

# Article ▶ Pathway Differences in the Amblyopic Brain: A Review Based upon Pupillary Reflex Studies

Matthew Walsh, OD, Nova Southeastern University College of Optometry, Fort Lauderdale, Florida

## ABSTRACT

Amblyopia is much more than decreased vision, it is a syndrome. The variety of deficits is a result of structural and functional differences in the visual pathway from the retina to the cortex. Historically, it was thought that amblyopia did not cause a relative afferent pupillary defect, but recent studies suggest otherwise. Research into the thalamic and cortical influences on the pupillary pathway has provided insight into some of the differences that occur in the amblyopic brain. Current research has cast light onto the complexity of the pupillary pathway, yet the exact mechanism is unknown. The neurological changes, which have long explained the visual deficits of amblyopia, may now also explain associated abnormal pupillary reactions. However, similar to some of the visual deficits of amblyopia, pupillary abnormalities have also been shown to be reversible with amblyopia treatment. This paper reviews research illustrating the increased awareness of pupillary involvement in those with amblyopia and the associated potential impact on optometric treatment of amblyopia.

**Keywords:** amblyopia, pupillary function, visual pathway

## Introduction

Amblyopia is much more than decreased vision, it is a syndrome. Amblyopia is a unilateral or bilateral condition due to abnormal visual experience during the first few years of life.<sup>1</sup> An amblyogenic factor, such as strabismus, anisometropia, high bilateral refractive error, or form deprivation must be present to make the diagnosis. Clinically, the first detected sign of amblyopia is reduced visual acuity. When amblyopia is seen as a syndrome resulting from poor spatial perception, then the full extent of amblyopic deficits may be present. These include increased sensitivity to contour interactions (crowding phenomenon), unsteady fixation, inaccurate and delayed saccadic movements, incorrect accommodative responses, and decreased stereopsis.<sup>2-9</sup> Additionally, amblyopic eyes have abnormal temporal and motion processing as well as abnormal spatial distortions due to deficits in contrast acuity, contrast sensitivity, positional acuity, and spatial localization.<sup>10</sup>

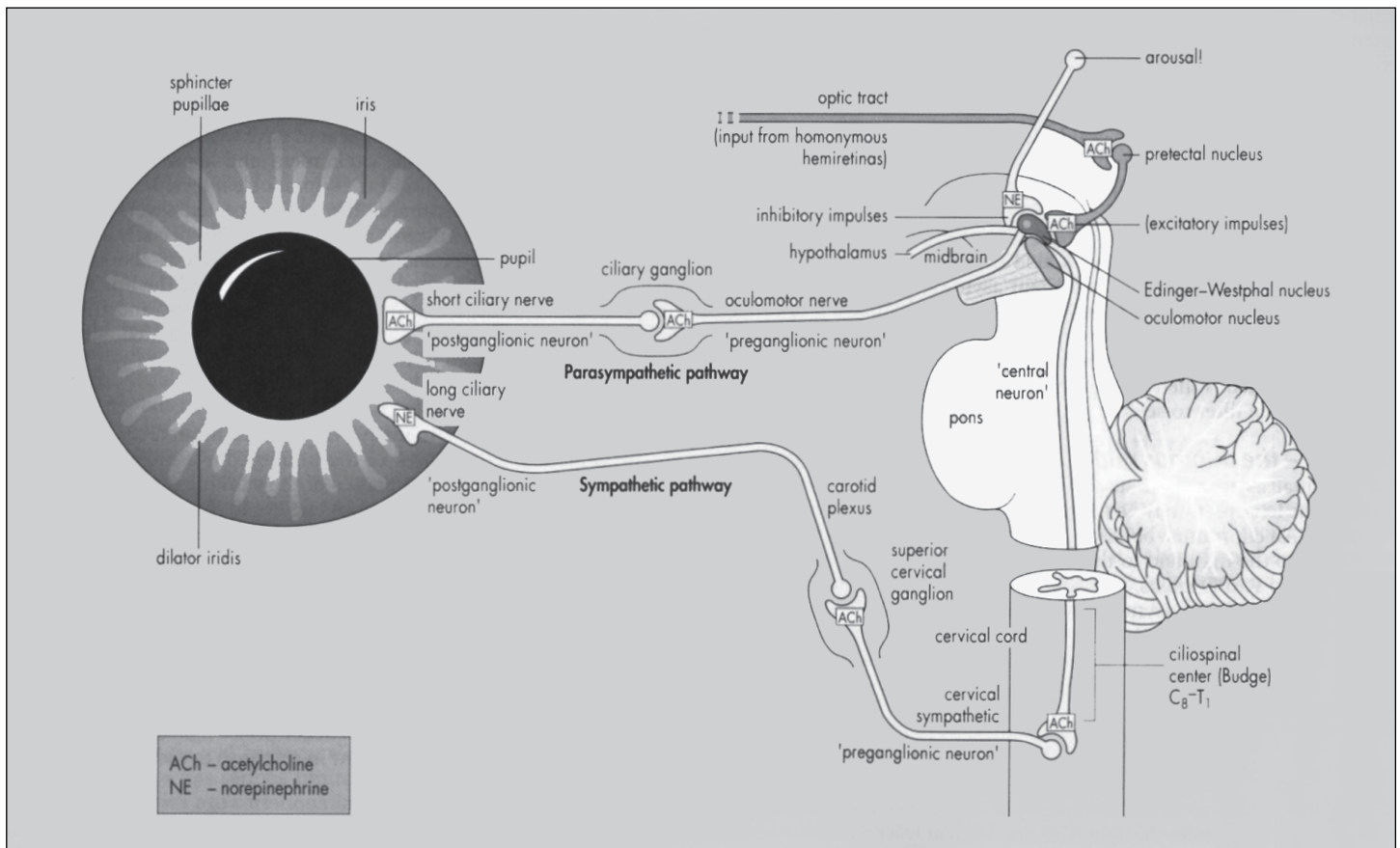
Zinn<sup>11</sup> wrote that a negative swinging flashlight test would be present in amblyopia. Portnoy et al.<sup>12</sup> wrote that eye care practitioners, like himself, believed in the early 1980s that a relative afferent pupillary defect (RAPD) was unlikely in an amblyopic eye. This belief arose from the concept that amblyopia resulted from central suppression and not damage to the eye or along the optic nerve.<sup>12</sup> However, many studies have shown the contrary; now, it is accepted that a subtle, clinically insignificant RAPD can be present in unilateral amblyopia.<sup>13,14</sup> As pupillary studies were conducted, more hypotheses began to emerge regarding the structural and functional integrity of the pupillary light reflex in amblyopes. The results of these studies made necessary the reconsideration of the pupil pathway as a simple reflex arc. Some investigators speculated that the deficits of the pupillary pathway involved higher-order influences, similar to the visual pathway.<sup>14-16</sup>

