16 Intraoperative Research during Deep Brain Stimulation Surgery

Shane Lee, Meghal Shah, Peter M. Lauro, Wael F. Asaad

Abstract

In this chapter, we discuss the process of conducting intraoperative research during deep brain stimulation surgery. Microelectrode recordings, which are routinely used for intraoperative mapping, present a unique opportunity to listen to and record from neurons in the brain. These recordings, with or without a behavioral task, offer a window into human neuronal circuit function with a granularity that is not otherwise available. This chapter will go over the types of research questions that are amenable to intraoperative neurophysiology research, patient selection, and the additional equipment needed. Considerations such as task development, data analysis, and related neuroimaging are covered. Finally, limitations and ethical considerations are discussed.

Keywords: deep brain stimulation, neurophysiology, microelectrode recordings, intraoperative research, methods, behavioral task, spiking activity

16.1 Introduction

Deep brain stimulation (DBS) surgery presents neurosurgeons with a rare opportunity to observe neural activity in the brain. DBS electrode targeting typically relies upon a combination of imaging and neurophysiology. Though magnetic resonance imaging (MRI) and computed tomography (CT) techniques are becoming more powerful, many gross structures and especially subregions within a therapeutic target of interest still remain difficult to visualize.[1] In conjunction with preoperative—and increasingly intraoperative—imaging, microelectrode recordings (MERs) are often used for intraoperative mapping to delineate structural borders and identify subareas within a region of interest (ROI) that may lead overall to improved patient outcomes.[2,3,4,5,6]

In combination with carefully designed behavioral assays, recording and analysis of intraoperative neuronal data can provide insight into the functions of these structures and how their activity relates to other areas of the brain, behaviors, or disease processes. This approach has been employed in a growing number of studies, helping to improve understanding of basic and pathological neural activity in essential tremor,[7,8] Parkinson's disease,[8,9,10] Tourette's syndrome,[11,12,13] obsessive-compulsive disorder,[14,15,16] and others. Other types of neural recordings are also being used increasingly in conjunction with MER, including electroencephalography (EEG) and electrocorticography (ECoG), adapting techniques largely pioneered within the context of epilepsy monitoring.[17,18,19]

For Parkinson's disease, the subthalamic nucleus (STN) and globus pallidus pars interna (GPi) are the most common therapeutic targets. Patients have performed tasks manipulating joysticks or haptic gloves while single neuron, multiunit, and local field potentials (LFPs) were recorded in STN or GPi.[5,20] Single neurons in these areas have demonstrated movement-related and direction-specific spike rate modulations, and STN neurons further showed oscillations at 3 to 5 Hz "tremor" frequencies or 15 to 30 Hz "beta" frequencies.[5,6,21] Other studies have engaged awake patients with tasks designed specifically to correlate neural activity with precise aspects of behavior. Both Zavala et al and Zaghloul et al demonstrated in distinct decision-making tasks that neuronal firing in the STN is correlated with conflict.[22,23] Using simultaneously recorded scalp EEG, Zavala et al showed that this STN activity was driven by activity in the frontal cortex.

In this chapter, practical considerations for conducting human intraoperative neurophysiology research are discussed.

16.2 Formulating Hypotheses

In developing a neurophysiology research study with human subjects, investigators must address the following questions while designing an experiment:

1. What cortical or subcortical structures are of interest?
2. What disease processes are of interest or would provide access to the structure in question?
3. Will this be an observational study or will there be behavioral task or measure?
4. What type(s) of neurophysiological recordings will be acquired?

The greatest potential limitation of intraoperative research is that by nature of the procedure, only patients with neurological disease will undergo DBS surgery. This may limit the interpretation of the data and may also limit the structures available for MER. Thus, the most common targets accessible in this fashion are the STN and GPi (with Parkinson's patients, the latter also for primary dystonia)[24] and the ventral intermediate nucleus (Vim) of the thalamus (with essential tremor patients).[8,25] MER can help localize specific substructures within these areas that are most desirable for electrode implantation.

In addition to these movement disorders that are now routinely treated with DBS, treatment of a number of psychiatric conditions has been explored with DBS therapy. For example, in extreme cases of obsessive-compulsive disorder and Tourette's syndrome (a combination of both motor and psychiatric pathology) the ventral internal capsule/ventral striatum (VC/VS) or cingulate cortex has been targeted for DBS with potentially impressive benefits in some patients.[14,15,16] For intractable obsessive-compulsive disorder, others have targeted the STN or the ventral anterior internal capsule/inferior thalamic peduncle.[26]

Recordings can be made through nontarget structures that are encountered along the trajectory to the target structure, such as frontal cortex and striatum, and in some cases just beyond the target structure, such as the substantia nigra, if such regions are routinely mapped to define a target's distal border.[27] In some cases, with the proper approvals, cortical recordings can be made

Deep Brain Stimulation | 04.03.19 - 16:32

with subdural electrodes, not typically required for DBS surgery, inserted through the standard burr holes.[10]

Often, a roadmap regarding what types of behaviors may be mediated by particular structures is available in the form of prior human or nonhuman primate functional MRI (fMRI) studies and in the wide body of literature describing electrophysiological correlates of behavior in animal studies. Adapting these behavioral paradigms to humans offers the opportunity to extend our knowledge of the neural correlates of behavior, especially those behaviors which may be elaborated in or are unique to humans.

16.3 Patient Selection and IRB Approval

Approval of the research protocol by an institutional review board (IRB) is mandatory even for observational studies. Patients who are considered for DBS are ideally first evaluated by a multidisciplinary team of clinicians. Appropriateness and fitness for surgery is determined by the surgeon, neurologist, anesthesiologist, and any other clinicians who are involved in the patient's care. Once patients are considered appropriate for surgery, they can be approached by a member of the clinical or research team per their specific IRB protocol to obtain voluntary consent after explaining the potential risks of the research-specific procedures (outlined in greater detail below). Because patients typically desire to please their physicians, especially in situations where they think this could improve the care or attention they receive, one should explain clearly that the quality of care provided will not depend on their participation. In addition, respecting a patient's decision-making autonomy extends throughout the process such that they should be allowed to withdraw from participation at any time, including during the procedure.[28]

Potential risks of intraoperative research include those related to additional time incurred during surgery to carry out the experimental procedures, such as behavioral tasks, the placement of additional electrodes (e.g., subdural electrodes) that are not typically required for the clinical procedure, and discomfort of the patient or anxiety related to task performance. Particular research protocols may incur other risks. In general, risks accrue as a result of any nonstandard surgical maneuvers or deviations from the clinical procedure. For example, the placement of subdural ECoG electrodes is not required for routine DBS procedure. While placement has been reported as generally safe, there is nonetheless a nonzero risk associated with any additional maneuver, and there may be risks not immediately considered (e.g., the additional time required to insert an ECoG electrode may result in increased pneumocephalus which could affect the accuracy of final DBS electrode placement).[29] While in some studies ECoG electrodes are used in hopes of improving the future efficacy of neuromodulation (such as a source of control signals for closed-loop DBS), in other cases the goal may be basic science. It may be easier, therefore, to justify the additional maneuver in the former case than in the latter, so careful deliberation over these issues is mandatory. Simply because an IRB may be convinced that a particular protocol is reasonable does not mean that the protocol is necessarily in a patient's best interest.

