Nicolelis MAL, editor. Methods for Neural Ensemble Recordings. 2nd edition. Boca Raton (FL): CRC Press/Taylor & Francis; 2008.

Chapter 5 Chronic Recordings in Transgenic Mice

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INTRODUCTION

Previous chapters of this book have highlighted technical advances made in recording ensembles of neurons in primates and rats. These advances have created a novel window through which to study brain function, allowing us to interpret an ever-growing body of data describing how the normal brain operates. On the other hand, these techniques have only provided a limited picture of how alterations in brain function generate behavioral pathology, requiring new recording techniques to be manufactured. In this chapter, we describe a novel method for extending previously described electrophysiological recording techniques for use in transgenic mice. This fusion of genetic and neuroscience technologies provides a promising tool for elucidating how changes in gene expression result in the behavioral alterations characteristic of central nervous system (CNS) disease.

During the course of the last century, great strides were made in treating diseases involving the CNS. Much of this progress resulted from an explosion of neuroscience research, which led to the discovery of action potentials, neuromodulators, and the principles of organization of neural circuits. Although these findings facilitated the development of drugs to treat neurological and psychiatric illnesses such as schizophrenia, Alzheimer's disease, Parkinson's disease, and depression, little headway was made in elucidating the pathophysiological mechanisms associated with many of these diseases. Thus, treatment options typically focused on managing symptoms, and not on curing the underlying disease. Currently, one of the primary challenges of behavioral brain research lies in the complexity of understanding how changes in patterns of gene expression alter the spatiotemporal firing of widely distributed populations of single neurons that define the large-scale neural interactions underlying the generation of behavior. This issue is further complicated by ethical concerns associated with genetic manipulation in humans and limitations inherent to the techniques currently used to study electrophysiological changes in the brain.

The primary techniques used to study human brain activity are functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Unfortunately, fMRI, which measures changes in blood flow resulting from activation of neural networks, has significant limitations in temporal resolution, and EEG, which utilizes scalp electrodes to measure brain activity, has significant limitations in spatial resolution. Although intraparenchymal

recording protocols can be used to enhance spatial and temporal resolution of brain activity, these techniques are invasive and are thus not typically suitable for studying neurological and psychiatric illness in human populations. To overcome these issues, we have created a protocol for chronically recording brain activity in animal models of CNS disease.

Recently, transgenic mice have gained greater acceptance as models of CNS disease (Dennis 2005). These genetically modified mice display behavioral alterations similar to those observed in humans with neurological or psychiatric illness, and recapitulate several endophenotypes characteristic of these diseases. By chronically implanting these mice with intraparenchymal microelectrode arrays, one is able to assess how changes in gene expression result in changes in neural ensemble firing patterns. Moreover, one can conduct longitudinal observations in animals given drugs used to treat the CNS diseases they model, providing a detailed picture of how changes in neuronal firing patterns result in neurological and psychiatric pathology.

CONSTRUCTION OF IMPLANT

The transgenic mouse recording protocol is very similar to that utilized in rats, with one major difference: mice are typically one-tenth the size of rats. This, of course, necessitates several modifications to the previously described implant.

Construction of Electrodes

The main design used to conduct electrophysiological recordings in mice consists of an array of 16 S-isonel-coated tungsten microwire electrodes, a printed circuit board (PCB) connected to the microwire electrodes, and a high-density, miniature connector attached to the opposite side of the PCB (Nicolelis et al. 2003).

We investigated the advantages and disadvantages of several array designs: (1) 16 single-ended wires spaced 250 μm apart (Figure 5.1A); (2) Four groups of four microwires separated by 100 μm in a square arrangement (each group separated by 250 μm; Figure 5.1B); (3) Eight pairs of two adjacent electrodes (maximum 50 μm between wire centers in each pair, pairs separated by 250 μm; Figure 5.1C). We also tested two wire diameters: 50 μm, with an impedance of about 1.2 MO; and 35 μm, with an impedance of about 1.5 MO. The arrays and headstage were miniaturized (weight ~0.26 g per array), allowing mice to move freely.

In our experiments, 32 microwires were implanted per mouse (an array of 16 microwires in each hemisphere) in the dorsal striatum and the motor cortex. To test the different designs, we recorded in single-channel mode (for all designs), tetrode mode (for design 2) or stereotrode mode (for design 3), (using MAP, Plexon Inc.). We used differential recording in which one of the channels with no neural activity was used as a reference electrode. Using

the single-channel recording mode, we were able to record well-isolated single units from single channels in all three designs (Figure 5.1D). With both designs 2 (tetrode mode) and 3 (stereotrode mode), we were unable to record simultaneous activity from the same unit in adjacent electrodes, even when very well-isolated single neurons could be recorded from each of the adjacent electrodes in single-channel mode. In this context, our results differ from previous studies using stereotrode and tetrode recording methods (Harris et al. 2000). Likely, this difference results because we used electrodes with an impedance 4 to 5 times higher than in other studies, larger wire diameter, different array design geometry, and we also recorded from sparsely distributed (in striatum 2–4 cells 35 μm^3 or 6–12 cells 50 μm^3 [Rosen and Williams 2001]) and very small (~12 μm cell body diameter for striatal medium spiny neurons [Rafols et al. 1989]; and ~15 μm for pyramidal cortical cells [Faherty et al. 2003]) neurons. Using the specific parameters described here, we observed no advantage in using triangulation to isolate single units. This observation could be different when recording in other brain areas or when using other parameters. We therefore opted to employ single-channel recording mode in all the experiments. In the striatum, we obtained better results with the 50 μm wires (both in terms of number of units isolated and longevity of the recordings), whereas in motor cortex both wire diameters produced similar outcomes.

