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A Novel Lead Design for Modulation and Sensing of Deep Brain Structures

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Abstract

Goal—Develop and characterize the functionality of a novel thin-film probe technology with a higher density of electrode contacts than are currently available with commercial deep brain stimulation (DBS) lead technology. Such technology has potential to enhance the spatial precision of DBS and enable a more robust approach to sensing local field potential activity in the context of adaptive DBS strategies.

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Methods—Thin-film planar arrays were microfabricated and then assembled on a cylindrical carrier to achieve a lead with 3D conformation. Using an integrated and removable stylet, the arrays were chronically implanted in the subthalamic nucleus and globus pallidus in two parkinsonian non-human primates.

Results—This study provides the first *in vivo* data from chronically implanted DBS arrays for translational non-human primate studies. Stimulation through the arrays induced a decrease in parkinsonian rigidity, and directing current around the lead showed an orientation dependency for eliciting motor capsule side effects. The array recordings also showed that oscillatory activity in the basal ganglia is heterogeneous at a smaller scale than detected by current DBS lead technology.

Conclusion—These 3D DBS arrays provide an enabling tool for future studies that seek to monitor and modulate deep brain activity through chronically implanted leads.

Significance—DBS lead technology with a higher density of electrode contacts have potential to enable sculpting DBS current flow and sensing biomarkers of disease and therapy.

Keywords

current steering; deep brain stimulation; neural engineering; implantable biomedical electrodes

I. Introduction

Since the early 1970s, the design of deep brain stimulation (DBS) lead implants for human use has largely followed the pioneering work of Hosobuchi and colleagues [1]. This design consisted of a linear stack of cylindrical electrodes that provided several options for tuning stimulation along the long axis of the thalamic ventral posterior medial (VPM) nucleus for treating chronic pain. The current state-of-the-art DBS lead similarly consists of a linear stack of four or more cylindrical electrode contacts, each with diameter, height, and axial pitch dimensions greater than or equal to 1 mm. While this lead design has proven useful and effective for treating a range of medication-refractory brain disorders [2, 3], it is particularly sensitive to surgical targeting errors that are tangential to the lead's primary axis. Indeed, numerous studies have noted that targeting errors of only 1-2 mm can result in unwanted side effects that mask the intended therapy [4-8].

This clinical outcome sensitivity to surgical targeting error stems in part because nearly the same DBS lead design is used regardless of the targeted nucleus or fiber pathway. For example, in most cases, the stack of cylindrical electrodes provides adequate flexibility for stimulating in the relatively large VPM nucleus of thalamus in cases of slight surgical misplacement; however, targeting smaller and more oblong nuclei like the subthalamic nucleus [5] or pedunculopontine nucleus [6] through relatively large cylindrical electrodes is likely to modulate a range of neuronal pathways around the DBS lead, many of which are thought to evoke unintended side-effects when stimulated [9, 10]. These examples motivate a clinical need for new DBS lead designs that enable directing electrical current around [5] and along the lead [11] as well as closer to the spatial scale of the local cytoarchitecture.

Segmentation of the stacked cylindrical electrodes into a three-dimensional array of electrodes along and around a DBS lead may facilitate more spatially targeted stimulation and recording from deep brain structures. Computational modeling studies have indicated that subdividing each cylindrical electrode's circumference into four rectangular electrodes [16] or four ellipsoidal electrodes [4, 5, 12] can improve the lead's capacity to steer, shift, and sculpt regions of stimulated tissue within the brain. Such refinement in the spatial activation volumes has potential to 'rescue' therapy from a DBS lead implant in which side effects emerge at lower stimulation amplitudes than are necessary for delivering optimal therapy [4]. Such advances may also be particularly important for the success of adaptive, closed-loop DBS therapies [13-15]. Reducing the electrode size and populating more electrodes around the DBS lead has potential to enable recording local field potential (LFP) oscillatory activity at finer spatial resolution than what is currently available with the relatively large cylindrical electrodes [16]. Such an approach may limit the degree of shunting of the underlying oscillatory sink and source heterogeneity within the targeted brain region [17, 18].

Previously, two DBS array designs, with electrodes around and along the DBS lead, have been tested in acute insertion experiments in humans prior to implantation of a commercial

DBS lead with the standard design containing a stack of four cylindrical electrodes. One lead design had four segmented contacts around the lead perimeter [8], whereas the other design had three segmented contacts [7]. Both studies provided proof-of-concept feasibility data that radially directed stimulation is superior to radially uniform stimulation in terms of reduction in power consumption and augmentation of the therapeutic window, which describes the quantitative difference between strength-duration curves for generating therapy and evoking side effects.

