

Study on surgical approaches and electrode implantation of oculomotor nerve and inferior obliquus in beagle dogs

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ABSTRACT

الأهداف: دراسة التشريح والطرق الجراحية للعصب المحرك للعين (OMN) والزوايا المائلة السفلية (IO) وطرق تطبيق المسرى الكهربائي لهما في نموذج الكلب.

الطريقة: أجريت هذا البحث على 30 كلب بكلية الطب بجامعة شنغهاي جيونتونق - شنغهاي - الصين، خلال الفترة ما بين نوفمبر 2007م وحتى أغسطس 2008م. تم إخضاع جميع الحيوانات لطريقة التحول الجبهي المداري الأيمن إلى عصب محرك العين (OMN) داخل القحف، والتحول الملتحمي إلى الزاوية المائلة السفلية (IO) والتحفيز العصبي، وتسجيل تطبيق المسرى الكهربائي تحت التخدير العام. تم تحفيز العصب المحرك للعين (OMN) وتم تحليل وتسجيل التخطيط الكهربائي للزاوية المائلة السفلية (IO) باستخدام نظام باورلاب (Powerlab System). تم التحقق من أمان واعتمادية المسرى الكهربائي المطبق.

النتائج: تم وصف التشريح الجراحي والطرق لكلا من العصب المحرك للعين (OMN) الذي ينشأ من منتصف الدماغ إلى مدخل الجيب الكهفي والزوايا المائلة السفلية (IO). المزيد من ذلك، تم عرض تطبيق طرق تحفيز المسرى الكهربائي للعصب المحرك للعين (OMN) والمسرى الكهربائي لتسجيل التخطيط الكهربائي للزاوية المائلة السفلية (IO). كانت المسريات الكهربائية المطبقة آمنة ومعتمدة. تم الحصول على بعض بيانات التخطيطات الكهربائية الفسيولوجية للزاوية المائلة السفلية (IO) في الكلاب السليمة. كذلك تم عرض بعض الاحتراس قبل العملية الجراحية للإجراءات الجراحية داخل الجمجمة والعين في الكلاب. بلغت نسبة الوفيات لدى الكلاب 0% ولم يتم ملاحظة مضاعفات بعد العملية الجراحية.

خاتمة: مع البيانات المتوفرة، ومع هذه الطرق الجراحية وطرق تطبيق المسرى الكهربائي تعرض خيارا بناء نموذج حيواني لدراسة مختلف الجوانب لتجدد العصب المحرك للعين (OMN).

Objectives: To study the surgical anatomy and approaches of intracranial oculomotor nerve (OMN) and inferior obliquus (IO), and the methods of their electrode implantation in dogs.

Methods: The research was performed on 30 adult beagle dogs at Shanghai Jiaotong University Medical College, Shanghai, China from November 2007 to August 2008. All animals were subjected to a right transfrontotemporal approach to intracranial OMN, a transconjunctival route to IO, and the neuro-stimulating and recording electrode implantation under general anaesthesia. The OMN was stimulated and the electromyography of IO recorded and analyzed with the Powerlab System. The security and reliability of the implanted electrodes were investigated.

Results: The surgical anatomy and approaches of both the OMN from its exit from midbrain to the entrance into cavernous sinus and the IO were described. Moreover, the implantation methods of OMN stimulating electrode and the electromyographic recording electrode of IO were displayed. The implanted electrodes were safe and reliable. Some electrophysiologic data of IO were obtained in the healthy dogs. Also, some perioperative precautions for intracranial and ophthalmic surgical procedures in dog were exhibited. The mortality rate of the dogs was 0%, and no operative complications were observed.

Conclusions: With the data provided, these surgical approaches and the methods of electrode implantation offer a choice to construct an animal model for studying various aspects of OMN regeneration.

