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REVIEW

Docosahexaenoic Acid and Visual Functioning in Preterm Infants: A Review

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Abstract Preterm children are at risk for a number of visual impairments which can be important for a range of other more complex visuocognitive tasks reliant on visual information. Despite the relatively high incidence of visual impairments in this group there are no good predictors that would allow early identification of those at risk for adverse outcomes. Several lines of evidence suggest that docosahexaenoic acid (DHA) supplementation for preterm infants may improve outcomes in this area. For example, diets deficient in the long-chain polyunsaturated fatty acid DHA have been shown to reduce its concentration in the cerebral cortex and retina, which interferes with physiological processes important for cognition and visual functioning. Further, various studies with pregnant and lactating women, as well as formula-fed infants, have demonstrated a general trend that supplementation with dietary DHA is associated with better childhood outcomes on tests of visual and cognitive development over the first year of life. However, research to date has several methodological limitations, including concentrations of DHA supplementation that have been too low to emulate the in utero accretion of DHA, using single measures of visual acuity to make generalised assumptions about the entire visual system, and little attempt to match what we know about inadequate DHA and structural ramifications with how specific functions may be affected. The objective of this review is to consider the role of DHA in the context of visual processing with a specific emphasis on preterm infants and to illustrate how future research may benefit from marrying what we know about structural consequences to inadequate DHA with functional outcomes that likely have far-reaching ramifications. Factors worth considering for clinical neuropsychological evaluation are also discussed.

Keywords Docosahexaenoic acid (DHA) · Visual processing · Preterm infants · Retina · Dorsal stream

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Introduction

Docosahexaenoic acid (DHA, 22:6 n-3), an (omega-3) n-3 long chain polyunsaturated fatty acid, is found in high concentrations in both the cerebral cortex and the retina and is important for a number of physiological processes. The neural networks involved in visual processing are extensive and early disruption to this integrated system may have detrimental consequences for the processes important for vision, which may in turn compromise other functional skills. Animal studies have illustrated that diets deficient in

n-3 fatty acids, including α-linolenic acid and DHA, have negative consequences for visual and behavioural functioning, leading to speculation that supplementation with n-3 fatty acids in human infants might improve functioning in a range of visual and cognitive domains.

During the last trimester of pregnancy a substantial amount of DHA is transferred from mother to fetus; thus infants born early (e.g. very preterm infants; <32 weeks' gestational age) are denied adequate intrauterine supply of DHA at a stage when brain growth is at its greatest. Consistent with the premise that visual processes are reliant on adequate DHA concentrations early in development, very preterm children exhibit higher than expected rates of refractive errors, strabismus, amblyopia, and deficient visual perceptual skills (Cioni et al. 2000; Downie et al. 2003; Fielder 1998; O'Connor et al. 2002, 2004; Powls et al. 1997; Stephenson et al. 2007). To understand how DHA affects visual processing, very preterm infants may serve as a useful model. The objectives of this review are to i) consider the role of DHA and how it relates to visual processing beyond what is already known about visual acuity, ii) discuss why preterm infants may be more susceptible for visual impairments due to inadequate DHA, iii) examine evidence for the effects of DHA supplementation in preterm infants, and iv) highlight areas that warrant further research.

Prematurity

Preterm birth, defined as a birth of less than 37 completed gestational weeks (WHO 1970), is a major public health concern. It is associated with more than two-thirds of all perinatal deaths (Lumley 2003) and approximately 75 % of neonatal morbidity, e.g. neurocognitive, pulmonary, and ophthalmological problems (Wen et al. 2004). Children born preterm are at increased risk for a range of neurodevelopmental difficulties compared with their full term peers, such as attention difficulties, memory and learning problems, academic underachievement, and visual motor integration deficits (e.g. (Anderson and Doyle 2003; Aylward 2005; Bhutta et al. 2002; Hack et al. 2005)). Visual processing is an area of particular concern, with deficits reported in visual acuity (Evensen et al. 2009; Stephenson et al. 2007), contrast sensitivity (Cooke et al. 2004; Powls et al. 1997), stereopsis (Cooke et al. 2004; Stephenson et al. 2007), motion processing (Jakobson et al. 2006; MacKay et al. 2005; Pavlova et al. 2006; Taylor et al. 2009), and spatial perception (Pavlova et al. 2007), all skills that are important for more complex and adaptive visual tasks such as classroom learning, and overall school performance (Cooke et al. 2004; Grisham et al. 2007; Maples 2003; Powls et al. 1997), as well as social interaction and cognition (Aylward 2002; Mitchell 2006; Pelphrey and Carter 2008).

