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The Photic Blink Reflex as an Index of Photophobia

Steven A. Hackley[1] and Lenworth N. Johnson[2]

[1]Department of Psychological Sciences, University of Missouri, Columbia

[2]Department of Ophthalmology, Warren Alpert Medical School of Brown University

Author Note

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Steven A. Hackley: ORCID ID #0000-0002-8036-5055

Correspondence concerning this article should be addressed to Dr. Steven Hackley, Dept. of Psychological Sciences, 210 McAlester Hall, Columbia, MO 65211, USA.

E-mail: HackleyS@Missouri.edu.

Abstract

Two recent studies of eye closure triggered by intense luminance increase suggest that this behavior reflects the melanopsin-based retinal activity known to underlie photophobia, the pathological aversion to light (Kardon, 2012; Kaiser et al., 2021). Early studies of the photic blink reflex (PBR) are reviewed to help guide future research on this possible objective index of photophobia. Electromyographic recordings of the lid-closure muscle, orbicularis oculi, reveal distinct bursts with typical onset latencies of 50 and 80 ms, *R50* and *R80*, respectively. The latter component appears to be especially sensitive to visual signals from intrinsically photosensitive retinal ganglion cells (ipRGCs) and to prior trigeminal nociceptive stimuli. The authors argue that the R80's function, in addition to protecting the eyeballs from physical contact, is to shape the upper and lower eyelids into a narrow slit to restrict incoming light. This serves to prevent retinal bleaching or injury, while allowing continued visual function.

Keywords: Photic blink reflex, pupillary light reflex, intrinsically photosensitive retinal ganglion cells (ipRGCs), photophobia, migraine headache

1. Photic Blink and Light Sensitivity

Like other contributions to the 50th anniversary issue of *Biological Psychology*, this review paper highlights early research topics that merit renewed consideration. More

specifically, we discuss recent findings in neuro-ophthalmology (Kaiser et al., 2021; Kardon, 2012) concerning photophobia and migraine and the new light they cast on early studies from psychology concerning the two-component blink reflex to sudden illumination. This research emerged from such diverse fields as conditioning (Grant, 1943), attention (Anthony & Graham, 1985), emotion (Bradley, Cuthbert, & Lang, 1990), motor control (Manning & Evinger, 1986), and prepulse inhibition (Burke & Hackley, 1997). We propose that the late component (R80) of the photic blink reflex (PBR) is primarily controlled by afference of intrinsically photosensitive retinal ganglion cells (ipRGCs). Duration of the R80 component is known to conform to that of the stimulus (Manning & Evinger, 1986), so we assume that it constitutes the onset of squinting behavior (Burke & Hackley, 1997). This is important because prior research had shown squinting behavior to be intimately correlated with the discomfort induced by bright light in the general population, not just in individuals who suffer from migraines (Berman et al., 1994; Murray, Plainis, & Carden, 2002; Stringham, Fuld, & Wenzel, 2003).

Photophobia is defined broadly as a sensory state in which light causes discomfort or pain in the eye or head, or that light causes an avoidance reaction (e.g., seeking to be or remain in darkness), even without the presence of overt pain (Digre & Brennan, 2012; Katz & Digre, 2017). If protective blinking evolved with the first terrestrial vertebrates 375M years ago (Aiello et al., 2023), if ipRGCs are the most ancient of our five photoreceptors (Davies, Hankins, & Foster, 2010), and if light-induced pain evolved to discourage looking at the sun (Fishman, 2017), then the connection between the PBR and photophobia could be a very old one.

Although early photic blink research was not focused on nociception (discomfort or pain perception), it can help us to better understand this putative objective index of photophobia. The first of the recent, neuro-ophthalmological studies that motivated this review of the early literature was a brief report (Kardon, 2012) in which orbicularis oculi electromyogram (EMG) responses were recorded in healthy individuals and in patients evaluated in an ophthalmology clinic with unspecified etiologies who reported light sensitivity. The eyelid EMG reflex began, as did the concomitantly recorded pupillary light reflex (PLR), with a transient response to the full-field, 1000-ms, red (640 nm) or blue (485 nm) luminance increments that varied in intensity over a 6 log-unit range. On trials in which the stimuli were blue and of high intensity, the transient response was followed by a sustained one. Patients with photophobia exhibited significantly larger eye-lid responses than controls. The rapid onset of these responses, measured

in a follow-up study with only control participants (*M* = 100 ms; Poolman, Pienta, Full, Anderson, & Kardon, 2014), indicated that they were likely reflexive in nature. Larger amplitudes were again observed for blue than red lights, matched for photopic luminance.

These results support the assumption that the PBR sustained component originates primarily in melanopsin-driven ipRGCs. As reviewed by Do and Yao (2010), these recently discovered photoreceptors (Berson, Dunn, & Takao, 2002) contain the photopigment melanopsin, which is somewhat similar to rhodopsin and cone opsin found in retinal photoreceptors (Davies, et al., 2010). These opsins bind 11-cis retinal, which is converted to all-trans retinal when exposed to light, causing phototransduction (Hoffman & Lamb, 2023; Kim & Sparrow, 2021). The ipRGCs account for less than 3% of retinal ganglion cells. Melanopsin-driven ipRGCs have a peak spectral sensitivity of 480-485 nm and a prolonged integration time, yielding responses that long outlast the stimulus. In addition to their intrinsic, melanopsin-based response, ipRGCs can also be driven synaptically by signals that originate in rods or cones.

