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Angélica Pérez Fornos[1], Jörg Sommerhalder[1], Lyndon da Cruz[2], Jose Alain Sahel[3], Saddek Mohand-Said[3], Farhad Hafezi[1], and Marco Pelizzone[1]

[1] Ophthalmology Clinic, Geneva University Hospitals, Geneva, Switzerland
[2] Vitreoretinal Surgery, Moorfields Eye Hospital, London, United Kingdom
[3] Ophthalmology Department, Quinze-Vingts National Eye Hospital, Paris, France

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Corresponding Author:

Angélica Pérez Fornos, PhD
Geneva University Hospitals
4 Rue Gabrielle-Perret-Gentil
1211 Geneva 14
Tel: +41(22)382-28290
Fax: +41(22)372-8287
Angelica.Perez-Fornos@hcuge.ch

Temporal properties of visual perception upon electrical stimulation of the retina

Angélica Pérez Fornos[1], Jörg Sommerhalder[1], Lyndon da Cruz[2], Jose Alain Sahel[3], Saddek Mohand-Said[3], Farhad Hafezi[1], and Marco Pelizzone[1]

[1] Ophthalmology Clinic, Geneva University Hospitals, Geneva, Switzerland
[2] Vitreoretinal Surgery, Moorfields Eye Hospital, London, United Kingdom
[3] Ophthalmology Department, Quinze-Vingts National Eye Hospital, Paris, France

Abstract

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

Methods: 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 described the brightness time dependence using a joystick while auditory feedback of joystick position was provided.

Results: All subjects described a bright, well-localized percept at stimulus onset. Only 1 subject reported such a bright, well-localized visual sensation during an entire 10 seconds stimulation trial. For the remaining 8 subjects, it faded more or less rapidly (in 4 cases <0.5s) and was often followed by a percept described as less bright, poorly localized, and having different color. Only initial percepts at stimulation onset seemed bright and localized enough to reconstruct a patterned image. Changing stimulation pulse rate influenced the time course of perception only in some cases but the effect was not systematic.

Conclusion: Percepts differed considerably across subjects, probably due to the considerable variations in the progression and remodeling processes associated to the disease. Appropriate coding of a patterned image under such conditions appears challenging. Further research of the underlying mechanisms of visual perception upon electrical stimulation of the retina is required to optimize stimulation paradigms and to better establish patient selection criteria.

Introduction

The first efforts to develop an electronic visual prosthesis started in the late 1960's[1–4]. 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)[5,6]. 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[7–10]. 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., [6,11–16]). 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[17–19]. 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[20,21]. 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.[22,23] (Palo Alto, California, USA) 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[24] 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[25] (Reutlingen, Germany) 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 G, et al. *IOVS* 2008; 49: ARVO E-Abstract 1786) 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[26] that matches the stimulation patterns to those seen by the patient. Unfortunately, little information is available on this trial. Rare public reports[27] (Keserue M, et al. *IOVS* 2008; 49: ARVO E-Abstract 1785) 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/cm^2. (4) EpiRet GmbH[28] (Giessen, Germany) 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[29]. 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 MS, et al. *IOVS* 2010; 51: ARVO E-Abstract 2022). 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[32,33]. 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[34] and more complex tasks such as character and word recognition (da Cruz L, et al. *IOVS* 2010; 51: ARVO E-Abstract 2023; Stanga PE, et al. *IOVS* 2010; 51: ARVO E-Abstract 426) have been presented. Three “star patients” in the trial have even been able to read short 4-word sentences, two of them reaching maximum rates of 2-5 words/min (Sahel JA, et al. *IOVS* 2011; 52: ARVO E-Abstract 3420).

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

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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[6]. Patients reported discrete phosphene perception upon stimulation and 3 of them performed better-than-chance on simple visual tasks[30,31].

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 temporal properties of the 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 Governmental Health Agencies 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 the patients' worse-seeing eye. More details on the trial and the Argus™ II device can be found in previous publications[32,34].

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.

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

** Estimated from fundus photos.*

[2] Measured by an adaptive four alternative forced choice (4FAC) square wave grating test[31].

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 rate (5, 20, 60 pulses per second - pps). To complete the characterization of the time-course of brightness perception 3 stimulus durations were evaluated (1, 10, 60 seconds - s). 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 (i.e., to maximize the available dynamic range[3]) 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; see Fig. 1). 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

[3] Please note that the upper safety limit for the system (during psychophysical testing in the clinic) is of 1mC/cm^2. We never exceeded this limit in any of the experiments mentioned in the manuscript.

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).

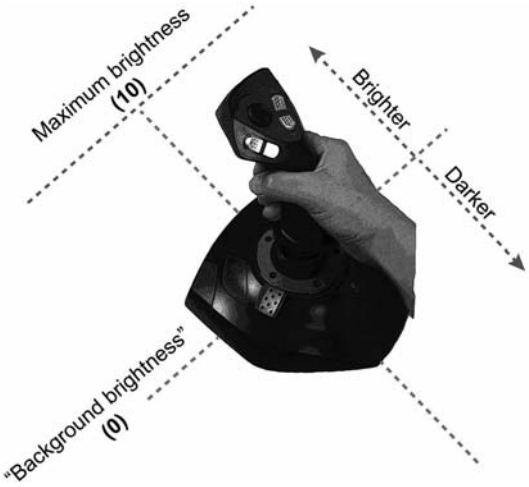


Figure 1. Plotting the time course of brightness: subjects had to describe the variations in the brightness of percepts during a stimulation trial using the vertical axis of a joystick. The central position of the joystick corresponded to "background brightness" while "push" and "pull" positions were used to correspondingly depict percepts brighter or darker than "background brightness".

For each stimulus condition, subjects were allowed to practice *ad libitum*. Figure 2 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 2, 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 2 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.

