Brain (1996), **119**, 507–522

Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex

E. M. Schmidt,[1] M. J. Bak,[1] F. T. Hambrecht,[2] C. V. Kufta,[3] D. K. O'Rourke[3] and P. Vallabhanath[4]

[1]*Laboratory of Neural Control, the* [2]*Neural Prosthesis Program, the* [3]*Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health and the* [4]*Howard Hughes Medical Institute, Bethesda, USA*

Correspondence to: E. M. Schmidt, Laboratory of Neural Control, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 49, Room 3A50, Bethesda, MD 20892-4455, USA

Summary

The feasibility of producing a visual prosthesis for the blind using intracortical microstimulation (ICMS) of the visual cortex was studied in a 42-year-old woman who had been totally blind for 22 years secondary to glaucoma. Thirty-eight microelectrodes were implanted in the right visual cortex, near the occipital pole, for a period of 4 months. Percepts reported as small spots of light, called phosphenes, were produced with 34 of the 38 implanted microelectrodes. Threshold currents for phosphene generation with trains of biphasic pulses were as low as 1.9 μA, and most of the microelectrodes had thresholds below 25 μA. Phosphene brightness could be modified with stimulus amplitude, frequency and pulse duration. Repeated stimulation over a period of minutes produced a gradual decrease in phosphene brightness. Phosphenes did not flicker. The apparent size of phosphenes ranged from a 'pin-point' to a 'nickel' (20 mm diameter coin) held at arm's length. Phosphene size usually decreased as stimulation current was increased but increased slightly as the train length (TL) was increased. At levels of stimulation near threshold, the phosphenes were often reported to have colours. As the stimulation level was increased, the phosphenes generally became white, greyish or yellowish. Individual phosphenes appeared at different distances from the subject. When two phosphenes were simultaneously generated, the apparent distances of the individual phosphenes sometimes changed to make them appear to be at about the same distance. When three or more phosphenes were simultaneously generated, they became coplanar. Except for rare occasions, phosphenes extinguished rapidly at the termination of the stimulation train. When stimulation TLs were increased beyond 1 s, phosphenes usually disappeared before the end of the train. The duration of phosphene perception could be increased by interrupting a long stimulation train with brief pauses in stimulation. Intracortical microelectrodes spaced 500 μm apart generated separate phosphenes, but microelectrodes spaced 250 μm typically did not. This two-point resolution was about five times closer than has typically been achieved with surface stimulation. With some individual microelectrodes, a second closely spaced phosphene was sometimes produced by increasing the stimulation current. Phosphenes moved with eye movements. When up to six phosphenes were simultaneously elicited, they all moved with the same relative orientation during eye movements. All phosphenes were located in the left hemi-field with the majority above the horizontal meridian. There was a clustering of most of the phosphenes within a relatively small area of visual space. The potentially greater microelectrode density and lower power requirements of ICMS compared with surface stimulation appears encouraging for a visual prosthesis. However, further studies with blind subjects are required to optimize stimulation parameters and test complex image recognition before the feasibility of a visual prosthesis based on ICMS can be established.

Keywords: human; electrical stimulation; visual cortex

Abbreviations: AF = anodic-first; BB = 4 mm diameter pellet; CF = cathodic-first; F = frequency; I = current; ICMS = intracortical microstimulation; IPI = inter-phase interval; ITI = inter-train interval; PD = pulse duration; TL = train length

Introduction

The concept of a cortical visual prosthesis for the blind is based on the fact that localized electrical stimulation of the human visual cortex can excite topographically mapped visual percepts called phosphenes. Early experiments by Brindley (Brindley and Lewin, 1968; Brindley *et al.*, 1972; Rushton and Brindley, 1977), Dobelle (Dobelle and Mladejovsky, 1974; Dobelle *et al.*, 1974, 1976), Pollen (1975) and others were designed to study the effects of visual cortical stimulation with relatively large electrodes placed on the pia-arachnoid surface in individuals who were totally blind, following lesions of the eyes and optic nerves. The results from these studies indicated that a prosthesis based on cortical surface stimulation would have limited usefulness because of factors such as the high levels of current required to produce phosphenes, interactions between phosphenes when electrodes were spaced closer than 2.4 mm, the production of multiple non-contiguous phosphenes as current was raised above threshold, and the occasional elicitation of pain due to meningeal or scalp stimulation.

As an alternative approach, we began the systematic design, development and evaluation of safe and effective means of microstimulating cortical tissue. By implanting floating microelectrodes within the visual cortex, with exposed tip sizes the same order of magnitude as the excited neurons, much more selective stimulation can, in principle, be achieved, resulting in more precise control of neuronal function. For a visual prosthesis, we hypothesized that ICMS would result in reduced phosphene interactions, a higher possible density of microelectrodes, and lower overall power requirements due to a greater reduction in current per microelectrode than increase in the total number of microelectrodes.

In order to derive engineering design data for a prototype chronic implant, acute ICMS studies were performed in sighted patients undergoing occipital craniotomy for other reasons (Bak *et al.*, 1990). The results from those studies were encouraging and provided the necessary engineering specifications to develop a long-term implant for a blind subject.

The initial questions to be answered by this implant were: (i) Does the visual cortex of a person, blind for a long period of time, remain responsive to ICMS and, if so, what visual percepts can be elicited by ICMS? (ii) Are the visual percepts stable over months of stimulation? (iii) With stimulation of many sites, do the elementary visual percepts (phosphenes) integrate to form meaningful spatial patterns that can be recognized by the subject? The present work provides partial or complete answers to these questions. The results are encouraging for the development of a prosthesis that might assist the blind in daily activities such as reading and mobility.

Material and methods

Subject selection

Although we did not actively solicit a research subject, over 50 blind individuals contacted us following several articles about our work in the popular press. From this group, four were brought to the National Institutes of Health for preliminary medical and psychological evaluation. A 42-year-old woman who had been blind without light perception for 22 years secondary to glaucoma was selected.

The human research protocol was approved by the Institute's Clinical Research Subpanel. The procedures and risks were fully explained to the subject prior to the experiments and informed consent obtained. The implant design was not permanent and the subject was fully aware that she would receive no direct benefit from this experiment. She understood that its main purpose was to gain knowledge essential to the future development of a visual prosthesis for the blind.

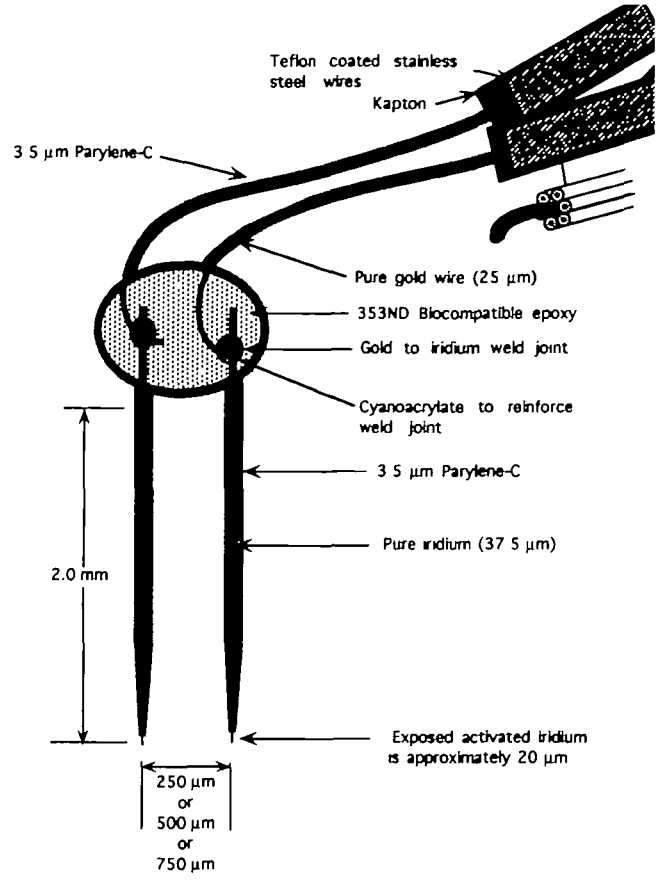

Fig. 1 Schematic diagram (not to scale) of a dual 'Hat-Pin' microelectrode used in this study for intracortical microstimulation (ICMS).

Microelectrodes

To fabricate each microelectrode (*see* Fig. 1), a 3 mm length of iridium wire, 37.5 μm in diameter, was micro welded to a flexible 25 μm gold wire with a free length of 12–40 mm. The gold wire was the centre conductor of a seven strand Teflon insulated cable. Six strands of 25 μm stainless steel wire surrounded the gold wire to provide strength so that the

cable could be passed through the scalp and attached to an external connector. The non-welded end of the iridium wire was electroetched to a length of 2 mm and a tip diameter of ~2 μm (Loeb *et al.*, 1977). In addition to 12 single microelectrodes, 13 pairs were constructed by fastening two iridium microelectrodes together with interelectrode spacing of 250, 500 or 750 μm. The microelectrodes and connecting leads were insulated with Parylene-C. The insulation was removed from the tip of each microelectrode with a high voltage arc discharge (Loeb *et al.*, 1977) to expose ~200 μm^2 of iridium. Activated iridium oxide was formed on the exposed iridium surface to increase the charge-carrying capacity of the microelectrodes (Robblee *et al.*, 1983). The microelectrode leads were assembled into three groups with eight or 10 microelectrodes per assembly. The Teflon coated cables in each group were passed through one of four silicone tubes and terminated on one of four miniature printed circuit connectors. Platinum ground leads were wrapped around each of the silicone tubes. These leads provided a return current path for the microelectrodes during stimulation.

