Measurement of Evoked Potentials after Electrical Stimulation of the Human Optic Nerve

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Purpose. To examine the visual evoked potentials (VEP) and electroretinograms (ERG) generated during electrical stimulation of the human optic nerve using the optic nerve visual prosthesis.

Methods. Two volunteers blind from retinitis pigmentosa (RP) and with no light perception each received a chronically implanted optic nerve visual prosthesis. Cortical evoked potentials were recorded using 16 scalp electrodes, and antidromic ERGs were obtained using DTL electrodes while the optic nerve was electrically stimulated. The results were compared with flash and eye surface electrical stimulation results in normal-sighted control subjects.

Results. The VEPs obtained in our two volunteers with implants had a waveshape similar to that obtained in normal-sighted volunteers during flash stimulation, but latency was reduced by approximately 25 ms. The VEPs recorded during surface eye stimulation are similar in both normal-sighted and RP volunteers. The VEPs were compared at sub- and suprathreshold stimulation strength and with different electrode configurations. Finally, the antidromic ERG recordings obtained in our implanted volunteers show a unique inner retinal potential generated by retrograde stimulation of the eye from the optic nerve.

Conclusions. Evoked potentials can be used to examine how a visual prosthesis generates visual sensations. This provides an objective means to investigate various aspects of the visual prostheses. (*Invest Ophthalmol Vis Sci.* 2010;51:5351–5355) DOI:10.1167/iovs.09-4346

A visual prosthesis is a device that aims to restore a meaningful sense of visual perception to blind volunteers by electrically stimulating their visual system. There are many devices being researched that differ according to the position along the visual system used to interface the stimulating electrode. They are broadly divided into the subretinal,[1–3] epiretinal,[4] optic nerve (Sakaguchi H, et al. *IOVS* 2008;49:ARVO E-Abstract 4044),[5] and visual cortex prostheses.[6–8] For a review of this topic, see Margalit et al.[9] or Veraart et al.[10] The optic nerve visual prosthesis (ONVP) uses a self-sizing spiral cuff electrode to electrically stimulate the optic nerve and thus create the perception of small flashes of light called phosphenes. By controlling the stimulation parameters, it is possible to vary the position of these phosphenes[11] and thus convey information regarding the surrounding environment.[12] Two volunteers each received a chronically implanted ONVP. In the first, the electrode was implanted on the intracranial section of the optic nerve.[5] In the second, it was implanted intraorbitally.[13]

Thus far, the ONVP has been used in psychophysical experiments such as pattern recognition,[14] identifying and localizing objects placed on a table,[15] and mobilizing in foreign environments. Results are encouraging and show that the ONVP can be used for visual rehabilitation.[16] Similar psychophysical results are now being reported from other research teams with chronically implanted human volunteers.[4] However, little work has been published on the evoked potentials generated by a visual prosthesis in humans. All the work on evoked potentials relates to animal studies during the initial trial phases of visual prosthesis development.

This study investigated the evoked potentials generated electrically in volunteers implanted with visual prostheses. A comparison is made between the electrical evoked potentials in visual prosthesis volunteers and flash evoked potentials in normal-sighted control subjects. Thresholds for activating the optic nerve are objectively measured. Furthermore, evoked potentials can be electrically generated in both normal-sighted and blind volunteers by a noninvasive technique previously reported by us using eye surface stimulation.[17] This allows direct comparison to be made when the visual pathway of the two groups are stimulated electrically in the same manner.

Methods

This study complied fully with the Declaration of Helsinki, and written informed consent was obtained from all volunteers involved in the study. All studies received approval from the ethics committee of St.-Luc University Hospital, UCL, Brussels, Belgium.