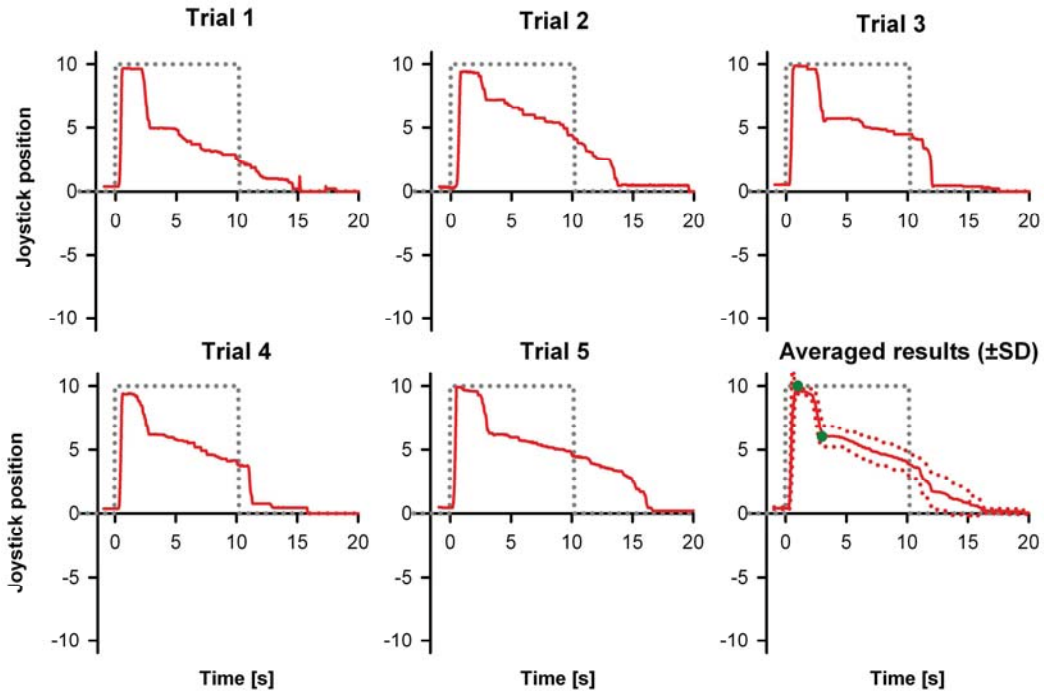


Figure 2. Plots of joystick position versus time for 5 consecutive trials as well as their corresponding averaged result (±SD – red dotted lines) to 20pps-10s duration stimuli for subject S3. Joystick responses are presented as red lines and stimulus duration is represented as a gray dotted line. The green dots in the averaged joystick plot (bottom right) correspond to verbal brightness estimations made at critical time points.

Results

Figure 3 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 lit up immediately 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.