16.4 Equipment and Setup

In most of human acute recordings, the operating theater also serves as the laboratory. In this unique arrangement, some of the equipment serve a principally clinical purpose but may also serve research goals with no or minimal modification.

MER in DBS allows an assessment of somatotopic responses, in which high bandpass filtered neural recordings at multiple sites are monitored over audio speakers while a clinician elicits various neural responses by manipulating the face/jaw and limbs. Typically, 1 to 5 microelectrodes arranged in a Ben-Gun array are advanced toward a predefined target structure while somatotopic assessments performed at various locations along the trajectories.

In general, neural data recording requires electrodes, signal amplifiers, and an acquisition system. Depending on the research questions, additional systems may be necessary to measure movement or administer tasks to awake patients while recording. An example of multichannel neural and behavioral recording is shown in ▶ Fig. 16.1.

Typical sharp tungsten or platinum-iridium electrodes with impedances around 300 to 1000 kΩ are typically used to record single- and multiunit spiking activity. Online during a case, signals measured with these electrodes are typically bandpass filtered from approximately 300 Hz to around 10 kHz, appropriate for isolating action potentials from neurons surrounding the recording tip.

The Nyquist sampling theorem sets a lower bound on the appropriate sampling rate of the digital acquisition system. Nyquist states that the sampling rate must be two times greater than the maximum frequency of the activity of interest. For example, if one wants to sample single-unit activity at 10 kHz, then the minimum sampling rate according to the Nyquist theorem would be 20 kHz. In practice, due to the noisy nature of these data, it is generally advised to allocate spectral "overhead" to this calculation which helps to guarantee that the signal of interest will be recorded faithfully; though higher sampling rates require greater data storage and an analog-to-digital interface capable of handling these rates. Data storage is relatively inexpensive, and acquisition systems' capabilities are growing, so sampling rates of 30 to 50 kHz are commonly employed.

If one wishes to test hypotheses about single- or multiunit spiking activity, then the typical 300 Hz to 10 kHz band will be appropriate. If one is testing hypotheses involving lower frequency LFPs (approximately 0.5–600 Hz), the neural recordings must be filtered appropriately with a very low high pass band stop (~ 0.1 Hz) and a low pass band stop of at least 1200 Hz to capture the highest frequency signal (2 × 600 Hz). Alternatively, if filtered data is not needed "online" as it is being acquired, data can be saved in its "raw" form, with the bandpass filter characteristics set to be the most permissive, for offline filtering as needed.

There are sometimes options available for online spike detection. Though they may be useful for rapid online analysis, in principle there are no benefits to online-only spike detection if not immediately required for closed-loop control or feedback. Saving raw data and performing offline spike sorting is preferable, because spike sorting can be performed in a more systematic manner without the limitations of the often-busy surgical environment.

Deep Brain Stimulation | 04.03.19 - 16:32

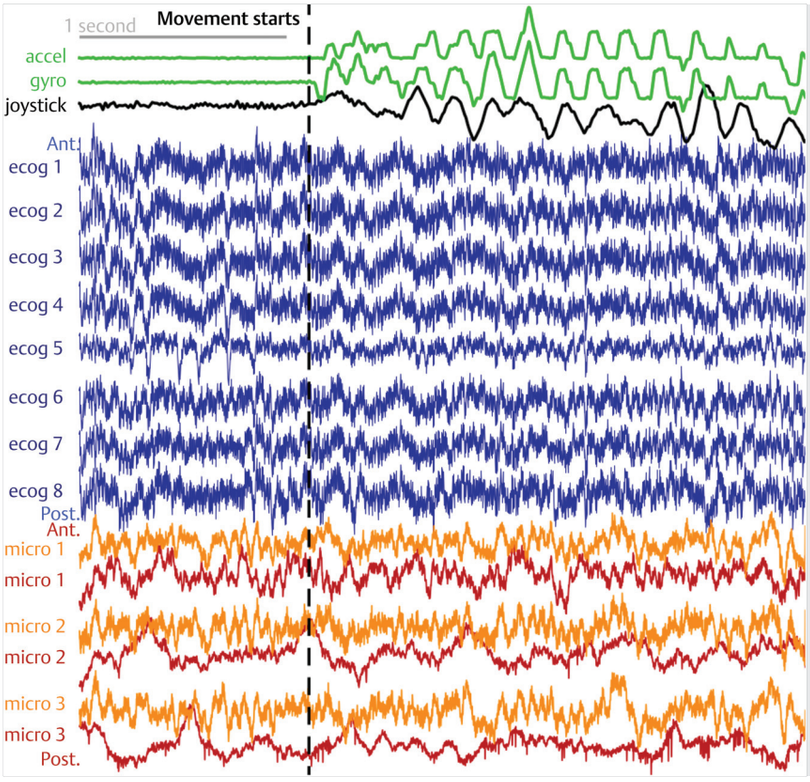

Fig. 16.1 Synchronization of behavioral and neural data.
Intraoperative data recorded from ventral intermediate nucleus of the thalamus (LFPs) and somatomotor cortices (ECoG). Examples of 3.5 seconds of composite three-axis accelerometer and three-axis gyroscope (*green*), task joystick (*black*), 8 channels of ECoG (*blue*, from anterior to posterior), and 3 channels of depth electrodes (*orange*/*red*, from anterior to posterior). Macro tip is 3 mm above the micro. Electrodes are 2 mm from each other. LFP on both, also single unit responses on micro. Movement starts at the black line.

Signal amplifiers and acquisition systems should be selected to suit current and anticipated future requirements. The role of the signal amplifier is to faithfully capture very small, noisy neural signals with high fidelity, while the acquisition system must be able to write multiple channels of data rapidly with no loss. The number of channels also depends on the specific clinical and research aims. For a minimal system, the number of channels might equal the number of microelectrodes implanted for recording, but it is more likely that a research system requires additional analog and digital inputs. Having a primary, clinical system that can serve as a data hub for other recording streams is convenient, as this will implicitly synchronize any data streams for which it is responsible (see below). These additional channels often come in a wide range of connector types and can be sampled at widely varying sampling rates, often with both an upper limit on the maximal signal amplitude or a bound on the amplitude resolution.

