

A Top–Down and Bottom–Up Component of Visual Attention

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Abstract A new constituent of visual attention theory is proposed based on research in an animal model system. That showed that the neuromodulators released by efference from that animal’s brain can accelerate or retard the potentials produced by visual stimulation of that animal’s photoreceptors. Such a possibility has never been considered in human behavioral research even though it has been clearly demonstrated that attention can alter the temporal window of visual perception. We therefore propose that attention theory should include new top–down and bottom–up components (TBC) with a top–down component that involves efferents that go from the brain to the photoreceptors and a bottom–up component that involves consequent neuromodulatory alterations of the timing of the afferent photoreceptor potentials evoked by light stimuli. Not long ago, it would have been infeasible to test the validity of TBC in humans. However, newly developed multifocal electroretinogram

(mfERG) technology makes it possible to obtain comfortable and objective measures of the timing of human retinal potentials while obtaining quantitative behavioral measures of both the observer’s state of attention and of visual performance. If the present prediction is confirmed by such measures, it would allow the mfERG technique to be used for both the objective diagnosis of and the quantitative evaluation of treatments for a variety of attention disorders. These would include attention deficit hyperactivity disorders as well as several psychoses that involve attentional difficulties. The costs of testing TBC are modest; the potential benefits of applying this neurocomputational technology to assist sufferers could be substantial.

Keywords Efference · Photoreceptor · Receptor potential · Latency · Neuromodulator · Neurocomputation · Octopamine · Substance P · Multifocal electroretinogram · Attention deficit hyperactivity disorder · Psychoses

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Introduction

All visual information flows through the photoreceptors. But unlike the inconsequential informational alterations intrinsically produced by the keyboard switches that are used to input information into computers, these most distal visual neurons impose significant changes on both the temporal [1] and the intensive [2] aspects of the information that they convey to the rest of the nervous system. In other words, a photoreceptor executes neurocomputations.

Despite its 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 [3] 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 [4] or of top-down neural influences in general [5], 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 postsynaptic 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 whether 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 just do not exist in humans nor do they exist 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 the history of this issue at some length elsewhere [6].

But we would here briefly note that appropriate investigations in humans by Honrubia and Elliott [7] found that efferent projections to the retina certainly do exist in us. These authors also cited a number of comparable findings in some of our mammalian relatives. They used a silver impregnation technique to analyze retinæ taken from healthy human eyes that had been donated to eye banks, and they found clear light micrographic evidence of retinal efference. This work did not determine whether or not such efferents directly reach the photoreceptors. But more recent work has demonstrated that human retinal ganglion cells have intraretinal axon collaterals [8]. And this last observation is given even greater impact by the recent finding that lamprey [9] ganglion cells make clear contacts with their photoreceptors. It is therefore clear that there is ample room for further work in this area and particularly for the application of modern fiber tracing techniques along with electron microscopy to the determination of whether or not

efferent fibers actually do contact human photoreceptors themselves.

In the absence of such a determination, there is no longer any legitimate reason for flatly excluding photoreceptor efference from consideration by workers in the area of visual attention. True enough, it is not now the case that definitive evidence exists with regard to this question. Therefore, we will proceed cautiously and speak of retinal efference in humans when we discuss the modifications of attention theory that emerged from our studies of the clear-cut photoreceptor efference that exists in an animal model system. And we will propose below a series of functional experiments in humans that would use new technology to markedly contribute to a clear resolution of this question.

In making this proposal, we recognize the fact that substantial evidence [10, 11] indicates that the central nervous system (CNS) of mammals clearly has a major role in visual attention. We do not question this view in the least; there is absolutely no doubt that the CNS is strongly invested in this function. We simply propose to add to that body of knowledge, so that it incorporates a contribution from retinal efference.

And it is also necessary to note that we call our proposal “neurocomputational” precisely because the computations involved are radically different from those that are characteristic of digital computers. Instead, neural computations involve the active and passive interplay of graded and prolonged bioelectric potentials propagating decrementally in the complex three-dimensional interior spaces provided by neuronal membranes. Such neurocomputations have powerful effects over distances that are less than or equal to the space constant of a given neural system. Characteristically, that distance is a millimeter or so. This approach leads to a very different view of neurocomputation than the one which was once derived from an analogy between the all-or-none action potentials (APs) of neurons and the electronic pulses of digital computers. Such APs do indeed play a role in neural *conduction*, but they are just a specialization for communication over long distances that are greater than a millimeter or so, and they have little to do with neuronal *computation*. Indeed, except for some contrived circumstances, all APs are born alone, travel alone, and end alone without ever being in either spatial or temporal contact with any other AP. The integration of the information they conduct is actually mediated by the postsynaptic potentials (PSPs) that are produced by APs, not by the APs themselves.

