Temporal properties of visual perception on electrical stimulation of the retina

PEREZ FORNOS, Angelica, et al.

Abstract
To investigate the elementary temporal properties of electrically evoked percepts in blind patients chronically implanted with an epiretinal prosthesis.

Reference

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Elementary visual perception upon electrical stimulation of the retina

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Abstract

We investigated the elementary features of percepts evoked by electrical stimulation of the retina within the context of a multicenter clinical trial evaluating an epiretinal prosthesis chronically implanted in patients blind from retinitis pigmentosa.

Nine subjects were presented with isolated stimuli of variable duration and pulse rate. Stimulation amplitude was set to the upper comfortable level and a group of 2x2 adjacent electrodes was simultaneously activated. First, subjects were asked to verbally describe their visual perception paying particular attention to the time course of brightness. Then, in subsequent trials, they were requested to describe the brightness time dependence using a joystick while auditory feedback of joystick position was provided.

While electrically stimulating the retina for 10s, all subjects described a bright and well-localized percept at stimulus onset. Only 1 out of the 9 tested subjects reported such a bright, well-localized visual sensation during the entire stimulation trial. For the remaining 8 subjects, this bright and well-localized percept faded more or less rapidly and was often followed by a visual sensation described as less bright, poorly localized (covering large areas of the visual field), and having different color. We found significant correlations between the duration of this initial well-localized, high brightness percept and some performance measures (closed-set character recognition rates and grating visual acuity scores). Changing stimulation pulse rate did not have a systematic effect on electrically evoked visual percepts.

Percepts elicited by electrical stimulation of the retina can be very different across subjects. In this study, initial percepts at stimulation onset seemed to be bright and localized enough to reconstruct a patterned image. However, for most subjects this initial phase lasted only a fraction of the entire stimulation duration (in four cases even less than 0.5s). Appropriate image coding under such conditions appears challenging and will require careful selection of stimulation parameters. In the future, it is fundamental to devote significant research efforts towards better understanding the underlying mechanisms of visual perception upon electrical stimulation of the retina. This will allow us to optimize stimulation paradigms and eventually lead to improved patient selection criteria.
Introduction

The first efforts to develop an electronic visual prosthesis started in the late 1960’s (Brindley & Lewin, 1968; Brindley, 1970; Dobelle et al., 1974; Dobelle & Mladejovsky, 1974). Since then, different approaches for restoring vision via electrical stimulation have been proposed. Among these, retinal prostheses are probably the most advanced approach, as demonstrated by ongoing human clinical trials.

Electrical stimulation of the retina is envisioned as a promising means for restoring some kind of visual perception to blind patients suffering from degenerative diseases of the retina like retinitis pigmentosa (RP) and age-related macular degeneration (AMD) (Jacobson & Cideciyan, 2010; Chader et al., 2009). In these diseases, the light sensitive cells in the retina (photoreceptors) are lost while second order retinal neurons (bipolar and ganglion cells) are relatively preserved (Stone et al., 1992; Santos et al., 1997; Kim et al., 2002; Eng et al., 2011). Thus, an electrode array implanted on the inner (epiretinal implant) or outer (subretinal implant) retinal surface could be used to directly stimulate the surviving cells and attempt to transmit an “artificial image” to the brain.

Significant research efforts have paved the way from the initial concept to the development of prototypes ready to be tested in human clinical trials (see e.g., Zrenner, 2002; Hetling & Baig-Silva, 2004; Loewenstein et al., 2004; Alteheld et al., 2007; Tombran-Tink et al., 2007; Bertschinger et al., 2008; Chader et al., 2009). The feasibility of the approach was established through acute in-vivo experiments on normally-sighted subjects and blind patients. The first studies yielded encouraging results (Humayun et al., 1996; Humayun et al., 1999; Weiland et al., 1999). Electrical stimulation was delivered to the surface of the retina under local anesthesia and visual percepts were successfully elicited in all patients tested. In general, the localization of percepts corresponded well to the site of stimulation and when multiple electrode stimulation was used, multiple discrete phosphenes forming shapes corresponding to that of the stimulation pattern were reported. Another group attempted to further investigate perception thresholds and the relationship between the pattern of electrical stimulation and the perception induced (Rizzo et al., 2003a; Rizzo et al., 2003b). Despite important inter-subject variations, this study yielded similar basic proof-of-concept results. These studies were followed by substantial technical efforts to develop devices adequate for chronic human use.

