Chronic multisite brain recordings from a totally implantable bidirectional neural interface: experience in 5 patients with Parkinson's disease

Nicole C. Swann, PhD,¹ Coralie de Hemptinne, PhD,¹ Svyetlana Miocinovic, MD, PhD,² Salman Qasim, BS,¹ Jill L. Ostrem, MD,² Nicholas B. Galifianakis, MD,² Marta San Luciano, MD,² Sarah S. Wang, PhD,² Nathan Ziman, BS,² Robin Taylor, MSN, FNP,² and Philip A. Starr, MD, PhD^{1,3,4}

Departments of ¹Neurological Surgery and ²Neurology; ³Kavli Institute for Fundamental Neuroscience; and ⁴Graduate Program in Neuroscience, University of California, San Francisco, California

OBJECTIVE Dysfunction of distributed neural networks underlies many brain disorders. The development of neuro-modulation therapies depends on a better understanding of these networks. Invasive human brain recordings have a favorable temporal and spatial resolution for the analysis of network phenomena but have generally been limited to acute intraoperative recording or short-term recording through temporarily externalized leads. Here, the authors describe their initial experience with an investigational, first-generation, totally implantable, bidirectional neural interface that allows both continuous therapeutic stimulation and recording of field potentials at multiple sites in a neural network.

METHODS Under a physician-sponsored US Food and Drug Administration investigational device exemption, 5 patients with Parkinson's disease were implanted with the Activa PC+S system (Medtronic Inc.). The device was attached to a quadripolar lead placed in the subdural space over motor cortex, for electrocorticography potential recordings, and to a quadripolar lead in the subthalamic nucleus (STN), for both therapeutic stimulation and recording of local field potentials. Recordings from the brain of each patient were performed at multiple time points over a 1-year period.

RESULTS There were no serious surgical complications or interruptions in deep brain stimulation therapy. Signals in both the cortex and the STN were relatively stable over time, despite a gradual increase in electrode impedance. Canonical movement-related changes in specific frequency bands in the motor cortex were identified in most but not all recordings.

CONCLUSIONS The acquisition of chronic multisite field potentials in humans is feasible. The device performance characteristics described here may inform the design of the next generation of totally implantable neural interfaces. This research tool provides a platform for translating discoveries in brain network dynamics to improved neurostimulation paradigms.

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MUCH about brain networks in Parkinson's disease (PD) has been learned from invasive brain recordings in patients undergoing neurosurgery in the awake state. Intraoperatively studied signals include basal ganglia single-unit discharge,⁴⁴ basal ganglia local field potentials (LFPs),²⁴ and motor cortex electrocorticog-

raphy (ECoG).²⁵ LFPs and ECoG potentials mainly reflect summed, synchronized synaptic activity from neuronal populations close to the recording electrode. Local field potentials have also been studied through temporarily externalized basal ganglia deep brain stimulation (DBS) leads, allowing recording for several days postoperatively.¹⁵ To-

ABBREVIATIONS DBS = deep brain stimulation; ECoG = electrocorticography; EKG = electrocardiogram; FDA = Food and Drug Administration; IPG = implanted pulse generator; LFP = local field potential; PD = Parkinson's disease; PSD = power spectral density; RMS = root mean square; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale.

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gether, these recording approaches have redefined PD as a circuit disorder characterized by excessive neuronal synchronization,²⁴ have led to a mechanistic understanding of the effects of acute DBS,¹³ and have suggested strategies to improve DBS therapy by incorporating feedback control.¹⁶

However, intraoperative and short-term perioperative recordings from externalized leads suffer from several disadvantages: severe time and logistical restrictions; the confounding influence of the “microlesion” effect, in which brain circuits are perturbed by edema around recently inserted leads;¹⁸ increased infection risk;⁵ and the inability to assess the chronic effects of therapies or to prototype strategies for chronic closed-loop control (automated adjustment of DBS stimulation parameters based on brain signals).

To address these shortcomings, we launched an investigational protocol utilizing a first-generation, totally implantable, “bidirectional neural interface,” a prosthesis that delivers clinically indicated stimulation therapy and senses and stores brain activity. This device, Activa PC+S (Medtronic Inc.), allows chronic, intermittent collection of field potential data over years, and this collection can be initiated by investigators in the clinic, by patients in their homes, or by automated algorithms.^{1,4,30,35,36} The device is available to research groups worldwide under investigator-initiated protocols or under CE Marking in European countries.^{17,22,27,32,39,40,42} In our study, the stimulation and sensing pulse generator was attached to both a subcortical and cortical electrode array to allow multisite recordings for network-level analyses. Here, we describe our initial experience with the device in 5 PD patients for over 1 year, focusing on the implantation technique, complications, recording capabilities, technical limitations, and solutions for researchers to mitigate these limitations.

Methods

Patients

Inclusion criteria for this study were a diagnosis of idiopathic PD by a movement disorders neurologist and clinical justification for DBS surgery based on the presence of motor fluctuations or medication-induced dyskinesia after treatment with antiparkinsonian medications at maximal tolerable levels. Patients with prominent tremor were excluded.

