Development of Chronic Implantable Electrodes for Long-term Visual Evoked Potential Recording in Rabbits

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Abstract Development of direct neural interface (DNI) including visual prostheses absolutely requires confirmation of their long-term safety and stability. Functional evaluation by electrically evoked potentials (EEPs) is effective in this regard, although the recording system must be stable for chronic use. In addition, control of anesthetic depth is important for stable recording of the evoked potentials. The purpose of this study was to develop a chronically implanted electrode capable of recording visual evoked responses safely during repeated anesthesia over long periods, which would allow more effective safety evaluations of not only visual prostheses but also DNI. We developed two types of electrodes, and implanted them into rabbits. A general screw electrode was used for comparison with the novel electrodes. Structurally, the newly developed platinum (Pt) ball-tip screw electrode consisted of a plastic screw with smoothly surfaced Pt balls on the tip. The depth of implantation into the brain was adjustable via a threaded insert installed in the skull. The newly developed platinum/iridium (Pt/Ir) ball-tip planar multi-electrode array (MEA) comprised Pt/Ir ball electrodes placed in a two-dimensional lattice pattern, which was implanted just beneath the skull. These electrodes recorded variations in visual evoked potentials (VEPs) in response to 20 J flash stimuli over a period of 48 weeks. After 48 weeks of implantation, the ability of the electrodes to continue recording EEPs was confirmed (500 µA, 500 µs, cathodic first biphasic). During the recording of VEPs and EEPs, stable anesthesia was maintained with isoflurane (end-tidal 2.4%). The depth of anesthesia using isoflurane could be adjusted safely, and allowed stable recording of evoked potentials throughout the long-term study. However, stable recording using the general screw electrode was possible only for a short period. We also obtained stable latency and N1 amplitude readings over the 48 weeks using the newly developed electrodes, and successfully recorded EEPs after the 48-week period. These results suggest that the novel electrodes work well over the entire duration of the study, and may allow assessment of long-term safety and stability of not only visual prostheses, but also other devices utilizing brain machine interfaces or direct neural interfaces.

Keywords: direct neural interface, visual prostheses, long-term recording, visual evoked potential, electrical evoked potential.


1. Introduction

Substantial research has kindled an enormous interest in the development of brain machine interface (BMI), brain computer interface (BCI), and direct neural interface (DNI), aiming to achieve the next generation of man-machine interfaces to restore damaged hearing, sight and movement [1]. Visual prostheses for treating acquired blindness are one of the devices using such type of interface [2]. Visual prostheses transmit visual information directly to the brain via electrical stimulation of the visual nervous system. In cases of retinitis pigmentosa (RP) and age-related macular degeneration (AMD), a large percentage of ganglion cells remain despite degeneration of photoreceptor cells [3]. Thus, vision may be reproduced with phosphenes generated via electrical stimulation to the residual nervous system.

In the development of visual prostheses, it is important to evaluate the effect of the stimulation on cells, as for DNI. Moreover, the ability to stably record electroencephalographic (EEG) data over a long period is necessary for research and development of BMI and BCI [4]. Additionally, for visual prostheses, the Food and Drug Administration (FDA) guidelines require implantation of the final form of the fully functional retinal prosthetic device in the eye of a model animal for at least 6 months [5]. However, visual evoked response tests such as electroretinography (ERG), flash visual evoked potentials (VEPs) or electrically evoked potentials (EEPs) are not required, because it is prohibitively difficult to establish a long-term experimental system. On the other hand, EEPs elicited by stimulation of the retina are one of the most effective methods for evaluating the effects of cell stimulation. Such evaluation is beneficial for initial development of BMIs such as visual prostheses. EEPs can be used to evaluate changes in the efficiency of stimulus, performance of the electrode, and safety of the device.

Various types of intracortical electrodes have been used as recording electrodes for BMIs [6–8]. In experimental animals, a
general screw electrode is generally used for recording cerebral evoked potentials [9]. However, in this type of electrodes, it is difficult to obtain stable long-term recordings, because the characteristics of the electrode change or the electrode becomes less viable over time [10–13]. A previous study reported that the extent of brain tissue inflammation is influenced in part by electrode design factors [13]. Thus, the shape of the electrode required for chronic implantation must be that which is less damaging to the brain tissue.