Pupillary responses are more complex than previously thought. Studies have shown that pupillary responses do not share one common pathway and occur in response to luminance, color, movement, and structure.<sup>17-19</sup> Papageorgiou et al. proposed two separate pathways: a primitive luminance conduit from the retina to the pretectal nucleus and a higher level channel with cortical involvement for color, motion, and spatial relations.<sup>19</sup> However, based on his work with pupillary reactions to luminance and color, Young et al.<sup>20</sup> reported that the pathways may be divided more appropriately into transient and sustained stimuli. This paper reviews the pupillary studies in amblyopes to describe the structural and functional differences in the amblyopic light reflex pathway, from retina to cortex.

## Classical Model of the Pupillary Light Reflex Pathway

In the textbook model, the pupillary light reflex pathway consists of three subcortical parts: the afferent pathway, the parasympathetic efferent pathway, and the sympathetic efferent pathway.<sup>11,21</sup>

The consensual and direct reactions should be theoretically equal in intensity, quality, and timing.<sup>22</sup> The afferent pupillary light reflex pathway begins with the photoreceptors. Light stimulation causes the photoreceptors to initiate a cascade of events, and the photoreceptors synapse to retinal ganglion cells via the bipolar cells. The axons of the ganglion cells travel along the optic nerve to the optic chiasm. At the chiasm, the nasal fibers decussate and continue down the optic tract. The pupillary fibers diverge from the visual pathway just prior to the lateral geniculate nucleus. These afferent pupillary fibers enter the midbrain, pass through the superior brachium of the superior colliculus, and synapse at the olivary pretectal nucleus. The pupillary fibers exit the pretectal nucleus and separate in



**Figure 1:** The afferent, parasympathetic efferent, and sympathetic efferent pupillary pathways.<sup>19</sup> Reprinted with permission by Elsevier from Yanoff M, Duker JS, eds, *Ophthalmology* (2009), page 1052.

approximately equal amounts to the ipsilateral and contralateral Edinger-Westphal nuclei. Whether the fibers travel to the ipsilateral or contralateral Edinger-Westphal nucleus, they are now termed intercalated neurons or the pretecto-oculomotor tract. The nearly equal decussation of fibers at the optic chiasm and the pretectal nucleus is the basis for the observed bilateral and symmetrical miosis during the swinging flashlight test (Figure 1).