When constructing implants, individual electrodes should be geometrically spaced and cut according to mouse stereotaxic coordinates to ensure appropriate spacing for target brain structures.

Electromyographic Electrodes

Electromyographic (EMG) electrodes provide an external measure of behavior. These electrodes are particularly useful when studying locomotor behavior, or classifying electrophysiological changes across sleep–wake states. To avoid damage to muscle tissue, smaller single-wire EMG electrodes are utilized in transgenic mice implants. EMG electrodes are created using 50 μm tungsten wire, and are connected to the microwire arrays as described in chapter 1. They should be cut to a length of no less than 7 cm to facilitate muscle implantation. Importantly, multiple EMG wires can be attached to each microwire array, allowing for muscle activity to be simultaneously recorded from the eyes, whiskers, neck, and other peripheral muscles.

IMPLANTATION SURGERY

Transgenic mice necessitate several adjustments to the rodent implantation surgery described in chapter 3. These modifications result from the decreased body mass of the mice in comparison to rats and primates, and the smaller surgical implantation field.

Anesthesia

After selecting a mouse for implantation, rapidly induce the animal using halothane/isoflourane (as described in chapter 3). Once the animal is induced, the mouse should be injected with a single dose of ketamine 100 mg/kg IM, and xylazine 10 mg/kg IM. This combination of anesthetic agents should be sufficient to provide 2–3 h of controlled anesthesia. If the mouse should require additional anesthesia during the course of the surgery, prepare a 20 mg/ml ketamine solution, and inject 0.1 mL IM as needed. At least 5 min should elapse between subsequent maintenance doses of ketamine to avoid causing unanticipated respiratory depression.

Microarray Implantation

The mouse cranium has a very thin skull, making the implantation surgery a technically challenging procedure. Once the cranium is exposed as described in the rat implantation surgery (chapter 3), target locations are marked off using a felt tip pen. First, small craniotomies for placement of anchoring screws are drilled using a ¼ mm drill bit. Screws (1 mm diameter) are used to anchor the implant. The size of such screw craniotomies should be approximated to tightly secure each screw. Two screw craniotomies are usually drilled for each surgery, but only one is necessary if numerous multiarrays are being implanted or cranial space is limited. After the screw craniotomies are opened, the anchor screws should be inserted using a screwdriver. Next, the electrode ground wire should be wrapped around the secured ground screw. The process should be repeated for each electrode. Two and a half revolutions should be sufficient. Finally, after lowering the electrodes to the desired depth, the ground wire should be covered and screwed with dental acrylic (as described in chapter 4). Care should be taken to avoid covering any of the other implant target sites with dental acrylic.

EMG Wires

EMG wires should be placed after microwire arrays are implanted and covered with dental acrylic. To implant EMG wires, pass a 27-gauge needle through the target muscle. Next, insert the EMG wire into the opening of the needle, and retract the needle through the target muscle. Repeat this procedure 2–3 times to ensure that the EMG wire is properly secured. Only one pass is necessary to secure eye and whisker EMG wires. Finally, remove the insulation coating from the EMG wire using a scalpel, and cut the EMG wire at the muscle.

RECORDING PROTOCOL

The transgenic mouse recording protocol is similar to that utilized for conducting electrophysiological recordings in rats. After mice are implanted, connect them to the recording setup using a 16-channel headstage and connector. The neural ensemble recording setup is identical to that utilized to record rats.

Recording Paradigms

Various recording paradigms can be used to uncover behavioral phenotypes in transgenic mice (Crawley 1999). By conducting the transgenic mouse recording protocol using these alternative recording paradigms, one can investigate the electrophysiological alterations underlying specific behavioral changes. Thus, this section will focus on describing the specific behavioral phenotypes isolated by each recording paradigm.

Gross Locomotor Behavior

Neural activity associated with changes in gross locomotor activity can be assessed by conducting recordings in an open field. Open-field recordings are conducted by placing mice in an open environment in which they can move freely. This environment can be stimulated using a specialized setup for tracking movement, or even an empty mouse cage and a video recorder. The open-field recording paradigm is particularly useful when studying genetic alterations that are known to generate changes in gross locomotor activity, such as hyper- or hypolocomotion, or stereotypic behavior such as grooming and licking. These phenotypes are displayed in human diseases such as Parkinson's disease, obsessive-compulsive disorder, schizophrenia, and attention-deficit hyperactivity disorder.

Motor Coordination

The accelerating rotarod (Crawley 2000) is particularly useful for studying changes in neural activity underlying deficits in motor coordination. During the rotarod recording setup, mice are placed on a rotating cylinder that is accelerated over time. Motor coordination is then assessed as the latency for the animal to fall off the rotating cylinder. To avoid injury to the animal, the rotarod cylinder is suspended only 6 in. from the bedding-covered floor. By conducting neural ensemble recordings in transgenic mice using the rotarod, one can study electrophysiological alterations associated with disorders of the motor system. This recording paradigm would be particularly useful for studying pathophysiological mechanisms underlying human neurological disorders such as amyotrophic lateral sclerosis and Huntington's disease.

