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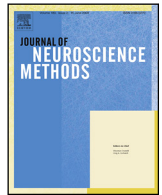

Basic Neuroscience

A new, behaving, head restrained, eye movement-controlled feline model for chronic visual electrophysiological recordings

Tamás Nagypál[a], Péter Gombkötő[b], Györgyi Utassy[a], Robert G. Averkin[c], György Benedek[a], Attila Nagy[a,*]

[a] Department of Physiology, Faculty of Medicine, University of Szeged, Dóm tér 10, Szeged H-6720, Hungary
[b] Center for Molecular and Behavioral Neuroscience Rutgers University, 197 University Ave, Newark, NJ 07102, United States
[c] Research Group for Cortical Microcircuits of the Hungarian Academy of Sciences, Department of Physiology, Anatomy and Neuroscience, University of Szeged, Közép fasor 52, Szeged H-6726, Hungary

HIGHLIGHTS

- A new model for chronic visual electrophysiological recordings in behaving cat.
- A novel body position for recording (suspension).
- Rigorous control to avoid the confounding effects of eye movements.
- Stable recording for over two years.

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ABSTRACT

Background: Anesthetized, paralyzed domestic cats are often used as model organisms in visual neurophysiology. However, in the last few decades, behaving animal models have gathered ground in neurophysiology, due to their advantages over anesthetized, paralyzed models.
New Method: In the present study a new, behaving, awake feline model is described, which is suitable for chronic visual electrophysiological recordings. Two trained, head- fixed cats were suspended in a canvas harness in a specially designed stand. The animals had been trained to fixate the center of a monitor during static and dynamic visual stimulation. Eye movements were monitored with implanted scleral coil in a magnetic field. Cell-level activity was recorded with eight electrodes implanted in the caudate nucleus.
Results: Our two trained cats could maintain accurate fixation, even during optic flow stimulation, in an acceptance window of $\pm 2.5^{\circ}$ and $\pm 1.5^{\circ}$, respectively. The model has yielded accurate recordings for over two years.
Comparison with Existing Method(s): To our knowledge, this is the first awake, behaving feline model with rigorous eye movement control for chronic, cell-level visual electrophysiological recordings, which has actually proven to work during a longer period.
Conclusions: The new model is optimal for chronic visual electrophysiological recordings in the awake, behaving domestic cat.

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1. Introduction

The domestic cat is a classical mammalian model organism in visual neurophysiology and neuroanatomy. Several high-impact discoveries have been based on the feline model, of which the most well-known may be those of the Nobel laureates Hubel and Wiesel (1961, 1962). In the last few decades, animal research has seen a clear tendency toward the use of awake, behaving animals, instead of the previously used anesthetized, paralyzed models.

In visual electrophysiology the anesthetized, paralyzed feline model was optimal for the analysis of visual receptive field properties of single neurons, as the confounding effect of eye movements was eliminated by the paralysis. However, the exclusion of the effects of the eye movements in awake, behaving experiments is not less necessary, as several visually active structures (e.g. the superior colliculus or the basal ganglia) show saccadic responses too (Hikosaka et al., 2000; Munoz and Fecteau, 2002). This necessitates

* Corresponding author at: Department of Physiology, University of Szeged, Dóm tér 10, H-6720 Szeged, POB 427, Hungary. Tel.: +36 62 545869; fax: +36 62 545842.
E-mail address: nagy.attila.1@med.u-szeged.hu (A. Nagy).

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a continuous monitoring of eye movements. For this purpose, implantation of scleral magnetic search coils was introduced (Fuchs and Robinson, 1966; Judge et al., 1980; Robinson, 1963). The model was developed for primate models, but it was successfully adapted to cats too. Awake, behaving animal models have two major advantages over anaesthetized ones: first, significantly fewer animals are required. Second, this way, the modulatory effects of anesthetics can be excluded. Such a modulatory effect was clearly demonstrated in the superior colliculus, a multisensory midbrain structure of the mammalian brain, where the large enhanced multisensory responses, which were described in anesthetized animals (Stein, 1998), could never be recorded from awake, behaving cats (Populin and Yin, 2002). Furthermore, different anesthetics have different effects on the visual sensitivity of the brain, which undermines the comparability of the results (Villeneuve and Casanova, 2003). Behaving animal models are often used in primate experiments, but they have rarely been utilized in cats, due to technical difficulties. In visual electrophysiology, only a few research groups are known that have performed visual experiments on eye-movement controlled, behaving cats. Pigarev and his colleagues investigated the visual cortical areas (Pigarev and Levichkina, 2011; Pigarev and Rodionova, 1998). Populin and Yin performed mainly auditory and auditory-visual experiments on the superior and inferior colliculi (Populin and Yin, 1998, 2002; Tollin et al., 2005). Huxlin and Pasternak (2004) investigated the training-induced recovery of visual motion perception after extrastriate cortical damage in adult cats. In each case, the head of the animal was fixed and its body was put either in a box or on a trolley, which could move along a 3-m long railway or in a canvas bag on a platform.