Computer controlled stimulators

A Digital Equipment PDP-11 computer was used to generate the stimulation waveforms that controlled four optically isolated constant current stimulators. Each stimulator was connected to 10 microelectrodes via relays with open and closure times of <1 ms. Each stimulator could also be connected to any one of the microelectrodes through a patch panel. Multiple microelectrodes could be activated from a single stimulator by interleaving the stimulation waveforms during a stimulation train. The stimulators were equipped with optically isolated voltage monitors so that the voltage across each microelectrode, as referenced to the platinum ground leads, could be observed on an oscilloscope during all stimulation sequences. By monitoring these voltages, problems such as open or shorted lead wires could be detected.

The basic stimulation parameters that were under computer control are shown in Fig. 2. The frequency of the charge-balanced pulses was usually constant during a pulse train, but a number of frequency modulated pulse trains were also tested.

Surgical procedures

The implantation of the intracortical microelectrodes was carried out in two stages. In the first procedure, an occipital craniotomy centred on the right occipital pole was performed under general anaesthesia. Four ramp-like channels were fashioned in the skull and the bone plate in order to allow future compression-free passage of the microelectrode cable groups. The second procedure was performed 8 days later under local anaesthesia with the intention of mapping the visual cortex with a 1 mm diameter platinum surface electrode prior to implanting the microelectrodes. The surface stimulation parameters employed were constant current,

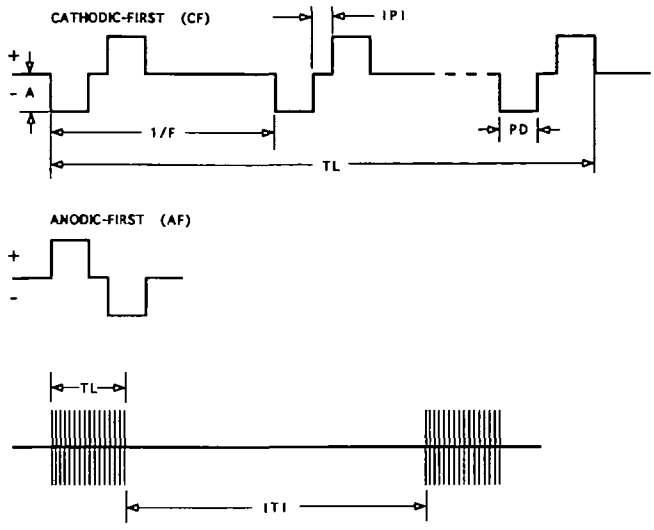

Fig. 2 Diagram illustrating the parameters that were used for the biphasic pulse waveforms. The polarities of the pulses were either cathodic-first (CF) or anodic-first (AF). The frequency (F) of stimulation was the reciprocal of the time between pulses. The inter-phase interval (IPI) was the time between the leading phase of the pulse and the repolarization phase. The pulse duration (PD) was the duration of one phase of the pulse. The train length (TL) was the time duration of the burst of stimulating pulses. The inter-train interval (ITI) was the time between stimulation trains. A = amplitude.

capacitor-coupled, anodic-first (AF) charge-balanced biphasic pulses [amplitude = 1.0–2.5 mA, frequency (F) = 100 Hz, pulse duration (PD) = 200 μs, TL = 2 s]. These parameters had produced phosphenes in our sighted subjects (Bak *et al.*, 1990) but failed to do so in this blind subject. Despite this failure to produce phosphenes with surface stimulation, 38 microelectrodes were implanted, normal to the cortical surface to a depth of 2 mm, in a wedge-shaped region near the pole of the right occipital cortex (Fig. 3), as planned from MRI studies of the subject. The microelectrode cables were placed on the skull ramps, tunnelled beneath the scalp and exteriorized through four separate scalp incisions.

At the completion of 4 months of testing, a final surgical procedure was performed under general anaesthesia for the removal of all of the percutaneous leads and five of the microelectrodes. The four scalp incisions were closed at this time. There were no intra- or post-operative complications.

Subject testing

The cables from the computer controlled stimulators were attached to a lightweight bicycle helmet, worn by the subject, to provide strain relief between them and the percutaneous leads. A quadrant of the helmet was removed to provide easy access to the connectors. At the end of each testing session, the helmet was removed and a head dressing was applied to minimize movements of the percutaneous leads.

Initial stimulation of individual microelectrodes was carried out with charge-balanced biphasic pulses that had the

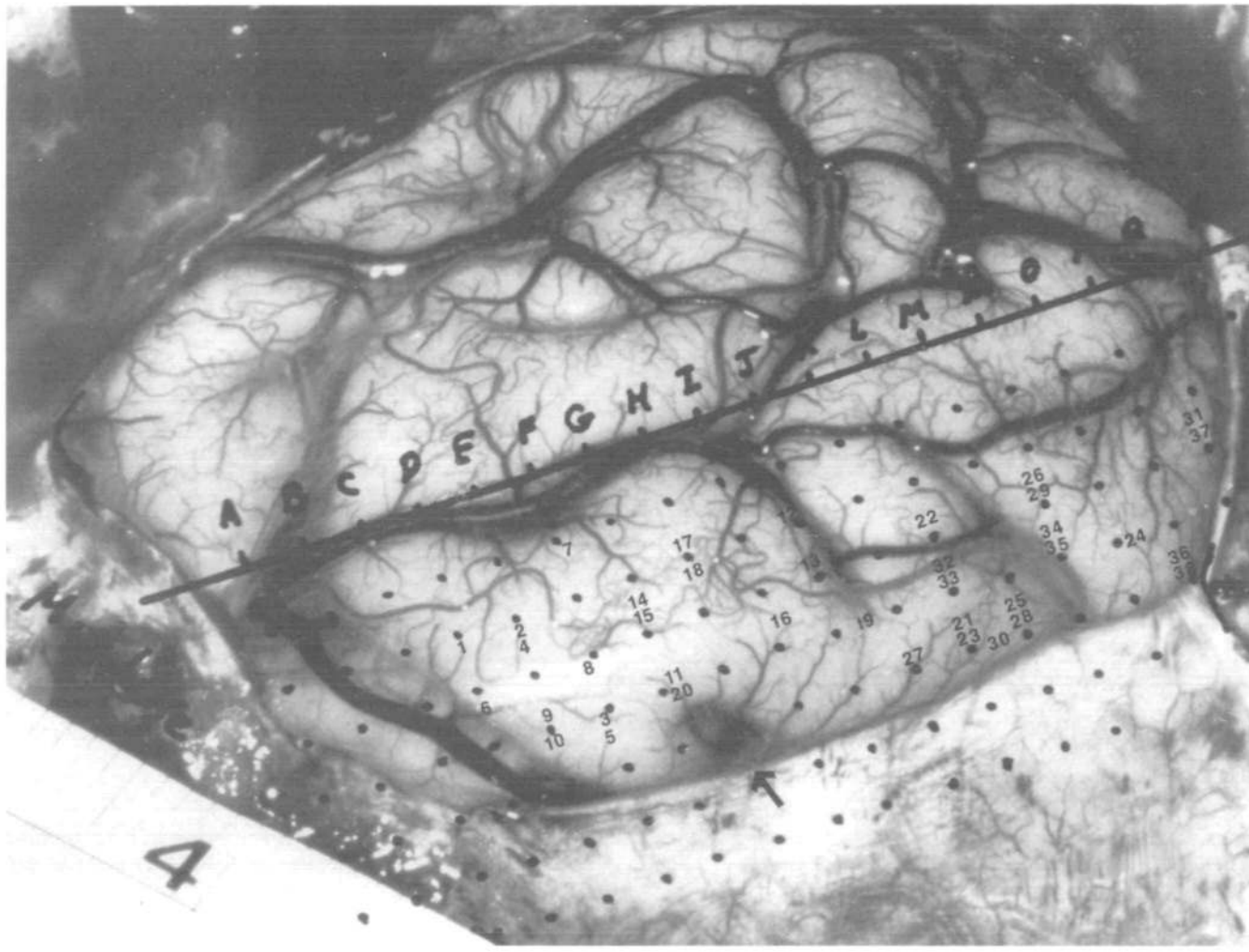

Fig. 3 Photograph of exposed surface of the right visual cortex of the blind subject. The overlaid dots, at ~2.4 mm spacing, were reference points for surface stimulation. The numbers in the figure have been placed on the approximate positions of the intracortical microelectrodes. The anatomical pole of the occipital cortex is estimated to be near microelectrodes 14 and 15. The terminal portion of the calcarine fissure is marked by an arrow and superior is to the left of the arrow. A centimetre scale is shown at the lower left.

following parameters: cathodic-first (CF), F = 100 Hz, PD = 200 μs, TL = 3000 ms and currents (I) up to 20 μA. After stimulus presentation, the subject was requested to describe the visual percepts. Audio and video tape records were made of all testing sessions in order to preserve details of subject responses.

Microelectrode testing

On each day of post-implant testing, the impedance of each microelectrode was measured by recording the voltage drop produced during passage of a 100 nA, 1 kHz, sine wave current. This determined the electrical integrity of the microelectrode, lead wire and connector assembly. Moisture occasionally accumulated in the cable connectors, producing a low impedance shunt. When this occurred, the connectors were flushed with alcohol and dried with an air stream. Impedances were also measured at the end of each testing session.

Threshold testing

The threshold current required to produce a phosphene with a given microelectrode was determined using a successive approximation convergence technique. One-half of the maximum current for threshold testing (CF = 30 μA, AF = 80 μA) was used as the initial value of stimulation current. The other parameters for the charge-balanced biphasic pulses were F = 200 Hz, PD = 200 μs and TL = 250 ms. After each stimulation train, the subject depressed one of three push buttons: the first if a phosphene was not perceived, the second to repeat the stimulus with the same parameters, and the third if a phosphene was perceived. At the beginning of each stimulation train, a tone was generated to alert the subject that a response was required. If a phosphene was perceived, the current for the next stimulation was reduced to a value halfway between the present value and either 0 μA or the highest value of current for which a phosphene had not been perceived. If a phosphene was not perceived, the current for the next stimulation was increased to a value

halfway between the present value and the lowest value of current for which a phosphene had been perceived, or the maximum current for threshold testing, whichever was lower. The process of determining threshold current continued until the change in current was <0.1 μA. Threshold current for an individual microelectrode was the lowest current for which the subject perceived a phosphene.