Among the diverse projections of ipRGCs, those innervating the olivary pretectal and suprachiasmatic nuclei contribute, respectively, to the pupillary light reflex and circadian photoentrainment. These are image-free forms of vision. Given that the PBR does not vary as a function of stimulus laterality (whether defined in terms of eye or hemifield, Hackley & Johnson, 1996), it is presumably also an image-free, luminance response. The ipRGCs' projections to the olivary pretectal nuclei (OPN) and other brain regions are overwhelmingly contralateral/crossed (Hattar et al., 2006). The notable exception involves the projections to the suprachiasmatic nucleus (SCN), where the projections are bilateral and symmetrical (Hattar et al., 2006).

Like the PBR, the PLR is an image-free luminance response originating in part from ipRGCs. When there is unilateral damage to the optic nerve, the PLR is asymmetric and results in a relative afferent pupillary defect (rAPD) that is evident when the eyes are alternately stimulated for 3-s intervals in the "swinging flashlight" test. The relative impairment can be quantified by imposing neutral density filters in front of the unimpaired eye until the imbalance is corrected (Thompson, Corbett, & Cox, 1981). Using a similar method to quantify fused binocular vision, stereoscopic acuity, and visual field contraction, Johnson (1996) observed a high correlation (r = .85) between rAPD and fusion, but there was no effect of neutral density filters on stereopsis. This raises the possibility that ipRGCs contribute to binocular fusion but not stereopsis.

Because rods, cones, and ipRGCs are broadly tuned chromatically within the electromagnetic spectrum below wavelengths of 700 nm, a simple contrast between lights of two specific wavelengths such as in the photic blink study of Kardon (2012) does not strongly implicate a particular photoreceptor category. Kaiser and colleagues (2021) improved on the methods of Kardon by using the *silent substitution* technique (Estevez & Spekreijse, 1982; Nugent & Zele, 2022). Stimuli with carefully structured spectra were created so as to selectively activate only cones, only ipRGCs, or both. Ramped, 4000-ms pulses were administered to three groups of participants—patients with migraine and aura, patients with migraine but who did not report visual disturbance/aura prior to their headaches, and headache-free controls. Patients with migraine with and without aura reported greater visual discomfort than controls, but only those with a history of aura exhibited larger orbicularis oculi EMG responses and more persistent blinking during stimulation. Comparisons across trials with distinct spectral contrasts led the authors to conclude that reflexive lid closures were triggered by integrated cone and melanopsin signals.

A separately reported analysis (McAdams et al., 2020) of data from the same experiment failed to identify any difference across the three groups with respect to pupil responses (but cf. Zele, Dey, Adhikari, & Feigle, 2021). Given the similar presumed function and afferent pathway of the PLR and PBR (see Sections 3 & 4, below), concordant findings would be expected. Psychophysical analyses showed that more intense ipRGC- and cone-targeted stimuli elicited greater discomfort than weak stimuli in all three groups, but participants with migraine with or without aura reported greater discomfort than did the controls. This is consistent with abundant prior research (reviewed by Digre & Brennan, 2012) indicating a prominent role for intrinsic (melanopsin) and extrinsic (cone-driven) ipRGC signals in photophobia. An animal model using mice has been developed for squinting, as measured by the interpalpebral fissure area between the upper and lower eyelids (Rea et al., 2022). This model was found to provide an objective quantification of dose-dependent pain response to a migraine trigger, calcitonin gene-related peptide.

The above data argue that the PBR holds promise as an objective measure of photophobia. What little research has been conducted on this response is scattered across diverse fields. Key publications may be inaccessible because of age, language, or obscure theoretical

context (Exner, 1874; Feger, Boulu, & Rossignol, 1972; Grant, 1945). A brief review to orient potential new investigators is in order.

2. Early and Late Components

The PBR was first investigated by prominent Viennese physiologist, Sigmund Exner (1874), using a mechanical recording device. Comparing onset latency of the reflexes to that of voluntary manual reactions to the same light-flash stimuli, he was surprised to find that voluntary reactions were faster (*M* = 113 vs. 216 ms). We now know, however, that delayed onset responses are not unusual for ipRGC-mediated responses (e.g., photic sneeze reflex, ~ 3 s, García-Moreno et al., 2005). Exner also provided evidence for cross-modal summation of photic and cutaneous blink reflexes.[1] When an electro-cutaneous stimulus was presented to one eye and a flash to the other, blink reflex latency was shorter on trials in which the visual stimulus was 5 cm as compared to 9 cm away (*M* = 57 vs. 66 ms).

Systematic investigation of these reflexes began in the 1930s and 1940s as eye-blink displaced salivation as the measure of choice in studies of classical conditioning. One methodological problem with eye-blink was that the typical conditioned stimuli (CS; tones and lights) would elicit eyelid responses—albeit small ones—even before they were repeatedly paired with the unconditioned stimulus (UCS; an air puff directed at the eye). This is quite different from Pavlov's (1927/2010) original paradigm in which the buzzer CS did not elicit salivation prior to training. In the late 20th century, Eric Kandel faced a similar challenge in his Nobel prize-winning research regarding the physical substrate of memory. He and his colleagues needed to show that "Aplysia learn not only to strengthen the magnitude of a previously existing reflex response (alpha conditioning), they also can learn to develop a new type of response to the CS (beta conditioning)" (Hawkins, Lalevic, Clark, & Kandel, 1989). The distinction between an alpha response (an unconditioned reflex to the CS) and a beta response (more commonly known as a *conditioned response*, CR) was introduced by Hull (1934).

