

## Telemetric recordings of single neuron activity and visual scenes in monkeys walking in an open field

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### Abstract

This paper describes a portable recording system and methods for obtaining chronic recordings of single units and tracking rhesus monkey behavior in an open field. The integrated system consists of four major components: (1) microelectrode assembly; (2) head-stage; (3) recording station; and (4) data storage station, the first three of which are carried by the monkey and weigh 800 g. Our system provides synchronized video and electrophysiological signals, which are transmitted by a wireless system to a distance of 50 m. Its major advantages are that neuronal recordings are made in freely moving monkeys, and well-separated action potentials with amplitude five times higher than the background noise are usually recorded and readily kept for many hours. Using this system, we were able to study “place cells” in non-human primate brains. The described methods provide a new way to examine correlations between single neuron activity and primate behaviors, and can also be used to study the cellular basis of social behaviors in non-human primates.

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**Keywords:** Monkeys; Freely moving; Open field; Microelectrode assembly; Unit recording; Portable recording system; Hippocampus

### 1. Introduction

In recent years, recording neuronal activity in the brain of awake, behaving animals has become a major tool in behavioral electrophysiology. Recording systems for freely moving monkeys have been previously developed (Ludvig et al., 2001; Ma et al., 2003), but they are limited by the area in which the subjects could walk (typically, 2 m) and do not permit the manifestation of many natural behaviors. Furthermore, these conditions are stressful for the monkeys, which may affect the generated data. Single unit recordings in these conditions may also suffer from many limitations, par-

ticularly in studies of hippocampal neurons. By modifying the method that O’Keefe and Dostrovsky (1971) originally designed for rats, we recorded hippocampal neuron activity in freely moving monkeys, to study hippocampal “place cell” in primates (Wilson et al., 1998). In these preliminary experiments, a multi-wire cable (3–5 m long) and the weight of the main amplifier limited the area in which the monkey could walk, and the testing laboratory was small relative to studies in rats, which are generally tested in an environment that is 10 times their body length (Trullier et al., 1999).

In contrast to the findings in rats (Markus et al., 1995; McNaughton et al., 1983; Muller et al., 1991; O’Keefe, 1984), we did not find “place cells” in the primate hippocampus. In recordings made in the primate hippocampus under similar conditions to those in which place cells had been found in rats, Rolls (1999) did not find any place cells possibly because the testing room was very small, and suspect that the walking area (about 3 m × 3 m) used in that study

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was too small to find a place cell because monkeys are accustomed to traveling several kilometers a day in open fields. To extend our previous studies on “place cells”, it was then necessary to examine the monkeys as they roam freely over a larger area (for example, several square kilometers). The only way we can accomplish this is to examine monkeys in an open field outside the confines of a typical testing laboratory. This requires the ability to record from neurons while the animal is at a distance of up to 50 m.

In this work, we describe a system that eliminates some of the limitations of currently used apparatus by using: (1) a miniature amplifier system; (2) a wireless signal transmit-fial system; (3) a bipolar microelectrode assembly and a dc power supplies in order to obtain clear and stable action potential recordings from freely moving monkeys. With this method, we were able to study “place cells” when the monkey was walking in a large open field.

**2. Materials and methods**

*2.1. Recording system*

This system can be divided into four parts according to the configuration shown in Fig. 1: (1) microelectrode assembly; (2) head-stage; (3) recording station; and (4) data storage station.

*2.1.1. Microelectrode assembly*

The microelectrode assembly was modified from the design of other investigators (Gray et al., 1995; McNaughton et al., 1983; Recce and O’Keefe, 1989). To make fine wire