To date, five groups have launched human chronic clinical trials: (1) Optobionics, Inc. (Palo Alto, California, USA; Chow et al., 2004; Chow et al., 2010) carried out the first attempts of implantation on human volunteers. Improvement of visual perception and/or slowing of vision loss were reported in areas adjacent and distant to the implant. Only 4 out of the 10 implanted patients reported intermittent “phosphene-like lights” at the actual location of the implant. These results combined with animal studies (DeMarco et al., 2007) suggested that this device induced some kind of neurotrophic effect, but that the improvements in visual function observed were unrelated to electrically evoked visual percepts. (2) Retina Implant AG (Reutlingen, Germany, Zrenner et al., 2011) led a clinical trial during which eleven blind patients were implanted with a subretinal prosthesis for a period of 4 months. The device consisted in an array of 1500 microphotodiodes (each with its stimulation electronics) and another array of 16 externally controlled (wired) electrodes allowing for direct stimulation of the retina. Results of psychophysical testing have been reported for 3 patients. All three were able to perform simple visual tasks, such as discriminating the orientation of a group of 4 adjacent electrodes stimulated simultaneously (e.g., horizontal, vertical, oblique), detecting light projected onto the microphotodiode array, and localizing bright large objects (e.g., dishes) on a dark table. One patient achieved more complex tasks, like identifying large (5-8cm) single letters and putting them together to form words. (3) IMI Intelligent Medical Implants, GmbH (Bonn, Germany, Richard et al., 2008) launched another clinical trial designed to test their IRIS™ system over a 4-month period. This is an epiretinal device containing 49 electrodes and incorporating a “learning” retina encoder (Eckmiller et al., 2005) that matches the stimulation patterns to those seen by the patient. Unfortunately, little information is available on this trial. Rare public reports indicate that no damage to the retina has been observed in implanted patients and that visual percepts have been elicited at charge densities below 1mC/cm² (Keserue et al., 2008; Matthaei et al., 2011). (4) EpiRet GmbH (Giessen, Germany, Klaue
et al., 2011) conducted a clinical trial designed to evaluate the EPIRET3 visual prosthesis prototype. This epiretinal 25-electrode system was completely implanted within the eye and was tested on 6 volunteers over a 4-week trial. Safety data and surgical techniques have been presented (Roessler et al., 2009). Four patients consistently reported visual sensations at stimulation currents below safety limits. When presented with the same stimulation parameters, the description of percepts varied substantially across subjects and three of them were able to achieve simple pattern discrimination tasks. (5) Finally, the largest clinical trial is led by Second Sight® Medical Products, Inc. (Sylmar, California, USA, Humayun et al., 2010). It is a long-term study (3 to 5 years) offering the possibility of conducting detailed psychophysical testing on human subjects with electrodes implanted chronically on the retina. The device evaluated is the Argus™ II epiretinal prosthesis, a second generation device with 60 retinal electrodes\(^1\). The system includes a camera that captures the visual scene and a microprocessor which wirelessly powers an implanted device and controls the currents that are to be delivered to the retina. To date, 32 patients have been implanted worldwide (Humayun et al., 2009; Humayun et al., 2010). All patients reported the perception of visual phosphenes upon electrical stimulation. Performance results for simple visual tasks, such as localizing a white square presented at random locations on a dark screen (Ahuja et al., 2011) and more complex tasks such as character and word recognition (da Cruz et al., 2010; Stanga et al., 2010) have been presented. Three “star patients” in the trial have even been able to read short, 4-word sentences at average rates of 1-3 words/min (Sahel et al., 2011).

What are the elementary characteristics of visual percepts elicited upon continuous electrical stimulation of the retina? This key issue is interesting for our fundamental understanding of the visual system as well as of practical importance for the development of efficient visual prostheses. There is little background information on this, mainly because most of the human studies cited above were of short duration, which limited the amount of data that could be collected. Since our center in Geneva participates in the Argus™ II clinical trial, we took advantage of the possibility of long-term access to human experimental subjects to study in detail the elementary visual perception evoked by electrical stimulation of the retina and the influence of some basic stimulation parameters.