It was in this context that the two-component structure of the PBR was discovered by David A. Grant (1943, 1945). Eyelid movements were recorded using an optical system with mm- and ms-level resolution. The 1945 experiment involved disk-shaped, 750-ms, luminance increments ranging across conditions from 4.9 to 582 millilamberts. Frequency distributions of the observed lid-closure latencies were distinctly bimodal, with peaks in the 40-110 and 120-240

ms range. He identified the initial component as the *alpha response*, based on its short latency and stability across trial blocks. The later component, which increased across trial blocks, he designated the *beta response*. Although it became clear in subsequent studies that the second component was also an unconditioned reflex, the name *beta* was retained. In view of this confusion and the fact that the vocabulary of neuroscience is replete with alphas and betas, we introduced an alternative nomenclature, R50 and R80, based on typical onset latencies of the orbicularis oculi EMG bursts (Hackley & Johnson, 1996).

Congruent with our hypothesis that the late component of PBR is sensitive to both visual and cutaneous discomfort (e.g., dry eyes), Grant (1945) reported that beta/R80 responses increased in frequency across three 8-min fixation periods. A significant interaction[2] showed that this increase was greater for more intense visual stimuli, which would have been especially effective at activating high threshold ipRGCs.

In a follow-up study (Grant, Norris, & Boissard, 1947), ocular discomfort was induced with a series of 40 corneal air puffs in half of the participants and via prolonged fixation in the others. This was crossed factorially with dark versus light adaptation. Pre- and post-testing of the PBR to 750-ms, 270-millilambert, disk-shaped, 9.5° diameter, light pulses was conducted under scotopic conditions. The observed increase in frequency and amplitude of beta/R80 responses was greatest for participants who received corneal air puffs and extended dark adaptation.

Interpretation of these findings in terms of sensitization of the visual reflex pathway by noxious air puffs nicely fits the thesis of the current paper and Grant's own interpretation. However, it should be kept in mind that defensive reflexes, including photic blink (Bradley, Cuthbert, & Lang, 1990),[3] are potentiated by negative emotion. Photic blink potentiation following the serial 8-min fixation tasks of Grant (1945) might well have been due to bored annoyance rather than dry eyes.

In the 1947 paper, Grant and colleagues noted that alpha/R50 and beta/R80 responses were uncorrelated with respect to amplitude or frequency of occurrence. Further evidence that these components are functionally distinct emerged in a study of the effects of weak pre-stimulation (Burke & Hackley, 1997).

Prepulse inhibition is said to occur when a weak, preliminary stimulus reduces the amplitude or delays onset of the response to a subsequent intense, reflexogenic stimulus (RS). Modulation in the opposite direction, relative to no-prepulse control trials, is termed *prepulse*

facilitation. According to the most widely accepted theory (Graham, 1975; Blumenthal 2015), the function of prepulse inhibition is to protect perceptual processing of the weak first stimulus from interruption by the more salient second stimulus and, more importantly, interruption by the reflex itself. Certainly, a reflex that closes the eyes could interfere with perceptual processing in the visual modality. Experiments in which selected prestimuli are the focus of attention support Graham's theory. Prepulse inhibition is found to be stronger and longer lasting if the preliminary stimulus is task relevant (Filion, Dawson, & Schell, 1998; Hackley & Graham, 1987) or intrinsically interesting (Bradley, Codispoti, & Lang, 2006). Prepulse inhibition has been extensively researched due to its proven utility in studies of the pharmacological treatment of psychiatric disorders, particularly schizophrenia (Geyer et al., 2001).

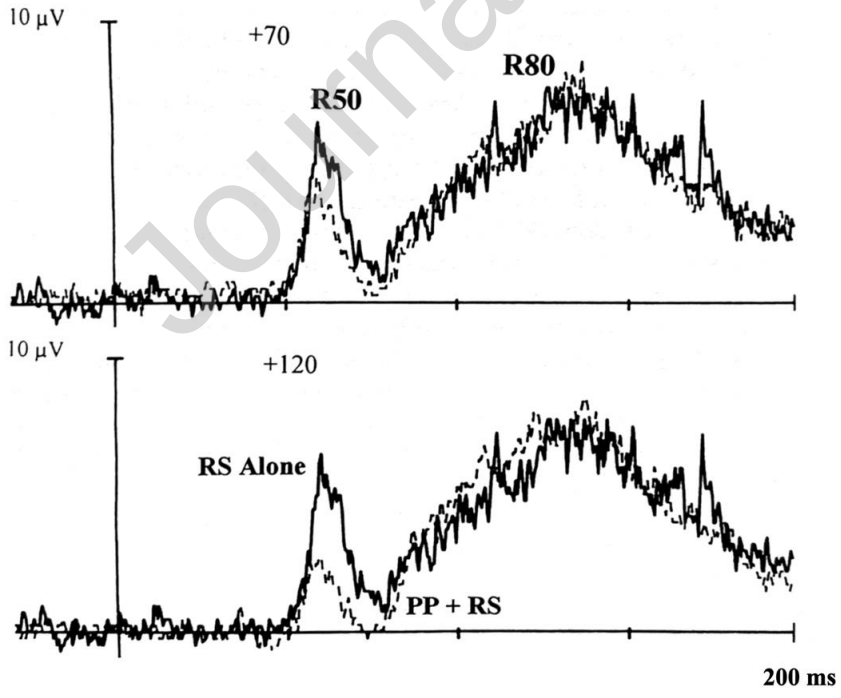
The main goal of Burke and Hackley's (1997) experiment was to determine whether the two components of the PBR are modulated similarly to those of the cutaneous blink reflex (elicited by air puff or electrical stimulation of the supra-orbital nerve). In the case of cutaneous blink, amplitude of the early (R1) and late (R2) EMG bursts exhibits facilitation and inhibition, respectively (Sanes & Ison, 1979; Sonnenberg, Johnson, Jurkowski, & Hackley, 2006).

