Interim Safety Profile From the Feasibility Study of the BrainGate Neural Interface System

Daniel B. Rubin, MD, PhD, A. Bolu Ajiboye, PhD, Laurie Barefoot, APRN, Marguerite Bowker, BSN, RN, Sydney S. Cash, MD, PhD, David Chen, MD, John P. Donoghue, PhD, Emad N. Eskandar, MD, Gerhard Friehs, MD, Carol Grant, BSN, RN, CCRN, CCRP, Jaimie M. Henderson, MD, Robert F. Kirsch, PhD, Rose Marujo, RN, Maryam Masood, MS, Stephen T. Mernoff, MD, Jonathan P. Miller, MD, Jon A. Mukand, MD, PhD, Richard D. Penn, MD, Jeremy Shefner, MD, PhD, Krishna V. Shenoy, PhD, John D. Simeral, PhD, Jennifer A. Sweet, MD, Benjamin L. Walter, MD, Ziv M. Williams, MD, and Leigh R. Hochberg, MD, PhD

Correspondence
Dr. Rubin
drubin4@mgh.harvard.edu

Abstract

Background and Objectives

Brain-computer interfaces (BCIs) are being developed to restore mobility, communication, and functional independence to people with paralysis. Though supported by decades of preclinical data, the safety of chronically implanted microelectrode array BCIs in humans is unknown. We report safety results from the prospective, open-label, nonrandomized BrainGate feasibility study (NCT00912041), the largest and longest-running clinical trial of an implanted BCI.

Methods

Adults aged 18–75 years with quadriparesis from spinal cord injury, brainstem stroke, or motor neuron disease were enrolled through 7 clinical sites in the United States. Participants underwent surgical implantation of 1 or 2 microelectrode arrays in the motor cortex of the dominant cerebral hemisphere. The primary safety outcome was device-related serious adverse events (SAEs) requiring device explantation or resulting in death or permanently increased disability during the 1-year postimplant evaluation period. The secondary outcomes included the type and frequency of other adverse events and the feasibility of the BrainGate system for controlling a computer or other assistive technologies.

Results

From 2004 to 2021, 14 adults enrolled in the BrainGate trial had devices surgically implanted. The average duration of device implantation was 872 days, yielding 12,203 days of safety experience. There were 68 device-related adverse events, including 6 device-related SAEs. The most common device-related adverse event was skin irritation around the percutaneous pedestal. There were no safety events that required device explantation, no unanticipated adverse device events, no intracranial infections, and no participant deaths or adverse events resulting in permanently increased disability related to the investigational device.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Glossary

AEs = adverse events; **BCIs** = brain-computer interfaces; **CPM** = characters per minute; **DBS** = deep brain stimulation; **IDE** = Investigational Device Exemption; **NORSE** = new-onset refractory status epilepticus; **RNS** = responsive neurostimulation; **SAEs** = serious adverse events; **SCI** = spinal cord injury; **UADEs** = unanticipated adverse device effects.

Discussion

The BrainGate Neural Interface system has a safety record comparable with other chronically implanted medical devices. Given rapid recent advances in this technology and continued performance gains, these data suggest a favorable risk/benefit ratio in appropriately selected individuals to support ongoing research and development.

Trial Registration Information

ClinicalTrials.gov Identifier: NCT00912041.

Classification of Evidence

This study provides Class IV evidence that the neurosurgically placed BrainGate Neural Interface system is associated with a low rate of SAEs defined as those requiring device explantation, resulting in death, or resulting in permanently increased disability during the 1-year postimplant period.

For many people with paralysis, the cortical substrates of motor activity, speech, and cognition are intact but functionally disconnected from the nerves and muscles that enable movement and communication. Among the most physically disabled are individuals with locked-in syndrome, who have limited or no volitional muscle control.[1] Cervical spinal cord injury (SCI), brainstem stroke, muscular dystrophy, or motor neuron disease can cause similar impairments in communication and functional independence. Brain-computer interfaces (BCIs) bypass the site of pathology, transmitting information directly from cerebral cortex to an assistive technology to restore communication and improve independence.[2]

There are several classes of BCIs under development that use different sensors and decoding algorithms.[3] Intracortical BCIs use sensors that are surgically implanted on the cortical surface and can access information-rich single neurons and local field potentials without degradation in signal content from spatial averaging and bone filtering seen with nonsurgical approaches.[4] Any implanted medical device must have an adequate safety profile before clinical use so that patients, caregivers, and healthcare professionals can make informed decisions about risks and benefits.

Two reviews have addressed the safety of implanted BCIs.[5,6] One is limited to endovascular stent-electrode arrays and reports primarily on electrode performance and structural characteristics of the implanted venous sinus, which are not directly related to this study.[5] The other review includes an analysis of intracortical microelectrode arrays (including some data inferred from BrainGate trial participants); however, the only safety metric reported was duration of device implantation, which was used as a surrogate marker of days without major complication.[6]

In 2004, the first trial of the BrainGate Neural Interface System was launched.[7] The objectives of the ongoing prospective, open-label, nonrandomized feasibility trial are to assess the safety of the BrainGate system and its feasibility to control assistive technology by people with paralysis. The BrainGate trial has accrued more than 12,000 participant-days of safety data, with more than 17,000 array-days (some participants received 2 arrays simultaneously), including 2 research participants who used the system for more than 5 years.[8,9] In this study, we report all safety data from all BrainGate clinical trials from 2004 to December 31, 2021. We compared BrainGate's safety profile with other implanted devices approved for neurologic disorders including epilepsy and movement disorders and seek to answer the primary research question of whether the neurosurgically placed BrainGate Neural Interface System was associated with a low rate of serious adverse events (SAEs) defined as those requiring device explantation, resulting in death, or resulting in permanently increased disability during the 1-year postimplant period.

Methods

The BrainGate consortium is engaged in a multicenter, prospective, open-label, nonrandomized feasibility study (ClinicalTrials.gov Identifier: NCT00912041) of an implanted BCI system (Figure). The study is performed under an Investigational Device Exemption (IDE) from the US Food and Drug Administration and approved by the Mass General Brigham Institutional Review Board (Protocol #: 2009P000505; CAUTION: Investigational Device. Limited by Federal Law to Investigational Use). Adults aged 18–75 years with quadriparesis caused by SCI, brainstem stroke, motor neuron disease, or

Figure Components of the Investigational BrainGate Neural Interface System
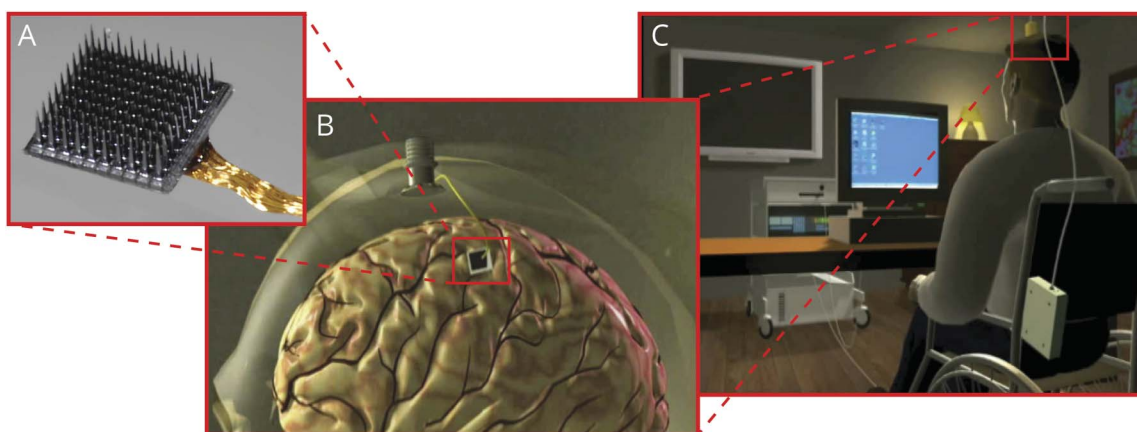
(A) The recording sensor is a "Utah" microelectrode array (NeuroPort, prior manufacturer: Cyberkinetics Neurotechnology Systems; present manufacturer, Blackrock Neurotech; both, Salt Lake City, UT) consisting of 96 electrodes arranged on a 4 × 4-mm platform. During surgical placement, the microelectrode array is placed onto the cortical surface of the predetermined brain region of interest and a pneumatic inserter wand is used to apply a precise amount of force to the array, inserting the microelectrodes through the pial surface and into the upper layers of cortex. (B) The microelectrode array is connected through a bundle of gold wires to a percutaneous pedestal, which is affixed to the outer table of the cranium by titanium surgical screws. When not in use, the percutaneous pedestal is covered by a disposable fitted cap. (C) Signals from the pedestal are transmitted either wirelessly[10] or through a cable to a signal processor, decoding computers, and output devices. Images published with permission from the authors.

