evaluations of an endovascular brain-computer interface

Panel A shows the signal bandwidth for all four subjects measured across a 12-month period. Shading depicts standard deviation across channels. **Panel B** shows the average (left) and single trial (right) spectrogram of neural activity during movement attempt for Subject 4. Feature selection for classification was subject specific, with beta band (13-30 Hz) power chosen in this example. The gray time-series trace depicts the 13-30 Hz bandpass filtered signal, and the black traces depict beta power normalized to the pre-movement rest period. Time 0 indicates cued attempted movement onset. Shaded areas indicate standard error of the mean across trials. **Panel C** shows offline movement classification balanced accuracy for all four subjects. Colored area shows the accuracy calculated with cross-validation; grey area shows chance-level accuracy calculated by shuffling the labels. **Panel D** shows performance of online BCI control for all four subjects. Left panel depicts correct characters per minute, middle panel depicts character accuracy, and the right panel depicts response accuracy from typing test. Errors bars indicate standard deviation across sessions.