Electrocorticography During Deep Brain Stimulation Surgery: Safety Experience From 4 Centers Within the National Institute of Neurological Disorders and Stroke Research Opportunities in Human Consortium

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BACKGROUND: Intraoperative research during deep brain stimulation (DBS) surgery has enabled major advances in understanding movement disorders pathophysiology and potential mechanisms for therapeutic benefit. In particular, over the last decade, recording electrocorticography (ECoG) from the cortical surface, simultaneously with subcortical recordings, has become an important research tool for assessing basal ganglia-thalamocortical circuit physiology.

OBJECTIVE: To provide confirmation of the safety of performing ECoG during DBS surgery, using data from centers involved in 2 BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative-funded basic human neuroscience projects.

METHODS: Data were collected separately at 4 centers. The primary endpoint was complication rate, defined as any intraoperative event, infection, or postoperative magnetic resonance imaging abnormality requiring clinical follow-up. Complication rates for explanatory variables were compared using point biserial correlations and Fisher exact tests.

RESULTS: A total of 367 DBS surgeries involving ECoG were reviewed. No cortical hemorrhages were observed. Seven complications occurred: 4 intraparenchymal hemorrhages and 3 infections (complication rate of 1.91%; CI = 0.77%-3.89%). The placement of 2 separate ECoG research electrodes through a single burr hole (84 cases) did not result in a significantly different rate of complications, compared to placement of a single electrode (3.6% vs 1.5%; $P = .4$). Research data were obtained successfully in 350 surgeries (95.4%).

CONCLUSION: Combined with the single report previously available, which described no ECoG-related complications in a single-center cohort of 200 cases, these findings suggest that research ECOG during DBS surgery did not significantly alter complication rates.

KEY WORDS: Deep brain stimulation, Electrocorticography, Functional neurosurgery, Movement disorders

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As part of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, in 2016, the National Institutes of Health (NIH) established a funding opportunity titled Research Opportunities Using Invasive Neural Recording and Stimulating Technologies in the Human Brain. This funding opportunity was an historic first in its requirement to focus on data collected during the course of functional neurosurgical procedures.[1] In addition, the National Institute of Neurological Disorders and Stroke (NINDS)-funded investigators joined a collaborative consortium of awardees to maximize learning and data sharing across these unique

ABBREVIATIONS: BRAIN, Brain Research through Advancing Innovative Neurotechnologies; **CI,** confidence interval; **ECoG,** electrocorticography; **ET,** essential tremor; **LFP,** local field potential; **MER,** microelectrode recording; **NIH,** National Institutes of Health; **NINDS,** National Institute of Neurological Disorders and Stroke; **PD,** Parkinson disease; **ROH,** Research Opportunities in Humans

human research paradigms. Two projects within the initial NINDS Research Opportunities in Humans (ROH) consortium were centered on the use of electrocorticography (ECoG) during the implantation of deep brain stimulation (DBS) leads, solely for research purposes.

DBS surgery provides one of the few opportunities to simultaneously record from the cortical surface and basal ganglia in humans. ECoG during DBS surgery has revealed physiological basal ganglia-cortical neural dynamics,[2-7] as well as cortical neurophysiological signatures in essential tremor (ET),[8-10] Parkinson disease (PD),[8,10-14] and dystonia.[12,15,16] Moreover, ECoG recording during active DBS has created a new era in our understanding of the mechanisms of therapeutic DBS in PD[17-20] by allowing the cortical effects of stimulation to be recorded directly from the brain surface. Additionally, ECoG studies have demonstrated the potential of cortical sensors to influence the future development of closed-loop basal ganglia DBS for movement disorders.[21-25]

Given that ECoG is not a clinically indicated step in the procedure of DBS lead implantation and that many centers worldwide are not yet familiar with implementation of this research technique, we sought to validate the original findings of Starr and colleagues.[26] These authors found that complications in patients who underwent research ECoG were not greater than historical controls. This knowledge is of critical interest to neurosurgeons, neurology partners, funding agencies, institutional review boards (IRB), and patients.