Preterm birth per se, early visual experiences, and various perinatal factors, such as retinopathy of prematurity (ROP), brain injury, and oxygen therapy during the neonatal period potentially contribute to adverse visual processing outcomes in this population. Despite the reported associations between certain perinatal variables and visual difficulties (Buksh et al. 2008; Cioni et al. 2000; Eken et al. 1995; Kushner 1982; Nissenkorn et al. 1983; Quinn et al. 1998; Ricci et al. 2011) it remains difficult to identify those preterm children at greatest risk for visual impairments. Different perinatal risk variables may differentially affect the developing visual system resulting in differing profiles of visual impairment. This is important because understanding the mechanisms for visual impairment in this population has ramifications for perinatal care, such as identifying optimal oxygen levels and specific nutrients and agents that might optimise ocular and cortical development.

Docosahexaenoic Acid (DHA)

Docosahexaenoic acid (DHA), in which very preterm infants are deficient, may be one perinatal factor associated with the high prevalence of visual deficits in this population. The relationship between preterm birth and DHA is an area that has not been sufficiently evaluated but may serve as a useful model to understand both the importance of DHA in neonatal visual development, as well as provide a better understanding of the etiology of visual deficits exhibited by preterm infants. In particular, research has shown that DHA differentially affects parts of the visual system, such as rod photoreceptors and M retinal ganglion cells, and yet visual functions that are most likely to be implicated by damage to these structures have not been assessed, either in the short- or long-term.

Humans have a limited ability to synthesise DHA from precursor n-3 fatty acids and thus it is mostly acquired through dietary sources such as fish, meat, seed oils, and eggs (Decsi and Koletzko 1994). The DHA status of a developing fetus depends on that of its mother, confirmed by data indicating a positive relationship between maternal DHA consumption and fetal DHA status, as reflected by increased concentrations of DHA in erythrocyte cell membranes, umbilical blood, and infant plasma (Birch et al. 1998; Connor et al. 1996; Le et al. 2009; Smuts et al. 2003; van Houwelingen et al. 1995; Velzing-Aarts et al. 2001). DHA is a crucial component for synthesis of brain tissue, metabolism of neurotransmitters, cellular differentiation, and synaptogenesis (Sabel et al. 2009). The placenta actively transports DHA into the fetal circulation during gestation (Crawford et al. 1997; Hornstra et al. 1995) and the rate of transfer increases substantially during the last trimester; in fact 80 % of the brain DHA accrues in the fetus

from 26 weeks' gestational age until term (Sabel et al. 2009). This coincides with the time where the velocity of brain growth is at its greatest (Huppi et al. 1998; Makrides et al. 1994; Smithers et al. 2008). Preterm infants are considered insufficient in DHA due to the loss of intrauterine supply during the last months of pregnancy.

DHA and the Visual System

The highest levels of DHA in the body are found in the retina and cerebral cortex (Neuringer et al. 1986). Depletion of DHA from the retina and the cortex is speculated to alter their physical and functional properties (Neuringer et al. 1986), which may affect functions important for accurate visual processing.

DHA is needed for photo-transduction, the process of transforming light into an electrophysiological signal (Litman and Mitchell 1996; Niu et al. 2001) and for the regeneration of rhodopsin, the light sensitive pigment in the retina; the absorption of light by rhodopsin is the first step in vision (Aveldano 1988; Bush et al. 1994; Chen et al. 1996). DHA accounts for 50 % of the total fatty acids in the structural phospholipids of the outer segment disk membranes of the photoreceptor (Anderson and Risk 1974), which creates a high degree of membrane fluidity (Neuringer et al. 1988). Experiments conducted by Rotstein et al. (1998) provide evidence that the availability of phospholipids enriched in DHA, required for building photoreceptor outer segments, at the correct developmental period is one factor that is critical for the survival and differentiation of photoreceptor cells. DHA is also important for brain myelination through its protection of premyelinating oligodendrocytes, which ensheath developing axons and are the precursors to myelin-forming oligodendrocytes (Volpe 2009), and stimulation of oligodendroglial cell differentiation (Brand et al. 2010; van Meeteren et al. 2006). Furthermore, Norcia et al. (1990) proposed that changes in the efficiency of photoreceptors might influence neuronal factors such as myelination of the optic nerve, or changes in synaptic efficiency, ultimately affecting the development of some visual functions. Consistent with this view, visual evoked potential (VEP) studies have demonstrated that preterm infants fed formulas without DHA have VEP wave latencies that are significantly longer in comparison with those with some DHA, suggesting slower maturation of optic pathways and the visual cortex (Birch et al. 1992; Faldella et al. 1996; O'Connor et al. 2001).

