Are long stimulus pulse durations the answer to improving spatial resolution in retinal prostheses?

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Abstract: Retinal prostheses can provide artificial vision to patients with degenerate retinae by electrically stimulating the remaining inner retinal neurons. The evoked perception is generally adequate for light localization, but of limited spatial resolution owing to the indiscriminate activation of multiple retinal cell types, leading to distortions in the perceived image. Here we present a perspective on a recent work by Weitz and colleagues who demonstrate a focal confinement of retinal ganglion cell (RGC) activation when using extended pulse durations in the stimulation waveform. Using real-time calcium imaging, they provide evidence that long pulse durations selectively stimulate inner retinal neurons, whilst avoiding unwanted axonal activations. The application of this stimulation technique may provide enhanced spatial resolution for retinal prosthesis users. These experiments provide a robust analysis of the effects of increasing pulse duration and introduce the potential for alternative stimulation paradigms in retinal prostheses.

Keywords: Retinal prostheses; retinitis pigmentosa (RP); calcium imaging; spatial resolution; retina

Submitted Sep 09, 2016. Accepted for publication Sep 11, 2016.
doi: 10.21037/atm.2016.11.24
View this article at: http://dx.doi.org/10.21037/atm.2016.11.24

Retinal prostheses ('bionic eyes') are a promising way to provide artificial vision to patients with inherited blindness caused by retinitis pigmentosa (RP), in which the outer retinal neurons (photoreceptors) are significantly lost but other retinal neurons remain preserved in varying levels. Some degree of vision can be provided by directly stimulating these inner retinal neurons by means of implanted microelectrodes, bypassing the non-functioning or absent photoreceptors, and utilizing the remaining visual pathway to transmit signals to the brain. Recipients perceive flashes of light ('phosphenes') when the implanted electrodes are stimulated, allowing them to interpret input from a video camera.

At present, the spatial resolution achievable through retinal prostheses is reported to be adequate for simple tasks involving object detection, localization, motion detection, and pattern discrimination (1,2), but is still largely inadequate for reliable identification of objects, faces, or letters. While some exceptional results for visual acuity have been reported; 20/1,260 (grating acuity) with an epi-retinal prosthesis (Argus II) (3) and 20/546 (optotype acuity) with a subretinal prosthesis (Alpha IMS) (2), these results have only been achievable in one patient from each group so far.

One way to improve resolution is to increase the number of physical electrodes in the implanted microelectrode array in order to try to increase the number of independent phosphenes. However, there are significant engineering constraints in adopting this approach including the minimum electrode size required to maintain safe charge density limits for electrical stimulation, and surgical complications associated with increased implant dimensions. Another factor that may significantly limit resolution is the spread of current, particularly from monopolar stimulation with square wave pulses, which may lead to indiscriminate activation of multiple cell types within the retina causing unwanted electrode interactions. Therefore, researching into methods that are able to reduce current spread e.g., (4) or minimise indiscriminate activation are more likely to increase the spatial resolution provided by such devices as opposed to simply increasing the electrode density.

The article by Weitz *et al*. (5) evaluates indiscriminate activation of multiple retinal cell types with epiretinal stimulation, particularly of retinal ganglion cell (RGC) axonal fibres, as an underlying cause of distortions in evoked phosphenes. Clinically in Argus II patients, it has been reported that phosphenes that should preferably be circular and confined are more-often perceived as elongated in the direction of axon fiber tracts passing directly below the stimulated electrode (6). Weitz *et al*. propose that a preferred way to improve spatial resolution is to modify the stimulation waveform, principally through increasing the pulse duration (leading phase only) of the predominantly used biphasic square-wave pulse in order to eliminate axonal activation. Clinical trials of retinal prostheses have most often used charged-balanced biphasic square-waves of around 0.5 msec duration per phase (7,8), or monophasic 1 msec pulses subretinally (2), with rates typically around 5 Hz (2,7), but ranging from 20 to 400 Hz in the case of suprachoroidal implantation (8,9).

