Visual development in preterm infants

Annotation

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Preterm birth can affect many neurological functions and is known to affect vision when damage to the visual cortex or optic radiations occurs. However, it is not known whether extreme preterm birth affects visual development, either favorably or unfavorably. Additional time in an extrauterine environment could conceivably allow the acceleration of visual abilities as a result of additional experience. Although recent studies suggest that even apparently healthy preterm infants may suffer some degree of loss of neurological function. In this paper we describe what is known about visual development in preterm infants, and we make the case that additional studies are needed to clarify the impact of preterm birth on vision. Because the visual system now lends itself to quantitative studies of function, it could offer researchers and clinicians a method of detecting subtle effects of preterm birth on neurological development and function.

Cortical and retinal injuries in infants occur against the background of a developing visual system. However, we know very little about visual development in preterm infants who have not experienced a cerebral or retinal insult, let alone those who have. Studies using technologies that are sensitive enough to discern subtle variations in acuity outcomes in preverbal infants are needed. Investigations to ascertain normal preterm infant acuity development are necessary to identify negative or positive effects of preterm birth on vision. In this paper we describe anatomical and physiological forces that make the preterm brain likely to experience alterations in visual development, and stress the importance of early detection of visual impairment in these infants. We also review our current knowledge of visual development in preterm infants.

Studies of blindness in children will have the greatest impact and likelihood of success if they concentrate on the first months after birth. The leading causes of blindness in children in western countries are cerebral or cortical visual impairment, retinopathy of prematurity (ROP), optic nerve hypoplasia, and congenital retinal disease.[1] All these conditions are congenital, with acquired blindness in children (i.e. blindness developing after the neonatal period) being uncommon. Data from several blindness registries show an important trend: low-birthweight children are more likely to be affected by bilateral visual impairment than are term children.[2] This finding undoubtedly reflects the fact that cortical visual impairment and ROP are the first and second leading causes of pediatric blindness, and both are associated with preterm birth.

Results from the Cryotherapy for ROP study show at least two important trends.[3] First, children with successful retinal ablation and favorable retinal outcome may still suffer impaired acuity. This is largely due to cerebral factors, although the incidence of cortical visual impairment in a cohort of very-low-birthweight infants without ROP is unknown. Second, a spectrum of acuity outcomes in infants with favorable retinal outcomes can be discerned in the Cryotherapy for ROP study, indicating that cortical and cerebral factors affect acuity in a continuous fashion.

Vision is a complex process with many different components, such as grating acuity (the ability to detect the thinnest possible line), vernier acuity (the ability to detect line offsets), and contrast sensitivity. These components are also referred to as functions. So far, large-scale trials of preterm infants have focused on grating acuity as an outcome measure, but there are many different types of acuity and each has its own developmental course. Logically, each function probably has particular vulnerabilities to injury, depending on the nature and timing of the insult. Studies on preterm infant vision should, therefore, consider other visual functions, e.g. contrast sensitivity, vernier acuity, and mid- and high-level visual processing, in an effort to discern effects of preterm birth and injury on vision development.

More subtle disorders of higher visual processing also occur as a result of either extreme preterm birth itself or damage from preterm birth. Cortical visual dysfunction is linked to preterm birth; it is defined as disorders of higher visual function.[4–7] Given the extraordinary rate of cortical/cognitive

See end of paper for list of abbreviations.

dysfunction in children born preterm, it would be surprising if visual dysfunction did not also occur. There are several factors that could place the preterm infant brain at risk for visual disturbances. These are discussed below.