Learning and Memory

Many behavioral paradigms have been developed to assess cognitive deficits in genetically altered mice. These paradigms include the light/dark and foot shock avoidance task, water maze, radial arm maze, and T/Y mazes (Crawley 2000). By conducting electrophysiological recordings while the transgenic mice are performing each of these tasks (with the exception of the water maze, which may present a problem with the recording equipment), one can probe alterations in neural circuits underling deficits in learning and memory that result from genetic manipulations. This recording protocol may be particularly useful in studying mouse

models of human diseases such as autism, schizophrenia, and Alzheimer's disease.

Sleep and Circadian Rhythms

A long-term recording setup can be used when experiments necessitate that recording periods last several days. The long-term recording setup is particularly useful when one is studying how genetic alterations generate changes in neural activity associated with the circadian and sleep–wake cycle. Long-term recordings are typically carried out in a modified mouse cage, which is placed in a behavior box that allows the temperature and light dark cycle to be closely controlled. Importantly, the modified mouse cage is filled with bedding and equipped with a modified feeding grate that allows for food and water to be accessed by the mouse ad libitum. Additionally, care must be taken ensure that the modified feeding grate does not cause the headstage connector to become tangled.

Pharmacological Manipulations

One can also conduct electrophysiological recordings in transgenic mice treated with pharmacological agents known to treat the human neurological diseases they model. The aforementioned recording paradigms can than be utilized to assess how these agents affect alterations in neural circuitry observed in untreated mice.

Data Collection

Once a mouse is implanted, connected to the recording setup, and the appropriate recording paradigm is selected, single-cell, multiunit, LFP, and EMG activity is recorded using the Multi Acquisition Processor (MAP) system (Plexon Inc., Texas) (Figure 5.2). The spike activity should be initially sorted using an online sorting algorithm. Only units that have a clearly identified waveform with a signal-to-noise ratio of at least 3:1, where no waveforms are dropped by the acquisition system (sampling rate of 40 KHz), should be used. At the end of the recording, units should be resorted offline based on waveform, amplitude, and interspike interval histogram using an offline sorting algorithm (Nicolelis et al. 2003). Concomitantly, we have also measured local field potentials (LFPs) in the same areas by low-pass-filtering the data (0.1–400 Hz range). Histological analysis demonstrated that chronic implants did not produce significant tissue damage besides the original implantation track.

DATA ANALYSIS

Spike Sorting/Waveforms

In our studies, single-cell and multiunit activity were recorded using the MAP system (Plexon Inc., Texas). In our protocol, the recorded neural activity is initially sorted using an

online sorting algorithm (Plexon Inc, Texas). At the end of the recording, potential single units should be resorted offline based on waveform, amplitude, and interspike interval histogram using an offline sorting algorithm (Nicolelis et al. 2003). Only units in which all the spikes have amplitudes well above the voltage threshold should be considered (to ensure that no spikes are lost). When the waveform, amplitude, and inter-spike-interval (ISI) do not allow unambiguous isolation (even with signal-to-noise ratios larger than 3:1), the signals should either be discarded or labeled multiunit activity. The criteria should be as follows: When the waveforms from a unit clearly result from two or more neurons that cannot be discriminated, the unit should be discarded. In the occasional cases in which not all the spikes of a single unit can be unequivocally isolated during offline sorting (owing to the proximity of two clusters or proximity to the noise cluster), the unit should be labeled multiunit. During three sessions, we found that the average number of multiunits per session was 11, 13, and 11%. Analyses of these units should be conducted separately. We observed that the waveform recordings across a session were generally very stable (Figure 5.3), allowing us to follow single units through time. The implants seemed to be well tolerated by the mouse brain, and single units could be recorded several months after surgery (Figure 5.4). These experiments revealed that several well-isolated single units can be obtained from a very high number of implanted electrodes, indicating that our methodology is appropriate for conducting long-term longitudinal studies in behaving mice. Additionally, we observed that changes in neural activity could be isolated from single units recorded across a behavioral learning task (Figure 5.5) (Costa 2004).

Behavioral State Analysis

Behavioral state scoring algorithms typically combine analysis of brain and EMG activity, with direct behavioral observations. We recently developed a novel technique in rats that can be utilized to predict behavioral states and their transitions based on LFP spectral ratios (Gervasoni et al. 2004). The first ratio (Ratio 1) produces cluster separation based on high-frequency gamma (33–55 Hz) spectral oscillations (Steriade et al. 1993), whereas the second (Ratio 2) produces cluster separation based primarily on theta (4–9 Hz) spectral oscillations (Vanderwolf 1969; Timo-Iaria et al. 1970; Cantero et al. 2003). We found that this method could also be used to predict behavioral states in mice using LFP oscillations recorded from hippocampus (Figure 5.6a and Figure 5.6b). Additionally, EMG data can be used to further discriminate points of behavioral state cluster overlap (Figure 5.6c). To determine EMG activity, the Fast Fourier transform was applied to the LFP signal using a 2 s window with a 1 s step. The Fourier transform parameters were chosen to allow for a frequency resolution of 0.5 Hz. EMG activity was then calculated by taking the root mean square of the spectral amplitude over selected frequency bands: 30–56 and 64–250 Hz. All EMG traces were high-pass-filtered at 30 Hz. Importantly, behavioral states predicted by the two-dimensional state space method correspond with those determined using standard sleep scoring methods

(Figure 5.7). Thus, this powerful technique facilitates high-throughput behavioral state analysis in mice, allowing for the observation of neuronal subpopulations across the sleep–wake cycle in animal models of CNS disease.