muscular dystrophy have been recruited primarily through referral by a neurologist or other clinician at 1 of 7 clinical sites in the United States (Tables 1 and 2). Please see the eMethods, links.lww.com/WNL/C565 section in the Supplement for additional details.

Results

Between 2004 and December 2021, 14 people enrolled in the BrainGate trial (Tables 2 and 3), of whom 2 are currently engaged in research. Four people were enrolled in a first-generation BrainGate clinical trial between 2004 and 2009. One participant was enrolled in a first-generation BrainGate trial when it ended in 2009; she transitioned into and enrolled in the second-generation BrainGate trial and participated for another 2 years. In addition to that "transitional" participant, 10 people, including 2 active participants, enrolled in the second-generation BrainGate trial.

Three participants were female and 11 were male. Eleven participants identified as White, 1 as Asian, 1 as Black, and 1 as Other. One participant identified as Hispanic ethnicity. All participants had quadriparesis, including 6 with SCI, 6 with ALS, and 2 with brainstem stroke. The median age at array implantation was 51 years (range 24–66). For participants with SCI or brainstem stroke, the median time from injury or stroke to implant was 8.5 years (range 3–11). For participants with ALS, the median time from diagnosis to implant was 5.5 years (range 2–7); we note that people with ALS often have symptoms for months or years before receiving a formal diagnosis. The median duration of device implantation was 774 days (range 296–1,994). There were 12,203 implant-days across all 14 participants (or 17,927 array-implant-days, counting participants with 2 arrays twice). Six participants

underwent elective explant of the BrainGate device at the conclusion of their participation in the trial; 1 participant requested removal of the percutaneous pedestal but not the intracranial microelectrode array. Six participants died of progression of their underlying neurologic disease while enrolled. In no case was a participant's death related to the investigational device or clinical trial; there were no unanticipated adverse device effects. Other than transitioning in 2013 from placing 1 to 2 arrays per participant and the introduction of a wireless signal transmitter in 2017,[10] there have been no substantial modifications to the underlying hardware.

Among the 14 participants, there were 342 adverse events (AEs); the median number of AEs per participant was 21, and the range was from 0–62 AEs (Table 3). Two hundred seventy-four of the 342 (80.1%) AEs were unrelated to the investigational device; most were medical events common in people with tetraplegia (e.g., urinary tract infection, pneumonia, and decubitus ulcer). There were no device-related AEs that resulted in a participant's death, a participant exiting the clinical trial, a need to explant the device, or the inability to continue participating in research sessions.

Of the 68 device-related AEs (median 2 per participant, range 0–17), approximately half (35/68) were related to irritation, sensitivity, a sense of tightness, or other changes of the skin around the surgical incision or pedestal site. In many cases, these were caused by overly enthusiastic preventive care of the pedestal site by a caretaker or family member, and these resolved after reeducating caregivers. One participant was treated with oral antibiotics for a localized skin infection around a pedestal site and required no further treatment. In more than 17,000 array-days of implant, there were no

Table 1 Clinical Trial Inclusion and Exclusion Criteria (as of December 31, 2021)

Inclusion criteria: patients must meet all the following inclusion criteria to be enrolled in the study

1. The patient must be between 18 and 75 y of age.
2. The patient must be able to speak understandably or if unable to speak understandably must have 1 reliable means of communication. (Note: All documents and materials involved with the BrainGate System will be in English. Patients who can speak must be able to speak in English. Ability to speak understandably or communicate reliably is determined by investigator opinion.)
3. If the patient has a diagnosis of spinal cord injury or stroke, the patient must be tetraplegic where tetraplegia is defined as follows:
   a. Complete or incomplete tetraplegia (bilateral C2-C4), or
   b. Complete or incomplete tetraplegia with muscle power grade in the dominant arm at specific cord levels as follows:
      i. ≤3/5 at C5
      ii. ≤2/5 at C6
      iii. <2/5 at C7–T1
   Note (1): Incomplete tetraplegia with muscle power grade in the dominant arm of 4/5 at C5 is acceptable if the patient's dominant arm motor function is not being used in any significant way for functional activities such as bathing, grooming, dressing, and mobility.
   Note (2): The participant may be using his/her nondominant arm for functional activities, though the nondominant arm must have a muscle power grade of ≤4/5.
4. If the patient has a diagnosis of ALS, progressive muscle atrophy, adult-onset spinal muscle atrophy, or muscular dystrophy, the patient must have severe physical impairment with impairment, defined as follows:
   a. Tetraplegia, or,
   b. Tetraparesis with muscle grade at C5-T1 cord levels ≤4/5. For patients who have 4/5 power at the C5-T1 muscle groups, patient must report either:
      i. A subjective decline in upper extremity function in the preceding 4 mo or
      ii. Anarthria or severe dysarthria with progressive decline in the preceding 4 mo.
5. For patients with ALS, confirmed clinical diagnosis of "Clinically Definite ALS," "Clinically Probable ALS," or "Clinically Probable Laboratory-Supported ALS" not caused by HIV.
6. If the patient is tetraplegic because of a spinal cord injury, a minimum of 12 mo must have elapsed postinjury and recovery must have plateaued at least 3 mo before baseline screening.
7. In the opinion of the Investigator, the patient must have a life expectancy greater than 6 mo.
8. The patient's chronic care environment must be within a 3-h drive of the study site.
9. The patient is expected to remain available (geographically stable) for at least 15 mo after enrollment.
10. The patient must be willing and committed to maintaining the evaluation schedule, which includes frequent visits to the Investigator's office and visits of sponsor personnel to the patients' home.
11. In the opinion of the investigator, the patient must have a stable psychosocial support system.
12. The cause of the patient's motor impairment must be identified.
13. The patient must be willing to allow the investigator to coordinate care with his or her primary care physician or neurologist, if necessary, for the duration of the study.
14. The patient must have previous experience with a personal computer.
15. The patient's scalp must be devoid of any lesions or skin breakdown precluding surgery.
16. The patient must be able to voluntarily provide informed consent in accordance with site institutional policies and permit the release of their personal health information from the date of the injury or disease onset through the completion of the clinical study.
17. The patient must have a caregiver capable of providing the necessary daily care of the patient's skin and pedestal site.