Here, we present the first chronic *in vivo* testing results of a high-density DBS array (rDBSA) lead, consisting of 8 rows of 4 ellipsoidal electrode contacts arranged around the circumference of 600 μm diameter DBS lead. A similar array design was reported previously from our group in 2011 for acute testing in non-human primates [5]. The current study provides the first chronic data with this array as well as the packaging and implantation approach to render this lead design applicable for chronic use. Additionally, we show that high-density DBS arrays enable (1) more precise spatial stimulation around the circumference of the lead and (2) provide finer spatially resolution of LFP recordings in the vicinity of the implanted DBS leads than can be achieved with annular clinical electrodes.

II. DBS Array And Packaging

A. Thin-film Electrode Array Design

The rDBSA design contained eight rows by four columns of ellipsoidal macroelectrode contacts and a single column of eight microelectrode contacts for a total of 40 contacts (**Fig. 1**). The dimensions and spacing of the macroelectrodes were tailored to fit the subthalamic nucleus (STN) or both segments of the globus pallidus (GP) of the rhesus macaque (**Table I**). The rDBSA targeting the STN had smaller contacts and an axial span of 4.9 mm, whereas the rDBSA targeting the GP had larger contacts and spanned 5.6 mm. In comparison, a

version of the clinical DBS lead, scaled down to the size of the primate brain, has 4 cylindrical contacts and spans 3.5 mm as used in previous studies [19, 20] (NuMed, Hopkinton, NY). In addition to the macroelectrodes, the rDBSA contained one column of 8 microelectrodes with circular contacts of 50 μm diameter, interspersed between rows of macroelectrodes. Both GP and STN designs had an integrated thin-film cable to carry signals to the proximal region of the implant package. Array design specifications were imported into NeuroNexus' custom layout algorithm to generate the required layers for the final design. The algorithm provided a method to equalize the resistance of all traces, an important characteristic for thin-film stimulation leads. Conventional integrated circuit layout software was then used to configure the designs onto a wafer frame from which photolithographic masks were made.

B. Microfabrication Process and Array Packaging

The arrays were fabricated using conventional microfabrication processes [21, 22] with five photolithographic mask steps. The arrays were comprised of platinum traces sandwiched between dielectric layers of silicon carbide and/or polyimide. Contact vias were opened through the top dielectrics and either platinum or iridium electrode sites were deposited and patterned. The planar 2D arrays were singulated, removed from the wafer, and then wrapped around a carrier tube to create a 3D cylindrical shape and a structure suitable for implantation with a stylet. Only the array portion of the thin-film device was adhered to the carrier probed with epoxy, allowing the insulated traces to be less susceptible to fracture during lead implantation. A stainless steel stylet was inserted through the carrier tube until reaching an epoxy-filled portion of the tube at a level slightly above the electrode array sites. The carrier tube was constructed with a rounded tip, consistent with commercial DBS leads and consistent with a shape that would blunt dissect tissue during the implantation process. In addition, a FlexPCB cable was bonded to the thin-film trace pad at the proximal end of the probe. This cable provided a means to interface with either a ZIF and/or Omnetics connector.

III. Experimental Methods

A. Pre-clinical Animal Studies

Functional rDBSAs were chronically implanted in two adult rhesus monkeys (*macaca mulatta*, subject P, ♀, 19 y.o., 9.6 kg; subject G, ♀, 17 y.o., 9.0 kg). All procedures were performed in compliance with the United States Public Health Service policy on the humane care and use of laboratory animals and were approved by the University of Minnesota's Institutional Animal Care and Use Committee. Under isoflurane anesthesia, each monkey was surgically implanted with a titanium headpost and two cephalic chambers that were oriented in sagittal (STN) and coronal (GP) orientations in the same hemisphere [20]. The STN and GP were identified using pre-operative magnetic resonance imaging at 7T (T2-weighted and susceptibility-weighted imaging). Following a 1-2 week recovery period, each animal received a computerized tomography scan to plan the DBS array implantation using *Monkey Cicerone* [23]. In a separate procedure, each monkey was rendered moderately to severely parkinsonian with systemic injections of the dopaminergic neurotoxin, MPTP (1-

methyl-4-phenyl-1,2,3,6-tetrahydropyridine) to quantify the therapeutic efficacy of the rDBSAs.

