Silicon-Substrate Intracortical Microelectrode Arrays for Long-Term Recording of Neuronal Spike Activity in Cerebral Cortex

Daryl R. Kipke, Rio J. Vetter, Justin C. Williams, and Jamille F. Hetke

***Abstract*—This study investigated the use of planar, silicon-substrate microelectrodes for chronic unit recording in the cerebral cortex. The 16-channel microelectrodes consisted of four penetrating shanks with four recording sites on each shank. The chronic electrode assembly included an integrated silicon ribbon cable and percutaneous connector. In a consecutive series of six rats, 5/6 (83%) of the implanted microelectrodes recorded neuronal spike activity for more than six weeks, with four of the implants (66%) remaining functional for more than 28 weeks. In each animal, more than 80% of the electrode sites recorded spike activity over sequential recording sessions during the postoperative time period. These results provide a performance baseline to support further electrode system development for intracortical neural implant systems for medical applications.**

***Index Terms*—Brain–computer interface (BCI), brain–machine interface, microelectrode, neuroprosthesis.**

I. Introduction

There is an increasing interest in using intracortical multichannel recording interfaces to provide control signals for neuroprosthetic systems [1], [3]–[6]. By recording from single neurons (units) or clusters of neurons, these types of interfaces provide increased spatial selectivity and a potential for corresponding increased information channel capacity compared to noninvasive electroencephalogram (EEG) recordings or subdural recordings [7], [8]. The tradeoff, however, is a degree of invasiveness that presents challenges in translating the interface technologies from animal studies to clinical brain–computer interface (BCI) and neuroprosthetic systems.

A number of engineering groups are currently working to develop viable neural implant systems for long-term neuronal recording for integration into control-related neuroprosthetic systems. These approaches encompass microelectrode technologies ranging from microwires [9], [10] to various types of silicon micromachining [11], [12], to polymers [13]. While the basic sensor and instrumentation requirements of neural implant systems for recording are well recognized [14], it is becoming increasingly clear that high-channel count-implantable microelectrode systems for medical applications will require a type of sophisticated integrated microsystem that is just now emerging from development efforts.

This paper reports on the use of a particular type of silicon-substrate microelectrode—the so-called "Michigan" microelectrode system—for chronic unit recording in the cerebral cortex. The various components of this electrode system have been developed over the past decade [11], [15] (recently reviewed in [16]) and have several favorable attributes, including: batch fabrication, high reproducibility of geometrical and electrical characteristics, easy customization of recording site placement and substrate shape, small size, and the ability to include on-chip electronics for signal conditioning. In addition, although the devices are planar, they can be microassembled into three-dimensional (3-D) arrays [17]. The objective of this feasibility study was to develop appropriate surgical techniques for permanently implanting the microelectrodes in cerebral cortex and to evaluate the resulting spike recordings over extended periods of time. The primary result is that in a consecutive series of six rats, 5/6 (83%) of the implants remained viable for more than six weeks with 4/6 (66%) remaining functional for more than 28 weeks. More than 80% of recording sites were found to record unit spike activity over multiple recording sessions. This paper provides the preliminary results to drive ongoing efforts to design implant systems appropriate for use in humans.

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II. Methodology

A. Silicon Probe Fabrication

The Michigan silicon probe process begins with selective diffusion of boron into a silicon wafer to define the shape and thickness of the device [17]. Lower dielectric layers of silicon dioxide and silicon nitride are next deposited using chemical vapor deposition. These layers provide insulation from the conductive boron-doped substrate. The conductive interconnect material, polysilicon for most applications, is deposited and patterned and then insulated with upper dielectrics as just described. Selective access through the upper dielectrics to the polysilicon layer to establish recording sites is achieved using a combination of wet and dry etching. Metal is next deposited and patterned to form the electrode sites (typically iridium) and bond pads (gold) using a lift-off technique. Dielectrics in the field area are removed using a dry etch. After the wafer is thinned, it is placed in ethylenediamine–pyrocatechol which selectively etches away the undoped silicon. This process uses eight photolithographic masks. It also enables the design of a wide variety of planar microelectrodes, with specific site configuration and physical layout customized to the targeted neural structure. The microelectrodes used in this study consisted of four penetrating shanks, each with four uniformly spaced recordings sites of the same size [Fig. 1(a) and (b)]. The complete microelectrode assembly included an integrated silicon ribbon cable [15] that was terminated on a flexible printed circuit board mounted to a commercially available microconnector (Nano connector, Omnetics Inc., Minneapolis, MN) [Fig. 1(c)].

