Quantifying Recording Quality in In Vivo Striatal Recordings

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The striatum mediates a variety of functions including movement, decision-making, motivation, and reward learning. In vivo recording is a powerful technique that allows for the interrogation of these striatal functions while an animal is awake and behaving. Here, we describe equipment needed and general setup for performing in vivo electrophysiology experiments, data processing, and quantification of recording quality. While this protocol is focused on striatal recordings, concepts should translate to other structures as well. © 2015 by John Wiley & Sons, Inc.

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In vivo electrophysiology is a powerful technique for recording neuronal activity in awake animals. As the striatum regulates a variety of behaviors that require alertness (i.e., movement, decision-making, motivation, reward learning), in vivo electrophysiology is an essential tool for studying this structure. Furthermore, dysfunction of the striatal dopamine system is implicated in several neurological disease including Parkinson's disease, schizophrenia, obsessive compulsive disorder, and addiction (Bergqvist et al., 1999; Avila et al., 2010; Brazhnik et al., 2012). In vivo electrophysiology in animal models of these disease states continues to provide significant insight into the striatal-related disease pathology.

Despite its widespread use, there is little standardization of recording methods or quantification of recording quality in in vivo recording studies. We advocate for quantifying and reporting measures of recording quality, which we believe will both improve the quality of striatal recordings and facilitate easier comparisons between studies. Topics covered in this protocol include quantifying noise in experimental setups, appropriate settings for acquiring neural data, processing data, and quantifying the quality of neural signals extracted from recordings.

Materials

Beaker of saline
Recording device (single electrode, micro-electrode array, silicone probe)
Recording chamber/Faraday cage
Data acquisition/analysis system
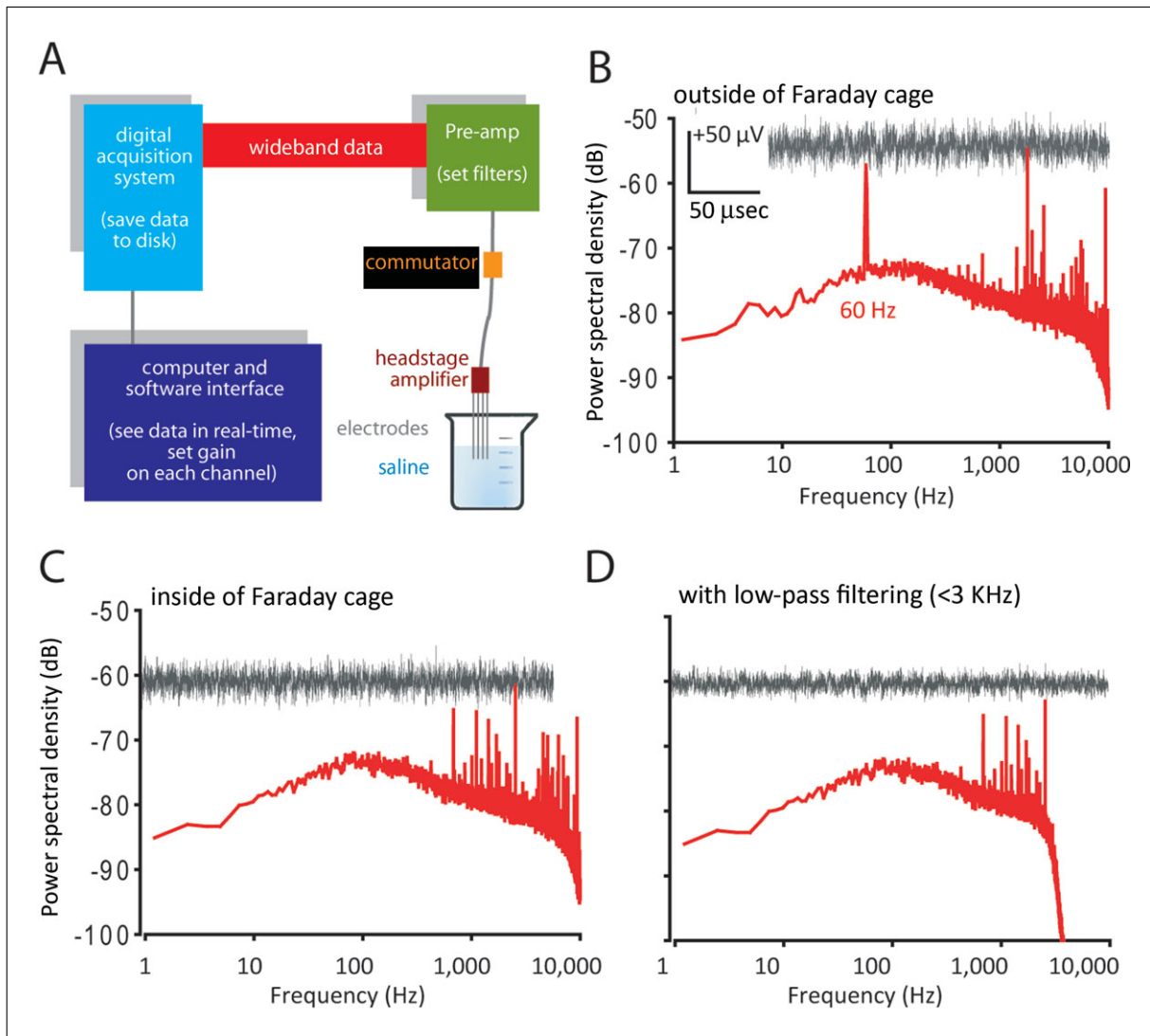High-pass and low-pass filters