Results And Conclusions

We recently utilized the method outlined in this chapter to examine the influence of dopamine on sleep–wake states. Dopamine transporter knockout (DAT-KO) mice were implanted with multiarray electrodes in the hippocampus, and electrophysiological recordings were conducted across the sleep–wake cycle (Dzirasa et al. 2006). DAT-KO mice lack the gene encoding the dopamine transporter, a transmembrane protein that is responsible for regulating the reuptake of synaptic dopamine and replenishing dopamine stores in the presynaptic terminal (Gainetdinov and Caron 2003). As such, the dopamine transporter plays the key role in controlling dopamine homeostasis. Because of the loss of the dopamine transporter, DAT-KO mice exhibit profound depletion of intraneural dopamine stores as well as a five-fold increase in extracellular dopamine levels (Gainetdinov and Caron 2003). Our results demonstrated that novelty-exposed DAT-KO mice display a new awake state characterized by electrophysiological signatures characteristic of REM sleep (Dzirasa et al. 2006). Moreover, when these mice were dopamine-depleted via administration of a tyrosine hydroxylase inhibitor (Sotnikova et al. 2005), they displayed another new sleep–wake state characterized by the complete suppression of REM sleep. These results indicated that dopamine directly regulates the sleep–wake states.

Our findings elucidate mechanisms central to the role that dopamine plays in mediating symptoms classically associated with neurological and psychiatric diseases. This work demonstrates that by combining in vivo electrophysiological recording techniques with techniques fundamental to genetics and pharmacology, one can gain novel insights into pathophysiological mechanisms underlying neurological and psychiatric disease. Furthermore, this approach is particularly promising given the ever-growing library of genetic alterations underlying brain diseases, and subsequent development of multiple novel transgenic mouse lines.

By expanding our electrophysiological recording technique to collect and analyze ensembles of single-unit neuronal data recorded simultaneously from multiple brain sites in various transgenic mouse lines, we believe that our method will ultimately demonstrate how genes interact to generate normal and altered behavior.

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Figures

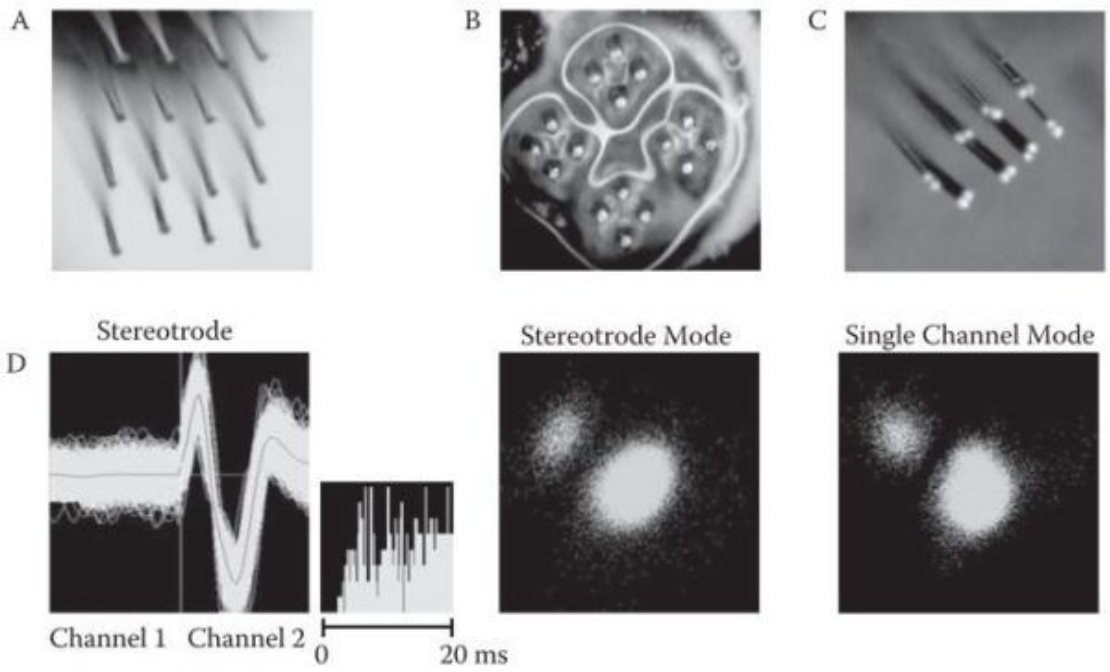

FIGURE 5.1

Comparison of different arrays and recording modes to record multiple single-neuron activity in awake behaving mice. A, B, and C are different microarray designs. (A) 16 single-ended wires spaced 250 μm apart. (B) Four groups of four microwires separated by 100 μm in a square arrangement—each group separated by 250 μm. (C) Eight pairs of two adjacent electrodes. (D) Example of a striatal single unit recorded in stereotrode mode. Although the signal recorded in channel 2 of the stereotrode is very prominent, no signal from this unit was captured in channel 1 of the stereotrode (note that the threshold is very close to zero). Also, the isolation quality of the cluster of this single unit is similar when the unit is recorded in stereotrode or single-channel mode.

