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Encoding Visual Information in Retinal Ganglion Cells with Prosthetic Stimulation

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Abstract

Retinal prostheses aim to restore functional vision to those blinded by outer retinal diseases using electric stimulation of surviving retinal neurons. The ability to replicate the spatiotemporal pattern of ganglion cell spike trains present under normal viewing conditions is presumably an important factor for restoring high-quality vision. In order to replicate such activity with a retinal prosthesis, it is important to consider both how visual information is encoded in ganglion cell spike trains, and how retinal neurons respond to electric stimulation. The goal of the current review is to bring together these two concepts in order to guide the development of more effective stimulation strategies. We review the experiments to date that have studied how retinal neurons respond to electric stimulation and discuss these findings in the context of known retinal signaling strategies. The results from such *in vitro* studies reveal the advantages and disadvantages of activating the ganglion cell directly with the electric stimulus (direct activation) as compared to activation of neurons that are presynaptic to the ganglion cell (indirect activation). While direct activation allows high *temporal* but low *spatial* resolution, indirect activation yields improved *spatial* resolution but poor *temporal* resolution. Finally, we use knowledge gained from *in vitro* experiments to infer the patterns of elicited activity in ongoing human trials, providing insights into some of the factors limiting the quality of prosthetic vision.

1. Introduction

In the healthy visual system, light is captured by the photoreceptors in the outer retina. Synaptic output from the photoreceptors then initiates activity in the retinal network and ultimately modulates the spiking patterns of retinal ganglion cells. These spikes propagate down the optic nerve and represent the sum total of information that the brain receives about the visual world. Outer retinal diseases such as macular degeneration and retinitis pigmentosa lead to degeneration of the photoreceptors. As a result, ganglion cells no longer transmit information about the visual world, and blindness ensues. However, a significant number of inner retinal neurons survive such diseases (Stone et al. 1992; Kim et al. 2002; Gargini et al. 2007; Mazzoni et al. 2008) (but see (Marc et al. 2003)), raising the possibility that functional vision can be restored by eliciting activity in remaining ganglion cells using electric stimulation from a retinal prosthetic (Rizzo et al. 2001; Zrenner 2002; Chow et al. 2004; Weiland et al. 2004; Palanker et al. 2005). With such an approach, an electrode array is brought in close proximity to surviving retinal neurons with the goal that individual electrodes each elicit a spatially-localized perception of light (i.e. phosphene). Figure 1 illustrates how individual phosphenes might be combined into a pixelized view of the visual

world; simulations suggest that several hundred electrodes may be needed to perform common visual tasks such as navigation (Dagnelie et al. 2007) or facial recognition (Thompson Jr. et al. 2003).

Results from clinical testing of retinal prostheses indicate much progress over the past decade (Chader et al. 2009). For example, electric stimulation of the retina has been shown to elicit phosphenes reliably in many patients (Ahuja et al. 2010; Zrenner et al. 2010). In response to a single pulse, the brightness of the elicited phosphene increases with stimulus intensity (Greenwald 2009). Subjects have also been able to distinguish between different orientations when multiple electrodes within an array are stimulated (Caspi et al. 2009; Benav et al. 2010). More recently, blind subjects have demonstrated the ability to read large, high-contrast letters, as well as to perform simple navigation tasks (Humayun et al. 2009; Humayun et al. 2010; Zrenner et al. 2010).

While these results are encouraging, the quality of elicited vision remains sub-optimal. For example, the time it takes to identify a single letter can be tens or even hundreds of seconds (Humayun et al. 2010; Zrenner et al. 2010). At least three aspects of the elicited percepts should be addressed in order to improve the quality of vision. First, the phosphenes resulting from single electrode stimulation are sometimes round, but also can be elongated or more complex (Rizzo et al. 2003; Greenwald 2009; Zrenner et al. 2010), particularly for higher stimulus amplitudes (Nanduri et al. 2008). Elongated percepts could potentially cause phosphenes elicited by neighboring electrodes to overlap, severely reducing control over the spatial pattern of the elicited percept. Second, the percepts elicited by multi-electrode stimulation tend to be more complex than would be predicted from stimulation with single electrodes. For example, stimulation with a 2 × 2 array of electrodes did not necessarily map to a 2 × 2 array of phosphenes (Rizzo et al. 2003; Horsager et al. 2010). Third, in response to sustained stimulation with pulses, the brightness of the elicited phosphene fades rapidly (Perez Fornos et al. 2010; Zrenner et al. 2010). Thus, control over the temporal pattern of brightness of the elicited percepts remains very limited. Taken together, these results suggest that control over the spatial and temporal pattern of the induced phosphenes must be improved in order to allow patients to interact with a complex and dynamic visual environment.

There are many factors that may contribute to the limited quality of prosthetic vision reported in clinical trials. One factor is that the level of ganglion cell degeneration may limit the quality of the elicited percepts (Stone et al. 1992). For example, there may be an insufficient number of ganglion cells to support vision with high spatial acuity. Another factor that may contribute is that patients who have been blind for many years may have significant rewiring of circuits in higher visual centers. This would prevent the ganglion cell spike trains from being processed and decoded properly by the brain. These factors that involve changes to the underlying neural substrate could preclude even the most advanced retinal prostheses from yielding high-quality vision.

Another factor that is likely to contribute to the limited quality of prosthetic vision is the inability to reproduce the patterns of ganglion cell spiking that are present under normal viewing conditions. Visual physiologists have produced a wealth of knowledge about how visual information is normally encoded in spike trains of ganglion cells (Field and Chichilnisky 2007; Gollisch and Meister 2010). For example, visual information may be carried in the precise temporal pattern of ganglion cell spiking (Victor 1999), as well as in spatial correlations of activity among populations of ganglion cells (Meister et al. 1995; Shlens et al. 2008). An understanding of how information is encoded in the spike trains of ganglion cells can be utilized to develop more effective stimulation strategies because

parameters of the prosthetic device can be adjusted (e.g. stimulus waveform, electrode size/shape) in order to elicit spiking patterns that better resemble those seen in the healthy retina.

Several groups are currently using *in vitro* preparations to study how retinal neurons respond to electric stimulation as a step towards developing more effective stimulation methods (Margalit and Thoreson 2006; Jensen and Rizzo 2007; Stett et al. 2007; Sekirnjak et al. 2008; Behrend et al. 2009; Fried et al. 2009; Tsai et al. 2009; Freeman et al. 2010a; Ryu et al. 2010). Here, we provide a review of these studies, detailing the extent to which ganglion cell activity can be controlled with existing stimulation techniques (Section 2). To help clarify the goals of these efforts, we discuss some key aspects of how visual information is encoded in ganglion cell spike trains in the healthy retina (Section 3). Finally, we examine a few clinical results in which the patterns of ganglion cell activity are unknown but can be inferred using (1) knowledge of the induced percepts and (2) an understanding of how retinal neurons respond to electric stimulation (Section 4).

2. The Response of Retinal Neurons to Electric Stimulation

Several groups are investigating how retinal neurons respond to electric stimulation in an effort to improve control over the spatial and temporal pattern of elicited spike trains (Margalit and Thoreson 2006; Jensen and Rizzo 2007; Stett et al. 2007; Sekirnjak et al. 2008; Behrend et al. 2009; Fried et al. 2009; Tsai et al. 2009; Freeman et al. 2010a; Ryu et al. 2010). In such experiments, stimuli are delivered from an electrode positioned either on the ganglion cell side (epi-retinal stimulation) or on the photoreceptor side (sub-retinal stimulation) of the retina. In either configuration, there are two ways in which ganglion cell spiking can be elicited: either through *direct* activation, where the electric stimulus acts directly on the ganglion cell, or through *indirect* activation, where presynaptic neurons are activated by the electric stimulus and this results in a modulation of synaptic input to the ganglion cell (Figure 2).

2.1 Direct Activation

Direct activation of the ganglion cell typically elicits a single action potential for each stimulus pulse (one-spike-per-pulse) (Figure 3a), although two-spikes-per-pulse has also been observed (Jensen et al. 2005b; Sekirnjak et al. 2006; Ahuja et al. 2008). The timing of the first elicited action potential is phase-locked to the onset of the cathodal pulse with a latency of ~0.5ms (Fried et al. 2006; Sekirnjak et al. 2008). Spikes have been elicited by direct activation not just with epi-retinal stimulation, but also with sub-retinal stimulation (Stett et al. 2000; Tsai et al. 2009). This result was somewhat surprising because for sub-retinal stimulation, the targeted ganglion cells are separated from the stimulating electrode by several layers of interneurons, spanning ~200μm (Boycott and Dowling 1969; Kim et al. 2010).

In response to direct activation, the most sensitive region of the ganglion cell is the initial segment of the axon (Sekirnjak et al. 2008). This is consistent with observations in other neuronal types throughout the nervous system (Ranck 1975; Tehovnik et al. 2006). This region of lowest threshold has been shown to correspond to a dense region of voltage-gated sodium channels in the initial segment, centered ~10–60μm from the soma (Fried et al. 2009). Although the site of spike initiation in response to electric stimulation has not been determined, the observation that threshold is lowest over the initial segment is consistent with spikes being initiated in this region. The length of the sodium channel ‘band’, as well as its location relative to the soma, differ among physiological types of ganglion cells (e.g. ON directionally-selective versus brisk transient). Such differences may be responsible for threshold differences among ganglion cell types. For example, the threshold for direct activation of brisk-transient cells is, on average, ~3 times lower than that of local-edge-

detector cells (Fried et al. 2009). Other factors may also contribute to differences in threshold among ganglion cell types, including axonal diameter, soma size, and/or the distribution and density of voltage-gated ion channels other than sodium.