B. DBS Implant Procedure

Microelectrodes (250 μm diameter, 0.8-1.2 $\text{M}\Omega$, FHC, Bowdoin, ME) were advanced through each chamber to verify coordinates for the STN and GP. Firing rates and patterns of single neurons were used to localize the borders of these nuclei, and sensorimotor territories within these nuclei were identified as those containing neurons whose firing rate was modulated by passive joint articulations [19] or in some cases volitional movement. The locations of the recording tracks relative to the corticospinal tract of the internal capsule were determined using microstimulation (10-150 μA , 300 Hz, 0.5 sec) to evoke movements about the face, upper extremity, and lower extremity. Based on the mapping results, a DBS implant trajectory was selected such that multiple rows of rDBSA electrodes would span the sensorimotor region of each target. For both monkeys, the GP target was mapped and implanted before mapping and implanting the STN target.

Prior to rDBSA implantation, a snap ring with a tongue (custom machined from Ultem) was inserted into a groove in the inner wall of each cranial chamber. Next, a stainless steel stiffening stylet was inserted into the lumen of the rDBSA and both were then guided into the brain using the same microdrive used for the initial mapping experiments. Once at the target, the lead was secured to the tongue of the snap ring with cyanoacrylate. The stiffening stylet was then retracted and the microdrive assembly was removed from the chamber. A slit-adaptor was custom machined from a PEEK rod to fit onto the top of each cranial chamber to allow for the flexPCB cable of the rDBSA to exit the chamber while also allowing for closure of the chamber with its original chamber cap (**Fig. 2**). A 3D printed cable guard was attached to the slit-adaptor with screws to protect the flexPCB cable as it exited the chamber. A dry chamber with space to accommodate the proximal connectors of two rDBSAs was secured to the headcap. The exposed portion of the flexPCB within and outside each cranial chamber was coated with silastic to form a waterproof barrier. Additionally, the portion of the silastic coated flexPCB outside the chambers was coated with a thin layer of dental acrylic to form another protective coating.

C. Electrochemical Impedance Measurements

After implantation, the 1-kHz impedance of each electrode site was monitored using a NiPOD (NeuroNexus, multiplexed measurement of 40 electrodes) or an impedance conditioning module (FHC, manual measurement). In addition, impedance spectroscopy was measured over 0.1 Hz to 25 kHz using an AutoLab potentiostat (Metrohm, Netherlands) to characterize the resistive and capacitive changes in the electrode-tissue interface over time [24-26]. All impedances were measured in a two-electrode configuration with the titanium headpost, attached with bone screws, serving as the counter electrode.

D. Deep Brain Stimulation Protocols

To investigate the capacity for the rDBSA implants to deliver sufficient charge to provide a therapeutic effect, biphasic, charge-balanced pulse trains were delivered through four electrodes in one row (100 μsec cathode-leading pulse width, 130 Hz, referenced to

headpost). The parkinsonian severity was measured using a modified Unified Parkinson's disease rating scale (mUPDRS). Muscle rigidity scores were assessed through passive manipulation of upper and lower extremity joints (i.e. wrist, elbow, shoulder, ankle, knee, hip) on a scale of 0-3 (0: no rigidity, 3: severe rigidity) by two investigators who were blinded to the stimulation settings, including whether the stimulation was on or off.

Additionally, the capacity of the rDBSA to direct current around the lead was evaluated by delivering pulse trains individually through each of the 32 macroelectrodes (biphasic, charge-balanced, 100 μ sec cathode-leading pulse width, 130 Hz). DBS amplitudes activating the corticospinal tract of internal capsule were assessed using motion capture of reflective markers placed on finger digits, wrist, elbow, shoulder, hip, knee, ankle, and foot digits (T-series system, Vicon, Centennial, CO). Evoked responses were repeated over several trials to establish consistency of threshold amplitudes.

E. Unit-Spike and Local Field Potential Recordings

Immediately following implantation and periodically thereafter, wide-band recordings digitized at 22 kHz were collected from the 8 microelectrodes (in reference to the titanium headpost). Resting-state LFP recordings were also acquired with a low-pass filter cutoff at 781 Hz and 1.5625 kHz sampling rate in reference to the titanium headpost. LFP recordings were re-referenced in bipolar montages by subtracting recordings from neighboring electrode contacts around each rDBSA row, yielding 32 bipolar LFPs. LFP recordings were collected in awake, resting-state conditions without DBS and during DBS at both subtherapeutic and therapeutic settings. Stimulus artifacts were removed from each recording using a template subtraction algorithm [27].