Subjects

The first volunteer implanted with the ONVP was a 65-year-old woman with autosomal dominant retinitis pigmentosa. She had no perception of light in either eye and received the implant in 1998 with a four-contact nerve cuff electrode around the intracranial section of the optic nerve.[5] Our second volunteer was a 72-year-old man with autosomal recessive retinitis pigmentosa. He also had no light perception in either eye and received the implant in 2005 with an eight-contact cuff electrode around the intraorbital section of the optic nerve.[13] The contacts are named according to the position around the cuff electrode, namely 0°, 90°, 180°, and 270° for the four-contact electrode and 0°, 45°, 90°, 135°, 180°, 235°, 270°, and 315° for the eight-contact electrode. Included were four normal-sighted control subjects aged between 25 and 32. Cortical evoked potentials to light and electrical surface eye stimulation were recorded in the control subjects.

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Stimulation Setup

Optic Nerve Visual Prosthesis. For a detailed description of the ONVP, see Delbeke and Veraart[18] or Delbeke et al.[19] In brief, the ONVP is made up of external and implantable components. The main external component is the processing unit, which receives stimulation commands from a computer running a data acquisition software program (Labview, Vernier, Beaverton, OR). The computer and external signal processor were connected wirelessly (Bluetooth). The processing unit is responsible for converting the commands into stimulation pulses, which are then transferred to the implantable neurostimulator by a radiofrequency telemetric link. This link allows data to be transferred across the scalp of the volunteer and is achieved using two antennas that are aligned and connected using magnets. The data are transferred at a rate of 3 Mb/s, and 250 mW power is generated for the implantable components. The neurostimulator, which is surgically embedded into the parietal cranium of the volunteer, works in the same way as the stimulators for cochlear implants. It has individually addressable current sources that send the stimulation pulses to the optic nerve cuff electrode.

To reduce the amount of noise in the recordings, the volunteer was placed inside a Faraday cage. The external components of the prosthesis were placed outside the cage, and a twisted-pair cable was passed from the external processor, through a grating in the cage, to the external antenna of the telemetric link. Preliminary experiments showed that this setup dramatically reduced the level of noise in the recordings.

In each recording session, the optic nerve was stimulated 100 times at 0.3 Hz with single-charge recuperated pulses with a ratio of 1:9. Each of the contacts around the optic nerve was used in turn; the pulse amplitudes were varied from 92 μA to 1040 μA, and the durations were varied from 213 μs to 426 μs.

Surface Stimulation. A detailed description of surface eye stimulation can be found in Delbeke et al.[17] The technique allows noninvasive electrical stimulation of the inner retina in both normal-sighted and blind volunteers. Pre-gelled self-adhesive electrodes are placed on the closed eyelids and held in position using a specially adapted pair of goggles. A reference anode is placed on the contralateral mastoid, and biphasic, charge-recuperating pulses are sent from the eyelids to the reference electrode. A custom made stimulator controlled by a computer running data acquisition software (Labview; Vernier) was used to generate stimulation pulses. During stimulation the volunteer perceives phosphenes, the details of which are described in Delbeke et al.[17] Both normal-sighted ($n = 4$) and RP ($n = 2$) volunteers were stimulated using this technique. Each recording session consisted of 100 stimulations with charge recuperating pulses at 4-ms duration and amplitudes between 2.01 mA and 5.34 mA. To reduce the impact of the stimulation artifact on the recording, the pulses were reversed so the anodal recuperation was delivered first.

Light Stimulation. Light stimulation was used in our normal-sighted control subjects to record flash visual evoked potentials (VEPs). The light was controlled by a computer outside the Faraday cage running the software program. The light source was a 5-W white light-emitting diode (Luxeon; Philips, San Jose, CA) placed behind a 2×4 cm diffuser positioned 20 cm from the subject's right eye. The light was calibrated to give a luminance of 1.5 cd $\cdot$ s/m^2, and the duration of each pulse was 1 ms. The background light intensity of the Farady cage was 19 cd/m^2. Each recording session consisted of 100 stimulations at a frequency of 0.3 Hz.