For direct activation, the total charge per pulse that is required to elicit a spike increases for larger diameter stimulating electrodes (Jensen et al. 2005b; Sekirnjak et al. 2006), but see also (Shyu et al. 2006). Also, the total charge required to elicit a spike increases with pulse duration (Jensen et al. 2005b; Shyu et al. 2006). Therefore, the use of short-duration pulses and small-diameter stimulating electrodes may be the most efficient way to elicit spiking through direct activation. Recent work suggests that outer retinal degeneration does not significantly affect the threshold for direct activation of the ganglion cell (Sekirnjak et al. 2009).

For direct activation, the higher sensitivity to shorter pulses likely results from the fact that the temporal integration of charge occurs rapidly; chronaxie values for ganglion cell activation are 0.1–0.4ms (Jensen et al. 2005b; Sekirnjak et al. 2006). Studies from non-retinal neurons show that chronaxies are shorter for the axon as compared to the soma (Tehovnik et al. 2006), suggesting that the short integration time found in ganglion cells is likely the result of spikes being initiated in the initial segment of the axon and not the soma. The difference in chronaxies between the soma and initial segment likely arises from differences in the passive electrical properties of the membrane (e.g. the low input resistance and high capacitance of soma, versus high input resistance and low capacitance of the initial segment). Whole-cell patch clamp studies have estimated the time constant of the soma of ganglion cells to be 4–80ms (O'Brien et al. 2002). Given the correspondence between chronaxie and time constant, it is likely that the chronaxie of the ganglion cell soma is also in this range, providing additional support that the rapid integration time of ganglion cells results from the activation of the initial segment, not the soma.

Spike trains elicited through direct activation can achieve high temporal resolution (50–500Hz) (Fried et al. 2006; Sekirnjak et al. 2006; Ahuja et al. 2008). For example, Figure 4a shows the response of a rabbit retinal ganglion cell to a train of pulses delivered at 225Hz. A single spike is elicited reliably following the cathodal phase of each pulse. Stimulation at high rates (>100Hz) is often performed for durations up to only 1sec, and it is therefore unknown whether longer term stimulation (e.g. >10sec) at high rates will continue to elicit spiking. Studies involving neurons in the hippocampus (Jensen and Durand 2007) and subthalamic nucleus (Beurrier et al. 2001) have found that in response to sustained stimulation, conduction block occurs, resulting in a loss of spiking.

The primary drawback associated with direct activation, including both the epi-and sub-retinal configurations, is the incidental activation of passing axons. Ganglion cell axons traverse the inner surface of the retina and are sensitive to electric stimulation. The activation of passing axons is likely to be interpreted by the brain as coming from ganglion cells with distant cell bodies (i.e. far from the stimulating electrode). The shape of the resulting percept is difficult to predict, but could be elongated in space, perhaps wedge-like (Greenberg et al. 1999) or slightly more complex (Rizzo et al. 2003) given the circuitous route some axons take towards the optic disk (Naito 1989). Regardless of the specific shape of the percept, it seems likely that the activation of passing axons would reduce the ability to create percepts that are spatially-localized.

The extent to which passing axons are activated in human trials is unknown (see Section 4.3), but several studies have begun to explore this question using electrical stimulation of the isolated retina. These studies indicate that the threshold for activation of passing axons is approximately 2–4 times higher than the threshold for activation of the initial segment (the

most sensitive region of the ganglion cell) (Jensen et al. 2003; Jensen et al. 2005b; Freeman et al. 2010a). For example, one study found that the threshold measured at the initial segment across a population of ganglion cells ranged from 10–31μA, while stimulation over the distal axon of these same cells ranged from 30–95μA (Freeman et al. 2010a). Although this suggests there is a range of stimulus amplitudes over which passing axons could be avoided, there are several reasons why this may be difficult to achieve in clinical practice. First, the threshold for direct activation is thought to vary across cell types. For example, brisk-transient cells are nearly twice as sensitive as ON-directionally selective cells, and three times more sensitive than local edge detectors (Fried et al. 2009). Therefore, passing axons of the highly sensitive brisk-transient cells might be activated at lower stimulus amplitudes than the initial segment of other types of cells that have higher thresholds. Second, a disc electrode placed at any point on the retina will likely overlay many more passing axons than initial segments. The activation of those few initial segments may not be sufficient to generate a visual percept, particularly for small diameter electrodes (e.g. 10 μm) that activate very few cells. This will require the stimulus amplitude to be increased in order to activate additional ganglion cells whose initial segments are slightly offset from the electrode. Unfortunately, increasing the stimulus amplitude will lead to the activation of passing axons.

A common assumption is that as stimulating electrodes become smaller, the spatial resolution of prosthetic vision will be improved. This notion is supported by the finding that small diameter (~10 μm) disk electrodes could activate a single parasol cell without also activating neighboring parasol cells (Sekirnjak et al. 2008). The ability to activate a single parasol cell is likely made possible by the fact that the electrode size is small compared to the distance between neighboring parasol cell bodies (and initial segments). This could potentially allow fine control over the spatial pattern of activity in parasol cells, but only if the passing axons were not activated. Unfortunately, the extent to which passing axons were activated could not be determined using the recording setup in this study. Therefore, the question still remains as to whether the use of small diameter electrodes can create vision with high-spatial resolution through direct activation of the ganglion cells.

2.2 Indirect Activation

Indirect activation of ganglion cells arises secondary to activation of neurons presynaptic to the ganglion cell. These presynaptic neurons respond to electric stimulation with modulations in their level of synaptic release, which leads to a spiking response in the ganglion cells. Because of the changes that occur following outer retinal disease (Gargini et al. 2007; Marc et al. 2007), the specific types of presynaptic neurons activated in response to electric stimulation may be different in the healthy and degenerate retina. For example, photoreceptors are largely absent in the degenerate retina and therefore an indirect response likely originates from activation of the bipolar cells (Jensen and Rizzo 2008). Conversely, in the healthy retina, the indirect activation of ganglion cells could be due to depolarization of either bipolar cells or photoreceptors.

In the healthy retina, there is evidence to suggest photoreceptors may be activated following stimulation with pulses (Jensen et al. 2005a; Jensen and Rizzo 2006) or low frequency sinusoids (5Hz) (Freeman et al. 2010a). In each case, it was observed that the anodal and cathodal phases of the stimulus had different effects on ON versus OFF ganglion cells. These results could be accounted for if photoreceptors were activated, since depolarization of the photoreceptors causes a depolarization in OFF bipolar cells but a hyperpolarization of ON bipolar cells. The observation that the threshold for indirect activation is significantly higher in degenerate retina as compared to healthy retina (Jensen and Rizzo 2008; Jensen and Rizzo 2009) could arise if (1) photoreceptors were activated in the normal retina and (2) bipolar cell responses were determined primarily by photoreceptor input and not by

activation from the electric stimulus. In other words, activation of the photoreceptors could contribute to ganglion cell depolarization in the healthy retina, thus lowering the threshold for eliciting a spiking response.

Studies employing whole-cell patch clamp recordings have provided insights as to the underlying synaptic activity responsible for indirect activation. For example, whole-cell current recordings have shown that synaptic input to the ganglion cell contains an excitatory current that peaks ~10–30ms after stimulus onset (Fried et al. 2006). The excitatory input is followed by a strong inhibitory input that peaks tens of milliseconds after stimulus onset, and gradually decays over hundreds of milliseconds (Fried et al. 2006; Margalit and Thoreson 2006). There is evidence that the activation of amacrine cells results secondary to activation of bipolar cells, and not from direct activation of the amacrine cell with the electrical stimulus (Margalit and Thoreson 2006).

Strength-duration relationships of the indirect response yield chronaxie measurements of ~14–18ms, significantly longer than that of direct activation (0.1–0.4ms) (Jensen et al. 2005b). This relatively long chronaxie indicates that the stimulus is being integrated over a long period of time. Consistent with this, the indirect response is relatively slow, generally peaking tens of milliseconds after stimulus onset (Freeman et al. 2010c; Freeman and Fried 2011). The reason that the indirect response occurs over this long timescale is likely related to synaptic communication between bipolar and ganglion cells. For example, following the release of glutamate from the synaptic terminals of bipolar cells, the clearance of glutamate from the synaptic cleft is relatively prolonged (Lukasiewicz 2005), thus causing the synaptic response of ganglion cells to also be prolonged. However, these slow response dynamics do not necessary imply that long-duration pulses are more effective than short-duration pulses at eliciting an indirect response. While it is true that longer pulse durations result in lower threshold currents for indirect activation (Fried et al. 2006; Tsai et al. 2009), the amount of stimulus energy (i.e. charge) required to reach threshold actually *increases* with pulse duration (Jensen et al. 2005b). Therefore, indirect activation is more efficient with short-duration pulses (in terms of charge required at threshold).

In response to a single pulse, the response to indirect activation typically consists of a burst of spikes. However, in response to a train of pulses, the response to indirect activation becomes desensitized, both for healthy (Jensen and Rizzo 2007; Ahuja et al. 2008; Freeman and Fried 2011) and degenerate retina (Ryu et al. 2009). Such desensitization is illustrated in Figure 4b for a rabbit retinal ganglion cell stimulated at 8Hz. A large burst of spikes is elicited by the first pulse, but the cell responds to subsequent pulses with fewer spikes. This suggests that the temporal resolution of indirect activation may be quite limited. The precise mechanisms of desensitization have not been resolved, but a recent study found that desensitization persisted in the presence of inhibitory blockers (Freeman and Fried 2011). This was surprising because is suggests that amacrine cell inhibition is not the sole mechanism underlying desensitization, or may not even contribute at all. Other potential mechanisms underlying desensitization could include AMPA receptor desensitization, depletion of synaptic vesicles, or spike-rate adaptation mechanisms in the ganglion cell itself.