Photic blink reflexes in the Burke and Hackley (1997) study were triggered by 2-ms flashes from one of two clinical strobe lamps, positioned 25 degrees to the left and right of a fixation light. The lamps were encircled by four light-emitting diodes, which delivered 50-ms prepulses at onset asynchronies of 1200, 600, 120, 70, 45, 20 or -50 ms. (The negative value means that the LED was illuminated *after* the strobe lamp was turned on.) As shown for the 70- and 120-ms conditions in Figure 1, R50 amplitudes were reduced on trials in which a prepulse preceded the reflexogenic stimulus (dashed line) as compared with RS-alone control (solid line) trials. There was no inhibition of R80 at any onset asynchrony, but the slight augmentation of its leading edge (90-140 ms) reached significance in the 120-ms asynchrony condition. This potentiation was observed in two participants who failed to exhibit an R50; therefore, R80 facilitation is unlikely to be secondary to R50 inhibition. The general pattern of modulation (inhibition of R50, facilitation of R80) makes it clear that these components differ functionally from one another, and that they are not entirely analogous to the cutaneous R1 and R2 components (facilitation of R1, inhibition of R2).

A finding that concerns the spatial relationship between strobe and stimulated eye also argues that R50 and R80 are functionally distinct. Participants wore a patch over one eye to

allow comparison of activation via the crossed versus uncrossed ascending pathway. To understand the rationale, recall that images projected onto the retina are inverted (upside-down) and right-left reversed. Images in the left field of vision are sent to the right side of both retinas (nasal retina left eye, temporal retina right eye), and subsequently to the right side of the brain. And images in the right field of vision are sent to the left side of both retinas (nasal retina right eye, temporal retina left eye), and subsequently to the left side of the brain. Note that the visual information projected to the nasal retinas will cross in the optic chiasm, while visual information in the temporal retinas will remain ipsilateral. Because ipRGC fibers are overwhelmingly more contralateral/crossing than ipsilateral (Hattar, et al., 2006), one might expect the eyelid contraction to light stimulation of the nasal retina would be slightly larger than the response to stimulation of the temporal retina. Burke and Hackley (1997) found that this was indeed the case for R80 but—highlighting the independence of these components—not for R50. As shown in Figure 2, bottom panel, the same pattern was observed by Hackley and Johnson (1996).

Figure 1. *Grand average (N = 16 participants) photic eyeblink reflexes on trials with and without a prepulse, collapsed across side of prepulse (PP), reflexogenic stimulus (RS, strobe flash), and eyepatch.*



Note. The solid line represents control trials in which the reflexogenic stimulus (RS) was presented alone. The dashed line indicates trials in which a brief, weak, prestimulus preceded the intense strobe flash by 70 ms (top panel) or 120 ms (bottom panel). Note that the peak and trailing edge of the R50 component are reduced in amplitude on PP + RS trials relative to control trials at these asynchronies. A similar pattern of prepulse inhibition is observed with the R2 component of the trigeminal blink reflex (e.g., Sonnenberg et al., 2006). This figure is adapted from Burke and Hackley (1997) with permission.

A secondary goal of the Burke and Hackley (1997) study was to assess modulation of R50 and R80 by spatial attention. No compelling evidence for stimulus-driven, spatial attention effects on either component was obtained. If abrupt onset of the task-irrelevant prepulse had automatically captured attention (Posner & Cohen, 1984), and if processing of brightness information were thereby enhanced, either response size or speed of onset should have been facilitated. Instead, the opposite was observed. R50 onset latencies were lengthened and R80 amplitudes reduced on ipsilateral trials, those in which the prepulse and strobe were presented on the same side.

An alternative interpretation is that these Prepulse x Strobe laterality interactions might have been produced by spatial summation. Given the highly integrative character of ipRGCs (Do & Yao, 2010), distant prestimulation on contralateral trials might have yielded greater summation than proximal prestimulation on ipsilateral trials, those in which the weak prepulse and intense reflexogenic stimulus were adjacent to one another. Slow response times of ipRGCs (Do & Yao, 2010; Karnas, et al., 2013) could account for the fact that the laterality interaction tended to be greater at longer lead times (maximum at 600 ms, $p < .06$).

3. Function and Kinematics

Burke and Hackley (1997) proposed that the purpose of the PBR is to compensate for the sluggish onset of the smooth-muscle, pupillary light reflex when there is a sudden, intense, luminance increase (see also Poolman et al., 2014). The levator palpebrae muscle, a striated muscle under control of the oculomotor nerve, along with Mueller's muscle, a smooth muscle under control of the sympathetic nervous system, are agonist muscles for eyelid elevation, while the orbicularis oculi muscle, a striated muscle under control of the facial nerve, is the agonist for

lid closure. These opposing muscles work together to quickly shape the eyelids into narrow slits. The eyelids function like Inuit snow goggles (early sunglasses made of bone or wood, with a horizontal slit to see through). Narrowing of the palpebral aperture reduces retinal bleaching and the risk of injury, while permitting at least some degree of continued visual function (Burke & Hackley, 1997; Poolman et al., 2014; Rea et al., 2022).

