Neurophysiological and medical considerations for better-performing microelectronic retinal prostheses

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1. Retinal prosthesis: a promising option for sight restoration

More than 350 blind individuals have received the Argus II implant of Second Sight, USA, which is the only US FDA-approved retinal prosthetic system, although it has been recently discontinued (Ayton et al. 2020). When incorporating the devices of other companies, such as Alpha IMS/AMS of Retinal Implant AG, Germany, and IRIS/PRIMA of Pixium Vision, France, over 500 subjects have been implanted with a retinal prosthesis to date (Ayton et al. 2020). Compared with other sight restoration approaches, microelectronic prostheses have demonstrated greater advantages such as long-term safety, minimal adverse events, and restoration of somewhat useful vision (da Cruz et al. 2016, Stingl et al. 2017, Palanker et al. 2020), making the most promising candidate for restoring vision above the legal blindness standard. Unfortunately, both Argus II and Alpha IMS/AMS have recently been discontinued, implying that their effectiveness remains limited even after considerable clinical testing. Due to the larger number of electrodes (i.e. pixels) than the Argus II, the Alpha IMS/AMS was expected to significantly enhance the quality of artificial vision (figure 1). However, the Alpha IMS/AMS has failed to reach its theoretical limit (~20/280) determined by its electrode size and pitch (Stingl et al. 2017). With state-of-the-art microfabrication technology, individual microelectrodes can be further miniaturized for higher electrode density. Yet, comparison of clinical outcomes of those two prosthetic systems (Ayton et al. 2020) suggests that miniaturization alone is insufficient to substantially improve the quality of electrically-elicted vision. Recent clinical trial of PRIMA has also reported the best performance that is below the visual acuity (~20/420) expected from electrode pitch (Palanker et al. 2020).

Although there have been numerous review papers summarizing the progress and challenges of retinal prostheses (Yue et al. 2016, Goetz and Palanker 2016, Mills et al. 2017, Manfredi et al. 2019, Ayton et al. 2020), additional studies are required to address essential issues for substantial performance enhancement. In the present work, we will discuss neurophysiological and medical considerations. But, engineering issues (e.g. wireless power transmission, hermetic sealing, mechanical property mismatch between substrate and retinal tissue) will not be covered.

2. Neurophysiological aspects of the retinal implant for performance break-through

Our understanding of retinal neurophysiology lags behind technological advances, leaving key challenges unresolved. As the first component of vision that provides the most sophisticated sensory information, the retina is incredibly complex in both anatomical (Helmstaedter et al. 2013, Bae et al. 2018) and functional (Baden et al. 2016, Bae et al. 2018) aspects. For instance, it has been well documented that diverse subtypes exist in each neuronal class of the retina, such as retinal ganglion cells (RGCs) (Rockhill et al. 2002, Baden et al. 2016, Bae et al. 2018), bipolar cells (BCs) (Helmstaedter et al. 2013, Euler et al. 2014), and amacrine cells (ACs) (Macneil et al. 1999). Due to the various combinations of those neuronal classes, the retinal circuitry is intrinsically and extremely heterogeneous, and so are neural signals transmitted from the retina to the brain. Therefore, natural normal vision, which is the encoded version of the complex visual world, cannot be restored through mere activation of RGCs. Rather, the ultimate goal of vision restoration should be duplication of the spatiotemporal characteristics of the heterogeneous population.
codes arising in RGCs (figure 2) (Im and Fried 2015a). This is the most significant challenge not only for microelectrode retinal prostheses, but also for other vision restoration approaches that need to mimic natural spiking patterns with artificial stimuli (e.g. optogenetic, magnetic, and chemical modalities). However, existing prosthetic systems have yet to achieve the remarkable complexity of neural signaling patterns.

