NO RETINAL EFFERENCE IN HUMANS: AN URBAN LEGEND

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Abstract

Visual attention involves the selective processing of sensory information. Animal model systems long ago demonstrated that such selectivity may be mediated by efferents that proceed from the brain to the eye in order to influence afferent input to the brain. However, such a mechanism seems to be absent from the literature on human visual attention. We here suggest that this omission is the result of an urban legend which holds that there are no retinal efferents in humans. We suggest that this legend exists because mammalian vision in general is degenerate relative to the ancestral vertebrate visual system that is clearly evident in birds. Further, our own work on an ideal animal model system has demonstrated that retinal efferents release neuromodulators that accelerate or delay photoreceptor responses to lights. If the same were true in humans, measurements of retinal response latencies would provide objective quantitative indicators of attention.

According to the *Oxford English Dictionary* (cf. Simpson, 1989), an urban legend is: "…a sensational but apocryphal story which through repetition in varying versions has acquired the status of folklore…." A common instantiation is the claim that alligators live in the sewers of large cities.

We encountered a powerful urban legend when our work on efferent mechanisms in the horseshoe crab, a classic animal model system, led us to wonder generally whether comparable mechanisms exist in humans and further, to wonder specifically whether they contributed to visual attention. We posed these questions because we had found that the retinal efferents that reside in these crabs release neuromodulators into their eyes which affect the timing and the amplitude of the receptor potentials (RPs) that light stimuli evoke in their photoreceptor neurons. We presented our questions along with a review of our animal results in a poster delivered at the Florida vision meeting (cf. Bolbecker, et al., 2005) and the title of this poster pointedly asked whether similar mechanisms might operate in human visual attention.

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We were quite surprised when visitors to our poster repeatedly informed us that our question had been definitively answered in the negative because no efferents coursed to the eyes of humans. The first author of the present contribution was particularly taken aback by these confident assertions because he still vividly remembered preparing for his doctoral qualifying examination a half century ago by thoroughly reviewing the then-recent literature on the olivocochlear bundle. How could it be, he wondered, that a peripheral feedback mechanism could be such a clearly significant and long-established property of audition and yet exist not at all in human vision?

Evolutionary Background

Our search for an answer to this question has convinced us that the view it encounters must reflect a pervasive urban legend that is shared by much of the vision research community. Although our understanding of this issue is still incomplete, we believe this view developed in some measure because it was well known that most of our early mammalian ancestors survived the dinosaur ascendancy by becoming nocturnally active. This produced what Polyak (1957, p. 969) called an "evolutionary bottleneck". As a result, there is absolutely no doubt that our vision is weak in some of the ancestral characteristics of the vertebrate visual system which were clearly retained by other lines of descent and especially in birds. A particularly well-documented example of this weakness is in the domain of color vision: Human color vision is largely trichromatic (cf. Wasserman, 1978; Ch. 4). Yet avian retinæ have preserved more of the ancestral spectrally-selective mechanisms than we have and so some birds clearly exhibit the behaviors of tetrachromats (Goldsmith, 2006).

All this notwithstanding, the difference in the domain of color vision is a difference in more versus less. However, the putative difference in the domain of retinal efference is believed by many to be an all or none difference with no role whatsoever for retinal efference in human vision. Such a belief was long enabled by the ease with which color vision could be tested in humans as opposed to the difficulty of assessing retinal efference. As a result, as we have said elsewhere (Wasserman, et al., 2011): "Despite their powerful role, the term 'photoreceptor' does not seem to appear in the current literature on visual attention. The basis for this relatively broad statement is provided by the regularity noted by de Solla Price (1961) to the effect that review articles appear whenever a certain number of research reports have been added to the archival literature of any particular research specialty. One can therefore do an electronic search of recent review articles that are relevant to visual attention in particular (Bergland, et al., 2002) or of top-down neural influences in general (Gilbert & Sigman, 2007) and one will readily see that the foregoing term is simply not retrieved. [It may perhaps be noted that the similar word "receptor" is sometimes found in this literature. However, that term will occur in contexts that make it clear that it deals with synaptic receptor sites, not with photoreceptors.]

Why does this omission exist? Mainly because it would be necessary for photoreceptors to receive efferent information in order for their known role in the transduction of visual stimuli to be modified in ways that would selectively alter the visual information that resides in the afferent signals they send back to the brain. If such modifications had been shown to be possible, then it would be reasonable to go further and to inquire if photoreceptors might play a role in accentuating visual information in ways that could affect visual attention. But if it were clear that such was just not the case, then it would simply be impossible for them to have any attentional role and the discussion would end at that point.

Critically for the current discussion, it indeed ended at exactly that point because an urban legend has persuaded much of the vision research community that such efferents to the eye neither exist in humans nor in the other mammals that are often used for research in this area. We are unaware of any written trace of this urban legend but we have repeatedly encountered it in oral discussions with colleagues. Indeed, some of them have invoked this legend to offer very strong criticisms of our work, which is why we have reviewed this issue at some length here."