Phosphene onset, extinction and duration

The onset and extinction of phosphenes were measured using a simple reaction time task. The subject initiated a trial by depressing a switch which started a stimulation train and a timer. The subject released the switch when a phosphene was perceived and the time was measured. This onset time was the time to the beginning of the perceived phosphene plus the subject's motor reaction time. The extinction time of phosphenes was measured in a similar fashion but the subject released the switch when the phosphene could no longer be perceived. Phosphene duration was estimated as the extinction time minus the onset time.

Phosphene mapping

Two mapping procedures were employed to estimate the location of phosphenes in the subject's perceived visual space. The first employed a circular dart board divided into the radial segments of a clock face, with five concentric annular zones to represent displacement between the fovea and the extreme visual periphery. The subject would concentrate on holding her eye position as if she were looking straight ahead prior to and during the generation of each phosphene. She would then place a dart in the board via tactile localization.

Computer mapping of phosphene location associated with each microelectrode was a modification of the procedure described by Mladejovsky *et al.* (1976). In their algorithm, the subject indicated the direction between two phosphenes with a touch-tone key pad indicating eight different directions. We expanded the resolution of this technique by using a joystick input to the computer that could indicate 16 different directions. Two phosphenes were elicited by activating two microelectrodes. One phosphene was the reference which had already been mapped and the other was the phosphene to be mapped. They were differentiated by order of presentation, differences in duration and/or brightness. The subject indicated the direction vector of the phosphene to be mapped with the joystick and pressed an acceptance button when a selection had been made. The computer determined the relative location of the phosphene from the directions of previously mapped phosphenes. A binary search, first in the x direction and then in the y direction, through the locations of phosphenes already mapped, determined the neighbours of the phosphene to be mapped.

Results

Stimulation was initiated 3 days after implantation of the microelectrodes [CF, F = 100 Hz, PD = 200 μs, inter-phase interval (IPI) = 0, TL = 3000 ms]. During the first eight stimulation sessions spanning 11 days, the described phenomena were disregarded because the subject reported visual experiences resembling phosphenes during sham trials, when the stimulating current was set to zero. Our subject had pronounced, spontaneous, visual background activity against which we were trying to superimpose phosphenes. It was thus necessary to establish whether she was reporting visual phenomena due to stimulation or to spontaneous fluctuations in her background activity. To aid the recognition of phosphenes, starting with the ninth stimulation session, the stimulation TL was reduced from 3000 ms to 200 ms and 10 trains were presented repetitively at 1-s intervals. As previously reported by Brindley (Rushton and Brindley, 1978), we found that this type of stimulus presentation greatly enhanced the subject's ability to distinguish phosphenes from background activity. When repetitive trains were first employed, the subject immediately reported that she saw a small spot of light that was blinking in synchrony with the trains. After this change, the subject never again reported a phosphene when sham stimulations were included in the testing sequence.

Phosphene threshold currents

Threshold currents for the detection of phosphenes were a function of all of the parameters shown in Fig. 2. A set of parameters that produced satisfactory phosphenes were initially chosen for threshold determinations. With CF pulses (F = 200 Hz, PD = 200 μs, IPI = 0, TL = 125 ms), 25 of the microelectrodes had threshold currents below 25 μA and the lowest threshold was 1.9 μA. Since activated iridium microelectrodes have a higher charge carrying capacity when pulsed in the AF direction (Robblee *et al.*, 1983), microelectrodes that did not produce phosphenes with CF stimulation at levels up to 30 μA were subsequently tested with AF stimulation at currents up to 80 μA. Threshold currents for nine additional microelectrodes with AF stimulation ranged from 40 to 77 μA.

Two of the microelectrode gold leads were broken at the time of implantation and only two of the 36 intact microelectrodes failed to produce phosphenes. During the sixth week of testing, four of the gold centre conductors in the cables to the microelectrodes were broken, where they exited the supporting stainless steel strands, due to accidental movement, during sleep, of the head dressing that protected the percutaneous cables between testing sessions. During the next few weeks, more of the gold leads broke which severely limited performance of a number of experiments.

Cathodic-first versus anodic-first stimulation

As noted above, the polarity of the leading phase of the charge-balanced biphasic stimulating pulses affected

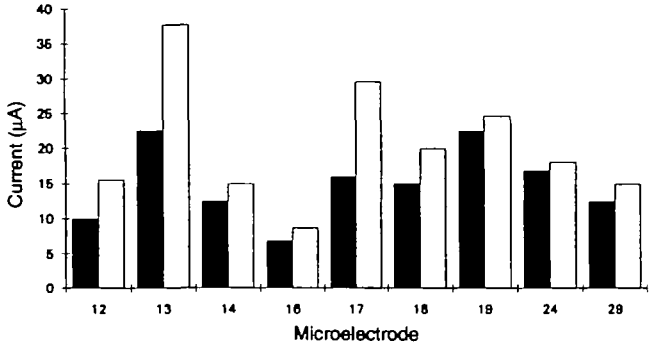

Fig. 4 Comparison of threshold currents of nine microelectrodes using CF (closed bars) and AF (open bars) stimulation. Stimulation parameters: F = 200 Hz, PD = 200 μs, TL = 250 ms.

threshold currents. Figure 4 illustrates the lower thresholds obtained with CF compared with AF stimulation for nine microelectrodes tested systematically (F = 200 Hz, PD = 200 μs, IPI = 0, TL = 250 ms). The average increase in current threshold with AF stimulation was 36.9%. However, only microelectrodes 13 and 17 required a sizable increase in current (75.3%), while the remaining microelectrodes required only a 21.6% increase in current.

Effects of TL and frequency

Threshold current tests were conducted with five individual microelectrodes to determine the relationship between current and TL over the frequency range of 75–200 Hz. The threshold currents were constant at frequencies between 150 and 200 Hz, but increased by ~50% at 75 Hz. The average thresholds at fixed frequencies for the 250 ms TL were 20% lower than those for the 125 ms TL. The subject reported that phosphenes produced with TLs of 250 ms were not as quick (i.e. of longer duration) as those produced with TLs of 125 ms, and were thus more easily recognized. Longer stimulation trains were investigated for prolonging phosphenes and the results are discussed below in the section on phosphene duration experiments.

Effects of pulse duration

The effects of stimulus PD were examined in detail for three microelectrodes. The reported average threshold currents decreased with increasing stimulus PD from 19.4 μA at PD = 200 μs to 11.7 μA at PD = 800 μs (F = 200 Hz, IPI = 0, TL = 250 ms). An unexpected finding was that the subject preferred the phosphenes produced with the wider PDs, indicating that 'they were more substantial'.

When narrow biphasic pulses were employed for stimulation, delay of the repolarization phase reduced the stimulation threshold. With a PD of 200 μs, the average threshold of five microelectrodes dropped by 5.4% when IPI was increased from 0 to 100 μs.

Threshold stability

As the experiment progressed, it was found that wider PDs provided a more pleasing percept to the subject. Thus the 'standard' parameters for establishing stimulation thresholds slowly evolved over the course of the experiment. For example, on day 35 post-implant, the threshold current for microelectrode 18 was 15.9 μA (F = 200 Hz, PD = 200 μs, IPI = 0, TL = 250 ms). The threshold initially dropped and then rose to 24.8 μA on day 78 (mean = 16 μA, SD = 3.8). Increasing the PD to 400 μs reduced the threshold current to 11.9 μA. When thresholds currents were determined with both 200 and 400 μs PDs on the same day, the 200 μs PD required, on average, 1.51 times more current than the 400 μs pulses. With these new parameters, the threshold current remained relatively stable through day 108 (mean = 12.8 μA, SD = 1.4). The stimulation parameters were again changed due to subject preference (F = 150 Hz, PD = 600 μs) resulting in a threshold current of 12.2 μA. The average threshold currents using the parameters (F = 200 Hz, PD = 400 μs) were 1.05 times higher than those obtained with the new set of parameters (F = 150 Hz, PD = 600 μs). The mean threshold current until the end of the testing with this last set of parameters was 12 μA (SD = 1.3). With the 400 or 600 μs PDs, there was less variation in threshold current values than with a PD of 200 μs.

Selected characteristics of phosphenes

Phosphene size

The size of the perceived phosphenes ranged from a 'pin-point' to a 'nickel' (20 mm diameter coin) held at arm's length. Systematic studies were not conducted on each of the different stimulation parameters, but sufficient data were obtained with current amplitude and TL to demonstrate that apparent phosphene size was slightly modified with variations in these parameters.

Phosphene sizes were estimated by the subject as stimulation currents were increased through 17 of the microelectrodes. With nine, the size of the phosphenes decreased as the current increased, while in the others, increasing current produced either no change in the size of the phosphenes or an increase and then decrease in size.

The sizes of the perceived phosphenes were tested with four microelectrodes as the stimulation TL was varied. All four produced larger phosphenes as the TL was increased from 200 to 500 ms.

Phosphene colour

When individual microelectrodes were stimulated near threshold, the subject usually reported the evoked phosphenes as having distinct colours such as yellow, blue or red, but not green. The results obtained with microelectrode 5 were typical. Its threshold was 7.5 μA (F = 100 Hz, PD = 200 μs, TL = 500 ms) and the colour reported was violet. As the

current was increased to 11.3 μA, the phosphenes were reported as sometimes white, sometimes violet and occasionally they consisted of both colours. At currents >12.5 μA, percepts during stimulation were generally white, yellowish or greyish.