The iris sphincter, which is responsible for iris constriction, is innervated via the parasympathetic efferent pathway. The parasympathetic efferent pupillary pathway starts at the Edinger-Westphal nucleus, which is located at the dorsal aspect of the third cranial nerve nucleus. Both nuclei are located in the anterior dorsal mesencephalon at the level of the superior colliculus. The pupillary fibers depart the Edinger-Westphal nucleus and join with the fibers of the third cranial nerve. The pupillary fibers are positioned superficially on the dorsomedial aspect of the nerve. The third cranial nerve courses through the cavernous sinus, where the pupillary fibers diverge with the branch responsible for innervation of the inferior oblique. The pupillary fibers enter the orbit through the superior orbital fissure and synapse at the ciliary ganglion. These postganglionic fibers then enter the eye via the short posterior ciliary nerves and synapse at the iris, choroid, and ciliary body.

The sympathetic nervous system influences pupillary dilation. The sympathetic nervous system is divided into three parts:

central (first-order) neurons, preganglionic (second-order) neurons, and postganglionic (third-order) neurons. The central neurons of the sympathetic efferent pupillary pathway start in the posterior and lateral areas of the hypothalamus. They descend in an uncrossed manner with synapses in the midbrain and pons. The fibers continue to descend and synapse at C8-T2 in the spinal cord. The preganglionic neurons begin as the fibers exit the spinal cord. They travel up the sympathetic chain and synapse at the inferior, middle, and superior cervical ganglia. The postganglionic neurons begin as the fibers exit the superior cervical ganglion. The fibers travel upward with the internal carotid artery, enter the cavernous sinus, and travel with the sixth cranial nerve. Upon exiting the cavernous sinus, the fibers run with the ophthalmic division of the fifth cranial nerve by passing through the superior orbital fissure. Once inside the orbit, the fibers travel with the nasociliary branch of the fifth cranial nerve's ophthalmic division. They pass through the ciliary ganglion without synapsing and continue through the long ciliary nerves to synapse on the dilator muscle in the iris.

### Methods of Measuring Pupillary Reactions

Over the years, various methods have been developed to evaluate pupillary reactions. In 1946, Alfred Kestenbaum, a neuro-ophthalmologist, created and explained a technique to demonstrate asymmetrical pupillary reactions to light. The patient was asked to fixate on a diffuse light throughout the

procedure. To rule out true anisocoria, he made an initial measurement of both pupils while both eyes were open. The procedure continued once it was determined that the pupils were of equal size. With the use of a pupillometer or ruler, the examiner measured the final diameter of each pupil while the other eye was sufficiently covered. Kestenbaum referred to the difference in pupillary diameters as the “pseudo-anisocoria sign.” The eye with the larger diameter had the RAPD.<sup>23</sup>

In 1959, Paul Levatin developed the “swinging flashlight test,” which is now clinically the most commonly used technique to determine the presence of an RAPD.<sup>24</sup> In 1981, Thompson et al.<sup>25</sup> explained the proper technique. The assessment should take place in a dimly lit room with a bright light, but they cautioned against using a light so bright that it would bleach the retina and impact the reactivity of the pupillary response. With both eyes open, the examiner placed the light along the visual axis of the eye for three seconds, and then quickly alternated to the other eye. Thompson recommended holding the light just below horizontal for two reasons. First, the corneal reflex would not block the pupillary response. Second, it would otherwise cast a shadow from the nose on the opposite eye. The “swinging flashlight test” amplified the difference in the pupillary reactions to light and aided examiners in determining the relative asymmetry between the two eyes.<sup>25</sup> In order to ensure correct alignment with the visual axis in strabismic patients, some examiners have presented alternating flashes of light using a synoptophore.

The swinging flashlight test alone allows the examiner to determine the presence or absence of an RAPD. Unfortunately, the grade of the RAPD depends on the subjectivity of the examiner. For this reason, Thompson<sup>25</sup> advocated quantification of the RAPD rather than estimation. He proposed the use of neutral density filters, which would measure the difference in log units. The neutral density filter decreases the transmittance of light onto the retina, producing a weaker impulse along the afferent pathway.<sup>26</sup> Neutral density filters of varying transmittance are placed in front of the unsuspected eye and a swinging flashlight test is performed until the examiner determines that the pupillary reactions are balanced.<sup>25</sup> The log unit value of the neutral density filter which equalizes the reactions is used as the measurement value for the RAPD.