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Technical developments have extensively promoted experimental and clinical study on cranial nerve regeneration, but intracranial nerve recovery is still an unexplored research area compared to peripheral nerve repair. A few authors have studied the regenerative mechanism of the oculomotor nerve (OMN) in many kinds of animal models, and proved anatomic nerve regeneration and functional restoration.¹⁻⁶ Oculomotor nucleus,^{1,2} nerve,²⁻⁴ and extraocular muscles,⁷ have been systematically investigated in histological and anatomic aspects in many experimental studies after OMN injury. Also, the reinnervation of extraocular muscles was observed by either the functional²⁻⁴ or electrophysiological examination.⁶ However, the description of the surgical anatomy and approaches of intracranial OMN and extraocular muscles is insufficient, and the present methods employed in neuroelectrostimulation and electromyographic recording in experimental and clinical study of cranial nerve regeneration are not suitable to the long-term and dynamic electrophysiological research.^{6,8} From an ethical, economical, and available point of view, the small animal was usually used in the study of cranial nerve regeneration,¹⁻⁴ but it is very difficult to perform more complicated intracranial and ophthalmic operation in them due to the limited operating field, such as electrode implantation on intracranial OMN or in extraocular muscles. As the protophase and basic work of our research on OMN regeneration, and the effectiveness of chronic neuroelectrostimulation on the nerve functional recovery, the aim of this present study is to investigate the surgical approaches and electrode implantation of both the OMN between its exit from midbrain and the entrance into cavernous sinus and the inferior obliquus (IO) in beagle dogs. Moreover, some perioperative precautions for intracranial and ophthalmic surgical procedures in dogs were discussed.

Methods. The study was approved by the local animal welfare committee, and performed at Shanghai Jiaotong University Medical College, Shanghai, China from November 2007 to August 2008. All experiments were carried out in accordance with the Chinese Institutional Ethical Committee guidelines for animal research. The surgical anatomy and approaches were based on 30 intracranial OMN and IO operations in beagle dogs (10-12 kg, from Shanghai Jiaotong University Agronomic College, license: SCXK Hu 20070004). Animals were handled and cared for in accordance with the Guide for the Care and Use of Laboratory Animals.⁹ All efforts were made to minimize the number of animals used and their suffering. General anesthesia was performed by intramuscular injection of a mixture of ketamine (10 mg/kg; Hengrui Med, Lianyungang, China),

neotachosleep (0.1 ml/kg; Academy of Military Medical Sciences, Changchun, China), diazepam (1 mg/kg; Xudonghaipu Pharm, Shanghai, China) and atropine (0.05 mg/kg; Hefeng Pharm, Shanghai, China). During the operation, the maintenance of anesthesia was practiced by intramuscular administration of semi-dose of the same anesthetic mixture, if needed.

All animals underwent a right transfrontotemporal approach to OMN, a transconjunctival route to IO and electrode implantation. Preoperatively, the right hemicephalous and buccal skin of the dogs was shaved, and the cranial and ophthalmic operating fields were degenerated with iodophors. During the operation, the animals were intravenously injected with 100 ml of mannitol 20% after the dura was opened and 1000 ml of glucose in normal saline, containing 3.2 million IU of penicillin and 0.16 million IU of gentamicin. Two hundred ml of normal saline 0.9%, containing 80,000 IU of gentamicin was used as rinse solution. Postoperatively, the dogs were placed on a smooth surface in individual, warmed cages with food and water ad libitum. An antibiotic eye ointment was prophylactically used to cover the operated eye twice daily for 7 days. Antibiotics (1.6 million IU of penicillin and 80,000 IU of gentamicin) were administered intramuscularly once daily for 7 days for prophylaxis, and analgesics for 1-2 days. The skin was sutured out on the postoperative 7 day. The common- and micro- neurosurgical instruments were used during the craniotomy, and the approach to OMN. When performing the operation on the nerve, the brain was retracted with a self-retaining brain retractor (Aesculap GMBH, Germany) and a small brain depressor (1 cm in width). The ophthalmological instruments were necessary for the transconjunctival approach to IO. Both the implantable recording and neuro-stimulating electrode were self-made monopolar rheophore, which comprised of a silver wire (diameter of 0.2 mm) and a 5F microtubule (as electrode sleeve) (Figure 1). For the recording electrode, a 10 cm silver wire was sheathed into an 8 cm 5F microtubule, then the uninsulated end (5 mm in length) to be inserted in the IO was bent into a hook-shape with a 10-15° angle between the uninsulated and insulated part (Figure 1a). As for the stimulating electrode, the length of the silver wire was 15 cm and 5F microtubular head end was 12 cm, and the 5 mm uninsulated silver wire to be encircled to the OMN was angulated to 30° with a hooklet on its tip (Figure 1b). The Powerlab System (AD Instruments Pty Ltd, New South Wales, Australia) was used in OMN stimulation and IO electromyographic examination. The proximal monopolar electrode on the OMN was connected to the anode of the stimulator and the distal one to the cathode. The stimulation pulse was 5 Hz, 0.1 millisecond (ms) duration and 0.5-1.8 volt.¹⁰