The visual cortex has the ability to reorganize its cortical functions (Burton 2003; Begenisic et al 2020), but it may be premature to expect the brain to be able to interpret too artificial signaling patterns. Indeed, retinal implant users did not show meaningful training effects during long-term follow-up (da Cruz et al 2016), suggesting that the current level of synthetic neural activities may be too far away from actual spiking patterns to take advantage of brain plasticity. In addition, sophisticated visual tasks require high visual centers (Tanaka 1992; Young and Yamane 1992), which are likely to be precisely activated by upstream neurons. Therefore, artificial neural signals produced in the retina should closely resemble physiological/natural signaling patterns to properly activate downstream pathways. In this sense, direct and indirect activations of RGCs have big contrast in ‘naturalness’ of their resulting spiking patterns. Due to the high-fidelity of direct activation (Fried et al 2006, Sekirnjak et al 2008, Tsai et al 2009, Jepson et al 2013, 2014, Shah et al 2019), a series of short electrical pulses can precisely mimic natural neural codes of RGCs if they are known (Fried et al 2006). However, it is thought to be challenging to design appropriate sequences of stimuli for individual RGCs as well as to selectively deliver them to target cells. Particularly, after the retinal degeneration removes their light responses, it would be like trying to copy something without having an original. In contrast to short pulses, one single long pulse activates presynaptic retinal network (i.e. indirectly activates RGCs), resulting in spike trains so called network-mediated responses (Freeman et al 2010, Eickenscheidt et al 2012, Lee et al 2013, Boinagrov et al 2014; Im and Fried, 2015a, Im et al 2018). Because the retinal network is used as incident light produces physiological signaling, the indirect activation has long been thought to be more advantageous than the direct activation in mimicking natural spiking patterns. Recently, it has been demonstrated that network-mediated responses of RGCs are quite similar to their natural light responses in ON but not OFF types of RGCs (Im and Fried 2015a). This indicates, at least for the ON RGCs, a single stimulus can trigger duplicating natural signaling even without knowing it. Although those network-mediated responses are required to compared with responses to complex natural movie clips (Puchalla et al 2005, Im and Fried 2016a) for further characterization of their naturalness, the ON pathway may have a key solution for better artificial vision.

If electric stimuli faithfully mimic physiological spiking patterns, artificial population codes would be as diverse as those arising from visual stimuli. For example, in our earlier work, the network-mediated responses of ON RGCs were not only more similar to their own light responses but also more diverse across cells than those of OFF RGCs (compare figures 2(Bi) vs. 2(Bii)). It has been thought that diverse spiking activities across RGCs may elicit higher quality of artificial vision (Gaub et al 2014) because the diversity is the central feature in encoding sensory information including vision (Chelaru and Dragoi 2008). Indeed, in a sight restoration study using chemically engineered photoswitches, mice performed better in behavioral tests when more heterogeneous spiking patterns were restored in RGCs (Berry et al 2017). This suggests the performance of prostheses is highly likely to be enhanced by restoring heterogeneity of natural population codes. However, retinal prosthetic studies have not paid enough attention to the cell-to-cell response diversity.
Figure 2. (Ai) During natural viewing, RGCs in the healthy retina produce heterogeneous population codes that precisely activate the primary visual cortex (V1) for visual percepts (Aii) If RGC spiking activities created by the retinal implant are too different natural spiking, the brain of a prosthetic user would be confounded. (Bi) Example of heterogeneous populational spiking responses: Correlation matrix shows high cell-to-cell diversity of network-mediated responses arising in ON RGCs of brisk sustained type in the rabbit retina. Spike time tiling coefficients (STTCs) were computed as a measure of correlation between two different spiking activities (Cutts and Eglen 2014) with data from our earlier work (Im and Fried 2015a). In a given cell, STTCs were computed across responses arising from seven repeats of an identical stimulus. Diagonal block indicates autocorrelation of each response. (Bii) Example of homogeneous populational spiking responses: Same as Bi but for OFF RGCs of brisk transient type.

Also, contrast is crucial in visual perception (Avidan et al 2002, Thiele et al 2009). In particular, central vision has the high contrast sensitivity (Rijsdijk et al 1980), which is known to be reduced by degeneration (Alexander et al 1995, 2004). Given that prosthetic vision showed 10 times lower contrast sensitivity than natural vision (Goetz et al 2015), the artificial vision is likely to be better perceived by introducing greater contrast between object and background (figure 3). Regarding the background, it is important to note that macular or ring scotomas are not perceived in black (Stoll 1950, Schuchard 1995, Zur and Ullman 2003) although most prosthetic literatures illustrate the lost central or peripheral visual space as black region. Unnoticed scotomas suggest sole activation of ON RGCs at center may not effectively encode contrast information without activating of OFF RGCs at surround.