Recording Setup

Recordings were made using a channel amplifier (Biosemi 16; BioSemi, Amsterdam, The Netherlands; http://www.biosemi.com). The electrodes (Active Two; BioSemi) have incorporated preamplifiers that can be plugged into a cap worn by the subject for the recordings of VEP or that can be attached, using a custom-made adapter, to a DTL cable for ERG recordings. Common mode interferences are reduced through a CMS (common mode sensing) and DRL (driven right leg) system. The system has a high-frequency cutoff limit of 3 kHz, after which the signal is sampled at 16.384 kHz per channel. The signal resolution is 24 bits. Recordings are transferred to the recording computer by a fiberoptic cable. To achieve the best quality recording, the volunteer and the recording amplifier worked from inside a Faraday cage.

Signal Processing

All signal analysis was made with technical computing software (Matlab Signal Processing Toolbox; The MathWorks, Natick, MA). Unless otherwise stated, all VEP recordings were filtered from 1 to 100 Hz using an IIR bandpass Butterworth filter. ERGs were filtered using the same filter but at a bandpass of 1 to 300 Hz. Each signal was filtered in forward and reverse to avoid any phase shift. Some of the channels that were close to the implanted neurostimulator picked up 50 Hz noise. The presence of a 50-Hz component was estimated from the frequency spectrum and subtracted as a constant amplitude sine wave. The amplitude and phase of the 50-Hz component were adjusted to best fit the data; no phase distortion was introduced. The epochs were then averaged, and the odd and even trials were averaged separately to show the reproducibility of the signal.

Results

Figure 1 shows a typical cortical evoked potential (Oz–Cz) after electrical stimulation of the optic nerve. In this sample contact, 180° was used in our first volunteer with a pulse duration of 213 μs and an amplitude 306 μA. This strength of stimulation was 20% above the perception threshold. The thin lines show the odd and even trials averaged separately ($n = 25$), and they correspond well with the overall average (thick line; $n = 50$) showing good reproducibility of the signal. There was minimal interference of the stimulating artifact, making it possible to record potentials with short latencies (<100 ms).

Similar components of the evoked potentials could be identified in our two volunteers with implants when their optic nerves were electrically stimulated. The black trace in Figure 2 corresponds to the first volunteer, who had an intracranial cuff electrode, and the dashed trace is a recording from the second volunteer, who had an intraorbital electrode. The VEP in the second volunteer was much smaller, and the two traces were therefore normalized to allow comparison. Similarly, a larger stimulation artifact (not shown) was produced in the second

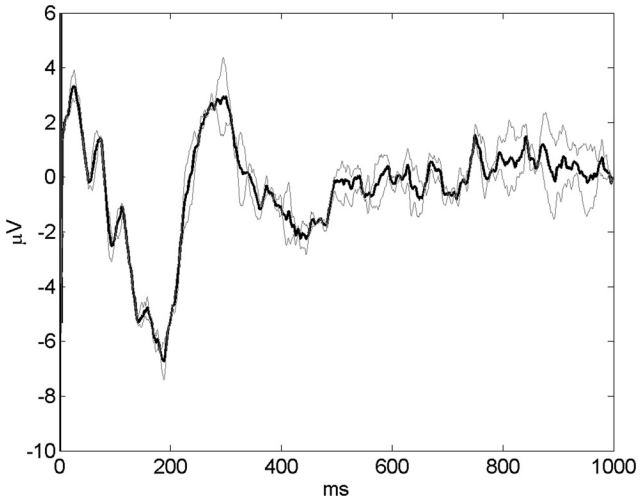

Figure 1. Cortical evoked potential (Oz–Pz) generated by stimulating the optic nerve in our first volunteer with 180° contact and 100 single pulses with a pulse duration of 213 μs and an amplitude of 306 μA. The odd- and even-numbered trials are averaged separately (*thin gray lines*) and correspond well to the overall average (*thick black line*).