**Methods**

The Argus™ II Retinal Stimulation System (Second Sight® Medical Products, Inc.; Sylmar, California, USA) comprises both implanted and external elements. The implanted device consists of a 6x10 electrode array (200µm electrode diameter, 575µm center-to-center spacing) tacked to the epiretinal surface and of a titanium case (attached to the outside of the eye with a scleral band) containing a receiver coil and a microprocessor driven stimulator. External components include a body worn video processing unit (VPU) and a pair of glasses on which a miniature camera and a transmitter coil are mounted. Briefly, the image captured by the camera is processed by the VPU and transformed into a custom pattern of electrical stimulation. The transmitter coil powers up and sends commands to the implanted stimulator that finally activates the retinal electrodes.

The Argus™ II Retinal Stimulation System Feasibility Protocol (www.clinicaltrials.gov NCT00407602) was designed and conducted in accordance with the Declaration of Helsinki, ICH Guidelines for Good Clinical Practices (GCPs), ISO 14155-1:2003, and applicable local and federal regulations pertaining to medical device clinical trials. Local approval from the Ministry of Health and from the Ethics Committee was obtained in each of the countries and institutions where the study is being conducted. All implanted subjects had a confirmed history of RP with remaining visual acuity of 2.9 logMAR\(^2\) or worse in both eyes. Written consent was obtained from all subjects and the device was implanted in

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\(^1\) The first generation epiretinal implant by Second Sight® Medical Products, Inc was the Argus™ I implant, a 16-electrode device tested on 6 RP patients (Chader et al., 2009). Patients reported discrete phosphene perception upon stimulation and 3 of them performed better-than-chance on simple visual tasks (Yanai et al., 2007; Caspi et al., 2009).

\(^2\) Measured by an adaptive four alternative forced choice (4FAC) square wave grating test.
the patients’ worse-seeing eye. More details on the trial and the Argus™ II device can be found in previous publications (Humayun et al., 2009; Ahuja et al., 2011).

Subject selection

Nine subjects, selected based on their availability for testing, were recruited from 3 European sites participating in the trial: the Geneva University Hospitals (Geneva, Switzerland), the Moorfields Eye Hospital (London, United Kingdom), and the Quinze-Vingts National Eye Hospital (Paris, France). Details on the subjects are presented in Table 1.

Table 1. Details on the subjects participating in the experiments.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age at Implant [years]</th>
<th>Date implanted</th>
<th>Eye implanted</th>
<th>Eccentricity of the QUAD tested [µm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>Male</td>
<td>72</td>
<td>03-Jun-08</td>
<td>Right</td>
<td>620</td>
</tr>
<tr>
<td>S2</td>
<td>Male</td>
<td>60</td>
<td>11-Feb-08</td>
<td>Right</td>
<td>3640</td>
</tr>
<tr>
<td>S3</td>
<td>Female</td>
<td>27</td>
<td>04-Mar-09</td>
<td>Left</td>
<td>1309</td>
</tr>
<tr>
<td>S4</td>
<td>Male</td>
<td>59</td>
<td>26-Mar-09</td>
<td>Right</td>
<td>5168</td>
</tr>
<tr>
<td>S5</td>
<td>Male</td>
<td>57</td>
<td>22-Jan-09</td>
<td>Right</td>
<td>350</td>
</tr>
<tr>
<td>S6</td>
<td>Male</td>
<td>49</td>
<td>28-May-09</td>
<td>Right</td>
<td>1227</td>
</tr>
<tr>
<td>S7</td>
<td>Male</td>
<td>62</td>
<td>16-Jun-09</td>
<td>Right</td>
<td>408</td>
</tr>
<tr>
<td>S8</td>
<td>Female</td>
<td>45</td>
<td>11-Aug-09</td>
<td>Right</td>
<td>1871</td>
</tr>
<tr>
<td>S9</td>
<td>Male</td>
<td>70</td>
<td>15-Apr-08</td>
<td>Right</td>
<td>2249</td>
</tr>
</tbody>
</table>

Experimental procedure

Subjects were presented with single stimulation trials separated by long pauses of at least 60s. Single trials consisted in biphasic pulse trains (cathodic first, 0.46ms per phase) of variable pulse rates (5, 20, 60 pulses per second - pps) and of variable durations (1s, 10s, 60s). A group of 2x2 adjacent electrodes (QUAD) was simultaneously activated and stimulation amplitude was set to the upper comfortable level (UCL). We used QUADs instead of single electrodes because they elicited larger visual percepts, easier for the subjects to describe accurately, and because their thresholds were lower. For each subject, the tested QUAD was selected: (i) to have low threshold and (ii) to be as close to the fovea as possible. The distance from the center of the tested QUAD to the fovea is presented in Table 1.