As an example, accelerometers can be placed on patient limbs to assess movements, and these signals can be sent to the amplifier and acquisition systems. But because relevant limb movements are biomechanically limited in speed and frequency, 10 kHz or greater sampling is potentially superfluous. Therefore, these inputs should be software-limited to an appropriate sampling rate that accounts for the trade-offs with storage mentioned previously. At our site, we routinely record accelerometer activity at 1000 to 3000 Hz, which results in manageably small data sizes but faithfully captures the fine details of movement.[30]

Routinely, the data recorded for three full-bandwidth channels of microelectrode data, three lower rate field recordings, and eight analog channels at lower sampling rates results in approximately 10 GB of data for 2 to 3 hours of recording. Including additional high-bandwidth channels, such as ECoG, can triple these data sizes for each case. Neurophysiology systems capable of recording high-bandwidth data should be capable of rapid transfer of these data to an external device for offline analysis.

Another important consideration in selecting a neurophysiology monitoring system is the software. Though hardware specifications may seem to be appropriate, it is the software that provides the interface that will be critical for both providing quality patient care as well as efficiency in processing the recorded data. Equipment and interfaces approved by a country's health and safety regulatory commissions may impose restrictions on how frequently software is updated, despite a company's best intentions, so the shipping product must be free of major issues. Good commercial vendors who appreciate the importance of intraoperative research and are committed to supporting it will work to mitigate issues with their hardware and software as they are identified. Wherever possible, open-source and cross-platform data formats and software tools are preferable to closed formats, as this will ensure longevity in data archival and future access.

16.5 Behavioral Task Control

In most cases, research involving human intracranial recordings requires quantitatively rigorous behavioral and precisely time-stamped metrics for correlation with neural signals. A simple

Deep Brain Stimulation | 04.03.19 - 16:32

accelerometer attached to a patient's wrist may be sufficient for some questions about the relationship of movement to neural activity, but for other behavioral activity, more interesting questions addressing complex motor behaviors and cognition will likely require a dedicated behavioral task control system. For example, our system uses a portable case with rack mounted hardware to house a standard desktop computer, a digital acquisition system used for behavior that is different from the neurophysiological system, and a multi-monitor mount. This system includes a monitor that can be positioned in front of the patient, as well as a joystick that controls the tasks. We present visual tasks to the patients while they manipulate a joystick or button box to provide behavioral responses. For other types of tasks, haptic gloves or other unique manipulanda might be employed for patient interaction. Irrespective of the input device selected for the tracking of behavioral data, patient comfort and reproducible placement are crucial to capturing performance accurately and reliably.

In our laboratory, tasks are programmed in MonkeyLogic, a free, MATLAB-based software toolbox[31,32,33] that enables millisecond precision in our psychophysical experiments (MonkeyLogic is currently supported and maintained at the NIH: https://www.nimh.nih.gov/labs-at-nimh/research-areas/clinics-and-labs/ln/shn/monkeylogic). Importantly, this software also sends precisely timed digital event codes to the neurophysiology acquisition system, enabling synchronization between the two systems. The goal of behavioral–neural synchronization in neurophysiology is to be accurate to ~ 1 millisecond timescale; in contrast, synchronization between behavior and slower modalities, such as fMRI, is often performed manually (the experimenter simultaneously initiates both systems by striking a key on each system, one with a finger of each hand).

16.6 Data Analysis

Creating a robust data processing and analysis pipeline is critical for an efficient and reliable research workflow. Even though most analyses can be performed post hoc and not online in the operating room, the acquisition system's hardware and data format serve as the starting point. When dealing with separate systems that are synchronized, custom software is often necessary to align the data according to the synchronizing signal.

Modern neuroscientific data analysis generally falls into two categories: continuous and point process. Continuous data consists of any time series, such as neurophysiological field potentials or accelerometer output. Point process data consists of discrete events, such as spiking activity or activity counts (e.g., number of choices A versus B). Specific methods exist for each class of data, though it is often necessary or desirable to convert between the two data types. Several neural data-specific guides are available that are balanced in presenting both theory and practical implementation.[34,35]

One of the most common and critical preprocessing steps in neurophysiology is spike sorting, which takes a continuous time series recording as input and converts it to a set of events that are labeled into one or many single "units." In general, spike sorting is a procedure to isolate an individual neuron's spikes from other neurons' spikes in an MER. Typically, MERs sampled at a high rate[3] (30 kHz) are bandpassed (approximately 0.3–10 kHz), resulting in a zero-mean noise baseline. A threshold is calculated based on the noise distribution and spike waveforms are isolated as threshold crossings. These waveforms are then analyzed using automated or semiautomated methods, such as principle components analysis and clustering algorithms (e.g., k-means algorithm). Manual methods that categorize waveforms on the basis of waveform features, fully automated methods, or a hybrid of approaches are commonly used, but knowing the ground truth is difficult, so accurate spike sorting remains an active area of research.[36] Both open-source and commercial solutions exist to perform spike sorting.

Even within a data type, different techniques that are commonly employed can lead to different qualitative and quantitative interpretations of neural activity. In ▶ Fig. 16.2, 2 seconds of ECoG data recorded from human somatomotor cortex of an essential tremor patient are shown with different spectral techniques demonstrating different results. The choice of analysis can make a substantial difference in the interpretation of the results. ▶ Fig. 16.2**a** shows the time series, referenced and z-scored. There was clear oscillatory activity that occurred at different times in the epoch, but the precise frequency characteristics need to be quantified. ▶ Fig. 16.2**b** shows a discrete Fourier transformed (DFT) power spectrum in which two distinct peaks were seen at 1.5 and 22 Hz. The DFT analysis assumed that the data were constant within the analysis window—a property called stationarity—which may be a poor assumption here, considering that different oscillatory activity was variable within this epoch.

Multiple methods are available for investigating time-varying spectral features. The most common is the short-time Fourier transform (STFT), which is also commonly referred to as a spectrogram (▶ Fig. 16.2**c**). In the STFT, small segments of time (in this case 0.5 s) were analyzed, and the window was slid across at short intervals (0.025 s) to provide a time-varying estimate of the activity. As the frequency interval is inversely proportional to the amount of time in the analyzed window, shorter time windows result in a larger frequency interval or poorer frequency resolution. The trade-off of frequency resolution, amount of data, and stationarity of data should be considered when using the STFT. Here, both low- and higher-frequency activities were seen, but the activity around 25 Hz was mostly limited near 1.2 s. Furthermore, the first estimate of data is centered around 0.25 s, and the last sample was centered around 0.75 s, and no estimates were available outside of those, meaning the data of interest needed to be within the boundaries set by the temporal window parameters. The timing information seen in the STFT was lost with a power spectrum (▶ Fig. 16.2**b**).