Technology has also been used to conduct pupillary reaction studies. The use of infrared pupillography enabled an examiner to compare both pupils simultaneously. In 1958, Lowenstein and Lowenfeld first introduced the instrument and its clinical implications.<sup>27</sup> Technological advancements have changed the setup throughout the years, but the basic principles remain unchanged. The setup includes a telephoto lens and double base-out prisms. The examiner can view a magnified image of the pupils located side-by-side on a monitor. Since pupil testing occurs in dimly-lit environments, the pupillometer would allow for easier comparison of the direct and consensual responses.<sup>21</sup> By recording the pupillary

reactions, the examiner can review each recording multiple times. Additionally, automated pupillometry has become a reality due to computerization of techniques. Examiners now have the option of creating specialized software and hardware, which could flash the light stimuli, record, and analyze the pupillary responses for the desired parameters, such as speed, latency, or diameter.<sup>21</sup>

### **Early Studies Describing the Pupillary Differences in Amblyopia**

Physicians have studied the relationship between pupillary reactions and visual acuity since the time of Galen in the 8th century.<sup>24</sup> However, it was not until the 20th century that pupillary reactions were studied in amblyopes. One of the first investigations into the presence of pupillary differences in the amblyopic eye was published in 1937 by Harms.<sup>13,16,22</sup> Using strabismic amblyopes and control subjects, Harms presented light stimuli to the central and peripheral fields. He then measured changes in pupillary size with a pupilloscopic system. He found that control subjects had greater constriction to central stimuli. In contrast, the study showed that the amblyopic eyes had a greater response to peripheral presentations. Harms concluded that a central sensory deficit existed in amblyopic eyes.<sup>13,16,22</sup> Several studies were published concerning pupillary abnormalities and retinal rivalry.<sup>16,28,29</sup> Retinal rivalry exists when the two eyes are presented with two different, unfusible images; subsequently, suppression of a part or all of one image occurs.<sup>28</sup> At the time of these studies,<sup>16,28,29</sup> there was a debate over the structural location of binocular suppression. While some argued that the pupillary and visual pathways only shared synapses within the retina, others said the visual cortex was the first location of binocular fusion. Central suppression was thought to cause poor fixation, and this, in turn, was responsible for the abnormal pupillary findings in amblyopes.<sup>12</sup> Barany and Hallden<sup>28</sup> experimented with only normal subjects. During retinal rivalry, they found that the suppressing eye would be less likely to experience pupil constriction in response to light as compared to the fellow eye. They postulated that motor inhibition of the pupil reflex can occur down to the retinal level. However, they did not discount the possibility of higher level influences upon the light reflex pathway despite the lack of experimental evidence at the time.<sup>28</sup> However, Lowe and Ogle<sup>29</sup> failed to replicate the findings that showed suppression of the pupillary light reflex during the phase of retinal rivalry inhibition in normal subjects.

Doesschate and Alpern<sup>30</sup> reported that normal subjects had smaller pupillary diameters (greater contracture) with binocular versus monocular light stimulation. When they tested strabismics, pupillary constriction was greater for the fixating eye compared to the nonfixating eye. It did not matter whether amblyopia was present or not. Furthermore, the pupillary constriction was no greater under binocular stimulation as compared to stimulation of the fixating eye

alone.<sup>30</sup> The lone exception to this finding was when unequal light stimuli were presented binocularly. If the nonfixating eye was given a stimulus of higher intensity, then the pupillary constriction was greater than for the fixating eye alone.<sup>31</sup> It was postulated that abnormal pupillary responses in strabismics may be correlated with the reduction of binocularly-driven cortical cells as reported by Hubel and Wiesel.<sup>31,32</sup> These findings suggested a commonality between the visual and pupillary pathways.

During the mid-20th Century, other researchers investigated other facets regarding abnormal pupillary findings in patients with amblyopia. Dolenek reported differences in the latency of the pupil reaction between amblyopic and normal eyes. He reported that the amblyopic eyes showed longer latencies of both constriction and dilation compared to normal eyes.<sup>22</sup>

Kruger used the “pseudo-anisocoria test of Kestenbaum” to measure pupil sensitivity in a study published in 1961.<sup>13</sup> He tested 100 functional amblyopes, as well as normal subjects and those with strabismus without amblyopia. Ninety-three percent of the amblyopes displayed abnormal responses, compared to 0% of the other groups. This finding suggested a link between amblyopia and abnormal pupillary reactions but did not establish a causal relationship.<sup>13</sup>

## Retinal Differences

Over time, some researchers began to question whether the presence of RAPDs in amblyopic eyes was simply due to poor fixation secondary to binocular suppression. In 1983, two studies used the swinging flashlight test with transilluminators specifically to detect the prevalence of RAPDs in amblyopia. Portnoy et al.<sup>12</sup> used the swinging flashlight test with neutral density filters to measure the magnitude of pupillary defects. The study included 55 amblyopic patients. None of the fellow eyes presented with an RAPD; however, 82% of subjects had an RAPD in the amblyopic eye. When the authors rejected an RAPD of less than 0.3 log units, then 53% of subjects still had an RAPD. The mean RAPD measured 0.317 log units when the 10 subjects with no RAPD were disregarded. Seventy-eight percent of the RAPDs measured 0.3 log units.<sup>11</sup> Based on their results, Portnoy et al. determined that it was “not possible” to predict the depth of amblyopia on the basis of magnitude of an RAPD, or vice versa. Portnoy et al. concluded that their results could not settle the debate between binocular suppression or a retinal lesion as the cause for the RAPD, which would have localized the pupillary defects to the visual pathway.<sup>12</sup>