The excitatory center and inhibitory surround are the basic feature of retinal receptive field (DeVries and Baylor 1997; Rathbun et al 2018) as well as in cortical response (Self et al 2014). The lateral inhibition from the surround is known to play a critical role in sophisticated neural computations (Cook and McReynolds 1998, Im and Fried 2016a, Turner et al 2018; Trenholm and Krishnaswamy 2020), suggesting accurate activation of an antagonistic surround is likely to enhance the performance of retinal prostheses (Goetz et al 2015, Stutzki et al 2016, Ho et al 2017). However, it is a tremendous challenge to exclusively activate RGCs of one type while deactivating RGCs of other types (e.g. activating only ON RGCs in the center and only OFF RGCs in the surround). This is because each type of RGCs tiles the retina in a mosaic arrangement at slightly different depths of stratification (DeVries and Baylor 1997). Although optimal stimulation parameters demonstrated more selective indirect activation of ON over OFF RGCs (Im and Fried 2016b, Im et al 2018, Lee and Im 2019), the selectivity needs to be further enhanced. Also, for the high contrast between center and surround, another selective activation of OFF over ON RGCs is indispensable as demonstrated in high-frequency direct activation (Twyford et al...
If the differential indirect activation of ON or OFF RGCs becomes available along with natural responses, bright and dark areas in visual space can be reconstructed without knowing RGC types in each area and their physiological spiking patterns. This is important in clinical settings with degenerate retinas because RGC types cannot be identified by their light responses (but see Richard et al 2015), stratification depth (Margolis et al 2008), and/or fluorescent labeling (Kim et al 2008).

Lastly, retinal prosthetic researches need to consider that degeneration alters baseline activities of RGCs as well as their responses to electric stimulation. For instance, increased spontaneous activity is a well-known feature of degenerate retina (Margolis et al 2008, Stasheff 2008, Borowska et al 2011, Goo et al 2011, Menzler et al 2014), which is thought to be an intrinsic noise in visual percept (Mcanany et al 2013, Stasheff 2018). Recent studies reported the reduction of spontaneous activity improves optogenetic responses (Barrett et al 2015, 2016) and/or light sensitivity (Barrett et al 2016, Telias et al 2019). Therefore, minimizing the noise is likely to enhance the quality of restored vision. Regarding this matter, indirect activation is favorable as long pulses stimulate not only excitatory but also inhibitory networks in both ON and OFF pathways, resulting in reduced spontaneous activities (Im and Fried 2016b; Lee and Im 2019). But, retinal remodeling (Marc et al 2003) alters network-mediated responses depending on the level of degeneration (Goo et al 2016, Lee et al 2017). It is particularly noteworthy that network-mediated responses of degenerate retinas become more inconsistent across repeats of an identical electric stimulus as degeneration advances (Lee et al 2017). This increased inconsistency of neural signals would be unfavorable in rehabilitation of prosthetic users. Along with the intrinsic capability of replicating neural spiking patterns in ON RGCs from healthy retinas (Im and Fried 2015a), it may be better to implant retinal prosthetic devices earlier than has been approved. In a clinical trial of gene therapy, young children showed better restored vision than adult cohorts (Maguire et al 2009), supporting the idea that earlier therapeutic intervention may be more effective (or too late intervention may limit therapeutic effects) in sight restoration due to retinal remodeling (McGregor 2019; Sahel et al 2019). Particularly, it may be ideal to target the time period of degeneration with still functional inner segments of photoreceptors (Busskamp et al 2010) because the retina during that interval would be blind but nearly electrophysiologically intact. Therefore, it may be best to screen potential implant users at such a stage (Busskamp et al 2010).