F. Histological Methods

The orientation of the rDBSA was determined by the orientation of the probe and flexible cable within the cephalic recording chamber. To confirm this orientation, direct current lesions were delivered through select electrodes one hour prior to euthanization. Each monkey was deeply anesthetized, given an overdose of pentobarbital (100 mg/kg), and transcardially perfused with a phosphate buffered saline solution (PBS) followed by 4% paraformaldehyde in PBS (PFA). Brains were blocked in the coronal plane, post-fixed in 4% PFA, and cryoprotected in 15% sucrose solution for 1-3 days. Coronal sections, 50 μ m thick, were taken using a freezing microtome in the coronal plane. The rDBSA implants were left in the brain during sectioning so the exact orientation could be visualized. Nissl staining was performed on both brains to verify the location and orientation of the rDBSA implants within the target nuclei.

IV. Results

The functionality and performance of the DBS arrays were assessed through a combination of (1) *in vivo* impedance measurements, (2) post-implant unit-spike recordings, (3) parkinsonian limb rigidity ratings during DBS, (4) upper and lower extremity limb movements while applying stimulation through electrodes around the rDBSA lead, and (5) resting-state LFP recordings across the array before and during DBS.

A. In Vivo Impedance Measurements

Pre-implant 1 kHz site impedances for macroelectrode and microelectrode contacts were on the order of 350-450 k Ω and 1-1.5 M Ω , respectively. Impedance spectroscopy was performed periodically to probe changes in the electrode-tissue interface over time. Contacts deemed viable for duration of the experiments (i.e. consistent 1 kHz impedance below 2 M Ω) were included in this analysis. For subject P, 23 contacts on the GP-lead and 30 contacts on the STN-lead were viable, while subject G had 30 viable contacts on the GP-lead and 32 viable contacts on the STN-lead. During the initial post-implantation period, impedance spectra on a Nyquist plot shifted to the right, indicating a change in the resistive component of the complex impedance. For subject P, 1 kHz impedances were measured every few days after the initial implant to track the development of the encapsulation layer around the lead (**Fig. 3A**). Over the first two weeks, the impedances increased slightly and plateaued. Site impedances also decreased after DBS (**Fig. 3B**), similar to findings from previous studies [28, 29].

B. Verification of Implantation Targeting

While co-registration of pre-operative MR imaging with post-operative CT imaging has been the gold-standard for estimating the location and orientation of implanted electrodes relative to a targeted nucleus within the human brain, the rDBSAs provided an additional means to verify targeting of the lead implant in the form of unit-spike recordings along the microelectrode column (**Fig. 4**). Single-unit spike activity was observed on a subset of the microelectrode channels at the time of implant in subject P (STN and GP leads) and subject G (only STN lead). In the case of subject P, the firing rate and pattern of the units was used to confirm the targeting of each lead within the sensorimotor GP or STN as assessed through passive joint manipulation. In all cases, no discriminable spike activity was observed one week after implantation.

C. Stimulation Capabilities of the rDBSA

Stimulating through a single row of electrodes in each array, DBS (130 Hz, total amplitude above 400 μ A) was able to reduce parkinsonian rigidity in both subjects (**Fig. 5**). Four individual current sources were used to deliver equal amounts of charge through four contacts in a single row. In both subjects P and G, low frequency (30 Hz) stimulation did not reduce rigidity regardless of the stimulation amplitude tested. Similarly, low stimulation amplitudes (total 50 μ A in subject P and 200 μ A in subject G) did not reduce rigidity regardless of frequency tested. Only the combination of high amplitude and high frequency reduced rigidity in both subjects when delivered to either the STN or the GP. Notably, the therapeutic effect on rigidity was less in subject P than subject G. Involuntary motor contractions were elicited at lower current amplitudes in subject P than subject G, which limited the magnitude of delivered current for the purposes of therapy.