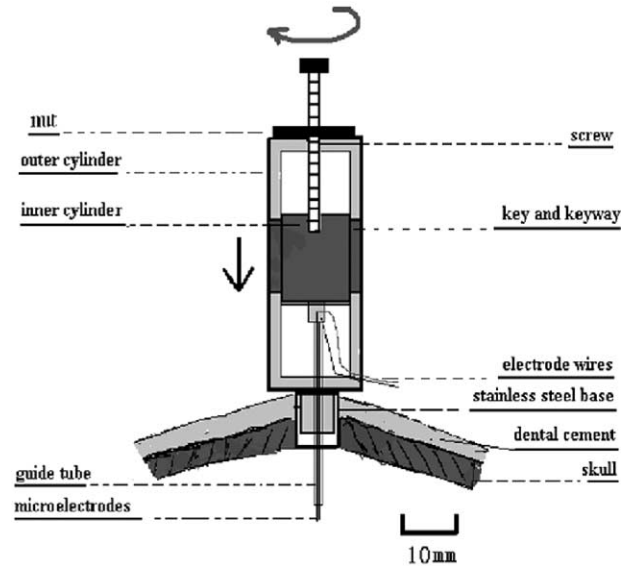


Fig. 2. The drivable microelectrode assembly. The entire assembly, which was fastened to the stainless steel base, was anchored to the skull with dental cement applied around the base and the outer cylinder.

electrodes, 15 μm diameter Formvar-coated nichrome wires (California Fine Wire, Grover Beach, CA) were used. Electrodes can be constructed in two ways: a common single fine wire electrode and a “tetraode” (a bundle formed with four fine wires).

As shown in Fig. 2, the microelectrode assembly contained electrodes and a micro-driver. The electrodes comprised a single electrode (or a tetraode) and a reference electrode. The diameter of the reference electrode was

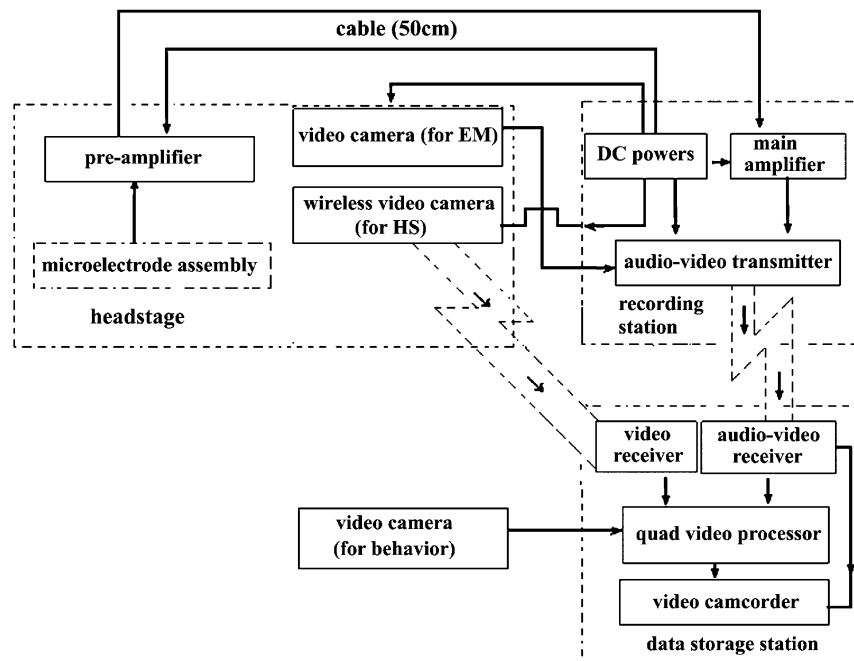


Fig. 1. The system flow chart.

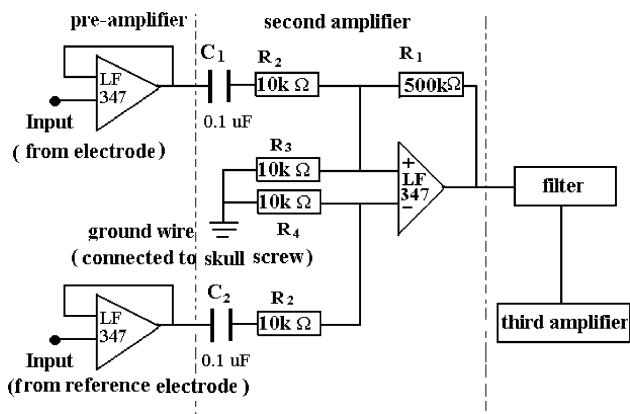


Fig. 3. A schematic diagram of the connections between the recording electrodes, the reference electrode and the ground wire in relation to the amplifiers. It shows the ‘bipolar’ electrode and the recording principle of common mode rejection (the filter and the third amplifier are omitted in the figure because their designs are similar to other designs (Bruce et al., 2001; Metting Van Rijn et al., 1994; Obeid et al., 2003)).