We write both to draw attention to this omission and also to suggest that a powerful and noninvasive new technology now makes it possible to determine whether retinal efference actually affects human visual function. We will particularly suggest that the data produced by this new technology might provide an objective indicator that

could aid in the diagnosis and treatment of attentional disorders.

Photoreceptor Dynamics and Behavior

The extraordinary temporal scope of photoreceptor dynamics is concretely illustrated in Fig. 1 [adapted from Fig. 1a of 12] that shows the waveform of an intracellular receptor potential (RP) that was evoked by a brief and intense flash of light. This extreme example came from a photoreceptor neuron that was in a strongly dark-adapted state after being excised from a cold-blooded invertebrate and placed in a chamber filled with isotonic seawater [13]. Under these conditions, as Fig. 1 clearly shows, RPs are very protracted, lasting for extraordinarily long times that are measured in full seconds.

There can be little doubt that quite similar phenomena occur in intact human observers because all of us have experienced the persistent afterimages that are produced when we are exposed to the same stimulating conditions, namely brief intense flashes delivered during dark adaptation. All that differs under “normal” viewing conditions is that the appropriate time scale of such persistence would be given in hundreds of milliseconds rather than full seconds. Similar evidence of temporal dispersion in RPs is given by the long latencies of their onsets and peaks. The importance of these dynamic properties of RPs stems from the fact that they have been clearly and directly related to other important visual phenomena including visual masking and metacontrast [14].

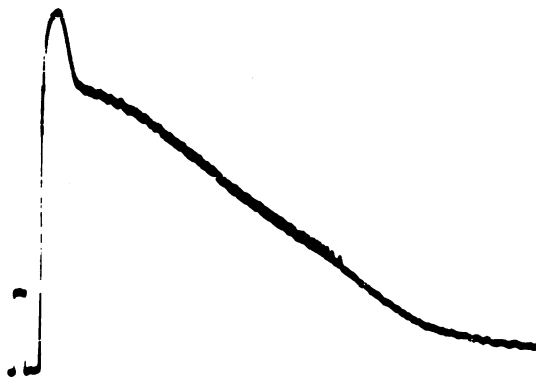


Fig. 1 An extremely prolonged (i.e., greater than 4 s) intracellularly recorded RP which was evoked in the lateral compound eye of *Limulus* by a brief (80 ms) and intense (250 W/m^2) light flash during perfusion with isotonic seawater. The square pulse at the beginning of the trace marks a calibration representing 100 ms by 10 mV. The onset of the light flash occurred 250 ms after the beginning of the trace. The thickening of the trace during its descending phase is produced by high-frequency action potentials that were electrotonically and decrementally conducted from the nearby optic nerve fiber. Reprinted from [12, Fig. 1a] with permission from Elsevier

Temporal Properties of Attention

Since Ptolemy, whose work was done circa 150 CE [cf. 15, p. 276], it has been understood that we cannot see movements that are too fast, as would currently be true in the case of a bullet, or too slow, as would currently be true in the case of the hour hand of a clock. However, more recent behavioral work, edited by Simons [16], has demonstrated that the margins of this temporal window can be shifted by selective attention. Events that are largely invisible to a relaxed or distracted viewer because they are either too fast or too slow become quite apparent when attention is focused on them. Simons has produced a series of DVDs that dramatically demonstrate such effects [17].

One possibility would be that central mechanisms employ variable neurocomputations to analyze fixed peripheral representations. That would require that all available sensory information always be transmitted centrally regardless of whether there is a present need for all of it. An alternative possibility, demonstrated compellingly by the anatomical, physiological, and behavioral work done by Miles [18] in domestic chickens, would be for the central nervous system (CNS) to instruct the periphery to adjust its representations so that they most effectively inform the CNS.

However, on purely a priori grounds, it is clearly the case that any given information transmission system must necessarily have a limited channel capacity. It therefore cannot be doubted that it would be highly adaptive to devote as much of that limited capacity as possible to the enhanced transmission of certain highly significant information rather than to transmit a more limited representation of all input information.

And there can be no doubt that such selectivity is often the case. Consider, for example, the commonplace effects of foveal overrepresentation in the transmission of retinal information to the CNS. There is no question that this foveal dedication of much of the limited capacity of this channel is responsible for the fact that we can see much more clearly when we stare directly at something than we can when we catch a view of it out of the corner of the eye. We hope that readers will understand that our proffering of this observation is not intended to denigrate the enormous contributions of central mechanisms to vision. We only wish that notice also be taken of the basic fact that CNS mechanisms can only operate on the sensory information that is actually provided to them by the periphery, and so they must therefore be affected by what they receive from their peripheral inputs and would benefit by specifying the nature of that information.