Wavelet-based time-varying spectral analyses are also commonly employed. These can provide estimates for an entire short window but also have their own shortcomings. In ▶ Fig. 16.2**d**, the power was calculated from a family of Morlet wavelets convolved with the time series. This method showed a consistent result with the STFT for the higher-frequency activity and its timing, but the lower- frequency activity was not clearly captured.

Finally, in ▶ Fig. 16.2**e**, a Hilbert transform spectral method was applied in a similar manner to the Morlet wavelets. This method captured the activity around 22 Hz well along with the lower-frequency activity which appeared to be primarily isolated to the first 0.5 s of the data. The power spectrum (▶ Fig. 16.2**b**) picked up this activity but not the timing, while

Deep Brain Stimulation | 04.03.19 - 16:32

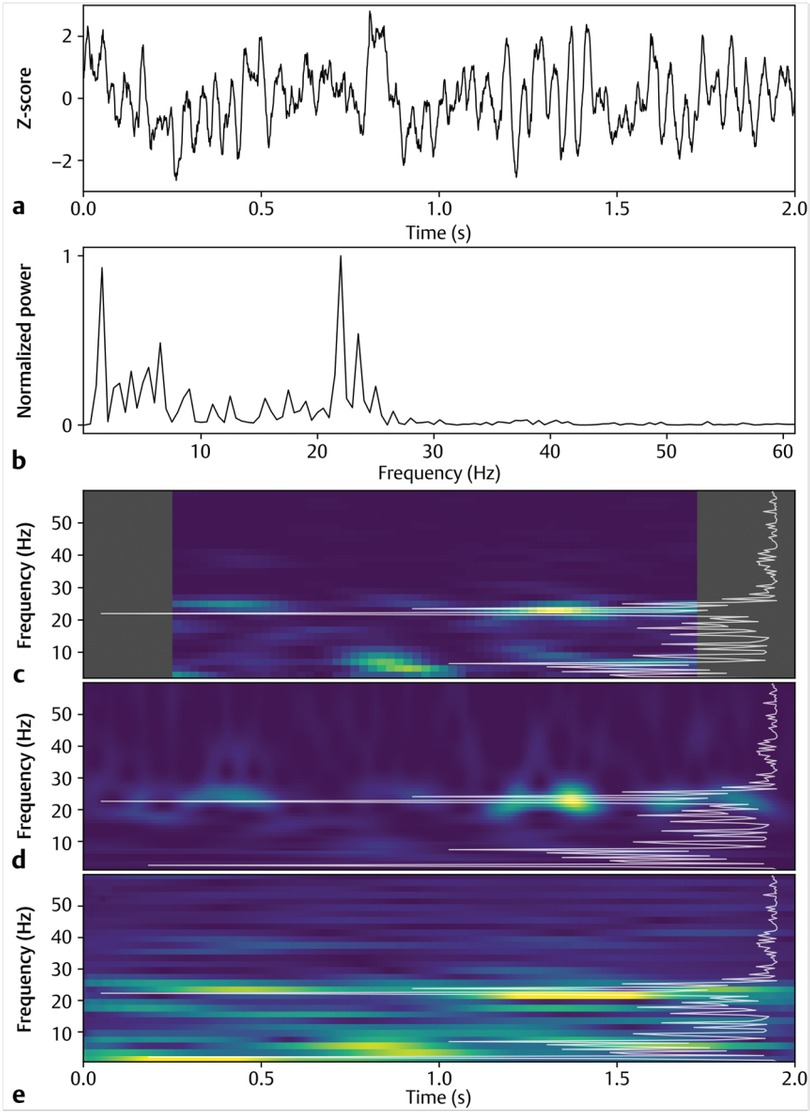

Fig. 16.2 Choice of analysis affects interpretation.
(a) Two seconds of human somatomotor ECoG data recorded from essential tremor patient. Recorded at 11 kHz. Downsampled to 1 kHz. Referenced, normalized. **(b)** Discrete Fourier Transform shows stationary peaks of similar height at 1.5 and 22 Hz. The stationarity assumption misses time-varying spectral changes. **(c)** Short-time Fourier Transform (STFT). 0.5 s windows, 0.025 s overlap for temporal estimates. Low-frequency peak and high-frequency peaks are observed with temporal information. No estimates for beginning and end of a short time series. Frequency resolution is limited by length of window. At 0.75 s, 5–10 Hz activity appears briefly. 1.5 Hz activity is not visible here. Mostly consistent with the Hilbert (E). **(d)** Morlet wavelet spectrogram. $\sigma = 7$. Due to scaling, only activity at ~ 25 Hz is visible, within a narrow temporal window. No low-frequency activity is resolved here. **(e)** Hilbert transformed power spectrum. Low-frequency and high-frequency activity is captured; suffers from potentially poor temporal resolution but estimates for entire sample of data. Mostly consistent with the STFT.

the STFT (▶ Fig. 16.2**c**) picked up this activity in its first estimate, though it was difficult to see represented in the figure, and the Morlet (▶ Fig. 16.2**d**) had these spectral features washed out by the much higher powered activity around 25 Hz. In general, the choice of spectral technique comes down to empirical questions about one's hypothesis and represents a trade-off between temporal precision and frequency precision. This example illustrates the necessity for these analyses to be selected on the basis of the hypothesis prior to analysis of one's data.

A substantial amount of data analysis can be done now on widely available computer hardware on all major computing platforms. In addition, depending on the type of analysis necessary, multiple commercial software solutions may exist, though these are often operating system (OS)-limited. Many free and non-free high-level programming languages (e.g., Python: https://www.python.org/) have fewer OS limitations and also have a large number of extensions or modules that are specifically tailored for scientific computing. Commercial programs (e.g., MATLAB, from Mathworks, Inc.) often have the benefit of customer support, while open-source solutions have third party paid support vendors who may be able to provide assistance. Both free and commercial software have large communities of users from which one might be able to get help.

