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Early Vision: Where (Some of) the Magic Happens

A recent study provides new insights into how the very different response characteristics of the main visual pathways from the eye to the brain may directly result from the presence or absence of a ‘spike trigger-zone’ in retinal bipolar cells.

Tom Baden and Thomas Euler

The visual system of primates, including that of humans, famously features both exquisite spatial acuity and a high temporal resolution. This dual focus on both ‘sharpness’ and ‘speed’ is made possible through different processing streams set up already in the retina. In a recent study, Puthussery *et al.* [1] now show that key differences in the processing streams that are thought to underlie these visual abilities are already set up right after the first synapse of the visual system — in retinal bipolar cells.

Origin of Magnocellular and Parvocellular Channels

The retina breaks the visual world into several parallel representations prior to transmission to the brain. Each representation, or ‘channel’, is based on a different type of retinal ganglion cell that carries information about specific features of the visual scene — such as edges, directed motion or ‘color’ [2]. Of the 20 or so types of ganglion cells that exist in the primate retina, two in particular

have attracted considerable attention since they were first described in the 1940s [3]: the parasol and midget cells. Parasol ganglion cells have large receptive fields, display transient visual responses and implement the ‘magnocellular’ (M) pathway. Midget ganglion cells, in contrast, have tiny receptive fields, slow responses and provide the ‘parvocellular’ (P) pathway (Figure 1A). Based on their physiology and projection targets in the brain, the magnocellular *versus* parvocellular channels have long been implicated as the source of high temporal precision and high spatial acuity in primate vision, respectively (for example [4]).

But how are the striking differences in midget *versus* parasol cell light responses derived from their respective retinal microcircuits? Much of the distinct response signature of ganglion cells is determined by their complement of synaptic inputs, namely excitatory drive from bipolar cells, and inhibition provided by amacrine cells [5,6]. Midget ganglion cells are driven by midget bipolar cells, while parasol ganglion cells receive major inputs from so-called ‘DB3’ and

‘DB4’ bipolar cells (DB referring to ‘diffuse bipolar’ cell). Hence, midget bipolar cells should exhibit a slow, sustained physiology, whereas DB3/4 cells should be more transient.