Our proposed addition to visual theory should be viewed as a proposal that there are overlooked temporal analogs of the spatial emphases provided by the selectivity of retinotopic projections. Imagine, for example, that an organism is

confronted with sensory stimuli that are changing more rapidly than its distal sensors can encode when they are in a relaxed condition. Without in any way trying to diminish the long-established evidence that the CNS can play an important role in such situations, would it not be advantageous if the brain were able to (say) accelerate the function of these distal sensors so that they could better transmit information about rapid environmental changes?

It is that specific possibility that concerns the present contribution. Evidence favoring it would require that it be shown that the CNS can indeed adjust the timing of peripheral mechanisms. We have demonstrated that precisely such an adjustment process exists in a favorable animal model system. Hence, the present contribution will next particularly examine the case of temporal neurocomputational processing in this model system. (It should be noted that many of the same studies of this model system also show that the intensive aspect of vision is involved in the sense that photoreceptor response magnitude can be altered by central feedback, thus providing yet another dimension to neurocomputing.)

Efferent Neuromodulation can Alter Photoreceptor Timing

Our group has spent the last decade exploring efference in the visual system of *Limulus polyphemus*, the horseshoe crab. Introduced into vision research almost a century ago by Hartline [19], this organism provides an almost ideal preparation because it is complicated enough to display important visual characteristics yet robust enough to provide very stable preparations which yield definitive results since the experiments last long enough to provide solid experimental control over all of their relevant aspects.

Much of the work done on this system in recent decades involved circadian rhythms [20]. That showed that a central pacemaker in *Limulus*' chief ganglion sent efferent fibers to its eyes [21]. These fibers particularly altered RPs in ways that indicated that such efference mediated a powerful circadian rhythm in visual function. Because of this research emphasis, experiments were done in which visual stimuli were regularly presented round the clock for many days while the resulting RPs and/or more proximal bioelectric signals were automatically recorded. It therefore became common practice for a single data point to be recorded, which represented the peak response of the particular bioelectric signal recorded during a given portion of a day while the rest of the waveform was either not stored or not examined. By limiting the data display in this way, it became possible to construct actograms that presented months and even years worth of data in a single chart. A necessary consequence of this approach was that no note

could possibly be taken of any circadian effects on temporal dynamics that might be occurring on a millisecond scale.

However, this approach did indicate that the basis of these circadian effects involved a process not previously recognized. This circadian work particularly taught that compounds that had long been thought of simply as synaptic transmitters whose effects were brief and transitory could actually produce prolonged effects [22]. This finding was assimilated into a growing literature on similar effects in many other neural systems. Such effects have come to be discussed under the rubric of “neuromodulation” meaning that the release of a synaptic transmitter can modulate the subsequent actions of a neuron and that such modulation can last a long time [23].

We quickly observed [24] that such was the case for efference in *Limulus*. Our first discovery came when we simply used our existing laboratory procedures to replicate the circadian findings of others who had studied this crab. As noted above, their work had implicated octopamine in the circadian fluctuations of RP amplitudes. But because our equipment and procedures were optimized for the study of the temporal properties of RPs, we readily saw that the neuromodulatory effects of octopamine radically altered the timing of RPs.

The first change we saw is illustrated in Fig. 2, taken from [24; Fig. 4]. These data clearly exhibit a very large and long-lasting increase in the duration of RPs evoked by brief flashes. Indeed, this kind of change would have markedly emphasized the slower properties of any given visual input.

We then turned to examine another neuromodulator that had been suggested to be involved in the function of this system by virtue of similar experiments [25]. This modulator is called substance P, and it had an effect that was exactly opposite to that of octopamine: As shown in Fig. 3, taken from [26; Fig. 6], a clear acceleration of the RP ensued, and this acceleration was quite striking at colder temperatures.