Patients provided written consent in accordance with the Declaration of Helsinki and the University of California, San Francisco, institutional review board. The study was also reviewed and approved by the US Food and Drug Administration (FDA) under a physician-sponsored investigational device exemption. The study was registered with the ClinicalTrials.gov database (<http://clinicaltrials.gov>), and its registration no. is NCT01934296.

Activa PC+S Recording Capabilities

The functional capabilities of the Activa PC+S system have been detailed in preclinical publications.^{1,4,30,35,36} Briefly, the device has 8-channel connectivity, but voltage time series can be recorded from only 2 bipolar channels simultaneously. Two additional channels can be selected for simultaneous calculation and storage of spectral power

in prespecified bandwidths, but we did not systematically test that capability. When sampling 2 time series channels continuously at the maximum sampling rate of 800 Hz, the maximum recording duration that can be stored, before one is required to download data to an external computer, is 8 minutes and 42 seconds. The Activa PC+S device is identical in shape and size to the standard FDA-approved Activa PC device commonly used for therapeutic neurostimulation in movement disorders.

Surgery

Quadripolar cylindrical leads with a 1.5-mm contact height and 0.5-mm intercontact spacing (model 3389-40, Medtronic Inc.) were implanted in the subthalamic nuclei (STNs), using techniques described previously.³⁷ A quadripolar paddle-type lead with a 12-mm² exposed surface area and 1-cm intercontact distance (model 3587A25, Resume II, Medtronic Inc.) was implanted over the primary motor cortex on one side of the brain only, except in the first patient whose cortical lead was a cylindrical lead with a 3-mm contact height and 4-mm intercontact spacing (model 3391-40, Medtronic Inc.). The cylindrical cortical lead was used only until regulatory approval was granted for the investigational use of the Resume II paddle lead in the subdural space. The cortical lead was passed through the same 15-mm frontal bur hole used for the STN lead but was directed posteriorly in the subdural space under fluoroscopic guidance such that at least one contact covered the arm area of the primary motor cortex, on the medial aspect of the hand knob,⁴⁵ approximately 3 cm from the midline. Adequate anatomical localization of the cortical electrode array was confirmed using intraoperative CT computationally merged to preoperative MRI in Framelink 5.0 (StealthStation, Medtronic Inc.).³¹ Functional localization of the cortical lead was verified by reversal of the N20 waveform of the somatosensory evoked potential.⁸

Subthalamic leads were secured to the skull using a standard lead anchoring device (Stimloc, Medtronic Inc.). On the brain side implanted with a cortical lead, the lead exited the bur hole in a bone trough underneath the Stimloc base ring and was secured to the skull with a titanium dogbone-shaped miniplate (Fig. 1). After removing the head frame and inducing general anesthesia, a 3-cm parietal incision was made, through which the free ends of the STN and cortical leads were accessed. These were attached to 40-cm lead extenders specifically designed for use with the Activa PC+S generator (model 3708740, Medtronic Inc.). The extenders were tunneled to an infraclavicular incision and attached to the pulse generator/recording unit, which was placed in a pocket over the pectoralis muscle. If bilateral therapy was clinically indicated, a second STN electrode was implanted, attached to an Activa SC pulse generator (without sensing capability), and placed in an infraclavicular pocket contralateral to the Activa PC+S device.

Patient Visits

For most patients, brain recordings were performed 1 day, 10 days, 3 weeks, 1 month, 2 months, 3 months, 6

FIG. 1. **A:** Schematic of cranial hardware implantation (bilateral brain leads) as viewed from the top of the head. **B:** Lateral skull radiograph showing cranial hardware and proximal lead extenders. The patient in this case has unilateral DBS. **C:** Case 4. Example lead locations. Black arrow indicates the central sulcus, and white arrow indicates the DBS electrode location in the STN. Electrode locations were determined by merging preoperative MRI to postoperative CT.

months, and 1 year after surgery. For the patient in Case 1, the recordings at 1 day, 2 months, and 3 months were not performed. Subsequent modification of our protocol allowed the additional recordings in Cases 2–5. During research visits, brain recordings were performed on and off medications and/or with DBS on and off. Programming for chronic therapeutic DBS was initiated during the 1-month visit.

Initiating Recordings and Data Downloading

At study visits, recordings were triggered by placing the Sensing Programmer Telemetry Module (SPTM) on the patient's chest over the Activa PC+S device. The Sensing Programmer (model 8181) was then used to initiate recordings, which either were set to last for a specified duration or were manually terminated. In addition to the recordings during formal study visits, patients could trigger brief recordings at home at any time by using the Medtronic Intercept patient programmer (model 37441). Study personnel had preprogrammed the recording duration for 1 minute for all home recordings. Data downloads were also performed with the Sensing Programmer and required at least 17–18 minutes (when memory was full).