Exclusion criteria: patients who have or meet any of the following exclusion criteria will not be enrolled in the study

1. Patients who have any active infection(s) or unexplained fever.
2. Patients who are blind or otherwise visually impaired such that extended viewing of a computer monitor would be difficult even with ordinary corrective lenses.
3. Patients who consume more than 1 alcoholic beverage per day.
4. Patients receiving medications (such as sedatives) chronically in doses that may significantly retard motor coordination and cognitive ability.
5. In the opinion of the investigator, the patient is being actively treated for another serious medical, neurological, or psychiatric disease or disorder that could seriously affect the patient's ability to participate in the study or undergo craniotomy and implantation of the NeuroPort Sensor.
6. Patients receiving chronic oral or intravenous steroids or immunosuppressive therapy.
7. Patients who have had active cancer within the past year (other than adequately treated basal cell or squamous cell skin cancer) or require chemotherapy.
8. Patients who have uncontrolled insulin-dependent diabetes mellitus.
9. Patients currently receiving anticoagulant medication for a clotting disorder. NOTE: Patients receiving prophylactic anticoagulation solely for the prevention of deep venous thrombosis are not excluded but must be able to have their prophylactic anticoagulation suspended temporarily for the surgical procedure and immediate postoperative period.
10. For patients with spinal cord injury, patients who have a history of autonomic dysreflexia within the past 3 mo that required urgent evaluation and pharmacologic intervention prescribed by a physician.
11. Patients who have had seizures in the past 3 mo.
12. Patients who require routine MRI.
13. Patients with osteomyelitis.
14. Patient has a severe skin disorder that causes excessive skin sloughing, lesions, or breakdown of the scalp.
15. Patients of childbearing age who are pregnant, lactating, or not using adequate birth control.
16. Patients whose condition in the opinion of the investigator would compromise the patient's safety in the study or whose condition poses an inordinately high surgical risk.
17. Patients with a history of myocardial infarction or cardiac arrest or with intractable cardiac arrhythmias, unless preoperative evaluation by a board-certified physician in internal medicine or anesthesiology indicates that an underlying cardiac abnormality presents no or only minimal additional perioperative risk to the patient.
18. Patients who have any type of cranially implanted generator, such as a cochlear implant or deep brain stimulator.
19. Patients with an implanted hydrocephalus shunt.
20. Patients who have attempted suicide in the past 12 mo.
21. Patients who are currently enrolled in any other investigational study that may interfere with the time commitments required of this study.

intracranial or deep tissue (e.g., bone) infections related to the investigational device or any device-related infections requiring hospitalization, intravenous antibiotics, or device removal.

Seven participants had perioperative AEs. In most cases, these were common postoperative problems such as low-grade fever, nausea, or headache. One participant had postoperative

Table 2 Enrollment by Clinical Site

Clinical site	No. of participants enrolled
Massachusetts General Hospital	5
VA Providence Health Care System	3
Stanford University	2
Case Western Reserve University	1
Spaulding Rehabilitation Hospital	1
University of Chicago	1
Sargent Rehabilitation Center	1

hypertension that required treatment with intravenous antihypertensives. A participant with a history of pulmonary embolism who was on chronic anticoagulation developed respiratory distress on postoperative day 3 (before the planned resumption of therapeutic anticoagulation on postoperative day 14). He was diagnosed with recurrent pulmonary embolus and restarted therapeutic anticoagulation with resolution of his symptoms. Given that anticoagulation was held for device placement, this event was classified as related to the study.

In 3 of the 5 participants who had elective array explantation after more than a year (a sixth participant had the pedestal but not the array explanted), array removal was without complications or AEs. In all participants who had elective array removal, it was noted that the arachnoid had grown over the array. For 1 participant who had the BrainGate array explanted at the conclusion of her participation in the trial, surgery revealed that the array was well adhered to the brain and that, as expected, a thin, semitranslucent layer of arachnoid had grown over the array. The arachnoid was incised to partially expose the array, which was then removed. A small piece of tissue secured within the forceps (approximately 5 × 5 × 1 mm intact; measured after dislodgement from the sensor as a triangular piece of tissue 7.0 mm in its longest dimension) was lightly adherent to the electrode side of the array. Histology confirmed that the tissue included meninges and underlying superficial cortex. There was no clinical impact on the participant, who returned to her residence and usual activities on the first postoperative day. In another participant who underwent explantation at the conclusion of trial participation, after removal of the array and all visible portions of reference wires, the surgical investigator noted that the dura was densely adherent to the brain in the area surrounding the array; it was felt unsafe to perform further dissection to retrieve the full length of the 2 15 cm × 0.127-mm diameter reference wires. Postoperative CT imaging demonstrated a short curvilinear hyperdensity within the extra-axial space, suggestive of either a short length of retained reference wire or calcification along the track of the prior location of a reference wire. There were no clinical sequelae.

Two participants, both of whom had a history of traumatic brain injury in addition to SCI, had seizures in the postimplantation period. In one case, the participant was noted intraoperatively to have a small but nonetheless atypical quantity (approximately 2 mL) of subarachnoid hemorrhage around 1 of the 2 implanted arrays. Four days later, he experienced 2 self-limited focal motor seizures, for which he was hospitalized and treated with levetiracetam. He continued levetiracetam as an outpatient, experienced no further seizures, and subsequently participated in the trial for 17 months without any other neurologic AEs. This participant had not received a prophylactic antiseizure medication postoperatively because this practice had not yet been incorporated into the study protocol. Another participant had a single seizure on postoperative day 4; he too was admitted to the hospital, started on levetiracetam, and had no further seizures. He remains enrolled in the clinical trial and has been participating in research sessions for more than 2 years. He had been prescribed a prophylactic antiseizure medication, but 2 doses were missed during the transition from hospital to home. These participants' prior traumatic brain injuries were believed to have increased their risk for seizures.

Before the 2 postoperative seizures described earlier, 1 participant experienced new-onset refractory status epilepticus (NORSE).[11] This person had quadriplegia and locked-in syndrome due to a brainstem stroke 5 years before enrollment. He had no history of seizures, traumatic brain injury, or other known predisposing comorbidities. After placement of a single array, he had been participating in research sessions for more than 18 months when this SAE occurred. On the morning of the event, the participant's family awoke to a ventilator dyssynchrony alarm and found him unresponsive, with chaotic eye movements. He was transported to Massachusetts General Hospital, where EEG demonstrated status epilepticus. He was treated with phenytoin, levetiracetam, lacosamide, and phenobarbital and intravenous anesthetics (propofol, midazolam, and ketamine) to achieve a burst-suppression pattern on EEG. The pedestal site was clean, and there was no evidence of localized skin infection or irritation. A CT scan of the brain demonstrated no acute structural pathology, and CSF analysis revealed normal levels of protein and glucose, 3–5 white blood cells per microliter, and negative results for viral and bacterial testing. Ultimately, the etiology of his seizures remained unknown, although pneumonia or urinary tract infections were included in the differential diagnosis. Continuous EEG monitoring demonstrated a left temporal lobe origin of his seizures, and the epileptologists involved in his care noted that the cortical location of the BrainGate array (the "hand-knob" of the precentral gyrus of the left frontal lobe) was comparatively less involved in ictal activity. By hospital day 4, he had resolution of all seizure activity. His EEGs evolved after the period of burst-suppression and initially showed generalized slowing with frequent epileptiform discharges; over subsequent days, the background rhythm improved considerably with re-emergence of a posterior dominant rhythm and only rare low-amplitude sharp waves. His antiseizure regimen was