In Greenwald and Folk's<sup>33</sup> study, one examiner evaluated 45 amblyopes, 44 subjects with equal vision (including nine patients who were successfully treated for amblyopia), and 5 subjects with pathological vision loss. The procedure did not include the use of neutral density filters. Nine percent of amblyopic eyes were noted to have a “probable” RAPD, but none were deemed unquestionable due to “the mildness of abnormality, less than perfect consistency of responses, and

testing difficulty.” This percentage of 9% greatly differed from Portnoy's 82%.<sup>12,33</sup> Anisometric and strabismic amblyopes were judged to have RAPDs of about equal frequency. They found no RAPDs in small angle or intermittent strabismics. Neither of the patients with form deprivation amblyopia from cataracts exhibited an RAPD, but they did have sluggish responses secondary to surgical iris trauma. From their results, Greenwald and Folk made several conclusions. First, and most clinically relevant, pathology should be suspected in the presence of a marked RAPD; yet, a subtle RAPD in conjunction with history and findings consistent with amblyopia requires no further workup. Second, in agreement with Portnoy et al.,<sup>12</sup> there was no relationship between visual acuity and the presence of an RAPD in amblyopia. Third, RAPDs were the result of the amblyopia itself since fundus examination and functional vision tests provided no evidence of pathology. They proposed that the presence of an RAPD suggested “a physiological disturbance” at the level of the retina, which is shared by the visual and pupillary pathways.<sup>33</sup>

It was not until 1984 that research provided evidence that the pupillary abnormalities in amblyopic eyes were confined to the afferent pathway. Kase et al.<sup>22</sup> used infrared pupillography to measure the pupillary reflex amplitudes, velocities, and latencies. The subjects comprised 15 unilateral amblyopes, either strabismic or anisometric, and eight recovered amblyopes who were successfully treated. Among the amblyopic subjects, the reflex amplitudes and maximum velocities did not reveal a statistically significant difference whether the amblyopic or fellow eye was stimulated; however, there was a difference in latency. Kase et al.<sup>22</sup> concluded that the afferent pathway accounts for this increased latency based upon three findings. First, the consensual reflex of the fellow eye had about the same increased latency as the direct reflex of the amblyopic eye. Second, the direct reflex of the amblyopic eye was statistically significantly longer than the direct reflex of the fellow eye. Third, the direct reflex of the amblyopic eye was statistically significantly longer than its consensual reflex. Additionally, “no significant correlation” was found between the degree of latency and the visual acuity measured (correlation of coefficient = -0.216). The authors suggested that the results varied because of the complexity of the pupillary system. They postulated that there are different sites or mechanisms responsible for pupillary reaction magnitude, speed, and timing. In agreement with Greenwald and Folk,<sup>33</sup> Kase et al.<sup>22</sup> suggested that the mechanism of the afferent pupillary defect lies in the retina rather than the optic nerve.

In 1990, Firth<sup>34</sup> published her study of the prevalence of RAPD in amblyopia. Like Brenner's group, Firth also used the alternating swinging flashlight test with a synoptophore. Firth used neutral density filters to confirm the presence of an RAPD, not to measure the size of the defect. The study included 65 amblyopes and 25 controls. About one-third of the amblyopes presented with an RAPD in their amblyopic eye, while 3% showed an RAPD in the fellow eye. Four percent

of the controls had a subtle RAPD, which Firth attributed to observer error or contraction anisocoria. Based on structural and functional changes of amblyopic retinas, Firth proposed that a defect located before the lateral geniculate nucleus (LGN) is the most likely explanation for an RAPD in amblyopia.

### **Pregenulate Differences**

Based on monkey studies suggesting retinal degeneration after long-term cortical damage, Hess postulated that amblyopic eyes may show retinal changes.<sup>35,36</sup> Unfortunately, there are no studies which investigate the retinal structure or function in the amblyopic eyes with an RAPD. Since both the pupillary and visual pathways begin in the retina, it is important to review the debate over the integrity of the structure and function of the amblyopic retina. Through his cat studies, Sherman et al.<sup>37</sup> concluded that “the ganglion cells of deprived retina appear normal in cell-body size, receptive field properties, axonal conduction velocities, and relative frequencies of Y-, X-, and W-cells.” Later, Kratz et al.<sup>38</sup> were also unable to discover any retinal anomalies following early monocular lid suture in cats. This finding is in stark contrast to other animal studies. During the same time frame, Ikeda and Tremain<sup>39</sup> published work detailing the abnormal retinal function of ganglion X cells. In separate studies with cats, Ikeda and Tremain<sup>39,40</sup> showed that the X cells in amblyopic eyes had reduced spatial resolving power. It did not matter whether the amblyogenic factor was surgically-induced unilateral strabismus or atropine-induced anisometropia.