16.7 Image-Based Reconstruction of Recording Sites

Offline analysis of MER data often requires the reconstruction of recording and/or stimulation sites in order to verify appropriate electrode placement and to understand the potential anatomical distribution of neural and/or behavioral data. Imaging data (cortical thickness, diffusion-tensor imaging) may also provide additional insight into the neural or behavioral features observed in intraoperative experiments. Clinical imaging used for surgical targeting and placement confirmation can be used,

Deep Brain Stimulation | 04.03.19 - 16:32

but multiple processing steps are needed for reproducible calculation of stereotactic coordinates.

16.7.1 Image Acquisition Considerations

Preoperative MRI is typically used to plan DBS implantation surgical trajectories and targets. Potential research-relevant sequences include:

- High-resolution T1-weighted images (e.g., MPRAGE) prior to gadolinium contrast to visualize anatomical structures.
- T2- or T2*-weighted images, ideally with fat suppression, for structural template for diffusion weighted images (DWI).
- DWI sequence for calculating tractography either for preoperative planning or postoperative analysis.
  - T1- and T2-weighted images are typically acquired as part of standard clinical imaging workflows. These images should be of high resolution (voxels should be 1.0 mm isotropic). DW images have several additional, important acquisition parameters. In general, DW images are formed by applying paired magnetic gradient pulses to the tissue, allowing the diffusion-related properties of tissue to emerge. Typically, the isotropy of spatial diffusion of protons in water (or lack thereof) is examined to differentiate white and gray matter, as it is assumed that proton diffusion is more constrained in fatty myelin sheathes. Tractography uses this anisotropic diffusion, assigning the diffusion orientation with the highest anisotropy in each voxel (i.e., the direction in which diffusion was the most constrained—this is thought to occur when this diffusion orientation is parallel with axons). These voxel-based orientations are then combined to form long-reaching estimations of white matter "tracts." This technique can help to identify target structures by their connections to other structures or provide additional anatomical context to neurophysiological or clinical data (e.g., stimulation to specific white matter tracts associated with more paresthesias). To estimate accurately the orientation of white matter tracts, multiple diffusion gradient directions are used during the acquisition sequence. For research purposes, a minimum of 64 gradient directions are recommended.[37] DWI sequences typically have one or more so-called B-values (expressed in seconds/mm^2), which describe the degree of diffusion weighting applied to tissue. Specifically, the B-value is the product of diffusion gradient amplitude, the duration of applied diffusion gradient pulses, and the duration between the first and second paired pulses. Different B-values allow different comparisons of diffusion-based tissue contrast.
  - For example, a DWI sequence with a single shell (b = 1000) is used for standard tensor-model diffusion tensor imaging (DTI). Multishell acquisition sequences (b = 1000, 2850) can be used for more advanced diffusion imaging techniques (e.g., neurite orientation dispersion and density imaging [NODDI] or diffusion spectrum imaging [DSI]). These latter techniques are typically used for disentangling neurite density, orientation dispersion index, and axonal coherence.

The surgical frame used for the DBS implantation surgery can also influence preoperative image sequences. Patient-specific frames, such as FHC's STarFix platform, typically require a preoperative CT scan, which is registered to preoperative MR images prior to planning. Patients with an Integra CRW or Leksell frame can also be imaged with preoperative CT. If patients are using an MR-compatible frame, magnetic field distortion of the frame and tissue should be considered and accounted for. In addition, affixed stereotactic frames may impact the duration of time patients will tolerate an MRI scan, which may limit the ultimate resolution of scans. A good review of frames, image registration, and other sources of error in stereotactic surgical planning is available.[38]

Intraoperative imaging provides valuable data for deep or surface electrode location and/or pneumocephalus. Intraoperative fluoroscopy and CT are fairly simple modalities for DBS surgery of awake patients. Intraoperative MRI (typically used for asleep DBS procedures) can provide more anatomical detail but is typically incompatible with MER.

Postoperative imaging (CT or MRI) can help to confirm the final location of electrodes. For direct visualization of DBS electrodes, postoperative CT can be acquired and registered back to preoperative MR images. Pneumocephalus-related brain shift (if a concern) is better identified with postoperative MRI. If postoperative MRI is used, it must be performed in a 1.5 T magnet, and performed sequences must have a specific absorption rate less than 0.4 W/kg in the head. Postoperative fMRI sequences are typically approved on a case-by-case basis and may require IRB approval.

16.7.2 Reconstructing the Recording Locations

Image processing steps are unique to the software package one decides to use. Software packages include the Analysis of Functional Neuroimages (AFNI; https://afni.nimh.nih.gov)[39,40] the FMRIB Software Library (FSL; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki),[41,42,43] the MATLAB-based Lead-DBS (http://www.lead-dbs.org),[44] and Statistical Parametric Mapping (SPM; http://www.fil.ion.ucl.ac.uk/spm) software packages. Many of the steps described below use AFNI, as it provides command-line flexibility for manipulating datasets, is compatible with other modality-specific software toolkits (TORTOISE, Freesurfer), and is free and open source.

Reconstructing DBS contact or MER coordinates can be useful for overlaying/understanding clinical, behavioral, or neural data in anatomical space. Generally speaking, the "bottom" or "final" location coordinate of a DBS electrode is typically considered the bottom of DBS contact 0 of a Medtronic 3387 or 3389 electrode or similar device. Semiautomated methods using AFNI for reconstructing postoperative DBS contacts[45] or MER locations from patient-specific platforms exist.[1]

To perform reconstructions, all images should be brought to a standard stereotactic coordinate space. Intra- or postoperative images can be registered to a preoperative plan in order to understand the location of recording or stimulating electrodes relative to planned implantation coordinates. However, this depends on the choice of stereotactic frame or platform. For example, Leksell frames are typically integrated with the Medtronic StealthStation or Brainlab systems, while FHC STarFix platforms require Waypoint software. At the time of writing, the former software does not export the registration matrices

Deep Brain Stimulation | 04.03.19 - 16:32

between images or any other information, while Waypoint can export registration matrices between images and coordinates of anterior commissure (AC), posterior commissure (PC), and targets as a plain text file that can be processed in external software packages.

To create a stereotactic coordinate space outside a surgical plan, AC and PC coordinates can also be manually determined in preoperative images. The preoperative volume should then be affinely transformed so that the midsagittal plane is aligned to the AC-PC axis. AC/PC determination can be performed using software such as AFNI, Medical Image Processing, Analysis, and Visualization (MIPAV; https://mipav.cit.nih.gov), or 3D Slicer (https://www.slicer.org). Consistent criteria are required for AC/PC delineation; for this, the neurosurgeon's determination can be used. From there, electrode coordinates can be manually delineated by navigating through planning software and locating the bottom of electrodes present within the images. Alternatively, coordinates can be reconstructed from Leksell frame arc and ring angles with the depth of the recording probe.