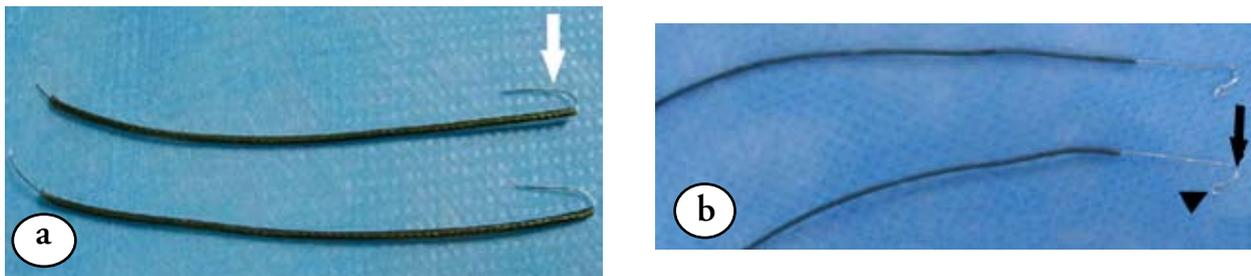


Figure 1 - Implantable recording and stimulating electrode. For the recording electrode a) its uninsulated end to be inserted in inferior obliques was bent into a hook-shape with 10-15° angle between its uninsulated and insulated part (white arrow). For the stimulating electrode b) the uninsulated silver wire to be encircled oculomotor nerve was angulated 30° (black arrow) with a hooklet on its tip (arrow head).