B. Surgical Procedure

Microelectrodes were implanted in either a somatosensory or auditory area of the cerebral cortex in rats. The animals were administered general anesthesia (mixture of 50 mg/ml ketamine, 5 mg/ml xylazine, and 1 mg/ml acepromazine), using intraperitoneal injection with an initial dosage of 0.1 ml/100 g body weight and maintained in an areflexive state throughout the surgical procedure using regular anesthesia supplements at 20% the initial dosage. The animal was attached to a standard stereotaxic frame and two or three stainless-steel bone screws were inserted into the skull. A craniotomy (approximately 3×2 mm) was made over the target cortical area and the connector assembly was attached to the skull using dental acrylic [Fig. 2(a)]. Several incisions were made in the dura overlying the cortical area and the resulting dural flaps were folded back to the edge of the bone. The bond-pad region of the microelectrode was grasped with microforceps and the penetrating shanks were inserted by hand through the pia into the cortex. The microelectrodes were inserted to the point where the recording sites were estimated to be 0.5–1.2 mm below the cortical surface. The dural flaps were kept away from the insertion area of the microelectrode. After the insertion, the external aspect of the probe assembly (bond-pad region

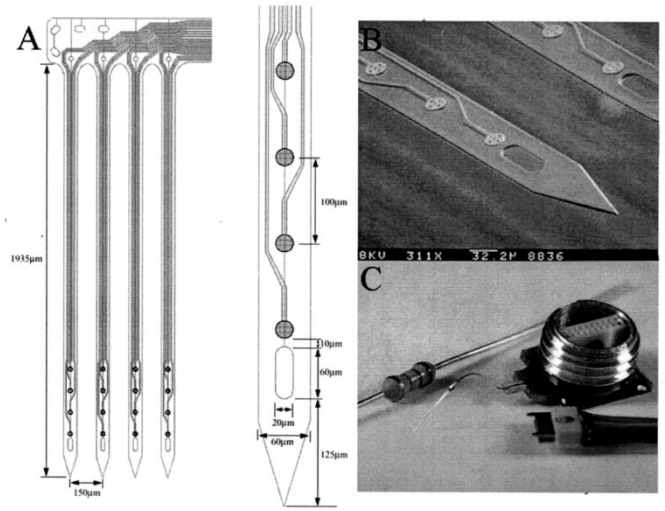

Fig. 1. Components of a chronic Michigan silicon microelectrode. (A) Left: Layout of one of the microelectrodes used in this study. Right: Detail of one of the shanks. (B) Micrograph of the distal end of one of the penetrating shanks The shanks were 15 × 60 microns in cross section. Four recording sites were located in the middle of each shank. The oval hole through the electrode substrate near the tip of each shank is intended to facilitate tissue ingrowth or provide a means for passive drug delivery through a gel. (C) Complete chronic microelectrode assembly included an integrated silicon ribbon cable and a percutaneous connector (resistor provided for scale). A and B show electrode type *flag1*; *C* shows a single-shank probe.

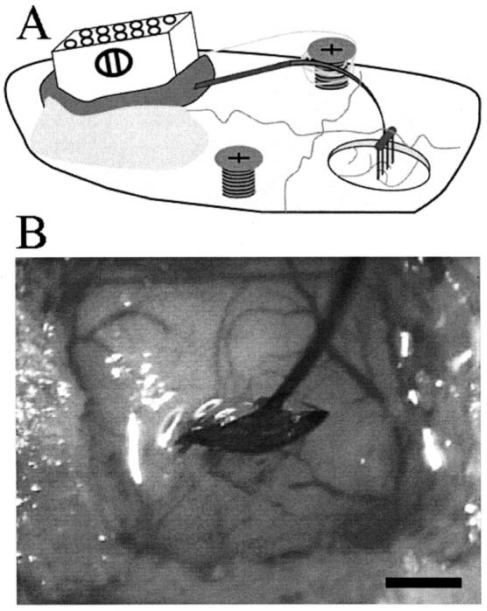

Fig. 2. Implant technique. (A) Illustration of the microelectrode assembly attached to the skull with dental acrylic, with the microelectrode cantilevered over the brain surface. (B) Micrograph of the cortical surface of an implanted microelectrode (MI-6, *siteover* electrode). The penetrating shanks are in the cortex, with the bond pad area and ribbon cable visible above the cortex. ALGEL (a clear polymer) has been applied around the electrode for stablization. Scale bar is 0.5 mm.

and several millimeters of the integrated ribbon cable) was covered using either small pieces of Gel Foam (Pharmacia and Upjohn Company) (animal MI-1 through MI-4) or a novel dural sealant polymer, calcium alginate [18] [animals MI-5 and MI-6; Fig. 2(b)]. A head cap was then fabricated using dental acrylic to further seal the craniotomy and permanently mount the connector assembly to the skull. All procedures complied with the United States Department of Agriculture guidelines for the care and use of laboratory animals and were approved by the University of Michigan Animal Care and Use Committee.