Using impressive real-time calcium imaging of an *in vitro* retinal preparation where they were able to load up to 80% of RGCs with a calcium indicator in both wild type and degenerated retinae, Weitz and colleagues investigated phase durations ranging from 0.06 to 100 msec duration and their effect on RGC responses. For phase durations of 8 msec or less, their spatial threshold maps (used as a measure of retinal selectivity) demonstrated focal responses at low stimulus amplitudes (only up to 40% above threshold, depending on electrode diameter) but clear axonal activation as the stimulus amplitude increased. Axonal activation was visible as a band of RGC activity extending from immediately under the 200 µm diameter electrodes out towards the originating somata of axon fiber tracts some 3 or 4 electrode diameters away. Multiple electrode stimulation with short pulses caused unwanted electrode interactions resulting in further distortion of percepts. This result is consistent with clinical reports that inter-electrode discrimination can be problematic in retinal prosthesis users (10).

Increasing the phase duration to 16 msec in the Weitz *et al*. study was shown to confine most of the RGC activity to within 100 µm of the electrode perimeter (i.e., one-half electrode diameter) and at phase durations 25 msec and longer the activity was focal, with no evidence of axonal stimulation. Furthermore, the high selectivity achieved with long phase durations was independent of stimulus amplitude and multiple electrode stimulation was able to achieve focal activation of patterns such as a shape of a line or a letter. Weitz and colleagues speculated that short pulses stimulated RGCs and passing axons directly, whereas longer pulses activated RGCs indirectly via the longer-time constant bipolar cells. This hypothesis was confirmed using synaptic blockers to block both excitatory and inhibitory input to RGCs, following which there were no threshold changes with 0.06 ms phase durations [implying direct RGC activation as also shown by other studies, e.g., (11)], elevated thresholds to mid-duration pulses (implying both direct RGC activation and indirect retinal contributions), and no evoked responses when using phase durations longer than 16 msec (implying selective indirect stimulation of inner retinal neurons).

While comparing the efficacy of long phase durations to other strategies capable of increasing resolution, Weitz *et al*. also showed that using long phase durations were more selective than using sinusoidal waveforms. In a comparison between 20 Hz sinusoidal and square-wave stimulation, square-wave thresholds were 22.8±35.5% higher, lending further credence to reports that sine wave stimulation preferentially elicits responses in RGCs whilst avoiding axonal activation (12,13). A subsequent human psychophysical comparison suggested that percepts to sinusoidal stimulation were round and confined, in contrast to the elongated arcs perceived with square-wave stimulation. Further, they also acknowledged that the strategy of using smaller electrode sizes did achieve focal retina activation but only up to 75 µm diameter with the obvious expense of increased charge density. In addition, a fascinating corollary of this study was the finding that bipolar cell thresholds become elevated during degeneration, whereas direct RGC thresholds remain unchanged. This would imply that a prosthesis that exclusively targets the inner retinal cells, say through the use of long pulse widths as shown by Weitz *et al*., would need to support higher charge requirements.

In the context of human psychophysics, an increased retinal selectivity may significantly improve inter-electrode discrimination, leading to realizable benefits in visual acuity (the authors propose a four-fold benefit to Argus II users, translating to a theoretical 20/300 achievable acuity). However, there are several practical considerations that may preclude the clinical application of long phase durations, some of which have been discussed by Weitz *et al*. As the preferred mode of addressing electrodes is sequentially, so as to avoid inter-electrode interactions (14), the use of a longer phase width will necessitate a reduction in the number of phosphenes communicable for each captured video frame and/or a reduction in the stimulation rate

[leading to increased charge requirements as thresholds increase with decreasing rate (8)].