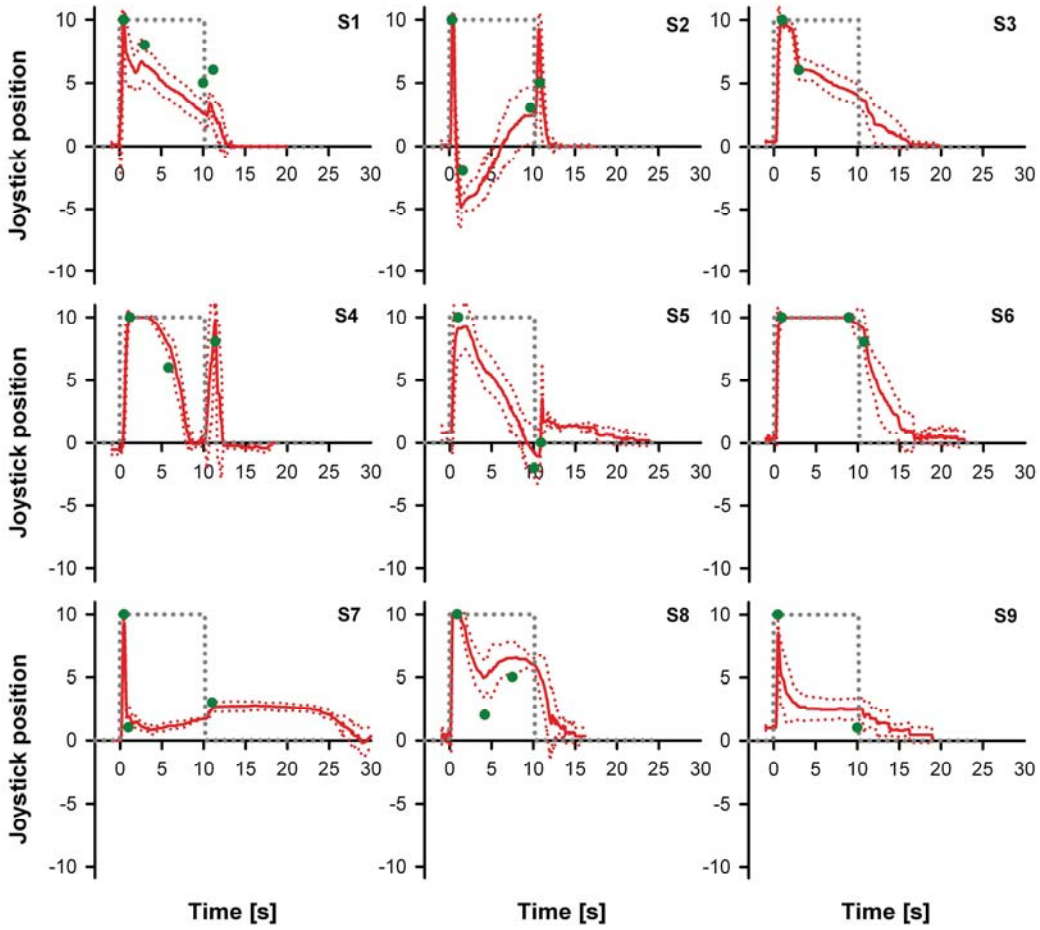


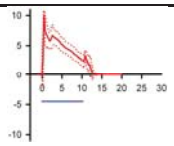
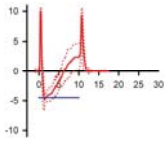
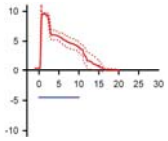
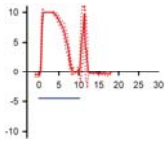
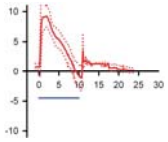
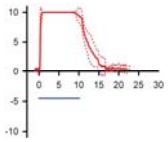
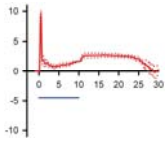
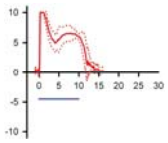
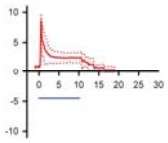
Figure 3. Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 10s duration stimuli presented at 20pps for 9 subjects. Each plot was calculated on the basis of 5 consecutive trials in this condition. The gray dotted plot represents stimulus duration. The green dots in the 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. 3) over the averaged joystick plots.

From the plots in Figure 3, 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 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.

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. 3) are included for comparison.

Subject	Joystick plot	Verbal description
S1		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.
S2		Brief (<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.
S3		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.
S4		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.
S5		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.
S6		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".
S7		Brief (<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.
S8		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.
S9		Brief (<0.5s), well-localized and bright percept of white/yellow color followed by a very dim « shimmering sensation » that disappears at stimulus offset.

Varying stimulation pulse rate

Figure 4 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. 3). For the remaining 6 subjects, lowering the stimulation pulse rate influenced the time course 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

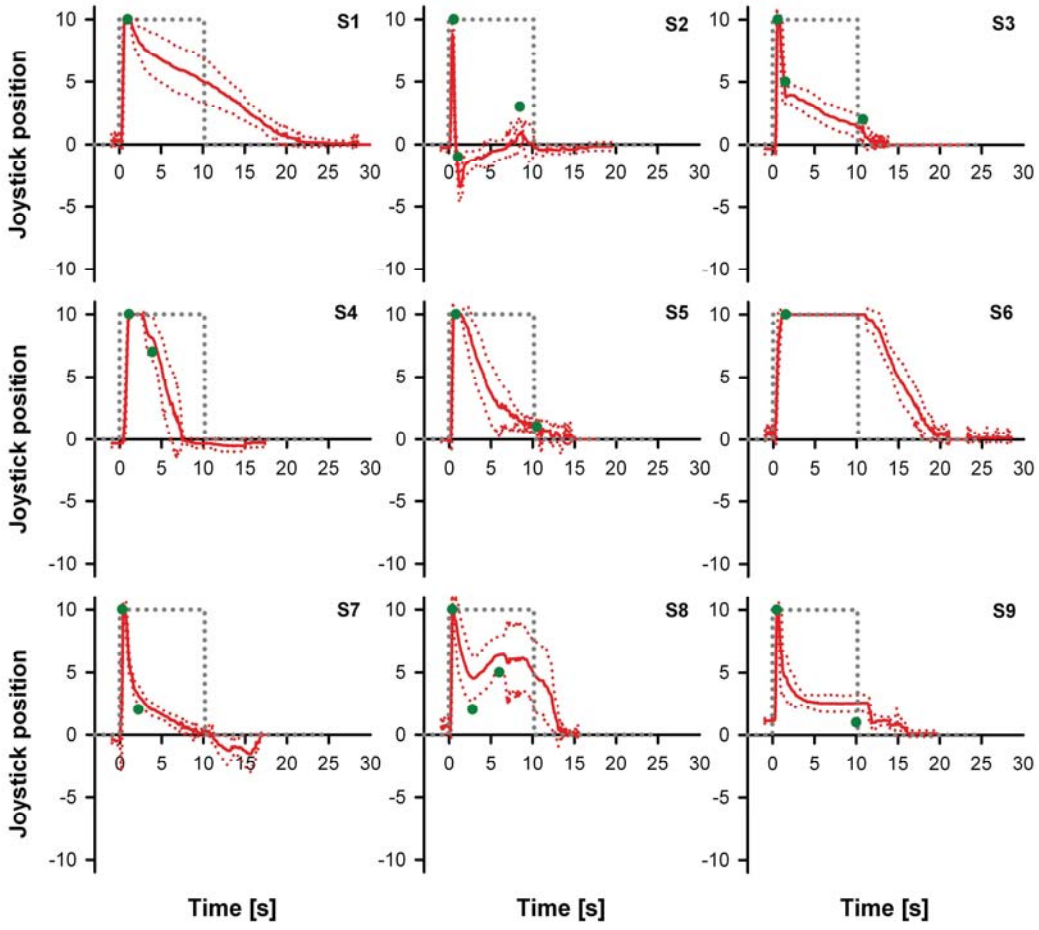


Figure 4. Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 10s duration stimuli presented at 5pps for 9 subjects. Each plot was calculated on the basis of the last 5 consecutive trials in this condition. The gray dotted plot represents stimulus duration. The green dots in the plots correspond to verbal brightness estimations made at critical time points. Each panel represents data from a single subject.

20pps. Finally, at 5pps both “darker than background” percepts and reincreases in brightness observed at stimulus offset at 20pps were practically suppressed.