While the temporal resolution for indirect activation is poor, the spatial resolution is thought to be better than that of direct activation because bipolar cells (the target of indirect activation) do not contain laterally projecting axons. Therefore, depolarization of bipolar cells near the stimulating electrode will result in spiking in only those ganglion cells that are close to the stimulating electrode. The threshold for indirect activation is relatively constant when delivered from a stimulating electrode positioned anywhere within the receptive field of the ganglion cell (Jensen et al. 2005b). Therefore, using stimulation with small-diameter

electrodes, the upper limit of spatial resolution for indirect activation is similar to that of ganglion cell responses to light, and it is limited by the spatial extent of the ganglion cell dendritic field. Conversely, if the electrode diameter is larger than the ganglion cell dendritic field, then the electrode size will limit the spatial resolution over elicited ganglion cell spiking. Regardless of the size of the electrode, indirect activation is likely to elicit neural activity that is spatially focal, yielding improved spatial resolution as compared to direct activation.

2.3 Selective Activation

Selective activation refers to the ability to activate one or more sub-populations of neurons without simultaneously producing a response in other neurons that are not targeted for stimulation. We will discuss findings related to the selective activation of the direct versus indirect response, as well as the selective activation of specific ganglion cell types (e.g. midget versus parasol) or classes (ON versus OFF). Then, we will discuss recent findings suggesting that the use of sinusoidal waveforms may offer advantages for selective activation as compared to conventional pulsatile stimulation.

Studies aimed at selectively activating the direct response without eliciting a response for indirect activation of the ganglion cells have shown some success. For example, using epi-retinal stimulation it is possible to selectively activate ganglion cells with short-duration pulses (<0.2ms) without eliciting an indirect response (Jensen et al. 2005b; Fried et al. 2006; Sekirnjak et al. 2006). One study reported that the threshold for direct activation was much lower than that of indirect activation; thresholds differed by a factor of ~8 for 500μm diameter electrodes, and a factor of ~20 for 125μm diameter electrodes (Jensen et al. 2005b). These results raise the possibility that selective activation of the direct response is optimal for small-diameter electrodes. A series of studies using small diameter electrodes (~10μm) examined only the response to direct activation (Sekirnjak et al. 2006; Sekirnjak et al. 2008). Although the difference in threshold for direct versus indirect activation was not examined, the authors report that indirect activation was rarely observed (personal communication, Chris Sekirnjak). However, another study using conical electrodes (equivalent in area to a 40μm diameter disk electrode) found that the threshold for indirect activation was only 2.5 times higher than that of direct activation (pulse duration: ≤0.15ms) (Fried et al. 2006). Taken together, these results suggest that short-duration pulses allow selective activation of the direct response over some range of stimulus amplitudes; it remains unclear whether smaller diameter electrodes facilitate this selective activation.

The ability to selectively activate the direct response offers a potentially powerful stimulation strategy in which any desired spike train can be generated using a one-spike-per-pulse paradigm (Fried et al. 2006). However, this stimulation strategy has the disadvantage that selective activation of the direct response may be possible only over a relatively small range of stimulus amplitudes (see above). An alternative stimulation strategy has recently been proposed that enhances selective activation of the direct response (Freeman and Fried 2011). The premise of this strategy is that indirect activation becomes greatly desensitized in response to repetitive stimulation at rates >2Hz. Therefore, delivering a pulse train continuously at a moderate rate (e.g. ~8–16Hz) will cause the indirect response to effectively shut down. However, the direct response continues to be elicited with only a modest increase in threshold (~30%). This allows any desired pattern of spikes to be elicited at one-spike-per-pulse through direct activation without interference from spikes elicited by indirect activation. Interestingly, this new stimulation strategy also allows the spontaneous firing rate of ganglion cells to be set to any desired level by modulating the pulse rate of the continuously delivered pulse train. Such an approach could potentially allow the brightness of the percept to be either increased or decreased (i.e. brighter or darker than the grayish background percept) by modulating the firing rate above or below the spontaneous rate; this

is not possible with existing stimulation methods. A disadvantage of this method is that passing axons would likely be activated by direct activation. Also, continuous stimulation would likely require more power than conventional stimulation methods.

Because direct activation of the ganglion cells can result in activation of passing axons, it may be desirable to selectively activate the indirect response. Given that selective activation of the *direct* response is best accomplished for short-duration pulses with small-diameter electrodes, it is conceivable that selective activation of the *indirect* response could be achieved with large-diameter electrodes and long-duration pulses (Greenberg 1998). However, using epi-retinal stimulation with 500μm diameter electrodes at pulse durations of 10–20ms, the threshold for direct versus indirect activation were similar in magnitude (Jensen et al. 2005b). Therefore, it may not be possible to selectively activate the indirect response for epi-retinal stimulation – at least when the stimulating electrode is in close proximity to the ganglion cell body. When the stimulating electrode is positioned far from the ganglion cell body but within the dendritic field of the ganglion cell, it is possible to selectively activate the indirect response (Jensen et al. 2005b). Presumably, this is because the stimulating electrode is closer to those bipolar cells that provide synaptic input to ganglion cell than it is to the ganglion cell soma or initial segment. However, even in this stimulus configuration, it is not possible to avoid direct activation of other ganglion cells whose cell bodies are near the stimulating electrode. Therefore, selective activation of the indirect response with epi-retinal stimulation has not been demonstrated with pulsatile stimulation.

It might be expected that the selective activation of the indirect response would be possible with sub-retinal stimulation because the stimulating electrode is significantly closer to the bipolar cells than the ganglion cells. One study using sub-retinal stimulation reports that selective activation of the indirect response could be achieved (although the relative thresholds for direct versus indirect activation were not reported) (Stett et al. 2000). However, another study found that for sub-retinal stimulation, the thresholds for direct versus indirect activation were statistically indistinguishable (Tsai et al. 2009). These studies were done in healthy retina, but other work has shown the threshold for indirect activation actually *increases* in the degenerate retina relative to healthy retina (Jensen and Rizzo 2008), while the threshold for direct activation is not affected by degeneration (Sekirnjak et al. 2009). This suggests that the ability to selectively activate the indirect response is reduced in the degenerate retina relative to the healthy retina. Further study is needed, particularly in the degenerate retina, in order to examine whether the indirect response can be selectively activated with sub-retinal stimulation.

The ability to selectively activate individual types of ganglion cells would offer significant advantages towards replicating normal physiological spiking patterns in ganglion cells (see Section 3.1). This is a major challenge because each point on the retina is represented by the full array of ganglion cell types, and therefore each stimulating electrode is in close proximity to many different types of ganglion cells. One possibility is that the ganglion cell types with the lowest threshold for direct activation could be selectively targeted. However, even though the threshold for direct activation varies by a factor of ~3 across some cell types (Fried et al. 2009), there are a large number of other ganglion cell types whose threshold has not been characterized. If any of these cell types have a threshold that is relatively low, then it may not be possible to selectively activate a single type. Furthermore, selective activation of those ganglion cell types with thresholds that are relatively high cannot be achieved with direct activation. Whether the threshold for indirect activation differs among different physiological types of ganglion cells has not yet been examined.

Multiple studies have also investigated the potential of selectively activating either ON or OFF type ganglion cells. In response to stimulation with light, ON and OFF ganglion cells representing the same point in space are known to fire temporally out of phase (e.g. ON cell firing rate increases to light stimulation while OFF cell firing decreases). For direct activation, the thresholds of ON versus OFF cells were not statistically different, both for epi-retinal (Sekirnjak et al. 2008) and sub-retinal (Tsai et al. 2009) stimulation. Therefore, in response to electric stimulation, ON and OFF ganglion cells representing the same point in space will fire temporally in phase. This is clearly an unnatural signal for the visual system, and may limit the quality of prosthetic vision. For indirect activation, the threshold for ON cells is lower than that of OFF cells (at least for cathodal pulses) (Jensen and Rizzo 2006), but this has only been demonstrated in the healthy retina. As discussed earlier, responses in the healthy retina may contain contributions from photoreceptor activation, potentially underlying the difference in threshold for ON and OFF cells. The threshold of ON versus OFF cells in the degenerate retina has not been tested, in part because of the difficulty of classifying ON versus OFF cells in the absence of light responses. Therefore, methods to selectively activate the ON versus OFF pathways have not yet been demonstrated unequivocally.

The use of more complex stimulus waveforms is currently being explored to determine if they can provide better selectivity over conventional pulsatile stimuli (Langille et al. 2008; Cantrell and Troy 2009; Freeman et al. 2010c; Foutz and McIntyre 2010). For example, a recent study found that low frequency sinusoidal waveforms (10–25Hz) produced robust synaptic responses (i.e. indirect activation) in the ganglion cell while producing little or no direct activation of the ganglion cell (Freeman et al. 2010a). Increasing the frequency of stimulation to 100Hz resulted in a strong spiking response arising from direct activation with very little influence from the synaptically mediated response. This suggests that the frequency content of the stimulus waveform can be tailored to provide optimal selectivity over the types of neurons being activated. Stimulus waveforms other than sinusoids, such as triangular pulses, are also being evaluated for their ability to selectively activate neuronal targets (Foutz and McIntyre 2010). The mechanisms underlying this frequency dependence have not been completely resolved. Modeling results suggest that differences in kinetics and activation/inactivation properties among voltage-gated ion channels may be involved (Freeman et al. 2010a). It is also possible that the passive electric properties of the cell membrane and surrounding tissue contribute as well. For example, different retinal cell types (e.g. bipolar versus ganglion cells) may exhibit unique temporal response characteristics due to differences in size and morphology. Because individual pulses contain broad spectral content, they will likely activate all retinal cell types indiscriminately, regardless of any differences in temporal dynamics. Conversely, sinusoidal stimulation contains energy at a single frequency and therefore may be more effective than pulsatile stimulation at achieving selective or preferential activation of neuronal targets.