Recording Parameters

We performed short-duration recordings (< 9 minutes, repeated 1–3 times) at each research visit. Two channels of time series recordings were obtained simultaneously at 800 Hz, the highest sampling rate available. We typically sampled one bipolar contact pair over the primary motor cortex and one bipolar contact pair in the STN. The selection of active cortical recording contacts was based on the pair showing the clearest somatosensory evoked potential reversal, the strongest movement-related high gamma response,⁶ and/or the strongest beta (13–30 Hz) peak in the power spectrum, at the time of initial surgical insertion. When these criteria were not in agreement, the intraoperative CT merged to the preoperative MRI was used to help select an optimal contact pair based on closest proximity to the posterior precentral gyrus. Additional recordings with other contacts were sometimes performed, particularly if more than one contact pair had shown strong movement-related signals as described above. The selection criteria for the STN recording configuration differed before and after therapeutic DBS was activated. Prior to stimulation, we selected the bipolar pair whose LFP power spectrum showed the largest beta peak the day of or the day after surgery, off antiparkinsonian medications. If selection was ambiguous, the center contacts (1–2) were used. After

initiating chronic therapeutic stimulation at 1 month, the contacts on either side of the stimulation contact(s), when available, were used to minimize artifacts. Since contacts used for stimulation could not simultaneously be used for recording, it is likely that the recording contacts used during chronic stimulation did not include the optimal therapeutic stimulation location within the STN. For all recordings, however, at least one of the recording contacts was in the motor STN or at the border of motor and nonmotor territories, based on intraoperative microelectrode recording.

Behavioral States

At each research visit and in each medication or stimulation state, brain recordings were performed with the patient in several different behavioral states, including at rest, while walking, and during an iPad reaching task, which has been previously described.^{10,29} Recording duration was 1–2 minutes for rest and walking and up to 6 minutes for the iPad task.

Assessing Signal Stability

To assess longitudinal signal stability, for each study visit, we calculated the root mean square (RMS) voltage for both the STN LFPs and motor cortex ECoG potentials. For this assessment, we used only resting-state recordings collected in the clinic, when patients were off both DBS and medications (except for the patient in Case 1, who had great difficulty tolerating the off-medication state and so maintained her regular medication regimen at her 10-day, 6-month, and 1-year visits). If more than one recording met these specifications for each visit, the RMS was calculated for each recording separately and then averaged across recordings to obtain 1 value per brain region and per patient at each time point. For STN recordings, we also omitted files contaminated by electrocardiogram (EKG) artifact (described below).²⁷

We also assessed signal stability by calculating both beta and gamma power for motor cortex ECoG potentials and STN LFPs over time. We calculated power spectral density (PSD) using the Welch method in MATLAB (pwelch, 512 ms window, 1024 FFT length, and no overlap). For beta, we averaged the log PSD between 13 and 30 Hz. For gamma, we averaged the log PSD in the broadband (high) gamma range (70–100 Hz), avoiding potential line noise at 60 Hz. We calculated the height of the beta peak normalized to baseline power using a previously described method.⁴³ Sometimes this local maximum was small and not readily distinguishable from baseline power. Therefore, data were also visually inspected to determine a threshold for reliable detection. In recording sessions in which multiple resting state data recordings were available, the PSD (for beta and gamma individually) or beta peak height was calculated for each recording, and the values were averaged across recordings. This analysis included the same recordings as the RMS analysis described above.

Reaching Task

Recording Paradigm

Twenty trials of the reaching task were performed for

each session. Each trial included at least 5 seconds of rest or movement preparation and then 2 seconds of continuous movement.^{10,29} During the reaching task, electromyography and accelerometry activity was recorded with an external recording system to determine movement onsets (ActiveTwo, BioSemi). Synchronizing the iPad to the external recording system has been described previously.^{10,29} To synchronize the external recording system to the Activa PC+S device, surface electrical stimulation was used to deliver 0.2-msec periodic pulses. Conductive pads were placed on the patient's head (near the forehead, but taking care to avoid large muscle groups to prevent uncomfortable muscle contractions during stimulation) and on the chest, near the implanted pulse generator (IPG). A train of pulses (approximately 10 mA) was then delivered at both the beginning and end of the task. During the train of pulses, the frequency of the pulse train was changed (from 1 to 2 Hz and then back to 1 Hz or vice versa). This improved the ability to synchronize the pulse artifacts from both recording systems since occasional pulses were missed due to the short pulse width.

Analysis

We analyzed all recordings during the iPad reaching task to determine the presence of canonical movement-related activity: beta amplitude decreases and gamma amplitude increases.^{4,6,7,20} Raw signals were visually inspected, and trials contaminated by artifact were excluded. Raw data were then filtered between 13 and 30 Hz for beta and 70–100 Hz for gamma, using a 2-way FIR1 filter (eegfilt from the eeglab¹¹ toolbox, with fir1 parameters). The Hilbert transform of the filtered signal was then calculated, and the absolute value of this transform was obtained to derive the analytical amplitude over time in each frequency range. Spectrograms were also generated for visualization using the same approach but filtering all frequencies from 5 to 250 with a 2-Hz bandwidth.

Changes during movement were determined by aligning data from all trials relative to the time of movement onset (time 0) and averaging across trials. The averaged amplitude was then normalized by a 500-msec baseline prior to movement onset (–2500 to –2000 msec relative to movement). Data were normalized by subtracting the average baseline amplitude and dividing by the baseline standard deviation. This z-score procedure was performed separately for each frequency.