Figure 5 presents the averaged joystick plots (±SD) of each subject for a 10s stimulus at **60pps**. The joystick responses of subjects S6, S8, and S9 were similar to those obtained at the two lower stimulation pulse rates. For the remaining subjects, the effect of increasing the pulse rate was again variable. Subjects S3 and S4 reported substantially shorter-duration percepts at 60pps than at 20pps. Subjects S2 and S5 reported enhanced “darker than background"

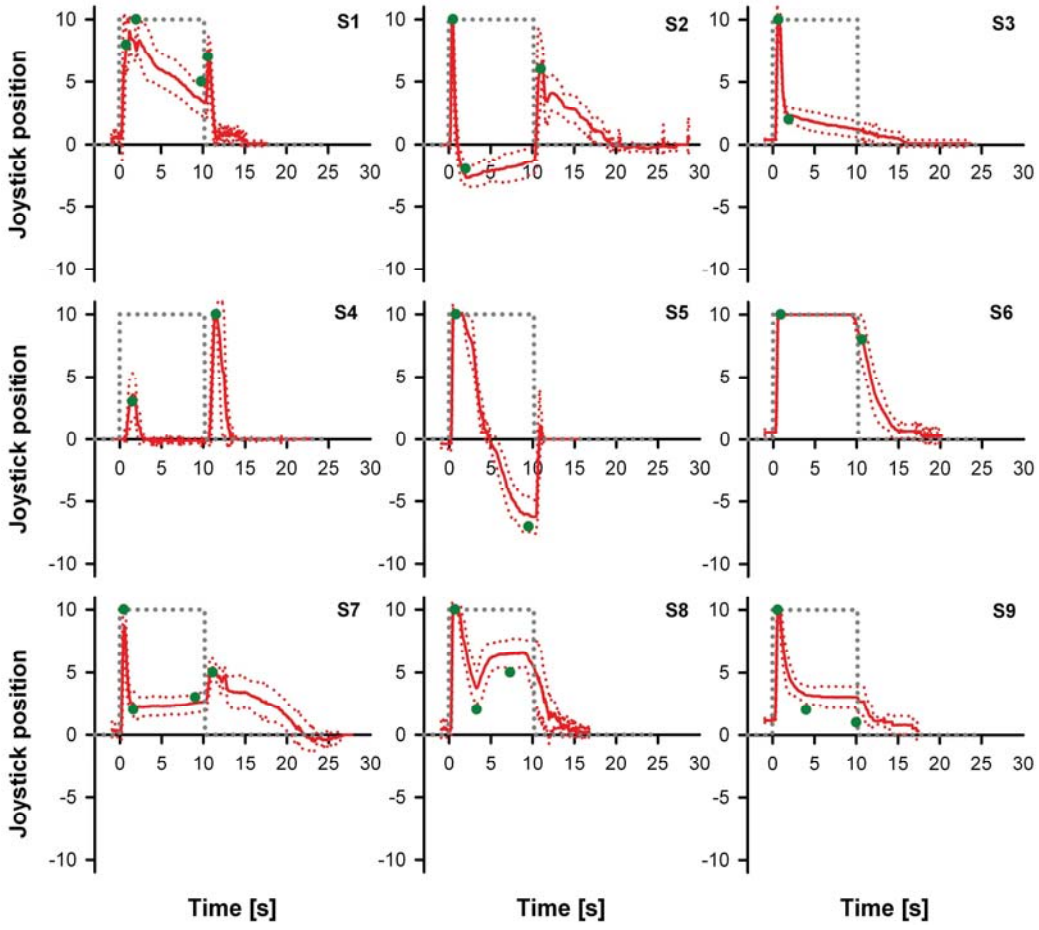


Figure 5. Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 10s duration stimuli presented at 60pps for 9 subjects. Each plot was calculated on the basis of the last 5 consecutive trials in this condition. The gray dotted plot represents stimulus duration. The green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

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 reincrease appearing at stimulus offset was considerably brighter than the initial flash-like percept appearing at stimulus onset.

Varying stimulus duration

Figure 6 presents the averaged joystick plots (±SD) of each subject for a **1s** stimulus at 20pps.

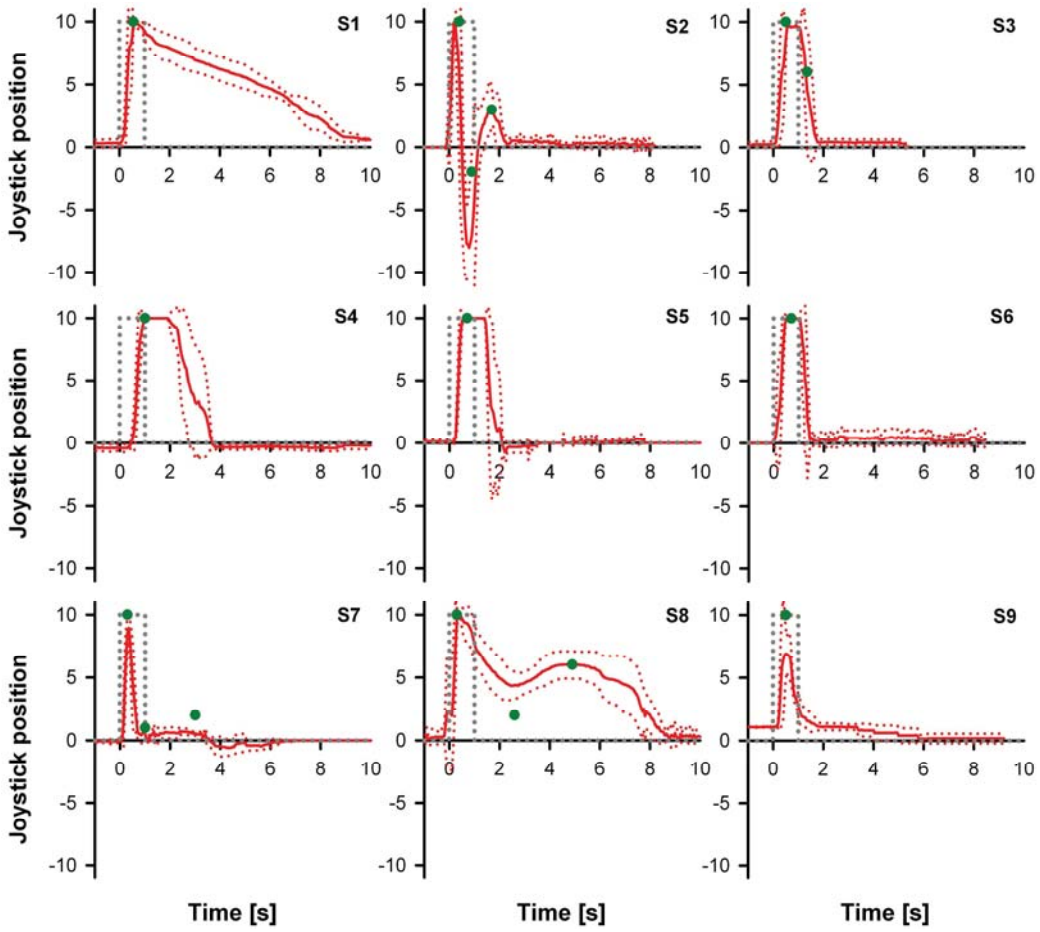


Figure 6. Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 1s duration stimuli presented at 20pps for 9 subjects. Note that the timescale used in the plots is different than in the previous figures. Each plot was calculated on the basis of the last 5 consecutive trials 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.