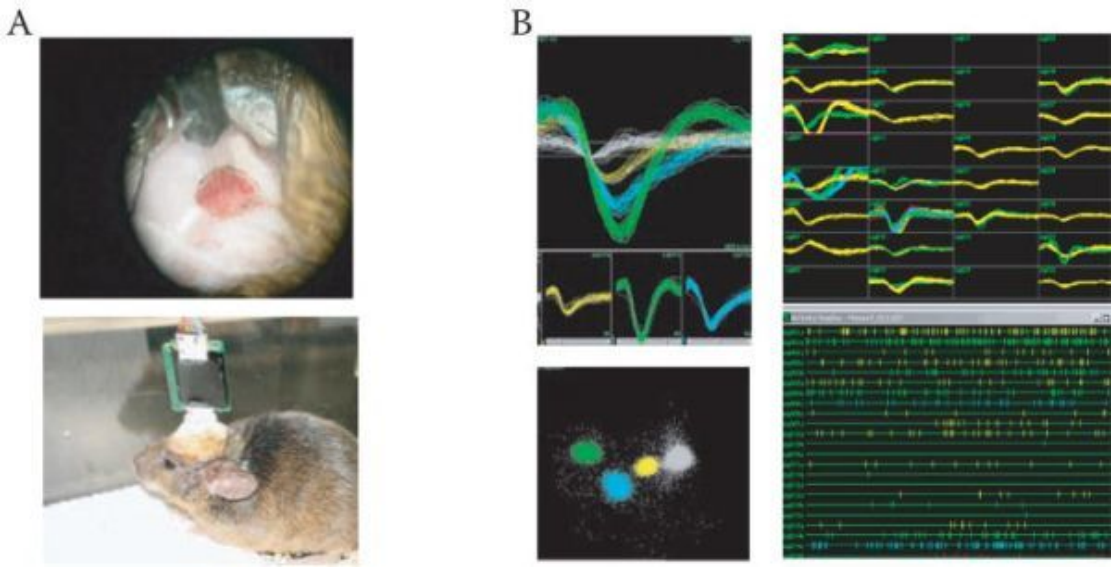

FIGURE 5.2

(See color insert following page 140.) (A) Upper-left panel. Craniotomy in the area above the dorsolateral striatum. An array of 16 microwires is ready for implantation. Lower-left panel. Awake mouse with 32 microwires inserted bilaterally in the dorsolateral striatum during a recording session. (B) Screen of our acquisition system during a recording session of the mouse presented in the left, one and a half months after surgery. The selected channel shows three clearly isolated cells recorded simultaneously from one electrode. Twenty-one other channels are also recording single-neuron activity. (Costa, R.M., Cohen, D., and Nicolelis, M.A. (2004). Differential corticostriatal plasticity during fast and slow motor skill learning in mice. *Curr. Biol.* **14**(13): 1124–1134.)