Recordings were categorized as having a detectable beta change if the z-scored values in the beta range (13–30 Hz) were at or below –1.96 (corresponding to $p < 0.05$, uncorrected) for more than 150 msec during the time period from 500 msec before to 1 second after movement initiation. This is a relatively liberal threshold (with no correction for multiple comparisons) since we were not trying to determine the effect of movement on electrophysiology (which is already well established^{6,7,20}) but were instead attempting to investigate the fidelity of the detection of this activity with the Activa PC+S system.

An analogous procedure was performed for broadband gamma (70–100 Hz), except that the threshold was set to a z-score value at or above 1.96 (since gamma *increases* are expected during movement). To avoid incorrectly categorizing

TABLE 1. Summary of characteristics of patients with PD

Case No.	Sex	Age (yrs)	Disease Duration (yrs)	Research Hemisphere	Baseline UPDRS (off/on antiparkinsonian medications)
1	F	47	15	Lt	68/16
2	M	62	8	Rt	30/14
3*	F	56	4	Lt	46/35
4	M	59	7	Lt	29/14
5	M	60	14	Rt	44/31

UPDRS = Unified Parkinson's Disease Rating Scale, Part III, scores.

* This patient was subsequently diagnosed with multisystem atrophy.

ricing cases in which noise in the signal caused increases across all frequencies as true movement-related broadband gamma increases, a recording was only considered to have a reliable high gamma increase if there was also a beta power decrease.

Results

Subjects

Five patients, 2 female and 3 male, were enrolled in the study and received the implanted device. Patients were 47–62 years old at the time of surgery and had had PD between 4 and 15 years (Table 1). Four of the 5 patients received bilateral DBS therapy, with the “non-research” side implanted with a quadripolar STN lead attached to an ipsilateral Activa SC single-channel generator.

Clinical Outcomes and Adverse Events

Four of the 5 patients had improved motor function with DBS 1 year postoperatively, as indicated by reduced Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores in the off-medication state (Table 2). One patient with minimal UPDRS improvement experienced a rapid progression in symptoms postimplantation, and subsequently developed features consistent with multisystem atrophy, parkinsonian subtype (MSA-P). Another patient, who had undergone unilateral implantation, experienced ipsilateral disease progression but did have a clinical benefit from DBS on the treated side. No patients reported any suicidal ideation during the study.

There were no serious adverse events related to the study protocol. Minor complications included the development of a painless, nonerythematous subgaleal fluid collection near the bur hole on the side implanted with the cortical lead, presumed to be CSF, which was self limited; thinning of the skin over the Activa PC+S battery implantation, which remained stable without the need for surgical revision; and an episode of lightheadedness during programming, which resolved with rest. Each of these events occurred only once. Two protocol violations occurred: the inadvertent performance of postoperative MRI in one patient, without clinical sequelae, and the inadvertent activation of cortical stimulation for 30–45 minutes, without clinical sequelae, in another patient.

Contact Localization

Cortical electrode arrays were successfully placed over

TABLE 2. Patient outcomes 1 year after implantation of Activa PC+S

Case No.	Baseline UPDRS, Off Medications	1-Yr Postop UPDRS, Off Medications, Off DBS	1-Yr Postop UPDRS, Off Medications, On DBS	Improvement 1 Yr Postop, Off Medications, On DBS*
1	16†	8†	5†	68%†
2	30	22	16	47%
3	46	51	50	9%
4‡	29	52	41	–41%
5	44	38	22	50%

* Relative to baseline off medications.

† Patient tested on medications.

‡ Unilateral implantation.

the left (3 patients) and right (2 patients) motor cortex and in the ipsilateral STN in all patients. See Fig. 1 for example lead locations and Table 3 for anterior commissure–posterior commissure coordinates for cortical contacts and the STN lead tip, measured from intraoperative CT fused to preoperative MRI. Comparing intraoperative to postoperative CT (acquired between 3 weeks to 3 months after surgery) revealed minimal migration of the cortical electrode array, with less than 3.5 mm of movement in each case (mean 1.7 mm, range 0–3.5 mm).

Signal Quality and Stability Over 1 Year

The quality of the recordings from the Activa PC+S device with the patient off stimulation a few hours after implantation was similar to the quality of the intraoperative recordings obtained with an FDA-approved external sys-

TABLE 3. Electrocorticography contact and DBS electrode tip coordinates

Case No.	Contact 3	Contact 2	Contact 1	Contact 0	DBS Electrode Tip
1	–26.24, –9.61, 63.07	–25.99, –16.79, 64.24	–25.52, –23.35, 64.24	–25.05, –30.15, 64.24	–10.54, –2.73, –4.87
2	30.40, –7.63, 65.36	29.23, –17.86, 66.22	29.23, –27.87, 65.79	29.23, –38.20, 65.47	11.31, –2.35, –4.44
3	–27.52, –4.71, 67.15	–26.35, –15.06, 67.15	–26.74, –25.22, 67.15	–26.94, –35.18, 67.15	–11.39, 0.23, –4.04
4	–38.02, –6.59, 64.21	–38.02, –16.55, 63.63	–38.02, –27.39, 62.75	–38.02, –37.94, 62.46	–12.56, –2.25, –5.96
5	28.43, 5.02, 63.59	28.43, –4.68, 65.94	28.43, –14.90, 67.61	28.43, –25.95, 69.62	12.50, –0.97, –5.51

Coordinates presented as distance from the midpoint of the line connecting the anterior and posterior commissures, expressed in mm. In each box the top number is the lateral coordinate; the middle number, the anteroposterior coordinate; and the lower number, the vertical coordinate. The positive direction is defined as right, anterior, and superior.