The development of the human retina requires a complex interaction of neural and vascular tissues which begins in early gestation and continues into mid-childhood. The processes involved in retinal maturation include generation of rods and cones and reorganisation and migration of photoreceptors (Hendrickson and Drucker 1992; Hollenberg and Spira 1973; Narayanan and Wadhwa 1998). During fetal development all cell types in the retina appear in a central-to-peripheral gradient (Provis et al. 1985). Mitosis in the fovea ceases by 14 weeks' postmenstrual age (PMA) but continues in the far periphery to at least 29 weeks' PMA (Provis et al. 1985). At 20–22 weeks' PMA, central and mid peripheral rods and cones are beginning to differentiate, and by 28 weeks all cell layers are present (Provis et al. 1985). The migration of cone photoreceptors toward the foveal pit and the movement of ganglion cells away from the foveal pit continues until beyond 57 weeks' PMA. Because DHA is important for retinal cell development and preterm infants are DHA deplete during the last trimester, the visual system for many of these children may be adversely affected.

The cones of the retina, except for foveal cones, are morphologically more mature than rods at the time of birth (Birch et al. 1990; Birch and O'Connor 2001; Hendrickson and Drucker 1992). Rods also experience significant changes postnatally (Uauy et al. 1990). Cultured rat retinal photoreceptors free from fatty acid undergo selective degeneration followed by apoptosis, but when DHA is added to the culture it increases its proportion in neuronal lipids and prevents the degeneration of photoreceptors (Rotstein et al. 1996). Consistent with these findings, studies on rats and primates have demonstrated low levels of retinal and brain DHA when fed diets deficient in n-3 fatty acids (Lamptey and Walker 1978; Neuringer et al. 1986; Wheeler et al. 1975), showing the greatest effect postnatally compared with prenatally (Neuringer et al. 1986). The brain and retina of human infants is less developed than rhesus monkeys, thus it has been speculated that postnatal deprivation of DHA might be especially problematic for human infants (Neuringer et al. 1986). Preterm infants are developing within an atypical environment and during a time when DHA accumulation is at its greatest, therefore it stands to reason that an immature visual system is particularly vulnerable to low levels of DHA. Indeed, the maturation of rod sensitivity appears to be slowed by preterm birth, likely influenced by environmental factors which adversely affect the development of photoreceptors, including nutritional insufficiency, such as DHA, and retinal vascularity (Hamilton et al. 2008). The implication appears to be that less mature structures may be at greater risk of dietary deprivation of DHA, resulting in specific functional consequences, which may be particularly relevant for preterm infants.

The functional distinctions of the visual pathways are usually described from the cortical regions of the brain, however there are also several functionally distinct populations of retinal ganglion cells. Of particular interest are the P and M ganglion cells, so called as most M retinal ganglion

cell axons project to the magnocellular layers of the lateral geniculate nucleus (LGN), whereas the P ganglion cells project to the parvocellular layers (Maunsell et al. 1990). M and P ganglion cells differ in terms of morphology and thus also have different functional properties. For example, M cells are fast responding and specialised in processing low spatial frequency information, such as the general size and shape of an object. Because they respond transiently to the presentation of visual stimuli M cells are important for motion perception, spatial relationships, and directing actions (Merigan and Maunsell 1990; Mitchell et al. 2007; Tanaka 1976). P cells respond in a sustained fashion and are specialised for processing high spatial frequency information, such as discrimination of colour, texture, fine shape, and pattern (Livingstone and Hubel 1988; Maunsell et al. 1990). The information from the magnocellular and parvocellular layers of the LGN remains separate at least in the initial stages of cortical processing; for this reason the terms magnocellular stream and parvocellular stream are often used to signify the pathways that transmit information derived from M and P ganglion cells. Importantly, M cells require high amounts of polyunsaturated fatty acids to function efficiently (Ahmad et al. 2002; Stein 2001) and thus visual functions reliant on efficiency are potentially affected by inadequate DHA concentrations following preterm birth. Additionally, DHA can be protective against oxidative and hypoxic stress-induced cell damage in retinal ganglion cells (Shimazawa et al. 2009). This point is crucial considering fluctuations in cerebral blood flow and hypoxaemic insults during apnoeic episodes are common in preterm infants.