All of the foregoing work was done in eye slices that were excised from the lateral compound eye of a crab and then maintained in a perfusion chamber mainly containing isotonic seawater along with small doses of neuromodulator. As these striking modulatory effects appeared, it therefore became important to determine whether such effects are really part of the normal physiology. This question was addressed by electroretinographic (ERG) work done in intact crabs [27]. In this work, the efferent system was engaged in several ways: noninvasively by variations in time of day as well as by extrinsic electrical stimulation of the efferent fibers themselves and also by direct infiltration of neuromodulators into otherwise intact eyes. These convergent ERG results were quite concordant with the

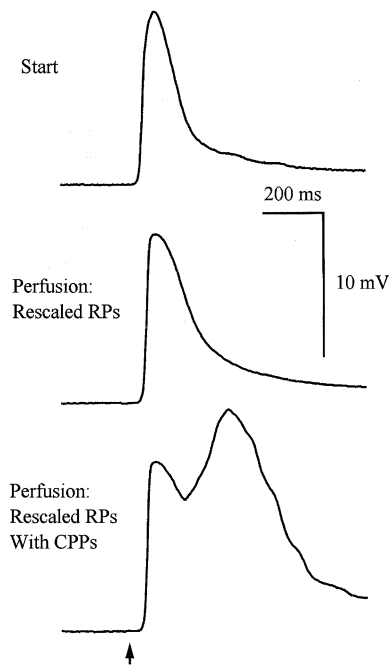


Fig. 2 Prolongation of intracellularly recorded RPs in *Limulus* by isotonic sea water perfusates containing $50 \mu\text{M}$ octopamine. Light flashes of 20 ms duration were delivered at the moment indicated by the arrow. Upper trace shows the average of 10 RPs obtained during perfusion by isotonic seawater alone. Middle and lower traces show the effects of adding octopamine to the perfusate. Lower trace shows the average of 29 responses which all produced very dramatic categorical and prolonged potentials (CPPs) which appear as an increase in the later amplitude of the RP along with a very dramatic prolongation of the response. These traces also showed a small increase in onset latency. Middle trace shows the average of 42 RPs of which none exhibited any CPPs; these traces instead exhibited temporal rescaling in the form of small increases in onset latency and large increases in the time for the response to decline to baseline. Reproduced from [22, Fig. 4]. Used with permission from S. Karger AG, Basel

intracellular results that had first been obtained. A sample of the retarding effect of octopamine is given in Fig. 4 [from 27; Fig. 4], and an illustration of the accelerating effect of substance P is shown in Fig. 5 [from 27; Fig. 5].

It should perhaps be noted that these ERGs are extracellularly recorded, and so their polarity is naturally opposite to that exhibited by the intracellular RPs presented above in Figs. 1, 2 and 3. Moreover, the ERG is a mass response, whereas the RP comes from a single cell. So, in relating the effect of octopamine as presented in Fig. 2 (say) to what is seen in Fig. 4, it is necessary to consider that the latter waveform is not only turned upside down relative to the former, but that it is more like a weighted average of the middle and lower traces of the former. And, by representing contributions from many cells instead of one, the ERG is further smoothed, and so the modulator effect is less dramatic. But the smoothing also makes these ERG effects crystal clear.

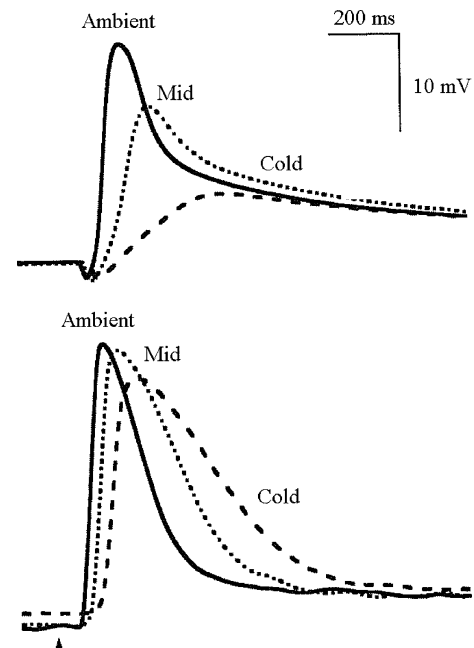


Fig. 3 Acceleration of intracellularly recorded RPs in *Limulus* by $50 \mu\text{M}$ substance P. Upper panel shows results obtained in isotonic seawater alone while lower panel shows results obtained in isotonic seawater containing substance P. Light flashes of 20 ms duration were delivered at the point indicated by the arrow. Slow infusion changes were necessary because three temperatures were employed, and the time required to change the temperature without cell loss was about 15–20 min. Ambient temperatures were near 22°C with Mid at exactly 16.7°C and with cold between 12 and 14°C . A dramatic interaction of temperature and modulation is evident in the extreme contrast between the RPs shown in the two panels, particularly in the cold condition. Reproduced from [26, Fig. 6]. Used with permission from Cambridge University Press