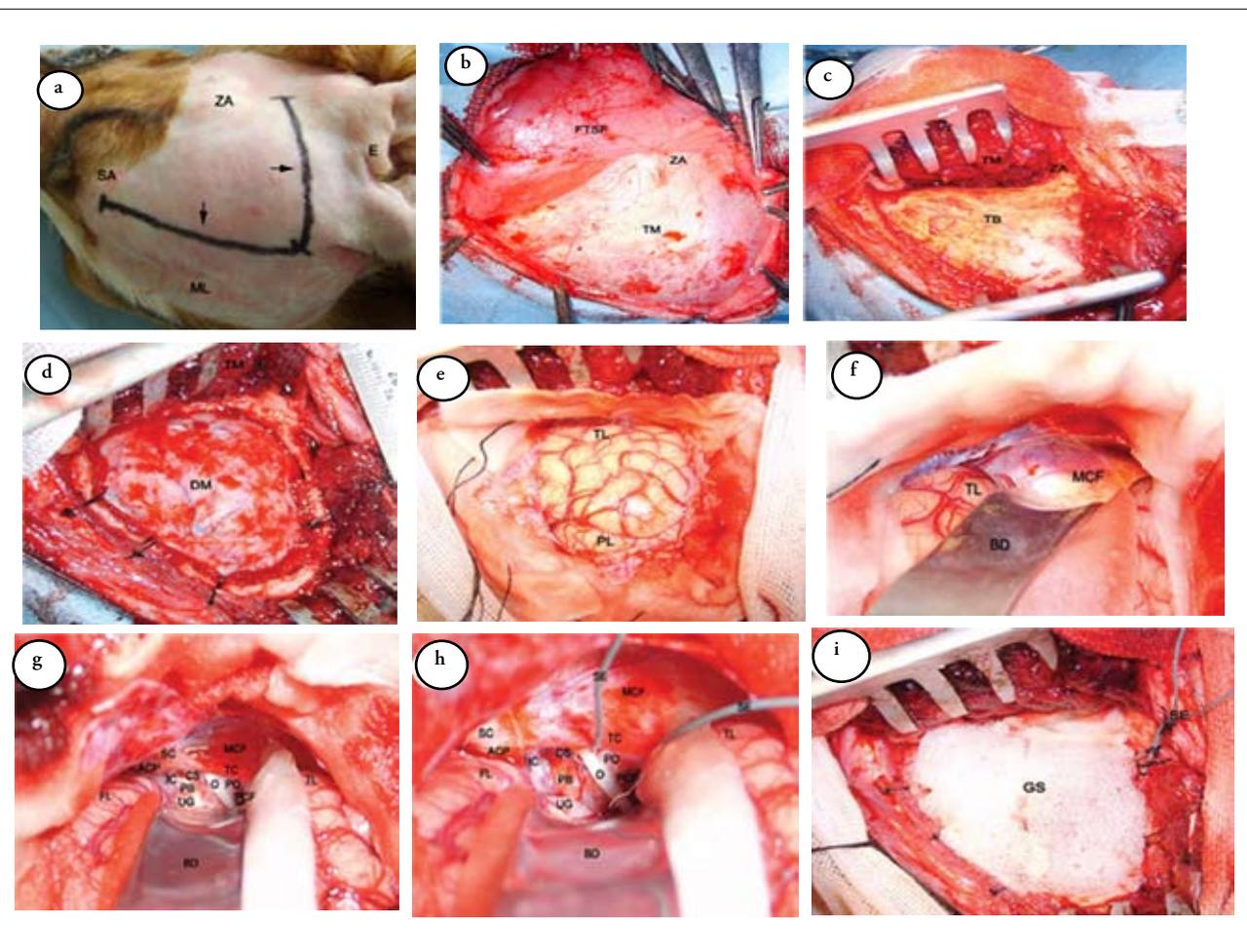


Figure 2 - Microsurgical approach and electrode implantation of the oculomotor nerve. a) Body position and frontotemporal dermatic incision (black arrows). b) Frontotemporal skin was incised and reflected. c) Temporal muscle flap was reflected and frontotemporal bone and zygomatic arch exposed. d) Craniotomy was accomplished. e) Dura was incised crosswise. f) Temporal lobe was retracted antero-supra-medially. g) Oculomotor nerve and some basicranial structures were identified after unciniate gyrus uplifted. h) Stimulating electrode was implanted on the oculomotor nerve. i) Bone defect was covered with gelatin sponge. GS - gelatin sponge, ZA - zygomatic arch, SA - superciliary arch, E - ear, ML - median line, FTSF - frontotemporal skin flap, TM - temporal muscle, TB - temporal bone, DM - dura mater, TL - temporal lobe, PL - parietal lobe, MCF - middle cranial fossa, BD - brain depressor, SC - sphenoidal crest, ACP - anterior clinoid process, FL - frontal lobe, IC - internal carotid, PB - pituitary body, CS - cavernous sinus, UG - unciniate gyrus, TC - tentorium of cerebellum, O - oculomotor nerve, PO - pyramis ossis temporalis, PCF - posterior cranial fossa, SE - stimulating electrode.