150 μm. The distance from the tip of the reference electrode to the tip of recording electrode is <1 mm. Hence, all electrodes formed a bipolar recording configuration. The connections between the electrode, ground wire (connected to the skull screw) and the reference electrode in relation to the pre-amplifier are shown in Fig. 3.

The micro-driver is detachable and small. As shown in Fig. 2, it consisted of two concentric transparent acrylic cylinders, an outer (the body, with a diameter of 6 mm) and an inner (moveable) cylinder. A key and keyway in the cylinders prevented rotation of the inner cylinder when the screw was manually turned. Manual rotation of the screw translated the linear motion of the inner cylinder up or down the

wall of the outer cylinder. A #0-80 machine screw, which provided the mechanism for driving the inner-cylinder vertically, was joined with a nut that was fixed at the opening of the outer cylinder. The gross weight of the microelectrode assembly was 3 g, and each full turn of the screw advanced the microelectrodes by 330 μm.

Before implantation, the tips of the microelectrodes were cut with sharp scissors, and the distance from the opening of the guide tube (30-gauge) to the tip of the microelectrodes is about 1 mm. The tips of the microelectrodes were then gold-plated, and the impedance (about 1 MΩ) of the electrode was measured to test in quality. In order to sterilize them, the microelectrode assemblies were subsequently soaked in ethanol, sonicated, and rinsed in deionized water.

2.1.2. The head-stage

The head-stage included a protective cap (containing the body and cover), the pre-amplifier and two video cameras (the resolution of the video cameras was 320 pixel × 240 pixel). As shown in Fig. 4, the protective cap, located on the head of the animal, mechanically supported two video cameras and protected the micro-electrode assemblies and pre-amplifier, which was anchored to the skull. The pre-amplifier with high-input impedance (10<sup>12</sup> Ohm) and common input mode (see Fig. 3) was used to amplify electric currents. One of the video cameras (203CA, Shen Zhen Company, China, 26 mm × 26 mm × 16 mm) was used to record eye movement (EM). The other was a wireless video camera (JLT-1.2G, Shen Zhen Company, China, 26 mm × 26 mm × 16 mm) that was used to record the ‘‘head scene’’ (HS). ‘‘HS’’ denotes the scene that the monkey was seeing and it could, therefore, provide some information about its head direction. Both cameras were attached to