METHODS

Consent Process

Data were collected separately at 4 centers performing intraoperative ECoG recordings during DBS lead implantation, in the context of 2 separate NINDS-funded studies. At all centers, patients scheduled for awake DBS surgery, after recommendation by a multidisciplinary movement disorders team, were considered for participation. Patients were recruited between April 2014 and March 2019 at center A, between February 2017 and August 2018 at center B, between September 2010 and January 2019 at center C, and between July 2013 and May 2019 at center D. Patients consented to these studies with written informed consent and at least one in-person meeting with the neurosurgeon prior to surgery under protocols approved by the respective IRB. Additional research time was limited to 30 to 45 min per surgery.

Clinical Methods

Preoperative 3T or 1.5T magnetic resonance imaging (MRI) was obtained at all centers as part of surgical planning, with the goal of identifying a trajectory optimized to avoid traversing brain sulci, vasculature, and the lateral ventricle. A small subset of patients with non-MRI compatible cardiac pacemakers underwent computed tomography (CT) scans only. The burr hole site was typically placed at the level of the coronal suture, and its location was selected based solely on clinical criteria. Leksell stereotactic frames (Elekta) were used at centers A, B, and C, and CRW stereotactic frames (Integra) were used at center D. Patients were positioned semi-sitting. Cortical targets for aiming ECoG strip electrodes were planned on surgical navigation software and marked on the scalp. Once burr holes were made, ECoG electrodes were placed in the subdural space prior to guide tube insertion. When multiple electrode strips were used, they were positioned unilaterally. In some patients, intraoperative median nerve stimulation-induced somatosensory-evoked potentials were recorded to identify the primary sensory and motor cortices and the location of the ECoG electrodes relative to that site. Lateral skull X-rays[24] or CT scanning was performed intraoperatively to document the location of the ECoG contacts (Figure 1). Depending on the research protocol, patients participated in behavioral tasks during microelectrode recording (MER) of regions of interest along the trajectory of the planned DBS target (eg, subthalamic nucleus, globus pallidus, putamen, and substantia nigra) for clinical subcortical mapping, or after the placement of the DBS lead, from which local field potential (LFP) recordings were made. All subdural strips were removed prior to final anchoring of the DBS lead. As part of routine care, postoperative CT or MRI was obtained to verify lead position and evaluate for postoperative hemorrhage within 24 h of surgery at all centers.

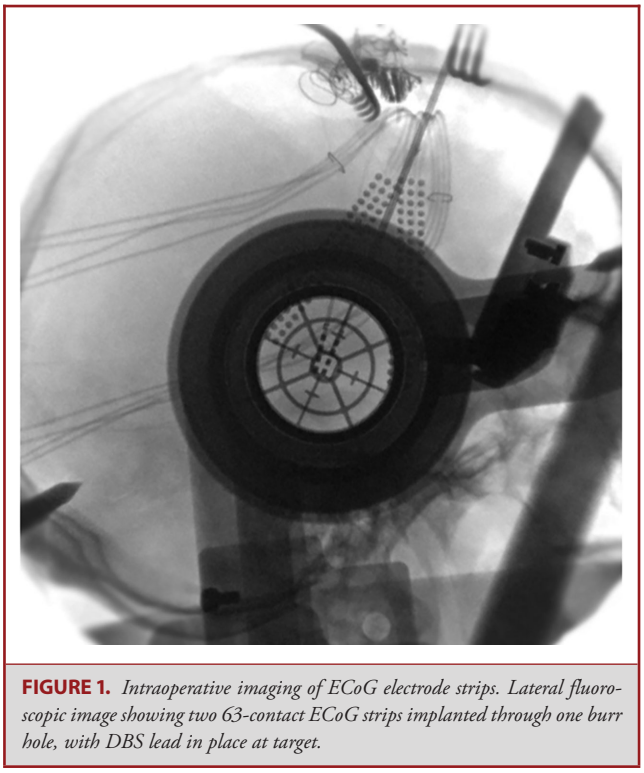

FIGURE 1. *Intraoperative imaging of ECoG electrode strips. Lateral fluoroscopic image showing two 63-contact ECoG strips implanted through one burr hole, with DBS lead in place at target.*

Study Design and Analysis

Information from each center was logged into a prospective database as part of the original interventional study design at each center. De-identified data from each institution were then compiled retrospectively using a common data dictionary and stored in a secure database. Basic demographic information was analyzed. The primary endpoint of this study was postoperative complication rate, defined as infection, intraoperative complication, or MRI abnormality that required clinical follow-up in the postoperative period. Imaging for patients with any abnormal finding on the radiology report was independently reviewed by each site's