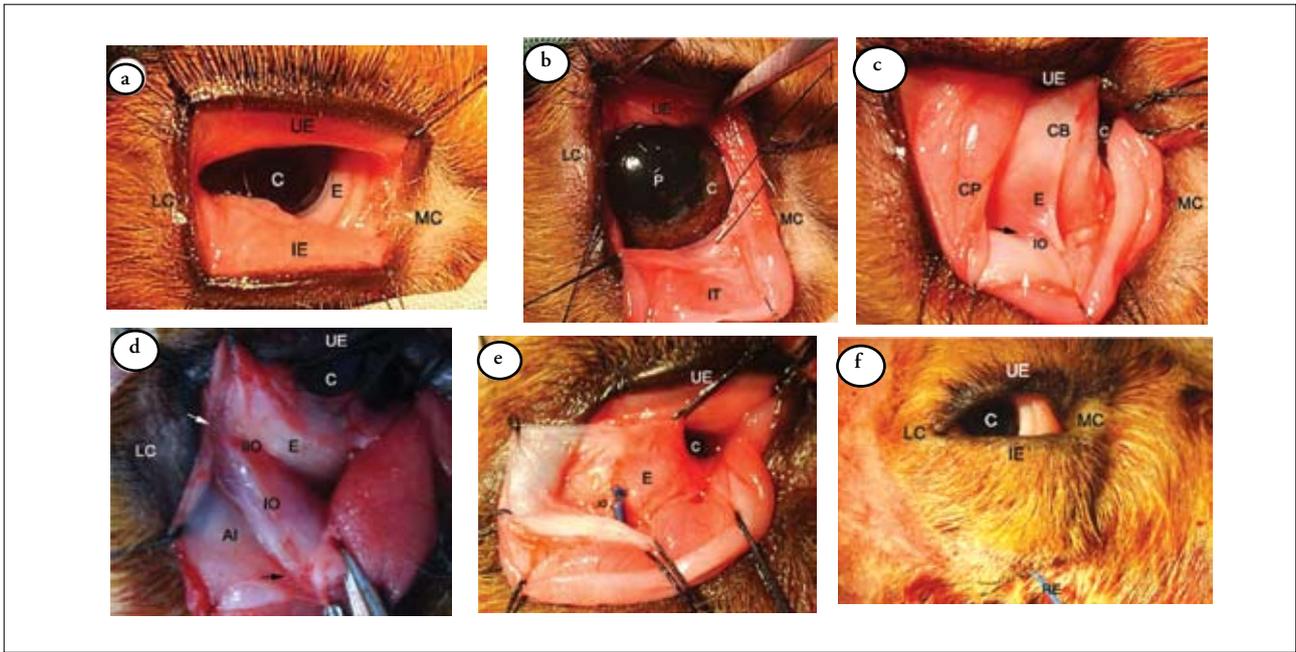


Figure 3 - Microsurgical approach and electrode implantation of inferior oblique (IO). a) Superior and inferior eyelid was retracted. b) Inferior tarsus was retracted downward. c) Inferior oblique was revealed and its insertion into sclera (black arrow) identified after the conjunctival flap was retracted (white arrow). d) Surgical anatomy of IO after opening aponeurosis of investment. White arrow indicates its insertion into sclera and the black arrow is the start. e) Recording electrode was implanted in IO. f) Photograph after electrode implantation. UE -upper eyelid, IE - inferior eyelids, MC - medial canthus, LC - lateral canthus, E - eyeball, C - cornea, P - pupil, IT - inferior tarsus, CB - conjunctiva bulbar, CP - conjunctiva palpebrae, AI - aponeurosis of investment, iIO - insertion of inferior oblique, RE - recording electrode.