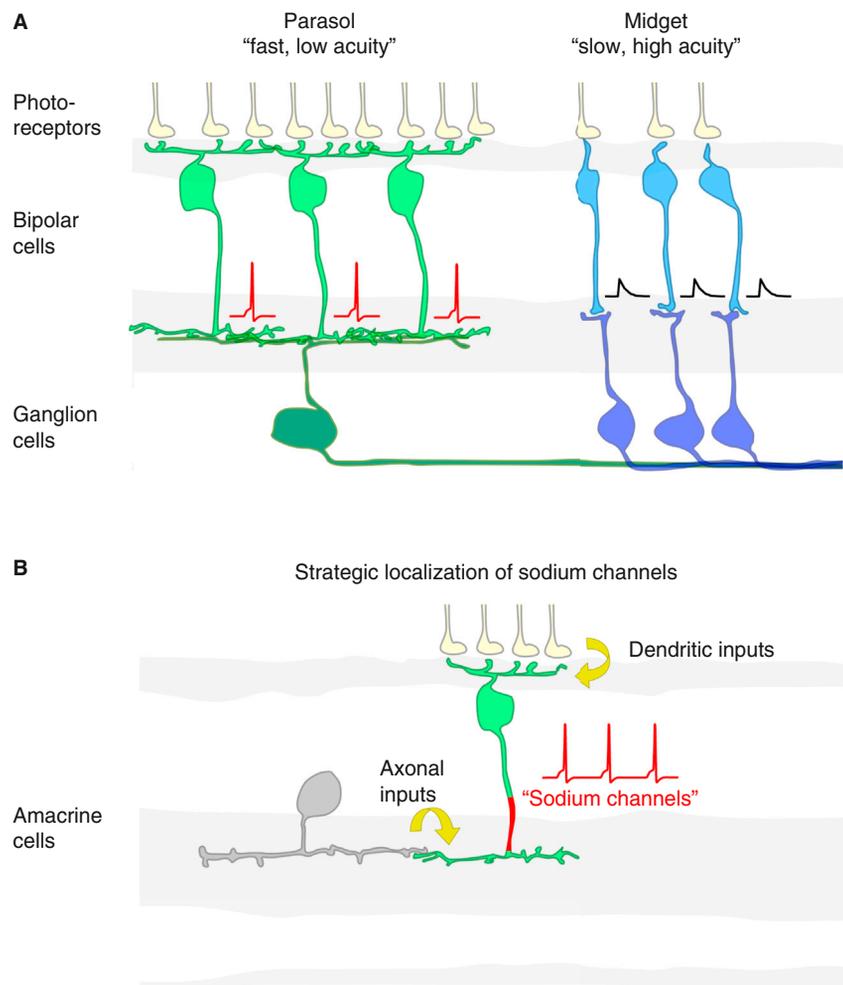
To address this long standing question, Puthussery *et al.* [1] investigated what active conductances are present in primate DB3/4 bipolar cells and how the underlying ion channels are distributed. In their beautiful study, the authors show that a specific set of ion channels is present in DB3/4 bipolar cells but completely absent in midget bipolar cells. These channels, most notably including voltage-gated sodium channels, appear to work together to render DB3/4 cells intrinsically highly transient and nonlinear. The channel complement of DB3/4 cells even allows them to generate full-blown action potentials — very much unlike the midget bipolar cells, which behaved in a fully graded, almost ‘passive’ manner (Figure 1A). Pharmacological blockage of these sodium channels resulted in much less transient light-driven inputs to parasol, but not to midget ganglion cells. In this way, Puthussery *et al.* [1] build on a growing body of evidence that active conductances and spikes in bipolar cells present a fundamental ingredient for high-precision temporal processing in the visual system [7–13].

The Design of a Retinal Bipolar Cell
The study by Puthussery *et al.* [1] goes beyond the ‘mere’ demonstration

of action potentials in a subset of primate bipolar cells. Using immunohistochemistry and computational modeling, the authors studied the subcellular localization and role of specific types of active conductances in these bipolar cells. In particular, they found that sodium channels were exclusively located within the axonal segment, just above the branching point to the terminal system. T-type calcium channels, on the other hand, were almost exclusively located in soma and dendrites — a result that the authors also confirmed in the presumed homologous bipolar cell types of the human retina.

The differential subcellular localization of conductances becomes of paramount importance when considering what bipolar cells actually do. Far from being simple passive ‘cables’ that relay the photoreceptor signal from the outer to the inner retinal layers, bipolar cells perform extensive signal pre-processing that goes beyond simply changing signal polarity to create the ‘classical’ light-ON and -OFF pathways [2,5,10]. The bipolar cell signal is fundamentally shaped by a multitude of cellular mechanisms as it passes from the dendrites to the output synapses in the terminals. At the dendrites, bipolar cells receive glutamatergic inputs from photoreceptors, which depending on receptor types [14] and other factors, can not only be excitatory or inhibitory but impart specific kinetic properties. This signal then ‘trickles’ through the soma into the largely passive axon. The axon branches into the terminal system consisting of 5 to 30 individual presynaptic compartments (boutons) within the retina’s ‘switchboard’ [5], the inner plexiform layer.

It is in the axon terminal system, where much of the ‘magic’ happens. Each bouton can be both pre- and postsynaptic to a vast barrage of inhibitory amacrine cell processes. Accordingly, the visual signal arriving at each terminal can be fundamentally transformed by a wide range of non-dendritic synaptic inputs. Therefore, bipolar cells have not one but two major sources of synaptic drive: dendritic and axonal. In this light, the detailed subcellular localization of active ion channels, such as voltage-gated sodium channels, becomes critical. Although, as Puthussery *et al.* [1] point out, the