TABLE 1. Summary of Demographics and Use of ECoG for Research

Characteristics	Parkinson disease	Essential tremor	Dystonia	Total
Median age (yr)	66 (40-82)	68 (36-84)	50 (18-70)	66
No. of procedures	264	81	17	367
No. of 2 ECoG strips used	53	22	9	84
No. of ECoG/microelectrode recording	151	11	12	177
No. of ECoG/microelectrode followed by ECoG/lead recording	119	41	4	166
No. of ECoG over sensorimotor cortex	165	77	5	250
No. of ECoG over prefrontal cortex	11	3	1	15

Note that totals may be greater than the sum of rows due to one of several uncommon indications, including obsessive-compulsive disorder (1), secondary tremor (1), atypical tremor (1), spinocerebellar ataxia (1), and refractory brachial plexopathy (1).

research team and neurosurgeon, with particular attention to whether the abnormality could be related to the placement of the research ECoG strip(s).

Complication rate 95% CIs were calculated using a Clopper-Pearson exact method. Point biserial correlations were used to test for correlation between a complication and either the number of contacts or the size (area) of ECoG strips. Fisher exact tests were used to compare complication rates in either the placement of 1 vs 2 research ECoG strips, the simultaneous use of ECoG strips and microelectrode for research recordings, or the simultaneous use of ECoG strips and DBS leads for research recordings. All statistical tests were performed using MATLAB 2017a (MathWorks) and R 3.6.1 (R Foundation for Statistical Computing).

RESULTS

A total of 433 ECoG strips were placed in 335 participants during 367 surgeries from 4 different academic medical centers in this study. Patients were implanted with DBS leads manufactured by Medtronic (263), Abbott Medical (74), or Boston Scientific (19). Simultaneous ECoG and microelectrode recording was undertaken in 177 surgeries, and simultaneous ECoG and DBS lead recording was undertaken in 166 surgeries (Medtronic, 132; Abbott, 28; Boston Scientific, 6). In 84 surgeries, 2 ECoG strips were placed. In 1 surgery, 3 ECoG strips were placed. The most common clinical indications for DBS were PD, ET, and dystonia (Table 1). ECoG strips were manufactured by PMT (99) or Adtech (334). The size of ECoG strips used varied from 55 to 95 mm in length and 8 to 9 mm in width, and the number of contacts ranged from 4 to 63 (Figure 2). Individual electrode contact sizes on ECoG strips were 1 mm (99), 2 mm (13), 4 mm (195), and 5 mm (126). The majority of electrodes covered regions that included sensorimotor cortex (250; hand = 157; vocal = 93). Other covered locations included premotor cortex (126), supplemental motor area (7), and dorsolateral prefrontal cortex (8).

Seven surgical complications occurred in total, comprised of 4 intraparenchymal hemorrhages and 3 infections, for an overall complication rate of 1.91% (CI = 0.77%-3.89%; Table 2). None of the intraparenchymal hemorrhages were observed in cortical locations, but rather occurred along the microelectrode or lead tract. No hemorrhages altered the course of a patient's care or recovery. The infection sites were the DBS generator chest pocket ipsilateral to ECoG strip placement, extender incision ipsilateral to the ECoG strip, and at the burr hole ipsilateral to ECoG strip placement. Two separate research electrodes were placed during the same surgery in 84 patients, a maneuver that did not result in a statistically significant difference in rate of complications as compared to placement of a single electrode (3.6% vs 1.5%; $P = .4$). There was no difference in outcomes when ECoG was recorded simultaneously with MER (177 patients) vs recorded simultaneously with recording from DBS leads (166 patients) (Table 3). Useable research data, defined as recordings that were sufficient in duration and fidelity to be included in the intended analyses, were obtained during 350 surgeries (95.4%). One ECoG placement was aborted because of difficulty with posterior placement, likely due to obstruction by a bridging vein, without encountering a complication. All patients were discharged on postoperative day 1 in accordance with standard clinical protocols for noncomplicated surgeries. No patients experienced delayed hematomas.