rDBSAs implanted in the STN were also able to generate directional stimulation such that the amplitudes of evoked involuntary muscle contractions were larger when stimulation was delivered through electrode contacts facing internal capsule (lateral) than for electrodes facing the medial direction (**Fig. 6**). The rDBSA position and orientation within the STN were confirmed with histology in both monkeys (**Fig. 6A**). Lower amplitudes were needed

to evoke limb movements in subject P (150-450 μ A) than in subject G (300-600 μ A), which corresponded to a more lateral implant trajectory in subject P compared with subject G (**Fig. 6B**). Additionally, the largest movements were evoked with stimulation through rows 3-6 in subject P, while deeper rows 1-4 evoked larger movements in subject G. These rows in subject G correspond to the rows on the probe that were located within or near the STN. Deeper contacts in subject P (rows 1-3) were located in the substantia nigra and shallower contacts in subject G (rows 5-8) were located in the zona incerta and thalamus and farther away from the internal capsule. Lastly, the contact and direction that evoked the largest amplitude movement differed across limbs (**Fig. 6C**). Stimulation through contacts in subject P, row 6 evoked the largest arm movements in the lateral direction, whereas stimulation in the dorsal direction evoked the largest leg movements. Similarly, dorsal stimulation through row 2 evoked the largest leg movements in subject G, whereas dorsal, not lateral stimulation evoked the largest arm movements in subject G (**Fig 6D**).

D. LFP Recordings during DBS

Bipolar LFPs were sensed from both STN and GP leads during DBS in the MPTP state. Due to crosstalk in the recording system, LFPs were sensed from the non-stimulated rDBSA during stimulation (i.e. GP LFPs sensed during STN DBS). As shown in **Fig. 7**, LFPs were recorded in both GPe and GPi during the onset of STN DBS at sub-therapeutic amplitude, sub-therapeutic frequency, and therapeutic settings. The order of stimulation settings was varied to account for long latency washout effects, and the recordings were repeated over 4 days. Spectrograms were calculated with a 2 sec wide, 200 msec step moving window. Before stimulation was turned on, there was prominent activity in the 10-20 Hz (beta) band, and the spectral power was variable across rows on the same rDBSA (**Fig. 7A,B**). Sub-therapeutic amplitude stimulation did not change the power in the beta band, sub-therapeutic frequency stimulation partially reduced the power in the beta band, and therapeutic settings nearly eliminated the power in the beta band.

To quantify this effect, the beta power was normalized by the power in the 70-80 Hz (gamma) band. This normalization was used to account for any broadband increase in power during stimulation as a result of any remaining stimulation artifact. The beta/gamma ratio was compared in the on-stimulation and off-stimulation cases. LFPs in the GP showed a reduction in beta/gamma ratio when stimulation was delivered to the STN (**Fig 7C**). This reduction was largest at high stimulation amplitudes (4 $\times$ 150 μ A across a row of macro-electrodes in the STN) (low frequency: min 0.37, max 0.95, high frequency: min 0.37, max 0.99) and for bipolar LFPs recorded between the medial and dorsal columns. Low amplitude high frequency stimulation showed a smaller reduction (min 0.50, max 0.90). Stimulation delivered to the GP did not consistently reduce beta/gamma power recorded in the STN (**Fig. 7D**). Low amplitude, high frequency GP stimulation caused a very small decrease in beta/gamma power in the STN (min 0.77, max 1.10). High amplitude GP stimulation caused a relative increase in the beta/gamma ratio in the STN (low frequency: min 0.97, max 1.35, high frequency: min 0.96, max 1.14). This effect was not likely associated with an increase in gamma power on stimulation compared to off stimulation, because the relative beta power on compared to off stimulation had the same trends as the beta/gamma power (data not shown). The high-density electrode sites on the rDBSA also revealed heterogeneity in the

resting-state LFPs around and along the lead's axis. This oscillatory activity was differentially modulated by DBS. For example, the medial-dorsal bipolar montage exhibited the strongest suppression of beta oscillations in globus pallidus during STN-DBS. This level of spatial resolution could not be sensed with clinical DBS leads, which are not segmented around the circumference of the lead and have fewer and larger electrode contacts along the axis of the lead.

V. Discussion

This study provides electrochemical, electrophysiological, and behavioral analysis from four implanted DBS arrays in two non-human primates, showing enhancements in the spatial direction of stimulation and in the spatial precision of LFP recordings along and around the implanted carrier probe in comparison with state of the art clinical technology.