3. Medical aspects for chronic retinal implants

Short pulses delivered from epiretinal side is known to distort artificial visual percepts (Nanduri et al 2012, Beyeler et al 2017, 2019) due to unintended activation of axon bundles (Jensen et al 2003, Behrend et al 2009, Grosberg et al 2017). In contrast, epiretinally-delivered long pulses can activate RGCs indirectly without stimulating passing axons (Freeman et al 2010, Weitz et al 2015). It is also notable that opposite polarity current stimuli applied from epi- and sub-retinal sides elicit largely similar network-mediated spiking patterns in a given cell (Im and Fried 2013b). This suggests that electrode location (i.e. epi- vs. sub-retinal) for indirect activation is neurophysiologically less critical than has been previously thought. However, epi- and sub-retinal approaches differ in several biophysical and surgical aspects. For example, the distance between the epiretinal electrode array and the retina may increase after implantation (Delyfer et al 2018, Finn et al 2018, Patelli et al 2018, Rizzo et al 2019, Yue et al 2015; but see, 2020 for no significance change in the gap), resulting in increased stimulation threshold due to current shunting through the conductive vitreous. This may cause decreasing number of effective electrodes over time (Delyfer et al 2018, Gregori et al 2018, Demchinsky et al 2019). Also, stimulation threshold for direct activation is sensitive on the lateral electrode position (Fried et al 2009, Yang et al 2018). Taken together, epiretinal electrodes should remain at constant positions in close proximity to the retina for chronic use. Probably, an implant needs to be pressured against the epiretinal surface but gently enough not to damage RGCs. Prosthetic devices may cause cumulative tissue damage and/or

**Figure 3.** Artificial visual percepts may be enhanced by introducing contrast between center and surround. White spot is more noticeable on higher contrast background.
retinal detachment due to significant inertia or friction during rapid accelerations of the eye; to avoid this potential adverse effect, light materials would be preferred (Maccarthy et al 2006). Recently, multielectrode arrays have been fabricated on flexible biocompatible material for conformal coverage of the epiretinal surface along the curvature of the eye (Ferrlauto et al 2018). But, it still remains a possibility that fibrous membrane formation between the electrode array and the retina in the epiretinal prosthesis may reduce stimulation efficacy (Delyfer et al 2018, Patelli et al 2018, Rizzo et al 2019).

Subretinal implants have an advantage over epiretinal prostheses in terms of tissue contact and stimulation efficiency. However, some issues should be considered for surgery of subretinal implantation. First, the implant placement at the central retina is essential for good clinical outcomes (Stingl et al 2013, Palanker et al 2020). Recent work recommended general over local anesthesia to avoid any movement of patients during the critical moment (Palanker et al 2020). Also, surgical methods to implant and replace the retinal prosthesis should be developed together (Stingl et al 2017, Gekelet et al 2018, Seuthe et al 2019) to ensure safe replacement of previously implanted devices with next-generation versions. Otherwise, the initial device design should possess every desired function for chronic use, which seems to be challenging. Usually, epiretinal prostheses are considered easier to implant than subretinal prostheses, which have been implanted in an ab-externo approach because it requires an external power supply by way of a connecting wire. However, recently available photovoltaic type retinal prostheses, which do not require a connecting cable between the intra- and extra-ocular components, can be implanted subretinally through the ab-interno approach (Lorach and Palanker 2017; Gekeler et al 2018). The ab-interno approach is advantageous to the ab-externo approach due to the 2- to 3-fold shorter operation time and the decreased amount of custom training required of the surgeon (Lorach and Palanker 2017). The one small drawback of this approach is that the retinotomy should be created at least as large as the device width in the mid-peripheral retina or near the outside of the vascular arcade of the posterior pole to insert an electrode array under the macula (Lee et al 2016).

To minimize retinal damage during insertion, it needs to develop a surgical device delivering or dribbling the chip from the far peripheral retinotomy site to the macular center safely and easily. In summary, for both ab-externo and ab-interno approaches, a new surgical technique and instrumentation are essential to enhance the surgeon’s performance and decrease operation time.

Suprachoroidal or scleral pocket approach is designed to guarantee operational and long-term safety as a top priority (Lee et al 2009, Fujikado et al 2011, Ayton et al 2014). As the electrodes do not contact the retinal tissue directly, retinal damage during/after the surgery is minimal. Surgical technique is relatively simple and less invasive compared to the other two (i.e. epiretinal or subretinal) approaches. However, because of the long distance between electrodes and retinal neurons, the suprachoroidal approach needs a high stimulation amplitude (Yamauchi et al 2005, Shivdasani et al 2010, Aplin et al 2016), which limits the miniaturization of electrodes and integration of high-density electrodes.