There may be far reaching consequences on the visual system for preterm infants who receive inadequate DHA during postnatal development (Bourgeois et al. 1989; Mirabella et al. 2006; Wiesel 1982). Beyond the occipital cortex the visual system divides into two hierarchically arranged and anatomically and functionally separate pathways; the dorsal and ventral streams (Goodale and Milner 1992; Livingstone and Hubel 1988). Visual information from the magnocellular pathway remains relatively segregated at the level of the primary visual cortex, as well as predominates the innervations of the dorsal stream, such as areas V2, V3, and V5 (V5 is also called the middle temporal area (MT)) (Goodale and Milner 1992; Maunsell et al. 1990; Mendes et al. 2005; Morand et al. 2000). Anatomical, physiological, and behavioural studies have demonstrated strong links between functions of the magnocellular and dorsal stream and between the parvocellular and ventral stream (Heinrich 2007; Kubova et al. 1995; Merigan and Maunsell 1993). As DHA appears to be particularly important for M cells, inadequate dietary intake of DHA may have specific ramifications for visual functions subsumed by the magnocellular/dorsal stream.

Functional Assessment Considerations

Despite physiological evidence which has highlighted the importance of DHA for specific structures and processes important for vision, research to date has focussed on only a narrow range of visual outcomes and thus our understanding of the role of DHA on the development of the visual system is limited. In order to truly understand the influence of DHA on the developing visual system a comprehensive range of assessment tools are required. This may have significant ramifications for children with visual impairments, especially those born preterm.

The mechanisms related to visual impairment in preterm children are likely to be multi-factorial, including DHA insufficiency, exposure to early visual stimuli, and brain injury. However, the specific role of DHA deficiency may be partially untangled by studying different visual functions, as their developmental trajectories differ (Madan et al. 2005) and some functions may be more vulnerable to DHA insufficiency. For example, visual acuity is measured with high contrast (e.g. logMAR visual acuity chart), and thus it is not representative of many visual situations. In contrast, contrast sensitivity, measures the ability to detect slight changes in luminance across space (Mirabella et al. 2006), is a measure of the minimum contrast required to identify a stimulus against its background (O'Connor and Fielder 2007) and can provide additional information about the functional ability of the visual system. Low spatial frequencies (e.g. coarse scale information) develop more rapidly and over a shorter time course than high spatial frequencies (e.g. fine scale details) (Norcia et al. 1990) thus low spatial frequencies may be more vulnerable to DHA insufficiency, particularly in preterm infants during the neonatal period. Grating acuity, which is the ability to distinguish the elements of a fine grating composed of alternating dark and light stripes, shows slower development, and thresholds are maximal when foveal architecture is fully developed at around 5 to 8 years of age (Madan et al. 2005; Mirabella et al. 2006). Because development of grating acuity has a protracted time course, adequate intake of dietary DHA may be important throughout early school-age years. Vernier acuity on the other hand, which measures the minimum offset that can be detected between two line segments (Mirabella et al. 2006), requires significant cortical input to obtain maximal thresholds (Skoczenski and Norcia 1999) and thus inadequate DHA may affect the initial rapid maturation of vernier acuity over the first few months of life (Manny and Klein 1984; Shimojo et al. 1984; Skoczenski and Norcia 1999). Given the potential role DHA has for the visual system structures, broader evaluation, beyond measures of visual acuity, should be considered in future investigations, including contrast sensitivity and vernier acuity.

Studies evaluating the effect of DHA on visual processing, in both full term and preterm infants, have used either visual evoked potentials (VEP) or grating acuity, both of which assess very low level visual function (Madan et al. 2005). The visual system is complex and a single measure is unlikely to be an accurate representation of functional vision as a whole. For example, grating acuity is affected very differently from either contrast sensitivity or vernier (positional) acuity in patients with amblyopia (McKee et al. 2003). Specifically, amblyopia has little effect on low spatial frequency contrast sensitivity, a moderate effect on grating acuity, and a strong effect on vernier acuity (McKee et al. 2003). Amblyopia is the result of abnormal visual experience during early postnatal development and is usually associated with unequal refractive error in the two eyes (Levi and Klein 1982, 1992). Research utilising VEP suggests that the visual cortex may undergo accelerated maturation in preterm birth (Madan et al. 2005) raising important questions about the long-term relevance of studies that have reported improved VEP outcomes following supplementation with DHA. For example, this may suggest that evaluating visual functioning via VEP may be more useful and relevant later in development. These functional and developmental considerations highlight the importance of evaluating the effect of DHA supplementation on different aspects of functional vision and beyond the first months of life. The neural mechanisms underlying dietary effects on visual acuity for preterm infants are not well understood thus examining additional measures of visual function would help to clarify the extent and nature of the effects of DHA on the developing visual system.