C. Neural Recordings and Data Analysis

Neural recordings were obtained using a Many-Neuron-Acquisition-Processor (Plexon Inc., Dallas, TX). The extracellular signals were bandpass filtered from 450 to 5000 Hz. Action potentials were discriminated using an interactive procedure based on amplitude thresholds and waveform templates. The extracellular recordings and isolated spike waveforms were analyzed offline using custom software. The animals were awake or lightly sedated during regular postoperative recording sessions lasting up to two hours.

III. Results

This study included a consecutive series of six rats that were implanted using similar silicon microelectrodes and surgical methods (Table I). The type of electrode used in each animal is listed in Table I, with the layout detail provided on the University of Michigan Center for Neural Communication Technology website.[1] The first four animals were implanted at the same time and were monitored intermittently over a period of either 28 weeks (MI-1, MI-2, MI-4) or 55 weeks (MI-3). The final two animals (MI-5 and MI-6) were implanted as part of a follow-up set of animals with more frequent recording sessions during shorter postoperative assessment periods (1 and 6 weeks, respectively). In all animals, the microelectrodes were functional (i.e., recording unit activity) at the end of the assessment period. Electrode impedances were obtained in the final two animals. In MI-6, the magnitude impedance at 1 kHz increased from the nominal value of approximately 1 MΩ over the first two postoperative weeks and then stabilized at approximately 1.6–2.0 MΩ.

[1]http://www.engin.umich.edu./center/cnct/.

TABLE I
IMPLANT SUMMARY

Animal	Post-operative weeks (days)	Remarks
MI-1	28.6 (200)	Barrel cortex, *flag1* electrode, Scheduled end-point
MI-2	28.6 (200)	Barrel cortex, *flag1* Scheduled end-point
MI-3	54.6 (382)	Barrel cortex, *4x4_3mm100chron* electrode, Head-cap failed
MI-4	28.6 (200)	Barrel cortex, *4x4_3mm100chron,* Scheduled end-point
MI-5	1 (9)	Auditory cortex, *siteover* electrode, Terminated because of respiratory complication
MI-6	6.7 (47)	Auditory cortex, *siteover* electrode, Head-cap failed

High-quality unit recordings were obtained from each of the animals in this series. Across any given microelectrode array, spike amplitudes ranged from 50 to 800 μV peak-to-peak, with nominal 30-μV noise floors. On most recording sites, single units or multiunit clusters typically persisted over consecutive recording sessions. It was not possible to discern whether the unit activity resulted from activity of the same neurons over these periods. This is highlighted in Fig. 3, which shows 5-s extracellular recordings in auditory cortex from the same electrode site on postoperative day 1 and postoperative day 47 in the same animal.

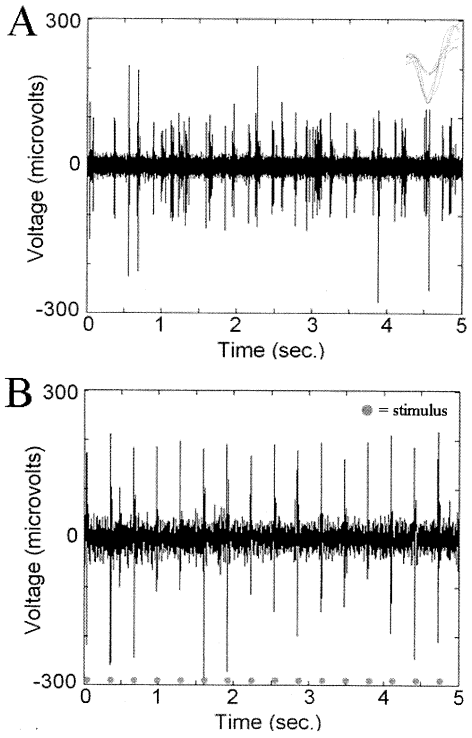

Fig. 3. Representative extracellular signals illustrate the recording quality of the microelectrodes. Each panel shows a 5-s snapshot from the same site in the same animal (MI-6). The microelectrode was implanted in auditory cortex. (A) Postoperative day 1. The inset illustrates several waveforms of two isolated units on this site. (B) Postoperative day 45. The small circles indicate the time of brief auditory clicks used to evoke neural activity during this recording session.