FIG. 2. Example of motor cortex ECoG potentials and STN LFPs raw data (A) and their power spectra (B) from the Activa PC+S system versus an external recording system designed for intraoperative electrophysiology (MicroGuide). Both recordings were obtained on the same day, a few hours apart, from the patient in Case 5. Note that notch filtering was used to remove line noise at 60 Hz in the intraoperative data. Line noise was not present in the Activa PC+S data.

tem designed for human electrophysiology (MicroGuide, Alpha Omega; Fig. 2), with the exception of some artifacts discussed below. This comparison has also been made in nonhuman primates.⁴ Subthalamic nucleus LFP amplitudes were lower than those of simultaneously recorded motor ECoG potentials⁹ (Fig. 3A). The average RMS voltage at rest, off DBS was $5.1 \pm 0.38 \mu\text{V}$ (mean $\pm$ standard deviation) for STN and $20.4 \pm 2.79 \mu\text{V}$ for cortex. These RMS values remained relatively stable over time (Fig. 3B).

Electrode impedances for both cortical and STN leads increased over time (Fig. 4E). This increase occurred mainly in the first months following surgery. An initial impedance increase followed by long-term stabilization has also been observed for other implanted neural prostheses.³³

Detection of Physiologically Important Frequency Bands

Prominent oscillatory activity in the beta band (13–30 Hz) is expected in field potential recordings from structures in the motor system. Gamma band activity in the cortex, over a broad frequency range (50–200 Hz), is a useful marker of local cortical activation.¹⁹ A major goal of this study was to document the ability to record these canonical physiological signatures using the novel Activa PC+S device. Log beta power (Fig. 4A) and log gamma power (Fig. 4B) at rest while off DBS varied between patients but were relatively stable over time within subjects, similar to observations in nonhuman primates.⁴ The amplitude of the PSD beta peak with respect to baseline

power (see *Methods*) was more variable, but still there was not a systematic change in beta peak height over time (Fig. 4C–D). Consistent with the experience of other users of Activa PC+S,²² an STN beta peak was not always clearly detected. Visual inspection suggested that any beta peak values with a height $< 0.25 \log_{10} (\mu\text{V}^2/\text{Hz})$ were difficult to distinguish from the rest of the spectrum and probably unreliable (Fig. 4F). Thirteen (31%) of 42 recordings in the STN and 5 (8%) of 62 recordings in the motor cortex failed to show a beta peak by this criterion (Table 4).

Variable beta peak detection may be unrelated to Activa PC+S recording capabilities. Beta oscillatory activity is known to dynamically change with behavior including movement and cognition,^{7,26} and in PD it is also affected by the medication state.¹⁵ Of note, our patient with the lowest rate of beta peak detection (Case 3) was eventually diagnosed with multisystem atrophy.

Movement-Related Changes

Examples of time-frequency plots showing movement-related changes in motor cortex ECoG potentials during the iPad-based arm movement task are provided in Fig. 5. For all such recordings, we classified movement-related beta power decreases and gamma power increases as present or absent (see *Methods*). Almost all motor cortex recordings (54 [98%] of 55) had a beta power decrease at movement initiation, and most exhibited a gamma power increase (37 [67%] of 55). Since movement-related corti-

FIG. 3. Signal quality and evolution over time. **A:** Example signals and their power spectra from the patient in Case 2, 10 days postoperatively, for both STN and motor cortex. For the STN PSD, the sharp peak at 32 Hz (arrow), on the right shoulder of the beta peak, is artifactual (further elaborated in Fig. 6). **B:** Evolution of RMS voltage over time for all patients. Data for the patient in Case 1 at 1 day, 2 months, and 3 months are missing because the initial protocol did not include research visits at these time points. The STN recordings contaminated by EKG artifact (see Fig. 6) were also excluded.

cal gamma changes were reliably detected intraoperatively when the cortical paddle leads were connected to an external recording system, we suspect that the Activa PC+S noise floor at high frequencies may have partially obscured movement-related gamma changes (Fig. 5C). Beta and gamma power changes were more difficult to detect in the STN than in cortex (Table 5). Note, though, that movement-related gamma is not always detected in the STN using intraoperative recording systems.

The ability to detect beta and gamma band changes during therapeutic neurostimulation will be important for the eventual use of neural interfaces for feedback-controlled stimulation. During DBS, movement-related signals in the motor cortex were still detectable at a similar level: 34 (94%) of 36 recordings had detectable beta and 25 (69%) of 36 recordings had detectable gamma. In the STN, however, signal detection was much reduced: only 4 (15%) of 26 recordings had detectable beta and 0 (0%) of 26 recordings had detectable gamma (Table 5). We noted that the patient in Case 5 had very few cortical recordings with detectable movement-related gamma increases prior

to stimulation initiation and had more such events detected during stimulation. It is possible that this change could reflect a stimulation-induced improvement in cortical activation, but this was only observed in one patient.