Because rods have different functional properties and are more adversely affected by inadequate DHA than cone cells, there may be specific functional consequences. Rod cells are located mostly in the peripheral part of the retina; they are about 500 times more sensitive to light than cone cells, enable night vision and are more sensitive to motion than cone cells. Consequently, visual functions such as contrast sensitivity, perception of motion, and visual fields may be influenced by DHA supplementation, in addition to visual acuity. This premise is supported by research on animals; in rats, deficient n-3 fatty acids results in decreased amplitude of the electroretinogram (Wheeler et al. 1975) and impairment in the ability to learn a visual discrimination task (Lamptey and Walker 1978), whereas in primates the deficient animals have reduced visual acuity (Neuringer et al. 1986) and an abnormal electroretinograph (Birch et al. 1992). Importantly, several studies following up infants born preterm have reported difficulties in numerous sensory functions (Cioni et al. 2000; Cooke et al. 2004; Dowdeswell et al. 1995; Jakobson et al. 2006; Pavlova et al. 2006; Powls et al. 1997; Stephenson et al. 2007).

Dorsal Visual Stream and DHA

Several authors have suggested that preterm infants display a particular vulnerability of dorsal stream processing (Atkinson and Braddick 2007; Jakobson et al. 2006; Olsen et al. 1998; Pavlova et al. 2006). For example, development of the motion processing system, a major attribute of the dorsal stream, which typically develops between 2 months to 3 months, is delayed in preterm infants by approximately 4 weeks (Atkinson and Braddick 2007). Additionally, several other studies have reported that preterm infants exhibit a clustering of deficits that rely on accurate processing within the dorsal steam, such as spatial memory, visual motor integration, visuospatial manipulation, and spatial navigation (Atkinson and Braddick 2007; Olsen et al. 1998; Pavlova et al. 2006, 2007). The reason preterm children may have a particular vulnerability to dorsal stream functioning is unclear, as MRI studies have shown diffuse white matter injury affecting both the dorsal (occipito-parietal pathway) and ventral streams (occipito-temporal pathway) (Hagberg et al. 2002; Huppi 2004). Importantly however, it has been shown that M cells need high amounts of polyunsaturated fatty acids to preserve their membrane flexibility crucial for allowing physiological processes, which underlie M cells transient sensitivity important for detecting motion (Stein 2001). Thus, damaged or inefficient M cells in the magnocellular pathway and dorsal stream may affect processing within these pathways and in turn functions subsumed by these regions/pathways. The notion that dorsal stream processing may be related to DHA deficiency is supported by dyslexia research. Numerous studies report that dyslexics who have clinical signs of essential fatty acid deficiency (Richardson et al. 2000; Taylor et al. 2000), demonstrate a specific vulnerability to magnocellular dysfunction. This has been consistently shown by testing sensitivity to moving stimuli. Motion engages not only the peripheral M cells within the occipital cortex but also parts of the dorsal stream such as up to at least area V5/MT in the extrastriate cortex.

Stereopsis, which is the perception of depth achieved from two slightly different images that fall on the retinas of the two eyes, has also been speculated to be a unique attribute of the magnocellular and dorsal processing stream (Backus et al. 2001; Nishida et al. 2001; Schechter et al. 2006). Stereopsis is dependent on equal visual acuity by the two eyes, normal eye alignment, and history of binocular experience. Stereopsis plays a vital role in many visual motor activities including reaching, manipulation of objects, motion perception, and spatial navigation within varying environments (Coren and Hakstian 1996; Jakobson et al. 2006). Preterm children exhibit more impairments in stereopsis than children born at term (e.g. (Cooke et al. 2004; Dowdeswell et al. 1995; Stephenson et al. 2007)), which

may partly explain the increased incidence of impaired motor performance in preterm groups, particularly those without focal white matter lesions. According to Banks et al. (1975) the critical periods for susceptibility of binocular vision are between 3 and 6 months, and between 12 months and 20 months, potentially implicating a critical role of DHA in the neonatal period. DHA insufficiency could have a two-fold effect on stereoacuity and the subsequent processing reliant on its accuracy. Indeed, there is some evidence to suggest that stereopsis is enhanced in children who have been breast-fed compared with those infants who were formula-fed (Williams et al. 2001), which may reflect lower concentrations of DHA in infant formula in comparison with maternal breast-milk.