Historical Basis

This situation is quite extraordinary because, according to the excellent review by Honrubia & Elliot (1968), the first evidence of efferents to a mammalian retina was actually provided by work done in dogs by von Monakow in 1889. And Honrubia & Elliot found that Cajal quickly confirmed his dog work in 1892. Moreover, Honrubia & Elliot reviewed a century-long series of findings of retinal efference in mammals of which not the least relevant is a 1956 report of efferents to the *human* retina by Wolter & Liss. True, most of the contributions cited by Honrubia & Elliot were written in French, German, or Spanish and this may have kept knowledge of their contents from binding to the apperceptive mass of more ethnocentric English speakers. Such parochialism is not unprecedented.

However, pointed inquiries orally directed by us to supporters of this view suggest that it may stem from the events attending the mid-century publication of Stephen Polyak's (1957) masterwork *The Vertebrate Visual System.* That document provided an authoritative and very comprehensive review of the knowledge of visual anatomy and physiology that had been gained up to that time by means of light microscopy and gross electrophysiology. Unfortunately, Polyak died before this document went through the press. Instead, its publication was generously handled by his good and loyal friend, Heinrich Klüver [cf., p. ix].

We take particular note that the general state of knowledge at that time about efferents to the vertebrate retina included many of the reports reviewed by Honrubia & Elliot. Indeed, Polyak's own extensive bibliography specifically included citations to the original von Monakow paper (p. 1246) and to many post-1889 papers of Cajal (p. 1278). Yet the 1390 pages of Polyak's tome devoted less than one page of text to this particular aspect of vision (i.e., Section 7, Efferent or

Exogenous Fibers of the Retina). Here, Polyak mainly took note of the work of Cajal (1909-11) saying [p. 250]: "This is most probable in the case of avian retinae. It is less certain in other Vertebrates, particularly Mammals. However, similar [structures] have been found by this author [i.e., Polyak] in the retina of the Chimpanzee." Moreover, he called for [p. 250]: "A detailed study of this category of neurons…."

In retrospect, it is clear that Cajal's work had substantially benefited from his extensive use of avian specimens because of the fact that their visual system is topographically organized throughout. Specifically, a closed path can be traced in such systems that begins in the retina and proceeds to the optic tectum and on from there to the isthmo-optic nucleus from which it finally returns back to the very same portion of the retina which had been the origin of that path. More recent investigators have further exploited this favorable anatomy to add to the foundation laid by Cajal. Notable is the magnificent anatomical, physiological, and behavioral work of Miles (1972) on domestic chickens. He clearly demonstrated that this utterly topographic system could be rigorously used to test detailed predictions about how such efference could powerfully control visually guided behavior in general and visual attention in particular.

It seems to us that some readers must have over interpreted Polyak's text as indicating that, even though he had explicitly looked for efferents to the primate retina, he had failed to find them instead of simply taking his brief comment as an indication of how preliminary the state of knowledge had been at the time when Polyak himself passed on. We believe that such over interpretations gave rise to the widespread urban legend that circulates orally in the vision research community and which holds that there are no efferents to our own eyes or to the eyes of our closest relatives. However, when this matter is reviewed more deliberately, it is evident that it would be more correct to say that Polyak had begun to look at primate retinal efferents, that he commented very cautiously on this work, and that he died before he finished his work, leaving a gap in the state of knowledge of visual efference.

Recent Data

But this gap no longer exists because other workers have subsequently investigated retinal efference (e.g., Honrubia & Elliott, 1968) and found that such efferents certainly do exist in humans and other primates. This particular contribution was content with a demonstration of retinal efference but did not determine whether such efferents directly reach the photoreceptors. However, later work has demonstrated that human retinal ganglion cells have intraretinal axon collaterals (Peterson, et al., 1998). And this last observation is given even greater impact by the finding that lamprey ganglion cells make clear contacts with their photoreceptors (Rio, et al. 1998). So there is no longer any legitimate reason for excluding photoreceptor efference from consideration by workers in the area of visual attention. There is room for further study of primate efferent pathways.

Our own group's recent contributions have augmented the province of retinal efference by showing that the neuromodulators released into the horseshoe crab compound eye by efferents originating in its brain profoundly affect the timing of the RPs evoked by light stimuli that reach its photoreceptors. Experiments done on perfused excised eye slices showed that octopamine dramatically prolongs RPs while substance P sharply accelerates them (Lim & Wasserman, 2001). Electroretinographic (ERG) experiments done in intact crabs showed that these temporal changes are part of the natural physiology and not artifacts of excision and/or perfusion (Bolbecker, et al. (2009). And studies of the interactions of these two neuromodulators showed that their joint actions are generally nonlinear combinants of their single actions and that these effects are quite similar to the effects produced by light and dark adaptation (Li, 2009).