Accurate signal averaging of event-related neural activity over multiple repetitions of a task depends on correct event alignment. This depends on the reliability of the data sampling rate over successive trials. We examined the consistency of the Activa PC+S sampling rate for all recordings with event-related activity (that is, during the iPad reaching task) by using the synchronization procedure described in *Methods*. We found that the sampling rate varied from 788 to 794 Hz in extreme cases and was typically between 792 and 794 Hz, when the nominal sampling rate was programmed at 800 Hz.

Artifacts

Brain sensing during stimulation is one of the most technically challenging aspects of totally implantable brain recording systems. During therapeutic stimulation, artifacts occurred at the stimulation frequency and also at its folded subharmonics (Fig. 6A). Stimulation artifacts were more prominent for the STN LFPs than the ECoG potentials, given the smaller signal amplitude as well as the proximity of the stimulation source to the recording array. For cortical recordings, detection of canonical movement-related changes in beta and gamma bands during DBS was similar to when DBS was off, whereas for STN recordings, DBS reduced the fidelity of detection of event-related changes (Table 5). In general, stimulation artifacts arise from 2 main sources: volume conduction through the brain and coupling between the stimulation and recording circuits with the stimulation/sensing device. While the former can be greatly reduced by signal detection at a distance from the stimulating electrode, the latter is more prominent than is the case for similar recordings from externalized leads connected to large external amplifiers,¹⁰ for which isolation of stimulation and recording circuits is technically simpler.

Several narrowband artifacts were also present in the Activa PC+S recordings even when stimulation was off. The frequency of these artifacts depended on the sampling rate used. For sampling rates of 800 Hz, the most obvious of these artifacts occurred at 200 and 32 Hz (Fig. 6B). The origin of the 200-Hz artifact (based on communications from Medtronic engineers) is an internal firmware processing step. The 32-Hz artifact is attributable to an internal Activa PC+S clock. Avoiding analysis of these frequencies can prevent the misinterpretation of data. This is straightforward for the 200-Hz artifact, but is more difficult for the 32-Hz artifact since it is close to the beta band, an important frequency band in the motor system and in movement disorders.^{7,12} When signal amplitude is low, this artifact could mimic or obscure a physiological beta signal (Figs. 3A, 4F, and 6B). High-amplitude signals, like those recorded from motor cortex or STN recordings with a robust LFP (Fig. 4F), are not strongly influenced.

Subthalamic nucleus recordings from Contact 0 (the most ventral contact) usually had EKG contamination (Fig. 6C). This is believed to originate from current leakage into the IPG at the insertion site of the device lead

FIG. 4. Power and impedance change over time. **A:** Average log beta PSD over time for all subjects. **B:** Average log broadband gamma over time for all subjects. **C:** Average log beta peak height in the STN over time for all subjects. Data for the patient in Case 1 at 1 day, 2 months, and 3 months are missing because the initial protocol did not include research visits at these time points. Moreover, the STN recordings contaminated by EKG artifact (see Fig. 6) were excluded. **D:** Average log beta peak height in the motor cortex over time for all subjects. **E:** Average monopolar impedances averaged across all electrode contacts for each region (motor cortex and STN). Impedances gradually increase over time. **F:** Example of an STN LFP power spectrum with (Case 4, 1 day after surgery) and without (Case 4, 10 days after surgery) the expected broad peak in the alpha-beta range. Note that the sharp peak at 32 Hz from the 10-day postsurgery recording is an artifact (see Results and Fig. 6).

TABLE 4. Recordings (at rest and off medications) with detected beta peaks in the LFP or ECoG power spectrum ($>0.25 \log_{10}[\mu V^2/\text{Hz}]$)

Case No.	Detected/Total	
	Beta Detected in STN	Beta Detected in Motor Cortex
1*	4/5 (80%)	5/5 (100%)
2	5/5 (100%)	10/10 (100%)
3	2/7 (28%)	14/14 (100%)
4	4/10 (40%)	13/15 (87%)
5	14/15 (93%)	15/18 (83%)
Total	29/42 (69%)	57/62 (92%)

* On-medication data are included for Case 1.

extender over the pectoralis muscle. Applying a sealant at the junction between lead extender and pulse generator may reduce the EKG artifact.²⁷ We also observed baseline deflections in the signal at the initiation of recordings. This channel startup transient decayed back to 0 V over 3–10 seconds (Fig. 6D). Sudden “jumps” in voltage were another type of transient baseline deflection observed, followed by decay back to 0 (Fig. 6E). These occurred infrequently. Of note, 60-Hz line noise and its harmonics were not prominent, as is expected based on the isolation of a totally implantable device from external sources of noise.