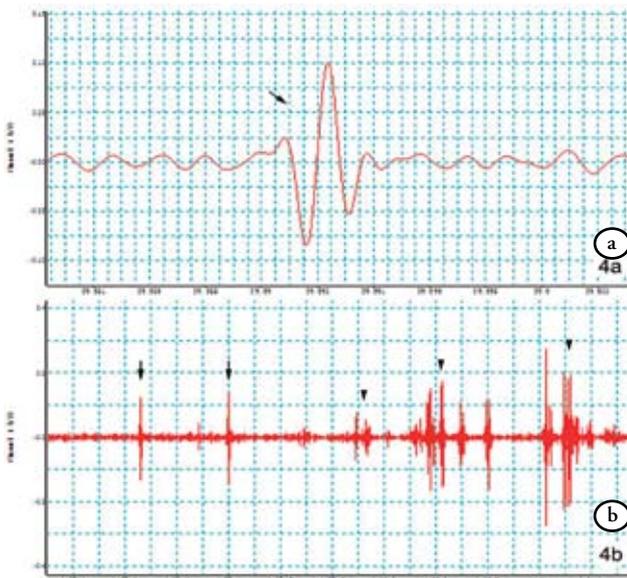


Figure 4 - The motor unit potential (MUP) of inferior oblique of a healthy dog. a) The normal MUP had 2 - 4 phases, its duration was 3.16 ± 0.15 msc and maximal amplitude $145 \mu\text{v}$ (black arrow). No multiphasic MUP was recorded. b) The shape of MUPs was uniform (black arrows) and the recruiting wave observed displaying interference pattern (black triangles). There was no abnormally spontaneous MUP recorded. msc - millisecond

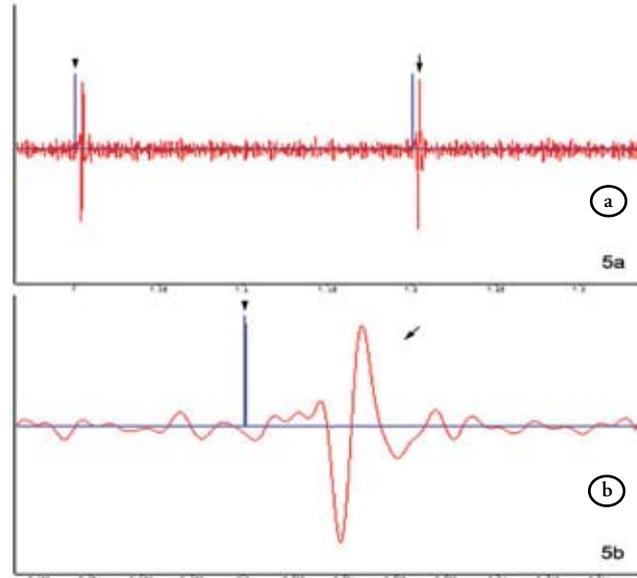


Figure 5 - The compound muscle action potential (CMAP) of inferior oblique of a healthy dog. a) The CMAP (black arrows) corresponding to the neurostimulation pulse (5 Hz, 0.1 msc duration, black triangles) was recorded synchronously. b) Its latency was 2.91 ± 0.03 msc, peak-to-peak amplitude $526.67 \pm 15.89 \mu\text{v}$ and duration 4.28 ± 0.21 msc with the supramaximal stimulation (1.8 volt). msc - millisecond

With the band pass set between 20 Hz and 10 kHz, the electromyography was recorded in IO, including the compound muscle action potential (CMAP) memorized synchronously during intra-/postoperative OMN stimulation and the motor unit potential (MUP) recorded while the phon-/photoinduced ocular movement occurred in the conscious animals. The ground electrode was connected to the oral lip of the animal with an alligator clip. All the electromyographic data were stored and analyzed off-line by the software package shipped with Powerlab System. The feasibility, availability, and reliability of the electrode implantation were assessed with electrophysiological method, and the security and stability of the implanted electrodes inspected every week during the experimental period from the end of the surgery to the postoperative 2, 4, 6, 8 or 12 weeks.