3. Signaling Strategies Employed by the Retina

Much research in retinal neurophysiology has been dedicated to understanding how visual information is encoded in the spiking patterns of retinal ganglion cells (Field and Chichilnisky 2007; Gollisch and Meister 2010). Knowledge of how a given pattern of spiking represents particular features of the visual stimulus will help guide the development of effective stimulation strategies with a retinal prosthesis. Here, we review some of the fundamental signaling strategies employed by the retina, including the use of different types of ganglion cells (Section 3.1), adaptation of retinal ganglion cells (Section 3.2), and the ability of ganglion cells to encode information using precise temporal (Section 3.3) and spatial (Section 3.4) patterns of spiking. Finally, we discuss the importance of considering saccadic suppression in developing a stimulation strategy (Section 3.5).

3.1 Ganglion Cell Types

Unlike a 1-Megapixel digital camera that samples visual space uniformly, the primate retina encodes each point in space with an array of ~17 ganglion cell types, each of which inform the brain about particular features of the visual stimulus (Field and Chichilnisky 2007). The most common types of ganglion cells in the primate retina are the midget and parasol cells. Midget cells are by far the most numerous, making up about 70% of all ganglion cells in human retina, as compared to 8–10% for parasol cells (Rodieck 1998). However, the proportion of midget cells varies significantly with eccentricity, making up 95% of ganglion cells in the central retina but only 45% in the periphery (Dacey 1993).

Midget and parasol cells have ON and OFF subtypes, each of which exhibit a concentrically organized receptive field with the classic excitatory center and antagonistic surround (for review, see (Kolb 2003)). Midget ganglion cells are characterized by their small dendritic fields, giving rise to small receptive fields that underlie high-spatial resolution vision. For example, near the fovea, midget ganglion cells typically receive synaptic input from a single bipolar cell, and these bipolar cells themselves receive input from a single cone (Kolb and Dekorver 1991; Wassle and Boycott 1991). In contrast to midget cells, parasol cells have large dendritic fields (Rodieck 1998), giving rise to large receptive fields and high contrast sensitivity (Kaplan and Shapley 1986). Even a very small change in luminance can be detected in parasol cells because they sum input from many presynaptic bipolar cells. In addition to the classic center and surround, a subset of parasol cells have an additional response mechanism referred to as nonlinear subunits (Benardete and Kaplan 1999; Victor 1999). These subunits are the defining feature of Y-type ganglion cells in lower mammals (Hochstein and Shapley 1976; Gollisch and Meister 2010), causing the ganglion cell to spike in response to the movement of any textured pattern through the receptive field, including the movement of high-spatial frequency stimuli that could not be resolved by the classical center and surround (Passaglia et al. 2009). Taken together, these properties allow midget and parasol cells to encode distinct features of the visual scene; midget cells convey information on fine spatial detail while parasol cells are well-suited for motion analysis (Kaplan and Benardete 2001) (for a discussion on color vision, see Section 4.5).

There are also ganglion cell types that extract more complex features of the visual stimulus. Studying the physiological characteristics of such cell types in primate is difficult because the majority of these cells are present at low densities (1–2% of the total population) (Dacey et al. 2003). In lower mammals, however, the relative number of each type of ganglion cell is more uniform than in primate (Masland and Martin 2007), allowing many different ganglion cell types to be characterized. For example, the most numerous ganglion cell type in rabbit retina is the local-edge detector; it responds strongly to edges within its receptive field, but weakly to other stimuli (Zeck et al. 2005). There are also two types of ganglion cells that fire strongly to motion in a particular direction, but weakly to motion in in the opposite direction (Barlow and Hill 1963). A more complete description of these non-midget and non-parasol cell types has been given in previous reviews (Troy and Shou 2002; Dacey and Packer 2003; Field and Chichilnisky 2007; Gollisch and Meister 2010).

In response to light, each ganglion cell type exhibits characteristic temporal response properties. For example, in response to a step change in local luminance, midget and parasol cells respond with a rapid increase in firing rate (i.e. ‘brisk’ response), while the response of many other cell types is relatively slow (i.e. ‘sluggish’ response) (Troy and Shou 2002). Most ganglion cell types are temporally bandpass (DeVries and Baylor 1997), indicating that there is a particular range of temporal frequencies to which the cells are optimally sensitive. For example, midget cells respond maximally to frequencies in the range of 4–8Hz while parasol cell respond maximally near ~16Hz (Kaplan et al. 1990). The temporal response properties are thought to be shaped by synaptic connections in the inner retina

(Roska and Werblin 2001), with smaller contributions arising from intrinsic physiological differences (O'Brien et al. 2002).

It may be important to replicate these cell-type specific responses using stimulation from a retinal prosthetic in order to transmit a complete and accurate representation of the visual stimulus. For direct activation, the ability to replicate the cell-type specific responses my not be possible because of the challenges associated with selectively activating particular types of ganglion cells – at least with existing stimulation techniques (see Section 2.3). In contrast, indirect activation may replicate aspects of the cell-type specific spiking patterns because it utilizes the existing inner retinal circuitry. Many response properties are known to be shaped by these circuits; for example, the transient response of parasol cells to a step change in luminance is partly due to amacrine cell feedback (Kaplan et al. 1990; Roska and Werblin 2001). In support of the view that such circuits may be recruited following electric stimulation, studies have found that in response to indirect activation, ganglion cells exhibit distinct temporal pattern of spikes that may be due to inner retinal processing (Jensen and Rizzo 2006). The extent to which these distinct temporal responses mirror the normal physiological spike patterns has not been examined in detail. It is encouraging, however, that even in the degenerate retina, ganglion cells can be classified into distinct categories based on their temporal spiking response (Jensen and Rizzo 2008).

Although the recruitment of inner retinal circuitry may replicate some of the cell-type specific patterns found across ganglion cell types, it will not replicate the phase differences exhibited by the ON and OFF pathways. This is because the mechanisms responsible for the differential response of ON and OFF cells to light stimulation are in the outer retina, at the photoreceptor-to-bipolar cell synapse. Replicating differential activity of the ON and OFF pathways in the degenerate retina will require selective activation of ON versus OFF bipolar cells, or ON versus OFF ganglion cells; such selectively is not currently possible (see Section 2.3).

3.2 Ganglion Cell Adaptation

One of the fundamental challenges in retinal physiology is to understand how a given pattern of spikes encodes information on the visual stimulus. For example, a starting hypothesis may be that the number of spikes in a given ganglion cell informs the brain as to the light intensity in some small region of space. However, this simple encoding scheme is not possible since the retina operates under a wide range of light levels (~10 log units) and the full range of luminance inputs cannot be encoded in the narrow dynamic range of spiking neurons (Shapley and Enroth-Cugell 1984; Walraven et al. 1990). For example, if a single spike were to encode the presence of a single photon, then signaling 10^6 photons/sec would require ganglion cells to fire at 10^6 spikes/sec. This is not possible because ganglion cell firing rate saturates at $<10^3$ spikes/sec (O'Brien et al. 2002).

The visual system deals with this challenge by adjusting retinal sensitivity to the ambient light level of a visual scene, a process referred to as light adaptation. The mechanisms responsible for such adaptation are primarily in the photoreceptors (Perlman and Norman 1998), with some contribution from the retinal network (Dunn et al. 2007; Freeman et al. 2010b). An important consequence of this adaptation is that under cone-dominated vision, the sensitivity of retinal ganglion cells to light changes in inverse proportion to background light level (Weber's Law). As a result, the firing rate of ganglion cells does not encode light intensity, per se, but *relative* light intensity, referred to as contrast (Shapley and Lam 1993; Troy and Enroth-Cugell 1993). The strategy of the retina to inform the brain on contrast, and not light intensity, should be considered in developing gain controls in the image acquisition device (e.g. an external camera). For example, if one were to deliver an electric stimulus whose amplitude scales proportionally with light intensity, then it may not be possible to

move from a dimly lit environment to a bright room without saturating (i.e. causing the stimulus intensity at each electrode to be near maximal). Instead, the stimulus amplitude at each electrode can be determined by the light intensity in some given region of space *normalized* by the background light level. Such gain controls would mimic light adaptation of the healthy retina and allow the patient to move between different lighting environments.

While light adaptation acts to adjust retinal sensitivity as we move between different background light levels, there are also mechanisms that adapt to the prevailing spatial and temporal contrast even under conditions with a constant background light level. Such mechanisms reduce retinal sensitivity and increase response speed in the presence of high contrast stimuli (Shapley 1997; Smirnakis et al. 1997; Chander and Chichilnisky 2001; Beaudoin et al. 2007; Freeman et al. 2010b). Mechanisms of contrast adaptation should be considered in conjunction with mechanisms of light adaptation in their ability to alter retinal sensitivity to repetitive electric stimulation. For example, the desensitization of the indirect response to repetitive electric stimulation could be due to the same mechanisms responsible for contrast and/or light adaptation (Freeman et al. 2010b; Freeman and Fried 2011). Adaptation in the photoreceptors will not be a concern for retinal prosthesis applications because the photoreceptors are absent in the degenerate retina. However, adaptive mechanisms in the inner retina could potentially be recruited in response to electric stimulation (Baccus and Meister 2002; Dunn et al. 2007).

3.3 Encoding Visual Information in the Temporal Pattern of Spiking

An important question in retinal signaling is the extent to which the precise temporal pattern of spiking is important; a topic generally referred to as ‘temporal coding’ (for review, see (Victor 1999)). The traditional view is that the total number of spikes within a given window of time (e.g. 50ms) is simply counted up by the brain without regard for the precise temporal pattern of spikes. This is referred to as firing rate, or spike count. However, there are two challenges associated with simply counting up the number of spikes. First ganglion cells fire spontaneously in the absence of any visual input (Troy and Lee 1994; Freeman et al. 2008). The brain must discriminate spikes elicited by dynamic stimulation with light from the spontaneous spikes. Second, in response to repeated presentations of the same stimulus, the number of spikes in a given window varies from trial-to-trial (Reich et al. 1997). To account for this experimentally, the response to a given stimulus is often averaged across trials to yield the mean firing rate. Of course, the visual system does not have the luxury of averaging over multiple stimulus repetitions, and therefore the *mean* firing rate of a given cell cannot be utilized (the potential to average across cells is discussed below).