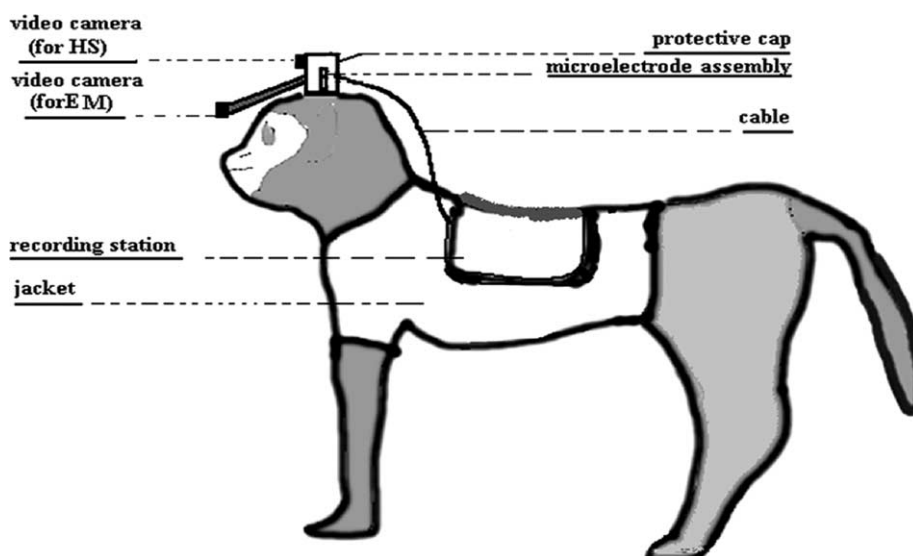


Fig. 4. Schematic diagram of system assembly on the animal. The devices which allowed simultaneous single-cell recording and behavior tracking were carried by the freely moving monkey. Note that the head-stage located on the head of the animal during the experiment mechanically supported two video cameras and protected the microelectrode assemblies and the pre-amplifiers anchored to the skull (the pre-amplifiers and the cover of the cap are omitted in the figure).

the protective cap at appropriate angles and powered by the same rechargeable battery (12 V, 1.3 Ah) packaged into the jacket. The protective cap plus the two video cameras weighed 127 g.

### 2.1.3. Recording station

The “recording station” (see Figs. 1 and 4), which were housed into two packages (each 20 cm × 13 cm × 4 cm), consists of the main amplifier, an audio–video transmitter, and a set of batteries. The packages were held in a jacket worn by the monkey. A multi-wire cable (Fig. 4) connecting the “head-stage” and the “recording station” was used to transmit electrophysiological and video signals from the pre-amplifier and the EM camera, respectively, to the “recording station”, and to supply power to the head-stage. A third video camera was held by the experimenter and was used for recording the animal behavior. The “recording station” plus a set of batteries weighed about 600 g. Hence, the weight carried by a monkey was likely not to affect its behavioral performance.

**2.1.3.1. The main amplifier.** The main amplifier was a differential amplifier, which consisted of the second amplifier, the third amplifier and band-pass filter (Fig. 3). The second and third amplifiers were powered, respectively, by a separate source, and this design was used to avoid interference caused by positive feedback. The second amplifier had a gain of 50 and the third amplifier of 100, so, the amplifier system provided a gain of 5000. When the monkey was moving or eating, electrical noise from muscles was quite strong. To filter such noise, each amplifier required a common mode of input. Bandpass filtering was set at 900–6000 Hz. The entire circuit of the main amplifier was laid out on a single-sided printed circuit board, and then packaged in a plastic box (200 mm × 50 mm × 25 mm high; gross weight, 140 g).

**2.1.3.2. The audio–video transmitter.** The signals of unit activity from the main amplifier were passed into the audio channel of the audio–video transmitter (Adth Co., VS-240, USA, 18 cm × 12 cm × 5 cm high) via a multi-wire cable, while the video signals of the eyes and their movements were fed into the video channel of the transmitter through the same multi-wire cable. These signals were then passed wirelessly from the transmitter to the audio–video receiver (Adth Co., VS-240, USA, 18 cm × 12 cm × 5 cm high), located in the “data storage station”. The telemetry range was over 50 m. At the same time, the video signals of the “HS” were wirelessly transmitted to another video receiver.

**2.1.3.3. dc power supply.** A set of rechargeable batteries packaged into the jacket supplied power to the pre-amplifier, EM, HS camera (on the “head-stage”) and the “data storage station” (the main amplifier and the audio–video transmitter). Pre-amp: ±9 V, main amplifier: ±9 V, two cameras and the transmitter shared the same rechargeable battery: 12 V, 1.3 Ah. The battery power was maintained for 5–6 h during

the recording session. The heat generated by the batteries and the battery-powered devices was negligible.

### 2.1.4. The data storage station

The “data storage station” (Fig. 1) included two video receivers, a quad video processor, a videotape camcorder and their dc power supplies. The station could be packaged inside a suitcase (26 cm × 16 cm × 20 cm high), weighed about 2.0 kg and was carried by the experimenter. One audio–video receiver (different from the one described below) was dedicated to the signals of unit activity and the video signals of the eye movements. Another receiver (JLT-1.2G, Shen Zhen Co., China, 11 cm × 5 cm × 2.2 cm) was used to receive the video signals from the HS camera. Video images from all three cameras were then fed into a four channel black–white quad processor (Goldbeam, Qb-Bnc, USA, 20 cm × 22 cm × 4.5 cm high); the composite picture of the three cameras as well as neuronal activity was sent to the videotape camcorder (Sharp Camcorder, VL-E660U; Sharp Corporation, Japan, or Panasonic, NV-MX300, Japan), where it was stored on 8 mm cassettes together with the simultaneously recorded neuronal responses (see Ro et al., 1998). A rechargeable battery (12 V, 7 Ah) was used to power all devices in the station except for the camcorder.