Results. The dog was laid in a left-lateral position with its right ear retracted dorsocaudally and fixed. A right frontotemporal L-shaped dermatic incision was performed (Figures 2a & 2b), and then the temporal muscle incised and reflected anterolaterally together with the skin flap (Figure 2c). The bone opening (4.5 x 4.5 cm) was made rostrocaudally from behind the superciliary arch to just in front of the transverse sinus and dorsoventrally from the beginning of middle fossa to one mm from the insertion of temporal muscle (Figure 2d), and then the dura incised crosswise up to the edge of craniectomy (Figure 2e). Under operating microscope, the postmedian temporal lobe was retracted antero-supra-medially with a small brain depressor along the facies anterior partis petrosae and the cerebrospinal fluid (CSF) gently sucked synchronously until the apex partis petrosae ossis temporalis (APPOT) and the edge of the tentorium of cerebellum (TC) were clearly visible (Figure 2f). Further anteromedially, the uncinate gyrus was gently uplifted, and the right OMN was observed (Figure 2g). To obtain more working place in the depth, the arachnoid of basal cistern could be sheared and CSF was aspirated. At this moment, the structures in the middle cranial fossa were clearly identified. The OMN between midbrain and cavernous sinus is approximately 7-8 mm in length, starting from interpeduncular fossa, elongating anterolaterally and entering the cavernous sinus via the edge of the TC at the APPOT. Medially from the OMN, the pituitary body can observe. The optic chiasm and nerve were located supra-anteriorly, and the internal carotid artery laterally from the pituitary body (Figure 2g). Paralleled to the OMN, the hook-shaped uninsulated end of the stimulating electrode was inserted via the interspace between the nerve and the APPOT. Then, the silver hook was made vertical to encircle the nerve and closed up by

the hooklet on its tip. The electrode sleeve was slowly pushed until its anterior end touched the silver loop. The distal electrode was placed near the entrance of the OMN into cavernous sinus and the proximal one close to its exit from midbrain, and the distance between them was 5-6 mm, which can be adjusted if needed (Figure 2h). Between the 2 electrodes, the experimental OMN injury can be performed and then a piece of 5 x 5 mm teflon clout or semithin gelatin sponge was put on the nerve. The intracranial electrodes were molded to match the form of middle cranial fossa and fixed on the dura and temporal muscle with suturation. The dura was not closed but the bone defect was covered with several pieces of gelatin sponge (Figure 2i). After the temporal muscle was closed, the extracranial portions of the electrodes were extracted subcutaneously from the dermatic incision in front of the auricle and fixed with suturation. The right superior and inferior eyelid was retracted upwards and downwards respectively, and the inferior tarsus reflected downwards (Figures 3a & 3b). Subsequently, the lateral part of the inferior conjunctival fornix was revealed by retracting the eyeball supra-medially with the retention sutures. A bracket-shaped conjunctival incision was made at 2 mm away from the corneoscleral junction between 5 and 9 o'clock. After retracting the conjunctival flap infra-laterally, the insertion into sclera of the IO was exposed (Figure 3c). Then, it was revealed after its aponeurosis of investment was bluntly dissociated and longitudinally incised from its insertion into the sclera to the start (Figures 3c & 3d). The recording electrodes were pre-extracted antidromically via the subcutaneous tunnel, which was made from the dermatic incision near the suborbital foramen to the start of the IO. Then their hook-shaped uninsulated ends were inserted infra-medially into the IO at 2 mm away from its insertion into sclera and deepened 5 mm along its longitudinal axis. The arc top of the silver hook was gently pinched with a microforceps to make the uninsulated and insulated portion of the electrode close to each other with a zero degree of angle between them. The 2 uninsulated ends in the muscle paralleled mutually with a 5 mm distance (Figure 3e). The intraorbital portions of the electrodes were invested and fixed by suturing the incised aponeurosis of investment and conjunctiva in layers with zero absorbable sutures, followed by the eyeball reset and the reliability of electrode implantation checked (Figure 3f). Their extraorbital portions were fixed with suturation on the maxillary periost near the infraorbital foramen, and then pulled out subcutaneously from and secured at the dermatic incision on the anterior end of zygomatic arch. Under the perioperative protocol and above surgical approaches, the mortality rate of the dogs was 0%. All dogs did well postoperatively and had no

signs of infection or neurological dysfunction except for total right OMN paresis due to the experimental nerve injury. During follow-up, all the implanted recording electrodes were secured in the same locations in the IO and subcutaneous tunnel as immediately after surgery. The neuro-stimulating electrodes were reliably fixed with no exodus and brisement. They worked effectively and did not cause intracranial or intraorbital inflammation and other complications. In the IO of the healthy dog, no spontaneous electric activity was recorded when the eyes were in the rest position. The normal MUP was displayed in **Figures 4a & 4b**. The CMAP corresponding to the neurostimulation pulse recorded synchronously, and its latency, peak-to-peak amplitude and duration with the supramaximal stimulation (1.8 volt)¹⁰ were exhibited in **Figures 5a & 5b**.