One line of evidence for this theory comes from the kinematics of blink reflexes. Drawing upon well-established findings in the oculomotor literature and their own experiments with parametrically manipulated stimulus duration and intensity, Manning and Evinger (1986) proposed that cutaneous and photic blinks are under two-stage control (for acoustic startle-blink, see Blumenthal & Berg, 1986). The early, phasic component is an open-loop, ballistic movement. That is to say, it is pre-programmed and feedback independent. Burst duration and motor neuron firing rates are determined by the rise-time and intensity of the reflexogenic stimulus. The late, sustained component is under closed-loop control, allowing duration and amplitude of lid closure to be controlled by stimulus duration and amplitude. For most responses to intense visual stimuli, the duration of the sustained component greatly exceeds that of the luminance increase.[4] In the case of the cutaneous blink reflex, early and late phases are manifest as R1 and R2 components of the orbicularis oculi EMG; correspondingly, the PBR is manifested by the R50 and R80. Manning and Evinger showed that the upper lid descends much more gradually in photic than cutaneous blink (Manning & Evinger, 1986). This slow descent is partly because the levator palpebrae continues to pull upwards until after the orbicularis oculi contraction is well under way. Under our account, descent of the upper lid is gradual and controlled because the goal is to initiate a squint of appropriate width.

In other research, Evinger (1995) has shown that control of lid elevation in the interval between blinks is controlled by levator palpebrae and the passive, downward-pulling elasticity of the palpebral ligaments. Given the limited evidence that eyelid muscles are endowed with functioning proprioceptors (Omstead et al., 2022), we propose that maintenance of optimal squint width is controlled by feedback from two sources: Mechanoreceptor afference from the eyelashes and luminance information from the retina, which combine to provide closed-loop control of the palpebral aperture. The lattice formed by interdigitating eyelashes can also help block bright light. During prolonged stimulation, squinting tends to have an uneven, spasmodic quality (Murray et al., 2002), with interspersed blinks (Kaiser et al., 2021). This may reflect the

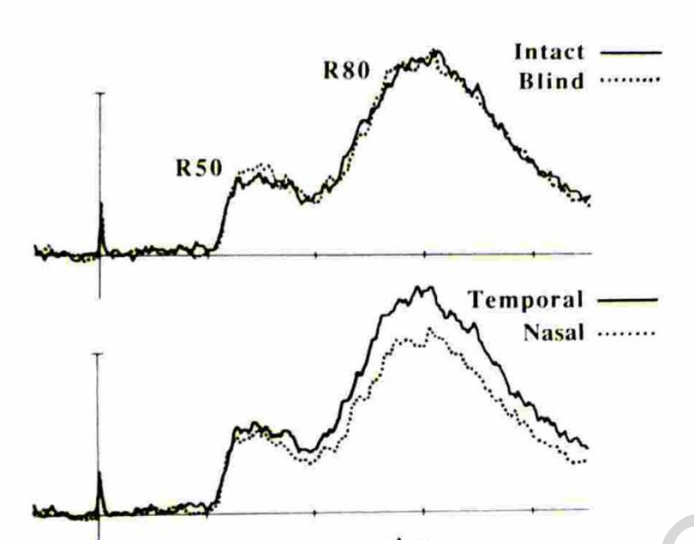
limited quality of non-proprioceptive feedback and an intermixing of voluntary and reflexive control.

4. Neural Pathways

It has been known since the 19th century that subcortical structures are sufficient for elicitation and control of the PBR (reviewed in Levinsohn, 1904). To determine whether this is true for both R50 and R80, we tested 12 patients with visual field defects due to unilateral occipital lobe damage (Hackley & Johnson, 1996). Signal-averaged EMGs for reflexes evoked by strobe flashes within versus outside of the scotoma were identical in latency, amplitude, and waveshape (Figure 2, top panel). Neither component appears to require or benefit from cortical-level processing. The lower panel documents a difference between the early and late components. Only the latter is significantly enhanced by temporal hemifield stimulation, that is to say, by reflexogenic afference via the crossed ascending pathway (discussed in Section 2, above).

There is only a modest amount of research concerning the subcortical pathways that mediate photic blink, and the findings are not entirely consistent. Anatomical tracing studies suggest that the olivary pretectal nucleus, OPN, is the first central synapse of the reflex arc. These studies have documented a direct connection from the OPN to the pontine blink premotor nucleus and the facial motor nucleus (Holstege, Tan, van Ham, & Graveland, 1986; Itoh, Takada, Yasui, & Mizuno, 1983; Takada et al., 1984). Tracing studies alone cannot distinguish mediating, modulating, and functionally silent pathways. Fortunately, an electrophysiological experiment has shown that stimulation of the pretectum yields excitatory post-synaptic potentials in the division of the facial nucleus where motor neurons innervating orbicularis oculi reside (Vidal, May, & Baker, 1988). The fact that OPN is the first central synapse for the functionally related PLR, and that OPN is heavily innervated by ipRGCs (Gamlin et al., 2007; McDougal & Gamlin, 2010) further supports this hypothesis regarding the pathway leading to orbicularis oculi activation.