Figure 6.28.1 Quantifying electrical noise. (**A**) Schematic of recording from a beaker of saline. (**B**) Raw trace and power spectrum of electrical noise. (**C**) Raw trace and power spectrum after placing the recording in a Faraday cage. (**D**) Raw trace and power spectrum of noise within a Faraday cage and after low-pass filtering (<3 kHz).

Quantify and mitigate noise in recordings

Electrical noise refers to electrical signals that interfere with the ability to detect a desired signal. Sources of electrical noise can include electronic instrumentation, the preparation itself, and equipment in the recording environment. Sources of noise can be identified by placing recording electrodes in saline and recording wideband electrical activity (Fig. 6.28.1A). Calculating the amplitude of this signal will help to determine whether the noise is small enough to allow for recording of the desired signal. Determining the power spectral density of this signal can help identify the source of the noise. For example, 60-Hz noise originates from the power grid and can often be mitigated with shielding, such as a Faraday cage (Fig. 6.28.1B,C). Once the source of noise is identified, it should be removed from the vicinity of the recording (if possible). If this is not possible, noise can often be mitigated by grounding the housing of the noise source and/or placing a grounded Faraday cage between the noise source and animal.

1. Attach recording device to the head stage. Place the electrodes and ground wire into a small beaker of saline (Fig. 6.28.1A).

2. Record wideband signals for ~30 sec.
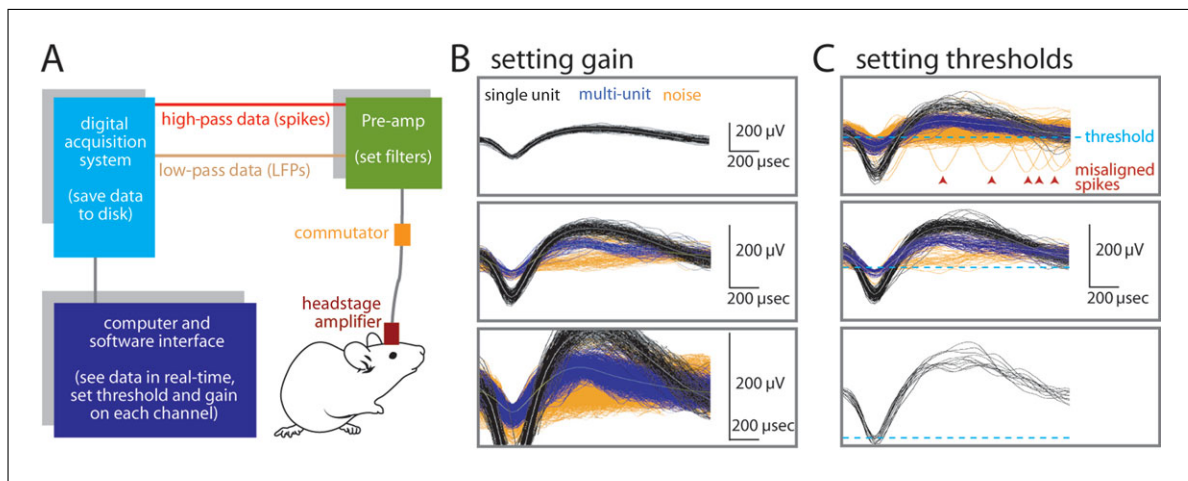
Figure 6.28.2 Setting up recording system. (**A**) Schematic of recording system indicating steps of system setup. (**B**) Setting recording system gain, with examples of gain settings that are set too low (top), too high (bottom), and appropriate (middle). (**C**) Setting recording threshold, with examples of threshold settings that are not stringent enough (top), too stringent (bottom), and appropriate (middle).