The purpose of this study was to develop a chronically implanted electrode capable of recording visual evoked responses safely during repeated anesthesia over long periods, which would allow more effective safety evaluations of not only visual prostheses but also DNI.

2. Method

2.1 Development of electrodes

We developed two types of electrodes in this study to concurrently investigate the long-term differences between local recording and widespread recording, as well as between recording from electrodes embedded in the skull and electrodes placed on the dura mater (Figs. 1–4). Multiple (four or nine) electrodes were developed with the intention of evaluating potential differences within various sizes of observation area. A standard general screw electrode (M2 stainless anchor steel screw; AM2-8, Unique Medical) was used to compare against the newly developed electrodes.

2.1.1 Platinum (Pt) ball-tip screw electrode

The Pt ball-tip screw electrode had the structure of a plastic screw made of polymethylmethacrylate (PMMA) or polytetrafluoroethylene (PTFE) with Pt balls at the tip (Fig. 1). The dimensions of the electrode included a 17.5 mm-long screw with thread diameter of 2.6 mm, then lathing screw threads to match the M2.6 × 0.45 specification. After cutting into the required length, the hexagonal head was machined to a width of 4 mm by a side cutter. The screw was tightened into a fixing jig with M2.6 female thread. Subsequently, the screw was formed with through holes at the tip using a long drill (0.3 mm diameter bit) to pass lead wires.

Pt ball electrodes were made from platinum wire (0.2 mm diameter; 351265, Nilaco). A mini-blowtorch (NT-PRO, Nippon Tansan Gas) utilizing an oxygen-liquefied petroleum gas flame was properly adjusted, and the Pt wire held by pliers was heated in the flame until the Pt wire tip curled up onto itself. Heating and cooling were repeated until the diameter of the Pt ball reached the target size of 0.7 mm, measured each time by calipers (CD-20CPX, Mitutoyo). The heating process imparts a smooth surface to the Pt balls (Fig. 2). The Pt ball electrodes were inserted into the holes of the plastic screw, and glued to the plastic screw; excess glue was wiped off with ethanol.

2.1.2 Platinum/iridium (Pt/Ir) ball-tip planar multi-electrode array (MEA)

The Pt/Ir ball-tip planar MEA was a sheet structure comprising Pt/Ir ball electrodes placed in a two-dimensional lattice pattern (Fig. 3). A silicone sheet 0.1 mm in thickness (0.1 t, Unique Medical) was put on an acrylic board supporting a 3 × 3, two-dimensional lattice form, and a needle was used to punch holes in the silicone sheet. Pt/Ir ball electrodes were made from Teflon-covered Pt-Ir wire (9 twist lines ϕ 0.2 mm; 967223, Nilaco) as de-

Fig. 1 Schematic view of the platinum (Pt) ball-tip screw electrode. (a) Specifications of the Pt ball-tip screw electrode. (b) Side view. (c) Bottom view. The Pt ball-tip screw electrode had the structure of a plastic screw with platinum (Pt) balls at the tip. To optimize recording of visual evoked potentials (VEPs), the depth of implantation into the brain is adjustable via a threaded insert installed in the skull.

Fig. 2 Scanning electron microscope image of the platinum (Pt) ball electrode developed for this study. Pt wire was heated in the flame until the Pt wire tip curled up onto itself. The size was around 0.7 mm in diameter. The smooth surface of the Pt ball was effective for long-term recording.

Fig. 3 Image of the platinum/iridium (Pt/Ir) ball-tip planar multi-electrode array (MEA) developed for this study. The Pt/Ir ball-tip planar MEA comprised Pt/Ir ball electrodes placed in a two-dimensional 3 × 3 lattice pattern in a sheet structure, which was implanted beneath the skull.
scribed in section 2.1.1. Pt/Ir ball electrodes were threaded through the holes, with the connected wire bent along the silicone sheet. A silicone tube 2 mm in outside diameter and 1 mm in inside diameter (986902, Asona) was used to bundle the individual wires. The tube was first swollen with dehydrated ethanol (321-D0025, Wako) to facilitate passage of the wires. The tip of the wire was soldered to a connector (HR25-9TR-12P, Hirose). The sheet was covered with silicone adhesive (KE-41-T, Shinetsu Kagaku). Then another silicone sheet 0.2 mm in thickness (0.2 t, Unique Medical) was placed on top (Fig. 4).