Because of the limits imposed by spontaneous spiking and response variability, it may not be possible for higher visual centers to decode the ganglion cell spike count unambiguously. This has led to the view that visual information may be encoded in the precise temporal pattern of spikes. For example, it has been suggested that information may be carried in bursts of spikes, so-called ‘firing events’(Berry et al. 1997). Supporting this view, ganglion cell responses to white noise stimulation exhibit brief bursts of spikes separated by long periods of silence (Berry et al. 1997; Berry and Meister 1998; Koch et al. 2004). Such bursts are extremely reliable, both in terms of the number of spikes per burst, and in the precise timing of these bursts (Uzzell and Chichilnisky 2003). Although the response of primate retinal ganglion cells to natural scenes has not been reported, data from guinea pig show ganglion cells also fire in a bursty fashion to natural scenes stimulation (Koch et al. 2006). Ganglion cells may also employ coding schemes other than the use of spike count or bursts. More abstract coding schemes could be used; for example, a neuron might respond to a small spot with a tonic change in firing rate but respond to a large spot with oscillatory type firing (Victor 1999).

Unfortunately, it is difficult to test experimentally between these coding schemes because both neural recordings and behavioral experiments are required to determine if a given feature of the neural response is utilized by visual centers of the brain (Victor and Nirenberg 2008). Because of the challenge of definitively answering how information is encoded in retinal ganglion cells, the importance of the precise temporal pattern of spiking for conveying visual information is still unresolved. However, it is possible that results from clinical trials could yield insight into the temporal coding schemes employed by the retina. For example, the use of prosthetic stimulation to elicit bursts of spikes in a population of ganglion cells, as compared to simply elevating the mean firing rate of those cells without bursts, might yield insight as to the functional role of bursts in generating visual percepts. Unfortunately, the ganglion cell spiking patterns elicited during human clinical trials are unknown due to the technical limitations of such recordings. However, knowledge gained from ongoing *in vitro* stimulation experiments (Section 2) can be used to infer the patterns of spiking elicited by stimulation, potentially providing a means to test experimentally between neural codes employed by ganglion cells.

3.4 Encoding Visual Information in the Spatial Pattern of Spiking

Each type of ganglion cell tiles the retina with slightly overlapping receptive fields (DeVries and Baylor 1997; Gauthier et al. 2009). Due to this slight overlap, it is expected that neighboring cells of the same type would exhibit correlations in their firing rates, particularly for naturalistic stimuli where there are significant spatial correlations in luminance. However, neighboring ganglion cells have a tendency to fire synchronously more than would be predicted by having shared visual input (Mastronarde 1989). This has led to the view that correlations in spiking among multiple ganglion cells may constitute a population code, conveying information on the visual stimulus that is not present if ganglion cells acted as independent encoders (Meister et al. 1995; Shlens et al. 2008).

Synchronized spiking is present in the dark, and therefore does not require visual stimulation (Schnitzer and Meister 2003). The synchronization in spike timing can be very precise, parasol ganglion cells in primate often fire within ±5ms of a neighboring parasol cell of the same class (ON or OFF) (Shlens et al. 2006). The observation that correlations in spike timing occurs only between *neighboring* ganglion cells suggests that such synchronization is a local phenomenon. However, other work has observed synchronized firing between distant ganglion cells that depends on specific parameters of light stimulation (see below for discussion) (Neuenschwander and Singer 1996). For the synchronization that occurs locally, evidence suggests that the mechanism responsible is primarily shared synaptic input, with minor contributions from electrical coupling (Trong and Rieke 2008).

Whether synchronized spiking between neighboring ganglion cells will occur in response to stimulation with a retinal prosthetic has not been investigated. In response to direct activation, it is likely that some synchronized activity will occur because responses are phase-locked to the stimulus onset. Therefore, the timing of elicited spikes in neighboring ganglion cells is likely to be similar. Experiments to determine whether the spike trains that result from indirect activation are synchronized have not yet been performed. However, the observation that shared synaptic input is the primary contributor to synchronization (Shlens et al. 2008) raises the possibility that prosthetic activation of bipolar cells (i.e. indirect activation) might result in physiological levels of synchronization.

It is possible that direct activation could induce too much synchronized spiking and thereby pose a problem for postsynaptic neurons in the thalamus. Consider the number of ganglion cells that may be simultaneously activated by a given electrode; in humans, the dendritic field diameter of ganglion cells 4mm from the fovea is ~30μm for midget cells and ~200μm for parasol cells (Dacey and Peterson 1992). For an electrode diameter of 260–520μm

(Greenwald 2009), approximately 75–300 midget cells and 2–7 parasol cells are located within the area of each electrode. Modeling work suggests this may cause preferential activation of cells near the edge of the electrode due to (1) a larger spatial gradient in electric field near the edges of the electrode (Rattay 1986) and/or (2) charge collecting near the edges of the electrode (Behrend et al. 2008). However, such preferential activation has not been demonstrated physiologically; results from one study indicate that stimulation with 200μm diameter disc electrode yields uniform ganglion cell activity across the area of the electrode (Behrend et al. 2009). This suggests that stimulation of the primate retina with a 520μm diameter electrode could simultaneously activate ~300 midget cells. Such a large pattern of simultaneous activity is unlikely to occur naturally and may underlie some of the inconsistencies in the induced phosphenes. The use of smaller diameter electrodes would likely reduce the number of ganglion cells being simultaneously activated, and therefore reduce the level of synchronization

Another concern is that the timing of the synchronization will be too precise when elicited by prosthetic stimulation. For example, under natural conditions, synchronized spiking between neighboring ganglion cells often has a timing precision of ±5ms, while direct activation will elicit simultaneous spiking with a timing precision of <1ms. Therefore, ganglion cells may fire with excessively high timing precision in response to direct activation. The consequence that such timing precision will have on the resulting percept is unknown.

In addition to synchronization in spike timing between neighboring ganglion cells, there is also synchronization between cells that are significant distances from one another (up to 20° visual angle)(Neuenschwander and Singer 1996; Neuenschwander et al. 1999). Interestingly, these long-range synchronizations are induced only under specific stimulus conditions. Regions of the retina that are simultaneously stimulated by a contiguous light stimulus respond with synchronous oscillations (60–120Hz) across large populations of ganglion cells (Ariel et al. 1983; Neuenschwander and Singer 1996). However, if two regions of the retina are simultaneously stimulated with separate spots of light (i.e. no contiguous region of stimulation), the synchronized oscillations are not present. These results suggest that synchronous oscillations may encode global aspects of the visual scene, such as stimulus continuity. It has been suggested that such oscillations originate from spiking amacrine cells that are excited through gap-junctions with ganglion cells, and in turn, produce inhibition on surrounding ganglion cells (Kenyon et al. 2004). Evidence for the involvement of synchronized oscillations in human vision has been reported with ERG recordings (Carli et al. 2001).

3.5 Saccadic Suppression

Under natural viewing conditions, the eyes make rapid shifts in position about 2–3 times per second. These are referred to as saccadic eye movements and they fall into two categories: (1) large saccadic eye movements, such as when we change our direction of gaze, and (2) small shifts in eye position (<1° visual angle) during fixation on a given point in space, including microsaccades and small drifts (Steinman et al. 1973; Rucci 2008). Saccades cause frequent movement of the image projected on the retina. Therefore, one might expect our view of the world would be similar to a shaky video camera. However, the visual system is able to filter out this motion to create a stable view of the visual world, a process referred to as saccadic suppression (Krekelberg 2010). Psychophysical studies have shown that visual sensitivity is suppressed during a saccade (Burr et al. 1994); the mechanisms responsible could be in the retina and/or in higher visual centers of the brain. However, since visual sensitivity is suppressed not just during a saccade, but immediately preceding the movement of the eye, mechanisms in higher visual centers must be involved (Wurtz 2008).

The existence of saccadic suppression in higher visual centers suggests that the relationship between ganglion cell spiking activity and the resulting visual percept is not a simple one-to-one mapping. Instead, visual perception depends both on the spiking pattern of ganglion cells and the activity of the oculomotor system. Consider an experiment in which a single electrical pulse is applied to the retina and the patient is asked to report on the brightness of the elicited phosphene. If the stimulation is delivered *during* a saccadic eye movement, then there is the possibility that saccadic suppression higher visual centers may attenuate or filter out the incoming burst of spikes. Conversely, if the same pulse is delivered *between* saccades, suppression will presumably not be present. As a result, the reported brightness and/or other features of the phosphene may be very different in each case even though the signal from the retinal is identical. Therefore, it may be necessary to take saccadic eye movements into account with an eye tracker such that stimulation can be delivered only between saccades. The effect of stimulating *during* versus *between* saccades has not been examined in clinical trials.

While the existence of saccadic suppression is well established, its mechanistic origin remains an area of ongoing debate. Physiological recordings from primary visual cortex (V1) have found little evidence for the suppression of V1 neurons during saccadic eye movements (Wurtz 2008), suggesting that saccadic suppression does not originate in the retina, thalamus, or V1 (but see (Thilo et al. 2003)). Conversely, there is strong evidence to suggest that suppression occurs in higher visual areas of the brain, including the middle temporal area and superior colliculus (Robinson and Wurtz 1976; Thiele et al. 2002; Bremmer et al. 2009). The origin of the neural signal underlying this suppression is thought to result from a so-called corollary discharge (sometimes referred to as an efferent copy) in which the neural signals that are sent to the eye muscles to produce a saccadic eye movement are simultaneously sent to other regions of the brain to inform them that a saccade is being initiated (Sommer and Wurtz 2008). This ‘copy’ of the motor command then suppresses the response of visual neurons, thus accounting for suppression of visual sensitivity during saccades. Note that suppression of visual sensitivity occurs during large saccadic eye movements, but is not thought to occur during smaller eye movements that occur during fixation (Ross et al. 2001).