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.

Figure 7 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

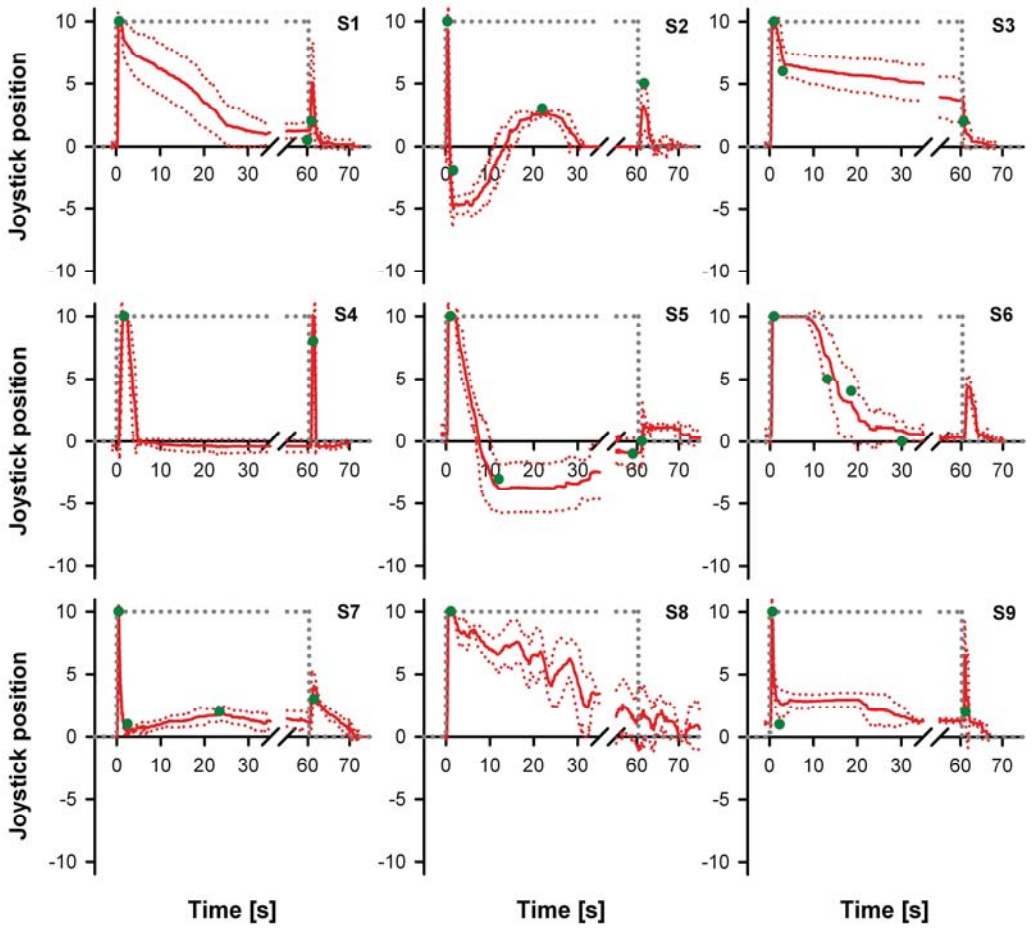


Figure 7. Averaged joystick responses (red solid plots) ±SD (red dotted plots) versus time to 60s duration stimuli presented at 20pps for 9 subjects. Note that the timescale used in the plots is different than in the previous figures. Each plot was calculated on the basis of the last 5 consecutive trials 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.

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, the only subject who reported the “ideal” time course of brightness for 10s duration stimuli at 20pps (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.

Additional experiments

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). As observed when varying stimulation pulse rate, we observed no general, 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 a 10s stimulation trial. The others also reported well localized and high brightness percepts at stimulus onset, but 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.

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. Then, 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? It is well known that in “normal” vision visual information is exclusively gathered during fixations[4], except special situations[35]. Normally-sighted viewers have typical fixation durations of 200-250ms during reading and of 260-330ms during scene perception[36,37]. 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[38]. Current electronic retinal

[4] Fixations are brief periods of time during which the eyes remain fairly stationary, between saccades[36].

prostheses provide very low resolution and a very limited “visual span”. Therefore, patients using these devices might require significantly longer “fixation” or “perceptual” times to grasp the necessary information. Indeed, we observed that in the visual tasks tested within the framework of the clinical trial[32,33], performance was generally poor for subjects where the duration of the initial, well-localized and high brightness percept was below 2s. This was particularly true for tasks having the most stringent spatial vision requirements such as character recognition (da Cruz L, et al. *IOVS* 2010; 51: ARVO E-Abstract 2023) and grating visual acuity[31]. For example, the best score achieved to date in the grating visual acuity test[33] (1.8 logMAR) was achieved by S6, the only subject for whom the initial well-localized percept lasted the entire duration of the 10s stimulation trial. To our knowledge, none of the subjects participating in this study that experience flash-like percepts have been able to score reliably on this test (1.6 – 2.9 logMAR scale). We did not perform statistical analyses against performance data given the limited dataset available. However, this observation suggests a “minimum percept duration” to make practical use of the Argus™ II retinal implant.

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[39–41], 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 RP[7,8,10] and AMD[9], making them good targets to electrical stimulation. 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[42–46]. 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[47]. Once the best neural targets in severely degenerated retinas have been identified, selective stimulation methods should allow for a better general outcome across patients.