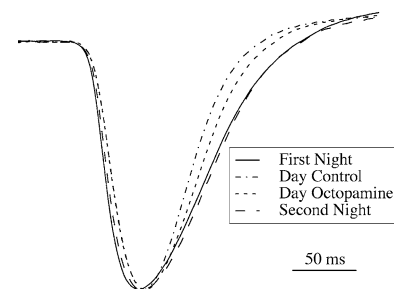


Fig. 4 Daytime infiltration of 2.5 mM octopamine into intact *Limulus* eyes increases electroretinogram (ERG) latency and prolongs its duration. ERGs recorded during the day and night in the absence of extrinsic octopamine are provided so that the clear effects of this neuromodulator during the day (when endogenous octopamine is at its minimum) can be more easily discerned. Reproduced from [27, lower panel of Fig. 4]. Used with permission from The American Physiological Society

Finally, we examined whether and how the effects of these two modulators on the responses of the *Limulus* lateral eye to light would interact when both modulators are present. Such experiments [28] demonstrated that

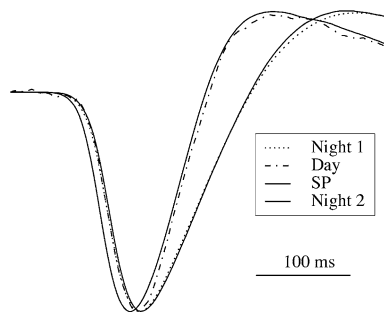


Fig. 5 Daytime infiltration of 2.5 mM substance P into intact *Limulus* eyes sharply decreases electroretinogram (ERG) latency. ERGs recorded during the day and night in the absence of extrinsic substance P are provided so that the clear accelerative effects of this neuromodulator during the day can be easily discerned. Reproduced from [27, lower panel of Fig. 5]. Used with permission from The American Physiological Society

modulator interactions do occur and that they exhibit complex nonlinearities. In particular, such comodulation normally increases the effects on RP amplitude that are produced by single modulation. But this is a nonlinear enlargement, given that a new phenomenon emerges: comodulation actually modifies the adaptation state of an eye. Indeed, as shown in Fig. 6 [from 28; Fig. 27b), membrane potential hyperpolarizations appear. These membrane potential changes are of the same character as those produced by changes in the state of light adaptation [29].

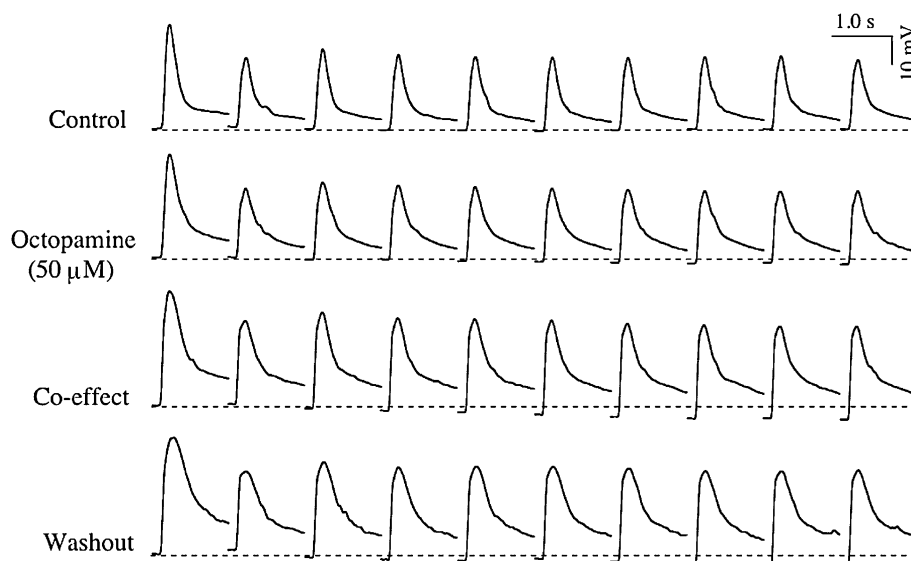


Fig. 6 Comodulatory adaptation produced by perfusion by isotonic seawater containing 50 μM octopamine and/or 50 μM substance P adapts intracellularly recorded receptor potentials (RPs) by increasing their amplitude and by hyperpolarizing the baseline membrane potential from which the next RP arises. Each trace is an individual RP evoked by 20 ms light flashes of 30 W/m^2 radiance. Each row displays ten successive RPs stimulated at intervals of 5.5 s.

In summary, our electrophysiological investigations demonstrated that efference powerfully alters the temporal and intensive properties of the afferent signals generated when light impinges on the photoreceptors of this animal. Efference thereby necessarily affects the neural computations that are based on the size and timing of those biogenic potentials.