While saccadic suppression is known to occur in higher visual centers, it is possible that there is also a retinal component. In support of this view, physiological recordings from ganglion cells have shown that rapid, saccadic-like shifts of the visual scene causes transient inhibition of ganglion cells (at least in some ganglion cell types) (Olveczky et al. 2003; Roska and Werblin 2003). The retinal component of saccadic suppression may influence the percepts induced by prosthetic stimulation, although this will depend on whether ganglion cells spiking is elicited by direct or indirect activation. For example, the saccadic suppression of ganglion cells seen physiologically is the result of transient inhibition from amacrine cells (Roska and Werblin 2003). If ganglion cell spiking is elicited by indirect activation, such amacrine cells could be activated. This will cause inhibition of the bipolar cell terminals and ganglion cell dendrites, likely influencing the resulting pattern of spiking in the ganglion cell.

If ganglion cells are elicited purely by direct activation, then amacrine cells will not be activated, and the retinal component of saccadic suppression will not be recruited. This raises the possibility that ganglion cell spikes might be elicited *during* a saccade even though these spikes would normally be absent due to retinal suppression. It is possible that such spikes would be suppressed in higher visual centers (as discussed above) and therefore do not contribute to visual perception. However, another possibility is that, at least for some ganglion cell types, spikes elicited during a saccade are not influenced by saccadic suppression in higher visual centers. For example, psychophysical evidence suggests that

saccadic suppression is specific to the magnocellular pathway (e.g. parasol cells), while not affecting the parvocellular pathway (e.g. midget cells) (Ross et al. 2001). Therefore, it is possible that direct activation will elicit spikes in midget cells during a saccade that (1) would have normally been absent due to the retinal component of suppression, and (2) are not affected by saccadic suppression in higher visual centers. The influence that such spikes would have on the induced percepts is unknown.

4. Understanding the Patterns of Ganglion Cell Activity Elicited in Clinical Trials

4.1 Why Do Percepts Fade over Time?

The ability to control the brightness of a given percept over time is limited with existing stimulation techniques. Following sustained electric stimulation of the retina, the brightness of a given phosphene fades over time (Perez Fornos et al. 2010; Zrenner et al. 2010). In response to moderate stimulation rates (5–60Hz), the time course of brightness fading contains two temporal components; a rapid fading that occurs within <0.5sec, as well as a slower reduction in brightness that occurs over several seconds (Perez Fornos et al. 2010). Interestingly, a recent *in vitro* study found that in response to sustained stimulation at 16Hz, the indirect response of rabbit retinal ganglion cells desensitized with two temporal components, one occurring rapidly (τ = 0.18sec), and the other occurring over many seconds (τ = 14.0sec) (Freeman and Fried 2011). The correlation between the timing of the *in vitro* data and the clinical results raises the possibility that the reduction in ganglion cell firing rate over time may contribute to the fading of brightness.

Another possibility is that saccadic eye movements contribute to the fading of brightness in clinical trials. In the healthy visual system, the presence of saccadic eye movements causes the light intensity observed by each ganglion cell to be constantly changing (see Section 3.5). The importance of such eye movements can be illustrated by the following observation: when an image is stabilized on the retina, the perception of this image fades in time (Rucci 2008). This suggests that dynamic stimulation with light may impart unique spatial (Desbordes and Rucci 2007) and temporal (Passaglia and Troy 2004) patterns of spiking that are necessary to maintain perception. Therefore, it may be necessary to replicate such patterns of spiking with prosthetic stimulation in order to maintain perception.

The use of sub-retinal microphotodiode arrays may allow saccadic eye movements to be incorporated naturally by delivering stimulation as a function of light input to the eye (Zrenner et al. 1997; Peachey and Chow 1999; Palanker et al. 2005). This is in contrast to head-mounted cameras in which such eye movements are not accounted for (Ahuja et al. 2010). A recent study found that stimulation delivered from a microphotodiode array achieved more stable percepts (i.e. percepts that did not fade in time) as compared to percepts induced by repetitive stimulation of a single electrode (Zrenner et al. 2010). It is possible that the increased stability with microphotodiode arrays was the result of more natural patterns of ganglion cell spiking arising from saccadic eye movements. However, another possibility is that the percept did not fade because a freely moving eye causes each electrode to be stimulated infrequently. As discussed earlier, the indirect response becomes desensitized in response to repetitive stimulation (see Section 2.2). Therefore, if there are brief periods of time in which each electrode is not active, this allows time for nearby ganglion cells to re-sensitize between stimulus pulses. In other words, the observation that brightness fades in time in response to repetitive stimulation could be unrelated to saccadic eye movements, but instead result purely from desensitization of the indirect response (Jensen and Rizzo 2007; Freeman and Fried 2011).

It is important to note that the ability to generate stable percepts does not necessarily address the need to generate percepts whose brightness can be dynamically modulated in time with some temporal resolution. For example, in order to support vision with a temporal resolution of 10Hz, it is presumably necessary that the ganglion cell firing rate can also be modulated at ≥10Hz. The temporal resolution of the indirect response is severely limited by desensitization (Jensen and Rizzo 2007; Freeman and Fried 2011), and therefore it may not be possible to generate vision with high temporal resolution when ganglion cells are activated indirectly. However, direct activation of the ganglion cells can be achieved at very high rates without desensitization, raising the possibility that artificial vision with high temporal resolution could be achieved via direct activation.

4.2 Limitations to Generating Spatially Patterned Vision

In clinical trials, the ability to control the spatial pattern of brightness consists of two primary challenges: (1) stimulation from a single electrode should elicit a phosphene that is spatially localized, and (2) multi-electrode stimulation should result in a percept that is a predictable combination of individual phosphenes.

In response to stimulation from a single electrode, patients report a percept that covers approximately 2–3° visual angle; this is twice as large as the size of each stimulating electrode (1–2° visual angle)(Horsager et al. 2009). It is not clear why the percepts are much larger than the size of the electrode. A contributing factor could be the distance between the stimulating electrodes and the targeted neurons. One study reported these distances ranged from approximately 100 to 1000μm (10^{th}–90^{th} percentile of 30 –350μm) (de Balthasar et al. 2008). Presumably, increasing the distance between the electrode and the retinal surface results in a larger area of activation, thereby expanding the size of the percept. As stimulus amplitude is increased beyond threshold, patients report that the shape of the percept becomes larger, and also changes from round to elongated, or to something more complex (Nanduri et al. 2008; Greenwald 2009). The fact that larger percepts occur for larger stimulus amplitudes is not surprising since a larger area of retinal neurons will be activated. However, it is unclear why the shape of the percept becomes more complex; future work will be necessary to understand the mechanisms underlying this observation. Also, because percepts become larger for higher stimulus amplitudes, spatially-localized percepts may be possible only at relatively low stimulus amplitudes. Penetrating electrodes that are inserted into the retina will likely bring the stimulating electrodes closer to the target neurons (Winter et al. 2007), and therefore may reduce the spread of current and generate a smaller percept.

Following multi-electrode stimulation, patients can reliably identify the orientation of the percept (Caspi et al. 2009). Also, the ability to read large letters has been demonstrated for both epi-retinal (Humayun et al. 2010) and sub-retinal (Zrenner et al. 2010) implants. While these results suggest that the visual percept shows a general correspondence to the spatial pattern of electrodes, the complexity of the percept tends to be much greater for multi-electrode stimulation than would be predicted from stimulation with single electrodes. For example, stimulation with a 2 × 2 array of electrodes did not necessarily map to a 2 × 2 array of phosphenes. (Rizzo et al. 2003; Horsager et al. 2010).

A recent study examining the percepts induced by multi-electrode stimulation found interactions between electrodes that were separated by relatively large distances (>1mm) (Horsager et al. 2010). The authors proposed three potential mechanisms that may account for this interaction. First, simultaneous stimulation from multiple electrodes can cause interactions between the electric fields generated by each electrode. Such interactions were shown to affect the elicited percept and can be avoided by phase-shifting the timing of stimulus pulses, a strategy commonly employed with cochlear implants (Wilson et al. 1993).

Second, neuronal interactions can occur, in which a single ganglion cell can be activated by two or more electrodes (either from direct or indirect activation). Third, it is possible that the interactions do not occur in the retina, but instead occur in higher visual centers. For example, the precise timing of individual spikes arising from distant ganglion cells is thought to encode global features of the visual stimulus (see Section 3.4). As a result, the percept elicited by a given electrode may be influenced by stimulation from other electrodes even in the absence of neuronal interactions or electric field interactions. Future work will be needed to better understand the extent to which multiple electrodes interact on the neuronal level, and the contribution of the precise spike timing among populations of ganglion cells to the elicited percept.

4.3 Are Percepts Induced by Direct or Indirect Activation of Ganglion Cells?

The neural activity underlying the generation of phosphenes is not well understood. For example, it is not known whether phosphenes are the result of direct activation of ganglion cells, indirect activation, or some combination of both. However, the shape of the elicited percepts may provide some insight as to whether ganglion cells are activated directly and/or indirectly. Clinical trials employing both epi-retinal (Humayun et al. 2003; Rizzo et al. 2003; Horsager et al. 2009) and sub-retinal (Zrenner et al. 2010) stimulation report a combination of round and oval-shaped percepts. Oval-shape percepts are consistent with the activation of passing axons and therefore suggest ganglion cells are activated directly (see Section 2.1) (Greenberg et al. 1999). However, round percepts could potentially result from indirect activation or from direct activation of the ganglion cell bodies (without activating passing axons); these possibilities are discussed below.