Discussion

We used a novel, investigational, totally implantable,

FIG. 5. Detection of movement-related changes in motor cortex ECoG potentials and their relationship to the device noise floor. Movement-related spectrograms (plotted on a log scale) aligned to movement onset (time 0) for a recording session that did (A, Case 2, 10 days postoperative) and did not (B, Case 3, 3 weeks postoperative) exhibit a movement-related gamma increase. Both examples have a beta decrease. The same plots on a nonlog scale (C and D, respectively). The PSD plots (E) for recordings shown in panels A–D, as well as the maximum manufacturer-specified device noise floor. Note that gamma activity may be difficult to detect reliably in panels B and D because gamma activity in that recording is near the device noise floor.

bidirectional neural interface to record motor cortex ECoG potentials and STN LFPs in 5 PD patients over 1 year. There were no serious surgical complications, no unintended interruptions in DBS therapy, and no major malfunctions in the recording features of the device. Signal amplitudes in both cortex and STN (measured as both RMS voltage and detection of beta and gamma power) remained relatively stable despite an increase in average monopolar contact impedances over time in both regions. In motor cortex, the canonical movement-related beta frequency decrease⁷ was reliably detected, the movement-related high gamma increase⁶ was seen in two-thirds of the recordings, and therapeutic stimulation did not preclude detection of these signals. The detection of movement-related changes in the STN was less reliable and more strongly influenced by stimulation artifacts. The STN LFP signal can, however, be improved by utilizing specific stimulation and recording configurations. These findings should be of use to investigators planning research protocols using Activa PC+S, as well as device companies designing the next generation of bidirectional neural interfaces.

TABLE 5. Recordings with movement-related changes in beta and gamma frequencies

Case No.	No. of Recordings w/ Detected Changes/ Total No. of Recordings			
	Beta Frequencies		Gamma Frequencies	
	STN	Motor Cortex	STN	Motor Cortex
Off DBS				
1	2/5 (40%)	8/9 (89%)	0/5 (0%)	6/9 (67%)
2	11/12 (92%)	12/12 (100%)	5/12 (42%)	12/12 (100%)
3	4/11 (36%)	11/11 (100%)	1/11 (9%)	5/11 (45%)
4	8/11 (72%)	12/12 (100%)	4/11 (36%)	12/12 (100%)
5	9/10 (90%)	11/11 (100%)	3/10 (30%)	2/11 (18%)
Total	34/49 (69%)	54/55 (98%)	13/49 (26%)	37/55 (67%)
On DBS				
1	2/5 (40%)	3/5 (60%)	0/5 (0%)	3/5 (60%)
2	1/9 (0%)	9/9 (100%)	0/9 (0%)	9/9 (100%)
3	1/6 (17%)	6/6 (100%)	0/6 (0%)	1/6 (17%)
4	0/6 (0%)	8/8 (100%)	0/6 (0%)	8/8 (100%)
5	NA*	8/8 (100%)	NA*	4/8 (50%)
Total	4/26 (15%)	34/36 (94%)	0/26 (0%)	25/36 (69%)

NA = not applicable.

* This patient had no STN data during the iPad task on DBS because his DBS utilized 3 contacts (1+2-3-) to achieve maximal clinical benefit, leaving no recording contact pairs available.

Neural Interfaces for Invasive Recording in Humans

Activa PC+S is one of a few chronic, invasive recording devices available for human use. Others are the RNS device (Neuropace Inc.),^{23,38} the first fully implanted responsive neurostimulation device approved for use in humans for epilepsy treatment, and the BrainGate device (BrainGate Co.), a brain-machine interface designed for patients with paralysis.^{14,41} While all 3 of these devices allow invasive electrophysiological recording, there are important differences, advantages, and limitations to each. Both the RNS and Activa PC+S devices are fully internalized devices, whereas the BrainGate device has an externalized component. The internalized devices have the significant advantage of a reduced risk of infection and the capacity for ambulatory recording outside of a specialized laboratory, at the expense of limited bandwidth. In contrast, the BrainGate system allows simultaneous recording from many more electrodes, as well as much higher sampling rates that permit detection of single-unit activity in addition to field potentials.

Both BrainGate and Activa PC+S allow rapid, immediate streaming of data to external computers, facilitating brain-machine interface applications such as real-time control of a motor prosthesis^{14,41} or prototyping of feedback-controlled stimulation algorithms.¹⁷ Feedback control may improve DBS therapy by real-time adjustment of stimulation parameters in response to fluctuating signs and symptoms.^{16,28} Long-term studies utilizing the BrainGate and RNS devices indicate stable recordings for up to 5 years for both, based on direct inspection of the signals (BrainGate) or continued clinical efficacy (RNS).^{2,3,34}

A. Stimulation artifacts **B. Narrowband artifacts** **C. EKG artifact** **D. Baseline Deflection Artifact** **E. Putative Movement Artifacts**

FIG. 6. Illustration of common Activa PC+S electrical artifacts. **A:** Example of DBS stimulation artifacts for constant current and constant voltage settings as well as off DBS in both motor cortex and STN in the same patient (Case 4). Stimulation parameters: c+1-, 160 Hz, 3 V, 60-µsec pulse width versus c+2-, 130 Hz, 4.9 mA, 90 µsec. Constant voltage recording occurred at 1 month postoperatively, and constant current and off-stimulation recordings occurred at 1 year postoperatively. Note that in all cases, the STN recordings were obtained from bipolar contact pairs bordering stimulation to minimize artifact (0–2 for constant voltage recording and 1–3 for constant current and off stimulation). Motor cortex recordings were obtained from contacts 9–11 in all recordings. **B:** Example of narrowband frequency artifacts (arrows) associated with intrinsic firmware or clock configuration properties in Activa PC+S (see *Results* for more information). **C:** Example of EKG artifact in the STN. **D:** Example of baseline deflection artifact associated with a filter startup transient. This occurred at the beginning of each recording for both electrode contacts. **E:** Example of transient baseline deflections of unknown etiology. These deflections can occur in motor cortex or STN.