Even with the assumption that the amblyopic eye has proper retinal structure, there is no assurance that the amblyopic retina functions normally. Not surprisingly, there are disagreements on this topic as well. Electroretinography (ERG) studies have yielded varied results. Some proponents suggested that amblyopic eyes have longer latencies or reduced amplitudes compared to normal eyes based upon ERG studies.<sup>35,41,42</sup> Other researchers have claimed that the retinal function of amblyopic eyes remains equivalent to normal eyes.<sup>35,41,43</sup>

The retinal nerve fiber layer (RNFL) carries the impulse away from the retina to the next destination, which differs depending on whether the specific fibers are part of the pupillary or visual pathways. The structure of the RNFL in amblyopes has been the subject of much research over the past decade since the advent of more technologically advanced diagnostic equipment. These instruments include the scanning laser polarimeter with variable corneal compensation (Zeiss GDx), confocal scanning laser ophthalmoscope (Heidelberg Retina Tomograph, or HRT), and optical coherence tomographer (OCT). Yen et al.<sup>44</sup> and Yoon et al.<sup>45</sup> have published studies using time-domain OCTs that show statistically significant differences in RNFL thickness between amblyopic eyes and fellow eyes. Interestingly, both cases found that the RNFL of the amblyopic eyes was thicker. However, numerous and more recent studies using time-domain OCTs

dispute this claim and have found no significant difference either between the amblyopic and the fellow eye or between amblyopic eyes compared to eyes of normal subjects.<sup>46-51</sup> One of these studies also found no difference in RNFL thickness between amblyopic eyes or those who had recovered following successful treatment.<sup>51</sup> Although Kase<sup>22</sup> may not be entirely wrong, most research regarding RNFL differences does not support the likelihood that the RNFL is the location of the differences leading to pupillary abnormalities in amblyopes. Additionally, a 2010 study using a spectral-domain OCT found no significant difference in RNFL thickness between the amblyopic and fellow eyes.<sup>52</sup> GDx and HRT studies have also shown no significant difference of RNFL thickness between either the amblyopic and the fellow eyes or between amblyopic and normal eyes.<sup>53-55</sup> As Hess<sup>35</sup> reported, although the retina is most likely not the primary site of the amblyopic defect, it does not mean that the amblyopic retina is completely normal.

### **Higher-Order Differences**

Several studies suggested that changes in higher-order influences within the amblyopic neural pathway explain the abnormal pupillary findings. In 1969, Brenner et al.<sup>16</sup> used the alternating swinging flashlight test with a synoptophore to ensure direct alignment with the visual axis of strabismic amblyopes. The subjects included seven normals and nine amblyopes. In both groups, the fixating eye demonstrated greater contraction amplitude than the nonfixating eye during retinal rivalry. This finding was exaggerated in the amblyopes. The authors also inferred that the pupillary response in the amblyopic eye decreased as the binocular suppression deepened. As a result, the authors suggested that the mechanisms of visual and pupillomotor suppression traveled along similar pathways. However, they could not pinpoint whether the defect occurred along the lines of retina to midbrain or whether higher-order cortical influences were involved.

Barbur et al.<sup>15</sup> studied the constriction amplitudes and latencies of amblyopic and normal eyes in response to light and pattern stimuli. The study included six normals and 19 amblyopes. The amblyopia group was subdivided further (seven anisometropes and 12 strabimics). The results revealed some of the complexity in the pupil pathway. First, the authors discussed the results in response to a light stimulus. There was no statistical difference between the amplitude of the direct and consensual responses of the amblyopic and fellow eye ( $p > 0.1$ ), thus confirming an intact efferent pathway. There was a statistically significant difference in latency of the pupil response between the amblyopic eye and its fellow eye ( $p < 0.05$ ), as well as between the amblyopic and normal eyes ( $p < 0.001$ ). Second, the authors discussed the results with the patterned stimulus. Compared to the fellow eye, there were reduced response amplitudes for strabismic amblyopic eyes across the spatial frequencies of 1.2-6 cycles per degree (cpd) ( $p < 0.01$ ). In contrast, the anisometric amblyopic eyes were reduced only for spatial frequencies of 6 cpd (0.245 versus

0.142 millimeters,  $p < 0.1$ ). In comparison to amplitudes in normal eyes, the amplitudes of the fellow eyes of all amblyopes were significantly reduced ( $p < 0.001$ ). The strabismic group had significantly longer latencies in their amblyopic eyes, as compared to the fellow eye (46 milliseconds,  $p < 0.05$ ). In addition, the strabismic amblyopes' fellow eye showed a significantly longer latency than the eye of a normal subject ( $p < 0.05$ ). Based on these findings, the authors suggested that the pupillary light reflex pathway is more complex than previously thought. These authors support a descending cortical influence on the pupillary pathway, which may be located along the geniculostriate route.