When reporting coordinates, it is important to differentiate between patient-specific and atlas coordinates. Patient-specific coordinates allow for the faithful reporting of targets relative to a patient's individualized surgical plan, while using a standardized atlas allows for reporting of group-level coordinates to account for anatomical or surgical variability. To normalize patient anatomy to an atlas, perform a nonlinear registration (e.g., AFNI's 3dQwarp) between the patient's high-resolution preoperative images (typically T1-weighted) and the atlas template volume. Montreal Neurological Institute (MNI) atlases are typically used, such as the 2009 152-subject average brain (http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009).[46,47,48] Disease-specific and more subcortically oriented atlases also exist, including the multi-contrast PD25 atlas, which is based on the Schaltenbrand atlas (http://nist.mni.mcgill.ca/?p=1209).[49,50,51] The Lead-DBS project maintains comprehensive listings of subcortical (http://www.lead-dbs.org/?page_id=45) and cortical (http://www.lead-dbs.org/?page_id=1004) atlases. Each atlas has its own limitations, so validation of group-level results may require two or more atlases (▶ Fig. 16.3).

Reconstruction of ECoG electrode locations is typically done with intra- or postoperative CT images. As ECoG electrodes conform to the cortical surface, they are more susceptible to brain shift and deformation due to pneumocephalus or the electrodes themselves. While electrode position can be approximated with sensory- or motor-evoked cortical potentials, there remains a research need to accurately determine electrode position.

Some groups have used fluoroscopy to localize ECoG electrodes[52], and others have used image-based methods to reconstruct cortical surfaces and spring energy functions to characterize the deformation of tissue and electrodes.[17]

16.7.3 Additional Image-Based Analyses

Investigating the topographic properties of a specific target nuclei (e.g., the difference between dorsal and ventral STN) can be performed with patient-specific anatomical segmentation or with atlas-based ROIs. Patient-specific cortical and subcortical segmentation can be performed using Freesurfer's "recon-all" command (https://surfer.nmr.mgh.harvard.edu).[53] For ease of use, the input T1-weighted volume should be already registered to the preferred coordinate space. If Freesurfer does not adequately delineate the ROIs/structures of interest, atlas-based ROIs in patient or atlas space can be used. Regardless of method, one can delineate topographic distribution of recording or stimulation coordinates by comparing them to the ROI's center-of-mass coordinates.

16.7.4 Diffusion-Weighted Imaging Analysis

For DTI analysis, one should affinely register T2- and DW images to the surgical plan coordinate space. Preprocessing of DWI data can be performed by TORTOISE's "DIFFPREP" function (https://science.nichd.nih.gov/confluence/display/nihpd/TORTOISE).[54] As DW images are prone to various forms of distortion (see review[37]), it is important to correct these sources of error. Preprocessing steps include (but are not limited to) eddy

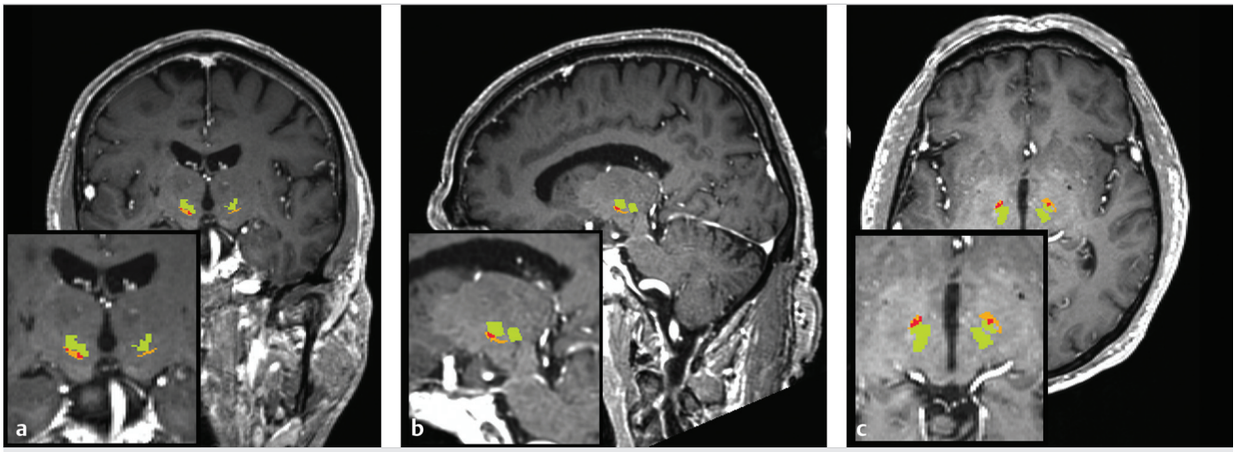

Fig. 16.3 Subthalamic nucleus (STN) volumes from two separate atlases (TT_N27, MNI PD25) overlaid in patient's T1-weighted volume native space in **(a)** coronal, **(b)** sagittal, and **(c)** axial views. Insets in lower-left corners represent the center of each panel. *Orange voxels* represent STN volume from MNI PD25 atlas, *green voxels* represent STN volume from TT_N27 atlas, and *red voxels* indicate overlap between the two.

Deep Brain Stimulation | 04.03.19 - 16:32

current correction, motion correction, and noise reduction. Regardless of the selected DTI software, these preprocessing steps should be performed with analogous functions.

With tractography estimation in AFNI, a network of ROIs must be specified to characterize what each tract "connects" to. Again, a patient-specific segmentation from Freesurfer can be used or atlas-based ROIs. In addition, ROIs can be generated around a coordinate of interest (e.g., a 2 mm radius sphere centered on a particular recording coordinate) or from voxels where a specific neural/behavioral feature was observed (e.g., high beta oscillatory activity). For research purposes, probabilistic tractography should be performed, as deterministic tractography can be susceptible to bias within the source DWIs and mask multiple fiber crossings.

16.8 Limitations

Though DBS surgery presents a fairly unique opportunity to observe neurons directly from the human brain, there are notable limitations. Perhaps the greatest limitation is the ability to record only from patients with neurological illness. Thus, activity related to apparently "normal" functions may be distorted by the pathological context, even if behavioral metrics appear grossly normal. In some cases, it may be possible to record data from the same structure in the setting of different diseases (such as the GPi in patients with Parkinson's disease or dystonia); this may add some measure of generalizability to the interpretation of the data, but even in such cases, the diseases may share common pathological mechanisms (such as the frequently observed presence of dystonic movements in Parkinson's disease patients) that limit our ability to generalize results beyond these patient populations.