Table 3 Summary of Demographic and Safety Data

Participant	Sex	Etiology	SCI motor level–ASIA impairment scale	Age at implant	Time from injury/ diagnosis to implant (y)	No. of arrays	Duration of implant (d)	Array-implant d	Status	Total AEs	Total SAEs	Possibly, probably, or definitely device-related or procedure- related AEs	Possibly, probably, or definitely device-related or procedure- related SAEs	Skin-related device AEs[a]	Surgery-related AEs[a]
S1	M	SCI	C4-A	24	3	1	484	484	Explanted	0	0	0	0	0	0
S2	M	SCI	C4-A	55	6	1	790	790	Explanted	2	1	0	0	0	0
A1	M	ALS		36	7	1	298	298	Deceased	3	2	1	0	1	0
S3	F	Stroke[b]		51	10	1	1,994	1994	Explanted	21	1	5	0	3	2
T1	F	ALS		48	7	1	307	307	Deceased	13	3	2	0	2	0
T2	M	Stroke[b]		66	5	1	950	950	Explanted	35	10	2	1	0	0
T3	M	ALS		52	2	1	440	440	Deceased	21	6	1	0	0	1
T5	M	SCI	C4-C	63	9	2	1,962	3,924	Enrolled	27	14	3	0	3	0
T6	F	ALS		50	7	1	1,216	1,216	Explanted	62	9	11	0	6	1
T7	M	ALS		57	3	2	552	1,104	Deceased	48	5	10	1	6	3
T8	M	SCI	C4-A	53	8	2	1,104	2,208	Deceased	12	8	3	0	2	0
T9	M	ALS		51	4	2	759	1,518	Deceased	54	13	17	1	6	3
T10	M	SCI	C4-A	34	9	2	518	1,036	Explanted	14	10	5	2	2	1
T11	M	SCI	C4-B	35	11	2	829	1,658	Enrolled	30	5	8	1	4	1

Abbreviations: AEs = adverse events; ASIA = American Spinal Injury Association; SAEs = serious adverse events; SCI = spinal cord injury.
[a] Possibly, probably, or definitely device-related or procedure-related AEs are inclusive of skin-related device AEs and surgery-related device AEs.
[b] Participants S2 and T2 enrolled after tetraplegia caused by ischemic brainstem stroke.

Table 4 Detailed Adverse Event Summary Table

	Total no. of AEs (SAEs)	No. of participants w/AE (SAE)	Median [range] no. of AEs per participant	Total no. of device-related or study-related AEs (SAEs)	No. of participants w/device-related AE (SAE)
Skin/soft tissue/musculoskeletal					
Skin reaction (at/near pedestal)	35 (0)	10 (0)	2 [0–7]	35 (0)	10 (0)
Rash, skin/soft tissue reaction (remote from pedestal; including decubitus ulcers and soft tissue injury)	45 (7)	11 (5)	2 [0–13]	1 (0)	1 (0)
Musculoskeletal pain/injury (remote from pedestal)	9 (3)	6 (3)	0 [0–3]	2 (0)	2 (0)
Infectious					
Urinary tract infection	35 (13)	10 (6)	1 [0–9]	0 (0)	0 (0)
Pneumonia	24 (16)	6 (6)	0 [0–8]	0 (0)	0 (0)
Fever	13 (0)	7 (0)	0.5 [0–4]	3 (0)	3 (0)
Sepsis	15 (15)	7 (7)	0.5 [0–5]	0 (0)	0 (0)
Cellulitis	1 (0)	1 (0)	0 [0–1]	1 (0)	1 (0)
Otitis media/upper respiratory infection	5 (0)	2 (0)	0 [0–4]	0 (0)	0 (0)
Respiratory					
Other respiratory event/respiratory failure (e.g., tracheostomy complication, aspiration, mucus plug, etc)	34 (11)	7 (6)	0.5 [0–9]	0 (0)	0 (0)
Pulmonary embolus	2 (2)	2 (2)	0 [0–1]	1 (1)	1 (1)
Gastrointestinal					
Constipation	11 (4)	7 (4)	0.5 [0–3]	0 (0)	0 (0)
Nausea/vomiting	6 (1)	3 (1)	0 [0–4]	1 (0)	1 (0)
Complications of gastrotomy tube	5 (0)	3 (0)	0 [0–2]	1 (0)	1 (0)
Diarrhea	2 (0)	2 (0)	0 [0–1]	0 (0)	0 (0)
Bowel perforation/volvulus	4 (4)	2 (2)	0 [0–2]	0 (0)	0 (0)
Colitis	2 (2)	1 (1)	0 [0–2]	0 (0)	0 (0)
Hepatitis/cholelithiasis	2 (0)	2 (0)	0 [0–1]	0 (0)	0 (0)
Ileus	1 (0)	1 (0)	0 [0–1]	0 (0)	0 (0)
Genitourinary/renal					
Nephrolithiasis/hydronephrosis/hematuria/ suprapubic catheter complications	11 (6)	4 (2)	0 [0–6]	0 (0)	0 (0)
Acute kidney injury/renal failure	3 (2)	3 (2)	0 [0–1]	0 (0)	0 (0)
Urinary retention	1 (0)	1 (0)	0 [0–1]	0 (0)	0 (0)
Neurologic/psychiatric					
Headache	13 (0)	4 (0)	0 [0–6]	8 (0)	4 (0)
Fatigue	5 (0)	4 (0)	0 [0–2]	3 (0)	2 (0)
Delirium	5 (2)	4 (1)	0 [0–2]	1 (0)	1 (0)
Spasticity	5 (3)	4 (2)	0 [0–2]	0 (0)	0 (0)
Anxiety	4 (0)	3 (0)	0 [0–2]	0 (0)	0 (0)
Seizure	3 (3)	3 (3)	0 [0–1]	3 (3)[a]	3 (3)

Continued

Table 4 Detailed Adverse Event Summary Table *(continued)*

	Total no. of AEs (SAEs)	No. of participants w/AE (SAE)	Median [range] no. of AEs per participant	Total no. of device-related or study-related AEs (SAEs)	No. of participants w/device-related AE (SAE)
Miscellaneous					
Abnormal laboratory values (e.g., hyperglycemia, hyponatremia, and hyperkalemia)	22 (3)	6 (2)	0 [0–9]	0 (0)	0 (0)
Anemia	11 (4)	6 (1)	0 [0–4]	2 (0)	2 (0)
Abnormal blood pressure	7 (1)	3 (1)	0 [0–4]	1 (1)	1 (1)
Abnormal heart rate	4 (3)	2 (2)	0 [0–3]	0 (0)	0 (0)
Conjunctivitis	2 (0)	2 (0)	0 [0–1]	0 (0)	0 (0)
Anaphylaxis	1 (1)	1 (1)	0 [0–1]	0 (0)	0 (0)
Benign prostatic hypertrophy	1 (0)	1 (0)	0 [0–1]	0 (0)	0 (0)
Chest pain	1 (1)	1 (1)	0 [0–1]	0 (0)	0 (0)
Sore throat/dry mouth	2 (0)	2 (0)	0 [0–1]	0 (0)	0 (0)
Trace (approximately 2 mL) intraoperative subarachnoid hemorrhage	1 (1)	1 (1)	0 [0–1]	1 (1)	1 (1)
Muffled hearing	1 (0)	1 (0)	0 [0–1]	1 (0)	1 (0)
Deep vein thrombosis	1 (0)	1 (0)	0 [0–1]	0 (0)	0 (0)

Abbreviations: AEs = adverse events; SAEs = serious adverse events.
[a] Two participants had *definitely related* postoperative seizures; 1 participant had seizures that were not believed to be device-related or study-related but were formally characterized as "*possibly related*" because a device relationship could not be definitively ruled out.

slowly tapered down to only lacosamide, and he was discharged to a rehabilitation setting. He resumed participating in research sessions approximately 4 months after this AE and participated in research sessions for another 8 months before concluding his participation in the trial.

While not an AE, we also note that for the participants who had the investigational device (array(s) and/or pedestal) electively explanted at their conclusion of participation in the trial, additional surgical consideration was required to close the well-healed scalp site(s) after removal of the pedestal(s). In participants with a thicker scalp, clean debridement and closure of the healed pedestal site was directly achieved. In a participant with a thinner scalp, additional loosening of the underlying tissue was necessary to close the site, which contributed to postoperative headaches. In addition, and while also not AEs, 2 participants in the first IDE had unexpected abrupt changes (or initial absence) of recording quality. In 1 participant, nonoperative provisional repair of an external component of the percutaneous pedestal was performed 6 months after device placement; the wire bonds had failed at the landing grid assembly within the pedestal, and conductive epoxy was manually placed on each bond site to attempt to restore connections. The initial source of this failure was attributed to the method of sterilization of the devices, which was subsequently changed.