In our laboratory we investigate the sensory properties of the basal ganglia and the connected ascending tectofugal visual system. We have hitherto performed our experiments on anaesthetized and paralyzed cats (Gombkoto et al., 2013; Nagy et al., 2006, 2008). Our main goal was to introduce a feline model, which would be suitable for chronic visual and multisensory electrophysiological recordings in the awake, behaving cat. Here we present the entire experimental setup and demonstrate how eye-movements were monitored and controlled for. The applicability of the new model is demonstrated through recordings of neuronal responses from the caudate nucleus.

2. Materials and methods

Experiments were performed on one male (3.5 kg) and one female (2.5 kg) adult domestic cats. All experimental procedures were carried out to minimize the number and the discomfort of the animals involved, and followed the European Communities Council Directive of 24 November 1986 (86 609 EEC) and the National Institutes of Health guidelines for the care and use of animals for experimental procedures. The experimental protocol was accepted and approved by the Ethics Committee for Animal Research of the University of Szeged.

2.1. Animal preparation and surgery

The animals were initially anesthetized with ketamine hydrochloride (Calypsol (Gedeon Richter®), 30 mg/kg i.m). To reduce salivation and bronchial secretion, a subcutaneous injection of 0.2 ml 0.1% atropine sulphate was administered preoperatively. A cannula was inserted in the femoral vein and after intubation of the trachea the animals were placed in a stereotaxic headholder. All wounds and pressure points were treated regularly with local anesthetic (1%, procaine hydrochloride). Throughout the surgery, the anesthesia was maintained with 1.5% halothane in a 2:1 mixture of N_2O and oxygen. The depth of anesthesia was monitored by continuously checking the end-tidal halothane concentration and heart rate (electrocardiogram). The minimum alveolar anesthetic concentration (MAC) values calculated from the end-tidal halothane readings were kept in the range recommended by Villeneuve and Casanova (2003). The end-tidal halothane concentration, MAC values and the peak expired CO_2 concentrations were monitored with a capnometer (Capnomac Ultima, Datex-Ohmeda, ICN). The O_2 saturation of the capillary blood was monitored by pulse oxymetry. The peak expired CO_2 concentration was kept within the range 3.8–4.2% by adjustment of the respiratory rate or volume. The body temperature of the animal was maintained at 37 °C by a computer-controlled, warm-water heating blanket. Craniotomy was performed with a dental drill to allow a vertical approach to the target structures. The dura mater was preserved, and the skull hole was covered with a 4% solution of 38 °C agar dissolved in Ringer's solution. Then a reclosable plastic recording chamber (20 mm in diameter) was installed on the skull. Following this, the eight electrodes were implanted in the brain with the help of an adjustable microdrive system (a modified Harper-McGinty microdrive for the first animal, see McKown and Schadt (2006), and a modified Korshunov microdrive for the second animal, see Korshunov (1995)). The implanted chamber and microdriver system allowed a stable recording background for long-time (at least two years in the first cat). In order to monitor the eye movements of the animals, a scleral search coil was implanted into the eye. Although this method was originally developed for primates (Fuchs and Robinson, 1966; Judge et al., 1980; Robinson, 1963), **it was later adapted to cats, too** (Huxlin and Pasternak, 2004; Pigarev and Levichkina, 2011; Pigarev and Rodionova, 1998; Populin and Yin, 1998, 2002; Tollin et al., 2005). Additionally, a stainless steel headholder was cemented to the skull for head fixation purposes.

Surgical procedures were carried out under aseptic conditions. Before the surgical procedure, a preventive dose of antibiotic was given (1000 mg ceftriaxon, i.m., Rocephin 500 mg (Roche®)). The first five postoperative days 50 mg/kg antibiotic was provided intramuscularly. Nalbuphin and non-steroidal anti-inflammatory drugs were administered until the seventh postoperative day.

2.2. Behavioral training of the animals

The experimental animals were selected with distinguished care, in a one-year process, during which the animals were adapted to the laboratory environment and their temper was also observed. It was only after this selection and training process that the insertion of the recording electrodes took place. Water deprivation was not used. Cooperative behavior and adaptation to the laboratory environment was formed by a feeding routine. Independently of behavioral training or recording, the animals received food only in the laboratory (150–250 g/day). During the weekends, the animals had access to food in their cage ad libitum, without any weight control. Once the cat got accustomed to the laboratory environment, it was carefully clothed into the canvas harness. This harness leaves the head, tail and legs free. Initially, the cat spent only a few minutes in the harness, which was extended to two hours. It was also during this period that we gradually shifted to pulpy food provided trough a plastic tube. The next step in training, which is a novelty of our model, was the suspension of the animal. Cats, by nature, like to lie in a hammock; therefore, it is relatively easy to get them accustomed to the canvas harness in a suspended position. In this specific case, it was done as follows: First, we lifted the animal manually only a few centimeters from the floor in the canvas harness, while it was being fed. When the animal got used to being suspended this way, it was gradually introduced to the experimental stand (Fig. 1). The experimental stand is a cubical structure with each side open, in which the suspension harness is fastened at two points in by a rope pulley block. Before the implantation of the electrodes, it

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