Flicker

When a single continuous train of stimulation was delivered, the subject perceived a phosphene that did not flicker regardless of TL. When multiple trains were delivered, the subject perceived a temporally separate phosphene for each train as long as the inter-train interval (ITI) was >~25 ms. When the ITI was reduced below this value, the subject perceived a continuous, non-flickering phosphene.

Perceived distance of phosphenes

The subject reported that phosphenes appeared at various distances, ranging from 8 cm in front of her face to far away, like a 'distant star'. The apparent distance of most phosphenes was under 60 cm.

Phosphene onset, duration and extinction

Onset response latency

The average onset reaction time for phosphene perception (*see* Material and methods) was 395 ms when microelectrode 18 was stimulated (F = 150 Hz, PD = 600 μs, TL = 250 ms, current = 1.5 times threshold). The average onset reaction time for phosphene perception with stimulation of microelectrode 12 was 452 ms, but the subject reported that the phosphenes were harder to see than those generated by stimulation of microelectrode 18. Microelectrodes 32 and 33 were stimulated simultaneously and the average onset reaction time for phosphene perception was 418 ms.

Onset latency versus stimulation frequency

The frequency of stimulation influenced the subject's reaction times to stimulus detection and cessation. Increasing the frequency of stimulation reduced the reaction time to both the onset of phosphene detection and cessation when stimulus intensity was set to 1.5 times threshold at F = 150 Hz. Beyond 150 Hz, the onset reaction times were relatively constant at 412 ms, while the reaction times to cessation of the phosphenes appeared to stabilize at 470 ms for F ≥250 Hz.

Phosphene duration

When microelectrodes were tested with a stimulation TL of 250 ms, the estimated phosphene durations were slightly longer than the duration of the TL (259, 276 and 481 ms). The estimated phosphene durations remained slightly longer than the stimulation TL for both 500 and 750 ms TLs. When the stimulation TLs were increased to 1000 and 1500 ms, the estimated phosphene durations were less than the duration of stimulation and never exceeded 930 ms.

Method of increasing phosphene duration

The subject described phosphenes produced by long stimulation trains as having a rapid onset and cessation even though the stimulation continued beyond the time that the phosphene was perceived. To increase the apparent duration of phosphenes, interrupted stimulation was investigated. With a TL of 125 ms, an ITI of 50 ms and 12 repetitive trains, the subject reported seeing 'a bunch of phosphenes that were close together in time'. They looked like 'they were receding in space, but did not get dimmer'. The total time of the stimulation was 2050 ms and the subject indicated that the total duration of the phosphenes was 2177 ms.

When the ITI was reduced to 25 ms and 13 trains were presented, the subject reported seeing 'one phosphene that receded in space, maintained the same brightness, but appeared to get smaller'. The total period of stimulation was 1925 ms and the subject indicated that the phosphene lasted ~2200 ms. Increasing the number of trains to 26 (period of stimulation = 3875 ms) the subject reported the same visual percept as before and indicated that it lasted ~2760 ms. This percept duration indicated that the phosphene ended before the end of stimulation, but was present for a much longer time than when continuous stimulation was employed.

Accommodation to repeated stimulation

During stimulation of a microelectrode, the apparent brightness of a phosphene reported by the subject decreased. To quantify this phenomenon, the subject calibrated her perception of phosphene brightness by assigning a maximum brightness value of 5.0 to the first stimulus presentation. Brightness of each subsequent phosphene was rated relative to the first on a scale of 0–5. Stimulation trains were presented every 4 s which allowed sufficient time for the subject to respond. Microelectrodes 2, 21 and 25 were stimulated at twice the threshold current level of each (F = 200 Hz, PD = 100 μs, IPI = 100 μs, TL = 125 ms). Figure 5 shows the results of ~50 repeated stimulations of each microelectrode. The accommodation in brightness was very pronounced for all three microelectrodes. There was a sudden drop in the brightness of the second phosphene produced by microelectrode 21, but then the slope of the accommodation curve was very similar to the accommodation curves for microelectrodes 2 and 25.

The threshold current for each of the three microelectrodes was determined prior to and immediately after the 50-trial sequence of stimulation. The average increase in threshold current was 52%. On the day following the repeated stimulation, the average threshold current of these microelectrodes had returned to their initial value for the preceding day.

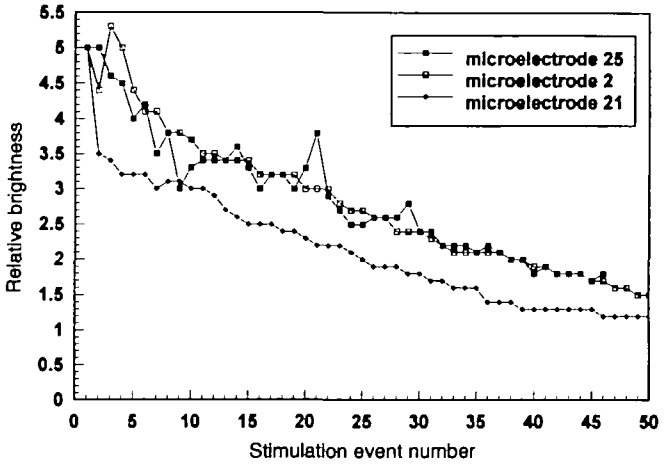

Fig. 5 The perceived relative phosphene brightness produced by repeated stimulation, at 4 s intervals, of three different microelectrodes. Microelectrode 25 was stimulated with 46 trains followed by stimulation of microelectrode 2 with 50 trains and then microelectrode 21 was stimulated. Stimulation parameters: F = 200 Hz, PD = 100 μs, IPI = 100 μs, TL = 125 ms.

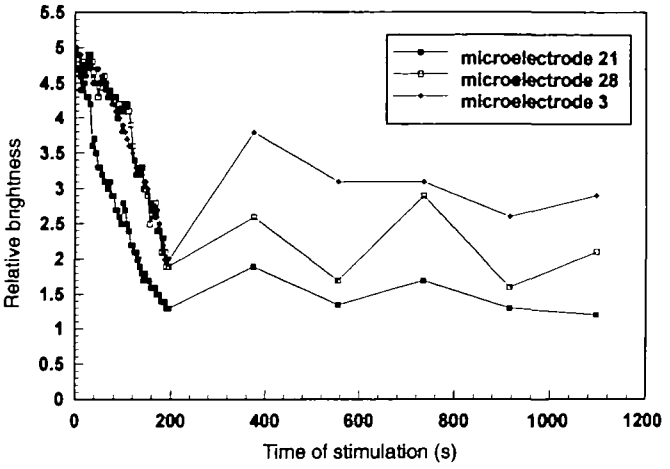

Fig. 6 Phosphene brightness accommodation and recovery produced by repeated stimulation of the three microelectrodes. The order of microelectrode stimulation was 21, 28 and 3. The microelectrodes were stimulated first at 4 s intervals for the accommodation portion of the test followed by stimulation once every 200 s to ascertain the level of brightness recovery. Stimulation parameters: F = 200 Hz, PD = 200 μs, TL = 125 ms.

Another series of accommodation experiments was conducted with microelectrodes 3, 21 and 28. Stimulation was again given at twice the threshold current level with the same parameters as used on the first accommodation series conducted the previous day, except that the PD was increased to 200 μs and the IPI was reduced to zero. The brightness accommodation curves for all microelectrodes declined at a slower rate than those of the previous day. The average increase in threshold current of these three microelectrodes produced by the repeated stimulation was 20%.

To rule out the possibility that the accommodation curves were due to the subject's scaling of perceived brightness, two sequential accommodation experiments were performed. At the completion of the first 50 stimulations the subject was asked to recalibrate the perceived brightness of the next observed phosphene to a value of 5.0 and report the brightness of the next 49 phosphenes on this new scale. The perceived brightness of the second set of 50 phosphenes decreased at a slower rate than the first set of 50 phosphenes.

To determine the rate of brightness recovery following repeated stimulation, the brightness was subsequently assessed at 3-min intervals with a single stimulation train. Figure 6 shows the accommodation curves on a longer time-scale, illustrating that apparent brightness does not recover over a 16-min period following an initial 50 stimulation sequence lasting 200 s.

Wider stimulation PDs appeared to reduce the effects of brightness accommodation with repeated stimulation. Figure 7 shows the brightness accommodation with PDs of 400 and 800 μs. Three hundred trains were first presented with PD = 400 μs (I = 28 μA, F = 200 Hz, TL = 250 ms, ITI = 4000 ms). The subject reported an initial decay in brightness over the first 25 trials, a relatively constant brightness for the next 130 trials and then a gradual decay to the end of the experiment. After 2 h of rest, a second

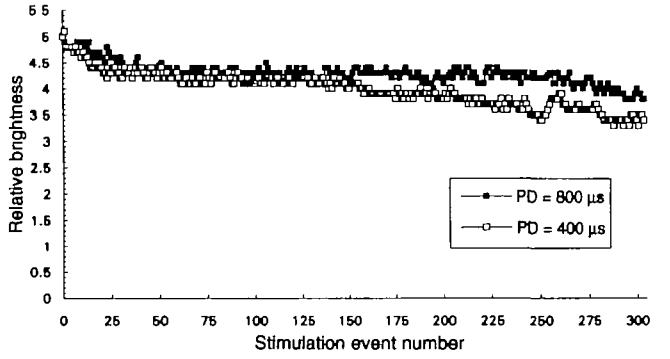

Fig. 7 Repeated stimulation with two different pulse widths. The perceived relative phosphene brightness produced with PDs of 400 μs (I = 28 μA, F = 200 Hz, TL = 250 ms, ITI = 4000 ms) and after 2 h of rest with PDs of 800 μs (I = 19 μA, other parameters the same).

accommodation experiment was conducted with the same parameters except PD was 800 μs and I was 19 μA. The brightness again rapidly decreased during the first 25 trials and then remained relatively stable for the next 250 trials. The brightness accommodation curves for both the 400 and 800 μs PDs were similar over the first 150 stimulations with the phosphenes produced at 800 μs being slightly brighter. Beyond 150 stimulations, there was a consistent separation in the brightness curves, with the perceived brightness of the phosphenes produced by the 800 μs PDs being greater than those produced by the 400 μs PDs.