## 2.2. Animal preparation and surgical implantation

Three healthy adult rhesus monkeys, weighing 3.0–5.5 kg, were used in the study. They were obtained from the animal husbandry center of the Kunming Institute of Zoology, Chinese Academy of Sciences. All procedures were approved (protocol no. 13888988490) by the Animal Experimental Committee, Kunming Institute of Zoology, Chinese Academy of Sciences, and were conducted in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals (NIH Guidelines).

Animals were trained for several weeks to walk along a road marked with numbers and do other tasks related to the experiment. After the first surgical procedure, each monkey was trained to become accustomed to wearing the “head-stage”, as well as to the experimental procedures such as the turning of the micro-driver.

The surgery was performed aseptically following anesthesia, induced by administration of hydrochloric acidulated ketamine (4 mg/kg, i.m.), followed by sodium pentobarbital (30 mg/kg, i.m.). Deep surgical anesthesia was maintained with supplementary doses as needed. There were two steps for the surgical implantation: Step 1, for the implantation of the head-stage; and Step 2, for implantation of the microelectrode assembly. At first, the scalp was incised and retracted, together with the muscles overlying the skull. The surface of the skull was cleaned of all fascias and thoroughly dried. The head-stage and the stainless steel bases were secured to the skull at appropriate positions. At the same time, a ground wire connected to the skull screw was prepared. The animal was then given an-

tibiotics and returned to the cage for recovery. Two weeks after the first surgical procedure, when the monkey had become accustomed to the head-stage and recovered from surgery, the second surgical procedure was performed under the same condition as described above. The microelectrode assembly was implanted in the parietal cortex or the hippocampus.

### 2.3. Recording procedure

Usually, the recording procedure was initiated in the laboratory. To commence recording, the cover of the protective cap was removed. The wires (one of the electrodes, the reference and the ground wire) were connected to the pre-amplifier (as shown in Fig. 3), and the HS and EM camera were fixed to the “head-stage” using two bolts. The “recording station” was carried in the monkey’s jacket (during the recording session). The multi-wire cable was then connected to the “head stage” and the “recording station”. When all connections were made, we searched for single neurons by advancing the electrodes in 40  $\mu\text{m}$  increments by rotating the driving screw (1/8 turns was the minimum advancement). The audio signal (neuronal firing) was monitored by an earphone (connected to the audio channel of the audio–video receiver) that was worn by the experimenter. Neuronal firing was usually detected within a 30 min “cell-searching” period, which is consistent with the experience in previous studies (Ludvig et al., 2000, 2001). Once stable unit activity had been established, the monkey was led to recording site and walked along the road (length: 300 m) six times while the experimenter with the data storage station followed the monkey to collect the data. All recorded data were analyzed off-line.

## 3. Results

### 3.1. Animal behavior

At the beginning of the adaptation period, animals attempted to remove the jacket and the protective cap using their teeth or hands. One week later, the animals had become completely accustomed to the jacket and the “head stage”, and were thereby able to move freely in an open field wearing the apparatus. No abnormal behaviors were observed. Monkeys implanted with the device cooperated very well with experimenters. Thus, recording was performed while the animal was in a normal state, in as much as the monkey was moving freely in an open field, and tolerating the presence of the recording device. In general, the presence of the recording apparatus did not affect the behavioral performance, and the behavioral performance did not compromise the stability of neuronal recordings.