Global and Local Form Processing and DHA

Global precedence occurs when general information is processed without interference from local information (Antes and Mann 1984). A common visual stimulus employed to investigate levels of visual analysis is the Navon stimulus (Navon 1981), which for example would present a large H (global) consisting of small Es (local)(see Fig. 1 for an example of a Navon stimulus). If the individual preferentially identifies the H over the Es the visual analysis is dominated by global information. Global precedence is related to spatial frequency, in that the large H is processed by low spatial frequency mechanisms, while the Es are processed by high spatial frequency visual mechanisms (Antes and Mann 1984). It has been argued by Hughes (1986) that

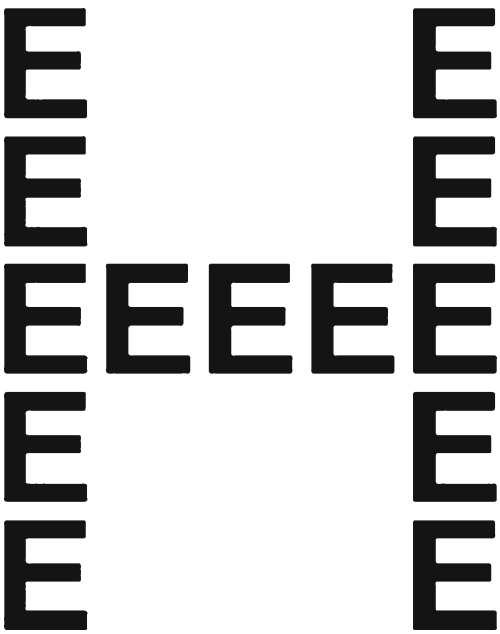

Fig. 1 Example of navon stimulus

global precedence is reliant on the speed advantage of the coarse scale information, which, when abolished, also abolished the global precedence. There has only been the one study examining the visual analysis of global and local information in preterm children; Santos et al. (2010) reported that preterm children demonstrated an atypical pattern of visual processing, in that they preferentially relied on local information rather than on a global analysis when performing a visual perceptual task. As such, preterm children may display a local precedence. One explanation for this finding is that inadequate DHA in the neonatal period affects the development of the magnocellular/dorsal pathway that consequently abolishes the "typical" speed advantage of low spatial frequency information usually associated with visual processing. This may have ramifications for visual perception and visual learning. For example, low spatial frequency information is important for face emotion recognition (Butler et al. 2009).

Visual Perception and DHA

If DHA deficiency is found to be associated with visual sensory outcomes such as visual acuity, then one may expect a secondary influence on visual perception that must, in part, rely on the accuracy of early visual processing. Visual perception deficiencies are common in preterm children both with (Ito et al. 1996; Koeda and Takeshita 1992; Ploner et al. 1999) and without (Davis et al. 2005; Feder et al. 2005; Hard et al. 2000; McGrath and Sullivan 2002) focal brain injury. Preterm children have difficulties with a range of visual perceptual tasks, ranging from basic visual discrimination to more complex visual closure and figure-ground tasks. Perceptual closure processes and perception of figure-ground are related to specific activation of the (right greater than left) lateral occipital complex. The lateral occipital complex has also been implicated in other aspects of object perception, such as visual discrimination. Further, perceptual closure tests require identification of whole figures from incomplete versions of various forms (Wasserstein et al. 2004). Perceptual closure and facial discrimination tests have classically been used as critical measures of right hemisphere "Gestalt" functioning (e.g. Benton and Van Allen 1968; Bogen et al. 1972; De Renzi et al. 1968; Warrington and James 1967). Deficient visual perception has been correlated with visual acuity (van den Hout et al. 2000), strabismus (Koeda and Takeshita 1992), and amblyopia (Koeda and Takeshita 1992) in preterm children, however due to the paucity of studies testing the relationship between visual function and visual perception it is less clear whether these deficiencies can be attributed to sensory abnormalities.