The data collected from single-neuron MERs provide relatively limited spatial sampling, so it may not be representative of the circuit as a whole. This is not unique to human electrophysiology but is rather a long-appreciated trade-off between the high spatial and temporal resolution of this method and broader sampling of neural activity at coarse resolution by other methods, such as noninvasive imaging. Indeed, the combination of these modalities may be especially interesting.[55]

Furthermore, the nature of the intraoperative environment may pose challenges. For example, patient positioning can make it difficult to comfortably allow the patient to move freely in order to complete the task and may contribute to accelerated fatigue during task performance. In addition, awkward patient positioning may distort motor symptoms. As patients are not free to stand and walk, testing of major subgroups of symptoms, such as those affecting gait, is not possible. Similarly, intraoperative eye-tracking is challenging due to the positioning and lighting constraints, as well as electrical and mechanical noise within the intraoperative environment. Modifying the behavioral tasks, when appropriate, may be a necessary compromise for the operating room.

The duration of a behavioral experiment is limited during surgery compared to the typical length of similar experiments in a nonsurgical environment. As neuronal responses (especially those of single units) are variable (or "noisy"), many repetitions of a behavioral condition are typically desirable in such experiments. Therefore, ideal tasks for intraoperative experiments may have relatively few conditions and may be simpler in overall structure. This may limit the ability to study more complex cognitive functions or nonstationary cognitive phenomena such as learning.

In addition, rapidly identifying and holding reliable neurons is challenging because signals can drift due to physical changes in the positioning of the tissue relative to the electrode (physical drift) or as a result of slow changes in excitability or neuronal integrity (physiological drift). In nonhuman electrophysiological experiments, isolated neurons may be allowed to stabilize for hours in the case of acute recordings or for many days or weeks in the case of chronic recordings. Semichronic, extraoperative recordings in patients undergoing invasive electrophysiological monitoring for epilepsy also allows for longer stabilization of neural signals. In contrast, intraoperative human neurophysiology often allows only a few minutes for recording stabilization.

Patients may experience subtle, prolonged changes in alertness, cognition, or affect due to transiently administered anxiolytic medications at the beginning of a case or may develop such changes during the surgical procedure, perhaps due to anxiety, somnolence, or physical discomfort (such as due to the pressure of a standard stereotactic frame). In case of Parkinson's disease, patients are typically off their anti-Parkinsonian medications for several hours and often experience increasing discomfort as the time since the last dose increases, due to the primary symptoms of the disease (such as painful dystonias). These factors can result in unreliable behavioral data or abandonment of the task. The reliability of even simple motor task behavior is contingent upon the patient's state that can be influenced by seemingly mundane variables such as the patient's position on the bed. Every aspect of intraoperative research must, therefore, be designed to optimize these often-challenging conditions so as to record meaningful data.

16.9 Conclusions

Although there are many potential limitations and pitfalls that complicate the undertaking of intraoperative neurophysiological experiments, the rare opportunity to observe the human brain in action on the level of individual neuronal spikes is, nonetheless, enormously attractive and important. Well-designed and executed experiments can shed light on pathoneurophysiological mechanisms directly, without the need for an intermediate animal model. Likewise, well-designed tasks that investigate abstract concepts may elucidate cognitive functions that are unique to or elaborated in humans at the neuronal level.

References

[1] Lauro PM, Lee S, Ahn M, Barborica A, Asaad WF. DBStar: An open-source toolkit for imaging analysis with patient-customized deep brain stimulation platforms. Stereotact Funct Neurosurg. 2018; 96(1):13–21

[2] Seifried C, Weise L, Hartmann R, et al. Intraoperative microelectrode recording for the delineation of subthalamic nucleus topography in Parkinson's disease. Brain Stimul. 2012; 5(3):378–387

[3] Reck C, Maarouf M, Wojtecki L, et al. Clinical outcome of subthalamic stimulation in Parkinson's disease is improved by intraoperative multiple trajectories microelectrode recording. J Neurol Surg A Cent Eur Neurosurg. 2012; 73: 377–386

Deep Brain Stimulation | 04.03.19 - 16:32

[4] Gross RE, Krack P, Rodriguez-Oroz MC, Rezai AR, Benabid AL. Electrophysiological mapping for the implantation of deep brain stimulators for Parkinson's disease and tremor. Mov Disord. 2006; 21 Suppl 14:S259–S283

[5] Williams ZM, Neimat JS, Cosgrove GR, Eskandar EN. Timing and direction selectivity of subthalamic and pallidal neurons in patients with Parkinson disease. Exp Brain Res. 2005; 162(4):407–416

[6] Moran A, Bergman H, Israel Z, Bar-Gad I. Subthalamic nucleus functional organization revealed by parkinsonian neuronal oscillations and synchrony. Brain. 2008; 131(Pt 12):3395–3409

[7] Holdefer RN, Cohen BA, Greene KA. Intraoperative local field recording for deep brain stimulation in Parkinson's disease and essential tremor. Mov Disord. 2010; 25(13):2067–2075

[8] Hubble JP, Busenbark KL, Wilkinson S, Penn RD, Lyons K, Koller WC. Deep brain stimulation for essential tremor. Neurology. 1996; 46(4):1150–1153

[9] Weinberger M, Mahant N, Hutchison WD, et al. Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson's disease. J Neurophysiol. 2006; 96(6):3248–3256

[10] Miocinovic S, de Hemptinne C, Qasim S, Ostrem JL, Starr PA. Patterns of cortical synchronization in isolated dystonia compared with Parkinson disease. JAMA Neurol. 2015; 72(11):1244–1251

[11] Israelashvili M, Loewenstern Y, Bar-Gad I. Abnormal neuronal activity in Tourette syndrome and its modulation using deep brain stimulation. J Neurophysiol. 2015; 114(1):6–20

[12] Priori A, Giannicola G, Rosa M, et al. Deep brain electrophysiological recordings provide clues to the pathophysiology of Tourette syndrome. Neurosci Biobehav Rev. 2013; 37(6):1063–1068

[13] Hampson M, Tokoglu F, King RA, Constable RT, Leckman JF. Brain areas coactivating with motor cortex during chronic motor tics and intentional movements. Biol Psychiatry. 2009; 65(7):594–599

[14] Mian MK, Campos M, Sheth SA, Eskandar EN. Deep brain stimulation for obsessive-compulsive disorder: past, present, and future. Neurosurg Focus. 2010; 29(2):E10

[15] Visser-Vandewalle V, Kuhn J. Deep brain stimulation for Tourette syndrome. Handb Clin Neurol. 2013; 116:251–258