Importance of Spatial Targeting in DBS Therapy

Expanding the design space for DBS leads is of strong clinical importance for future DBS therapies given the known relationship between surgical targeting precision of DBS lead implants and successful delivery of DBS therapy [30, 31]. In the STN, for instance, surgical targeting errors in the ventral, lateral, and anterior directions can lead to stimulus-induced tonic muscle contractions stemming from activation of the corticospinal tract of internal capsule. The likelihood of these side-effects is readily apparent when considering that the STN is nestled along the lateral extent of internal capsule and has a relative volume (non-human primates: $2 \times 4 \times 6$ mm [32], human: $3 \times 5 \times 12$ mm [33]) that is on the same order of magnitude as the contact spacing along the DBS lead. In addition to tonic muscle contractions, DBS about the STN region can evoke paresthesia, contralateral conjugate eye deviation, apraxia of eyelid opening, weight gain, and limbic side-effects [34]. The sensorimotor globus pallidus is an alternative target for treating Parkinson's disease and dystonia with DBS. The GP is a larger structure than the STN, approximately 10-15 mm medial to lateral in the human [33], but it is also bordered by the internal capsule and placement of a lead too medial or posterior within the structure will cause tonic muscle contractions [30, 35]. Similarly, DBS lead placement in the ventral intermediate (Vim) nucleus of the thalamus for treatment of tremor is also sensitive to location because of the elongated morphology of the nucleus [30] and interdigitation with other thalamic nuclei. Misplacement of the DBS lead in this brain region can result in stimulus-induced paresthesia, tonic muscle contractions [36], as well as deficits in speech and swallowing [37].

The rDBSA as reported here has a geometric advantage over the current clinical leads, providing improved spatial targeting of DBS. The rDBSA manufacturing process enabled tailoring the electrode height and array spacing to interface with the nucleus of interest at a higher spatial resolution than has been currently available. For example, the rDBSA designed for the STN had five rows of four electrodes each (effectively 20 macroelectrodes) in the same space occupied by four cylindrical electrodes on a scaled-down version of the human DBS lead. For the rDBSA designed for the GP, electrodes were spread out to span

both internal and external segments of globus pallidus with 32 macroelectrodes as compared with four cylindrical electrodes on the scaled-down version of the human DBS lead.

The arrangement of segmented electrodes around the lead circumference enabled directing stimulation in three dimensions, as identified by the generation of spatially heterogeneous stimulus-evoked muscle contractions (**Fig 6**), a finding that has clinical importance in reducing the emergence of DBS side-effects through more advanced current steering approaches [7]. Further, more stimulation contacts within the target brain region will allow for variation in the location of the stimulating electrode over time [38], which may contribute for example to long-term reduction of motor signs through network desynchronization stimulation patterns that leverage multiple contacts [39]. The number and arrangement of electrodes on the DBS arrays was chosen to provide a balance between flexibility of stimulation direction and limits on the applied charge density necessary to drive therapeutic effects on parkinsonian motor signs and the packaging requirements that go along with higher density neural probe implants. It is important to note that the DBS arrays reported here did not have the spatial resolution to make inferences on the optimal spatial scale of electrode sizes and configurations for current steering or LFP recordings. DBS arrays with even higher site density [40] and computational models of high-density DBS arrays [12] may be able to better probe this question. However, the DBS array dimensions in this study did show improved functional resolution over current DBS lead designs.

Circumferential Segmentation of DBS Lead Electrodes

DBS leads with segmented electrode contacts around the lead circumference have been hypothesized to improve targeting of stimulation within the brain [5, 7, 8, 38]. In a computational modeling study of STN neural activation, Buhlmann et al. showed comparable neuronal activation between a Medtronic 3389 DBS lead and a circumferentially segmented version of that same lead [38]. To create the segmented lead, each cylindrical contact was split into four rectangular electrodes for a total of 16 contacts that enabled current-steering around the lead. In practice, the geometry of these electrodes could be problematic due to higher current densities at the corners of the contacts during stimulation. Toader et al. utilized computational modeling to assess a DBS-array with 64 disc contacts (16 rows of 4 contacts), each with 0.5 mm diameter and 0.25 mm spacing. This design was also able to direct current around the lead and alter the shape of a theoretical volume of activated tissue [41]. This computational study was followed by acute implantation of a prior version of the rDBSA reported here [5].