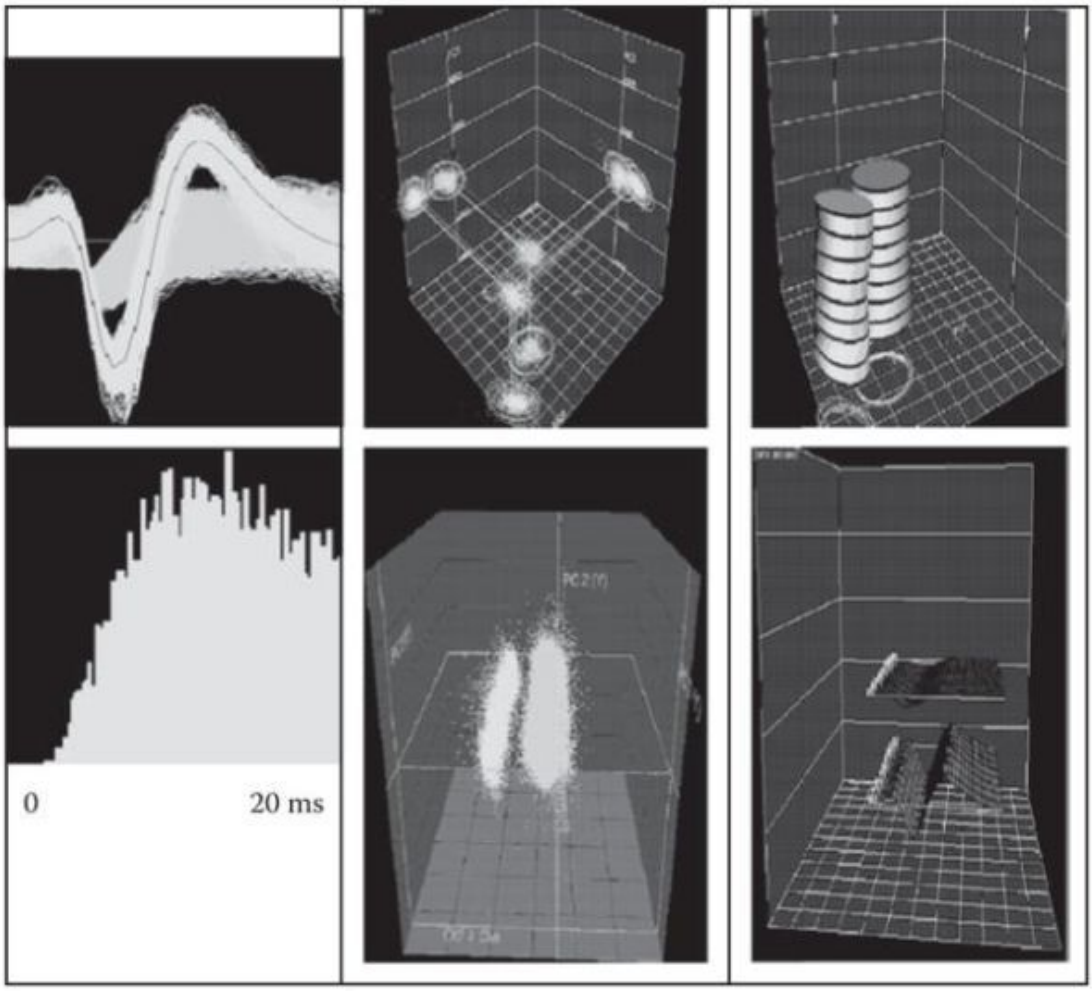

FIGURE 5.3

Stability of the recordings during a session. Example of a striatal unit recorded 4 months after surgery. Left Panel. Waveforms (top) and inter-spike-histogram (bottom) of a selected unit. Center Panel. Top—Projection of the three first principal components (PCs) of the waveform shows that the waveforms of the unit cluster distinctively. Bottom—Projection of the two PCs of the waveform across time shows that they remain relatively constant across time. Right Panel. Stability of the PC cluster based on the first three PCs (top) and waveform (bottom) across time. (Costa, R.M., Cohen, D., and Nicolelis, M.A. (2004). Differential corticostriatal plasticity during fast and slow motor skill learning in mice. *Curr. Biol.* **14**(13): 1124–1134.)

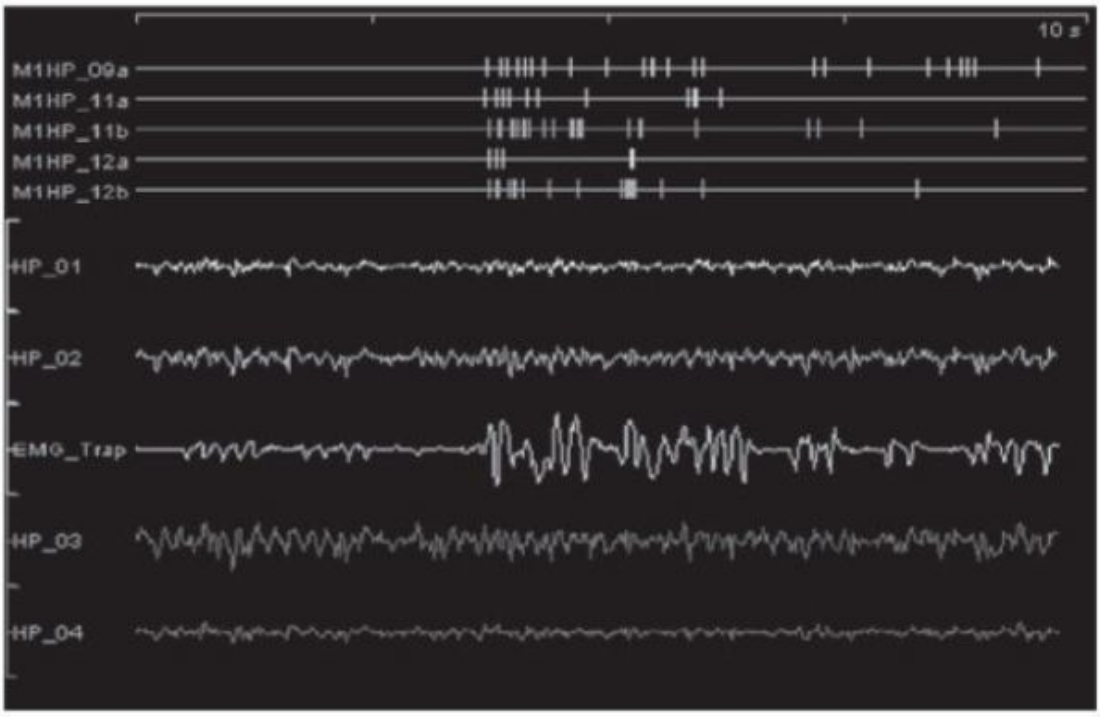

FIGURE 5.4

Electrophysiological recording protocol in mice. Screen of our acquisition system during a recording session 10 weeks after surgery. Along with five isolated cells (top), hippocampal LFP oscillations are also being recorded from four channels, and electromyographic activity is being recorded from the trapezius muscle. (Costa, R.M., Cohen, D., and Nicolelis, M.A. (2004). Differential corticostriatal plasticity during fast and slow motor skill learning in mice. *Curr. Biol.* **14**(13): 1124–1134.)