[16] Kim W, Pouratian N. Deep brain stimulation for Tourette syndrome. Neurosurg Clin N Am. 2014; 25(1):117–135

[17] Trotta M, Cocjin J, Whitehead E, et al. Surface based electrode localization and standardized regions of interest for intracranial EEG. Hum Brain Mapp. 2018; 39:709–721

[18] Yang T, Hakimian S, Schwartz TH. Intraoperative ElectroCorticoGraphy (ECog): indications, techniques, and utility in epilepsy surgery. Epileptic Disord. 2014; 16(3):271–279

[19] Greiner HM, Horn PS, Tenney JR, et al. Preresection intraoperative electrocorticography (ECoG) abnormalities predict seizure-onset zone and outcome in pediatric epilepsy surgery. Epilepsia. 2016; 57(4):582–589

[20] Hanson TL, Fuller AM, Lebedev MA, Turner DA, Nicolelis MA. Subcortical neuronal ensembles: an analysis of motor task association, tremor, oscillations, and synchrony in human patients. J Neurosci. 2012; 32(25): 8620–8632

[21] Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. J Neurosci. 2000; 20(20):7766–7775

[22] Zavala BA, Tan H, Little S, et al. Midline frontal cortex low-frequency activity drives subthalamic nucleus oscillations during conflict. J Neurosci. 2014; 34 (21):7322–7333

[23] Zaghloul KA, Weidemann CT, Lega BC, Jaggi JL, Baltuch GH, Kahana MJ. Neuronal activity in the human subthalamic nucleus encodes decision conflict during action selection. J Neurosci. 2012; 32(7):2453–2460

[24] Vidailhet M, Vercueil L, Houeto JL, et al. French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med. 2005; 352(5):459–467

[25] Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology. 1998; 51(3):850–855

[26] Tierney TS, Abd-El-Barr MM, Stanford AD, Foote KD, Okun MS. Deep brain stimulation and ablation for obsessive compulsive disorder: evolution of contemporary indications, targets and techniques. Int J Neurosci. 2014; 124(6): 394–402

[27] Ramayya AG, Zaghloul KA, Weidemann CT, Baltuch GH, Kahana MJ. Electrophysiological evidence for functionally distinct neuronal populations in the human substantia nigra. Front Hum Neurosci. 2014; 8:655

[28] Patel SR, Sheth SA, Martinez-Rubio C, et al. Studying task-related activity of individual neurons in the human brain. Nat Protoc. 2013; 8(5):949–957

[29] Panov F, Levin E, de Hemptinne C, et al. Intraoperative electrocorticography for physiological research in movement disorders: principles and experience in 200 cases. J Neurosurg. 2017; 126(1):122–131

[30] Schaeffer EL, Liu DY, Guerin J, Ahn M, Lee S, Asaad WF. A low-cost solution for quantification of movement during DBS surgery. J Neurosci Methods. 2018; 303:136–145

[31] Asaad WF, Eskandar EN. A flexible software tool for temporally-precise behavioral control in Matlab. J Neurosci Methods. 2008; 174(2):245–258

[32] Asaad WF, Eskandar EN. Achieving behavioral control with millisecond resolution in a high-level programming environment. J Neurosci Methods. 2008; 173(2):235–240

[33] Asaad WF, Santhanam N, McClellan S, Freedman DJ. High-performance execution of psychophysical tasks with complex visual stimuli in MATLAB. J Neurophysiol. 2013; 109(1):249–260

[34] Cohen M. Analyzing Neural Time Series Data: Theory and Practice. MIT Press; 2014

[35] Kass R, Eden U, Brown E. Analysis of Neural Data. In: New York, NY: Springer; 2014

[36] Wood F, Black MJ, Vargas-Irwin C, Fellows M, Donoghue JP. On the variability of manual spike sorting. IEEE Trans Biomed Eng. 2004; 51(6):912–918

[37] Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. Neuroimage. 2013; 73:239–254

[38] Zrinzo L. Pitfalls in precision stereotactic surgery. Surg Neurol Int. 2012; 3 Suppl 1:S53–S61

[39] Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res. 1996; 29(3):162–173

[40] Saad ZS, Reynolds RC. SUMA. Neuroimage. 2012; 62(2):768–773

[41] Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004; 23 Suppl 1:S208–S219

[42] Woolrich MW, Jbabdi S, Patenaude B, et al. Bayesian analysis of neuroimaging data in FSL. Neuroimage. 2009; 45(1) Suppl:S173–S186

[43] Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. Neuroimage. 2012; 62(2):782–790

[44] Horn A, Kühn AA. Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations. Neuroimage. 2015; 107:127–135

[45] Lauro PM, Vanegas-Arroyave N, Huang L, et al. DBSproc: An open source process for DBS electrode localization and tractographic analysis. Hum Brain Mapp. 2016; 37(1):422–433

[46] Collins D, Zijdenbos A, Baaré W, Evans A. ANIMAL+INSECT: Improved Cortical Structure Segmentation. In: Information Processing in Medical Imaging. Berlin, Heidelberg: Springer; 1999

[47] Fonov V, Evans A, McKinstry R, Almli C, Collins D. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. Neuroimage. 2009; 47(Suppl)(1):S102

[48] Fonov V, Evans AC, Botteron K, Almli CR, McKinstry RC, Collins DL, Brain Development Cooperative Group. Unbiased average age-appropriate atlases for pediatric studies. Neuroimage. 2011; 54(1):313–327

[49] Xiao Y, Beriault S, Pike GB, Collins DL. Multicontrast multiecho FLASH MRI for targeting the subthalamic nucleus. Magn Reson Imaging. 2012; 30(5):627–640

[50] Xiao Y, Fonov V, Bériault S, et al. Multi-contrast unbiased MRI atlas of a Parkinson's disease population. Int J CARS. 2015; 10(3):329–341

[51] Xiao Y, Fonov V, Chakravarty MM, et al. A dataset of multi-contrast population-averaged brain MRI atlases of a Parkinson's disease cohort. Data Brief. 2017; 12:370–379

[52] Randazzo MJ, Kondylis ED, Alhourani A, et al. Three-dimensional localization of cortical electrodes in deep brain stimulation surgery from intraoperative fluoroscopy. Neuroimage. 2016; 125:515–521

[53] Fischl B. FreeSurfer. Neuroimage. 2012; 62(2):774–781

[54] Pierpaoli C, Walker L, Irfanoglu M, et al. TORTOISE: An Integrated Software Package for Processing of Diffusion MRI Data. Stockholm, Sweden; 2010

[55] Sheth SA, Mian MK, Patel SR, et al. Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. Nature. 2012; 488(7410): 218–221