Another interesting observation to be highlighted is the variability observed in the results, within and across subjects. In a given condition, the time course of brightness perception described by subjects was considerably different from one to the other. In addition, varying stimulation pulse rate had very different effects in each subject. This non-systematic behavior is very difficult to interpret. Therefore, to further explore these variations we tried to analyze separately the initial well-localized, high brightness percept described by subjects as "useful" to construct an image. We calculated the duration of the initial "stable" percept - which we called the First Well Localized High Brightness (FWLHB) phase – at the three stimulation pulse rates tested. 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. Figure 8 compares the duration of the FWLHB percept for all 9 subjects, at the three pulse rates tested. The effect of stimulation pulse rate on the duration of the FWLHB percepts was also very variable. 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[5] 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. 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). Yet, an

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

interesting outcome of this analysis is that, for some subjects, there is an “optimum” stimulation pulse rate for obtaining the best FWLHB percept duration results.

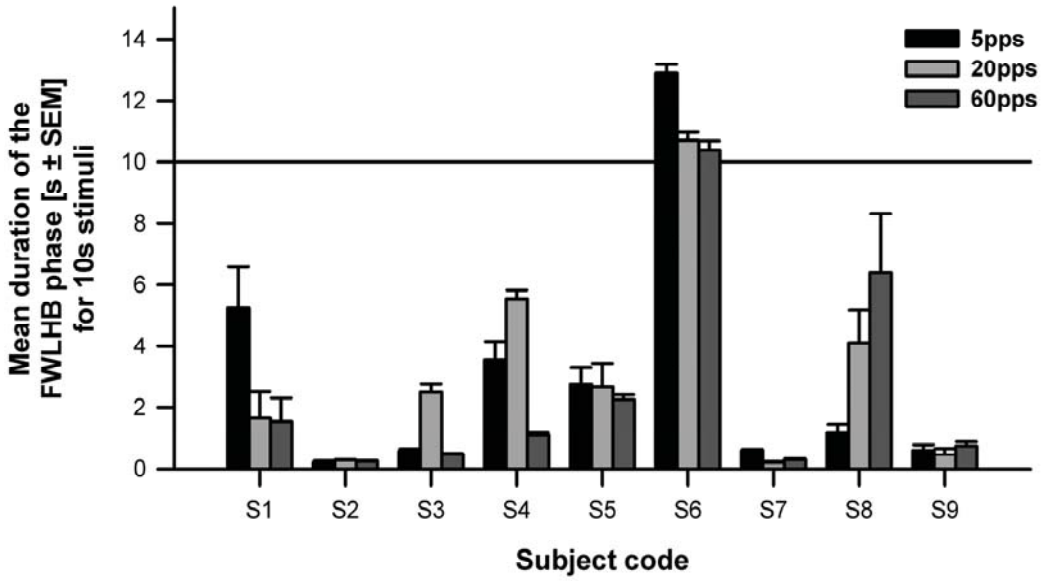


Figure 8. Mean duration [s±SEM] of the FWLHB phase per subject for 10s duration stimuli at 5pps (black bars), 20pps (light gray bars), and 60pps (dark gray bars). This value was calculated as the duration of the first interval during which the joystick response remained ≥7. Results were computed on the basis of 5 consecutive trials per subject and per condition. The black solid reference line shows the duration of the stimulus.

What are reasons underlying this large variability? We checked for possible correlations between the duration of the FWLHB phase and relevant patients’ data, such as age at implant and time blind before implant. Due to the heterogeneous distribution of the different cell populations across the retina[48], we also investigated correlations between the duration of the FWLHB phase and the eccentricity of the tested QUAD. None of these variables correlated with the duration of the FWLHB phase (see Table 3). All the previous non-systematic observations go in line with concerns raised by experts in the field of retinal remodeling. In retinal diseases like RP, retinal circuits are progressively remodeled through ongoing neural death, cell migration, and rewiring resulting in anomalous synapses[49–52]. Furthermore, there is considerable variation in the progression of the disease and the remodeling process depending on the different RP variations. If the retinal circuitry is significantly remodeled and in different ways for

Table 3. Simple (Pearson's) correlations of relevant patients' and performance data versus the duration of the FWLHB phase for 10s duration stimuli at 20pps.

Age at implant	R = -0.34; p = 0.36
Time blind before implant	R = 0.58; p = 0.10
QUAD eccentricity	R = 0.09; p = 0.80

each subject, it is reasonable to assume that the perceptual response to electrical stimulation would also differ considerably. Indeed, 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[52]. In future studies, the relationship between the implanted patients' particular phenotype-genotype and the nature of their perceptual response to electrical stimulation of the retina should be thoroughly investigated. In addition, other retinal degenerations suitable for rehabilitation with a retinal prosthesis (e.g., AMD) should also be considered.

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[17–21,25,28,53,54]. The present study demonstrates that the temporal properties of 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

1. Brindley GS, Lewin WS. The visual sensations produced by electrical stimulation of the medial occipital cortex. *J Physiol (Lond)* 1968;194:54-55P.
2. Brindley GS, Lewin WS. The sensations produced by electrical stimulation of the visual cortex. *J Physiol (Lond)* 1968;196:479-493.
3. Dobelle WH, Mladejovsky MG, Girvin JP. Artifical vision for the blind: electrical stimulation of visual cortex offers hope for a functional prosthesis. *Science* 1974;183:440-444.
4. 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;243:553-576.
5. Jacobson SG, Cideciyan AV. Treatment Possibilities for Retinitis Pigmentosa. *N Engl J Med* 2010;363:1669-1671.
6. Chader GJ, Weiland J, Humayun MS. Artificial vision: needs, functioning, and testing of a retinal electronic prosthesis. In: *Neurotherapy: Progress in Restorative Neuroscience and Neurology* Elsevier; 2009;Vol.175:317-332.