DISCUSSION

The placement of subdural strip electrodes during DBS surgery to record from the cortical surface is a powerful research tool. Each site in this study contributed the entirety of its research ECoG during DBS surgery experience, which included several years of experience prior to U01-funded work. Given that individual patients do not receive direct therapeutic benefit from these maneuvers, it is imperative that we understand the risks associated with research ECoG during DBS surgery. In a multi-institutional cohort, we verified that intraoperative use of ECoG for research purposes during implantation of DBS electrodes does not result in higher complications rates than would be expected to occur with standard DBS surgery.[26]

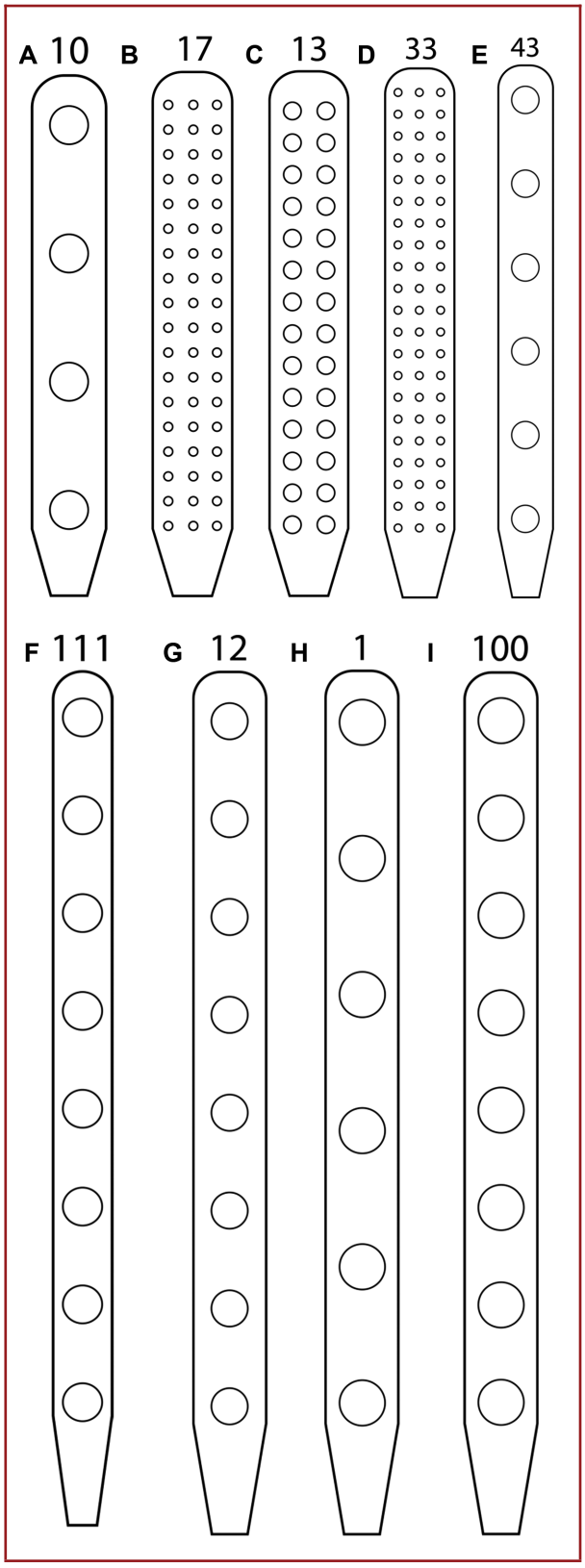

FIGURE 2. *Subdural strips used for research ECoG recordings. Strips and contacts are drawn to scale, with number of times used above each strip.* **A**, *Ad-tech 55 × 8 mm strip with four 4-mm contacts.* **B**, *PMT 59.5 × 9 mm strip with fifty-four 1-mm contacts.* **C**, *Ad-tech 60 × 9 mm strip with twenty-eight 2-mm contacts.* **D**, *PMT 68.5 × 9 mm strip with sixty-three 1-mm contacts.* **E**, *Ad-tech 75 × 8 mm strip with six 4-mm contacts.* **F**, *Ad-tech 90 × 6 mm strip with eight 4-mm contacts.* **G**, *Ad-tech 95 × 8 mm strip with eight 4-mm contacts.* **H**, *Ad-tech 95 × 8 mm strip with six 5-mm contacts.* **I**, *Ad-tech 95 × 8 mm strip with eight 5-mm contacts.*