These findings support the idea that long-term stable electrophysiological recording in humans is possible.

Of the available implantable devices with a sensing capability, Activa PC+S is the only one designed for continuous stimulation and thus is suitable to deliver therapy for any disorder treatable with open-loop DBS.²¹ The use of Activa PC+S in humans with PD for single-site subcortical recording with continuous stimulation was recently reported.^{22,27} Here, we describe the use of a multisite recording configuration (cortex and basal ganglia) via the Activa PC+S device in humans.³⁹

Device Limitations and Mitigation Strategies

Many of the technical limitations of Activa PC+S are attributable to the constraints associated with integrating the sensing function into a small, totally implantable device. Canonical movement-related high gamma changes in motor cortex, reliably detected using ECoG arrays attached percutaneously to external recording systems,^{6,7,20,29} were not always apparent using Activa PC+S. Broadband gamma (also called “high gamma”) activity tracks local cortical function and is thought to be a surrogate for local neural activity.¹⁹ The optimal frequencies for gamma power detection are above 70 Hz, for which signal amplitudes are near or below the device noise floor of Activa PC+S in some patients (Fig. 5B and D). Further, cross frequency interactions between the amplitude of high gamma and the phase of lower frequency rhythms may provide important control signals for adaptive (closed loop) stimulation.^{9,10} underscoring the importance of high gamma sensing.

The stimulation artifact is more pronounced with Activa PC+S than when stimulating and recording from externalized leads.¹⁰ This is probably due to coupling of the stimulation and recording circuits within the pulse generator. The stimulation artifact is particularly challenging for STN because of its low signal amplitude and proximity to the site of stimulation. This may limit the feasibility of close-loop DBS approaches using STN LFP beta power as a control signal.¹⁶ Stimulation artifacts may be reduced by the use of the 100-Hz low pass filter. The use of constant voltage rather than constant current stimulation aids in common mode rejection of stimulation artifacts. Stimulation frequency may be selected judiciously to align stimulation artifacts away from the frequency bands of interest (for example, 140-Hz stimulation sampled at 422 Hz results in artifacts above 130 Hz or below 10 Hz, away from the frequency bands of greatest interest for many applications). Recording from a bipolar configuration that brackets a monopolar stimulating contact is ideal for stimulation artifact reduction, but this may not be possible if the clinically optimal stimulation contact is on one end of the contact array. Finally, a calibration procedure can be performed prior to each recording to determine optimal STN gain.²⁷

Fully implantable devices pose a trade-off between the recording capability of the device and the longevity of the power supply. Using the maximum available sampling rate of 800 Hz for 2-channel recording affords less than 9 minutes of data storage prior to download. Memory capacity in Activa PC+S can be improved by lowering the sampling rate, recording only spectral power at a prespecified frequency instead of time domain signals, sampling only one channel, or using the data compression (which may reduce the signal/noise ratio and is not recommended when stimulation is on).

Characterizing the variability in the sampling rate was critical for the analysis of task-related activity since this variability affects precise event alignment when signal averaging over multiple trials. Without changing the nominal programmed sampling rate, the actual sampling rate can vary between patients and between recording sessions within a patient. To address this, we delivered synchronization pulses at the beginning and end of each task record-

ing and calculated the sampling rate from the number of samples collected and the length of the interval between pulses. For longer recordings, additional synchronization pulses may be necessary.

Conclusions

We report our initial experience with subcortical neurostimulation combined with chronic cortical and subcortical recording for 1 year in 5 PD patients using a bidirectional neural interface. The acquisition of high-quality, long-term ECoG and LFP data is achievable. For most disorders, brain network abnormalities underlying disease expression are yet to be discovered. Totally implantable sensing devices hold promise both for signal discovery and for feedback-controlled stimulation. These developments will be facilitated by improvements in the signal/noise ratio, increased bandwidth and memory, reduced time for data downloading, and better methods of synchronizing internal data sampling with external monitors and computers.

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Author Contributions

Conception and design: Swann, de Hemptinne, Ostrem, Starr. Acquisition of data: Swann, de Hemptinne, Miocinovic, Qasim, Galifianakis, San Luciano. Analysis and interpretation of data: Swann, de Hemptinne, Miocinovic. Drafting the article: Swann, Starr. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Swann. Statistical analysis: Swann. Administrative/technical/material support: Wang, Ziman, Taylor. Study supervision: Starr.

Correspondence

Nicole C. Swann, Department of Neurological Surgery, University of California, San Francisco, 513 Parnassus HSE 8, Rm. 823, San Francisco, CA 94143. email: nicole.swann@ucsf.edu.