Brightness modulation

Effects of pulse duration

The relative brightness of phosphenes was determined from 20 consecutive trials at PDs of 400, 800 and 1000 μs,

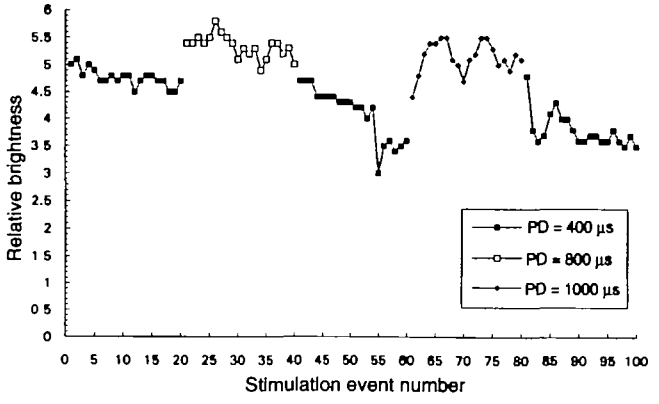

Fig. 8 Relative brightness using microelectrode 18 with different stimulation PDs. Twenty stimulations were performed at each PD. Stimulation parameters: I = 20 µA, CF, F = 200 Hz, TL = 250 ms, ITI = 4000 ms.

respectively. Figure 8 shows that the majority of phosphenes produced by the 800 and 1000 µs pulses were brighter than those produced with 400 µs pulses. The current for all trials was the same but the total charge injected per stimulation pulse was a function of the PDs.

Effects of TL

Three different TLs were evaluated for their effects on perceived brightness (microelectrode 18: F = 200 Hz, PD = 400 µs, AF, TL = 65, 125 or 250 ms). The level of current (33 µA) was selected to be 1.5 times threshold for the shortest TL. When the TL was alternated between 250 and 65 ms, the phosphenes were always brighter with the longer train of pulses. On two occasions, the phosphenes were not observed with the 65 ms pulse train. When the TL was either 125 or 250, the 250 ms train usually produced a slight increase in brightness over the 125 ms train. However, the decrease in brightness from accommodation during the periods of repeated stimulation at each TL was greater than this increase. The subject reported that all of the phosphenes in the TL experiments looked alike, except for the difference in brightness.

Effect of stimulation frequency

When either the TL or the number of stimulation pulses was held constant, the threshold current declined as the F of stimulation increased from 50 to 200 Hz.

To determine the effects of F on the perceived brightness of phosphenes, the stimulation F was alternated between 100 and 200 Hz while the current and TL were held constant (microelectrode 18: I = 25 µA, PD = 400 µs, TL = 250 ms, CF, ITI = 4000 ms). Except for three consecutive stimulations when the brightnesses were equal, the brightness of the 100 Hz stimulation was always lower than the preceding 200 Hz stimulation. During two stimulation trials at 100 Hz, a phosphene was not observed.

Visual phenomena caused by after-discharge

Visual phenomena apparently caused by after-discharges following stimulation occurred on three occasions, all with the same microelectrode (number 18). The first was detected during stimulation with a continuous 20 Hz pulse train (PD = 200 µs, CF, biphasic pulses) that was interrupted with a high frequency 125 ms pulse train (F =200 Hz, PD = 200 µs, CF, biphasic pulses) occurring every 4 s. The current level was twice threshold (42 µA) for the high frequency burst of stimulation, but was below threshold for the 20 Hz pulse train. After the third high F stimulation train, the phosphene did not extinguish. The stimulator was turned off but the subject continued to see something, apparently produced by an after-discharge. During stimulation, the phosphene was reported to be an amorphous white–grey pea-sized spot. The visual percept persisted for 6 min after cessation of stimulation. Over this period it became more diffuse, gradually expanding from pea size to fill the upper left quadrant of the visual field, becoming multi-coloured as it grew larger.

Four minutes after the end of the after-discharge a threshold current determination was performed. During the first stimulation train at 15 µA, a phosphene appeared and remained on after the termination of the train. The new after-discharge started in the periphery of the visual field where the last after-discharge had ended, and proceeded to fill the upper left quadrant. The second after-discharge lasted for 9 min. Further stimulation of this microelectrode was aborted for the day.

Two weeks later, another after-discharge was produced with stimulation of the same microelectrode. Approximately 640 stimulation trains were presented prior to the development of an after-discharge. After a set of 165 stimulus trains at 25 µA (CF, F = 50 Hz, PD = 400 µs, TL = 250 ms), a 2-s train of continuous stimulation (same parameters except TL) produced an after-discharge. The original phosphene was reported to be a 'BB' sized (4 mm diameter) greyish-white spot of reflected light. After cessation of stimulation, as the after-discharge progressed, the phosphene became larger and brighter. Four minutes after the end of stimulation it was the size of a 'quarter' (24 mm diameter coin), with different parts appearing as different colours. It moved as the subject moved her eyes. By 7 min, the size had grown to that of a 'half dollar' (30 mm diameter coin). It slowly enlarged to fill the left hemi-field with the brightest area near the periphery. Although this visual phenomenon disappeared after 25 min, the subject felt that a bright light was pulsating beyond the extent of her visual field, especially in the region between 9 and 12 o'clock. There were no further after-discharges during the remaining stimulation sessions, and at all times the subject remained fully alert; she never showed any signs of motor seizures.

While the after-discharge triggered by stimulation of microelectrode 18 was still present, the phosphene produced by stimulation of microelectrode 12 (~4.3 mm from

microelectrode 18) was determined to have a threshold of 22.5 μA, to be light yellow in colour and was easily perceived superimposed on the visual phenomena generated by the after-discharge. Five hours earlier, the threshold of microelectrode 12 had been 15 μA, and the resulting phosphene was white. Thirty-five minutes after the end of the after-discharge, the threshold of microelectrode 12 had dropped to 15.4 μA. The threshold of microelectrode 6 (~10 mm from microelectrode 18) was tested 1 min after the end of the after-discharge and found to be 29.9 μA. Four hours earlier, the threshold had been 20 μA. The threshold of microelectrode 6 dropped in value as time progressed after the end of the after-discharge. After 33 min the threshold was 24 μA, and 21.5 μA after 42 min.

Multiple phosphenes from a single microelectrode

Depending on stimulation parameters, an individual microelectrode could either produce a single phosphene or a pair. Stimulation of microelectrode 18 at 3.6 μA (F = 150 Hz, PD = 600 μs, TL = 250 ms) produced a single phosphene. Increasing the current to 7.75 μA produced a pair. The high threshold phosphene appeared above the low threshold phosphene, was 'fuzzy' while the low threshold phosphene was 'distinct, the size of a BB and just touching the high threshold phosphene'.

Microelectrode 12 also produced either one or two phosphenes depending on the stimulation current level. The low threshold phosphene appeared at 15.2 μA, while the pair appeared at 19.8 μA. These two phosphenes were described as being white–grey, round and solid, equal or greater in size than a pin-point and almost touching. These two phosphenes appeared above the phosphenes produced by microelectrode 18, were in a straight line and all four phosphenes were almost touching.

Microelectrodes 32 and 33 were 250 μm apart in the cortex and their stimulus fields were found to interact. Because the electrical characteristics of the two microelectrodes were almost identical, they were connected in parallel to the output of a single stimulator. With simultaneous stimulation of the two microelectrodes, approximately one-half of the total current flowed through each. The first phosphene appeared at a current level of 22.4 μA (AF), and 'looked like a yellow–orange light, greater than a pin-point in size'. The second phosphene appeared at a current level of 36 μA, was 'bluish, less than a BB below the first and in a straight line with the phosphenes produced by microelectrodes 12 and 18'.

Phosphene maps

A typical phosphene 'dart board' map referred to the subjective centre of gaze (*see* Material and methods) is shown in Fig. 9. All of the phosphenes were in the left hemi-field with all but two above the horizontal meridian. There was a large clustering of phosphenes from 10 microelectrodes at ~22° eccentricity and slightly above the horizontal meridian.

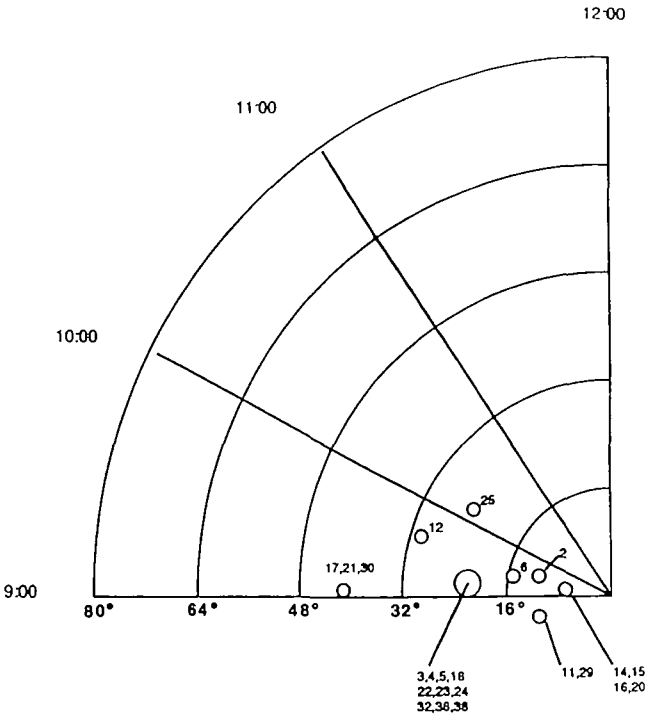

Fig. 9 Phosphene map obtained by having the patient place a dart in a dart board at the perceived location in visual space after each microelectrode was stimulated. The circular dart board was divided as the face of a clock with five concentric annular zones representing angular deviations from the most central (0°) to the most peripheral (80°) the subject remembered when she had vision. The large circle at ~22° represents a region that contained 10 phosphenes whose individual locations could not be separated by this mapping technique.