Direct activation could potentially elicit a round percept if ganglion cell bodies near the stimulating electrode are preferentially activated over the passing axons. The threshold for activation of passing axons is approximately 2–4 times higher than the threshold for activation of the initial segment (the most sensitive region of the ganglion cell) (Jensen et al. 2003; Jensen et al. 2005b; Freeman et al. 2010a). Therefore, it may be that round percepts occur when the number of passing axons being activated is much less than the number of ganglion cells that are activated at their initial segment. Conversely, elongated percepts occur when the number of passing axons being activated is equal or greater than the number of ganglion cells that are activated at the initial segment.

Indirect activation would be expected to produce a round percept because only ganglion cells in the vicinity of the stimulating electrode will be activated (i.e. the activation of bipolar cells results in activation of only nearby ganglion cells). In support of the view that indirect activation can contribute to the elicited percepts, the time course of ganglion cell desensitization observed *in vitro* matches the time course of brightness fading seen in human subjects (see Section 4.1) (Perez Fornos et al. 2010; Freeman and Fried 2011).

The possibility exists that both direct and indirect activation contribute to phosphenes. For example, in response to a single pulse, passing axons are activated directly, eliciting a single spike in each cell. Indirect activation arising from that same pulse would lead to a burst of spikes, but only in ganglion cells whose cell bodies are relatively close to the stimulating electrode. Because a burst of spikes may be more likely to be detected by higher visual centers, the percept would appear round even though passing axons were activated. The shape of the percept would shift from round to oval when the indirect response component was weak or missing. In this case, the visual percept elicited would be due to activation of a sufficient number of passing axons. The relative contributions of direct and indirect activation will depend on many factors (see Section 2), including stimulation parameters and the desensitization of the indirect response.

Further insight into whether percepts are induced by direct or indirect activation comes from a recent study examining the effect of stimulation rate on perceptual threshold (Horsager et al. 2009). The threshold for detection was found to decrease as pulse rate was increased. The results were fit with a quantitative model, which found that the relationship between the applied stimulus and the resulting percept involved two primary stages of integration: one acting rapidly with a time constant of 0.24–0.65ms, and one acting more slowly with a time constant of 24–33ms. The authors hypothesized that the rapid integration is due to direct activation of the ganglion cells, and the slower integration results from processing in higher visual centers. If true, this would indicate that the percepts are due to direct activation. However, the time course of the slow stage of integration in the model is similar to the timing of spikes elicited by indirect activation (Jensen and Rizzo 2008; Freeman et al. 2010c), raising the possibility that indirect activation may be involved as well. Taken together, results from clinical trials provide evidence that both direct and indirect activation contribute to phosphene perception. It will be important to understand the conditions under which direct and indirect activation are recruited in order to interpret data from clinical trials, and ultimately to improve the quality of elicited vision.

4.4 Stimulation of the Central versus Peripheral Retina

Evidence from clinical trials suggests that the location of the stimulating electrode, in terms of retinal eccentricity, may have an impact on the resulting percept. Using microphotodiode arrays implanted in the sub-retinal space, it was noted that precise localization of the array under the fovea seemed important for generating “useful percepts” (Benav et al. 2010; Zrenner et al. 2010). Data from acute epi-retinal stimulation indicate that the threshold is lower for stimulation nearer to the fovea (Humayun et al. 1999). Also, there was found to be a more consistent correlation between stimulus current and brightness for stimulation near the fovea, while percepts elicited in the periphery tended to be dim, and did not exhibit the same relationship between stimulus level and brightness (Humayun et al. 2003).

There are several potential reasons why the elicited percepts may vary with retinal eccentricity. First, approximately half of visual cortex is dedicated to a portion of the retina located within ~7° of the fovea (Rodieck 1998). This overrepresentation of the small central portion of the retina suggests the manner in which visual signals are processed differs for central versus peripheral retina. Second, the relative number of each type of ganglion cell being stimulated varies with retinal eccentricity. For example, the ratio of the number midget to parasol cells in human retina decreases from 30:1 in the central retina to 3:1 in the peripheral retina (Dacey and Peterson 1992). The relative number of cell types being stimulated is important because the relationship between firing rate and stimulus contrast are very different for each type of cell. For example, parasol cells have much higher contrast sensitivity than midget cells, producing robust spiking responses in response to very low contrast stimuli (Kaplan and Shapley 1986). Therefore, a burst of spikes in a parasol cell may inform the brain on the presence of a relatively dim spot, while the identical burst of spikes in a midget cell is informing the brain on the presence of a much brighter spot.

4.5 Color Vision

Color vision is made possible with multiple types of cone photoreceptors – each type is maximally sensitive to a different wavelength of light (Dacey 2000). Humans have trichromatic vision, with three cone types showing maximal sensitivity to long (L-cones), middle (M-cones), or short (S-cones) wavelengths. There are two parallel pathways used by ganglion cells to carry color information: the red-green and blue-yellow pathways. Midget cells are thought to underlie the red-green pathway by combining signals from L-cones and M-cones antagonistically in a center-surround configuration (e.g. excited by L-cones (red) in the center and inhibited by M-cones (green) in the surround)(Dacey 2000). There are also

several types of ganglion cells that carry blue-yellow information (Dacey and Packer 2003; Schein et al. 2004). Other ganglion cell types sum the inputs from multiple cone types indiscriminately, carrying only luminance signals (i.e. no color information).

The fact that some ganglion cell types convey information on color and others do not may provide insight as to which cells are being activated in human trials. Patients report that the elicited percepts are often white or yellow (Greenwald 2009), but occasionally red-orange (Humayun et al. 2003) or blue (Humayun et al. 1999). Red-orange percepts could result from the preferential activation of ganglion cells types carrying information on the red-green color axis, such as midget cells. Conversely, blue percepts could arise from activation of one of many ganglion cell types carrying information on the blue-yellow axis (Dacey and Packer 2003). In one study, blue colored percepts were reported to occur after the offset of stimulation (Humayun et al. 2003). Interestingly, the blue percept was elicited at high but not low pulse rates, indicating that the types of ganglion cells activated may vary as a function of stimulation parameters. Other studies have also reported that the color of the elicited percepts varies with pulse rates (Horsager et al. 2009), but a systematic study on perceptual color versus stimulation parameters has not yet been performed.

4.6 Why Are Percepts Generally Brighter than Background?

In the absence of any stimulation, patients report their visual fields have a grayish background (Horsager et al. 2010). In response to electric stimulation, patients usually report the presence of a percept that is brighter than background (Humayun et al. 1999; Rizzo et al. 2003; Zrenner et al. 2010). Occasionally (~1/10 trials), a given electrode will elicit a dark percept rather than a bright percept (Horsager et al. 2009), and increasing stimulus amplitude will often cause such a percept to change from dark to bright (de Balthasar et al. 2008). Also, there are reports of a dark annulus surrounding a bright spot (Humayun et al. 2003), as well as dark spot following the offset of a stimulus that initially produced a bright percept (Perez Fornos et al. 2010).

The fact that percepts are primarily bright rather than dark may have implications as to whether the ON or OFF pathways are being activated. One possibility is that ON and OFF ganglion cells are activated identically by electric stimulation; in this case, the bright percept is produced because the signal from the OFF pathway is negated or outweighed by the signal from the ON pathway when processed in higher visual centers. Another possibility is that bright percepts result from preferential activation of ON versus OFF type ganglion cells. The potential for such preferential activation depends on whether ganglion cells are activated directly or indirectly. For example, OFF ganglion cells outnumber ON ganglion cells by nearly a factor of two (Balasubramanian and Sterling 2009), and therefore it would seem likely that direct activation of the ganglion cells would activate more OFF cells than ON cells since the threshold for ON versus OFF cells do not differ. Conversely, ON cells (both midget and parasol) have dendritic trees that are 30–50% larger than OFF cells (at least in human) (Dacey and Peterson 1992). Therefore, a response mediated by indirect activation might produce preferential activation of ON cells because they pool from a larger number of bipolar cells. However, since the relative threshold of ON versus OFF cells in response to indirect activation has not been reported for *in vitro* studies of the degenerate retina, it remains unknown whether ON cells are preferentially activated in clinical trials. Another factor that may contribute to the preferential activation of ON cells is that ON bipolar cells have longer processes than OFF bipolar cells, stratifying in the inner most layer of the inner plexiform layer (Famiglietti and Kolb 1976). Therefore, ON cells are closer to the stimulating electrodes than OFF cells (at least for epi-retinal stimulation). In summary, the reason that percepts are generally brighter than background remains an open question. Further testing is needed both clinically and with *in vitro* degenerate models to better understand this phenomenon.

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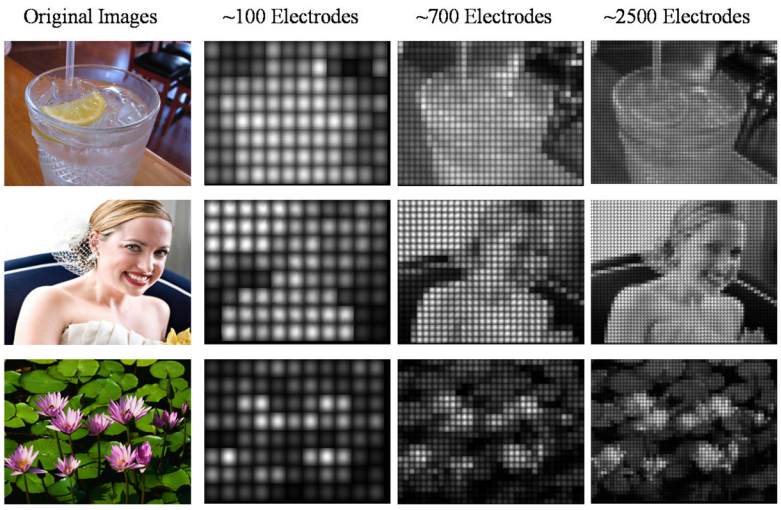

Figure 1. Illustration of Visual Percepts Induced by Prosthetic Stimulation

Simulations of how an image could be constructed by eliciting individual phosphenes of varying brightness. The simulation was performed by dividing the original photo into approximately 100, 700, or 2,500 segments (simulating arrays with varying numbers of electrodes) and then averaging the luminance that falls within that segment in the original photo. Each segment is then multiplied by a 2-D Gaussian filter to reproduce the circular shape of each phosphene.