During the initial trials in each experimental condition, subjects were asked to verbally describe their visual perception paying particular attention to the time course of brightness. The same stimulus was repeated as many times as necessary, until they felt comfortable with the words they used for their description. They were also asked several questions regarding the time course of brightness.

In subsequent trials subjects were requested to mimic or “plot” the time course of brightness using a joystick (vertical axis only). The resting (central) position of the joystick corresponded to “background brightness” perceived in absence of stimulation. The uppermost (“full push”) position of the joystick corresponded to the highest brightness level perceived during the whole trial. Positions below the central position (“pull positions”) were offered to describe “darker than background” percepts. Joystick position was sampled at 20Hz and mapped to a ±10 scale, where 10 corresponded to the uppermost position (highest brightness perceived during the trial) and 0 to “background brightness”. In addition, auditory feedback of joystick position was provided via a sound of variable pitch (highest joystick position 3200Hz – central joystick position 800Hz – lowest joystick position 200Hz).
For each stimulus condition, subjects were allowed to practice *ad libitum*. Figure 1 presents examples of data collected during the last 5 trials of a 20pps, 10s duration stimulus for S3. The subject systematically perceived a very bright phosphene (10/10 rating) at stimulus onset, but this bright percept lasted only a fraction of the entire stimulus duration. Then, brightness dropped rapidly to 5/10 – 7/10 ratings and slowly faded to background brightness. Stimulus offset was not accurately perceived. As it can be seen from the plots in Figure 1, trial-to-trial reproducibility was remarkable despite the relative complexity of the task. We therefore decided to merge the 5 last trials collected in each condition and to present averaged data (±SD) in all subsequent results presented in this paper.

Finally, to verify the accuracy of subjects in providing a quantitatively precise estimation of brightness with the joystick, they were also asked to provide verbal estimates of brightness in a ±10 scale at critical time points of the response. Figure 1 shows an example of these brightness estimations for S3, superimposed to the averaged joystick plot (green dots in the bottom right plot). As it can be seen in the graph, this particular subject was quite accurate in matching verbal estimations with joystick data.

**Results**

Figure 2 presents the averaged joystick plots (±SD) of each subject for a 10s stimulus at 20pps. They all reported that a well-localized spot in their visual field suddenly lit up at stimulus onset. All subjects attributed a brightness level of 10 to this event. However, out of the 9 subjects tested, only S6 described that this initial well-localized percept remained stable and lasted for the entire duration of the stimulus. For subjects S3, S4, S5, and S8 this initial percept lasted only 2 to 5s, while the remaining subjects (S1, S2, S7, S9) experienced a short duration, flash-like initial percept that lasted less than 0.5s. Afterwards, this well-localized percept “exploded” into a much less localized and lower brightness visual sensation. In addition, some subjects reported a brightness reincrease at stimulus
offset that was most often brief (S1, S2, S4) but could also last several seconds (S7). Finally, note that subject S2 described a percept that became “darker than background” upon ongoing stimulation.

Figure 2. Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 10s duration stimuli presented at 20pps for 9 subjects. Each plot was calculated on the basis of 5 consecutive trials in this condition. The gray dotted plot represents stimulus duration. The green dots in the plots correspond to verbal estimations of brightness made at critical time points. Each panel represents data from a single subject.

The considerable differences observed across subjects cannot be explained by experimental error. First, trial-to-trial reproducibility was very good in all cases (look at the small experimental SDs in each subject’s plot). Second, for every subject we replicated the same measurements in the same experimental condition in sessions that were several weeks apart. The result was always virtually the same (within experimental error). Finally, we also observed that overall subjects were quite accurate when estimating brightness with the joystick, as revealed by the superposition of subjective brightness estimations (green dots in the plots of Fig. 2) over the averaged joystick plots.
From the plots in Figure 2, it is clear that the time course of brightness perception is complex and that, except for one case, it differs substantially from the time course of stimulation. During these joystick experiments we asked subjects to concentrate exclusively on brightness. However, this was a difficult task because they spontaneously and persistently reported that the size and color of percepts also