With a second position mapping technique the relative direction between pairs of phosphenes as indicated by a computer-coupled joystick was plotted (*see* Material and methods). Figure 10 shows a map generated by this technique. A number of the phosphenes that appeared at the same location with the dartboard technique (*see* Fig. 9) were found to be at separate locations with joystick mapping. This second map provided more information as to the relative location of the phosphenes, but did not contain information on the absolute spacing between phosphenes or the location of the map in the perceived visual space. This latter information was obtained from the subject through verbal descriptions of the size, location and spacing between specific phosphenes.

There was a fairly good relationship between an inverted map of computer located phosphene positions shown in Fig. 10 and the placement of microelectrodes in the visual cortex shown in Fig. 3. Stimulation of microelectrode 3 produced a phosphene that was the lowest in the visual field, near the horizontal meridian. This microelectrode was located superior to the calcarine fissure. Stimulation of microelectrode 25 produced a phosphene that was highest in perceived visual space and the microelectrode was inferior to the calcarine

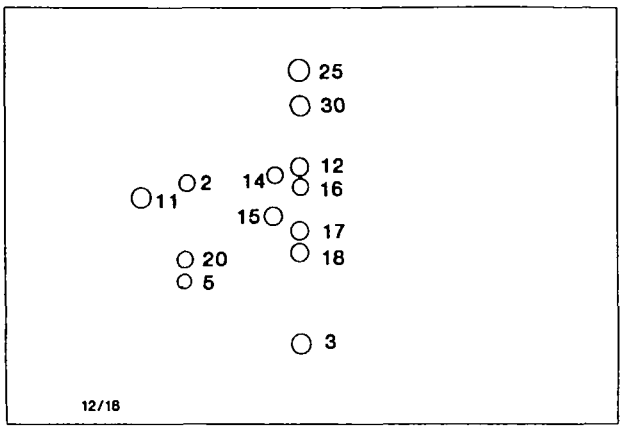

Fig. 10 Computer generated phosphene map. The subject positioned a joystick indicating the direction between two phosphenes presented as pairs. The computer quantized the joystick position into 16 vectors. At the time these data were collected, lead wire breakage prevented mapping many of the phosphenes.

fissure. Phosphenes that were located between these extremes were produced by stimulation of microelectrodes that were located between microelectrodes 3 and 25.

Interactions between phosphenes

Microelectrode spacing

Interactions between pairs of microelectrodes with inter-electrode spacings of 250 μm, 500 μm and 750 μm were examined (F = 200 Hz, PD = 100 μs, IPI = 100 μs, TL = 125 ms). Three pairs of microelectrodes were utilized that had an inter-electrode spacing of 250 μm. The phosphene locations for the individual microelectrodes in two of the pairs were reported as being very close together, but the phosphene locations produced by each microelectrode of the third pair were reported as being the same.

The threshold currents for phosphene production usually increased after repeated stimulation. When one micro-electrode of a 250 μm pair (microelectrodes 2 and 4) was repeatedly stimulated, its threshold value increased by 69%. During this time the threshold value of the unstimulated microelectrode in the pair dropped by 12%. Microelectrodes 32 and 33 did not produce phosphenes when stimulated with CF pulses at levels up to 30 μA. Phosphenes were produced with AF stimulation (TL = 250 ms, F = 200 Hz, PD = 800 μs, IPI = 0) with a threshold of 45.7 μA for microelectrode 32 and 47.4 μA for microelectrode 33. When microelectrode 33 was stimulated at 0.5 times threshold simultaneously with microelectrode 32, the threshold for microelectrode 32 dropped to 39.9 μA (−13%). Likewise, when microelectrode 32 was stimulated at 0.5 times threshold simultaneously with microelectrode 33, the threshold for microelectrode 33 dropped to 30 μA (−37%).

Three pairs of microelectrodes were tested that had an inter-electrode spacing of 500 μm. During one test session, the phosphenes produced by each of the microelectrodes in two of the pairs were reported as having the same locations. On at least two other occasions the phosphenes were reported as having separate locations. The phosphenes produced by the third pair of microelectrodes were always reported at separate locations. Simultaneous sub-threshold stimulation of one microelectrode of a pair (microelectrodes 3 and 5) reduced the threshold of the other microelectrode by 13%.

Two pairs of microelectrodes were evaluated that had an inter-electrode spacing of 750 μm. The phosphene locations produced by each of the separate microelectrodes from both pairs were always reported as being different. When one microelectrode of one of the pairs was stimulated at a sub-threshold level, there was no change in the threshold value of the other microelectrode. Elevation of threshold by repeated stimulation of one microelectrode of a pair had no effect on the threshold of the unstimulated microelectrode.

Phosphene interactions

A number of stimulation tests were conducted with two microelectrodes (12 and 18) that were separated spatially (4.4 mm) but produced phosphenes that were very close together. When microelectrode 18 was stimulated (F = 200 Hz, PD = 200 μs, TL = 250 ms, I = 1.5 times threshold), the subject reported perceiving 'a small round grey solid spot that was between a BB and pin-point in size'. When microelectrode 12 was stimulated with the same parameters, the subject reported perceiving 'an object that was smaller than the phosphene produced by stimulation of microelectrode 18, was light grey, smooth inside, thick outline and looked like a drop of water'. Stimulation of microelectrode 12 with three trains followed by microelectrode 18 with three trains or alternately stimulating the two microelectrodes at an ITI of 1000 ms resulted in both phosphenes appearing in the same spot, grey–white in colour, with no outline. Repeated stimulation of either microelectrode alone resulted in the phosphenes that were distinct for that microelectrode. However, repeated alternating stimulation of the pair at an ITI of ≤1 s resulted in the loss of individual characteristics of the phosphenes.

Reduction of the ITI to 500 ms, with alternating stimulation of the two microelectrodes resulted in phosphenes appearing at two separate points, one-half a BB apart with the phosphene from microelectrode 18 below the phosphene from microelectrode 12. When the ITI was reduced to 250 ms the subject reported perceiving 'two similar looking phosphenes vertically displaced by one-half a BB and no apparent time interval between the appearance of the two phosphenes', yet the subject was able to report the exact number of phosphenes that were generated.

Further reduction of the ITI to 125 ms resulted in the phosphenes becoming blurry, 'like a photographic double exposure'. Maintaining an ITI of 125 ms between the end of stimulation of microelectrode 18 and the beginning of stimulation of microelectrode 12 but increasing the time when this sequence was repeated (burst interval) to 875 ms,

the subject reported that 'phosphenes were now clear and separated in space by one half a BB'. Reducing the ITI to 75 ms and the burst interval to 400 ms resulted in blurry phosphenes, but an accurate count of the number of phosphenes generated was maintained.

The last interaction experiment involved alternately stimulating microelectrodes 12 and 18 with interleaved biphasic pulses separated by 1 ms (F = 200 Hz, TL = 250 ms), i.e. microelectrode 18 was stimulated with one biphasic pulse pair followed 1 ms later with stimulation of microelectrode 12. The subject reported 'two vertically oriented phosphenes that appeared at the same time, were touching each other, and were at the same general location as in the previous experiments'.

Current adjustments for multiple phosphenes

When multiple phosphenes were produced by stimulation of two or more microelectrodes, dim phosphenes could be overshadowed by bright phosphenes and not perceived. For the subject to perceive all phosphenes in a group, adjustments of the individual stimulating currents were required. Near the end of testing when up to six phosphenes could be simultaneously generated, the subject was allowed to adjust the current levels of the individual microelectrodes such that all six phosphenes could be perceived. Allowing the subject to make adjustments of stimulation parameters significantly enhanced the perception of multiple phosphenes.

Perceived distance of multiple phosphenes

When pairs of phosphenes were produced by the simultaneous stimulation of two microelectrodes, the distances of individual phosphenes were modified, but usually did not become equidistant. For example, when microelectrode 5 was individually stimulated, the perceived distance was 25 cm in front of the subject. However, when this microelectrode was stimulated together with any one of five other microelectrodes, the apparent distance of the phosphenes produced by microelectrode 5 ranged between 20 and 60 cm. In experiments when three or more phosphenes were simultaneously generated, they appeared equidistant from the subject.

Percepts from multiple phosphenes

When three single phosphenes were produced with currents near threshold (microelectrodes 12, 18 and 32 in parallel with 33) the subject described them as closely spaced in a vertical orientation. When currents were increased to a level when six phosphenes were perceived, the subject felt that the initial phosphenes moved to allow space for the new phosphenes. During the presentation of these six simultaneous phosphenes that were in a vertical orientation and all just touching, the subject reported that the size of the resultant image was adequate to form a letter of the alphabet, such as 'I' or the branch of a letter such as 'M'. The subject stated that, because the multiple phosphenes looked alike and were equidistant from her, more complex patterns or images should be easier to interpret than if each phosphene had its own unique depth, size, colour, shape and texture.

Perceptual changes with multiple phosphenes

When multiple phosphenes were simultaneously generated, some of the distinctive characteristics of the individual phosphenes were lost. For example, when six phosphenes were simultaneously generated, all phosphenes appeared to be equidistant from the subject and similar in appearance. The subject could no longer identify which microelectrode produced which phosphene.