The results of the current study showed that the rDBSA was able to deliver directionally-selective stimulation to the internal capsule by activating individual contacts around a single row as well as across the entire electrode array (**Fig. 6**). By thoroughly surveying the effects of stimulation at each viable contact, we were able to show topographical differences in the electrode locations with the lowest threshold for inducing muscle contractions about the upper and lower extremities, which may reflect differences in the orientation of corticospinal tract fibers within internal capsule related to each extremity. The heterogeneity of thresholds in adjacent contacts for both animals, and especially for monkey P, likely stem from the

known variability in motor thresholds [42, 43] and potentially some fabrication variability within the DBS array. In both cases, however, stimulation directed towards internal capsule resulted in the lowest threshold for muscle activation. If a patient were implanted with a similar electrode array, a similar procedure could be used to identify the contacts and directions evoking the largest movements. Then the current steering techniques could be employed to direct therapeutic stimulation away from these movement-inducing directions and towards directions that maximally reduce symptoms. These results suggest that the DBS arrays may have potential usefulness in improving or rescuing therapy for patients with low-threshold stimulation-induced side effects, consistent with prior subject-specific computational modeling results in motor thalamus [4] and brainstem [6].

In clinical studies, a different circumferentially segmented DBS electrode array was acutely implanted in the STN or Vim thalamus of 13 human patients [7]. These investigational leads contained two cylindrical contacts on the dorsal portion and two rows of three lead-conforming square contacts on the distal portion of the lead (Aleva Neurotherapeutics SA, Lausanne, Switzerland). DBS through the square contacts was deemed to be superior to the cylindrical contact because less voltage was required to achieve a therapeutic effect, and there was a larger therapeutic window between improvement in parkinsonian motor signs and stimulus-evoked side-effects. Along with previous modeling studies, this study by Pollo and colleagues showed that DBS leads with electrodes segmented around the lead circumference can be superior to current DBS lead technology with cylindrical electrodes. The results presented herein build on these studies as well as our previous rDBSA experiments now demonstrating the capacity for arrays to circumferentially direct current using a *chronic* implant despite an encapsulated tissue response.

Implications for Adaptive DBS Therapies

The accumulation of improvements in DBS technology is driving towards implementation of adaptive DBS that can meter stimulation and provide a more consistent level of therapy for each individual patient. Several studies have shown how relatively simple implementations of on-demand or threshold based control algorithms can improve parkinsonian motor signs in acute settings. For example, an algorithm that used the amplitude of beta power to turn STN DBS on and off showed slight benefits over continuous, therapeutic DBS in a cohort of patients [13]. Improved sensing and stimulation electrode geometries are likely to enhance the isolation of salient biomarkers and provide improved spatial selectivity for stimulation. Examination of intraoperative STN LFPs has shown a depth-dependence in the amplitude of beta power, with the largest signal being detected in the dorsal or central part of the STN [44-47]. As shown in **Fig. 7**, sensing through the rDBSA revealed heterogeneity of LFPs around the circumference of the lead in STN and GP, which may not be sensed with larger, cylindrical contacts.

Detection of salient biomarkers of disease pathophysiology and stimulation therapies is of high clinical interest. LFPs are considered fairly robust in chronically implanted devices [48], while still providing useful data regarding the underlying neuronal activity of the sampled population. In the context of brain nuclei and sub-nuclei, it is important to consider the spatial scale of LFPs, as highlighted in this study. LFPs related to pathophysiology and

mechanisms of DBS, will likely be more informative at a smaller spatial scale than what is currently offered by the relatively large cylindrical electrodes on commercial DBS leads [49]. It is possible that the optimal size and spacing are below the spatial resolution of the rDBSA, and future studies would be important to further investigate this possibility.

Conclusions

DBS leads with segmented electrodes around and along the lead shank have potential to further the study of mechanisms of DBS therapy by (1) enhancing the targeting of stimulation, (2) recording LFPs at a finer spatial scale. Here, we provide the first *in vivo* evidence from chronically implanted DBS arrays in primates supporting these concepts. Such DBS technology is poised to create a much richer space from which to develop closed-loop stimulation protocols.

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Figure 1. rDBSA dimensions

Comparison of scaled-down versions of the (A) human DBS lead and rDBSA leads with electrode configurations for the (B) STN and (C) GP. (D) Images of the GP version of the rDBSA fully assembled (top) and of the planar thin-film electrode array before wrapping around the carrier tube (bottom). Scale bar: 1 mm.

Figure 2. rDBSA implant procedure

(A) Cephalic recording chambers were surgically attached to the skull and the target area of the brain was mapped with microelectrode recordings (B). The rDBSA was implanted with the microdrive (C). The flexPCB cable was folded over the chamber (D) and secured within the slit adapter and cable guard (E). The omnetics connectors were secured in a dry chamber with setscrews and silicone and allowed access to the electrical connection for each rDBSA (F).