Table 2. Subjects’ verbal descriptions of the time course of brightness perception to 20pps, 10s duration stimuli. The corresponding average joystick plots (see also Fig. 2) are included for comparison.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Joystick plot</th>
<th>Verbal description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td><img src="chart1.png" alt="Joystick plot" /></td>
<td>Well-localized and bright percept of white color in the beginning followed by gradually decreasing brightness and becoming a very poorly defined blue “fat” line (“a light without shape”). Poorly localized and small reincrease in brightness at stimulus offset.</td>
</tr>
<tr>
<td>S2</td>
<td><img src="chart2.png" alt="Joystick plot" /></td>
<td>Brief (&lt;0.5s), well-localized and bright percept of white/yellow color followed by an immediate decrease in brightness that changed rapidly to a “darker than background” percept. Poorly localized and medium reincrease in brightness at stimulus offset.</td>
</tr>
<tr>
<td>S3</td>
<td><img src="chart3.png" alt="Joystick plot" /></td>
<td>Well-localized and bright percept of yellow/orange color in the beginning, which after 2s-3s gradually decreases in brightness and “grows like an explosion” to fade into the “background”. Stimulus offset difficult to detect.</td>
</tr>
<tr>
<td>S4</td>
<td><img src="chart4.png" alt="Joystick plot" /></td>
<td>Well-localized and bright percept of white/yellow color remaining stable for about 5s which then disappears into the “background”. Well-localized and large reincrease in brightness at stimulus offset.</td>
</tr>
<tr>
<td>S5</td>
<td><img src="chart5.png" alt="Joystick plot" /></td>
<td>Well-localized and bright percept of yellow color in the beginning, fading into a “darker than background” percept at the end. “Background” at stimulus offset.</td>
</tr>
<tr>
<td>S6</td>
<td><img src="chart6.png" alt="Joystick plot" /></td>
<td>Well-localized and bright percept of white/yellow color that remains stable for the entire duration of the stimulus. At stimulus offset the percept changes to a blue light that fades into the “background”.</td>
</tr>
<tr>
<td>S7</td>
<td><img src="chart7.png" alt="Joystick plot" /></td>
<td>Brief (&lt;0.5s), well-localized and bright percept of white color, immediately followed by a “dim reddish light” extending all over the visual field. Poorly localized and small reincrease in brightness at stimulus offset.</td>
</tr>
<tr>
<td>S8</td>
<td><img src="chart8.png" alt="Joystick plot" /></td>
<td>Well-localized and bright percept of white/silvery color in the beginning, followed by a dimmer orange light extending all over the visual field. Stimulus offset difficult to detect.</td>
</tr>
<tr>
<td>S9</td>
<td><img src="chart9.png" alt="Joystick plot" /></td>
<td>Brief (&lt;0.5s), well-localized and bright percept of white/yellow color followed by a very dim « shimmering sensation » that disappears at stimulus offset.</td>
</tr>
</tbody>
</table>
changed during electrical stimulation. It thus appeared mandatory to complement brightness measurements with subjects' verbal reports describing the evolution of the quality (e.g., color and/or shape) of percepts. Table 2 summarizes subjects' descriptions. After analyzing all their comments, two general observations can be drawn. First, it is clear that only initial white/yellow percepts seem to be localized and bright enough to be used to construct a "useful" image. All subjects agreed on that statement. Second, past these initial instants, perception changed into what was most often described as dimmer and "shapeless" percepts covering large regions of the visual field and having different color. This second perceptual phase was qualified as much less useful (if useful at all) to reconstruct an image.

