NeuroImage 178 (2018) 649–659

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Early nutrition influences developmental myelination and cognition in infants and young children

Sean Deoni [a,*], Douglas Dean III [b], Sarah Joelson [a], Jonathan O'Regan [c], Nora Schneider [d]

[a] Advanced Baby Imaging Lab, Memorial Hospital of Rhode Island, Pawtucket, RI, United States
[b] University of Wisconsin-Madison, Waisman Centre, Madison, WI, United States
[c] Nestle Development Centre, Askeaton Co, Limerick, Ireland
[d] Nestle Research Centre, Nestec Ltd, Neurodevelopment & Cognition, Lausanne, Switzerland

ARTICLE INFO

Keywords:
Infant brain development
Cognitive development
Brain MRI
Myelination

ABSTRACT

Throughout early neurodevelopment, myelination helps provide the foundation for brain connectivity and supports the emergence of cognitive and behavioral functioning. Early life nutrition is an important and modifiable factor that can shape myelination and, consequently, cognitive outcomes. Differences in the nutritional composition between human breast and formula milk may help explain the functional and cognitive disparity often observed between exclusively breast versus formula-fed children. However, past cognitive and brain imaging studies comparing breast and formula feeding are often: cross-sectional; performed in older children and adolescents relying on parental recall of infant feeding; and generally treat formula-fed children as a single group despite the variability between formula compositions. Here we address some of these weakness by examining longitudinal trajectories of brain and neurocognitive development in children who were exclusively breastfed versus formula-fed for at least 3 months. We further examine development between children who received different formula compositions. Results reveal significantly improved overall myelination in breastfed children accompanied by increased general, verbal, and non-verbal cognitive abilities compared to children who were exclusively formula-fed. These differences were found to persist into childhood even with groups matched for important socioeconomic and demographic factors. We also find significant developmental differences depending on formula composition received and that, in particular, long-chain fatty acids, iron, choline, sphingomyelin and folic acid are significantly associated with early myelination trajectories. These results add to the consensus that prolonged and exclusive breastfeeding plays an important role in early neurodevelopment and childhood cognitive outcomes.

Introduction

Infancy and early childhood are sensitive and rapid periods of brain growth that coincide with the emergence of nearly all cognitive, behavioral, and social-emotional functions (Johnson, 2001). Throughout this period, the brain's eloquent networks are shaped and refined through processes that include myelination, dendritic arborisation and synaptogenesis, and synaptic pruning. These adaptive processes are modulated by neural activity and are responsive to environmental, genetic, hormonal, and other influences (Stiles and Jernigan, 2010). The development and pattern of myelination follows a well-described neuroanatomical arc (Brody et al., 1987), progressing in a posterior-to-anterior and centre-outwards spatiotemporal pattern that corresponding to maturing cognitive functions (McGee et al., 2005; Markham and Greenough, 2004). That is, there is a strong overlap in the emergence of a specific cognitive function and the myelination of brain regions and networks subserving that function (Fornari et al., 2007; Van der Knaap et al., 1991; Pujol et al., 2006). Beyond this temporal association, prior studies have further shown the importance of white matter and cortical myelination to cognitive development and brain plasticity (McGee et al., 2005; Pujol et al., 2004, 2006; Fields, 2008; Fornari et al., 2007), and altered myelination and white matter maturation in a variety of intellectual, behavioral, and psychiatric disorders (Bartzokis et al., 2003; Flynn et al., 2003; Davison and Dobbing, 1966; Wolff et al., 2012). We have further shown that early trajectories of myelination are associated with cognitive abilities and outcomes (O'Muircheartaigh et al.,

* Corresponding author. Advanced Baby Imaging Lab, 184 Hope Street, Box D, Providence, RI 02912, USA.
E-mail address: sdeoni@mac.com (S. Deoni).

https://doi.org/10.1016/j.neuroimage.2017.12.056
Received 1 August 2017; Received in revised form 3 November 2017; Accepted 18 December 2017
Available online 20 December 2017

2014; Deoni et al., 2014).

The assembly and maintenance of the myelin sheath requires a carefully orchestrated delivery of nutrients, including lipids and fatty acids, proteins, minerals, and other micronutrients (Dobbing, 1964). Long-chain polyunsaturated fatty acids (LC-PUFAs), choline, iron, zinc, cholesterol, phospholipids, and sphingomyelin play essential roles in myelin elaboration, as key components of the myelin sheath and/or energy sources (Oshida et al., 2003; Saher et al., 2005; Hadley et al., 2016; Chang et al., 2009). Deficiencies in these nutrients throughout infancy can significantly alter myelin content, composition, and morphology, potentially disrupting normal brain function and impairing cognitive outcomes.

Compositionally, human breastmilk provides many of the nutritional building blocks that support healthy physical growth, immune system development, and brain maturation (Kramer et al., 2008; Jacobi and Odle, 2012; Hoi and McKerracher, 2015; M'Rabet et al., 2008; Reynolds, 2001). This includes micro and macro-nutrients, short and long-chain PUFAs, phospholipids, neurotrophic factors, biofactors, and hormones that are important for myelination. While many of these nutrients are also provided by infant formula, their concentration often varies considerably from human milk, and does not mimic the changing nutritional composition of human milk across an individual feed (from foremilk to hindmilk), or from colostrum to mature milk (Ballard and Morrow, 2013). It is possible, therefore that given the importance of these nutritional components to brain development, nutritional differences between breast milk and infant formula, or between formula, may influence trajectories of brain myelination and, subsequently, affect cognitive development.