Figure 3. In vivo impedance measurements

(A) Averaged 1 kHz impedances of an STN rDBSA implant in Monkey P (mean $\pm$ SE). Stimulation was delivered on day 34 (red diamond) and impedance spectroscopy on days 27 and 72 (grey diamonds). (B) Impedance spectroscopy Nyquist plots measured after implant before stimulation (left column) and on the final day of the study after stimulation (right column). Macroelectrode contacts are labeled 1-16 and 25-40 (green), and the microelectrode contacts are labeled 17-24 (blue). Impedance values measured at low frequencies (1 Hz) are in the top right region of each plot, and impedance values measured at high frequencies (25 kHz) are in the bottom left. Impedances from only viable contacts are shown.

Figure 4. Post-implant unit-spike recordings

(A) Location of rDBSAs within the GPe/GPi (left) and STN (middle) in subject P, as well as the STN (right) in subject G. No discriminable spike activity was detected on the GPe/GPi rDBSA in subject G. (B) rDBSA microelectrode recordings from the GP (top) and STN (bottom) on the day after implant. D: dorsal, M: medial, A: anterior.

Figure 5. Therapeutic effects of DBS using four electrodes in a single row

Contralateral rigidity mUPDRS sub-scores off (MPTP) and on stimulation at sub-therapeutic frequencies (30 Hz), sub-therapeutic amplitudes (50-200 μ A), and at therapeutic levels (130 Hz, >200 μ A) summed over all joints. Error bars display standard deviation over multiple assessments. Asterisks indicate significant differences with $p < 0.05$ according to the Wilcoxon rank sum test.

Figure 6.

Directional stimulation. (A) Coronal histological slices (cresyl violet) of Subjects P and G at a level where the rDBSA passed through the subthalamic nucleus (STN) adjacent to the internal capsule (IC). (B) Color map of the maximum amplitude of displacement (disp) of the knee and hip joints in Subjects P and G, respectively, evoked by individual stimulation through each of the 32 macroelectrodes. (C) Examples of directional stimulation through row 6 of the STN implant in Subject P near the border with internal capsule. Cross-section of row 6 of the rDBSA shows electrodes facing dorsal (D), lateral (L), ventral (V), and

medial (M) in the context of histology. Hashed boxes show non-usable contact sites. Stimulation was delivered at 130 Hz at increasing amplitudes of 150 μ A (cyan), 300 μ A (green) and 450 μ A (magenta). (D) As in (C), examples of directional stimulation through row 2 of the STN implant in Subject G.

Figure 7. LFP changes induced by DBS in subject G

(A) Example spectrograms recorded from one column of bipolar LFPs recorded from the GP rDBSA during stimulation through the STN rDBSA. DBS was turned on at time 0. The cartoon on the left shows the columns used for recording in the GP (green filled circles) referenced between columns (brackets). DBS was delivered at high frequency/low amplitude (left column), low frequency/high amplitude (middle column), and high frequency/high amplitude (right column). (B) Example power spectral densities off (blue) and on high frequency/high amplitude (red) stimulation recorded from one pair of contacts in the GP (right) and STN (left). The blue shaded area spans the beta band (10-20 Hz) and the green shaded area spans the gamma band (70-80 Hz). (C) Colors show the amplitude of beta/gamma power recorded in the GP with STN stimulation on relative to off stimulation. (D) Colors show the amplitude of beta/gamma power recorded in the STN with GP stimulation on relative to off stimulation. All values were averaged over four recording sessions.

Magenta outlines show bipolar contacts displayed in part B. Hashed boxes show unviable contacts.

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TABLE I

Comparison Between a Standard DBS Lead and an rDBSA Lead Customized for Targeting the STN and the GP

	Scaled-down Clinical Lead	STN rDBSA	GP rDBSA
Contact Height (μm)	500	360	470
Contact Width (μm)	n/a	360	370
Contact Surface Area (μm^2)	982,000	98,537	149,361
Axial Pitch (μm)	1000	572	750
Radial Pitch	N/A	90°, 471 μm	90°, 471 μm
Lead Diameter	625	600	600
1 kHz Impedance ($\text{k}\Omega$, $\text{M}\pm\text{SD}$):			
macroelectrodes	4.55 $\pm$ 2.02	364 $\pm$ 220	443 $\pm$ 255
microelectrodes	N/A	956 $\pm$ 571	1480 $\pm$ 478