The unique structure of fovea in primates mediates high visual acuity at the central retina, suggesting the restored foveal function is likely to determine clinical performance of prostheses (McGregor 2019). Due to the differing density and arrangement of retinal neurons, clinical outcome may deviate from experimental results from non-foveate animals (McGregor 2019). To minimize translational gap, retinal prostheses are preferred to be implanted into non-human primates (NHPs) for preclinical testing (McGregor 2019, Prévot et al 2020). NHP genetic models of eye disease have been also developed (Sasaki 2015, Sato and Sasaki 2018, Moshiri et al 2019). However, given the economical and ethical issues associated with NHPs, other animal models of medium to large size would be good alternatives for successful verification of long-term safety and efficacy. For instance, leporine (Jones et al 2011, Komimani et al 2019, Ahn et al 2019a, 2019b) and swine (Noel et al 2012, Monés et al 2016, Scott et al 2017) models would be more attractive than murine models (Cameron et al 2013, Menzler et al 2014, Stutzki et al 2016, Jalligampala et al 2017) due to their large ocular size. In particular, the eyeballs of swine models are similar in size to those of humans (Noel et al 2012, Monés et al 2016, Scott et al 2017). In addition, prosthetic devices are likely to function more efficiently in clinical settings if they are tested in animal models that simulate outer retinal degeneration as well as subsequent remodeling of the retinal neural network. Genetically-modified retinal degeneration models of medium to large animals are typically difficult to mass produce, making them economically unfriendly. The outer retina can be degenerated by drugs like N-methyl-N-nitrosourea (Ahn et al 2019a), sodium iodate (Monés et al 2016, Ahn et al 2019a), and iodoacetic acid (Noel et al 2012). However, systemic administration often requires a high dose of chemicals, which can be fatally harmful to the health of animals. To reduce this dose, such drugs can be locally administered either intravitreally or subretinally or without vitrectomy (Monés et al 2016, Ahn et al 2019a, 2019b). Drug-induced degeneration has several advantages. First, degree of degeneration can be controlled by adjusting the dose or concentration of the drugs. Second, degeneration is confined in a single eye, allowing the other eye to be available as a control. These steps will result in greater acceptance in terms of animal ethics.
Several characteristics of drug-induced degenerate retinas are similar to those of their genetically-modified counterparts. For example, drug-induced degenerate retinas exhibit oscillatory rhythms in neural activities (Ahn et al 2019a). In addition, RGC responses of drug-induced degenerate retinas to electric stimulation showed lower saturated spike counts and higher thresholds than those of normal retinas (Halupka et al 2017). It was also reported that threshold for electrical stimulation for retinal and/or cortical responses was proportional to degree of gliosis of the retina (Aplin et al 2016). Lastly, electrically evoked potential (EEP) was reported to decrease much more severely than the extent of degeneration (Kominami et al 2019) because stimulation efficiency is strongly reduced in degenerate retinas, particularly when abnormal activities such as oscillations and rhythmic firing of spike bursts are observed (Haselier et al 2017). Taken together, these findings indicate that medium- to large-sized retinal degeneration models using localized drug administration can be a useful platform for development of retinal prostheses and for determining more effective stimulation strategies.

4. The future of microelectronic retinal implants: fulfilling unmet needs

Spatial resolution should be significantly improved for clear artificial visual perception. Prosthetic devices with local return electrodes have demonstrated tighter spatial confinement of electric stimulation, resulting in better performance in animals (Lorach et al 2015) as well as in human patients (Palanker et al 2020). For the improved visual acuity, it is thought that even higher local confinement of electric currents should be achieved using novel electrode configurations such as 3D structures (Flores et al 2019). However, it is worth noting that earlier studies demonstrated the possibilities of advancement even without additional changes in electrode architecture. For instance, optimal pulse duration successfully enhanced spatial confinement (Weitz et al 2015), suggesting that optimization of stimulation strategies may further improve spatial resolution. The rationale of such optimization should be more realistic duplication of neural signaling aspects as evidenced by a previous study that improved animal behavior testing by restoring heterogeneous population codes (Berry et al 2017).

To develop more effective and reliable retinal implants, the community of retinal prosthetics needs to address more fundamental questions such as precise mechanism underlying electrically-elicited retinal responses. Unfortunately, our knowledge remains incomplete in not only electrically-evoked, but also visually-evoked responses, even in healthy retinas. Therefore, more basic studies are essential to deepen our understanding of the visual system as well as to create new ideas for innovative electrode designs for retinal prostheses. In the future, vivid colorful artificial vision may be achieved using technologies including photosensitive materials with different spectral sensitivities that correspond to those of human cones (Park et al 2018). But, without comprehensive understanding of the neurophysiological aspects of normal vision, the impact of technological advances is likely to be limited.

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Competing interests

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