In summary, a broader range of neuropsychological measures should be considered when clinicians evaluate children who are born preterm. Whilst it is not always practical to assess some of the visual functions mentioned above, screening for basic visual functions such as visual acuity and stereopsis are relatively simple and quick to administer. Difficulties with contrast sensitivity, depth perception, motion and global processing may have secondary consequences, which are worth considering when designing the assessment protocol, such as visual perception, visual motor integration, and spatial navigation. Further research may elucidate other important relationships between DHA, visual processing and multifactorial cognitive skills that could better inform clinical neuropsychologists.

DHA Supplementation in Humans

Animal research served as a good basis for DHA supplementation in human infants by documenting the effect of inadequate DHA for structures important for visual processing (Lamptey and Walker 1978; Neuringer et al. 1986; Wheeler et al. 1975). Preliminary evidence of randomised controlled trials (RCTs) involving formula-fed term and preterm infants provides some initial support for the concept that inadequate dietary intake of DHA early in life is related to adverse visual processing outcomes in preterm children (Birch et al. 1992; Carlson et al. 1993, 1996b; O'Connor et al. 2001; Smithers et al. 2008).

There have been a number of trials that have evaluated the short term effect of DHA supplementation on cognitive and visual functioning in both term and preterm infants. These are typically difficult to compare as they differ in the type and dose of fatty acid, duration and commencement of supplementation, age of subjects when assessed (Eilander et al. 2007), and outcome measures. The major outcome measures used to assess the effect of DHA supplementation on visual development, reflected by retinal and cortical visual function, have been electroretinography (ERG) and visual acuity as assessed by visual evoked potential (VEP) and/or preferential looking techniques. The outcomes reported in RCTs involving term infants have varied between studies; some have demonstrated a benefit for visual function (Birch et al. 2010; Birch et al. 2002; Carlson et al. 1996a; Hoffman et al. 2003; Makrides et al. 1995), while others show no difference (Auestad et al. 1997; Jensen et al. 2010; Jorgensen et al. 1996). RCTs involving preterm infants have demonstrated more consistent benefits for visual acuity following DHA supplementation, at least over the first six months of life (e.g. (Birch et al. 1992; Carlson et al. 1993, 1996b; O'Connor et al. 2001; Smithers et al. 2008).

A meta-analysis conducted by SanGiovanni et al. (2000) aimed to determine the combined estimates of visual resolution acuity differences between preterm infants who received different compositions and ratios of essential fatty acids and DHA. They reported that there were significant differences in visual resolution acuity at 2 and 4 months of age between preterm infants fed formula supplemented with DHA compared with preterm infants not supplemented with DHA (SanGiovanni et al. 2000). A number of Cochrane reviews have also been undertaken, which consistently conclude that DHA supplementation of infant formula increases the rate of visual maturation in preterm infants but ascribe no clear long-term benefits greater than 6 months (Schulzke et al. 2011; Simmer 2000).

Human brain composition studies have provided valuable information about the effect of deficient DHA on the brain and retina. For example, term infants fed formula without DHA who died suddenly have been found to have lower DHA concentrations in their frontal cortex, in comparison with term infants who were breastfed and consequently received a dietary source of DHA (Makrides et al. 1994). Further, the brain and retinal DHA composition of preterm infants at matched ages is lower than that of term infants regardless of feeding mode (Martinez 1992). Importantly, supplementation with DHA during pregnancy has been shown to increase the level of this fatty acid in both maternal and infants' erythrocyte cell membranes, umbilical blood levels, and infant plasma levels (Birch et al. 1998; Connor et al. 1996; Le et al. 2009; Smuts et al. 2003; van Houwelingen et al. 1995; Velzing-Aarts et al. 2001). In turn, and according to a randomised trial involving healthy full term infants, better visual acuity and stereoacuity at 17 weeks of age are correlated with higher concentrations of DHA in plasma, and better visual acuity at 52 weeks of age is associated with higher concentrations of DHA in plasma and red blood cells (Birch et al. 1998).