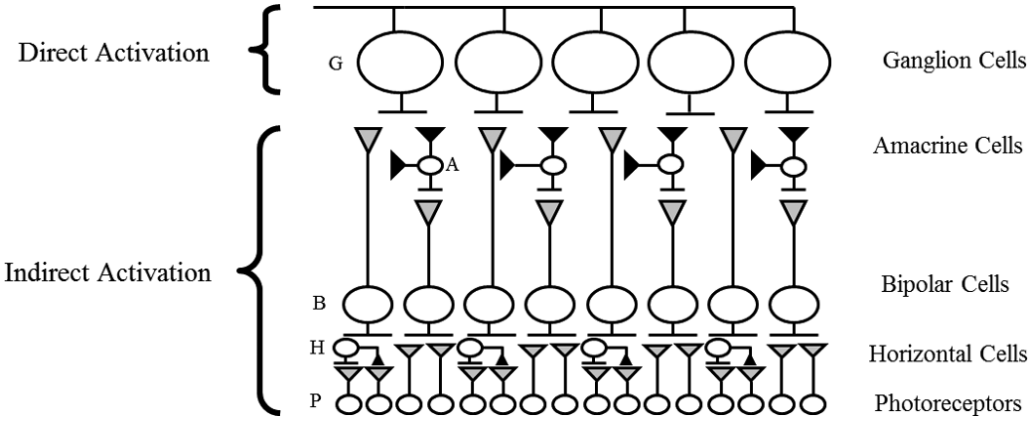

Figure 2. Direct versus Indirect Activation of Ganglion Cells with Electric Stimulation

The retina contains five major neuronal types: photoreceptors (P), horizontal cells (H), bipolar cells (B), amacrine cells (A), and ganglion cells (G). Direct activation elicits ganglion cell spiking as a result of the electric stimulus acting directly on the ganglion cell. Indirect activation elicits ganglion cells spiking when the electric stimulus acts on presynaptic neurons, producing a synaptic release at both excitatory (gray) and inhibitory (black) synapses. Ganglion cells receive excitatory and inhibitory synaptic input from bipolar and amacrine cells, respectively.

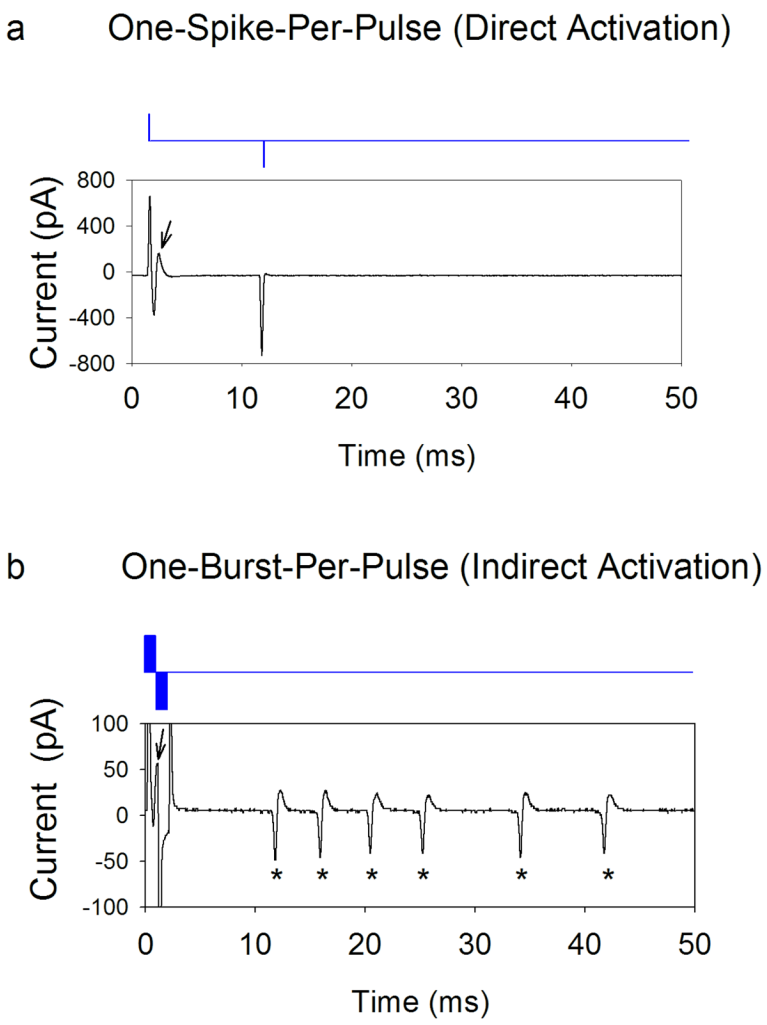

Figure 3. Retinal Ganglion Cell Spiking Responses to Direct versus Indirect Activation

Spikes were recorded from a rabbit retinal ganglion cell in response to epi-retinal stimulation with a 10kΩ Pt-Ir electrode. **a**. A cathodic pulse of 0.2ms duration was applied, followed by a 10ms delay, and then an anodal pulse. This delay was used in order to reveal the elicited spike (arrow) embedded in the stimulus artifact. This spike was elicited by direct activation (one-spike-per-pulse). **b**. A 1ms duration pulse (cathodic-first, with zero delay between cathodal and anodal phases) elicits a burst of spikes (asterisks) through indirect (i.e. synaptic) activation of the ganglion cell (one-burst-per-pulse). In response to this pulse, a spike was also elicited through direct activation (arrow).

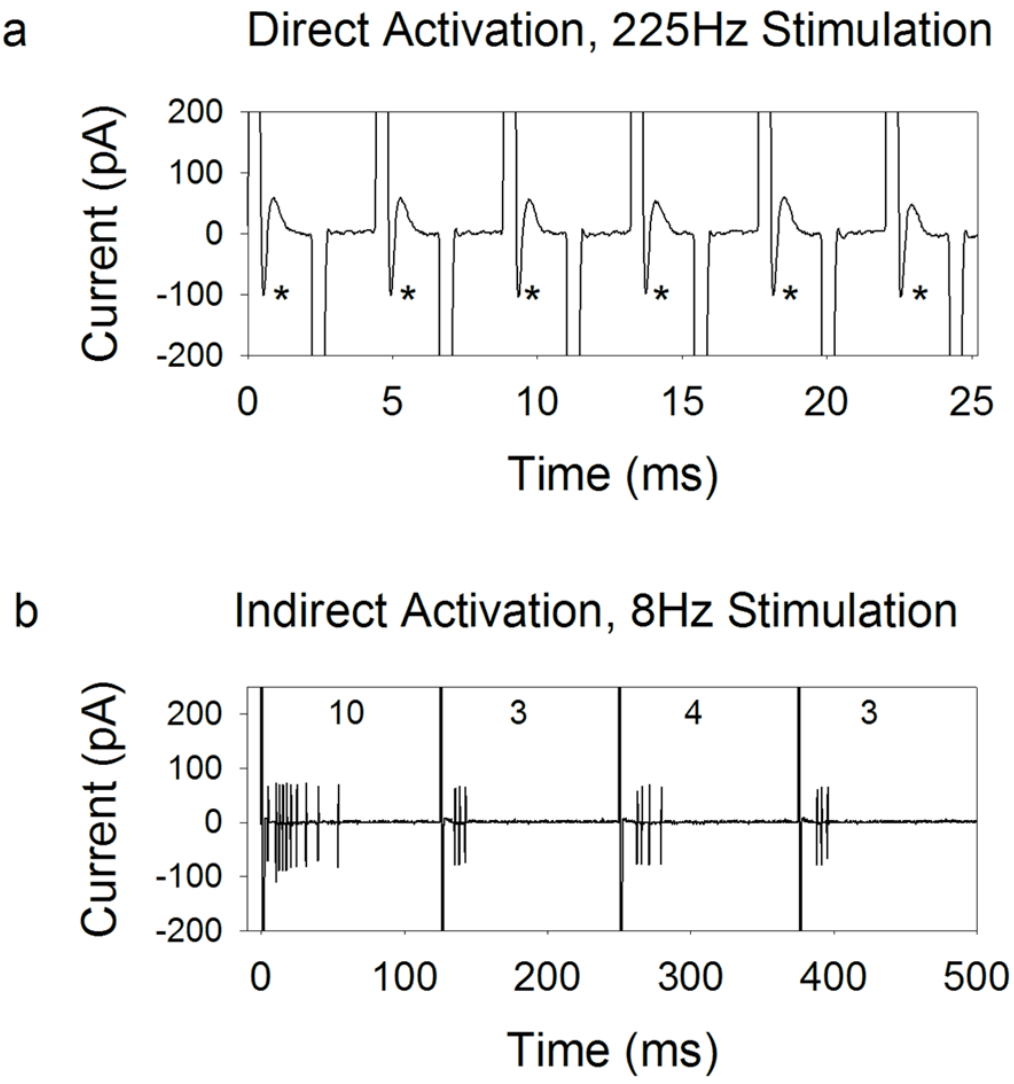

Figure 4. Temporal Resolution for Direct versus Indirect Activation

Spikes were recorded from two rabbit retinal ganglion cells in response to epi-retinal stimulation with a 10kΩ Pt-Ir electrode. **a**. Direct activation with 0.2ms pulses delivered at 225Hz elicits one-spike-per-pulse, where spikes (asterisks) are phase-locked to the cathodal phase. **b**. Indirect activation elicits one-burst-per-pulse at 8Hz, but the number of spikes per burst decreases dramatically after the first pulse due to desensitization. The number of spikes per pulse is given above the response to each pulse.