The prime concern with long phase durations is that threshold charge density was shown to increase to the point where the practical operating range (to provide sufficient contrast and dynamic range) would be likely to enter electrochemically unsafe charge densities if used in humans with platinum electrodes (7). Indeed, the human psychophysical result reported in this paper found a required charge density of 0.73 mC/cm^2 for 25 msec pulses on a 260 µm diameter Argus I electrode—implying a threshold charge density of 1.23 mC/cm^2 on a smaller 200 µm diameter Argus II electrode. As the authors state, this exceeds published limits on safe charge densities for acute and chronic stimulation with platinum black electrodes (currently used in the Argus II) and newer electrode materials with higher charge injection capabilities are likely to be necessary in order to support high charge density stimulation if electrode size is to remain small. This is the catch-22 of this study; longer phase durations at present necessitate larger electrodes to ensure operation in a safe therapeutic window, but larger electrodes will stimulate a larger area of retina and decrease the theoretical spatial resolution. It is also important to note that the present electrochemical limits for platinum are determined from short pulse durations, the possibility remains that long phase durations are within yet-to-be established safety limits since it is known that charge injection capacity increases with phase duration (15). Furthermore, the long leading phase could behave like a monophasic pulse, potentially allowing greater accumulation of electrochemical products and rendering the second phase ineffective in fully reversing the electrochemical reactions at the electrode-tissue interface. This could significantly increase the risk of tissue damage that has been shown with the use of monophasic waveforms (16-19).

Ultimately, one must bear in mind that waveforms optimized for selective physiological stimulation may not be optimal for balanced electrochemical processes (20). On the positive side, metabolic damage due to depression of neural activity or electroporation, shown to occur when using high current densities (21-23), may be less of a concern when using long phase durations. This would primarily be due to the reduced current densities and reduced voltage requirements compared to shorter phase durations.

A clinical consideration of the study is that the authors made use of retinal activation as a predictive measure of human perception. It is important to note that while they showed that longer phase durations evoked focal percepts in one subject implanted with the Argus I device, this result was obtained on only 2/5 electrodes tested. The other three electrodes tested in this subject either failed to evoke enough percepts with long phase durations (but correspondingly evoked sufficient numbers of percepts at short durations), or did not show a significant difference in the elongation of percepts between short and long phase durations. It is therefore entirely plausible that results achieved in the retina may not fully translate into perceptual outcomes as some of the perceptual distortion of phosphenes could be caused by central mechanisms and plasticity associated with long-term blindness (24). Finally, the perceptual benefits achieved with long phase durations may only apply to patients implanted with an epiretinal prosthesis, as perceptual distortions shown to be a result of axonal activation has not primarily been observed with subretinal (2) or suprachoroidal (25,26) stimulation.

In conclusion, Weitz *et al*. have performed a thought provoking study, since low spatial resolution is a key obstacle for all retinal prostheses to move forward. Increasing the spatial resolution through longer pulse durations may indeed prove to be an effective measure, but the safe delivery of the increased charge density requirements is currently a concern. The preliminary human psychophysical data is enticing, but it remains to be seen if this will ultimately result in safe high-resolution vision and "sharper sight with sustained stimuli".

Acknowledgements

Funding: The Bionics Institute acknowledges the support it receives from the Victorian Government through its Operational Infrastructure Support Program. MAP is supported by a project grant from the National Health and Medical Research Council of Australia (GNT#1082358) and a Ramaciotti Foundations Health Investment Grant. MNS is supported by a project grant from the National Health and Medical Research Council of Australia (GNT#1063093).

Footnote

Provenance: This is a Guest Perspective commissioned by Managing Editor Bing Gu, MD (Department of Laboratory Medicine, the Affiliated Hospital of Xuzhou Medical University, Xuzhou, China).

Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Weitz AC, Nanduri D, Behrend MR, *et al*. Improving the spatial resolution of epiretinal implants by increasing stimulus pulse duration. Sci Transl Med 2015;7:318ra203.

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Cite this article as: Petoe MA, Shivdasani MN. Are long stimulus pulse durations the answer to improving spatial resolution in retinal prostheses? Ann Transl Med 2016;4(21):434. doi: 10.21037/atm.2016.11.24