Until recently, it would have been impossible to test this notion in humans. Traditional ERGs recorded from humans yielded extremely noisy and rather inscrutable data bearing little evidence of photoreceptor activity (Dowling, 1987). However, a new noninvasive technology has now been provided in the form of the mfERG or multifocal ERG (Poloschek & Sutter, 2002). It produces large clear waveforms with an extremely high signal to noise ratio. Yet it only requires the placement of a small gold leaf electrode near the margin of an eye. All else is determined by the visual stimuli that are presented to the observer.

That should make it possible to test the notion that human attention is influenced by changes in the timing of retinal signals caused by efference. The prediction is simple: the latencies of mfERG recordings should be alterable by changing the instructions so as to incent observers to pay attention either to the more rapid or to the more sluggish aspects of visual stimulation. Critical to any definitive test would be the incorporation of rigorous psychophysical methods that would objectively quantitate both the observer's state of attention and his'er behavioral performance.

If this new theory is confirmed, the door would be opened to objective testing of patients suffering from attention disorders and that would make it possible to assess the effects of therapies in an objective way. Millions of children suffer from attention disorders, as do many psychotics. The potential benefits of this new approach therefore far outweigh the modest costs of evaluating it.

References

Bolbecker, A.R., Lim, C.C.M., Li, J., Traverso, V., Orchard, A., Christadoss, C.S., Brahmbhatt, J., Beck, K.E., Lewis, A.R., Fleet, J., Carlson, K.W., Hoyt, C., Collins, M.D. Jr., Swan A., & Wasserman, G.S. (2005). Are photoreceptors in the attention spotlight? Efferent neuromodulators accelerate and/or retard the time course of photoreceptor responses evoked by light. *Journal of Vision, 5,* 680a. Presented in Sarasota FL at the annual meeting of the *Vision Sciences Society,* 2005, abstract #226.117001.

Bolbecker, A.R., Lim-Kessler, C.C.M., Li. J., Swan. A., Lewis, A., Fleets. J., & Wasserman, G.S. (2009). Visual efference neuromodulates retinal timing: In vivo roles of octopamine, substance P, circadian phase, and efferent activation in *Limulus. Journal of Neurophysiology, 102,* 1132-1138.

Cajal, S. Ramón y, (1909-11, 2 vols.). *Histologie du Système Nerveux de l'Homme & des Vertébrés.* Paris: A. Maloine.

Dowling, J.E. (1987). *The retina: An approachable part of the brain.* Cambridge: Harvard University Press.

Gilbert, C.D. & Sigman, M. (2007). Brain states: Top-down influences in sensory processing. *Neuron, 54,* 677-696.

Goldsmith, T.H. (2006). What birds see. *Scientific American, 295,* 68-75,

Honrubia, F.M. & Elliott, J.H. (1968) Efferent innervation of the retina. I. Morphologic study of the human retina. *Archive of Ophthalmology, 80,* 98-103.

Li, J. (2009). Comodulation of *Limulus* lateral eye photoreceptors by efferent neuromodulators. Doctoral dissertation; W. Lafayette, IN: Purdue Univ.

Lim, C.C.M. & Wasserman, G.S. (2001). Categorical and prolonged potentials are evoked when brief, intermediate-intensity flashes stimulate horseshoe crab photoreceptors during octopamine neuromodulation. *Biological Signals and Receptors, 10*, 399-415.

Lim-Kessler. C.C.M., Bolbecker, A.R., Li, J., & Wasserman, G.S. (2008). Visual efference in *Limulus: In vitro* temperature-dependent neuromodulation of photoreceptor potential timing by octopamine and substance P. *Visual Neuroscience, 25,* 83-94.

Miles, F.A. (1972). Centrifugal control of the avian retina. I-V. *Brain Research, 4,* 65-156.

Peterson, B.P. & Dacey, D.M. (1998). Morphology of human retinal ganglion cells with intraretinal axon collaterals. *Visual Neuroscience, 15,* 377-387.

Poloschek, C.M. & Sutter, E.E. (2002). The fine structure of multifocal ERG topographies. *Journal of Vision, 2,* 577-587.

Polyak, S. (1957). *The Vertebrate Visual System.* Chicago: University of Chicago Press.

Price, D.J. de Solla (1961). *Science Since Babylon.* New Haven: Yale University Press.

Rio, J.P., Vesselkin, N.P, Repérant, J., Kenigfest, N.B., Versaux-Botteri, C. (1998). Lamprey ganglion cells contact photoreceptor cells. *Neuroscience Letters, 250,* 103-106.

Simpson, J., (1989). *Oxford English Dictionary Online, 2nd Edition.* Oxford: Oxford University Press.

Wasserman, G.S. (1978). *Color Vision: An Historical Introduction.* New York: Wiley.

Wasserman, G.S., Bolbecker, A.R., Li, J., & Lim-Kessler, C.C.M. (2011). A top-down and bottom-up component of visual attention. *Cognitive Computation,* DOI: 10.1007/s12559-010-9058-z, in press.