7. Stone JL, Barlow WE, Humayun MS, de Juan Jr E, Milam AH. Morphometric analysis of macular photoreceptors and ganglion cells in retinas with retinitis pigmentosa. *Arch Ophthalmol* 1992;110:1634-1639.

8. Santos A, Humayun MS, de Juan Jr E, Greenberg RJ, Marsh MJ, Klock IB, Milam AH. Preservation of the inner retina in retinitis pigmentosa. A morphometric analysis. *Arch Ophthalmol* 1997;115:511-515.

9. Kim SY, Sadda S, Humayun MS, de Juan Jr E, Melia BM, Green WR. Morphometric analysis of the macula in eyes with geographic atrophy due to age-related macular degeneration. *Retina (Philadelphia, Pa)* 2002;22:464-470.

10. Eng JG, Agrawal RN, Tozer KR, Ross-Cisneros FN, Dagnelie G, Greenberg RJ, Chader GJ, Weiland JD, Rao NA, Sadun AA, Humayun MS. Morphometric Analysis of Optic Nerves and Retina from an End-Stage Retinitis Pigmentosa Patient with an Implanted Active Epiretinal Array. *Invest Ophthalmol Vis Sci* 2011;52:4610-4616.

11. Zrenner E. Will retinal implants restore vision? *Science* 2002;295:1022-1025.

12. Hetling JR, Baig-Silva MS. Neural prostheses for vision: designing a functional interface with retinal neurons. *Neurol Res* 2004;26:21-34.

13. Loewenstein JI, Montezuma SR, Rizzo JF. Outer retinal degeneration: an electronic retinal prosthesis as a treatment strategy. Arch Ophthalmol 2004;122:587-596. Available at: [Accessed January 19, 2011].

14. Alteheld N, Roessler G, Walter P. Towards the bionic eye--the retina implant: surgical, opthalmological and histopathological perspectives. *Acta Neurochir Suppl* 2007;97:487-493.

15. Tombran-Tink J, Barnstable CJ, Rizzo JF eds. Visual Prosthesis and Ophthalmic Devices New Hope in Sight. Totowa, New Jersey, USA: Humana Press; 2007.

16. Bertschinger DR, Beknazar E, Simonutti M, Safran AB, Sahel JA, Rosolen SG, Picaud S, Salzmann J. A review of in vivo animal studies in retinal prosthesis research. *Graefes Arch Clin Exp Ophthalmol* 2008;246:1505-1517.

17. Humayun MS, de Juan Jr E, Dagnelie G, Greenberg RJ, Propst RH, Phillips DH. Visual perception elicited by electrical stimulation of retina in blind humans. *Arch Ophthalmol* 1996;114:40-46.

18. Humayun MS, de Juan E Jr, Weiland JD, Dagnelie G, Katona S, Greenberg R, Suzuki S. Pattern electrical stimulation of the human retina. *Vision Res* 1999;39:2569-2576.

19. Weiland JD, Humayun MS, Dagnelie G, de Juan Jr E, Greenberg RJ, Iliff NT. Understanding the origin of visual percepts elicited by electrical stimulation of the human retina. *Graefes Arch Clin Exp Ophthalmol* 1999;237:1007-1013.

20. Rizzo JF 3rd, Wyatt J, Loewenstein J, Kelly S, Shire D. Methods and perceptual thresholds for short-term electrical stimulation of human retina with microelectrode arrays. *Invest Ophthalmol Vis Sci* 2003;44:5355-5361.

21. Rizzo JF 3rd, Wyatt J, Loewenstein J, Kelly S, Shire D. Perceptual efficacy of electrical stimulation of human retina with a microelectrode array during short-term surgical trials. *Invest Ophthalmol Vis Sci* 2003;44:5362-5369.

22. Chow AY, Bittner AK, Pardue MT. The artificial silicon retina in retinitis pigmentosa patients (an american ophthalmological association thesis). *Trans Am Ophthalmol Soc* 2010;108:120-154.

23. Chow AY, Chow VY, Packo KH, Pollack JS, Peyman GA, Schuchard R. The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. *Arch Ophthalmol* 2004;122:460-469.

24. DeMarco PJ, Yarbrough GL, Yee CW, McLean GY, Sagdullaev BT, Ball SL, McCall MA. Stimulation via a Subretinally Placed Prosthetic Elicits Central Activity and Induces a Trophic Effect on Visual Responses. *Invest Ophthalmol Vis Sci* 2007;48:916-926.

25. Zrenner E, Bartz-Schmidt KU, Benav H, Besch D, Bruckmann A, Gabel VP, Gekeler F, Greppmaier U, Harscher A, Kibbel S, Koch J, Kusnyerik A, Peters T, Stingl K, Sachs H, Stett A, Szurman P, Wilhelm B, Wilke R. Subretinal electronic chips allow blind patients to read letters and combine them to words. *Proc Biol Sci* 2011;278:1489-1497.

26. Eckmiller R, Neumann D, Baruth O. Tunable retina encoders for retina implants: why and how. *J Neural Eng* 2005;2:S91-S104.

27. Matthaei M, Zeitz O, Keserü M, Wagenfeld L, Hornig R, Post N, Richard G. Progress in the Development of Vision Prostheses. *Ophthalmologica* 2011;225:187-192.

28. Klauke S, Goertz M, Rein S, Hoehl D, Thomas U, Eckhorn R, Bremmer F, Wachtler T. Stimulation with a Wireless Intraocular Epiretinal Implant Elicits Visual Percepts in Blind Humans. *Invest Ophthalmol Vis Sci* 2011;52:449 -455.

29. Roessler G, Laube T, Brockmann C, Kirschkamp T, Mazinani B, Goertz M, Koch C, Krisch I, Sellhaus B, Trieu HK, Weis J, Bornfeld N, Röthgen H, Messner A, Mokwa W, Walter P. Implantation and Explantation of a Wireless Epiretinal Retina Implant Device: Observations during the EPIRET3 Prospective Clinical Trial. *Invest Ophthalmol Vis Sci* 2009;50:3003-3008.