2.2 Electrode implantation

Four Dutch-belted pigmented rabbits (1.6–2.6 kg, 19 weeks of age, male) were used in this study. We measured VEPs with a general screw electrode in 1 rabbit, a Pt ball-tip screw electrode in 2 rabbits, and a Pt/Ir ball-tip planar MEA in 1 rabbit. The general screw electrode and Pt ball-tip screw electrode were implanted 6 mm anterior and 6 mm lateral from the lambdoid suture as recording electrodes. The inactive electrode (M2 stainless anchor steel screw; AM2-8, Unique Medical) was screwed into a skull burr hole created 14 mm anterior from the lambdoid suture (Fig. 5).

A threaded insert made of SUS303 (Ensat 302000025.500, kkv) was installed in the skull beforehand and fixed with cement (UNIFAST TRAD, GC). To allow optimization of VEP recording, the depth of screw electrode implantation was adjustable via the threaded insert (Fig. 1). A craniotomy of the right skull was performed using an electric saw, then the Pt/Ir ball-tip planar MEA was inserted and the lead wire was exited through a groove in the cut end. The bone flap was restored and fixed with cement.

2.3 Measurement of evoked potentials

An individual rabbit allowed only water for 2 h prior to the experiment, the anesthesia apparatus (NS-3000, Acoma) at a flow rate of 4 L/min. Room lights were turned off, and the recovery box was covered with a blackout curtain; the rabbit was dark-adapted for 15 min [9]. Then 5% isoflurane anesthesia (Forane, AbbVie) was introduced via a vaporizer. Gas flow was adjusted to a concentration of 2.5% isoflurane and monitored with a biological information monitor (BP-608EV, COLIN).

Once sufficient anesthetic depth was achieved, the oxygen flow was reduced to 1 L/min and isoflurane maintained at 2.5%. The pupils of the eye to be stimulated was dilated with tropicamide (MydriP, Santen), and additional local anesthesia was applied (oxybuprocaine hydrochloride; Benoxil, Santen). The eyelids were held open mechanically beginning 5 min after local anesthesia. The stimulated eye was coated with hydroxyethyl cellulose (SCOPISOL, Senju) to prevent drying and avoid corneal clouding. The contralateral eye was shaded from light with gauze after also being coated with hydroxyethyl cellulose. Illuminance of the room was maintained at 0.2–0.3 lx. Anesthetic depth was monitored throughout and maintained at 2.4% isoflurane. Experiments were started at least 5 min after isoflurane inhalation reached steady state. We recorded changes in VEPs over time, and then attempted to record an EEP at the end of the 48-week implantation period. The VEPs were recorded over 8 weeks for the screw electrode, and 48 weeks for the Pt ball-tip screw electrode and Pt/Ir ball-tip planar MEA.

We recorded VEPs using a photonic stimulator (SLS-3100, Nihon Kohden), biomeamal amplifier (ML135, AD Instrument) (high-cut: 100 Hz, low-cut: 1 Hz), and data acquisition system (PowerLab/8SP, AD Instrument). VEPs in response to photonic stimulation delivered 30 cm in front of the eye [14] contralateral to the Pt ball-tip screw electrode were averaged over 32 trials. Stimulation parameters were: 20 J setting, 3-sec repetition, time-integrated luminance 3.74 cd·s/cm², peak luminance 29.5 cd/cm², half-value width with respect to the peak luminance 75 ms, and a flash time course as shown as Fig. S1. Luminance measures represent the actual measured luminance properties obtained by a luminance meter (BM-7, TOPCON) and oscilloscope.
(Wave Surfer 424, LeCroy). The earlobe was grounded using a clip electrode (NE-103A, Nihon Kohden) attached with an electroencephalograhic paste.

An electrode array of gold electrodes 200 µm in diameter was inserted into the scleral pocket at the end of the 48-week period, and EEPs were measured using a custom-made stimulator designed by us, a biological amplifier (MEG-6116, Nihon Kohden), and an induction potential research software (ElyzerII, Kissei Comtec). EEPs were recorded following electrical stimulation with parameters of cathodic first biphasic, 500 µA current and 500 µs duration. EEPs were averaged over 1000 times, after band-pass filtering from 1.5 Hz to 1 kHz.