Top-Down and Bottom-Up Contributions

A brief summary of the foregoing evidence would be that this crab demonstrably possesses a powerful neural mechanism that has two components: A top-down component in the form of efferent signals coming to the eye's photoreceptors from the CNS and a bottom-up component in the form of the resulting intensive and temporal modifications in the waveforms of the afferent signals that inform the CNS about the environment. Aside from the fact that these profound alterations were found by us simply because our group's history of research led us to examine the entire RP waveform, nothing that has been discovered to this point can possibly be unique to this crab. There is simply no reason to believe that a system much like this one cannot exist in any other organism that is at least as complex as this crab. Certainly, all of these neuronal elements exist in the human visual system generally and, *pari passu*, in children in particular.

Experiment begins with the elicitation of the control RPs shown in the *top row*. The next row shows what happens when octopamine is delivered while the third row shows the co-effect produced when substance P is added so that both are comodulating the preparation. The *bottom row* shows what happens when the perfusate is washed out with isotonic seawater [unpublished data from 28; Fig. 27b]

Moreover, the functional benefits of TBC would come about because of the way it increases the neural channel capacity that is effectively available for the transmission of visual information. Instead of evolution advancing afferent signals that vainly try to provide all possible information about all aspects of a visual scene, TBC would have made it possible for evolution to foster the development of neural signals that could preferentially emphasize just that information which is currently adaptive. This is so obvious that we will not belabor this point because the question now in hand is whether TBC actually exists in humans, not whether it would be adaptive for us to have one.

Testing TBC Electroretinographically

Not too long ago, it would have been unlikely that a clear test of TBC could ever have been done in intact humans. The only available method would have been to record conventional ERGs from awake and intact human observers. But the clearest components of such ERGs were those that represented more proximal postreceptor activity, while the more distal photoreceptor component of the conventional ERG itself is almost invisible at low to moderate light intensities because the signal-to-noise ratio of conventional ERGs is badly degraded by electronic noise [30, Chap. 6]. Although later retinal components could be retrieved from such ERGs to a degree that made them useful medically, photoreceptor contributions were essentially unfathomable at moderate light intensities while the high intensities needed to demonstrate any evidence of such contributions would have been incompatible with behavioral research on attention. Moreover, the electrodes used in conventional ERG work are difficult to tolerate for any length of time, making prolonged experiments problematic.

Recently, a new technology [31] has substantially altered this situation. The multifocal electroretinogram (mfERG) presents an observer with a widescreen display containing multiple adjacent hexagonal subfields. Each of these subfields can be independently illuminated at different times. The observer is fitted with a small and lightweight gold foil electrode placed comfortably on the lateral margin of an eye, and the resulting electrical signal is led to a conventional bio-amplifier whose output is analyzed by a conventional digital computer. The central ingredient is a sophisticated signal-processing program that examines the interactions among the responses to illumination of the various hexagons. This program extracts mfERGs, which consist of clear thin lines that trace out quite large excursions. In other words, the signal-to-noise ratio of the mfERG is quite substantial. The result is that it has been possible to identify variations in the mfERG in a rigorous way and that makes behavioral tests of TBC feasible.

However, to our knowledge, no attempts have been made to use the mfERG to identify efferent effects in humans. Moreover, as was already noted above with regard to human anatomy, it is necessary to note here that the present functional discussion currently can only be held to apply generally to the human retina with its more particular extension to human photoreceptors still only being a possibility in future.

Behavioral Rigor is Absolutely Necessary

The way to proceed is therefore obvious: Manipulate the state of attention of a human observer fitted for an mfERG and measure the effect that such attentional state changes have on the temporal properties of the mfERG. If clear attention-dependent changes in mfERG timing do occur, TBC will be confirmed in humans; if not, then it will be refuted.

However, no such test will be compelling unless it includes rigorous behavioral measurements that provide prima facie evidence that the observers are actually attending to specified properties of a visual stimulus at a given moment in the research. An ideal test would be provided if were possible for the hexagons of the mfERG to be used to lay out spatio-temporal visual patterns that would not interfere with the recording of the mfERG yet still permit quantitative psychophysical tests of visual performance to be employed in assessing the temporal aspects of the stimulus: The basic approach would be to generate (say) a pattern that comes early, and TBC would be supported if paying attention to that pattern causes the timing of mfERGs to become quicker and vice versa. Such a result would justify the application of TBC in other domains.