Anatomical vulnerability of preterm brain

The blood supply to the brain of a preterm infant brain differs from that of the term infant. The germinal matrix that supplies the periventricular region in the preterm brain is literally a watershed region, such that hypoxic and ischemic injury will attenuate the blood supply to this region. These two factors, hypoxia and ischemia, are by no means synonymous. Hypoxia could trigger certain neuronal or other cellular events without necessarily engendering cell death. Nevertheless, it follows that hypoxia is a natural consequence of inadequate blood supply (ischemia). The fragile vessels in the germinal matrix are vulnerable to the erratic changes in blood pressure and oxygen tension seen in preterm infants. Eventually, the germinal matrix regresses, giving rise to a blood supply and distribution that characterizes the more mature brain (i.e. anterior, middle, and posterior cerebral artery distribution). The spectrum of visual disturbance in preterm infants can be understood in the light of a continuum of potential injury to the preterm child's developing brain. Two broad mechanisms for neurological damage/effect to the preterm child's brain have been succinctly described by Volpe.[8]

In the first mechanism, damage to cerebral white matter occurs as a result of germinal matrix and/or intraventricular hemorrhage.[8] As a result, ischemia occurs in the germinal matrix and vulnerability of differentiating oligodendroglia to hemorrhage or hypoxia, causes damage to myelinated fibers, resulting in the characteristic neurological findings of cerebral palsy (long motor tracts are in the periventricular region) and vision impairment (optic radiations are in proximity to the lateral ventricles) seen in very-low-birthweight infants. Invoking damage to white matter cannot explain the high rate of disorders of attention and cognition seen in very-low-birthweight infants. To understand the potential damage of preterm birth to cortical function, we, and others, attribute damage to subplate neurons as causative.[8–10]

In this second mechanism, subplate neurons have a pivotal role. These neurons reside in the subependymal germinative zones and have a crucial function in synaptogenesis and cortical development.[11–14] The formation of the cortical plate along with its architecture and function is controlled by the subplate system.[15] Subplate neurons provide a site for synaptic contact for axons ascending from the thalamus and other cortical sites between roughly 22 and 34 weeks' gestational age.[16] However, at this gestational age the cortical plate has not even developed and so subplate neurons function as a holding region for these ascending afferent pathways. This region is in close proximity to the germinal matrix and is, therefore, vulnerable to the same ischemic effects that damage the periventricular white matter.

Thus, damage to subplate neurons will disrupt the development of cortical architecture. For example, ocular dominance columns fail to develop in the visual cortex when subplate neurons are damaged at this crucial developmental time.[17,18] Very preterm infants are likely to suffer damage to visual function, just as they are likely to develop damage to other cortical functions (cognition and attention) even when such damage cannot be imaged. The spectrum of disability to the developing visual system, therefore, begins with frank intraventricular hemorrhage and hemorrhagic necrosis of white matter (causing periventricular leukomalacia), both of which can be detected by various imaging modalities. The spectrum of injury probably extends to the damaging effects of extreme preterm birth on cortical development.

EFFECTS OF PRETERM EXPOSURE TO VISUAL STIMULATION

Very-low-birthweight infants are vulnerable to the impact of preterm birth on subplate neuron and cortical plate development. Intraventricular hemorrhage, which occurs in 11% of very-low-birthweight infants, also poses a significant risk to visual function. This alone makes the study of visual development in these infants of great interest and importance. Consider also that, even in the best of circumstances, the preterm infant's brain is exposed to visual stimulation months before nature intended. An assessment of visual function in healthy, high-risk, preterm infants will offer important insights into visual cortex development. Even if visual development is unaffected by preterm birth, this would be of great interest. Why should the visual cortex behave differently from other cortical functions (in terms of damage)? Is the visual cortex non-plastic (not subject to the effects of deprivation, light, or vision) before 32 weeks' gestational age?

Visual development in preterm infants

Preterm birth places infants in light and a visual environment at a time when the visual system is extremely immature. Consider the status of the retina at 24 to 28 weeks' gestational age.[19] Although central retinal photoreceptor cells are formed by 24 weeks, they still have only rudimentary outer segments at 24 weeks.[20,21] Retinal mitosis in the periphery continues until at least 29 weeks' gestational age, and rods are still developing at 40 weeks.[22] The secondary vitreous does not regress until 24 to 28 weeks' gestational age and causes haziness of ocular media, due to its cellular composition. Visual deprivation has a strong effect on developing synapses in the inner retina, indicating that development of the mammalian retina is dependent on activity,[23] just as it is in the visual cortex.