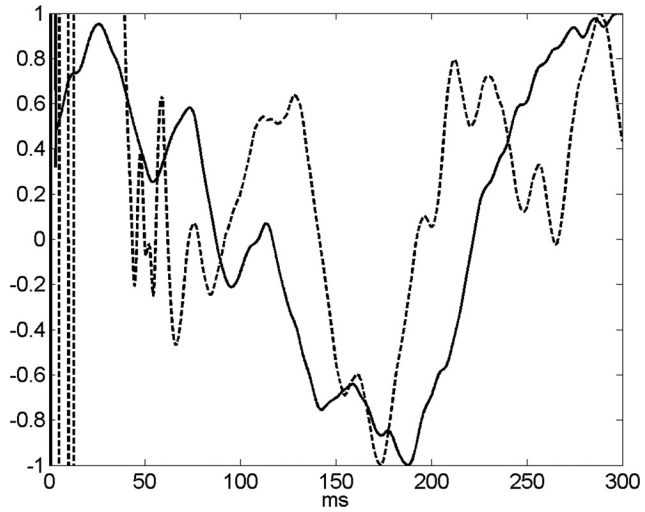

FIGURE 2. Comparison of evoked potentials generated by optic nerve stimulation in the two implanted volunteers. *Black line*: first volunteer with intracranially implanted electrode. *Gray line*: second volunteer with intraorbital electrode. Traces have been normalized to allow comparison.

volunteer because greater stimulation strength was required to elicit phosphenes. Both volunteers were stimulated at 20% above perception threshold.

Scalp recording across the visual cortex (O1–O2) shows that it was maximally activated at around 75 ms after stimulation of the optic nerve (Fig. 3). When stimulating with different contacts, the waveshape and amplitude of this positive peak remained relatively unchanged. However, the volunteers described visual sensations in different locations. All phosphenes generated remained within the central visual field; consequently, the evoked potentials did not change significantly with different stimulation parameters.

Figure 4 shows a comparison between the evoked potentials generated using a flash stimulus in a normal-sighted control subject (Fig. 4A) and surface eye stimulation in the first RP volunteer (Fig. 4B). The main difference was in the timing of

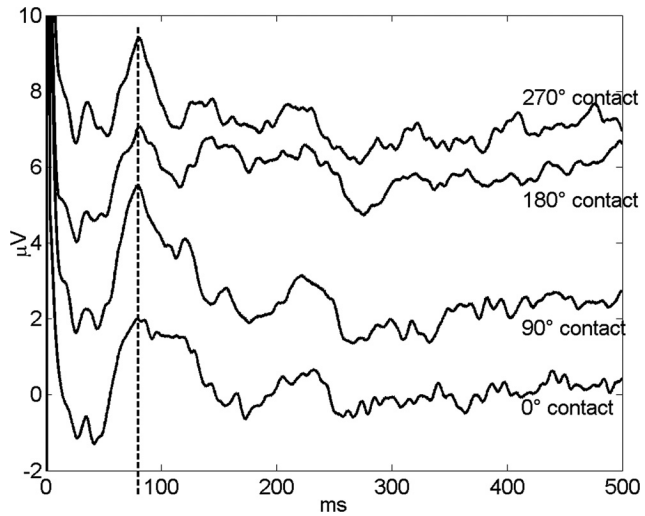

FIGURE 3. Evoked potentials generated when stimulating the optic nerve with different contacts around the optic nerve. Four-electrode contacts (0°, 90°, 180°, and 270°) were used individually to generate each evoked potential. The stimulation strength was set at 20% above perception threshold.