With specific reference to brain myelination, breastmilk is an important source of long-chain PUFAs, including docosahexaenoic and arachidonic acid (DHA and ARA), the together comprise more than 20% of the brain's fatty acid content (Chang et al., 2009), and phospholipids such as phosphatidylcholine that make up 10% of the lipid weight of myelin. Approximately 40% of the lipid content of mature human milk is sphingomyelin (Blaas et al., 2011), a sphingolipid that plays a critical role in development of the myelin sheath (Oshida et al., 2003; Jana and Pahan, 2010). Breastmilk is also an important source of cholesterol, which is essential for myelin synthesis (Saher et al., 2005). Even in otherwise healthy children, prolonged deficits in these and other nutrients have been associated with developmental abnormalities and cognitive impairments. For example, prolonged essential fatty acid deficiency or low blood levels of ARA and DHA have been associated with learning disorders, ADHD, dyslexia, and autism spectrum disorder (Hadley et al., 2016).

The nutritional composition differences between breast and infant formula milk may help to explain some of the observed difference in overall cognitive functioning and ability between breast and formula fed infants (Horwood and Fergusson, 1998). Even controlling for important confounds such as birth weight, pregnancy length, parent education level, and family socioeconomic status and demographics, the general consensus from prior studies is that children and adolescents breastfed as infants show improved performance on tests of cognitive functioning (Horwood and Fergusson, 1998; Anderson et al., 1999; Kramer et al., 2008; Mortensen et al., 2002; Huang et al., 2014). These results are also generally supported by brain imaging studies, which have shown increased white matter volume, total gray matter volume, and regional cortical thickness increases in association with breastfeeding duration and percentage of breastmilk in a infant's diet. These neuroimaging finds have further been associated with improved cognitive function as measured by IQ (Ou et al., 2015; Isaacs et al., 2010; Kafouri et al., 2013; Luby et al., 2016). Although these studies have been performed predominately in older children and adolescents, our group's prior work (Deoni et al., 2013a,b) extended these findings to infants, showing cross-sectional differences in early brain myelination between exclusively breastfed, exclusively formula-fed, and mixed-fed infants and toddlers. These differences were found to present prior to one year of age and extend throughout childhood, and were associated with duration of breastfeeding.

An important limitation of past neuroimaging (MRI) studies, however, has been their cross-sectional nature with children pooled across large age-ranges, making it difficult to draw causative conclusions. In addition, formula-fed children are often treated as a single group without consideration of the potential differences in formula composition. These limitations generally stem from the retrospective nature of most studies, with nutritional composition information often not remembered or readily available. Though infant formula is tightly regulated (e.g., http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048694.htm), there exists measurable differences in micronutrient, PUFA, and phospholipid content across different infant formulas.

To investigate nutritional influences on *longitudinal* infant and child brain development in a naturalistic setting, we longitudinally characterised myelination in a large group ($n = 150$, 57 females) of healthy and neurotypically developing children from 3 months to 9 years of age. A total of 452 total MRI and neurocognitive datasets were acquired on these children. These children were drawn from a larger study of normal brain development and were selected since knowledge of infant feeding habits, duration of exclusive breastfeeding, and main infant formula composition was known. Brain myelination was quantified using a multi-component relaxometry (MCR) technique termed mcDESPOT (Deoni et al., 2008), which decomposes the measured MRI signal into contributions from distinct sub-voxel anatomical water pools (MacKay et al., 1994). Through the acquisition of multiple T_1 weighted and T_1/T_2 weighted spoiled and fully-balanced steady-state images with different flip angles, mcDESPOT applies a 3-pool tissue model (Deoni et al., 2013a, b) to quantify the T_1 and T_2 relaxation and volume fraction properties for water pools associated with intra- and extra-cellular water, water trapped within the lipid bilayers of the myelin sheath, and a non-exchange free water pool (i.e., cerebral spinal fluid). The volume fraction of the myelin-associated water, termed the myelin water fraction (MWF) is used as a surrogate measure of myelin volume, and has been verified via comparisons with histology (Wood et al., 2016), and used previously to investigate trajectories of early brain maturation (Deoni et al., 2012), myelin-function relationships throughout childhood (O'Muircheartaigh et al., 2013; O'Muircheartaigh et al., 2014), and myelin loss in adults with multiple sclerosis and other demyelinating disorders (Kolind et al., 2013, 2012, 2015). For children up to 5 years and 8 months of age, cognitive function and development was measured using the Mullen Scales of Early Learning (MSEL) (Mullen, 1995), a population-normed tool that provides standardised measures of fine and gross motor control, expressive and receptive language, and visual processing. In addition to domain specific scores, computed early learning composite (ELC) and verbal and non-verbal development quotients (VDQ and NVDQ) composite values reflect overall cognitive, verbal, and non-verbal functioning. Each of these age normalized composite values has a mean of 100 and standard deviation of 15.

In addition to comparisons of brain and cognitive development trajectories associated with exclusive breast and formula-fed children, we further stratified the formula-fed children based on the main formula composition they received over the first 3 months of life and examined developmental differences between them. This analysis allowed us to more specifically investigate the role of nutritional composition on early brain growth. Finally, we extended this analysis to investigate the influence of individual nutrients on developmental myelin trajectories by examining the associations between specific formula nutrient levels and growth curve parameters.

Overall, we find that compared to exclusive breastfeeding for 3 months, children who exclusively received formula milk have lower overall neurodevelopment, including both neuroimaging measures of myelination and measures of cognitive performance that persist into later childhood, even with groups matched for important socioeconomic and demographic factors. In addition, significant deviations in development are evident across children who received different formula compositions.