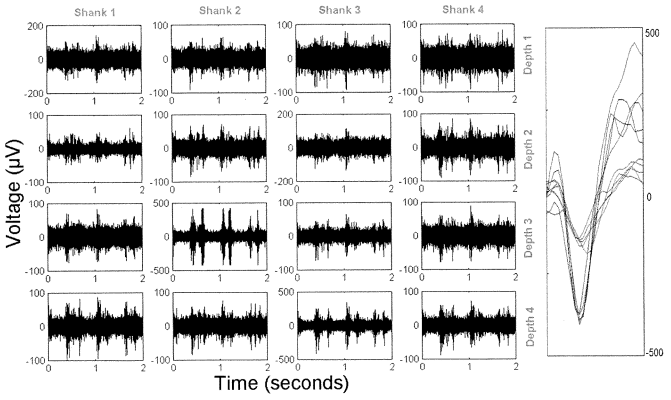

Fig. 4. Simultaneous extracellular neural recordings from the 16 recording sites on a microelectrode. (left) Unit activity was recorded from each site, with some variability in signal-to-noise ratios. The layout of these traces corresponds to the site layout of the electrode. Note the variable ordinate scales. (right) Isolated spike waveforms from two units recorded on one of the sites (shank 2, depth 3). Data from MI-3 on postoperative day 382.

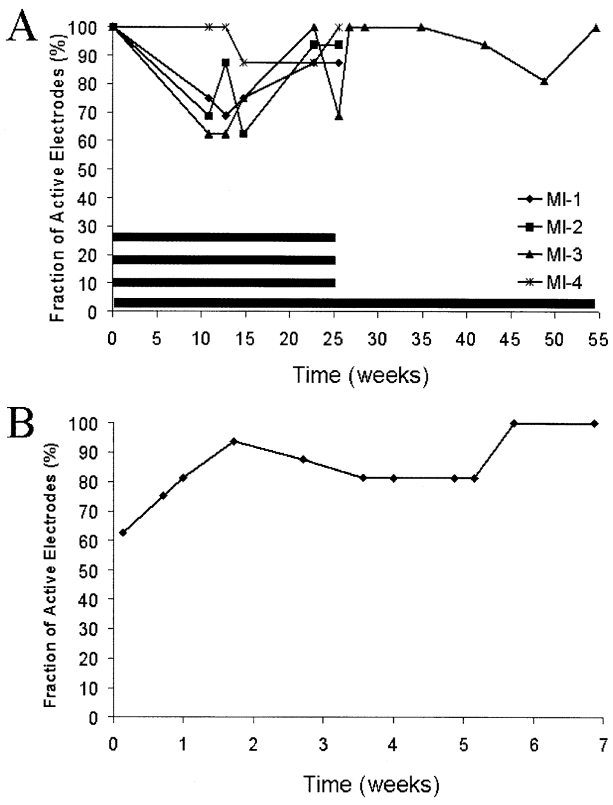

Fig. 5. Summary of the microelectrode reliability to record unit spike activity. (A) Percent of recording sites with detectable unit activity as a function of postoperative week for animals MI-1 through MI-4. (B) Same as in (A) for animal MI-6. Each datapoint summarizes responses from a single 30-min recording session with the animal lightly sedated.

The overall signal quality, as indicated by spike amplitudes relative to the background noise, provides for easily discriminable unit activity (Fig. 3(a), inset).

Most of the sites recorded unit activity. Fig. 4 provides a brief sample of simultaneous recordings across all 16 sites in one animal to illustrate the extent of the neural activity available from these implantable microelectrodes. These data are from a microelectrode in barrel cortex with the animal lightly anesthetized and undergoing intermittent stimulation of contralateral whiskers. The arrangement of the panels in Fig. 4 corresponds to the two-dimensional layout of the recording sites on the microelectrode. For this electrode, the shank separation and the spacing between sites along a shank were each 100 μm. The recording sites were approximately 0.7–1.0 mm from the cortical surface. At this site separation, adjacent sites may sometimes record the same unit.