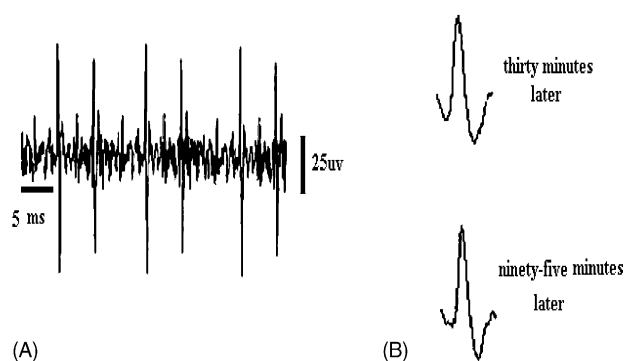


Fig. 5. Single-cell recording from the parietal cortex of a monkey moving freely in an open field. (A) Action potentials firing during the experimental session, showing a five-fold signal-to-noise ratio. (B) Action potential waveforms could be reliably kept for over 1 h.

### 3.2. Recording quality and stability

We were able to record 100 single neurons from the brains of monkeys moving freely in an open field. Stable action potentials with amplitudes five times higher than the background noise were consistently detected (Fig. 5A). In addition, a neuron could be recorded for 1–2 h without the risk of losing the signal when the monkey was moving during the recording sessions, also, the recordings were not disturbed by the animal movements. Fig. 5B shows single neuron action potential waveforms at different times during the experiment, so far, unfortunately we have not been able to hold a neuron overnight. Our precautions in the design of the amplification system resulted in very little noise from sources such as EEG and EMG, and usually could not be observed when recording took place in an open field, irrespective of whether the monkey was walking or eating.

### 3.3. Eye movement recording and behavioral recording

During recording, the behavior of the monkey and the view from the head scene camera were filmed using video cameras which had a wide-angle lens (60°), so that the landmarks around the monkey were easily captured. It was thereby easy to trace the walking routes of the monkeys. Fig. 6 shows a direct correlation of frame-by-frame video images with the neuronal activity from the microelectrode.

Usually, unlike the eyeball of humans, both the cornea and conjunctiva of rhesus monkeys are dark brown, so it is not easy for a computer to trace the eye position. However, we found that illumination using an infrared LED (light-emitting diode) allowed very good images of the eyeball, especially the pupil, which was quite clear and therefore good for eye position tracings. The use of an infrared LED anchored to the camera as a light source overcomes the fluctuations in light intensity that occur during locomotion and head movement, e.g. shadows as the monkey’s moves in relation to the sun.