Diagnosis and Treatment of Attention Disorders

There are two major attention disorder domains that might benefit from this new view of attention. One extremely attractive domain for such an application of TBC would come from using it to examine sufferers from attention deficit hyperactivity disorder (ADHD) [32]. If visual attention indeed has a retinal component in humans, then it would follow that one should be able to use this property to provide an objective and noninvasive electrophysiological diagnostic test for ADHD. Indeed, it might further be the case that the application of TBC would objectively differentiate ADHD into clear subgroups with different etiologies. That alone would constitute a major contribution.

But it could also be the case that such a test would provide a quantitative way of assessing the effects of ADHD therapies in general as well as of objectively

evaluating the progress of individual ADHD patients. Thus, the cost of examining the validity of a TBC approach to the ADHD problem would be quite modest, and its potential benefits would be very large.

In making this proposal, it should be clear that we are no more saying that ADHD is localized in the retina than one would infer that drawing a blood sample from a patient suffering from a physical disorder is tantamount to saying that such disorders only involve the blood and not any other aspect of organismic physiology. What we are saying is that it may be the case that diagnosis and treatment of ADHD might benefit from quantitative and objective retinal measurements.

Second, impaired attention is a central feature of a number of severe psychiatric disorders in addition to ADHD. For example, childhood ADHD is associated with adult onset schizophrenia and bipolar disorder [33]. Concordant with this finding, attentional impairment is a core deficit in schizophrenia [34], and there is strong evidence that it is an endophenotype of the disorder [35, 36]. In bipolar disorder, which is genetically and phenomenologically related to schizophrenia [i.e., 37], impaired attention is also increasingly recognized as a fundamental feature of the disorder which is present across all phases of the illness [38]. Particularly pertinent to the present review, top-down influences on sensory processing have been specifically identified as potential contributors to severe mental illness [i.e., 39].

Summary and Suggestions

Because it emerges directly from basic neuroscience research and involves the mechanisms that underlie neurocomputation, the foregoing presentation of TBC holds out the possibility that it may provide a more effective basis for understanding the attention disorders, and it might therefore provide a quantitative and objective method for improving their diagnosis and their current treatment modes. For example, TBC may lead directly to possible chemotherapeutic improvements if the efferent neuro-modulators were identified that putatively affect either human photoreceptors or some other part of the human retina. That might well provide a way of rationally designing new chemotherapies that could improve on the benefits now provided by (say) Ritalin for ADHD sufferers.

Alternatively, it might provide a rational basis for the design of new neuroleptics that would improve chemotherapeutic approaches to the psychoses. As we said above, the potential benefits of applying this knowledge to assist large numbers of sufferers are great, and the cost of determining whether such applications are effective is very modest.

Finally, it is now more than clear that state-of-the-art anatomical and functional studies of retinal efference in humans are long overdue.

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References

1. Wasserman GS, Kong K-L. Illusory correlation of brightness enhancement and transients in the nervous system. *Science*. 1974;184:911–3.
2. Wasserman GS, Felsten G, Easland GS. The psychophysical function: harmonizing Fechner and Stevens. *Science*. 1979;204:85–7.
3. de Solla Price DJ. *Science since Babylon*. New Haven: Yale University Press; 1961.
4. Pei F, Pettet MW, Norcia AM. Neural correlates of object-based attention. *J Vision*. 2002;2:588–96.
5. Gilbert CD, Sigman M. Brain states: top-down influences in sensory processing. *Neuron*. 2007;54:677–96.
6. Wasserman GS, Bolbecker AR, Li, J, Lim-Kessler CCM. No retinal efference in humans: an urban legend. In: Bastianelli A, Vidotto G, editors. *Fechner Day 2010*. Padova: International Society for Psychophysics. Lengerich, Germany: Pabst Science Publishers; 2010 (in press).
7. Hornruba FM, Elliott JH. Efferent innervation of the retina. I. Morphologic study of the human retina. *Arch Ophthalmol*. 1968;80:98–103.
8. Peterson BP, Dacey DM. Morphology of human retinal ganglion cells with intraretinal axon collaterals. *Visual Neurosci*. 1998;15:377–87.
9. Rio JP, Vesselkin NP, Repérant J, Kenigfest NB, Versaux-Botteri C. Lamprey ganglion cells contact photoreceptor cells. *Neurosci Lett*. 1998;250:103–6.
10. Corbett M, Patel G, Shulman G. The reorienting system of the human brain: from environment to theory of mind. *Neuron*. 2008;58:306–24.
11. Taylor JG. Paying attention to consciousness. *Prog Neurobiol*. 2003;71:305–35.
12. Wang LT, Wasserman GS. Direct intracellular measurement of non-linear postreceptor transfer functions in dark and light adaptation in *Limulus*. *Brain Res*. 1985;328:41–50.
13. Lim CCM, Bolbecker AR, Li J, Wasserman GS. Osmotic properties of *Limulus* seawaters and organ cultures: an unrecognized issue. *Vis Neurosci*. 2008;25:103–5.
14. Felsten G, Wasserman GS. Visual masking: mechanisms and theories. *Psychol Bull*. 1980;88:329–53.
15. Wasserman GS. *Limulus* psychophysics: temporal summation in the ventral eye. *J Exper Psychol:Gen*. 1978;107:276–86.
16. Simons DJ (Ed) *Change blindness and visual memory*. *Vis Cogn*. 2007;7(1–3):1–412.

