Clinical Trial of a Prototype Retinal Prosthesis

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Abstract
A prototype electronic retinal prosthesis has been tested in six blind subjects. The system features an implanted retinal stimulator and an external system for image acquisition, processing, and telemetry. Perceptual thresholds were as follows: S1: 35-1121 µA; S2: 16 – 777 µA; S3: 18 – 412 µA; S4: 20 – 385 µA; S5: 10 – 31 µA; S6: 6 – 41 µA. The subjects in general performed better than chance on simple visual tasks. Neurophysiologic testing showed pupil response to stimulation and localized brain activity.

1. INTRODUCTION
An electronic retinal prosthesis has been proposed as a means to treat retinal degenerative diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). RP and AMD are two leading causes of blindness.[1, 2] The disease primarily attacks the photoreceptor cells of the retina, but leaves the other retinal cells relatively intact. A retinal prosthesis that can electrically activate these remaining cells has shown increasing feasibility through animal and human trials.[3-5] The specific studies reported below involves the first clinical trial of a chronically implanted epiretinal prosthesis. We report here data examining perceptual threshold, visual task performance, and objective measures of visual system response to electrical stimulation.

2. METHODS
This study was conducted under an Investigational Device Exemption granted to Second Sight Medical Products, Inc. by the Food and Drug Agency. The University of Southern California Institutional Review Board approved the study protocol. Informed consent was obtained from volunteers who met the initial study parameters of clinical diagnosis of vision no better than light perception in the worse seeing eye. Potential subjects were screened with a battery of visual function tests including gross electrical stimulation of the eye.[6]

Six subjects who met study criteria were implanted with a Second Sight intraocular epiretinal prosthesis in the eye with worse vision. Implants consist of an extraocular microelectronic device and an intraocular electrode array, connected by a multiwire cable. The electrode array is a 4x4 grid of platinum electrodes embedded in silicone rubber. The electrodes were either 520 or 260 µm in diameter. The electrode array is held to the retina with a small retinal tack. The extraocular microelectronic device is controlled wirelessly by a wearable camera/video processing unit (VPU). The VPU commands stimulus current, which is generated by the microelectronics and delivered to the electrodes on the retina. Electrical stimulation was begun between 7 and 15 days post-operative.

Pupillography was performed on five subjects. All five patients were determined to be without a clinically apparent papillary light reflex (PLR) prior to implantation of the prosthesis. Evaluation of the consensual PLR was performed in a dark room with an infrared video camera monitoring pupil diameter at 29.97 frames/sec. Individual frames were analyzed using video and image editing software. Various electrical stimuli parameters were selected for each patient to allow for characterization of pupil constriction in terms of intensity, frequency, and duration of electrical stimuli. Multiple measurements were recorded and averaged for each set of stimuli parameters.

Multichannel evoked response testing was performed to localize cortical activity evoked by electrical stimulation. After patching the subject’s left eye (prosthesis in right eye), a 64
channel electrode skullcap was placed on her head in a standard 10-20 setup. Using a 500Hz sampling rate, a gain of 250, and a continuous data acquisition mode, all 16 electrodes of the prosthesis were stimulated with biphasic pulses (3ms). Data was recorded for 1140s repeating the stimuli every second. Data from 6 faulty channels (FP2, C2, F6, FT8, T4, TP10) resulting from eye movement or interference from electric fields of the stimulation device were removed. 416 epochs were selected manually and averaged to reject artifacts. For reconstruction from EEG data, a 3 shell sphere model and a warped generic realistic head model (Montreal brain phantom) were used to compute the bioelectric forward model. The warped brain phantom was also used to display results in an anatomical atlas. Point and distributed sources in the interval from 50-450ms were reconstructed using RAP-MUSIC and cortical constrained minimum norms.

3. RESULTS

The device was successfully implanted in all subjects. The intraocular stimulating array remained in position to activate the retina and produce phosphes in all 6 subjects.

Perceptual thresholds varied both within and across subjects. S1: 35-1121 uA; S2: 16 – 777 uA; S3: 18 – 412 uA; S4: 20 – 385 uA; S5: 10 – 31 uA; S6: 6 – 41 uA. Performance using the head mounted video camera suggests that patients are capable of interpreting patterned electrical stimulation. Subjects can localize the position of, or count the number of, high contrast objects with 74-99% accuracy (3 or 4 Alternative Forced Choice (AltFC)), and can discriminate simple shapes such as the orientation of a bar or an “L” (2 or 4AltFC) with 61-80% accuracy. There was a trend towards subjects performing better when stimulated using meaningful patterns of electrical stimulation, rather than all electrodes being stimulated identically. There was no improvement in perceptual acuity when the device was electrically inactive, suggesting that electrical stimulation did not improve the health or function of the retina.

All five patients demonstrated measurable pupil constriction in response to electrical stimulation with their IRP. Electrical stimuli parameters set to produce visual perception for 2 seconds resulted in an average percent pupil constriction of 23% SD 7.5%. The average time to maximum pupil constriction at these settings was 1557 msec SD 327 msec. Average latency of onset of constriction was 510 msec SD 195 msec after the initiation of the stimulus.

Evoked potential recording showed regions of cortex activated by electrical stimulation. Significant activity was noted in the parietal/occipital channels from 200-300 ms as compared to the pre-stimulus data. Minimum norm reconstruction showed activity on the cortical white matter of V1 at 144ms, 204ms, and 292ms with a shift in activation at these three time points from the right to the left and back to the right hemispheres respectively. The source localization technique RAP-MUSIC found 3 sources, 2 close to the visual cortex and 1 corresponding to the stimulation device which was localized to the right side of the subject (figure 2). Subspace correlation for this stimulation source was 0.98 (1=best). From activity in V1, one source was found deep in the cortex sitting between the hemispheres with a subspace correlation of 0.99. The second source close to the visual cortex was found at a shallower position relative to the first source and its subspace correlation was 0.95. The sources are similar to those found when light stimulus is used.

![Figure 1 – The model 1 retinal prosthesis in the eye of a test subject with RP. The implant is visualized through a dilated pupil. The optic disk is to the left of the array. Each electrode in this array is a 520 um diameter disk of platinum. The array is held to the retina with a tack.](image)
Figure 2 EEG source localization. Electrical stimulation was applied to the retina and signals recorded from the cortex. The algorithm RAP-MUSIC was used to solve the inverse problem and define current sources within the cortex. The source above is not in V1, but is in a location similar to that seen with visual evoked potentials.

4. DISCUSSION AND CONCLUSIONS

These results demonstrate that the implanted retinal prosthesis can activate the visual system in blind individuals. Electrical stimulus of the retina was sufficient to activate the afferent limb of the PLR. Pupillography in patients with an IRP provides an objective physiologic measure of prosthesis function. Visual evoked potentials as seen on EEG were used with source localization methods to positively identify two regions of cortex which are activated as a result of artificial electrical stimulation of the retina.


