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Marshall M. Parks Memorial Lecture: Ocular Motor Misbehavior in Children

Where Neuro-Ophthalmology Meets Strabismus

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Clinical diagnosis has been supplemented by neuroimaging advances, genetic discoveries, and molecular research to generate new neurobiological discoveries pertaining to early maldevelopment of ocular motor control systems. In this focused review, I examine recent paradigm shifts that have transformed our understanding of pediatric ocular motor disease at the prenuclear and infranuclear levels. The pathogenesis of complex ocular motor disorders, such as paradoxical pupillary constriction to darkness, benign tonic upgaze of infancy, congenital fibrosis syndrome, and the constellation of unique eye movements that accompany Joubert syndrome, are elucidated. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology*

Supplemental material is available at www.aaojournal.org.

Dr. Marshall Parks was larger than life. When I trained, he was an almost biblical figure. Much of how we practiced pediatric ophthalmology in the United States was justified because Marshall Parks had ordained it. He influenced every aspect of my practice and gave me important inroads into some of my research into infantile strabismus. But in this symposium, we are focused on pediatric neuro-ophthalmology. In discussing the efferent visual system, I want to touch on the many recent discoveries involving the prenuclear and infranuclear pathways that have occurred since I started my ophthalmology training more than 30 years ago.

Many of you are familiar with Thomas Kuhn, whose 1962 book[1] overturned our understanding of scientific research. According to Kuhn, intellectual progress is not steady and gradual. It is marked by sudden paradigm shifts. There is a period of normal science when everybody embraces a paradigm that seems to be working. Then there is a period of model drift: As years go by, anomalies accumulate, and the model begins to seem more shaky and flawed, until the prevailing model is interrupted by a sudden, revolutionary phase or paradigm shift in our thinking that generates turmoil, uncertainty, and angst.[2] So what are some of the paradigm shifts we have witnessed in pediatric neuro-ophthalmology?

Subcortical Ocular Motor Pathways May Reactivate When Higher Retinocortical Pathways Fail to Develop on Time

Among the most perplexing clinical signs we encounter is the paradoxical pupillary constriction to darkness that occurs in some children with infantile nystagmus.[3–6] This condition usually is associated with congenital stationary night blindness (a deficiency of rod function)[3] or achromatopsia (an absence of retinal cones),[4] although a variety of other associated conditions have been documented.[5,6] When the room lights are turned off, there is a short lag of approximately 1 second before a sustained pupillary constriction is seen (Video 1, available at www.aaojournal.org).[5] So how can an incremental *decrease* in ambient illumination elicit pupillary *constriction*?

Approximately 15 years ago, we witnessed an amazing discovery that most animals, including humans, have intrinsically sensitive photoreceptors in a subpopulation of their retinal ganglion cells.[7–9] These photosensitive retinal ganglion cells contain an evolutionarily ancient opsin, termed "melanopsin," which is selectively sensitive to blue light from the sky. These melanopsin pathways project subcortically to the suprachiasmatic nucleus of the hypothalamus, which controls our sleep-wake cycles, then down through the cervical sympathetic tracts and back up to the pineal gland to stimulate secretion of melatonin, and entrain our circadian rhythms (Fig 1).[9,10] This subcortical visual pathway also sends projections to the pretectal olivary nucleus in the midbrain, causing pupillary constriction.[9–11] We think it may be this melanopsin-dependent pupillary pathway that we see in action in patients with paradoxical pupillary constriction.

So how does this work? Randy Kardon, MD, PhD, has formulated the following hypothesis. In normal humans, a decrement of light causes a bipolar cell off-signal to trigger pupillary dilation, which overrides the intrinsic melanopsin pupillomotor signal. In achromatopsia and congenital stationary night blindness, however, this bipolar off-signal is absent or deficient.[12,13] The decrease in photoreceptor input to the melanopsin-containing retinal ganglion cells may increase the steady state pupil size in room light. Under

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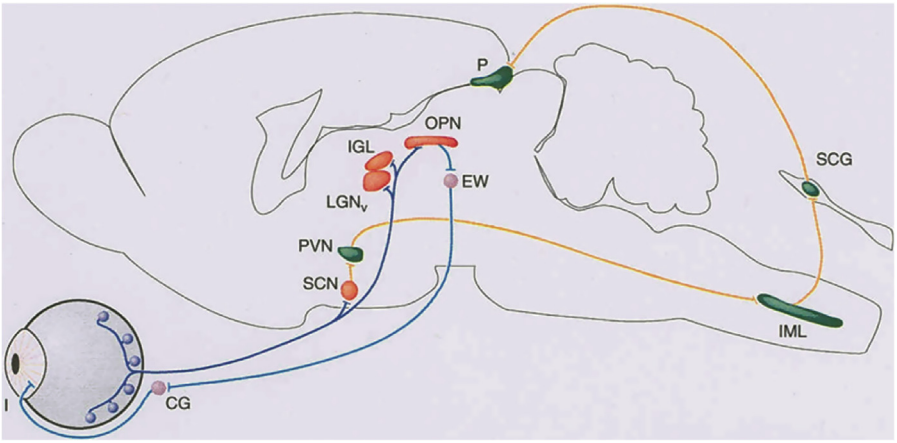

Figure 1. Graphic overview of the subcortical visual pathways influenced by melanopsin-containing retinal ganglion cells. CG = ciliary ganglion; EW = Edinger–Westphal nucleus; IGL = intergeniculate leaflet; IML = intermediolateral nucleus of the spinal cord; LGN = lateral geniculate nucleus; OPN = olivary pretectal nucleus; P = pineal gland; PVN = periventricular nucleus; SCG = superior cervical ganglion; SCN = suprachiasmatic nucleus. Reprinted with permission from Berson.[9]

these circumstances, the intrinsic melanopsin pupillomotor signal is slow to exert its effect, producing a delayed, sustained pupillary constriction. So when our retinal bipolar cells cease to function, what you see is an unmasking of the normal, tonic pupillomotor signal caused by the melanopsin-mediated visual pathways. It is likely that this melanopsin-mediated pupillomotor signal gives rise to paradoxical pupillary constriction in darkness.

Because our understanding of retinal bipolar cell physiology is becoming increasingly complex, accurate measurement of the time constants and dynamics of these components of the retinal circuitry will be necessary to experimentally confirm this putative mechanism. Intrinsically sensitive retinal ganglion cells have now been implicated in a number of other neurologic disorders,[14] including the photophobia of migraine[15] and in seasonal affective disorder (an *OPN4* melanopsin gene mutation being found in some individuals with this condition).[16] The melanopsin system tends to be relatively spared when mitochondrial disease affects the retina, but it is more severely affected in glaucomatous optic neuropathy, contributing to circadian dysfunction.[17,18] As a side note, this recurrent theme of subcortical visual pathways coming to life when higher pathways fail to develop on time also underlies the ocular motor misbehavior in infantile nystagmus[19] and infantile esotropia.[20] But that's a story for another day.

Paroxysmal Ocular Motor Misbehaviors May Have a Common Molecular Underpinning

Another enigmatic prenuclear ocular motility disorder is paroxysmal tonic upgaze of infancy. As depicted in Figure 2, affected infants present with tonic upgaze and a chin-down position. These babies all have some degree of ataxia and a wide-based gait when learning to walk.[19–22]

Figure 2. Tonic upgaze of infancy. **Left**: Photograph of affected infant showing tonic upgaze with compensatory chin-down position. **Right**: Photograph of her mother as an infant showing similar chin-down position before the tonic upgaze resolved. Reprinted with permission from Brodsky.[25]