3. Calculate peak-peak amplitude of the recorded signal.

4. Calculate power spectral density of the recorded signal.

5. Use the power spectra to identify sources of noise and either remove them or shield your experiment with a grounded Faraday cage (Fig. 6.28.1B,C).

6. Repeat recordings in saline as needed to determine if the source of noise has been eliminated.

7. If high frequency sources of noise cannot be removed, use low-pass filters to filter these out of the recorded signal. In our experience, filters <3 kHz can distort neural waveforms so we recommend setting the low-pass filter at ~3 kHz.

Set up the recording system and record experimental data

Inappropriate gain or threshold settings during the system setup can render recordings unusable. If you are only saving large events to disk, you will set the threshold before the recording starts, and this will determine what data is saved to disk. If you are recording wideband signals you will set the threshold after the data is written to disk. While recording wideband signals has traditionally presented storage and processing challenges, continuing decreases in prices for bulk/cloud storage and increases in computing power are beginning to make wideband recording more normative.

8. Connect your experimental preparation to the head stage amplifier.

9. Set the analog gain for the each channel making sure that the gain settings make good use of the linear range of the system (Fig. 6.28.2B).

   If gain settings are too low neural signals may be too small and may not resolve from noise. Conversely, setting the gain too high can have a number of deleterious effects, including truncating a portion of the neural signal (Fig. 6.28.2B), amplifying the effect of large artifacts due to saturation of the analog to digital converter, or reducing the dynamic range to the extent that low-frequency oscillations can truncate spikes.

10. Set the parameters of the high-pass and low-pass filters to the range used for action potentials (typically ~300 to 600 Hz and ~3000 to 6000 Hz).

11. Set thresholds for each channel to discard small amplitude signals that are unlikely to be of interest (Fig. 6.28.2C).

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If threshold settings are not stringent enough, the recording may contain large amounts of noise events, and can result in misaligned spikes (i.e., Fig. 6.28.2C). If the threshold settings are too stringent, the recording may fail to detect all of the spikes from a unit. An appropriate threshold will allow for the detection of a small amount of noise, and all of the relevant neural signals.

12. Choose an appropriate reference electrode. While it is possible to use the amplifier ground as a reference for each channel, a designated electrode within the brain will provide better final signal quality. In many cases, "dead" electrodes within the recording array—those which detect neural activity but are not capable of resolving spikes, typically due to large surface area or low impedance—often serve as good references. The reference channel should be observed for several minutes to ensure that the reference electrode is not detecting any neural signals. If the reference electrode can be moved, it should be targeted towards regions where the density of action potential signals is low, such as the corpus callosum.

13. Begin recording.

Preprocess data for analysis

Preprocessing the recorded data should be completed before extracting spikes from the recordings. Preprocessing can include artifact rejection, spike alignment, and restricting the analysis temporally to the data of interest.

14. Eliminate artifacts.

    Artifact rejection can be used to eliminate large erroneous events in a recording. Artifacts can be identified as large-amplitude events that occur on one or more channels that do not have neural waveform shape (multi or single unit). Automated procedures can be used to identify and reject artifacts that occur on multiple channels simultaneously.

15. Align spike waveforms. Waveforms may be aligned as they are recorded based on where they cross the established threshold. Aligning spike waveforms to the absolute minimum value or the center of mass may improve the spike clustering and better allow for spike sorting. The most reduction in variability can be achieved by up-sampling/interpolating the spike waveforms by a factor of $2\times$ to $8\times$, aligning the waveform in this higher sample rate space and then down-sampling to the original sample rate.