While testing the spatial orientation of the six simultaneously generated phosphenes, the stimulation TL was changed. At 250 ms, the subject reported that the phosphenes appeared simultaneously in a vertical line. When the TL was increased to 375 ms or greater, the phosphenes that formed a vertical line of touching dots appeared to come on quickly from bottom to top. When the TL was 333 ms or below, the subject reported that the six phosphenes appeared at the same time.

Phosphene movement

When the subject observed phosphenes, she concentrated on keeping her eyes straight ahead. When she was asked to move her eyes, the position of the perceived phosphene moved in the direction of eye movements. When six simultaneous phosphenes in a vertical line were produced, the phosphenes moved in the direction of eye movement and maintained the vertical alignment.

Discussion

After 22 years of blindness, our subject was consistently able to perceive small spots of light at stable locations in visual space, using ICMS. This is in contrast to the diffuse phosphenes produced by surface stimulation in a subject blind for over 30 years (Rushton and Brindley, 1978). The current levels for phosphene generation with ICMS are also very low, being two orders of magnitude less than is required when surface stimulation is employed.

Stimulation parameters

A number of different stimulation parameters was investigated to determine design information for a visual prosthesis. The initial studies centred on finding the most energy efficient set of stimulus parameters (Geddes and Bourland, 1985). However, the subject indicated that the most efficient parameters did not necessarily produce the most easily recognized phosphenes. Instead we determined a set of stimulation parameters (CF, charge-balanced biphasic pulses, F = 150 Hz, PD of ~500 μs, IPI = 0, TL = 250 ms, ITI of

1–4 s) that produced phosphenes the subject could easily detect and that we could use for assessment of phosphene stability over the several months of testing.

Pulse duration

With ICMS, our subject preferred the phosphenes generated by longer duration pulses (≥400 μs) because they appeared 'more substantial'. Phosphenes produced with 400 μs pulses required only 25% more energy than those generated with 200 μs pulses, because the peak currents were less.

Dobelle and Mladejovsky (1974), using surface stimulation, found that there was little effect on subjective sensation when PD was varied between 250 and 2000 μs. However, Brindley (1973) found that short pulses produced more spatially diffuse phosphenes than long pulses.

Flicker

With ICMS of the primary visual cortex in sighted subjects (Bak *et al.*, 1990) and in our blind subject, all phosphenes have appeared as a constant percept without flicker. This is in contrast to some of the reports from both sighted and blind subjects who have perceived phosphenes from stimulation of the surface of the visual cortex. With both of Brindley's blind subjects (Brindley and Lewin, 1968; Rushton and Brindley, 1978), all phosphenes flickered at a rate of ~10 s^{-1} regardless of stimulation parameters. Dobelle *et al.* (1974) found that surface stimulation of a subject who had been blind for 28 years caused flickering phosphenes. A subject blind for 7 years, experienced some phosphenes that flickered and some that did not when the primary visual cortex was stimulated, but all phosphenes flickered when surrounding association areas were stimulated. With sighted subjects, Dobelle and Mladejovsky (1974) noted that phosphenes may or may not flicker with surface stimulation. Pollen (1975) noted that phosphenes produced with surface stimulation of visual cortex in sighted subjects did not flicker. It is not clear why some subjects experience flicker nor whether it would be detrimental to the function of a visual prosthesis.

Phosphene distance

With ICMS of visual cortex, we found that individually elicited phosphenes usually appeared to be at different distances, but when two microelectrodes were simultaneously stimulated, the apparent distance of each phosphene approached an equidistant position. However, when three or more phosphenes were simultaneously produced, they appeared to be equidistant. In previous reports using surface stimulation (Dobelle and Mladejovsky, 1974; Dobelle *et al.*, 1974; Rushton and Brindley, 1978), subjects also have perceived phosphenes at different distances from their eyes when individual electrodes were stimulated and when two or more electrodes were simultaneously stimulated, the subjects reported that the phosphenes were at the same distance (Dobelle and Mladejovsky, 1974; Dobelle *et al.*, 1974). Since most images that would be produced by a visual prosthesis would result from the simultaneous activation of a number of microelectrodes, all of the resultant phosphenes would probably appear at the same distance from the subject. Our subject felt that this would make pattern recognition easier for her.

Phosphene latency

A subject's phosphene onset and extinction reaction times provide data on the possible rate at which visual information can be transferred to the CNS by stimulation of the visual cortex. Onset reaction time measures both the time for conscious perception of a phosphene plus the time required to produce a motor output signalling this perception.

With ICMS of two different microelectrodes, we obtained average onset reaction times of 395 and 452 ms. Pollen (1975) stimulated a surface electrode in one of his subjects and obtained onset reaction times of 480–650 ms at a threshold current of 1.0 mA. When the current was increased to 1.5 mA, the onset reaction times ranged between 292 and 365 ms. Rushton and Brindley (1978) measured an average onset reaction time produced by surface stimulation of 174.3 ms. The sizes of the phosphenes for this subject were quite large (~4°×11°). The onset reaction time values that we obtained with ICMS fall between those reported by Pollen (1975) at threshold and those at 1.5 times threshold stimulation, but are much longer than those reported by Rushton and Brindley (1978). Pollen's (1975) tests indicated that increased phosphene brightness was associated with reduced onset reaction time.

With the ICMS onset reaction times we have observed, a subject may only be capable of recognizing three to four individual phosphenes per second. Similar studies have not been conducted when two or more phosphenes are generated simultaneously. Since both increased size and brightness of a visual stimulus are associated with reduced reaction time (Kohfeld, 1971; Mansfield, 1973; E. M. Schmidt and J. A. Bragg, unpublished results), one would assume that the onset reaction time would decrease when multiple phosphenes are simultaneously elicited, resulting in useful information transfer rates for a visual prosthesis.

Phosphene extinction reaction time provides information on the actual duration of a phosphene. Pollen (1975), using surface stimulation and TLs of 2000 ms, found that some phosphenes could be longer than 2000 ms, suggesting persistence due to after-discharge. With Brindley's second subject (Rushton and Brindley, 1978), extinction reaction time measurements were not conducted because 'continuous trains of several seconds result in fading and persistence of the phosphene', again suggesting after-discharges.

Using ICMS with TLs up to 750 ms, our subject's perceived phosphenes were of similar durations, while with longer TLs the phosphenes extinguished prior to the termination of stimulation. We have tentatively concluded, pending further

study, that stimulation TLs should be <1 s to minimize the possibility of after-discharges or phosphene termination prior to the end of stimulation.

Phosphene repetition rate

In the present study, we found that interrupted pulse train stimulation (ITI = 25 ms) extends the duration of the perception of a continuous phosphene and also reduced the total energy transfer of the stimulation system. With surface stimulation, Pollen (1975) found that introduction of a 24 ms ITI resulted in a continuous phosphene that did not flicker. When the ITI was 30 ms, the phosphene seemed to flicker a little and at 80 ms the phosphene was definitely flickering. These results indicate that more efficient stimulation can be produced by introducing short gaps in the stimulation train.

Brightness accommodation

The first stimulations each day produced phosphenes that were much brighter than those produced after long periods of stimulation. One factor that might influence this brightness accommodation to repeated stimulation is the amount of neuronal activity that the cortex has experienced over time. The primary visual cortex of a person blind for a long time must experience significantly modified neuronal activity over this period. Initial electrical stimulation may produce a rapid fatigue of neuronal circuitry, but as stimulation is repeated over many days the neurons may become more fatigue resistant. There was some evidence to support this hypothesis from the large accommodation that occurred early in the study (Fig. 5) compared with the relatively small amount of accommodation seen after several months of testing (Fig. 8). The latter accommodation may also be due to the inactivation of neurons close to the microelectrode, where higher current densities are present, resulting in fewer neurons responding to each stimulus train as time progresses.

Knowing the rates of brightness accommodation and recovery after stimulation, one might, in principle, be able to predict phosphene brightness from the past history of stimulation, and adjust stimulation parameters to produce phosphenes of a more constant brightness. The rapid initial accommodation and slow and variable brightness recovery that we found with our subject suggest that it is not feasible to maintain phosphene brightness simply from knowing the past history of stimulation, at least in individuals blind for a long period of time.

With surface stimulation, the reports on brightness accommodation in the literature are varied. Brindley found that continuous stimulation of 30 min in a subject who was recently blind, produced a phosphene that did not fade (Brindley and Rushton, 1977). On the other hand, a subject, who had been blind for over 30 years, was unable to perceive continuous phosphenes of several seconds (Rushton and Brindley, 1978). With sighted subjects, Dobelle and Mladejovsky (1974) found that phosphenes faded after 10–15 s of continuous stimulation. Regardless of what causes accommodation, this phenomenon must be accounted for in the design of a useful visual prosthesis.

Brightness modulation

All of the stimulation parameters that we have investigated (I, F, PD and TL) have an effect on phosphene brightness, although brightness accommodation can mask brightness variations due to parameter changes. Previous studies that used surface stimulation (Dobelle and Mladejovsky, 1974; Dobelle *et al.*, 1974; Pollen, 1975; Rushton and Brindley, 1978; Evans *et al.*, 1979; Henderson *et al.*, 1979) have also indicated that most parameters affect the brightness of the perceived phosphenes. Evans *et al.* (1979) noted that current was the most potent variable in determining phosphene brightness. Rushton and Brindley (1978) estimated that their subject could distinguish at least 12 levels of brightness while Evans *et al.* (1979) estimated that one of their subjects could distinguish five to eight levels of brightness. All of the tests with surface stimulation were conducted with long time intervals between stimulation trains so that accommodation in phosphene brightness should not have been significant. In a practical visual prosthesis, phosphene repetition rates will undoubtedly be high enough that some brightness accommodation will occur, at least in some subjects. This accommodation might limit the number of brightness levels that can be utilized.