Discussion. Craniocerebral trauma and surgical treatment of lesions of the orbital cavity, superior orbital fissure, cavernous sinus, or skull base can frequently result in OMN injury, which severely impairs the patient's quality of life. Although the research on the functional recovery of OMN started as early as in 1938,¹¹ for many years, the OMN was not repaired, partly due to the technical difficulties, the belief that the cranial nerves did not regenerate, and the scepticism concerning the functional recovery of intracranial nerve after surgical repair. After the 1980s, some successful clinical cranial nerve reconstruction¹²⁻¹⁷ led to regained confidence in intracranial nerve regeneration. Especially in more recent years, the development of experimental conditions and techniques, such as neuroradiology, neurohistology, neuroimmunology, microsurgical technique, light, and electron microscope, have promoted systematical research on cranial nerve regeneration which proved anatomic nerve regeneration and possible functional recovery. However, to date, the rule of nerve regeneration is not clear, and the effective intervention study insufficient. As a consequence, reliable animal models on cranial nerves are needed to study various aspects of cranial nerve regeneration. Animal models on OMN regeneration comprised of the rat,^{1-3,18-20} guinea-pig,^{4,21} cat,⁵ dog,^{6,7,10} and monkey.^{11,22} On account of ethics, economy, and availability, small animals such as the rat and the guinea-pig were mostly used in research on experimental cranial nerve injury.²³⁻³⁰ However, it is very difficult, sometimes even impossible, to accomplish more sophisticated operative procedures in a small animal owing to the limited workplace, for example, intracranial neuroanastomosis and electrode implantation on cranial nerve and implanting rheophore in extraocular muscles, therefore, large animals were naturally considered in this situation.

Despite a number of general and specialized textbooks, monographs, and journals dealing with canine anatomy, information on basic and specialized techniques used in intracranial and ophthalmic surgery is far less available. The surgical anatomy and approach of both OMN and extraocular muscles were not described in detail in previous researches.^{1-6,10,11,18-21} On the basis of the sufficient study on canine craniocerebral anatomy, we designed the transfrontotemporal approach including frontotemporal craniotomy and uplifting the temporal lobe to reveal the OMN between its exit from the midbrain and the entrance into the cavernous sinus in dogs by imitating the human modified pterion approach. Moreover, we worked out the method of electrode implantation on the nerve for chronic neurostimulation *in vivo*. This intracranial surgical approach can be employed to research various aspects of OMN regeneration such as experimental nerve injury and intervention study on nerve regeneration. Also, we devised the transconjunctival approach to expose the IO and a method to an insert recording electrode into the IO after research on canine gross anatomy of extraocular muscles, and study of the human orthopia procedure atlas. This ophthalmic surgical approach can be used to implant recording electrodes for long-term and dynamical electrophysiologic study on extraocular muscles *in vivo* after OMN injury and besem other extraocular muscles besides the IO by appropriate modification. This study showed that the OMN, before its entrance into the cavernous sinus and the IO can be revealed sufficiently and electrodes implanted safely and reliably through these 2 surgical approaches with no increased additional injury. Moreover, under strict and befitting perioperative precautions for intracranial and ophthalmic surgical procedures, the mortality rate was very low (0% in this study) and all animals were free from severe complications such as intracranial and ophthalmic infection and injury resulting from the operation, except for the symptoms from the experimental OMN injury. The feasibility and security were verified for electrode implantation on intracranial OMN and in IO, and the long-term availability, stability, and durability for the implanted electrodes. Nevertheless, the surgical approaches described in this study need to be further improved when used in research on human OMN regeneration, due to the anatomic discrepancy.

In conclusion, we have shown that more sophisticated intracranial surgery on OMN and ophthalmic operation on IO can be performed effectively and safely with few complications in dogs. These surgical approaches can offer a choice to construct an animal model for OMN regeneration.

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