16. Restrict recording temporally. Recordings are often longer than the period of interest for data analysis. For instance, the experimental design may involve analysis of data only within the task, yet data may be collected for a 1-hr "baseline" period before the task. Due to drift and variation in the recording across time, extra periods of recording will decrease the quality of spike sorting, and should be removed prior to spike sorting.

Sort spikes and quantify the sorting quality

Spike sorting is used to identify single and multi-unit activity (Fig. 6.28.3). We will avoid discussion of spike sorting itself as it is a rich topic that is not suitable to a protocol. We refer readers to reviews on this topic for making decisions on the most appropriate spike sorting for their experiments (Lewicki, 1998; Einevoll et al., 2012). However the spikes are sorted, the results of the sorting should be quantified. In practice, we have found that each of the methods below has unique strengths, and recommend evaluating multiple metrics of sorting quality.

17. Sort spikes.

    Sorting is typically performed in a dimensionally reduced space (e.g., principal components; see Fig. 6.28.3 panels B and C, bottom).
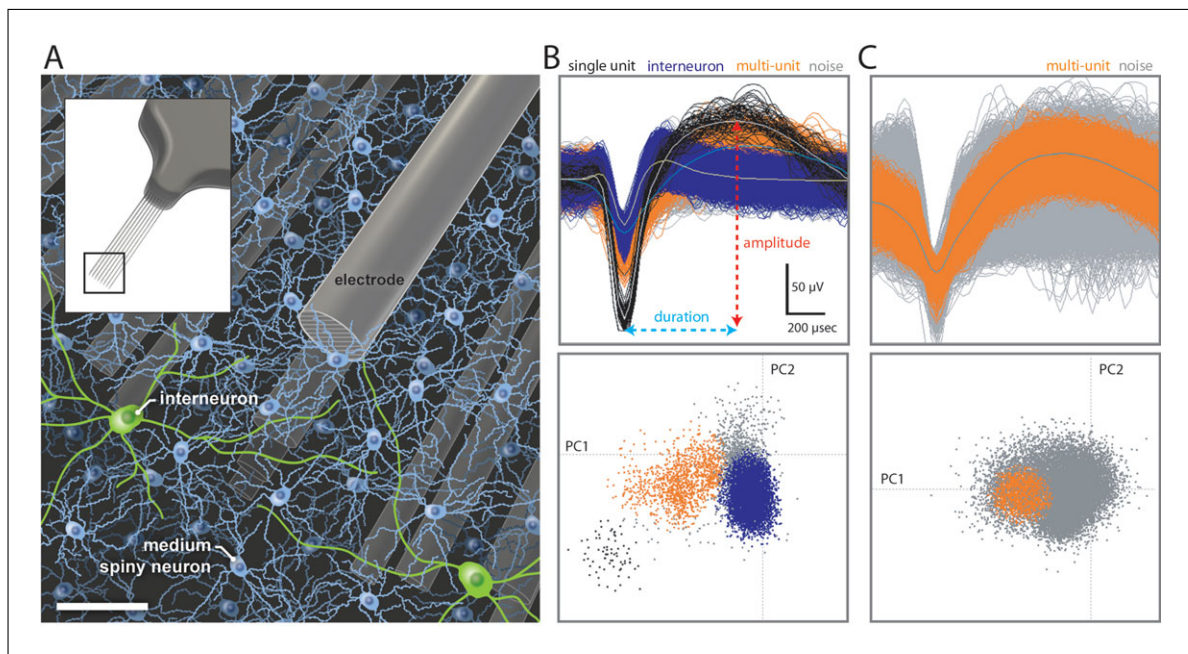
Figure 6.28.3 Quantifying recording quality. (**A**) Schematic of electrodes from a microwire electrode (inset) in relation to striatal neurons (scale bar = 50 μm). (**B**) Top: Waveforms of single-unit events of a single unit (black) and a putative fast-spiking interneuron (purple), multi-unit signals (orange), and electrical noise (gray) from a single channel. Bottom: Principal component analysis (PCA) clustering of these signals (same color scheme as above). (**C**) Top: Waveforms of multi-unit signals (orange) and electrical noise (gray). Bottom: PCA clustering of these signals (same color scheme as above).