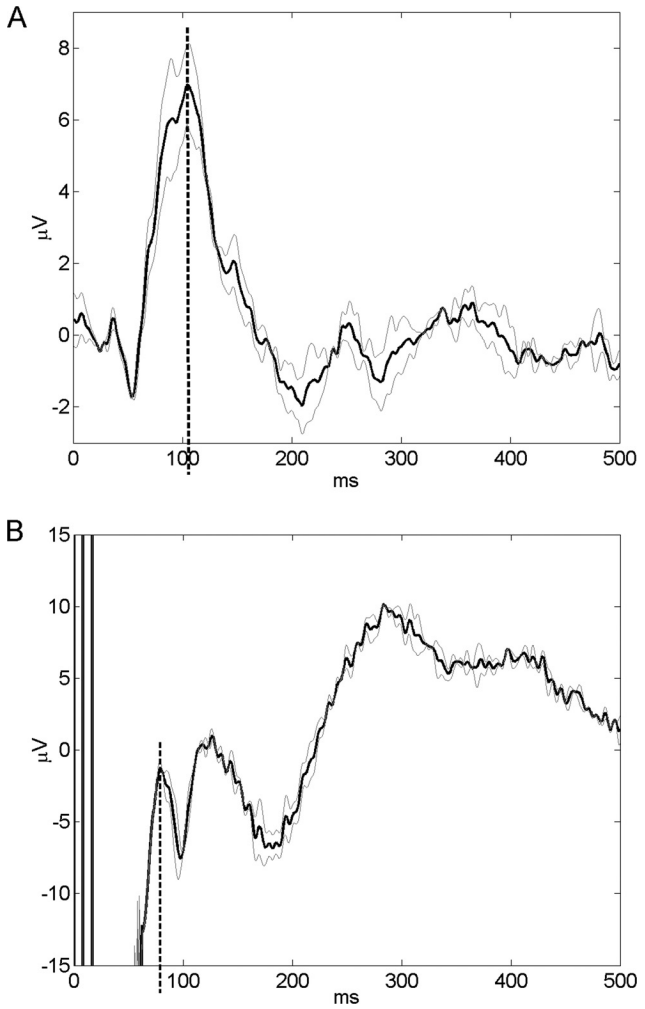

FIGURE 4. Comparison of flash stimulation in a normal-sighted control subject (**A**) and eye surface stimulation (**B**) in the first RP volunteer implanted intracranially. All evoked potentials have similar waveshapes in the 60- to 120-ms range.

the events, during which flash stimulation, which activated photoreceptors, was slower than eye surface stimulation, which electrically stimulated the inner retina. The main positive peak occurred at just after 100 ms for a flash stimulus (101 ms) and at 79 ms for eye surface stimulation. Similarly, optic nerve stimulation had the shortest latency because it stimulated the visual system the furthest downstream. Intraorbital optic nerve stimulation produced a latency of 76 ms compared with the intracranial cuff, which had a latency of 74 ms (Fig. 2). The recordings shown were all averages of 100 epochs between Oz and Cz and were filtered (with zero phase shift) between 1 and 100 Hz.

Figure 5 shows the evoked potential in a normal-sighted control subject when the inner retina was stimulated using eye surface stimulation (odd- and even-numbered responses have been averaged separately and shown as thin gray traces). The main positive peak occurred at 80 ms, which is the same as that of the RP volunteer (Fig. 4B).

As the amplitude of the stimulus was reduced, the early potentials disappeared first, and the later slower potentials disappeared at lower amplitudes of stimulation. The threshold was at the point where the evoked potential was reduced to baseline noise. Figure 6 shows the estimation of the threshold in our first volunteer while the optic nerve was stimulated for 213 μs at varying amplitudes. The stimulation threshold was

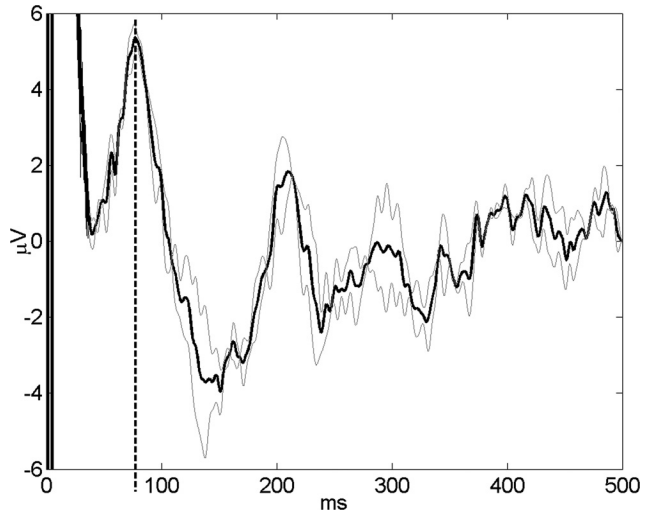

FIGURE 5. Cortical evoked potential in normal-sighted control subject when stimulating the eye electrically with surface eye stimulation. The positive peak at 80 ms is similar to that seen in RP volunteers, as shown in Figure 4.

given when all data points in the recording were within 2.58 SD (i.e., 99% confidence interval) of the mean. In the example shown in Figure 6, this occurred at a stimulation strength of 162 μA.