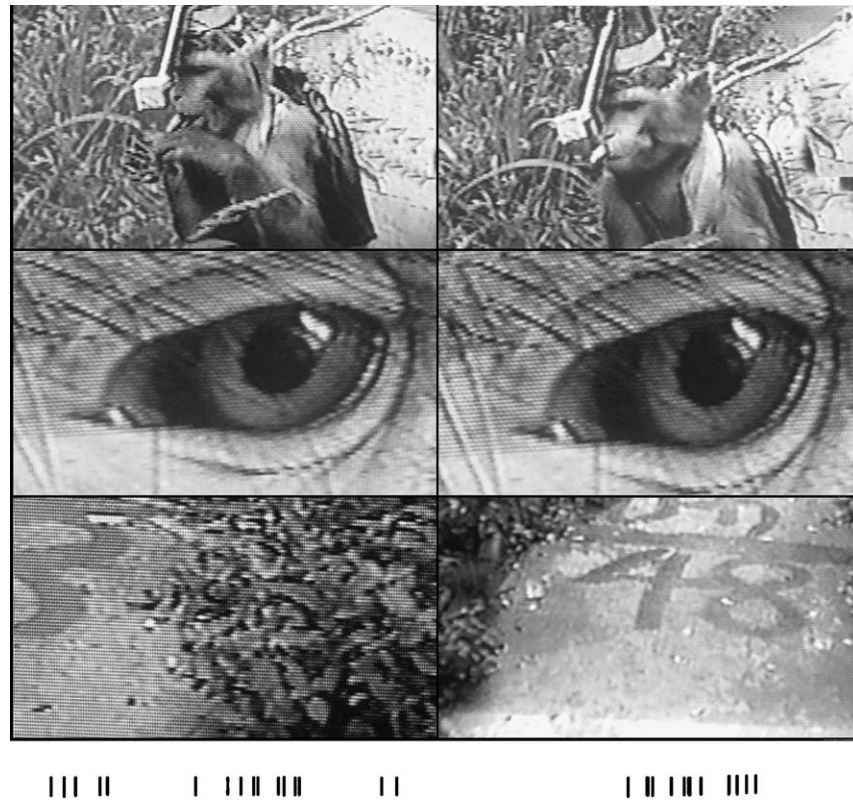


Fig. 6. Correlation of frame-by-frame video images with the neuronal activity recorded from the parietal cortex. Top row: two video images of the monkey taken from the investigator's camera: the monkey rotates his head to the left. Middle row: images of the eye synchronized with the frames from the investigator's camera. Bottom row: images from the "head scene" camera, showing the number "48" before and after rotation of the head to the left. Numbers written on the ground were used as landmarks in order to trace the walking routes of the monkeys. The actual spike trains that occurred during these head and eye camera scenes are shown at the bottom of this figure.

Pattern recognition techniques (Fenton and Muller, 1996) were used to trace and analyze eye movements and their position. As the spatial relationship between the camera and the eyes of the animal was geometrically fixed, the orientations of the eye-ball relative to the eye socket could be calculated with the positions of the pupil in the visual field of the camera. We used a Hopfield artificial network for this calculation. The network was trained with the following information. First, the signals of the eyeball orientations were divided using a two-valued process. Second, the network was programmed to filter the noise from the signals, allowing the edge of the pupil to be detected, with the center of the pupil calculated. Finally, the coordinates of the pupil were calculated (Marques de Sa', 2002).

### 3.4. Signal wireless transmission

The wireless transmission system could transmit two separate microelectrode signals via different channels without interfering crosstalk. This is consistent with the results of Nieder (2000). In addition, the transmitter relayed electrical signals from the recorded neuron to a receiver some 50 m distant, and no decrease in the quality of the signal was apparent.

## 4. Discussion

Our study demonstrated for the first time that it is possible to record the firing of single neurons, for a number of hours using a portable recording system connected to monkeys that are moving freely in an open field. The system we developed has three advantages: it is physically portable, electrically stable, and has multiple functions (it can be used in different conditions and for many purposes). Another major advantage of this system is the easy linkage of behavioral changes with electrophysiological correlates, as shown in Fig. 6. This provides the possibility of studying the relationship between brain and behavior at a cellular level, or studying the cellular basis of social behavior when monkeys are moving freely in an open field or even in a monkey colony. It allows maximum freedom for both the animal and the experimenter, and reduces stress to the animals. This is very important for studying animal behavior, and in particular social behaviors.

The key problem when developing this method was to design a portable recording system to obtain a stable, low-noise, high-quality recording from freely moving monkey in an open field. The following factors proved to be critical. First, it was necessary to ensure that all components

of the portable recording system were small and light. In addition, low dc power consumption and wireless signal transmission enables the recording system to be portable. The major limitation of the device is that only two audio input channels are available. Secondly, a bipolar recording configuration, allowing a common mode of input, was used in our microelectrode–amplifier system, thereby reducing the interference generated by animal movements or other noise. For amplification, a separate amplifier with a separate dc power supply was used to avoid oscillation caused by positive feedback. The independent dc power helped isolate external interference. The power input of the operational amplifier was bypassed with a capacitor to reduce the ripple, especially in the front-end stage. Further, a ground wire connected to the skull screw was important for noise reduction. Hence, our design negated the need for a shielded environment.

Our technique of using video imaging to track eye movements was successful, and greatly reduces problems associated with other eye tracking techniques. For example: (1) the scleral coil system (Fuchs, 1967; Robinson, 1963) requires a large coil (surrounding the head) to generate a magnetic field and this is not practical for freely moving monkeys in an open field; (2) using pairs of infrared sensors and an infrared LED, changes in the reflection of the infrared light represent the eye movements. However, our video imaging system uses the monkey's face as a reference, and has to be located in close proximity to the monkey's eye. Our eye movement camera was small, had high spatial resolution, and was located several centimeters from the eye. The time resolution using this monitor is lower (40 frames/s) than that produced by using the coil; however, it proved acceptable for analyzing eye movement in our experiment.

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