Another factor that may further limit the range of useful phosphene brightness modulation is the masking of dim phosphenes by nearby bright phosphenes. When six phosphenes were generated with ICMS, adjustments of individual microelectrode currents were required before the subject saw all of them simultaneously. This is similar to the results reported by Dobelle *et al.* (1974) with surface stimulation of the visual cortex.

Multiple phosphenes from a single microelectrode

Multiple phosphenes from a single electrode were originally reported by Brindley and Lewin (1968). Stimulation of individual electrodes on the cortical surface could produce one, two, three or a cluster of 10 or more phosphenes over 15° of visual field. In addition, some electrodes produced a single phosphene at low levels of stimulation and a second phosphene in another part of the visual field with high levels of stimulation. Two different mechanisms might be responsible. The first may involve the stimulation of multiple adjacent cortical columns that produce closely spaced phosphenes, while the second (particularly with surface electrodes) could result from current spread to adjoining gyri on the surface of the cortex resulting in widely spaced phosphenes.

Dobelle and Mladejovsky (1974) also reported clusters of

phosphenes produced from some surface electrodes and could not find a level of current that would produce just a single phosphene. They were also able to generate one or two phosphenes with other electrodes depending on the level of stimulation. The second phosphene was a conjugate of the first inverted about the horizontal meridian.

Shakhnovich *et al.* (1982) also reported the production of one or two phosphenes with intracortical stimulation that depended on the level of excitation, but did not indicate the relative locations of the two phosphenes.

With our subject, using ICMS, we were able to produce one or two phosphenes depending upon the current level. The production of the second nearby phosphene occurred when stimulation current levels were as low as 1.3 and as high as 2.2 times threshold for a single phosphene.

The generation of multiple phosphenes with individual microelectrodes appears to be a function of the stimulation parameters. If the second phosphene is always spatially close to the first, as has always been the case with ICMS, then the second phosphene could easily be included in the processing and presentation of images for a visual prosthesis. If the second phosphene is at a considerable distance from the first, as has been observed with surface stimulation, a significant problem might exist in image generation for a visual prosthesis.

Electrode spacing

When two electrodes on the surface of the cortex are simultaneously stimulated, subjects report either one or two phosphenes depending on the distance between the electrodes. Brindley and Lewin (1968) and Brindley (1973) reported that electrodes spaced 2.4 mm apart produced either single phosphenes or pairs of phosphenes depending on their location on the visual cortex. Dobelle *et al.* (1974) confirmed these results and stated that 2–3 mm separation between electrodes was required to produce separate phosphenes when electrodes were simultaneously stimulated. Pollen's results (Pollen, 1975) suggested that electrodes had to be spaced 5 mm apart before separate phosphenes were observed. These large spacings would significantly limit the number of electrodes and the ultimate resolution in a functional visual prosthesis based on surface stimulation.

Our earlier work (Bak *et al.*, 1990), with intracortical microelectrodes in sighted individuals, showed that simultaneous stimulation of two microelectrodes with a spacing of 0.3 mm produced a single phosphene, while stimulation of two microelectrodes spaced 0.7–1 mm produced two separate phosphenes. In our current study, we found that simultaneous stimulation of microelectrodes spaced 0.5 mm usually produced separate phosphenes, while at times microelectrodes spaced 0.25 mm apart could produce separate phosphenes. This resolution is about five times finer than with surface stimulation. These results suggest that the spatial density of intracortical microelectrodes can be roughly an order of magnitude greater than can be obtained with surface electrodes.

Phosphene movement

For a feasible visual prosthesis, simultaneously generated phosphenes must move as a group with eye movements and retain the same positional orientation. We found that a group of six phosphenes, produced with ICMS, moved with eye movements and maintained the same orientation regardless of eye position. When Dobelle *et al.* (1974) simultaneously stimulated a group of surface electrodes, the subject reported that all phosphenes moved proportionally with eye movement and that their relative position did not change. Thus both surface and intracortical stimulation can produce a pattern of phosphenes that remain stable with respect to each other during eye movements.

Pattern recognition

Due to the breakage of lead wires early in the experiment only limited tests were conducted on pattern recognition. When a group of six phosphenes were produced that formed a series of closely spaced dots with a vertical orientation, the subject felt that the size of the resultant image would be adequate to represent a letter 'I' or one leg of the letter 'M'. These results suggest that a 5×7 array of phosphenes might be adequate to represent the alphabet for a reading aid. To increase reading speed, multiple letters would probably need to be produced simultaneously.

Concluding remarks

The results of this study on visual cortex ICMS in a subject, blind for 22 years, are very encouraging in terms of the feasibility of a visual prosthesis. Because the currents required for the production of phosphenes with intracortical microelectrodes were two to three orders of magnitude smaller than those required for surface stimulation, microelectrodes can be placed about five times closer together before significant interactions occur. In addition, the overall power requirements of an intracortical stimulating system would still be smaller than a lower resolution surface stimulating system.

Further studies with blind subjects are required for optimizing stimulation parameters. In addition, the implantation of several hundred microelectrodes will be essential for determining a blind subject's ability to recognize complex images and evaluate information transfer rates. With this information, it should be possible to determine the feasibility of a visual prosthesis based on ICMS.

Acknowledgements

The authors would like to express their sincere appreciation to our research subject, Mary Anne, whose courage, enthusiasm and dedication will never be forgotten and to her

family for their understanding and steadfast support. We also wish to thank Drs E. Streicher, R. Burke, E. Oldfield, R. Porter and M. Goldstein for their encouragement. The original computer programs for patient testing were developed by S. Charagundla. The National Institutes of Neurological Disorders and Stroke provided support for this project. P. Vallabhanath is an NIH Research Scholar.

References

Bak M, Girvin JP, Hambrecht FT, Kufta CV, Loeb GE, Schmidt EM. Visual sensations produced by intracortical microstimulation of the human occipital cortex. Med Biol Eng Comput 1990; 28: 257–9.

Brindley GS. Sensory effects of electrical stimulation of the visual and paravisual cortex in man. In: Jung R, editor. Handbook of sensory physiology, Vol. VII/3. Berlin: Springer-Verlag, 1973: 583–94.

Brindley GS, Lewin WS. The sensations produced by electrical stimulation of the visual cortex. J Physiol (Lond) 1968; 196: 479–93.

Brindley GS, Rushton DN. Observations on the representation of the visual field on the human occipital cortex. In: Hambrecht FT, Reswick JB, editors. Functional electrical stimulation: applications in neural prostheses. New York: Marcel Dekker, 1977: 261–76.

Brindley GS, Donaldson PEK, Falconer MA, Rushton DN. The extent of the region of occipital cortex that when stimulated gives phosphenes fixed in the visual field. J Physiol (Lond) 1972; 225: 57P–8P.

Dobelle WH, Mladejovsky MG. Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind. J Physiol (Lond) 1974; 243: 553–76.

Dobelle WH, Mladejovsky MG, Girvin JP. Artificial vision for the blind: electrical stimulation of visual cortex offers hope for a functional prosthesis. Science 1974; 183: 440–4.

Dobelle WH, Mladejovsky MG, Evans JR, Roberts TS, Girvin JP. 'Braille' reading by a blind volunteer by visual cortex stimulation. Nature 1976; 259: 111–12.

Evans JR, Gordon J, Abramov I, Mladejovsky MG, Dobelle WH. Brightness of phosphenes elicited by electrical stimulation of human visual cortex. Sens Processes 1979; 3: 82–94.

Geddes LA, Bourland JD. The strength-duration curve. IEEE Trans Biomed Eng 1985; 32: 458–9.

Henderson DC, Evans JR, Dobelle WH. The relationship between stimulus parameters and phosphene threshold/brightness, during stimulation of human visual cortex. Trans Am Soc Artif Intern Organs 1979; 25: 367–71.

Kohfeld DL. Simple reaction time as a function of stimulus intensity in decibels of light and sound. J Exp Psychol 1971; 88: 251–7.

Loeb GE, Bak MJ, Salcman M, Schmidt EM. Parylene as a chronically stable, reproducible microelectrode insulator. IEEE Trans Biomed Eng 1977; 24: 121–8.

Mansfield RJW. Latency functions in human vision. Vision Res 1973; 13: 2219–34.

Mladejovsky MG, Eddington DK, Evans JR, Dobelle WH. A computer-based brain stimulation system to investigate sensory prostheses for the blind and deaf. IEEE Trans Biomed Eng 1976; 23: 286–96.

Pollen DA. Some perceptual effects of electrical stimulation of the visual cortex in man. In: Tower DB, editor. The nervous system, Vol. 2: the clinical neurosciences. New York: Raven Press, 1975: 519–28.

Robblee LS, Lefko JL, Brummer SB. Activated Ir: an electrode suitable for reversible charge injection in saline solution. J Electrochem Soc 1983; 130: 731–3.

Rushton DN, Brindley GS. Short- and long-term stability of cortical electrical phosphenes. In: Rose FC, editor. Physiological aspects of clinical neurology. Oxford: Blackwell, 1977: 123–53.

Rushton DN, Brindley GS. Properties of cortical electrical phosphenes. In: Cool SJ, Smith EL, editors. Frontiers in visual science. New York: Springer-Verlag, 1978: 574–93.

Schmidt EM, Bragg JA. Simple visual reaction time as a means of quantifying brightness of electrically produced phosphenes. Vision Res 1995. In press.

Shakhnovich AR, Ogleznev KY, Abakumova LY, Tishchenko LS, Razumovskii AE. Phosphene formation during electrical stimulation of the visual cortex. Hum Physiol 1982; 8: 34–9.

Received June 1, 1995. Revised August 23, 1995.
Accepted October 18, 1995