Complications

There were no cortical intraparenchymal hemorrhages or extra-axials collections in this cohort. Rates for all types of postsurgical complications, including infection, chronic subdural hematoma, intraparenchymal hematoma, and venous infarction were lower than published rates (Table 2). Further, neither the presence of more than one ECoG strip nor the presence of either simultaneous microelectrode recording or DBS lead recording was associated with a clinically significant increase in complication rate, in either univariate or multivariate analysis. All observed hemorrhages were associated with DBS lead or microelectrode tracts rather than the cortical surface and were not clinically significant in any patients. Thus, in this large retrospective cohort, the use of intraoperative ECoG strips for research recordings for all observed cortical targets (sensory, motor, premotor, supplemental motor, and dorsolateral prefrontal cortex) was found to be safe, with no identifiable negative effect on complication rates.

Project-Specific Scientific Rationale for ECoG Recording

A number of studies using multisite cortical and subcortical recording have allowed discoveries of patterns of physiological and pathological network activity that are relevant to movement disorders, including potential DBS mechanisms of action.[25] The 2 invasive human neuroscience projects from which the current report was derived seek to expand basic neuroscience knowledge more broadly in areas of normal motor control.

In one project, investigators are exploring the subthalamic and cortico-subthalamic coding of speech production. Despite the importance of the basal ganglia in modulating cognitive and motor behaviors, current models of speech production cannot adequately account for information transfer through basal ganglia-thalamocortical loops. A novel paradigm for simultaneous recording of neural activity in cortical and relatively inaccessible subcortical nodes of the speech network was developed (Figure 3). This strategy involves minimal disruption of standard intraoperative workflow yet allows for detailed examination of neural activity in multiple brain regions integral to speech circuitry alongside recordings from the subcortical DBS target while patients participate in reading or auditory response tasks.[27]

In the other study, investigators aim to understand cortical-basal ganglia circuits mediating action regulation. Despite numerous publications assessing the role of motor cortices and

TABLE 2. Summary of Postoperative Complications

Complication	No. of cases in current study	Reported rate in the DBS literature
Infection	3 (0.8%, CI = 0.2%-2.4%)	Up to 10%[23-25]
Chronic subdural hematoma	0 (0.0%, CI = 0.0%-1.0%)	0.8% to 3%[26,24]
Intraparenchymal hematoma	4 (1.1%, CI = 0.3%-2.8%)	0.5% to 2.2%[24,27]
Venous infarction	0 (0.0%, CI = 0.0%-1.0%)	0.8%[28]

TABLE 3. Summary of Univariate Analysis of Explanatory Variables for Correlation With Any Postoperative Complication

Explanatory variable	No. of complications	Effect strength/size	Significance
No. of ECoG contacts	7	rpb = –0.05 (CI = –0.14 to 0.05)	$P = .32$
Surface area of ECoG strip	7	rpb = 0.03 (CI = –0.09 to 0.15)	$P = .62$
Two ECoG strips	3	OR = 2.38 (CI = 0.34 to 14.40)	$P = .37$
ECoG/microelectrode recording	5	OR = 2.68 (CI = 0.43 to 28.52)	$P = .27$
ECoG/microelectrode followed by ECoG/lead recording	1	OR = 0.20 (CI = 0.00 to 1.65)	$P = .13$