### 2.4 Measurement of electrochemical impedances

We measured electrochemical impedances using an electrochemical instrument (Autolab PGSTAT32, Metrohm) with the following parameters: three-electrode method, 1 mV_{ras} single sine, constant voltage. The three-electrode method used the recording electrode as a working electrode, the inactive electrode as an auxiliary electrode, and a clip electrode on the earlobe as a reference electrode.

All in vivo experiments were conducted in accordance with the Association for Research in Vision and Ophthalmology statement for the use of animals in ophthalmic and vision research, and institutional guidelines for the care and use of laboratory animals. We conducted this experiment after obtaining permission from the animal experimental committee at Nidek Co., Ltd.

### 3. Results

We confirmed the presence of an inverted VEP wave during depthless implantation, as described in a previous study [9]. Then, the depth of implantation was adjusted to achieve the appropriate waveform to obtain maximum VEP amplitude. Figure 6(a) shows a typical VEP waveform recorded by the Pt ball-tip screw electrode. The first negative peak in the VEPs appeared around 20–40 ms, and was designated N1. The latency and amplitude of N1 were measured, and were evaluated along with the waveform over time. The amplitude of N1 was measured using the peak-to-trough amplitude to exclude difference in noise level [15]. The noise level was defined as the minimum-to-maximum potential difference for 10 ms after flash stimulation. The noise level was 1.2–11.1 µV for the general screw electrode, 1.2–16.6 µV for the Pt ball-tip screw electrode, and 1.2–25.3 µV for the Pt/Ir ball-tip planar MEA. These noise levels were primarily related to the external environment and noise from the biomedical amplifier itself, rather than to the characteristics of the electrodes. For the first 2–4 weeks, the amplitude of N1 was small and unstable in all the electrodes compared to the latter part of the experimental period (Figs. 6–8).

With the new Pt ball-tip screw electrode and Pt/Ir ball-tip...
planar MEA, but not the general screw electrode, clear VEP waveforms were obtained for 48 weeks (Fig. 6). The VEPs of the Pt ball-tip screw electrode and Pt/Ir ball-tip planar MEA were stable over 48 weeks, except the first 2–4 weeks after implantation. However, the general screw electrode was stable for only around 2 weeks (2 weeks after implantation), and in the recordings, the wave patterns representing the first and the second negative waves were fused. Stable recording with the general screw electrode was possible only for a short period.

For the Pt ball-tip screw electrode recordings, the latency period appeared to shorten with time. The N1 amplitude was stable for 48 weeks, except during the recovery period, (Fig. 7), although a decrease in N1 amplitude was observed in one case. For the Pt/Ir ball-tip planar MEA, a trend towards shortened latency described above, as well as stable N1 amplitude readings, were observed for 48 weeks except the first 2–4 weeks after implantation (Fig. 8). For both the Pt ball-tip screw electrode and Pt/Ir ball-tip planar MEA, the N1 peaks of the EEPs had a shorter latency than that of VEPs at the end of 48-week implantation (Fig. 9). The latency for EEP was the same for the Pt ball-tip screw electrode and Pt/Ir ball-tip planar MEA. The amplitude recorded for EEP with the Pt ball-tip screw electrode was larger than that recorded with the Pt/Ir ball-tip planar MEA (Fig. 9) because of the closer proximity of the cortical depth (screw) electrode to the signal source. In this study, the optimal insertion depth of the Pt ball-tip screw electrode was 5–7 mm from the surface of the skull with a thickness of approximately 2 mm.

The frequency characteristics of the electrochemical impedances are depicted in Fig. 10. The characteristics of both the Pt ball-tip screw electrode and Pt/Ir ball-tip planar MEA were typical of implanted electrode described by equivalent circuit, consisting of resistance and capacitance. Results for the other electrodes developed in this study are shown in Supplementary Figs. S2 and S3. Within the electrode type, the component electrodes produced similar (not significantly different) values. The electrical impedances were stable over time for each frequency level after 6 weeks of implantation (Fig. 11).