The most recent study of the prevalence of RAPDs in amblyopia occurred in 2008 by Miki et al.<sup>14</sup> The subjects included 10 unilateral strabismic and/or anisometropic amblyopes and eight normals. They used a binocular infrared video pupillographic device to measure the pupillary responses. They used an automated swinging flashlight test which presented a light stimulus along the visual axis. They defined a pupillary defect as a difference of 0.25 mm or greater between maximum and minimum contraction amplitudes. While none of the normal subjects had a pupillary defect, 10% of amblyopic eyes showed a reproducible RAPD. This percentage was most in agreement with Greenwald's finding of 9%.<sup>14,33</sup> Miki et al. found no correlation between visual acuity and contraction amplitude ( $p = 0.3965$ ). They concluded that a subtle RAPD could occur in amblyopia and urged clinicians to suspect pathology of the optic nerve or retina in the presence of a marked RAPD. While Miki et al. concluded the origin of an RAPD in amblyopia to be unknown, they suggested the possibility that anomalies in the visual cortex may influence the afferent pupillary pathway.<sup>14</sup>

### Geniculate and Postgeniculate Differences

The structural changes of the visual cortex of amblyopes have been known since the landmark studies by Hubel and Weisel.<sup>32</sup> More recently, researchers have been able to monitor brain activity of amblyopes using functional magnetic resonance imaging (fMRI) technology. These studies have shown decreased activity levels in the striate and extra-striate cortices.<sup>56,57</sup> A 2011 study found that fMRIs can confirm anomalous connections between the LGN and the cortex and between the striate cortex and extrastriate cortex.<sup>58</sup> Structural changes of the LGN have long been identified in amblyopia.<sup>59</sup> Post-mortem evaluation has demonstrated cell shrinkage of the ipsilateral LGN.<sup>60</sup> More recently, a decrease in gray matter was discovered.<sup>61</sup> These structural changes may account for the reduced activity compared to the fellow eye measured in fMRI studies.<sup>62</sup> The extent of the deficits throughout the entirety of the thalamocortical pathway caused researchers to propose a new query: should the visual deficits of amblyopia be attributed to specific sites or rather to anomalous connections between different locations?<sup>58</sup> Likewise, the same question could be raised regarding the pupillary pathway in amblyopes.

Since the control centers for the amblyopic syndrome reside in higher-level processes, the structural and functional changes of the cortex could explain these deficits. However, the pupillary findings have been harder to explain owing to the classical thought that the pupillary pathway is completely subcortical and does not involve the LGN or cortex.

Although the anatomy is still unknown, the pupillary pathway is more than just a simple reflex arc. Current research explains the potential complexity of the pupillary pathway.<sup>15,63</sup> Studies first suggested the possibility of a cortical influence on the pupillary light reflex pathway in cats and monkeys.<sup>64,65</sup> Later, Inoue et al.<sup>66</sup> studied rabbits and concluded that the "cortical pupilloconstrictor area and the pretectal region represented higher brain centers of the pupillary reactions, and that impulses from these cortical and subcortical centers share common peripheral nerve units with the pupillary light reaction." The literature describing cortical influences on the pupillary pathway did not stop with animals. Zinn<sup>11</sup> described that the corticothalamohypothalamic pathway sent inhibitory impulses to the Edinger-Westphal nucleus in humans.

Case studies on human subjects, who developed RAPDs from cortical and thalamic damage, began to build a case for geniculostriate pathway influence. In one study, about one-third of patients with geniculate or retrogeniculate lesions developed an RAPD. All of the lesions were within 18 millimeters of the LGN.<sup>67</sup> Other studies showed decreased pupillary contraction amplitudes in patients with central visual pathway damage.<sup>15</sup> Wilhelm<sup>67</sup> postulated that a lesion to intercalated neurons connecting the visual pathway to the pretectal nuclei caused the presence of an RAPD.

In 2008, the pupillary light reflex pathway was investigated using the most advanced technology to date. Papageorgiou et al.<sup>19</sup> imaged the brains of subjects who had homonymous visual field defects due to a unilateral vascular brain lesion in the cerebral cortex. The results showed that 43% of these patients had an RAPD greater than or equal to 0.3 log units. Based upon the prevalence and magnitude, this was unlikely due to normal physiology according to Kawasaki and Wilhelm's research.<sup>68-70</sup> These findings inspired the researchers to compare the T1-weighted MRIs of those with and without an RAPD. They found the subjects who presented with an RAPD were over seven times more likely to have a lesion at the "early beginning of the course of the optic radiation in the temporal white matter."<sup>19</sup> In agreement with Wilhelm et al.,<sup>70</sup> this location was close to the LGN. They concluded that the exact anatomic pathway is still unknown but believed that cortical influences upon the pretectal nuclei were responsible.<sup>19</sup> These findings support the argument that structural and functional abnormalities in higher-order structures can produce abnormal pupillary findings in amblyopes.