18. Calculate the following statistical measures to quantify sorting quality and help determine if identified clusters likely contain the activity of only one neuron (i.e., single-unit activity, Fig. 6.28.3B), or multiple neurons (i.e., multi-unit activity, Fig. 6.28.3B,C). While general quantitative guidelines are listed with each statistic below, these statistics can be affected by the amplitude of the noise band and units on the electrode. Therefore, absolute rules that apply to all electrodes are difficult to employ, and multiple measures should be examined to gain a holistic view of the recording quality on each electrode:

MANOVA: MANOVA uses parametric statistical tests to determine whether each sorted cluster is significantly different from the other sorted clusters. Pairwise statistics between the multiunit clusters and other putative units should be significant ($p < 0.05$).

J3 statistic: The J3 statistic is calculated based a ratio of within cluster to between cluster variance. A higher J3 ratio indicates better clustering and well-separated units (Wheeler, 1998). In general, J3 statistic will be >2 for well sorted channels, and >1 for intermediate sorting quality.

Pseudo-F: The Pseudo-F statistic is related to the J3 ratio; however, the Pseudo-F statistic adjusts for the number of waveforms and the number of units on the analyzed channel. A higher Pseudo-F value suggest better clustering and well-separated units (Wheeler, 1998). In general, Pseudo-F will be >100K for well sorted channels and >50K for intermediate sorting quality.

Davies-Bouldin Validity Index: The Davies-Bouldin criterion is based on a ratio of within-cluster and between-cluster distances. A lower Davies-Bouldin index suggests better clustering (Davies and Bouldin, 1979). In general, Davies-Bouldin index will be <0.3 for well sorted channels and <0.5 for intermediate sorting quality.

Dunn Validity Index: The Dunn validity index is calculated based the ratio of the distance from the centroid of unit A to the centroid of unit B and the average

distance of a point in unit B to the centroid of unit B. A higher Dunn index suggests better clustering (Dunn, 1973). In general, Dunn validity index will be >2 for well sorted channels, and >1 for intermediate sorting quality.

Isolation distance: For a cluster, C, the isolation distance is the Mahalonobis distance (in the feature space in which the clusters are defined) to the $n_C{}^{th}$-closest noise-waveform (i.e., waveform not assigned to cluster C), where n_C is the number of waveforms in cluster C (Schmitzer-Torbert et al., 2005; Joshua et al., 2007). An isolation distance in excess of 100 generally indicates well isolated clusters; values in the 20 to 100 range indicate intermediate quality.

L-ratio: The L-ratio is based on the Mahalobis distance to all noise waveforms, using a multi-variate normality assumption (Schmitzer-Torbert et al., 2005). In experimental data, the L-ratio will generally vary on a logarithmic scale, with values in the range of 10^{-5} to 10^{-4} indicates very well-isolated clusters, and 10^{-3} to 10^{-2} representing intermediate quality.

ISI plots/autocorrelation: Putative single units should also demonstrate clear refractory periods. Refractory periods can be examined by forming inter-spike-interval histograms or autocorrelograms. Single units will demonstrate a clear refractory period resulting from the inability of a single neuron to produce two spikes in close proximity. In the striatum, this period should be >2 msec for medium spiny neurons.

19. If statistics indicate that clusters are not well separated (above measures deviate from recommended guidelines) from one another, they should be combined and labeled as multi-unit activity.

20. Cluster stability should also be evaluated across the duration of the recording. Should a cell "drift" and the sorting of the cell no longer differentiate from electrical noise, analysis of the recording can be restricted to a more specific length of recording, or combined and identified as multi-unit activity.

21. The average waveforms for identified units should be exported and peak to peak amplitude, waveform duration, and average firing rates calculated. These parameters may be used to classify single units into putative striatal cell types (see Background Information).

Statistics used for quantifying recording quality (avg. noise and waveform amplitudes, clustering statistics) should be reported with experimental data.