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Figure 1. The bipolar cells driving parasol and midget ganglion cells in the primate retina. (A) The large parasol ganglion cells integrate inputs across many bipolar cells (left), while the small midget ganglion cells are driven by only one or few bipolar cells. Puthussery *et al.* [1] now show that the bipolar cells supplying parasol ganglion cells, but not those supplying midget ganglion cells, can generate fast spikes. (B) Spikes in the bipolar cells supplying parasol ganglion cells are made possible through voltage-gated sodium channels expressed specifically at a particular axon segment (marked red) — perhaps to allow both dendritic and axonal synaptic input to impart control over the cell’s spike pattern.

location of the sodium channels in these bipolar cells is reminiscent of a ‘trigger zone’ as commonly found adjacent to the soma of central neurons, the computational role of this bipolar cell ‘trigger zone’ may be very different. Central neurons typically feature long axons, such that synaptic input impinging onto the axon terminal system is too electronically distant to directly influence spike generation — the spike pattern that arrives at the terminal of these cells is thereby almost exclusively under the control of proximal inputs. However, the short axon of bipolar cells

likely means that presynaptic inputs to the terminal system can directly impact spike generation — a push and pull mechanism of sorts over spiking control of the cell (Figure 1B)?

The subcellular location of ‘spike-enabling’ active conductances in bipolar cells had long been suspected to lie somewhere within their terminal system, but the precise subcellular location of sodium channels could never be clearly ascertained [8,12]. A notable exception are L-type calcium channels which are present in all bipolar cells to support vesicle release and in some cases

do support spiking — these are clearly located within the axon terminals themselves [15,16]. Critically, the axon segment that Puthussery *et al.* found to be decorated with sodium channels in DB3/4 cells is not in the terminals themselves, but roughly half way between dendrites and axon terminals, thereby possibly allowing a more ‘balanced’ weighting of the axonal and dendritic synaptic input sites. However, a hypothetical strong inhibitory input near the active axon segment may permit direct gating control over spike generation.

If such a mechanism indeed exists, it would present one exciting possibility to explain ‘mode switching’ [9,13,15] — the idea that spiking in bipolar cells can be switched on and off depending on the system’s current demands or recent input history. Notably, once initiated, a spike propagating from the active axon segment throughout the remainder of the cell could contribute to synchronizing the activity across all synaptic boutons, thereby counteracting potential bouton-specific independent signaling [17] in spiking bipolar cells. Clearly, more work is needed to reach a comprehensive understanding of active processes that occur deep within the terminal systems of different types of bipolar cells.

But Now for Something Completely Different

The specific subcellular localization of active conductances in bipolar cells also bears a more practical, that is, experimental, consideration. Puthussery *et al.* [1] note that it was notoriously difficult to reliably ‘clamp’ the axonal membrane potential when having the recording electrode located on the electrotonically distant soma. Accordingly, they interpreted runaway potentials that they occasionally observed as the result of an incomplete voltage clamp. And indeed, using biophysically realistic modeling they could directly recreate the experimentally observed effect when locating sodium channels to the said axonal segment. With retinal research homing in increasingly on the intricate processing strategies enabled by the interactions of bipolar cells, amacrine cells and ganglion cells, electrical recordings from the bipolar cell soma can clearly only scratch the surface. Current experimental

strategies to complement classical electrophysiological approaches with optical imaging of calcium [18], glutamate release [19] and soon perhaps even voltage [20], will most certainly lead to exciting discoveries about the origin of parallel channels emerging from the retina.

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Conservation: Forest Fragments, Facts, and Fallacies

Most of the world’s remaining habitats are split into small fragments that lose species quickly. Knowledge of this fact can guide practical actions to prevent extinctions.

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Flights from Miami to Rio de Janeiro across the Amazon or from Detroit to Shanghai across Canada’s and Russia’s northern wilderness are exceptional journeys. They are exceptional because most plane

trips pass over human-dominated landscapes. Not merely have we destroyed natural habitats worldwide, but what remains are mostly fragments. Our world is in tatters. Habitat fragments cover millions of square kilometres of Earth’s surface. The fate of biodiversity depends on whether species will survive in them. Fragments