Figure 2. *Grand average photic eyeblink reflexes for 12 patients with homonymous hemianopsia due to retrochiasmal damage (e.g., occipital lobe stroke).*



Note. In the top panel, the dashed line (*Blind*) indicates trials in which photic blink was triggered by the flash of a strobe lamp positioned within the patient's perimetrically confirmed, visual-field defect. The solid line (*Intact*) represents trials in which the reflexogenic stimulus was the discharge of the lamp positioned at the mirror-image location within the patient's intact, sighted hemifield. In some participants there was a brief silent period between the early, phasic component, R50, and the late, sustained component, R80. Two of the 12 participants failed to exhibit an R50 burst, a proportion similar to that observed in healthy young adults (Sonnenberg et al., 2006). The bottom panel contrasts trials in which the reflexogenic stimulus was positioned within the *Temporal* (solid line) or *Nasal* (dashed line) hemifield. This figure is adapted with permission from Hackley and Johnson (1996).

Regarding the antagonist muscle, levator palpebrae, there is a direct projection from the pontine blink premotor nucleus to the oculomotor nucleus that likely provides inhibitory control (Guerra-Seijas, Garcia, & Gonzalez, 1993). A separate pathway to this muscle, originating in a cluster of cells called the "M group" (Horn & Büttner-Ennever, 2008), might play a role in the maintenance of prolonged squint, which presumably involves a mixture of voluntary and reflexive control.

An alternative model for the pathway mediating lid closure to intense luminance increases was proposed by Feger, Boulu, and Rossignol (1972). These authors reported that lesions of the OPN in cats did not influence PBR, nor did electrical stimulation at this site trigger the reflex. Feger and colleagues proposed that the first central synapse of the reflex arc is not in the OPN but rather in the ventro-posterior portion of the lateral geniculate nucleus (LGN). Their data indicate a latency of roughly 25 ms for activation of the LGN, which is similar to the mean of 27 ms for first spikes in the human LGN (during surgery for epilepsy; Wilson, Babb, Halgren, & Crandall, 1983). A delay of about 8 ms is interposed between arrival at and exit from the LGN, which the authors attributed to reverberatory connections that help shape the motor response. Based on their own lesion, intracerebral recording, and stimulation experiments, the authors argued for a direct, monosynaptic connection from the LGN to the facial motor nucleus.

This is an appealing hypothesis because the LGN receives ipRGC input and several nearby thalamic nuclei are sites of convergence for trigeminal nociceptive and ipRGC signals (Dacey et al., 2005). Convergence of ipRGC and trigeminal nociceptive afference in posterior regions of the thalamus is a presumed mechanism for photophobia (Digre & Brennan, 2012; Noseda, Copenhagen, & Burstein, 2019; Moulton, Becerra, & Borsook, 2009). However, to our knowledge there is no independent confirmation of a direct connection between LGN and the motor neurons that control orbicularis oculi (e.g., Morcuende, Delgado-Garcia, & Ugolini, 2002). Additional neurobiological research is needed, especially lesion studies of OPN and LGN.

5. Delayed Melanopsin Effects

We have emphasized that early and late components of the PBR are functionally distinguishable, yet it is possible that the same basic pathway mediates both. Because the extrinsic response of primate giant ipRGCs is as rapid as conventional RGCs (Dacey et al., 2005), ipRGCs could in principle trigger both components. Their differing spectral sensitivities suggest that, if this is the case, there is sequential activation first via the extrinsic and then the intrinsic mechanism. As discussed in Section 1, the initial, phasic component of photic blink is similarly responsive to red (640 nm) and blue (485 nm) light, but the sustained component is more responsive to blue light (Kardon, 2012; Poolman et al., 2014). Although existing neurophysiological evidence regarding latency do not rule out this possibility, the data generally suggest that the intrinsic response is too slow to trigger either R50 or R80. In the case of primate

giant ipRGCs, Dacey and colleagues (2005, Figure 4b) obtained latencies of 1400 ms or more. Studies of other cell types and other species have documented intrinsic ipRGC latencies ranging from one-tenth of a second to several seconds (Do & Yao, 2010; Karnas, et al., 2013).

An alternative hypothesis is that spectral properties of the PBR sustained component and its potentiation in cases of photophobia reflect delayed consequences of melanopsin that carry over from one trial to the next. Discomfort triggered by trigeminal nociceptive or melanopsin-based afference on early trials of an experiment might prime, sensitize, or otherwise enhance the excitability of some segment of the reflex arc for the remainder of the experimental session. Activation of this pathway by non-melanopsin afference on later trials would yield a more vigorous closure of the eye, especially when experimental conditions are blocked rather than mixed. The findings of Grant and colleagues (1947) that were discussed in Section 2 support this interpretation. A series of 40 air puffs directed straight into the eye, which certainly would have elicited blink reflexes and been perceived as unpleasant, potentiated the beta/R80 response to light flashes on later trials.

A closely related hypothesis is that a negative emotional state that develops across early trials with annoyingly bright lights could potentiate the PBR on subsequent trials. The mechanism would be affective priming—negative emotions broadly enhance protective reflexes, whereas positive emotions suppress them (Bradley, Codispoti, & Lang, 2001). One relevant study found that potentiation of blink reflexes to light flashes in healthy young adults as they viewed unpleasant slides (e.g., snakes, mutilated bodies, angry dogs) was significant only for those participants who reported the reflexogenic light flashes to be aversive (Bradley et al., 1990). In addition to this Slide Valence (pleasant/neutral/unpleasant) x Group (photophobic/non-photophobic) interaction, a main effect of group was observed. Congruent with studies reviewed in Section 1, Bradley and colleagues reported that healthy young adults who found the light flashes to be aversive exhibited larger PBRs than those who did not.