Approximately 4.5 months later, the number of useable signals recorded from the array again dropped abruptly, with moderate recovery of signals. There was no clinical change in the participant coinciding with this change in signals nor was this event believed to represent a risk to the health, safety, or welfare of the participant, and it was reported as an unexpected change in device performance. It is unknown whether this loss of signals was due to failure of the previous repair or an unrelated event, such as array dislodgement/displacement from coughing (which the patient had reported) or other participant-specific factors. After the initial device failure and discussion with the device manufacturer, modifications were made to the sterilization procedures used before delivery to investigators. In a second participant during this early period, caregivers inadvertently applied a sudden axial force to the participant's head and pedestal while placing the participant back into bed (by too forcefully contacting the headrest of the bed with the participant's head). There was a substantial return of recording quality within a month, though with considerably more day-to-day variability than previously seen. Overall, this study provides Class IV evidence that the neurosurgically placed BrainGate Neural Interface system is associated with a low rate of SAEs, defined as those requiring device explantation, resulting in death, or resulting in permanently increased disability during the 1-year postimplant period.

Table 5 Anti-infective Procedures/Protocols

Preimplantation anti-infective precautions

Methicillin-resistant *Staphylococcus aureus* (MRSA) screening is performed at the baseline evaluation or up to 6 wk before implant surgery. Patients with MRSA colonization may be treated and retested after the colonization is believed to have been eradicated (e.g., nasal bactroban treatment). If colonization is still present after the treatment period, implantation may be postponed for up to 4 mo until satisfactory results or the patient will be exited from the study. To reduce the chance of infection during surgery, the patient will be bathed once daily for the 3 d before the implant by a healthcare professional using a chlorhexidine-based antimicrobial solution (e.g., Hibiclens, ChloraPrep, DuraPrep) from head to toe. The hair must be thoroughly washed using the chlorhexidine-based soap on all 3 occasions. Before bathing, the patient should have a skin patch test to rule out any allergies to the antimicrobial wash. Antibiotics will be used perioperatively; antibiotic choices should follow current routine guidelines.

Postimplantation anti-infective precautions

To help reduce the risk of infection, all caregivers who are to come in contact with the patient above the neck are to have clipped nails (no long, artificial or polished nails) and must clean their hands with a waterless, alcohol-based hygiene product such as Purell before donning sterile nonlatex gloves.
A Biopatch will continue to be placed around the pedestal(s) to help reduce the potential for infection. The hair should be clipped periodically around the pedestal(s) to allow the Biopatch to maintain contact with the patient's skin.
A pedestal cap must remain on the pedestal(s) at all times with the exception of when the patient cable or wireless transmitter is attached. Pedestal caps may be reused. Pedestal caps should be visibly evaluated on removal and before placement, cleaned of any visible debris with a 70% isopropyl alcohol swab, and allowed to dry completely. Pedestal caps should be replaced with a new cap if debris cannot be removed or if the cap is damaged. The external surfaces of the pedestal caps are cleaned with ChloraPrep swabs after placement on the pedestal.

Instructions given to participants and caregivers for skin care around the pedestal connector

This procedure will require some assistance from your caregiver. The pedestal site(s) should be cleaned at least once every 3 d or as required. Do not clean with the Patient Cable headstage in place. Only clean around the pedestal site(s) when the Pedestal cap(s) is/are on. Instructions for the caregiver are as follows:
1. Open the suture removal kit, which contains scissors and tweezers, being careful not to touch the inside of the pouch or equipment. Set aside.
2. Carefully open 1 or 2 ChloraPrep pouches and 1 sterile gloves pouch, being careful not to touch the inside of the pouches or their contents. Open 1 ChloraPrep pouch if only 1 pedestal and 2 ChloraPrep pouches for 2 pedestals. Set these aside so that you can easily remove the ChloraPrep applicator(s) and gloves.
3. Open a Biopatch and drop the sterile Biopatch into the sterile suture removal kit. If there are 2 pedestals, open 2 Biopatches. Set aside.
4. Wash hands and then disinfect hands with alcohol gel.
5. Put on the sterile gloves using a sterile technique.
6. Using the tweezers, carefully remove the old Biopatch(es) from the pedestal site(s) and discard. Take time to observe the pedestal site(s) for clinical signs of infection, such as redness of the skin resulting from inflammation (erythema), drainage, skin discoloration caused by the escape of blood into the tissues (ecchymosis), pain, or unusual redness along lead tunnel or pedestal connector. If any clinical signs for infection are present, the study doctor should be contacted immediately.
7. Clean around the pedestal site with ChloraPrep:
   a. Carefully remove the ChloraPrep applicator from the pouch and activate ChloraPrep flow (typically by pressing side wings on the applicator).
   b. Apply the ChloraPrep solution to an area 2 inches in diameter surrounding the pedestal site by gently moving the friction pad from the pedestal outward while holding the Applicator downward and gently squeezing the wings to release the solution.
   c. After you have applied the solution to the skin, use the applicator to wipe the outside of the pedestal cap, working from the bottom up.
   d. Discard the applicator.
   e. If there are 2 pedestals, clean 1 pedestal completely (using this procedure from 7a to 7d) and when you have finished, immediately move on to the second pedestal using the second, already-opened ChloraPrep applicator to clean it (using this procedure from 7a to 7d).
8. Let the ChloraPrep solution dry completely. This may take a full 5 minutes.
9. Using a new Biopatch, enlarge the hole by using the sterile scissors to allow the Biopatch(es) to rest easily around the pedestal(s).
10. Place the Biopatch(es) around the base of the pedestal(s), ensuring contact with the surrounding skin. If you have 2 pedestals, place 1 Biopatch around the first pedestal and place another Biopatch around the second pedestal.
Note: To help reduce the risk of infection, it is important that all caregivers who touch the patient above the neck have clipped nails (no long, artificial, or polished nails).
Bathing: It is OK for you to bathe. If you are taking a shower, it is advised that you wear a shower cap. You should not wash your hair for the first 5 d after the surgery. After that, when washing your hair, it is important to keep the pedestal cap(s) on. After washing your hair or taking a shower, you should clean the area around the pedestal(s) with the ChloraPrep applicator and replace the Biopatch(es) by following the directions for "Skin Care around the Pedestal Connector" listed earlier. Do not shower with the patient cable in place, including the Wireless Headstage. Only shower when the pedestal cap(s) are on. The pedestal cap(s) should remain on the pedestal(s) at all times when a patient cable is not in place and should only be removed by an authorized study technician or your trained caregiver. If the pedestal cap(s) seem loose or comes off, please contact your study technician immediately.

Discussion

The investigational BrainGate Neural Interface system has an encouraging safety record, with more than 17,000 person-array implant-days of data. All 12 participants who were enrolled for more than 1 year met the primary safety endpoint of not having the device removed for safety reasons during the 1-year postimplant evaluation. Although 6 SAEs were classified as possible, probably, or definitely device-related or procedure-related, there were no device-related SAEs that resulted in death or permanently increased disability during the 1-year postimplant evaluation period (Two participants died of complications from ALS before the 1-year evaluation).

Device safety has also remained reassuring over the 2 to 5+ years that 8 participants have been enrolled.

The most common AE (Table 4) was local skin reaction and/or sensitivity around the pedestal, in most cases related to expected postsurgical changes or excessive cleaning with chlorhexadine solution as part of the infection control protocol. The most notable adverse safety events were postoperative seizures that occurred 4 days postdevice implantation in 2 participants, both of whom had a history of traumatic brain injury and had not received consistent postoperative seizure prophylaxis. Neither participant had any further seizures nor did these events affect their ability to continue to

participate in the clinical trial or in their usual activities of daily living. Although preclinical data did not suggest the need for seizure prophylaxis, the trial protocol now includes 1 week of postoperative prophylactic antiseizure medication (a common practice for supratentorial craniotomies). In a participant who had a BrainGate device for more than 5 years, a small amount of tissue was adherent to the array during explantation; for 4 other participants, the array was removed without any adherent tissue. A recently published study demonstrated comparable findings in 6 Utah arrays explanted from 2 other human research participants,[12] which may be an important consideration as this technology moves toward wider use.