4. Discussion

We found unstable N1 peak amplitude in VEP waveforms at all electrodes for the first 2–4 weeks after implantation surgery. Therefore, this could be interpreted as an appropriate recovery period. After this recovery period, recordings of the first and second negative peaks from the general screw electrode were still difficult to differentiate. Therefore, the general screw electrode
could only be used for evaluation of short-term VEP recording.

Long-term recording requires that the recording electrode has stable characteristics. However, the period of stable recording using a general screw electrode, as demonstrated here, is very short, because the electrical characteristics are unstable. This is likely due to sharp edges at the tip of the general screw electrode, which damage the surrounding tissue and cause inflammation. The inflammatory responses dynamically alter the recording characteristics of the electrode over time.

In contrast, the Pt ball-tip screw electrode and Pt/Ir ball-tip planar MEA have large recordable areas, and demonstrated more clear VEP waveforms than the VEP recorded with the general screw electrode.

Generally, a porous surface electrode is used due to its good performance. However, this type of electrode can only be used for short-term evaluation, because clogging of the pores by proteins in a living organism would change the characteristics of the porous electrode [16, 17]. Therefore, smooth surface electrodes such as a Pt ball-tip screw electrode or Pt/Ir ball-tip planar MEA is more appropriate for long-term evaluation (Fig. 2).

Regarding the Pt ball-tip screw electrode, the N1 amplitude was stable for the 48-week assessment period, although a decrease was observed in one case. We speculate that the decrease was caused by the adhesive of the electrodes loosening over the assessment period. Thus, filling a plastic screw with cement is likely to be a better method of securing the electrodes, because none of the plastic electrodes required adjustment according to the depth of implantation during the experiments. Covering the electrode or using shorter electrodes (minimum length 12 mm) helps to avoid breaking the plastic electrode. An electrode made of polyimide has appropriate hardness for a recording electrode, whereas a PMMA electrode breaks easily, and a PTFE electrode is too soft. Finally, a unipolar electrode is sufficient to record VEPs and EEPs for assessments such as those in this study, because no variation of VEPs is observed between electrodes in the multipolar electrode. Presumably, this is due to the narrow inter-polar area. Insertion of the threaded inserts used in this study was difficult owing to the narrow thread pitch. A self-tapping threaded insert (SUS303; Ensat 309000030.500, kkv) would allow easier implantation into the skull.

For both the Pt ball-tip screw electrode and Pt/Ir ball-tip planar MEA, latency of VEP waveform tended to shorten with the passage of time (Figs. 7 and 8). Knowledge of this trend may also be useful in prospective studies using long-term EEP recording.

Fig. 10 Bode plots of electrochemical impedance after 3-weeks implantation: (a) platinum (Pt) ball-tip screw electrode, and (b) platinum/iridium (Pt/Ir) ball-tip planar multi-electrode array (MEA). The impedance depends on the surface area of the electrode. Although both electrodes had the same size, impedance property was different due to the characteristic of peripheral structure.

Fig. 11 Changes of electrical impedance of the novel electrodes over time: (a) platinum (Pt) ball-tip screw electrode, and (b) platinum/iridium (Pt/Ir) ball-tip planar multi-electrode array (MEA). The solid lines were obtained by least-squares method, excluding the data for the first 4 weeks. The electrical impedance was stable for 48 weeks, except during the recovery period.
Parallel measurement of VEPs and EEPs allows differentiation of the responses evoked by different stimuli and changes in the recording system during long-term functionality assessment. After 48 weeks of implantation, EEPs with shorter latency than VEPs were observed (Fig. 9). The difference in latency between VEPs and EEPs reflects the delay of information processing in the retina [15]. EEP is generated by localized stimulation, hence vision information is transmitted to a circumscribed area in the striate cortex of the brain. Therefore, the magnitude of the amplitude depends on the positional relationship between the stimulating electrode and recording electrode (retinotopy). The depth of implantation also has an impact because EEP is recorded in a localized area. VEP, on the other hand, is generated by full visual field stimulation. Thus, strong vision information is transmitted broadly across the striate cortex. Large evoked potential waveform is obtained when recording anywhere in the striate cortex, and the amplitudes are larger in VEP than in EEP recording. Furthermore, the depth of implantation has less impact on VEP than on EEP. As a result, the resulting amplitudes in VEP recordings for the Pt ball-tip screw electrode and Pt/Ir ball-tip planar MEA (Fig. 6) were similar. The amplitudes were very similar between the Pt ball-tip screw electrode and the Pt/Ir ball-tip planar MEA, although the latter was perhaps slightly lower. The amplitude of EEP recorded with the Pt ball-tip screw electrode was larger than that with the Pt/Ir ball-tip planar MEA, because the Pt ball-tip screw electrode implanted below the dura mater was nearer to the cerebral cortex than the Pt/Ir ball-tip planar MEA, which was placed on the dura mater. In previous research, the threshold intensity of EEP in response to suprachoroidal-transretinal stimulation (STS) using a general screw electrode for recording was approximately 7.2 ± 2.8 nC in normal rats in an acute test [18].