COMMENTARY

Background Information

Determining cell types recordings from electrophysiological properties

The striatum is a heterogeneous structure containing two types of medium spiny neurons (direct and indirect pathway neurons), as well as multiple classes of interneurons. Experiments will provide greater insight if the cell type of recorded neurons are identified. Certain cells can be putatively identified based on electrophysiological properties. For example, striatal medium spiny neurons can be distinguished from striatal interneurons based on the width or shape of the waveform. Other characteristics including interspike intervals and average firing rates can also help to distinguish striatal medium spiny neurons from striatal interneurons. For example, striatal medium spiny neurons generally fire in bursts separated by periods of quiescence and maintain average firing rates of <5 Hz (Berke, 2008; Wan and Peoples, 2008; Gittis et al., 2011; Kravitz et al., 2012); therefore, neurons with average firing rates above 5 Hz may not be medium spiny neurons. For instance, such a neuron may be a PV+ fast spiking interneuron, which generally fire at ~10 to 30 Hz (Berke et al., 2004; Berke, 2008; Gittis et al., 2011). Alternatively, a unit that fires >5 Hz but has a waveform similar to medium spiny neurons may arise from multiple cells (multiunit activity) rather than a single unit.

Using optogenetics and imaging to identify genetically specified cell types

In addition to electrophysiological parameters, optogenetics can be used to identify specific neural types in in vivo recordings with "photo-tagging". Photo-tagging refers to the expression of an opsin such as channelrhodopsin-2 (ChR2) in a specific cell type, and identifying that cell type by its response to light pulses. While the approach is fairly straightforward, in practice several issues can interfere with the positive identification of neurons. Briefly, the main obstacles include synaptic activation of neurons that may appear to be light-responsive, and multi-unit activation near the electrode that can obscure spike sorting (Kravitz et al., 2013). Despite these issues, photo-tagging has been successfully used to record spike trains of genetically identified neurons, and for the first time allow insights to how they act within larger populations (Cardin et al., 2009, 2010; Lima et al., 2009; Jin et al., 2014).

A complementary approach that allows for unambiguous activity monitoring of genetically specified cell types involves Ca^{2+} imaging. Genetically encoded Ca^{2+} sensors can be expressed in a cell type of interest, and the Ca^{2+} signals of that cell type can be recorded either through a traditional fluorescence microscope in a head-fixed preparation, or in a head-mounted fluorescence microscope, through an implanted endoscope, or through a fiber optic that collects bulk-fluorescence (Barretto and Schnitzer, 2012a,b; Cui et al., 2013). While individual cells can be clearly identified via the shape of their soma there are a number of challenges to achieve stable recordings of neural activity using fluorescent indicators, and, to our knowledge, the "quality" of these recordings has yet to have been systematically analyzed or quantitated.

Making use of multi-units recordings

Due to the density of neurons in the striatum, and the fact that the diameter of most recording electrodes are ~2–5× the size of a medium spiny neuron, many electrodes in a device will record "multi-unit" activity (Fig. 6.28.3A). While this activity cannot be resolved into signals from individual neurons, it can still be useful. As described above, multi-unit activity is necessary for making comparisons between putative "single-units," which constitute clusters of points that are statistically distinct from multi-unit activity.

In addition, depending on the experimental goals, multi-unit activity can be useful in its own right. If the primary goal is to determine if overall activity in a structure is increased or decreased by a manipulation or in a certain phase of a task, multi-unit activity can often provide a richer evaluation of this goal than single unit activity. Multi-unit activity does not require the experimenter to make decisions concerning whether more than one unit contributed to a cluster, or the quality of the spike sorting. In addition, as most electrodes will pick up multi-unit activity, it is a higher yield process that can reliably provide estimations of spiking activity from most electrodes. In addition, by using cluster features (e.g., amplitude or principal components analysis projections), algorithms which extract information from multi-unit activity can be improved (Kloosterman et al., 2014).

Automated spike sorting

Spike sorting essentially involves separating recorded waveform shapes into groups. As such, this problem would seem ideally suited to automation. Reviews on automated spike sorting exist (Lewicki, 1998), and we will not discuss specific automated approaches in this protocol. The advantage of automated sorting is that the method is more objective and results in reproducible sorting. While many algorithms can sort channels that have large, easily distinguished spikes, many channels are not like this, and therefore the algorithm requires supervision and manual editing on these channels. For this reason, many researchers still employ manual or semi-automated sorting methods.

Critical Parameters and Troubleshooting

Sources of noise

When setting up an electrophysiology system, it is important to evaluate and minimize sources of noise that will enter the recording. In general, all non-essential equipment should be moved away from the recording area. Equipment that involves switching currents (such as motors and power supplies) can be particularly troublesome sources of noise and should be placed as far away from the recording area as possible. Extra shielding measures can be used if it is not possible to mitigate equipment noise completely. Finally, placing the entire recording setup inside of a Faraday cage can further help mitigate noise from electrical systems and lighting in the room. If a source of noise cannot be mitigated, it may be possible to filter it out, particularly if it is high frequency and outside of the

spectral content of action potentials. In practice, we have brought our low-pass filters down to 3 kHz without noticeable distortion of the neural waveforms.