The subjective visual perception threshold was similar to the threshold that could be obtained with the evoked potentials. However, around the threshold, the visual perceptions became variable, and it was often difficult to accurately determine the threshold psychophysically.

Figure 7 shows the antidromic ERG generated after electrical stimulation of the optic nerve. The signal was filtered from 1 to 300 Hz and was an average of 100 epochs. The signal had good reproducibility, as demonstrated by the similarity of odd and even traces averaged separately (gray traces). The antidromic ERG shows an unusual volley of activity generated by the inner retina.

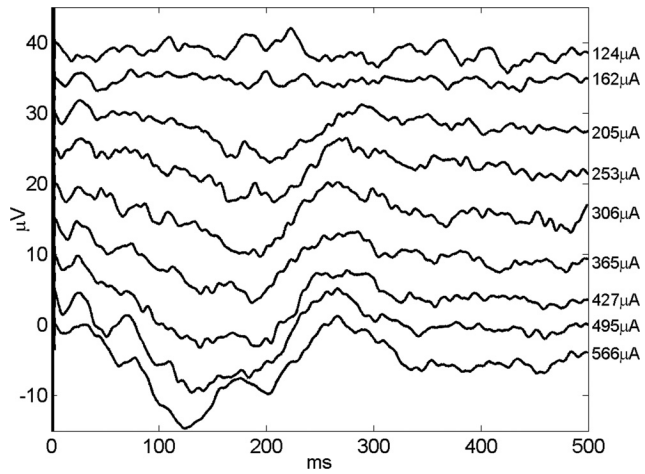

FIGURE 6. Threshold estimation for generating an evoked potential. The stimulation duration was constant at 213 μs, and the amplitude of stimulus for each evoked potential in μA is shown on the right. The early potentials are the first to flatten when stimulus amplitude is reduced. Threshold is defined as stimulus intensity at which no response is recorded (124 μA).

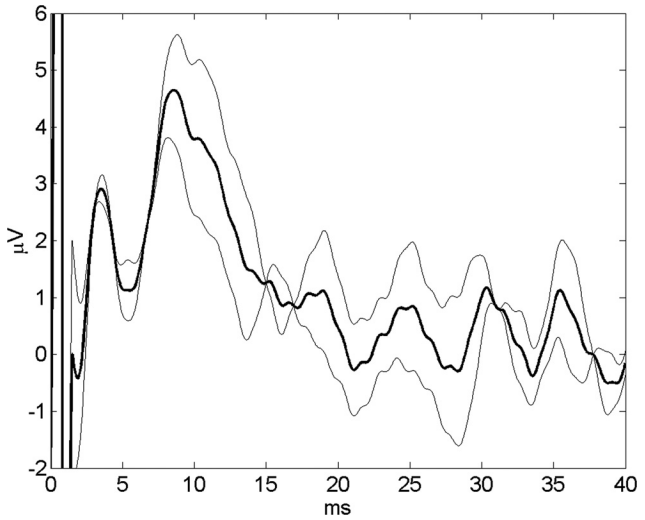

FIGURE 7. Antidromic ERG recording when the retina is retrograde stimulated from the optic nerve.

DISCUSSION

The recording method shown in this study was derived from the International Society for Clinical Electrophysiology for Vision standards for recording VEPs and ERGs.[20,21] One of the main difficulties in obtaining good recordings in our volunteers with implants was that the visual prosthesis itself creates electrical noise that could easily drown the signal. By placing the external components of the visual prosthesis outside a Faraday cage and the volunteer inside, the quality of the recordings improved dramatically. It was also necessary to cut the radiofrequency transmission to the implanted neurostimulator after the optic nerve was stimulated to minimize the impact of the stimulation artifact.