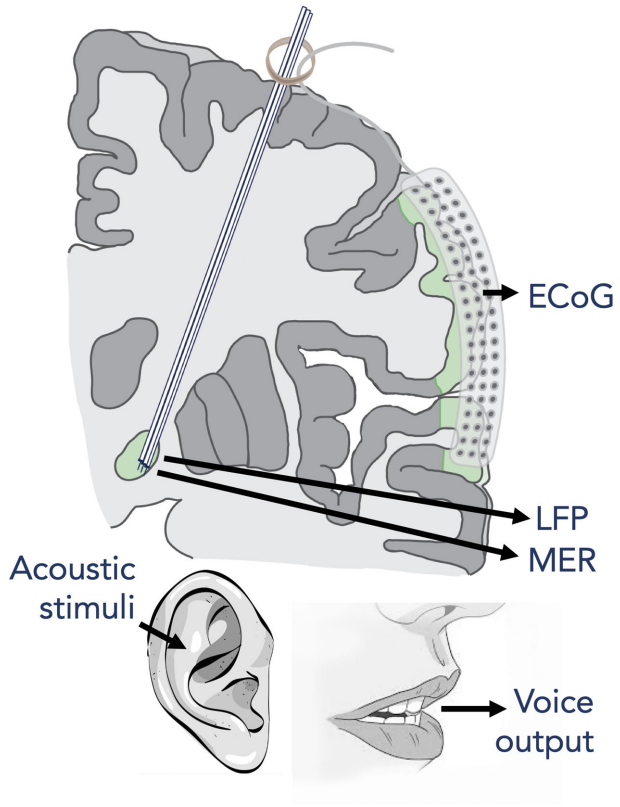

FIGURE 3. *Multiscale recording paradigm for speech research during DBS surgery. Simultaneous data streams are synced to allow correlation of behavior with cortical and subcortical neural activity: acoustic recordings of auditory stimuli and spoken responses, cortical LFP, subcortical LFP, and subcortical unit recordings.*

basal ganglia in movement,[28] few have specifically addressed the role of cortical-basal ganglia interactions in pausing or stopping motor actions during decision making.[29-31] Investigators hypothesize that distinct cortical-subthalamic nucleus circuits subserved by distinct hyperdirect pathways mediate distinct aspects of action regulation under different behavioral conditions. By simultaneously recording ECoG from multiple motor cortices (eg, supplementary motor, premotor, and primary motor) and subcortical structures (eg, subthalamic nucleus and globus pallidus), the goal is to demonstrate structural segregation of these circuits and to characterize the causal flow of signals regulating motor output.

Ethical Considerations

The US BRAIN Initiative has accelerated a new era in basic neuroscience research that benefits from direct access to brain recording and stimulation during invasive neurosurgical procedures. For this in Vivo neuroscience research to occur, patients already undergoing these procedures for clinical indications allow neurosurgeons and neuroscientists to administer behavioral tests during surgery that are driven by a research question typically unrelated to the clinical indication for surgery. As noted in a recent commentary on the integration of neuroethics within the BRAIN Initiative, these studies are reviewed and approved by IRBs and are guided by the ethical frameworks inherent to NIH policy and United States law, yet this cutting-edge work also raises common ethical questions about the balance between acceptable risk and informed consent.[32] Thus, for this type of work, it is critical that neurosurgeon-neuroscientists are able discuss with patients confidently the minimal risk associated with participating in this research. The current report provides objective evidence for the safety of research ECoG during DBS.

Another common scenario in which electrodes are implanted for research applications is in epilepsy patients undergoing seizure monitoring with hybrid depth electrodes containing microwire

bundles to record single unit extracellular action potentials. These experiments present similar ethical considerations as those for DBS surgery in that the research electrodes and data derived are used for research questions unrelated to clinical care and are of no benefit to the patients. Nonetheless, these research tools can provide invaluable insight into the network basis of cognitive processes.[33-36] Along similar lines, there are now safety data to demonstrate that these hybrid electrodes are equally as safe as standard depth electrodes.[37] Continued reporting of safety outcomes with the introduction of new invasive research techniques in patients undergoing functional neurosurgery procedures is important for ensuring the ethical advancement of the invasive human neuroscience field.

Limitations

This was a retrospective study, which limits the conclusions that can be drawn. As a multicenter retrospective study, surgical technique and equipment changed over time and were not standardized across sites. However, the use of ECoG for research purposes employs well-reported techniques with overall minimal variability in technical implementation. For example, the number and location of burr holes did not differ from standard clinical practice. The data needed to calculate lead placement error could not be readily obtained, and postoperative Unified Parkinson's DIsease Rating Scale scores were not regularly obtained at any of the study sites. Pneumocephalus itself was not considered to be a complication, and no sequelae attributable to pneumocephalus were observed. The results are potentially limited by confounders, such as comorbidities and disease severity. Patients who could not complete preoperative training materials or who exhibited mild cognitive impairment beyond that expected for their disease severity were not enrolled in intraoperative research. Finally, the number of complications identified in this study was small, which limited statistical sensitivity. Nonetheless, the overall complication rate in this cohort of DBS patients undergoing ECoG research did not exceed that of published complication rates for standard, clinical DBS placement.

CONCLUSION

The use of ECoG, an invasive recording technique, for research during DBS surgery is safe. This technique offers neurosurgeon-scientists and collaborators the unique ability to study human brain circuitry in Vivo. This type of research is crucial for continuing to develop our understanding of network-level human brain physiology and pathophysiology.

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