Although there appears to be some evidence that preterm infants benefit from diets supplemented with DHA very early in visual development, there are a number of methodological limitations that raise important questions of the validity and relevance of previous findings, and likely explains the inconsistency of results across studies, in particular beyond 6 months of age. Firstly, previous studies have used formula for supplementation rather than breast milk. Breast milk is the milk-feed-of-choice for the clinical management of preterm infants in the neonatal intensive care unit and has several nutritional advantages, including decreased risks of necrotizing enterocolitis (Lee and Polin 2003; Sisk et al. 2007) and sepsis (Furman et al. 2003; Hylander et al. 1998), and improved motor and cognitive development (Lucas et al. 1992; Vohr et al. 2006). Secondly, most trials have tested low concentrations of DHA that are comparable with the breast milk of women consuming a

Western-style diet, which is between approximately 0.2 and 0.3 % of total fatty acids (Gibson et al. 2001). However the quantity of DHA an infant would receive from this dose is well below what the fetus accrues during the last trimester (Makrides et al. 1994; Martinez 1992). It has been estimated that 1 % DHA emulates the in utero accretion of DHA (Makrides et al. 1994; Martinez 1992) suggesting that the concentration of DHA used in previous trials is inadequate, thus failing to either increase the level of DHA in the retina and cortex and/or is insufficient to influence functional outcomes. Consistent with this view, slightly higher supplemental concentrations of DHA, up to 0.6 %, have been more likely to result in positive outcomes concerning cognitive and motor development for preterm infants (Clandinin et al. 1980; Fewtrell et al. 2004). Further, there is some evidence of a dose–response relationship between dietary DHA concentration and neural function; Uauy et al. (2003) correlated the effect size in visual acuity against DHA dose and found that the higher the DHA content the greater the effect (Uauy et al. 2003). These studies suggest that the level of DHA supplementation is an important factor in achieving improved outcomes. It may be postulated that trials with experimental formulas close to the worldwide human milk average are more likely to yield functional benefits attributable to DHA than those providing only relatively low-dose supplementation. Despite these methodological limitations there is a general trend indicating that supplementation with DHA has a positive effect on visual function.

A study which overcomes many of the limitations outlined above has shown partial benefits for preterm infants fed high dose DHA (1 % of total fatty acids) breast milk in comparison with preterm infants fed standard DHA (approximately 0.3 % total fatty acids). Beneficial differences were documented in early cognitive development (Makrides et al. 2009), hay fever (Manley et al. 2011), and need for supplemental oxygen at 36 weeks' corrected age (Manley et al. 2011). This study also reported that preterm infants fed milk with high dose DHA concentrations had improved visual acuity at 4 months corrected age compared with infants receiving standard DHA doses (Smithers et al. 2008). The long-term significance of DHA supplementation on visual acuity and other visual functions is unknown.

Conclusions and Future Directions

Preterm children are at risk for a number of visual impairments, including difficulties with visual acuity, contrast sensitivity, stereopsis, and visual perception, which are important for a range of more complex and adaptive skills reliant of visual information. Despite the relatively high incidence of visual impairments in this group there are no good predictors that would allow early identification of those at risk for adverse outcomes. Several lines of evidence suggest that DHA supplementation for preterm infants may improve outcomes in this area. For example, DHA is important for a number of visual processes, such as phototransduction, regeneration of rhodopsin, and maturation of the cortical visual pathway; animals fed diets deficient in DHA demonstrate impaired visual acuity and visual learning; and human studies show short-term benefits for visual acuity following supplementation with DHA.

Future studies should address the significant research gaps, such as evaluating the effect of DHA supplementation on functions specifically related to the structural and physiological processes reliant on adequate DHA concentrations. Despite the possible link between inadequate DHA and specific visual structures and functions there is a lack of empirical evidence supporting this association. Thus well-defined studies that combine the knowledge we have about the structures and functions of the visual system that are reliant upon adequate DHA concentrations, with specific functional outcomes dependent on their integrity, may elucidate important associations between preterm birth, DHA, and visual processing. For example, it could be beneficial to explore the relationship between DHA supplementation and visual functions reliant on the efficiency of M cells, such as motion processing, contrast sensitivity, and stereopsis. Exploring the relationship between DHA supplementation and its possible role in influencing the documented dorsal stream vulnerability commonly described in preterm infants also warrants further attention. Further, research examining the long-term visual outcomes of DHA supplementation beyond 18 months of age in preterm children is a major research gap that requires greater follow up.

The clinical significance of DHA deficiency is substantial if it can be demonstrated to be associated with the development of visual processes. Early intervention comprising DHA supplementation would be relatively inexpensive and easy to prescribe. The possible short- and long-term benefits, especially for very preterm children, include improved quality of life, and reduced follow-up, medical care, and special education costs.

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