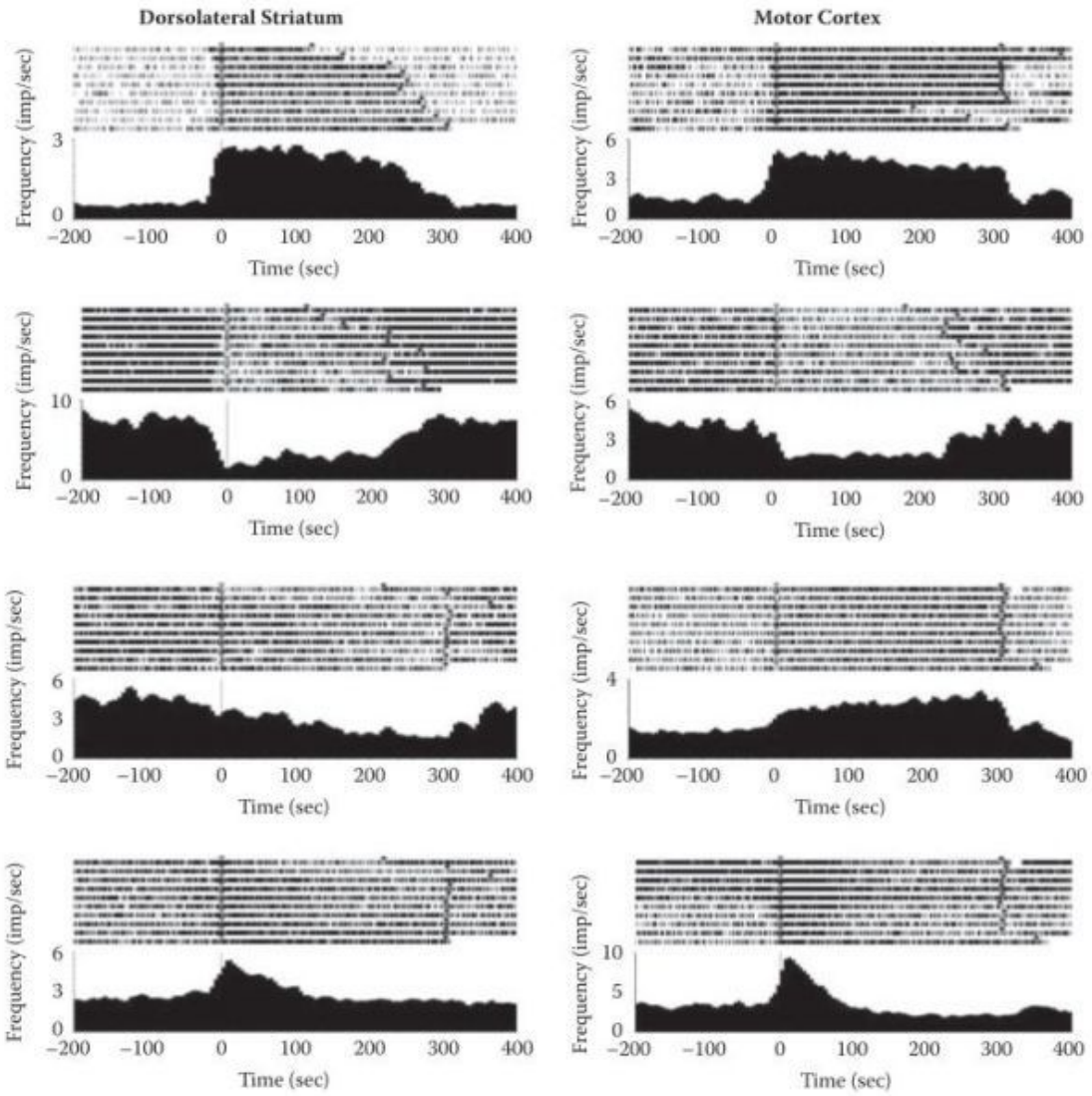

FIGURE 5.5

Modulation of neural activity during running on the accelerating rotarod. Left column: striatal neurons, right column: motor cortex neurons. Each panel displays the raster plots and corresponding peri-event time histogram (PETHs) for a particular neuron throughout one session. The beginning of each running period is aligned at time zero. In each graph, trials are presented top to bottom as they were presented during training. Dorsal striatum neurons are presented on the left column and motor cortex neurons on the right column. First row: Example of a striatal and a cortical neuron that abruptly increase their firing rate during the running period. Second row: Example of a striatal and a cortical neuron that abruptly decrease their firing rate during the running period. Third row, left: Example of a striatal neuron with a rather high firing rate at the onset of each trial; gradually decreases firing rate toward the end of the trial. Third row, right: Example of a cortical neuron that gradually increases its firing rate during the running period. Fourth row: Example of a striatal and a cortical neuron that transiently changed their firing rate at the beginning of the running period and then gradually decreased it throughout the trial.