Because affective modulation of startle-blink is reasonably well understood at the neural and behavioral levels (Bradley et al., 2006; Kuhn et al., 2020), the just described findings may offer avenues for pursuing the photophobia—PBR connection. Future research could, for example, assess carry-over across trials. A design similar to that of Bradley and colleagues (1990) would be employed, but with two trial types intermixed, those with unpleasant and those with neutral (e.g., clothes hangers, cleaning products) slides. An interaction of preceding and

current trial type would constitute evidence for carry-over. Simple effects analysis might show, for example, that blinks to bright blue light presented during a neutral slide preceded by a trial with an unpleasant slide would be of greater amplitude than those elicited on a neutral trial preceded by a neutral trial. A similar approach could be taken to determine whether carry-over can be modality-specific (e.g., intermixing bright blue and intense white-noise reflexogenic stimuli).

6. Data Acquisition Systems

There are many laboratories around the world that are set up to study affective modulation of acoustic startle-blink. The standard setup involves a monitor for displaying emotion-eliciting slides, a sound system for delivering brief but high-intensity noise bursts, a bio-amplifier and A/D convertor for recording orbicularis oculi EMG, and one or more computers for presenting the stimuli, recording the EMG, and analyzing the responses. (For general methods in eliciting, recording, and analyzing startle-blink, see Blumenthal et al., 2005.)

Only three basic changes are needed to study the PBR: (1) The sound system would be replaced or supplemented with apparatus for presenting sustained pulses of bright light; (2) the eye from which EMG is recorded would be covered with a patch so that retinal potentials do not contaminate the orbicularis oculi EMG (Hackley & Johnson, 1996; Hackley, Woldorff, & Hillyard, 1990; Yasuhara & Naito, 1982); and (3) the temporal window for measuring EMG amplitude would be adjusted to capture either R80 or the subsequent, sustained squint.

For research conducted in the ophthalmology clinic, a stand-alone, commercially available system (MonCV3 multifunction visual perimetry system; MetroVision, Perenchies, France) has proven suitable for investigating photic blink (Choi, Jang, Kim, & Jung, 2021). Because the near-infrared video camera of this system records lid position, findings would reflect the contributions of levator palpebrae as well as orbicularis oculi. This could be advantageous for assessment of sustained lid control during squint or pre-stimulus baseline. For some purposes, the fact that this system simultaneously records the PLR would also constitute an advantage over conventional EMG-only methods.

Optimal choices for stimulation and other methods will depend on the behavioral and physiological processes being investigated, as well as the patient group of interest. For distinguishing the contribution of rods, cones, and melanopsin afference, the silent substitution

technique (Estevez & Spekreijse, 1982; Nugent & Zele, 2022) is the gold standard. The use of this technique to specifically stimulate cones or ipRGCs in separate blocks of trials made Kaiser and colleagues' (2021) study of photophobia in migraine especially compelling (discussed in Section 1). This is a powerful technique, but not without weaknesses. Targeting of particular photoreceptor types can be impaired by chromatic aberration of the macular pigmentation or retinal vasculature, and the technique cannot easily distinguish extrinsic ipRGC input from cone input to conventional RGCs. In the near future, a useful alternative method may be available—two-photon excitation fluorescence. In its most basic form, the method has proven suitable for eliciting PLR via a targeted receptor category (rods, in this case; Zielińska, Ciąćka, Szkulmowski, & Komar, 2021). Given the spatial precision of some variants of this technology, it might be feasible for stimulation via two-photon excitation fluorescence to be confined to the retinal ganglion layer (for ipRGCs) or the photoreceptor layer (rods and cones). (For further information, see Diasporo, 2022; Palczewska, et al., 2014; Palczewska, Wojtkowski, & Palczewski, 2023.)

7. Clinical Applications

Although our review has emphasized migraine, use of the PBR as an objective measure of photophobia could find application in symptom assessment and treatment development for a broad range of disorders. It is important to note that photophobia is not a disease; rather it is a symptom in association with a disorder. The disorders and conditions associated with photophobia fall into four general categories (Albilali & Dilli, 2018; Digre & Brennan, 2012; Katz & Digre, 2016; Kooij & Bijlenga, 2014; Wu & Hallett, 2017):

(1) Ophthalmologic disorders, including blepharitis, dry eye disease, corneal disease (e.g., corneal abrasion, exposure keratopathy, corneal ulcer), infection or inflammation in association with iritis/uveitis, cataract, glaucoma, inherited retinal diseases (e.g., retinitis pigmentosa, cone dystrophies, albinism, rod monochromatism), optic neuritis, and arteritic anterior ischemic optic neuropathy in association with giant cell/temporal arteritis;

(2) Neurologic disorders, such as migraine and other headaches, blepharospasm and hemifacial spasm, dementia with Lewy bodies, infections such as meningitis and encephalitis, brain tumors, thalamic insult, progressive supranuclear palsy, and traumatic brain injury;

(3) Psychiatric disorders, including agoraphobia, attention deficit hyperactivity disorder, depression, and anxiety disorders; and
(4) Drug-induced photophobia, as triggered by anticholinergic drugs which paralyze the iris sphincter muscle causing pupillary dilation, barbiturates, benzodiazepines, and haloperidol.