Complicating retinal immaturity in preterm infants is the observation that these infants have fused eyelids until 25 weeks' gestational age. Fused eyelids function essentially as red filters, allowing only long-wavelength light to be transmitted to the retina.[24,25] Furthermore, during the second and third trimesters a considerable amount of axonal dropout and remodeling occurs, resulting in significant structural changes to the optic nerves and lateral geniculate bodies.[26] Myelination of optic nerves and radiations proceeds beyond 40 weeks' gestational age.[27] Therefore, a situation exists in which the extremely immature and vulnerable visual cortex is exposed to highly anomalous visual inputs, both temporally and spatially. To the extent that cortical development is dependent on visual activity, we would expect alterations of visual development in preterm infants. In animal models of dark rearing before natural eye-opening, 'visual stimuli presented through unopened eyelids robustly activate neurons in the dorsal lateral geniculate nucleus'.[28]

Receptive field maps after dark rearing show increased convergence of On- and Off-center responses, and neurons frequently respond to both bright and dark phases of drifting gratings. There is also increased selectivity for orientation

of the gratings. 'These abnormalities of On–Off segregation can be explained by the finding that the responses of immature On and Off cells to naturalistic stimuli are strongly anticorrelated.'[28]

Clinical studies of visual development in preterm infants

It is surprising, given the immaturity and vulnerability of the preterm infant's visual system, that clinical studies and observations of visual development in this population are inconclusive. Studies of human visual development have employed two techniques to measure visual acuity in preterm infants: behavioral and electrophysiological. These studies have usually been framed in terms of 'nature/nurture'; in other words, does earlier than expected visual experience promote visual development, or is visual development preprogrammed so that preterm birth has no effect on it? Behavioral techniques show no trend,[29] or only a slight trend toward a more rapid development of vision in preterm infants;[30] electrophysiological techniques have usually shown a more rapid maturation of the visual evoked potential (VEP) brought about by preterm birth.[31] All studies have tended to include a wide range of gestational ages of preterm infants, a fact that could obscure significant differences that might exist in the very smallest and most vulnerable infants. Furthermore, most visual development studies of preterm infants noted above are more than 10 years old, and they concentrated on larger, older gestational age infants.

VEP in preterm infants

The VEP is a non-invasive procedure for measuring the electrical activity of the brain and is specific to visual information processing. Numerous VEP studies have elucidated the maturation of components of the VEP in preterm infants.[32–34] In general, these studies show the feasibility of obtaining interpretable signals, even from preterm infants, and demonstrate a developmental sequence for cerebral visual pathways. Cortex growth and synaptic density begin to evolve earlier in gestation, followed by changes in myelination of the optic radiations, beginning at about 37 weeks.[34] A correlation between VEP changes and changes in the structural central nervous system seen at post mortem examinations in preterm infants validates the VEP findings that have been reported. For example, a rapid improvement in pattern VEP resolution has been shown to occur at a time when the lateral cortical connections are forming[34,35] and P100 VEP latency has been shown to decrease within myelin formation.[27]

Results of VEP studies in preterm infants also suggest that the visual cortex might undergo accelerated maturation in preterm birth, whereas myelination of the optic radiations does not.[36] In flash VEP experiments, maturation of the N1 waveform is accelerated in preterm infants, suggesting that development of the visual cortex proceeds faster in preterm infants. Meanwhile, peak latencies in flash VEP studies are not affected by preterm birth, suggesting that white matter tracts do not undergo a more rapid development in these infants.[37,38]

Visual development measured by pattern-reversal VEPs does not always demonstrate acceleration or alteration of visual development in preterm infants.[34,39] However, almost all studies of visual development in preterm infants have averaged a wide range of gestational ages, with the average usually being 32 weeks.[39] Variance in the findings of these studies is high, perhaps indicating that a collection of preterm infants, ranging in gestational age from 24 to 36 weeks at birth, is a rather heterogeneous group.[34] The smallest infants are most likely to experience any adverse effects of the extrauterine environment.