30. Yanai D, Weiland JD, Mahadevappa M, Greenberg RJ, Fine I, Humayun MS. Visual Performance Using a Retinal Prosthesis in Three Subjects With Retinitis Pigmentosa. *Am J Ophthalmol* 2007;143:820-827.

31. Caspi A, Dorn JD, McClure KH, Humayun MS, Greenberg RJ, McMahon MJ. Feasibility study of a retinal prosthesis: spatial vision with a 16-electrode implant. *Arch Ophthalmol* 2009;127:398-401.

32. Humayun MS, Dorn JD, Ahuja AK, Caspi A, Filley E, Dagnelie G, Salzmann J, Santos A, Duncan J, daCruz L, Mohand-Said S, Eliott D, McMahon MJ, Greenberg RJ. Preliminary 6 month results from the Argus II epiretinal prosthesis feasibility study. *Conf Proc IEEE Eng Med Biol Soc* 2009;2009:4566-4568.

33. Humayun MS, Dorn JD, da Cruz L, Dagnelie G, Sahel JA, Stanga PE, Cideciyan AV, Duncan JL, Eliott D, Filley E, Ho AC, Santos A, Safran AB, Arditi A, Del Priore LV, Greenberg RJ. Interim Results from the International Trial of Second Sight's Visual Prosthesis. *Ophthalmology* 2012;DOI: 10.1016/j.ophtha.2011.09.028.

34. Ahuja AK, Dorn JD, Caspi A, McMahon MJ, Dagnelie G, Dacruz L, Stanga P, Humayun MS, Greenberg RJ; Argus II Study Group. Blind subjects implanted with the Argus II retinal prosthesis are able to improve performance in a spatial-motor task. *Br J Ophthalmol* 2011;95:539-543.

35. Matin E. Saccadic suppression: A review and an analysis. *Psychol Bull* 1974;81:899-917.

36. Reichle ED, Rayner K, Pollatsek A. The E-Z reader model of eye-movement control in reading: comparisons to other models. *Behav Brain Sci* 2003;26:445-476.

37. Rayner K. Eye movements and attention in reading, scene perception, and visual search. *Q J Exp Psychol (Colchester)* 2009;62:1457-1506.

38. Rayner K, Bertera JH. Reading Without a Fovea. *Science* 1979;206:468-469.

39. Carandini M, Ferster D. A Tonic Hyperpolarization Underlying Contrast Adaptation in Cat Visual Cortex. *Science* 1997;276:949-952.

40. Baccus SA, Meister M. Retina versus Cortex: Contrast Adaptation in Parallel Visual Pathways. *Neuron* 2004;42:5-7.

41. Mante V, Frazor RA, Bonin V, Geisler WS, Carandini M. Independence of luminance and contrast in natural scenes and in the early visual system. *Nat Neurosci* 2005;8:1690-1697.

42. Fried SI, Hsueh HA, Werblin FS. A method for generating precise temporal patterns of retinal spiking using prosthetic stimulation. *J Neurophysiol* 2006;95:970-978.

43. Sekirnjak C, Hottowy P, Sher A, Dabrowski W, Litke AM, Chichilnisky EJ. Electrical stimulation of mammalian retinal ganglion cells with multielectrode arrays. *J Neurophysiol* 2006;95:3311-3327.

44. Jensen RJ, Rizzo JF. Responses of ganglion cells to repetitive electrical stimulation of the retina. *J Neural Eng* 2007;4:S1-6.

45. Ryu SB, Ye JH, Goo YS, Kim CH, Kim KH. Decoding of retinal ganglion cell spike trains evoked by temporally patterned electrical stimulation. *Brain Res* 2010;1348:71-83.

46. Tsai D, Morley JW, Suaning GJ, Lovell NH. Direct activation and temporal response properties of rabbit retinal ganglion cells following subretinal stimulation. *J Neurophysiol* 2009;102:2982-2993.

47. Freeman DK, Rizzo JF, Fried SI. Encoding visual information in retinal ganglion cells with prosthetic stimulation. *J Neural Eng* 2011;8:035005.

48. Dacey DM. Physiology, morphology and spatial densities of identified ganglion cell types in primate retina. *Ciba Found Symp* 1994;184:12-28.

49. Stone J, Maslim J, Valter-Kocsi K, Mervin K, Bowers F, Chu Y, Barnett N, Provis J, Lewis G, Fisher SK, Bisti S, Gargini C, Cervetto L, Merin S, Peér J. Mechanisms of photoreceptor death and survival in mammalian retina. *Prog Retin Eye Res* 1999;18:689-735.

50. Marc RE, Jones BW, Watt CB, Strettoi E. Neural remodeling in retinal degeneration. *Prog Retin Eye Res* 2003;22:607-655.

51. Marc RE, Jones BW, Anderson JR, Kinard K, Marshak DW, Wilson JH, Wensel T, Lucas RJ. Neural

reprogramming in retinal degeneration. *Invest Ophthalmol Vis Sci* 2007;48:3364-3371.

52. O'Brien EE, Fletcher EL, Meffin H, Burkitt AN, Grayden DB, Greferath U. Viability of the inner retina in a novel mouse model of retinitis pigmentosa. *Conf Proc IEEE Eng Med Biol Soc* 2010;2010:553-556.

53. Mahadevappa M, Weiland JD, Yanai D, Fine I, Greenberg RJ, Humayun MS. Perceptual thresholds and electrode impedance in three retinal prosthesis subjects. *IEEE Trans Neural Syst Rehabil Eng* 2005;13:201-206.

54. de Balthasar C, Patel S, Roy A, Freda R, Greenwald S, Horsager A, Mahadevappa M, Yanai D, McMahon MJ, Humayun MS, Greenberg RJ, Weiland JD, Fine I. Factors Affecting Perceptual Thresholds in Epiretinal Prostheses. *Invest Ophthalmol Vis Sci* 2008;49:2303-2314.

Precis

Electrically evoked percepts had a dynamic behavior and in most cases lasted only a fraction of the entire stimulation duration. There was considerable variability in the responses, probably related to ongoing remodeling processes associated to the disease.