Intuitively, the amount of time during which precise visual information is available to subjects should have an impact on the visual performance that could be achieved with the device. In other words, not only should percepts be sharp and well-localized, they should also last long enough for the brain to be able to reconstruct meaningful images. For example, it seems tremendously difficult to achieve accurate vision with flash-like percepts. We therefore decided to explore whether the duration of the initial percept - which we called the First Well Localized High Brightness (FWLHB) phase - correlated to performance measures gathered in the framework of the clinical trial, especially those having the most stringent spatial vision requirements: closed-set character recognition and grating visual acuity. We also checked for possible correlations with relevant patients' data, such as age at implant and time blind before implant. Finally, due to the heterogeneous distribution of the different cell populations across the retina (see e.g., Dacey, 1994), we also investigated correlations between the duration of the FWLHB phase and the eccentricity of the tested QUAD. The duration of the FWLHB phase was computed as the amount of time that the joystick response remained above a brightness level of 7. This brightness criterion is somewhat arbitrary, but subjects were consistent in reporting that perception became shapeless at lower brightness levels. The results of these statistical analyses are presented in Table 3. None of the patients' data correlated with the duration of the FWLHB phase. The only statistically significant correlations we found were between the duration of the FWLHB phase and performance on closed-set character recognition (r=0.66, p=0.04; see example in Fig. 3) as well as grating visual acuity (r=0.74, p=0.02). While based on a relatively small number of subjects, these significant correlations are consistent with the hypothesis that the duration of the phase during which subjects can experience well-localized, high-brightness percepts is important for performance on tasks requiring pattern recognition (i.e., true multi-channel performance).

**Additional experiments**

Results obtained in the remaining experimental conditions (5pps and 60 pps pulse rates, 1s and 60s duration stimuli) are presented in detail in the Appendix. Summarizing, we observed no systematic effect of stimulation pulse rate on the time course of brightness perception or the duration of the FWLHB phase. One way repeated measures analysis of variance confirmed that, overall, the stimulation pulse rate did not significantly influence the duration of the FWLHB phase ($F_{2,16} = 0.318$, $p = 0.73$). Varying stimulus duration revealed that four subjects (S1, S4, S5, and S8) failed to detect short-duration, 1s stimuli, reporting percepts lasting longer than stimulation. It is interesting to note that
higher stimulation pulse rates and longer duration stimuli tended to enhance (or in some cases revealed) “darker than background” percepts and brightness reincreases at stimulus offset.

Finally, in some subjects, we varied other parameters for control: stimulation amplitude (half and double the UCL), pulse width (3ms per phase), testing the four single electrodes composing the tested QUAD separately, and testing an additional QUAD located as far as possible from the originally tested QUAD. When changing the stimulation amplitude to half or double the UCL, subjects described percepts as less/more bright in general but the time course of perceived brightness was similar (within experimental error). Percepts elicited by single electrodes were always reported as being smaller and less bright, but the time course of perceived brightness was essentially the same (within experimental error). In general, we observed no systematic difference between the joystick plots obtained with a longer pulse width of 3ms or when testing a different QUAD.

Discussion

Nine blind subjects using the Argus™ II Retinal Stimulation System participated in this study. They were asked to characterize their elementary visual perception upon electrical stimulation of their retina. Out of the nine tested subjects, only one reported a well localized, bright percept appearing at stimulus onset and lasting the entire duration of the 10s stimulation trial. The others also reported well localized and high brightness percepts at stimulus onset. However, these percepts did not remain stable and well localized. Instead, they faded more or less rapidly, changing into different visual sensations which were described as being dimmer, poorly localized (covering large areas of the visual field) and having different color. Consequently, we can suppose that in every-day use of their retinal implant these subjects are confronted to a difficult task: that of reconstructing images based on fading and changing percepts.

How much time should a well-localized and stable percept last for the brain to be capable of grasping the necessary information to reconstruct a patterned image? For example, it is well known that in “normal” vision visual information is exclusively gathered during fixations\(^3\), except special situations (Matin, 1974). Normally-sighted viewers have typical fixation durations of 200-250ms during reading and of 260-330ms during scene perception (Reichle et al., 2003; Rayner, 2009). The simple fact of restricting the number of characters visible at once (visual span) during normal reading significantly increases average fixation duration, and more than 400-500ms are required for single character visual spans (Rayner & Bertera, 1979). Therefore, it can be assumed that retinal implant wearers might require significantly longer durations because of the very low resolution and very limited visual field provided by the device. It is interesting to note that the duration of the FWLHB phase correlated

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\(^3\) Fixations are brief periods of time during which the eyes remain fairly stationary, between saccades (Reichle et al., 2003).
significantly with results on a character recognition task: performance was generally poor for durations of the FWLHB phase below 2s, which give an experimental first estimate of the minimum duration required to make practical use of the Argus™ II retinal implant for reading. We also found a similar significant correlation between the duration of the FWLHB phase and the results of the grating visual acuity task.