In this regard it is relevant to note that VEP recordings provide a sensitive marker for subtle effects on the developing nervous system. Maternal smoking and fetal growth retardation affect development of the pN1 and pN23 waveform components respectively,[40,41] As these are long latency components of the VEP, this suggests that secondary (later) acidity in the visual cortex may be affected by growth retardation. Measures of vernier and grating acuity in infants with intrauterine growth retardation show that vernier acuity thresholds are significantly worse in growth-retarded children, whereas grating acuity thresholds are relatively unaffected.[42] These deficits in vernier acuity in infants at risk for neurological problems are probably caused by changes in cortical architecture and not in retinal architecture.[42]

Rationale for measuring multiple visual functions

With one exception,[42] electrophysiological studies of visual development in preterm infants have studied either flash VEP or grating acuity. These tasks concentrate on very low-level visual function, and development on a single function cannot be taken as representative of the entire visual system. This point is clearly illustrated by amblyopia, in which research in the past several years has demonstrated that grating acuity is affected very differently from either contrast sensitivity or vernier acuity. This finding is demonstrated in data from McKee and colleagues.[43] Amblyopia has very little effect on low-spatial-frequency contrast sensitivity, a moderate effect on grating acuity, and a strong effect on vernier acuity. Amblyopia is the result of abnormal visual experience during early postnatal development. It is plausible that preterm visual experience might also affect cortical development.

A new tool, termed the sweep VEP, may offer the opportunity to measure acuity thresholds and, thereby, provide a quantitative measure of different functions of visual acuity rather than an all-or-none measure. In this technique, a stimulus (e.g. grating, vernier, or contrast) is presented to an infant in the visible range. Then, over the course of a short trial lasting a few seconds, the stimulus gradually becomes less visible and then invisible. The stimulus is presented at a given temporal frequency, which presumably drives visual cortex neurons at that frequency for as long as the stimulus is in the visible range. The visual cortex can be sampled with appropriately positioned leads, and a threshold can be deduced as the stimulus-driven response drops into the background electroencephalogram noise.

The three visual functions – contrast sensitivity, vernier, and grating acuity – have different rates of development and, therefore, may show the effects of extrauterine life and trauma in different ways. Contrast sensitivity develops rapidly, whereas grating acuity shows a slower developmental rate and vernier acuity does not reach maturity until early adolescence.[44,45] Contrast sensitivity thresholds are maximal at low spatial frequencies and are not limited so much by foveal development. Grating acuity thresholds are maximal when foveal architecture is fully developed. With regard to vernier acuity, there is mounting evidence that its development undergoes a prolonged period of plasticity and that significant cortical input is required for maximal thresholds to be obtained.[46]

Because vernier acuity requires a patient to recognize spatial relationships, it may be a meaningful indicator of the integrity of higher-order visual cognitive functions. For example, the vernier acuity deficits in patients with strabismic amblyopia are associated with cognitive abnormalities. Sharma et al.[47] found that, in brief presentations, strabismic amblyopic patients are unable to count highly visible features accurately with their amblyopic eye. From a functional standpoint, there is more to vision than simply Snellen acuity. Deficits in contrast sensitivity, both at the high and the low end of the spatial frequency scale, have an impact on ambulation and motion processing. Vernier acuity offers a better estimation of optotype acuity, and is a better assay for higher cortical function and dysfunction.

Conclusion

Exciting advances in electrophysiology and imaging techniques now provide the opportunity to probe more sensitively the impact of perinatal injury on visual development and to learn the impact of preterm birth on visual development. The hope is that earlier measures of visual function will allow the identification of vulnerable or injured children at an earlier age. To understand the negative (or positive) effects of preterm birth on visual development will require an understanding of normal development in preterm birth. Multiple neurological and visual processes exist, and each can be assayed to gain a broader picture of visual function after preterm birth. That visual function is important in its own right is obvious, but visual function will also, to some degree, reflect neurological function in general.

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List of abbreviations

ROP	Retinopathy of prematurity
VEP	Visual evoked potential