Across this series of six animals, the microelectrodes were found to provide reliable unit recordings. In every implant, at least 10 of the 16 sites (63%) recorded unit activity (single units or multiunit clusters) during each of the recording sessions (Fig. 5). In three cases (MI-3, 4, and 6), more than 13/16 sites were active in most sessions. It is notable that each case in this series was terminated due to reasons other than the microelectrode not recording unit activity.

IV. Discussion

This study investigated the use of implantable Michigan silicon microelectrodes for long-term neuronal spike recording in cerebral cortex. The principal finding is that this electrode system proved effective for recording viable multichannel unit activity beyond a year in the rat. Moreover, the recordings were typically sufficient for supporting experimental studies aimed at developing neuron-level multichannel cortical interfaces that can be used as a source of control signals for next-generation neuroprosthetic or BCI systems.

Detailed analysis of the recording signal quality and the development of microelectrode optimization strategies are beyond the scope of this study. The variability in spike amplitudes—or, more generally, signal-to-noise ratios—simultaneously recorded on an electrode array during the same time period is attributed to a complex set of factors involving the overall electrode design, the relative position of the recording sites with respect to large and active neurons, and the dynamic tissue response to the implanted microelectrode. Most

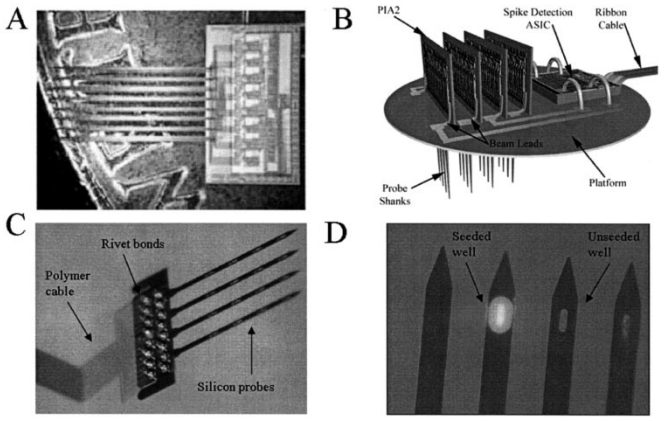

Fig. 6. Current and future developments and enhancements to the base Michigan microelectrode system. (A) Integration of active circuits for signal amplification, filtering, sampling, and site selection. (B) Concept drawing of a prototypical platform assembly for 3-D microelectrode arrays with on-board electronics. (C) Hybrid system that uses silicon-substrate microelectrodes with more flexible polyimide (polymer) ribbon cables. (D) Microelectrode shank with the hole in the shank filled with a gel for release of bioactive molecules into the micronenvironment around the shanks.

of the implants provided examples of both stable and unstable unit waveforms recorded over consecutive recording sessions, although most of the sites did record some level of unit activity. The results presented here provide baseline measures that can support further analysis and system optimization. It is noted that the unit recordings were generally comparable to recordings from implantable microwire arrays [9], [19], [20] or alternative silicon microelectrodes [21]. However, direct comparisons among chronic recording studies are difficult because of significant differences among the electrodes, surgical techniques, and animal preparations.

The particular Michigan microelectrodes used in this study represent a base configuration upon which various advanced functionalities can be integrated. Component- and system-level integration will result in reconfigurable neural implant systems optimized for BCIs and neuroprosthetic systems. Several device extensions are currently in development. On-board or closely integrated active circuits provide the requisite signal conditioning for low-power telemetry [22], [23] [Fig. 6(a)]. Advanced assembly and packaging techniques enable 3-D grids of precisely placed recording sites [17] [Fig. 6(b)]. Silicon-polymer hybrid electrode systems provide a means to assemble flexible and robust implant systems more appropriate for neurosurgical applications [24], [25]. Multifunctional electrode systems with bioactive, drug-delivery components provide a means to also affect the chemical microenvironment around the electrode shank [2], [26].

V. Conclusion

The Michigan microelectrode system was found to be feasible for long-term cortical recording. While there remains much work to do, this electrode system provides the adequate design space in order to provide a technology system for intracortical implant systems for BCI systems.