One fundamental issue to be addressed is why electrical stimulation of the retina in human subjects elicits such variable and dynamic visual percepts. While the contribution of adaptation mechanisms at structures high along the visual pathway cannot be excluded (Carandini & Ferster, 1997; Baccus & Meister, 2004; Mante et al., 2005), there is some evidence suggesting it might be related to the complexity of retinal circuitry. Retinal prosthesis development was based on the fact that bipolar and ganglion cells are relatively spared in retinal degenerations, making them good targets to electrical stimulation (Stone et al., 1992; Santos et al., 1997; Kim et al., 2002; Eng et al., 2011). We do not know which retinal cells are being primarily activated by electrical stimulation of the retina in our subjects, but primarily activating one type of cell or another could have a significant effect on the type/quality of the elicited percepts. On one hand, animal studies suggest that the best strategy to achieve good temporal resolution would be to activate ganglion cells directly and avoid indirect activation through the retinal network (Fried et al., 2006; Sekirnjak et al., 2006; Jensen & Rizzo, 2007; Ryu et al., 2010; Tsai et al., 2009). On the other hand, it has been postulated that the activation of the inner retinal network might result in better spatial resolution than the direct stimulation of ganglion cells (Freeman et al., 2011). Once the best neural targets in severely degenerated retinas have been identified, selective stimulation methods should allow for a better general outcome across patients.

Concerns raised by experts in the field of retinal remodeling should also be considered. In retinal diseases like RP, retinal circuits are progressively remodeled through ongoing neural death, cell migration, and rewiring resulting in anomalous synapses (Stone et al., 1999; Marc et al., 2003; Marc et al., 2007; O’Brien et al., 2010). For example, it has been proposed that patients with some residual cone function might be better candidates for retinal prostheses since the integrity of the inner retinal layers could be better preserved (O’Brien et al., 2010). In future studies, it will be interesting to investigate the relationship between the implanted patients’ particular genotype and the nature of their perceptual response to electrical stimulation of the retina.

Conclusion

The perceptual response to electrical stimulation of the retina can be very different across subjects. Previous studies both in blind and normally-sighted patients have already reported substantial differences in perception thresholds, shape/color of percepts, as well as performance (Humayun et al., 1996; Humayun et al., 1999; Weiland et al., 1999; Rizzo et al., 2003a; Rizzo et al., 2003b; Mahadevappa et al., 2005; de Balthasar et al., 2008; Wilke et al., 2010; Klaue et al., 2011; Zrenner et al., 2011). The present study demonstrates that the elementary percepts evoked by electrical stimulation of the retina have a dynamic behavior that can vary substantially from subject to subject. Furthermore, only initial percepts at stimulation onset seemed to be useful to reconstruct a patterned image. Unfortunately, for several subjects the duration of such initial percepts was very short.

Appropriate coding of a patterned image under such conditions appears challenging and will require careful selection of stimulation parameters. Significant research efforts are required to: (i) understand how and why perceptual responses vary across patients, (ii) determine the optimum stimulation strategies, and (iii) if necessary, improve screening methods so that the candidates having the best rehabilitation prospects can be appropriately identified.

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References


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Appendix to:

**Elementary visual perception upon electrical stimulation of the retina**

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**Varying stimulation pulse rate**

Figure A1 presents the averaged joystick plots (±SD) of each subject for a 10s stimulus at 5pps. Subjects S6, S8, and S9 reported similar joystick plots at this lower stimulation pulse rate than at 20pps (compare to Fig. 2 in the main article). For the remaining 6 subjects, lowering the stimulation pulse rate influenced the time course.

![Figure A1](image)

**Figure A1.** Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 10s duration stimuli presented at 5pps for 9 subjects. Each plot was calculated on the basis of the last 5 consecutive trials in this condition. The gray dotted plot represents stimulus duration. The green dots in the plots correspond to verbal brightness estimations made at critical time points. Each panel represents data from a single subject.
of brightness in different ways. For example, at 5pps S1 reported a substantially longer-duration percept (double the stimulus duration) than at 20pps. In contrast, in the same stimulation condition S3 reported a substantially shorter-duration percept than at 20pps. Finally, at 5pps both “darker than background” percepts and reincreases in brightness observed at stimulus offset were practically suppressed.