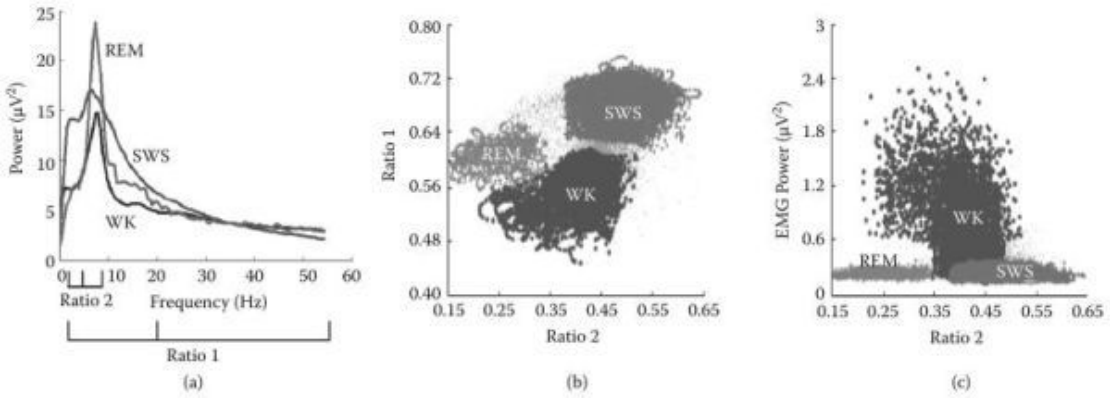

FIGURE 5.6

State-dependent local field potential oscillations and behavioral state map of adult mice. After a 1-week recovery period, normal mice were subjected to 12-h continuous LFP (hippocampus) and EMG (trapezius) recordings in their home cage. (A) The mice displayed state-dependent power spectral patterns characteristic of REM, SWS, and WK in rodents. REM was characterized by high-amplitude theta (4–9 Hz) and gamma (33–55 Hz) oscillations, SWS was characterized by high-amplitude delta (1–4 Hz) and low-amplitude gamma oscillations, and WK was characterized by high-amplitude gamma oscillations. (B) A two-dimensional behavioral state map was generated by plotting the following spectral ratios: x-axis, 0.5–4.5 Hz/0.5–9 Hz and y-axis, 0.5–20 Hz/0.5–55 Hz; (C) EMG data were used to disambiguate WK and REM clusters. All unassigned time points, typically corresponding to interstate transitions, were coded gray. (Dzirasa, K. and Ribeiro, S. et al. (2006). Dopaminergic control of sleep-wake states. J. Neurosci. **26**(41): 10577–10589.)

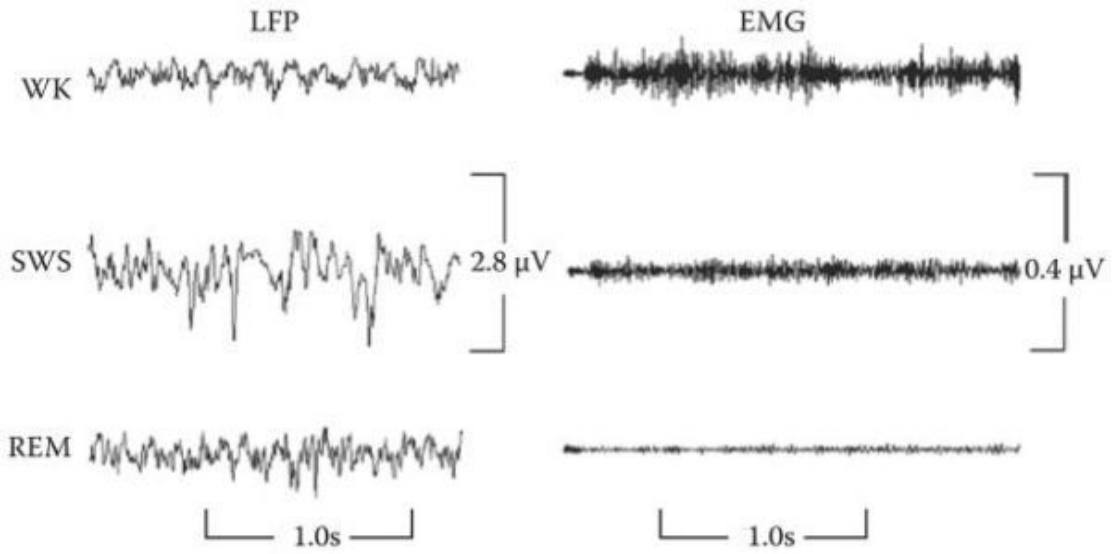

FIGURE 5.7

LFP and EMG activity during state-map-predicted behavioral states. Mice were introduced into a novel cage, and subjected to 12-h continuous LFP (hippocampus) and EMG (trapezius) recordings. Real-time two-dimensional behavioral state maps were generated by plotting the following spectral ratios: *x*-axis, 0.5–4.5 Hz/0.5–9 Hz and *y*-axis, 0.5–20 Hz/0.5–55 Hz. Raw LFP and EMG activity was analyzed during periods of WK, SWS, and REM sleep predicted by the two-dimensional state map. As previously demonstrated, WK was characterized by high brain activity and high muscle activity, SWS was characterized by low brain activity and low muscle activity, and REM was characterized by high brain activity and negligible muscle activity (atonia). (Dzirasa, K. and Ribeiro, S. et al. (2006). Dopaminergic control of sleep-wake states. *J. Neurosci.* **26**(41): 10577–10589.)

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