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Dynamical Dimension of a Hybrid Neurorobotic System

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***Abstract*—The goal of this work is to understand how neural tissue can be programed to execute predetermined functions. We developed a research tool that includes the brainstem of a lamprey and a two-wheeled robot interconnected in a closed loop. We report here the development of a framework for studying the dynamics of the neural tissue based on the interaction of this tissue with the robot.**

***Index Terms*—Brain–machine interface, dynamical dimension, neurocontrollers.**

I. Introduction

Recent studies on primates have shown that information measured in the motor cortex can be used to guide a robotic arm [1]–[3]. A critical challenge for brain machine interfaces is to train the neural system connected to a device in the execution of a variety of tasks. While some studies are focusing on learning mediated by visual feedback mechanisms, the focus of our work is on the control of plasticity at a specific synaptic site, through the interaction of pre- and post-synaptic activities associated with feedback and command signals. To address this issue, we have developed a research tool that includes a portion of living brain tissue of a lamprey and a two-wheeled robot interconnected in a closed loop [4].

The Lamprey is an eel-like fish, whose nervous system has been extensively studied, particularly for what concerns its ability to generate and modulate locomotor behavior [5]. We have selected a portion of the neural circuitry that in normal circumstances receives vestibular and other sensory signals and issues motor commands to stabilize the orientation of the body during swimming [6], [7]. This system has been shown to be adaptive, as unilateral lesions of the vestibular capsules are followed by a slow reconfiguration of neuronal activities until the correct postural control is recovered [6].

In our neurorobotic system, vestibular signals are replaced by light-intensity signals. Two electrodes apply stimulations to the axons of the octavomotor nuclei. The stimulations rates are proportional to the light intensity measured by sensors on the right and left sides of the mobile robot. The mobile robot has two wheels that receive velocity commands proportional to the population spike rates recorded by two electrodes in the spinal cord. Therefore, the natural stabilizing behavior—in which the lamprey tracks the vertical axis—correspond, in the hybrid system to tracking a source of light. Indeed, in most cases, the robot orients itself toward the source of light.

The nervous system between the four electrodes assumes the function of a controller, with two inputs and two outputs that determine the behavior of the robot in a closed feedback loop. In this communication, we focus on the identification of dynamical properties of neural tissue embedded in the neurorobotic system. In particular, we are interested to establish the dynamical dimension of the neural element, as this is a critical parameter to assess what can and cannot be learned.

Section II describes the neurorobotic system, i.e., the neural tissue, the robot, and the interface. Section III briefly describes previous research with the neurorobotic system, which laid the foundation for the work being reported. Section IV describes the experimental protocol. Section V describes the computational analysis method used to establish the dynamic dimension of the system. Then the results are presented in Section VI and discussed in Section VII.

II. Neurorobotic System

The neurorobotic system includes three elements: neural tissue, a robot, and an interface.

A. Neural Tissue

The neural component of the hybrid system is a portion of the brainstem of the Sea Lamprey (*Petromyzon marinus*) in its larval state. After anesthetizing the larvae with tricane methanesulphonate (MS222, 100–200 mg/L), the whole brain was dissected and maintained in continuously superfused, oxygenated, and refrigerated (9 °C–11 °C) Ringer's solution (NaCl, 100.0 mM; KCl, 2.1 mM; $CaCl_2$, 2.6 mM; $MgCl_2$, 1.8 mM; glucose, 4.0 mM; $NaHCO_3$, 25.0 mM), see details in [8].

We recorded extracellularly the activity of neurons in a region of the reticular formation, a relay that connects different sensory systems (visual, vestibular, tactile) and central commands to the motor centers of the spinal cord. We placed two recording electrodes among the axons of the right and left posterior rhombencephalic reticular nuclei (PRRN). We also placed two unipolar tungsten stimulation electrodes among the axons of the intermediate and posterior octavomotor nuclei (nOMI and nOMP). These nuclei receive inputs from the vestibular capsules and their axons form synapses with the rhombencephalic neurons on both sides of the midline. The recorded signals were acquired at 10 kHz by a data acquisition board (National Instruments PCI-MIO-16E4) on a Pentium III 2GHz computer (Dell Computer Corporation).

While the axons of the nOMI remain ipsilateral, those of the nOMP cross the midline. Accordingly, the activity of one vestibular capsule affects both the ipsi- and contralateral reticulospinal (RS) nuclei. We placed each stimulating electrode near the region in which the axons of the nOMI and nOMP cross [see Fig. 1(a)]. This placement of the electrodes induced predominantly excitatory responses in the downstream neurons. The recording electrodes were placed on either side of the midline, near the visually identifiable neurons of the PRRN. To verify the placement of the stimulating electrodes we delivered brief single stimulus pulses (200 μs) and observed the response in both the ipsi- and contralateral PRRN neurons. Once it was determined that the stimulation electrodes were properly placed, the recording electrodes were moved caudally in order to pick up population spikes.

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