Figure A2 presents the averaged joystick plots (±SD) of each subject for a 10s stimulus at 60pps. Stimulating at a higher pulse rate had no systematic effect on the time course of brightness perception. The joystick responses of subjects S6, S8, and S9 were similar to those obtained at the two lower stimulation pulse rates. Subjects S3 and S4 reported substantially shorter-duration percepts at 60pps than at 20pps. Subjects S2 and S5 reported enhanced “darker than background” percepts. Finally, the 60pps stimulation pulse rate tended to augment (or in some cases reveal) the brightness reincreases observed at stimulus offset. It is interesting to note that S4 reported that at 60pps the brightness reincr ease appearing at stimulus offset was considerably brighter than the initial flash-like percept appearing at stimulus onset.

Figure A2. Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 10s duration stimuli presented at 60pps for 9 subjects. Each plot was calculated on the basis of the last 5 consecutive trials in this condition. The gray dotted plot represents stimulus duration. The green dots in the plots correspond to verbal brightness estimations made at critical time points. Each panel represents data from a single subject.
Varying stimulus duration

Figure A3 presents the averaged joystick plots (±SD) of each subject for a 1s stimulus at 20pps. An interesting observation from this figure is that 3 out of the 9 tested subjects reported percepts that lasted longer than the stimulation. This was most striking for S1 and S8, where brighter than background percepts lasted as long as 10s. At this shorter stimulus duration, S2 was the only subject to report a reincrease in brightness at stimulation offset.

![Averaged joystick plots for 1s stimulus duration](image)

**Figure A3.** Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 1s duration stimuli presented at 20pps for 9 subjects. Note that the timescale used in the plots is different than in the previous figures. Each plot was calculated on the basis of the last 5 consecutive trials in this condition. The gray dotted plot represents stimulus duration. The green dots in the plots correspond to verbal brightness estimations made at critical time points. Each panel represents data from a single subject.

Figure A4 presents the averaged joystick plots (±SD) of each subject for a 60s stimulus at 20pps. Five subjects (S1, S3, S7, S8, S9) reported percepts whose time course was similar to that observed at 10s. For the remaining subjects, a few observations deserve to be highlighted. S2 described, after the initial flash-like and “darker than background” percepts, a brightness reincrease that disappeared beyond 30s of stimulation. S5 described a “darker than background” percept after approximately 5s which remained fairly stable for the remainder of the stimulation. Subjects S4 and S6 reported that, after the initial stable percepts that lasted approximately 5 and 12s, percepts disappeared completely for the remainder of the stimulation. It is interesting to note that S6,...
only subject who reported the “ideal” time course of brightness for 10s duration stimuli at 20 pps (i.e., a stable and bright percept lasting for the entire duration of stimulation), observed a fading percept beyond 12s of ongoing electrical stimulation. In other words, for very long stimulation durations, this subject’s perception also had a dynamic and fading behavior, as observed for the other 8 subjects. Finally, the brightness increases observed at stimulus offset were generally enhanced at this long stimulus duration.

Figure A4. Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 60s duration stimuli presented at 20pps for 9 subjects. Note that the timescale used in the plots is different than in the previous figures. Each plot was calculated on the basis of the last 5 consecutive trials in this condition. The gray dotted plot represents stimulus duration. The green dots in the plots correspond to verbal brightness estimations made at critical time points. Each panel represents data from a single subject.

FWLHB phase analysis

Figure A5 compares the duration of the FWLHB percept for all 9 subjects, at the three pulse rates tested. We did not observe a clear and systematic effect of the stimulation pulse rate on the duration of the FWLHB percepts. Subjects S2, S5, S7, and S9 showed virtually identical results in all stimulation conditions. For the others, changing the stimulation pulse rate influenced the duration of the FWLHB percept in different ways. For
example, subjects S1 and S6 had the longest FWLHB percept durations at 5pps. The longest FWLHB percept durations were obtained at 20pps for subjects S3 and S4, and at 60pps for subject S8. These results suggest that for some subjects there is an “optimum” stimulation pulse rate for obtaining the best FWLHB percept duration results.

Figure A5. Mean duration [±SEM] of the FWLHB phase per subject for 10s duration stimuli at 5pps (blue bars), 20pps (red bars), and 60pps (green bars). This value was calculated as the duration of the first interval during which the joystick response remained ≥7. Results were computed on the basis of 5 consecutive trials per subject and per condition. The black solid reference line shows the duration of the stimulus.

1 Note that in the case of S6 this results in a percept lasting approximately 3s longer than the stimulation.