All cortical evoked potentials, whether generated using flash stimulation in normal-sighted controls, eye surface stimulation, or optic nerve stimulation in the implanted volunteers, had similar waveshapes. In this study we found that maximal occipital cortex activation took place at around 75 ms after electrical stimulation of the optic nerve. A 2-ms shorter latency was, in fact, found when stimulation was performed with the intracranial rather than the intraorbital electrode because it was further downstream in the visual pathway.

Evoked potentials generated by eye surface stimulation are thought to arise from activation of the inner retina. Potts et al.[22] showed that rats with hereditary outer retinal degenerative conditions have absent ERG and VEPs but near-normal electrically evoked cortical potentials. Similarly, in humans, the electrically evoked response to surface eye stimulation is near normal in patients with rod/cone dystrophy[23] but reduced or absent in patients with inner retinal abnormalities such as central retinal artery occlusion[24] and optic nerve disease.[25] Electrically evoked potentials using surface eyelid stimulation shown in this study demonstrated a striking similarity between an RP volunteer and a normal-sighted subject. In both cases, the inner retina was noninvasively stimulated, and both groups had a peak response at around 80 ms.

It will be interesting to see how these recordings compare with those generated using an epiretinal or a subretinal visual prosthesis. It is likely that an epiretinal device will produce a latency similar to surface eye stimulation because both techniques stimulate the inner retina.[26,27] Similarly, subretinal or suprachoroidal stimulation of the outer retina should produce evoked potentials with longer latencies.

Our second volunteer, who had the intraorbital cuff electrode, had a higher stimulation threshold for perceiving phosphenes because of the position of the intraorbital cuff electrode, which was outside the meninges and not in direct contact with the nerve, as it is intracranially. Nevertheless, phosphenes can be created with both devices, and in both volunteers VEPs could be measured. VEP amplitude, in keeping with the subjective brightness described by our two volunteers, was smaller in the second volunteer than in the first. A greater stimulation artifact was produced in our second volunteer, but the waveshapes thereafter were similar in shape (Fig. 2). Once thresholds were reached, the amplitude of the VEP increased less in our second volunteer than in our first volunteer when stimulation strength was increased. Subjectively, the first volunteer also described more marked changes in the brightness, location, and size of the perceived phosphenes when increasing the stimulus amplitude.

When stimulating at different locations around the nerve, the waveshape and, hence, the equivalent source dipole changed very little in location or orientation even though, during stimulation with different contacts, both volunteers perceived phosphenes at different locations. All phosphenes elicited with the ONVP occurred within a limited central area of the visual field. In this study, single-pulse stimuli were used that produced phosphenes at the edge of this electrically inducible visual field.[11] Even so, with the setup used for this study, it was not possible to discriminate the different phosphenes elicited from evoked potentials alone.

The VEP recordings in our implanted volunteers were used to objectively estimate the thresholds for stimulating the optic nerve. By varying the amplitude of stimulation, it was possible to establish the threshold for activating the optic nerve. These thresholds form an integral part of the predictive models used to calculate the stimulation parameters required for the generation of phosphenes within discrete areas of the visual field.[11] Until now, these thresholds have been obtained psychophysically, and there was, in this study, good correlation with the objectively measured thresholds. Recently, it has been found that the threshold for stimulating the optic nerve diminishes over time (Delbeke J, manuscript submitted). Thus far, only our first volunteer has been implanted long enough for this phenomenon to be observed.

Our implanted volunteers showed unique ERGs that were generated by retrograde electrical stimulation of the optic nerve. There did not appear to have been any latent secondary activation of the inner retina, as seen in epiretinal devices.[26] However, further animal experiments will be needed whereby the optic nerve can be stimulated and recorded simultaneously to demonstrate this conclusively.

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