The specific disorders that would most benefit from systematic investigation of hypersensitivity to light and its relation to the PBR remain to be determined, but such research is of prima facie value in understanding chronic, pathological contraction of orbicularis oculi and other facial muscles. Among patients with dystonia of blepharospasm and hemifacial spasm, almost 80% report having photophobia and that bright light is the most frequent exacerbating factor causing worsening of the eyelid spasms (Anderson, Patel, Holds, & Jordan, 1998; Denuelle et al., 2011; Dutton & Buckley, 1988; Emoto et al., 2011; Wu et al., 2019). The facial dystonia of blepharospasm and hemifacial spasm often begins within one year after a person has experienced two or more major stressful life experiences within a 1-year period (e.g., death of a loved one, home foreclosure, bankruptcy, etc.) (Johnson et al., 2007). It might, therefore, be useful to assess potentiation of the PBR by negative emotion in patients with vs. without photophobia. Furthermore, it might be possible to recruit patients after they have had one major stressful life event, then prospectively test whether PBR or other indices of photophobia predict development of the facial dystonia.

Hypoactivity of the melanopsin system is also clinically relevant (e.g., seasonal affective disorder, Roecklein et al., 2013), and might be assessed in terms of reduced photic blink reactivity. People with dementia of the Alzheimer's type have poor circadian entrainment and a loss of ipRGCs that is disproportionate to their age (La Morgia et al., 2016; see also Santos et al., 2018; Snyder et al., 2016). Tisserand and colleagues (2023) found that Alzheimer's patients report photophobia at a frequency (19.3%) that is numerically (although not significantly) less than healthy controls (35.5%) and significantly less than those suffering from dementia with Lewy bodies (47.3%). Individuals with migraine headache are at increased risk for dementia, and patients with dementia—particularly Lewy body dementia—frequently have photophobia (30%) and dry eye disease (40%) (Blanc et al., 2022; Kim et al., 2023). Photophobia in Lewy body dementia could result from its association with migraine, dry eyes, or the dementia itself.

A briefly reported study of PBR supports the potential value of this measure in dementia research (Tavy, von Woerkom, Morré, & Slates,1985). An aggregated group of 15 patients with

either Alzheimer's or multi-infarct dementia were compared with 13 neurologically intact controls. Analyses of the latency of PBRs revealed a dramatic difference between the two groups. Controls showed latency values that are typical in the literature (mean = 49.7 ms, standard deviation = 2.2 ms, range = 47.0 – 53.3), whereas patients exhibited longer and much more distributed values (M = 104.3 ms, SD = 30.0 ms, range = 65.0 – 158 ms). We endorse the authors' conclusion from nearly 40 years ago that "these findings imply that further studies on the visual blink reflex in dementia are warranted."

8. Conclusions

The research covered in this review support our hypothesis that the main function of the PBR sustained component, R80, is to shape the eyelids into a narrow fissure so as to block painfully bright light. This response is driven primarily by ipRGC input and is potentiated by cephalic pain or even mild ocular discomfort (e.g., dry eyes following extended fixation). The PBR and subsequent squinting behavior have been found to be associated with visual discomfort during exposure to bright light in various patient groups, healthy adults, and mice injected with a substance known to induce migraine.

The PBR and pupillary light reflex work together to protect the retina from dangerously bright light and their neural pathways appear to overlap. It is clear that both are useful as objective indices of photophobia. In the case of migraine, though, a direct comparison of these two measures found PBR to be superior (Kaiser et al., 2021; McAdams et al., 2020). The availability of a stand-alone system for simultaneously measuring both responses (Choi et al., 2021) is a reminder that researchers and clinicians need not choose between them. The question then becomes whether to optimize the protocol for one or the other measure for the objective assessment of photophobia.

That the PBR would find this practical application might not have been predicted when Sigmund Exner initiated research on the phenomenon one-and-a-half centuries ago (Exner, 1874). His insight, though, that investigating "the simplest psychological processes" could lead to a better understanding of the human mind, has certainly held true. As brain and behavior researchers have followed this strategy over the decades, the PBR found a role in studies of conditioning, attention, expectation, emotion, and motor control. Basic research on simple neurobehavioral phenomena can lead to unexpected benefits.

Declaration of Generative AI and AI-assisted technologies in the writing process:

The authors declare that they did not use generative AI technologies in the preparation of this work.

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End Notes

[1]Historians of science are mistaken in crediting discovery of the trigeminal blink reflex to Overend, 1896 (e.g., Fine, Sentz, & Soria, 1992). [Call-out is on page 6.]

[2]Note that analyses of variance were calculated with pencil, paper, and slide rule in that pre-digital era. One of us (SAH) discussed the remarkably sophisticated methods employed in these early reflex modulation studies with David Grant's graduate advisor, Ernest Hilgard. Prof. Hilgard kept office hours at Stanford University well into his 90s. [Call-out is on page 7.]

[3]Margaret T. Bradley was Grant's last student and, with over 90,000 citations, surely his most influential. [Call-out is on page 7.]

[4]We recognize that the term "blink" is not optimal for prolonged lid closure in response to prolonged visual stimulation, but it may be worth retaining until the blink-squint transition has been more fully characterized. [Call-out is on page 11.]

Author Note

The authors declare that they have no known conflicts of interest to disclose.

Highlights:

- Recent findings indicate that blinking or squinting, reflexively triggered by bright light, is increased in patients with migraine headaches.
- Early research documented an interaction of visual and nociceptive stimulation on reflexive lid closure.
- The authors propose that the late, sustained component of the photic blink is driven primarily by melanopsin afference.
- This component shapes the eyelids into a squint, which helps block painfully bright light.