The participant who experienced NORSE illustrates how medical device research can raise dilemmas at the interface of research ethics and medical ethics. Similar to many trials of novel medical devices, the ethical premise under which participants are recruited and provide informed consent to this study is that there *is risk* to participation and *no benefit* to the individual; the only benefit is that gained by society through the development of a system that could improve communication and/or mobility for people with paralysis. In this context, the NORSE SAE raised important questions that required immediate decisions. As with any clinical trial, an SAE of uncertain relationship to study procedures required rapid and comprehensive evaluation. The decision whether to remove the array was explicitly made on clinical grounds alone, and on this basis, the recommendation was to not remove the array because the neurosurgical intervention would be without a clear clinical indication and could increase the risk for additional seizures and other complications. However, during extensive discussions with the participant's family, they conveyed that he had repeatedly expressed enjoyment and altruistic fulfillment by contributing to scientific advances that could benefit people with paralysis and would be saddened to learn that he could no longer participate in the trial because the investigational device had been removed. While his family's impression of the best patient/participant–centered approach was consistent with the clinical impression for managing this SAE, the investigational team realized that the original "no benefit" premise did not fully capture the factors involved in deciding whether to remove the device. The presence of personal intangible benefits such as altruistic fulfillment might be considered in the design, review, and conduct of trials that seem to be without benefit to individuals considering enrollment.

This work has some limitations warranting discussion. The most significant, from a clinical trials standpoint, is the lack of a control arm; for myriad ethical and logistical reasons, an experimental control (e.g., surgery without device use) would not be feasible. We are nonetheless reassured by our findings that the percutaneous BrainGate system has a safety profile, to date, in a population of people with tetraplegia, which is comparable with fully implanted deep brain stimulation (DBS) devices approved for the treatment of certain movement disorders and the responsive neurostimulation (RNS)

device approved for the treatment of partial-onset seizures refractory to 2 or more antiepileptic medications. Large studies with more than 100 patients undergoing DBS implantation have reported infection rates between 3% and 5% of patients,[6,13-15] of which up to half have required hardware removal.[15] Other complications included subcortical hemorrhage, subdural hematoma, venous infarction, and seizure; these were observed in 1%–5% of patients in case series.[16,17] A meta-analysis of 1,714 patients who underwent DBS for essential tremor reported an infection rate of 3.4%, hemorrhage rate of 2.4%, and seizure rate of 2.3%.[18] Device-specific complications, such as lead migration, misplaced leads, and implantable pulse generator failure have occurred at rates of approximately 3%–5%.[19] In the long-term trial of the NeuroPace RNS, a chronically implanted neurostimulator used in the treatment of medication refractory epilepsy, the only device-related SAE observed in >5% of the 230 enrolled participants was implantation site infection (in 12.1%),[20] with no instances of meningitis or parenchymal brain infection (although bone flap osteomyelitis was observed).[21] Some patients also required operative repair of damaged leads.[22] Seven patients (2.7%) had hemorrhage, 4 of which were associated with implantation surgery and had no neurologic sequaelae.[20]

Our clinical research experience with a percutaneously connected intracortical neural recording system has included only a single device-related skin infection and no bone or CNS infections. We ascribe this to a thorough preoperative skin cleansing protocol (consisting of 3 days of a daily preoperative full body wash with chlorhexidine soap); careful intraoperative attention to sterile procedure; a rigorous caregiver protocol for maintaining an aseptic environment around the percutaneous pedestals; and chlorhexidine-impregnated patches (BioPatch) around the pedestal site (Table 5). However, we recognize that our study is underpowered to detect rare events such as intracranial infection. Given the low incidence in the general population (1.38 cases per 100,000 population per year in 2006–2007),[23] our current study, with 33.43 person-years of observation, has a power of less than 1% to detect a doubling in the rate of intracranial infection at a 0.05 level of significance. Had we observed intracranial infections, we could query for a statistical deviation from the background rate, if present.

A second limitation in comparing the safety profile of this device with other chronically implanted neurotechnologies is that the people enrolled in the BrainGate trial have different neurologic conditions than the populations enrolled in other neurotechnology trials. People with quadriparesis may have greater contact with caregivers attending to health-related needs than those with epilepsy or Parkinson disease; consequently, comparisons with devices intended for ambulatory populations are imperfect. In addition, while our participants consented to the risk of worsening paralysis because of array placement on motor cortex (which has not been observed), given the significant baseline weakness required to enroll,

subtle changes in motor function may occur below the threshold of clinical perception. With that said, the ongoing BrainGate trial and subsequent studies using similar research protocols and the Blackrock NeuroPort array were informed by numerous animal studies of safety, histology, and chronic device function[24-27] and with the understanding that other research studies for participants with paralysis who could benefit from future intracortical BCI devices would continue to inform the field.[9,28-30] In addition to our 14 participants, as of April 2022, there have been approximately 21 other human research participants who have participated in chronic intracortical BCI trials at academic centers in the United States,[28,29,31-33] China,[34] and Germany.[35] Chronically implanted electrocorticography grids have been placed for similar research in the United States and The Netherlands,[31,36] and 4 investigational Stentrode devices have been placed in Australia.[37,38] Several neurotechnology companies are also preparing clinical trials of implanted BCI systems, reinforcing the growing interest in developing and deploying a clinically useful implanted BCI.

While safety is the *sine qua non* of any successful medical technology, quantifiable metrics of efficacy are important to establish clinical utility and to help individuals to evaluate the technology within their personal value system of risks and benefits. Our current feasibility study is being conducted partly to inform the development of metrics upon which efficacy could be evaluated in a subsequent pivotal trial. Prior publications from our group and others have demonstrated the potential for intracortical BCIs to improve the quality of life for people with paralysis. With highly accurate 2-dimensional cursor control that can be calibrated within minutes of initial use,[39] BrainGate participants have controlled a point-and-click interface to communicate at 30–40 correct characters per minute (CPM).[40,41] Using handwriting decoding techniques, a communication rate of 90 CPM has been demonstrated,[9] approaching the range of an able-bodied individual typing on a smartphone keyboard.[42] In addition to developing methods for improved communication, the investigational BrainGate system and related intracortical BCIs have been used to control assistive robotics[7,28,43] and a participant's own arm and hand through functional electrical stimulation.[33,44] These demonstrations suggest the potential to provide a meaningful improvement in quality of life.