In addition, control of anesthetic depth is important for stable recording of evoked potentials. Several problems impede safe and stable recording of evoked potentials with injected anesthetics such as ketamine/xylazine or pentobarbital. Most importantly, repetitive ketamine/xylazine anesthetic injections result in fluctuating depth of anesthesia and could cause death [19]. Additionally, the amplitude of VEPs tends to vary or even disappear at deeper levels of anesthesia when using ketamine/xylazine or pentobarbital anesthesia. For this reason, it was difficult to record evoked potentials under fixed conditions [20, 21]. When using isoflurane as an inhaled anesthetic, evoked potentials can be observed during deep anesthesia, and the anesthetic depth can be controlled more stably. As Fig. 10 depicts, the EIS results of both the ball-tip screw electrode and the Pt/Ir ball-tip planar MEA exhibit same characteristic as a typical implanted electrode. Although the impedance values were different between both novel electrodes. On the other hand, the impedance obtained from implanted electrodes with the same ball size and peripheral environment should be equal in theory. We believe that the different impedance values were related to the different characteristics of the peripheral structure of the two electrodes used in this study. Both VEP recording and electrical impedance were stable over the 48-week period, with the exception of the recovery period (see Figs. 7, 8, and 11). VEPs are affected by flash stimulus intensity, anesthetic depth, and electrode impedance. In this study, we measured VEP while maintaining constant flash stimulus intensity and anesthetic depth. The increase of electrode impedance causes attenuation of the evoked potential as well as recording artifacts [22]. Thus, the only source of electrode-related VEP changes is the electrode impedance. We obtained both stable VEP recordings and electrochemical impedances using the newly developed electrodes. Hence, we validated that the novel electrodes are capable of stable VEP recording over 48 weeks without failure.

5. Conclusion
The depth of anesthesia using isoflurane could be adjusted safely, which allowed stable recording of evoked potentials throughout the duration of this long-term study. The electrodes developed for this study were also capable of chronic stable VEP and electrochemical impedance recordings, as well as allow measurement of EEP for the entire 48-week assessment period. The present results suggest that such an experimental system may provide better evaluation of safety and function in the long term, as suggested by FDA guidelines [5].

EEP evaluation using these electrodes and management of anesthesia will allow assessment of the long-term safety and stability of visual prostheses. This evaluation system should also be a useful asset for the assessment of other devices that utilize brain machine or direct neural interfaces. Further studies are warranted to evaluate the relationships between electrochemical impedance spectroscopy of the electrode, histopathological, and physiological results. Additionally, spatial analysis of the type of widespread recording is planned as our future work. The electrode implantation depth needed to optimize VEP recording was confirmed by this study. In addition, a short-term electrical stimulation experiment using a non-adjustable recording electrode implanted to the most suitable depth was successful [23]. We also successfully developed a three-dimensional stimulating electrode array with improved charge injection capacity [24], as well as an evaluation system for long-term stimulation in freely moving animals [25]. We will investigate the safety of visual prostheses designed for chronic use using these novel recording electrodes, the new stimulation electrode [24], and the evaluation system [25] in subsequent experiments.

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Conflicts of Interest
H. Tashiro, T. Tokuda, J. Ohta, and T. Fujikado received a research grant from Nidek Co., Ltd. Y. Terasawa and K. Osawa are employees of Nidek Co., Ltd. M. Kuwabara declares no conflict of interest associated with this manuscript.

References


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