What type of recording device is best?

Many types of electrodes and styles of recording device can be used for in vivo recording. These differ in material and in configuration. The most widely used electrodes in striatum are arrays of single electrode micro-wires. These are relatively cheap, can be manufactured in house, and are a proven technology that provides reliable recordings over weeks or months. In the striatum, micro-wire arrays have been fabricated of steel, tungsten, nichrome, and platinum/iridium, and now silicone with successful results and the impedance of these wires is generally between ~250-1000 kOhms (Hubel, 1957; Csicsvari et al., 2003; Berenyi et al., 2014). Despite the low cost and reliability of microwire arrays, newer techniques have theoretical and practical promise over these arrays. By changing the configuration of the wires to a stereo-trode (2 wires twisted together) or tet-rode (4 wires twisted together), one can record the same neurons from multiple closely-spaced recording sites. This can allow for better sorting of multi-unit activity into its component units. In addition, micromachining processes have led to much higher densities of electrodes in much smaller volumes. For example, this technology was recently used to complete 512 channel recordings from rats, resulting recordings from large numbers of single units per recording session (Berenyi et al., 2014). Overall, the experimental goals, equipment in the lab, and cost of devices should all be considered when choosing which style of electrodes to use.

Locating recording sites after in vivo recording experiments

Once recording experiments have been completed, it is important to verify the locations of recording arrays and wires. The most common way to do this is by producing lesions through the wires in the recording array. Briefly, the animal should be anesthetized and the array connected to a power supply that sends current through each wire (~10 to 100 µA for ~3 sec, optimized to your particular set-up). Once this has been completed the brain can be removed, fixed and the tissue sectioned, mounted on slides, and the location of the array wires located based on site of the lesion (Fig. 6.28.4).
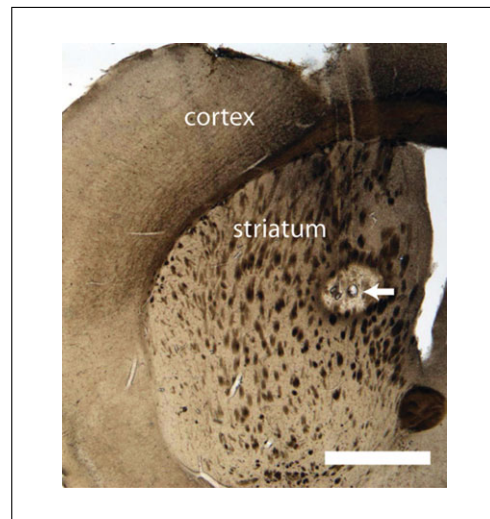
Figure 6.28.4 Histological identification of electrode sites. Micrograph of a coronal section of brain tissue demonstrating lesion sites (arrow) from passing 100 µA of current for 5 sec through each electrode. Scale bar represents 1 mm.

Anticipated Results

Once electrical noise has been identified and eliminated and recording quality optimized, and spike sorting has been completed, the experimenter will be able to quantify several parameters related to the cell types and/or structure recorded from. However, should the experimenter attempt spike sorting with unsuccessful results (statistical measures used to determine cluster quality do not reach significance, thus indicating poor clustering), the experimenter should optimize recording settings and reduce noise so that the next attempts result in well separated units (statistical measures used to determine cluster quality reach significance, thus indicating well clustered units). It is also possible that recording devices may not have appropriate impedance for recording single units, in which case these should be adjusted.

Time Considerations

The amount of time needed to complete recording experiments and data analysis will vary depending upon the experimental design. Generally speaking, preparations taken to begin in vivo recordings (identifying and eliminating electrical noise) can be completed within a couple of days. Depending upon the experimental goals, recordings can be completed within a few hours to one day, although repeated measures designs (recording from the same animal at several time points will consist of recordings conducted on several days. The most labor-intensive portion of in vivo

recordings is the processing and analysis of data, which can take several days to years depending on the experimental design and amount of data collected.

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