While an exhaustive review of the potential benefits of the iBCI approach is beyond the scope of this article, the "risk/benefit" analysis—particularly as considered by an individual with paralysis contemplating the use of different assistive technologies—will be central to the future success of these devices. For example, some participants have entered the study frustrated, for a host of reasons, by the utility of their eye-gaze systems. Despite relative preservation of eye movements in the earlier stages of ALS, subtle changes in motor control, slowness of saccades, fatigue in supporting musculature, and progressive ophthalmoparesis can all affect performance with these systems.[45] Limited data suggest communication rates of 10–20 CPM in people with ALS; in a limited head-to-head study, participants communicated faster using a manual letter board than a computerized eye-gaze system.[46,47]

Furthermore, for a person with severe speech and motor impairments, the ability to use an assistive technology while visually engaging with their dialog partner—which itself has communication value—is also important. Consequently, iBCIs provide not only theoretical advantages over eye-gaze systems but also over other BCIs (implanted or EEG based) that encumber eye movements specifically to navigate communication interfaces. Given iBCIs' early demonstrations of the ability to support multidimensional, dexterous reach-and-grasp movements, to restore sensation (with some further improvement in, for example, assistive robot control),[29] the broad potential for iBCIs is clear. Despite the flexibility and range of effector control that iBCIs may provide in the future, the current percutaneous component and substantial external hardware will remain suboptimal features when compared with fully implanted or nonsurgery-requiring approaches. Both our group and others continue to work on components and systems that would permit iBCIs to become fully implanted, available to users around-the-clock, and incorporate a suite of design characteristics previously proposed.[48]

Overall, we are reassured by our findings over the past 17 years that the investigational BrainGate Neural Interface System is being deployed safely. The development of a fully implantable system, which would reduce the infection concern presented by a percutaneous component and provide more acceptable cosmesis for many users, remains an important goal of our group and others. Moreover, this trial has been conducted during and continues to benefit from a revolution in machine learning/artificial intelligence and microprocessor technology. Advances in these fields have contributed to the ongoing improvement in performance that we have observed, and we anticipate that these technical gains will only accelerate in the coming years. Of importance, these same technological advances have led to improvements in consumer assistive technology available to people with paralysis. Voice control platforms such as Siri and Alexa may allow a person with quadriplegia and intact speech naturalistic control over their consumer electronics and home environment, and head-mounted virtual reality/augmented reality technology may provide additional channels of communication for people who have lost the ability to speak. However, no one technological solution will work best for everyone. Indeed, many able-bodied individuals prefer to type or text rather than use voice recognition to maintain the privacy of their communication from the people in their immediate surroundings, and much of the drive for iBCIs is not only to restore communication but also to restore mobility through intuitively controlled functional electrical stimulation or soft/wearable robotics. Intracortical BCIs also are being developed as key components of closed-loop neuromodulation therapies that may improve the management of disorders of mood or cognition.[49,50] Ultimately, the extraordinary potential utility

of implanted BCIs will reflect the personal risk/benefit assessment of the people for whom these devices are being developed.

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Neurotechnology Inc. to Stanford University and from there on to the inventors. This pertains to Patents 6, 8, 10, 12, and 13 as numbered below. Royalties are paid by Neuralink Corp to Stanford University and from there on to the inventors. This pertains to Patents 6, 8, 12, and 13 as numbered below. K.V. Shenoy is a consultant to Neuralink Corp and CTRL-Labs (Meta Platforms/Facebook), reports honoraria from a variety of universities (no corporations), reports honoraria from the NIH for reviewing grants (study section), reports support for attending meetings/travel from universities and professional societies to give invited talks, was on the Scientific Advisory Board of CTRL-Labs, Inc (now Meta Platforms/Facebook), is on the Scientific Advisory Board of MIND-X Inc, Inscopix Inc. and Heal Inc, and discloses the following patents: (1) Processed neural signals and methods for generating and using them. Patent Number: US 6,609,017 B1. Date of patent: Aug. 19, 2003. Krishna V. Shenoy, Richard A. Andersen, Sohaib A. Kureshi. California Institute of Technology. ISSUED. (2) Cognitive state machine for prosthetic systems. Publication Number: US 2003/0023319 A1. Date of patent: July 10, 2001. Richard A. Andersen, Bijan Pesaran, Partha Mitra, Daniella Meeker, Krishna V. Shenoy, Shiyan Cao, Joel W. Burdick. California Institute of Technology. ISSUED. (3) Cognitive state machine for prosthetic systems. International Publication No.: WO 03/005,934 A3. Date of patent: January 23, 2003. Richard A. Andersen, Bijan Pesaran, Partha Mitra, Daniella Meeker, Krishna V. Shenoy, Shiyan Cao, Joel W. Burdick. California Institute of Technology. ISSUED. (4) Decoding of neural signals for movement control. Patent No.: US 7,058,445 B2. Date of patent: June 6, 2001. Caleb T. Kemere, Gopal Santhanam, Byron M. Yu, Teresa H. Meng, Krishna V. Shenoy. Stanford University. ISSUED. (5) Brain-machine interface utilizing interventions to emphasize aspects of neural variance and decode speed and angle. Pub. No.: US 2015/0245928 A1. Publication Date: September 3, 2015. Jonathan C. Kao, Chethan Pandarinath, Paul Nuyujukian, Krishna V. Shenoy. Stanford University. ISSUED. (6) Brain machine interface. Patent No.: US 8,792,976 B2. Date of patent: July 29, 2014. Vikash Gilja, Paul Nuyujukian, Cynthia A. Chestek, John P. Cunningham, Byron M. Yu, Stephen I. Ryu, Krishna V. Shenoy. Stanford University. ISSUED. (7) Brain machine interfaces incorporating neural population dynamics. Patent No.: US 9,095,455 B2. Date of patent: August 4, 2015. Jonathan C. Kao, Paul Nuyujukian, Mark M. Churchland, John P. Cunningham, Krishna V. Shenoy. Stanford University. ISSUED. (8) Brain-machine interface utilizing a discrete action state decoder in parallel with a continuous decoder for a neural prosthetic device. Patent No.: US 9,373,088 B2. Date of patent: June 21, 2016. Paul Nuyujukian, Jonathan C. Kao, Krishna V. Shenoy. Stanford University. ISSUED. (9) Task-outcome error signals and their use in brain-machine interfaces. Patent No.: US 10,779,764 B2. Date of patent: September 22, 2020. Nir Even-Chen, Krishna V. Shenoy, Jonathan C. Kao, Sergey Stavisky. Stanford University. ISSUED. (10) Multiplicative recurrent neural network for fast and robust intracortical brain-machine interface decoders. Patent No.: US 10,223,634 B2. Date of patent: Mar. 5, 2019. David Sussillo, Jonathan C. Kao, Sergey Stavisky, Krishna V. Shenoy. Stanford University. ISSUED. (11) Systems and methods for virtual keyboards for high dimensional controllers. Patent No.: US 10,949,086 B2. Publication Date: March 16, 2021. Nir Even-Chen, Krishna V. Shenoy. Stanford University. ISSUED. (12) Systems and methods for decoding intended speech from neuronal activity. Pub. No.: US 2019/0333505 A1. Publication Date: October 31, 2019. Sergey Stavisky, Krishna V. Shenoy, Jaimie M. Henderson. Stanford University. PENDING. (13) Systems and methods for decoding intended symbols from neural activity. Pub. No.: US 2021/0064135 A1. Publication Date: March 4, 2021. Krishna V. Shenoy, Jaimie M. Henderson, Frank Willett. Stanford University. PENDING; J. D. Simeral reports no disclosures relevant to the manuscript; J.A. Sweet is currently on the scientific advisory board of Koh Young Inc. and was previously on the scientific advisory board and received stock options from Helius Medical Technologies; B.L. Walter has received consulting fees from Abbott Labs. Z.M. Williams reports no disclosures relevant to the manuscript. The MGH Translational Research Center has a clinical research support agreement with Neuralink and Synchron, for which L.R. Hochberg provides consultative input. Go to Neurology.org/N for full disclosures.