### Relative Afferent Pupillary Defects in Normal Subjects

An RAPD can occur in normal subjects. Indirect evidence suggests that the pupillary abnormalities found in patients

with amblyopia result from the neural deficits of the condition rather than normal physiological differences. Normal subjects have shown afferent pupillomotor asymmetry, typically of a small magnitude.<sup>68</sup> Not only can normal subjects exhibit an RAPD, but it can vary over time in laterality and magnitude.<sup>69</sup> The expected prevalence in the normal population differs depending upon the identification method. Wilhelm et al.<sup>70</sup> in a population of 102 subjects found by swinging flashlight test that 85% had no RAPD, 13% had an RAPD of 0.15 log units, and 2% had an RAPD of 0.3 log units. However, pupillography revealed that every subject had an asymmetry of some magnitude. The results revealed that 94% had an RAPD of 0.22 log units or less and 6% had an RAPD between 0.23 and 0.39 log units.<sup>70</sup> By disregarding RAPDs less than 0.3 log units, Portnoy et al.<sup>12</sup> eliminated a majority of false positives due to physiological asymmetry. The remaining 53% of amblyopic eyes with an RAPD of 0.3 log units or greater were more likely to be a true entity of the amblyopic syndrome.

### Effects of Vision Therapy on Pupillary Abnormalities

Evidence exists that vision therapy may improve specific facets of abnormal pupillary light reactions. Dolenc published findings that suggested that successful vision therapy could normalize the direct response latencies of the amblyopic eyes. The response latencies decreased from 240 to 180 milliseconds in the amblyopic eyes after treatment.<sup>13</sup> Greenwald and Folk reported that the RAPD of an eight-year-old subject “became increasingly difficult to observe” over the course of treatment for unilateral amblyopia.<sup>33</sup> Kase et al. reported that none of the eight subjects successfully treated for unilateral amblyopia showed a significant difference in latency of the direct or consensual pupillary reflexes of the treated eye ( $p > 0.05$  for both cases) compared to normal eyes.<sup>22</sup>

Evidence exists that sensory deprivation during sensitive periods can alter cortical and subcortical structures. A 2010 study of monaural deprivation did show changes to the auditory midbrain as well as the cortex.<sup>71</sup> It is possible that amblyopia could cause similar reorganization of midbrain pathways responsible for the afferent pupillary light reflex pathway, but more research is needed. New research involving neuroplasticity has found that even a mature nervous system can make new synaptic connections.<sup>72</sup> More research is necessary to determine whether the alterations occur in cortical or subcortical influences on the pupillary light reflex pathway.

### Conclusion

A review of the pupillary studies has confirmed changes in the amblyopic brain throughout the visual pathway. The location or locations of the defects responsible for an RAPD in amblyopia may be as elusive as the primary site of the amblyopia itself. As discussed, the amblyopic pupillary and visual pathways may be anomalous from the retina to the cortex. Unfortunately, the exact reason why some amblyopes present with an RAPD while others do not remains a mystery.

Beyond speculation, pupillary abnormalities can and do occur in amblyopic eyes with no consistent correlation to visual acuity. The defect is usually subtle, typically 0.3 log units or less, with the afferent pupillary pathway being responsible for the pupillary defect regarding the latency and magnitude of contracture. Likewise to other visual deficits of amblyopia, the RAPD has shown evidence of amenability to vision therapy. Clinicians who regularly treat visual deficits associated with amblyopia have found an explanation for the improvements made by vision therapy through the evidence of neuroplasticity. If neuroplasticity explains the positive effect of visual training on visual acuity, then maybe it also clarifies why some researchers found an improvement in the pupillary response. More research will determine whether cortical or subcortical neuronal alterations account for the specific improvements on pupillary abnormalities in amblyopic eyes.

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*Correspondence regarding this article should be emailed to Matthew Walsh, OD, at [mattwals@nova.edu](mailto:mattwals@nova.edu). All statements are the author's personal opinions and may not reflect the opinions of the representative organizations, ACBO or OEPE, Optometry & Visual Performance, or any institution or organization with which the author may be affiliated. Permission to use reprints of this article must be obtained from the editor. Copyright 2014 Optometric Extension Program Foundation. Online access is available at [www.acbo.org.au](http://www.acbo.org.au), [www.oepf.org](http://www.oepf.org), and [www.ovjournal.org](http://www.ovjournal.org).*

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