17. Simons DJ. Surprising studies of visual awareness, Vol 1+2 combo. Champaign: Viscog Productions; 2008.
18. Miles FA. Centrifugal control of the avian retina. I–V. Brain Res. 1972;48:65–156.
19. Hartline HK. A quantitative and descriptive study of the electric response to illumination of the arthropod eye. Am J Physiol. 1928;83:466–83.
20. Barlow RB Jr. Circadian rhythms in the *Limulus* visual system. J Neurosci. 1983;3:856–70.
21. Calman BG, Batelle BA. Central origin of the efferent neurons projecting to the eyes of *Limulus polyphemus*. Vis Neurosci. 1991;6:481–95.
22. Kass L, Barlow RB Jr. Efferent neurotransmission of circadian rhythms in *Limulus* lateral eye. I. Octopamine-induced increases in retinal sensitivity. J Neurosci. 1984;19:283–97.
23. Marder E, Bucher D. Understanding circuit dynamics using the stomatogastric nervous system of lobsters and crabs. Ann Rev Physiol. 2007;69:291–316.
24. Lim CCM, Wasserman GS. Categorical and prolonged potentials are evoked when brief, intermediate-intensity flashes stimulate horseshoe crab photoreceptors during octopamine neuromodulation. Biol Signals Recept. 2001;10:399–415.
25. Mancillas JR, Selverston AL. Neuropeptide modulation of photosensitivity. II. Physiological and anatomical effects of substance P on the lateral eye of *Limulus*. J Neurosci. 1984;4:847–859.
26. Lim-Kessler CCM, Bolbecker AR, Li J, Wasserman GS. Visual efference in *Limulus*: in vitro temperature-dependent neuromodulation of photoreceptor potential timing by octopamine and substance P. Vis Neurosci. 2008;25:83–94.
27. Bolbecker AR, Lim-Kessler CCM, Li J, Swan A, Lewis A, Fleets J, Wasserman GS. Visual efference neuromodulates retinal timing: in vivo roles of octopamine, substance P, circadian phase, and efferent activation in *Limulus*. J Neurophysiol. 2009;102:1132–8.
28. Li J. Comodulation of *Limulus* lateral eye photoreceptors by efferent neuromodulators. Doctoral dissertation. In: W. Lafayette, editor. Purdue University; 2009.
29. Easland G, Wasserman GS. Multiple intracellular contributions to light adaptation in *Limulus* ommatidia. Vision Res. 1979;19:1–8.
30. Dowling JE. The retina: an approachable part of the brain. Cambridge: Harvard University Press; 1987.
31. Poloschek CM, Sutter EE. The fine structure of multifocal ERG topographies. J Vis. 2002;2:577–87.
32. Hammerness PG. ADHD. Westport: Greenwood; 2009.
33. Rubino IA, Frank E, Croce Nanni R, Pozzi D, Lanza di Scalea T, Siracusano A. A comparative study of axis I antecedents before age 18 of unipolar depression, bipolar disorder and schizophrenia. Psychopathology. 2009;42:325–32.
34. Gilbert CD, Sigman M. Brain states: top-down influences in sensory processing. Neuron. 2007;54:677–96.
35. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160:636–45.
36. Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, Green MF, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL. The consortium on the genetics of endophenotypes in schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration. Schizophr Bull. 2007;33:33–48.
37. Nuechterlein KH, Luck SJ, Lustig C, Sarter M. CNTRICS final task selection: control of attention. Schizophr Bull. 2009;35(1):182–96.
38. Lin PI, Mitchell BD. Approaches for unraveling the joint genetic determinants of schizophrenia and bipolar disorder. Schizophr Bull. 2008;34(4):791–7.
39. Goldberg JF, Chengappa KN. Identifying and treating cognitive impairment in bipolar disorder. Bipolar Disord. 2009;11(Suppl 2):123–37.
40. Wasserman GS. Brightness enhancement in intermittent light: methods of measurement. J Exper Psychol. 1966;72:300–6.