Publication History

Appendix Authors

Name	Location	Contribution
Daniel B. Rubin, MD, PhD	Center for Neurotechnology and Neurorecovery (CNTR), Department of Neurology, Massachusetts General Hospital, Boston, MA; Department of Neurology, Harvard Medical School, Boston, MA	Additional contributions: verified underlying data; site-responsible investigator and clinical coinvestigator responsible for clinical monitoring and adverse event reporting for 1 or more participants; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
A. Bolu Ajiboye, PhD	Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH; Louis Stokes Cleveland Department of Veterans Affairs Medical Center, FES Center of Excellence, Rehab. R&D Service, Cleveland, OH; School of Medicine, Case Western Reserve University, Cleveland, OH	Additional contributions: scientific team leader responsible for directing neuroscientific inquiries including feasibility testing; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design

Name	Location	Contribution
Laurie Barefoot, APRN	Center for Neurotechnology and Neurorecovery (CNTR), Department of Neurology, Massachusetts General Hospital, Boston, MA	Additional contributions: clinical and regulatory staff who assisted in the collection and compilation of safety data; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Marguerite Bowker, BSN, RN	Center for Neurorestoration and Neurotechnology (CfNN), Rehabilitation R&D Service, Department of Veterans Affairs Medical Center, Providence, RI	Additional contributions: clinical and regulatory staff who assisted in the collection and compilation of safety data; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Sydney S. Cash, MD, PhD	Center for Neurotechnology and Neurorecovery (CNTR), Department of Neurology, Massachusetts General Hospital, Boston, MA; Department of Neurology, Harvard Medical School, Boston, MA	Additional contributions: site-responsible investigator and clinical coinvestigator responsible for clinical monitoring and adverse event reporting for 1 or more participants; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
David Chen, MD	Legs and Walking Lab, Shirley Ryan AbilityLab, Chicago, IL; Department of Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, Rehabilitation Institute of Chicago, Chicago, IL	Additional contributions: site-responsible investigator and clinical coinvestigator responsible for clinical monitoring and adverse event reporting for 1 or more participants; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
John P. Donoghue, PhD	Center for Neurorestoration and Neurotechnology (CfNN), Rehabilitation R&D Service, Department of Veterans Affairs Medical Center, Providence, RI; Department of Neuroscience, Brown University, Providence, RI; Robert J. and Nancy D. Carney Institute for Brain Science, Brown University, Providence, RI	Additional contributions: scientific team leader responsible for directing neuroscientific inquiries including feasibility testing; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design
Emad N. Eskandar, MD	Department of Neurological Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY	Additional contributions: surgical investigator; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Gerhard Friehs, MD	European University of Cyprus, Nicosia, Cyprus	Additional contributions: surgical investigator; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data

Name	Location	Contribution
Carol Grant, BSN, RN, CCRN, CCRP	Center for Neurotechnology and Neurorecovery (CNTR), Department of Neurology, Massachusetts General Hospital, Boston, MA	Additional contributions: clinical and regulatory staff who assisted in the collection and compilation of safety data; drafting/revision of the article for content, including medical writing for content; and major role in the acquisition of data
Jaimie M. Henderson, MD	Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA; Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA; Bio-X Institute, Stanford University, Stanford, CA	Additional contributions: site-responsible investigator and clinical coinvestigator responsible for clinical monitoring and adverse event reporting for 1 or more participants; surgical investigator; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
Robert F. Kirsch, PhD	Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH; Louis Stokes Cleveland Department of Veterans Affairs Medical Center, FES Center of Excellence, Rehab. R&D Service, Cleveland, OH; School of Medicine, Case Western Reserve University, Cleveland, OH; Department of Neurological Surgery, University Hospitals Case Medical Center, Cleveland, OH	Additional contributions: scientific team leader responsible for directing neuroscientific inquiries including feasibility testing; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
Rose Marujo, RN	Center for Neurotechnology and Neurorecovery (CNTR), Department of Neurology, Massachusetts General Hospital, Boston, MA	Additional contributions: clinical and regulatory staff who assisted in the collection and compilation of safety data; drafting/revision of the article for content, including medical writing for content; and major role in the acquisition of data
Maryam Masood, MS	Center for Neurotechnology and Neurorecovery (CNTR), Department of Neurology, Massachusetts General Hospital, Boston, MA	Additional contributions: clinical and regulatory staff who assisted in the collection and compilation of safety data; drafting/revision of the article for content, including medical writing for content; and major role in the acquisition of data
Stephen T. Mernoff, MD	Neurology Section, VA Providence Health Care System, Providence, RI; Department of Neurology, Alpert Medical School of Brown University, Providence, RI	Additional contributions: site-responsible investigator and clinical coinvestigator responsible for clinical monitoring and adverse event reporting for 1 or more participants; drafting/revision of the article for content, including medical writing for content; and major role in the acquisition of data

Name	Location	Contribution
Jonathan P Miller, MD	Louis Stokes Cleveland Department of Veterans Affairs Medical Center, FES Center of Excellence, Rehab. R&D Service, Cleveland, OH; School of Medicine, Case Western Reserve University, Cleveland, OH; Department of Neurological Surgery, University Hospitals Case Medical Center, Cleveland, OH	Additional contributions: surgical investigator; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Jon A. Mukand, MD, PhD	Sargent Rehabilitation Center, Warwick, RI; Department of Rehabilitation Medicine, Brown University, Providence, RI	Additional contributions: site-responsible investigator and clinical coinvestigator responsible for clinical monitoring and adverse event reporting for 1 or more participants; drafting/revision of the article for content, including medical writing for content; and major role in the acquisition of data
Richard D. Penn, MD	Section of Neurosurgery, Department of Surgery, University of Chicago, Chicago, IL; Department of Neurosurgery, Rush University Medical Center, Chicago, IL	Additional contributions: surgical investigator; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Jeremy Shefner, MD, PhD	Department of Neurology, Barrow Neurological Institute, Phoenix, AZ	Additional contributions: served as the medical monitor; drafting/revision of the article for content, including medical writing for content; and analysis or interpretation of data
Krishna V. Shenoy, PhD	Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA; Bio-X Institute, Stanford University, Stanford, CA; Howard Hughes Medical Institute at Stanford University, Stanford, CA; Departments of Electrical Engineering, Neurobiology, and Bioengineering, Stanford University, Stanford, CA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design; Additional contributions: scientific team leader responsible for directing neuroscientific inquiries including feasibility testing
John D. Simeral, PhD	Center for Neurorestoration and Neurotechnology (CfNN), Rehabilitation R&D Service, Department of Veterans Affairs Medical Center, Providence, RI; Robert J. and Nancy D. Carney Institute for Brain Science, Brown University, Providence, RI	Additional contributions: scientific team leader responsible for directing neuroscientific inquiries including feasibility testing; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design

Name	Location	Contribution
Jennifer A. Sweet, MD	Louis Stokes Cleveland Department of Veterans Affairs Medical Center, FES Center of Excellence, Rehab. R&D Service, Cleveland, OH; School of Medicine, Case Western Reserve University, Cleveland, OH; Department of Neurological Surgery, University Hospitals Case Medical Center, Cleveland, OH	Additional contributions: surgical investigator; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Benjamin L. Walter, MD	School of Medicine, Case Western Reserve University, Cleveland, OH	Additional contributions: site-responsible investigator and clinical coinvestigator responsible for clinical monitoring and adverse event reporting for 1 or more participants; drafting/revision of the article for content, including medical writing for content; and major role in the acquisition of data
Ziv M. Williams, MD	Department of Neurosurgery, Massachusetts General Hospital, Boston, MA; Program in Neuroscience, Harvard-MIT Program in Health Sciences and Technology, Harvard Medical School, Boston, MA	Additional contributions: surgical investigator; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Leigh R. Hochberg, MD, PhD	Center for Neurotechnology and Neurorecovery (CNTR), Department of Neurology, Massachusetts General Hospital, Boston, MA; Department of Neurology, Harvard Medical School, Boston, MA; Center for Neurorestoration and Neurotechnology (CfNN), Rehabilitation R&D Service, Department of Veterans Affairs Medical Center, Providence, RI; Robert J. and Nancy D. Carney Institute for Brain Science, Brown University, Providence, RI; School of Engineering, Brown University, Providence, RI	Additional contributions: verified underlying data; participated in the design and conduct of the original BrainGate trials and has been the IDE Sponsor-Investigator for this trial since 2009; site-responsible investigator and clinical coinvestigator responsible for clinical monitoring and adverse event reporting for 1 or more participants; scientific team leader responsible for directing neuroscientific inquiries including feasibility testing; drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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