

## **A milk for all ages: Benefits of breastfeeding on infant brain development**

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Infancy and early childhood are dynamic, yet vulnerable, periods of brain development. Throughout this period, brain networks are formed and refined in an adaptive process driven by diverse environmental and genetic influences<sup>1</sup>, including nutrition. Developmental processes, including the maturation of the myelinated white matter (myelination), play critical roles in establishing these brain networks, and mediate the brain messaging necessary for cognitive and behavioral skills<sup>2</sup>. The process of myelination is particularly sensitive to environmental conditions, and is highly dependent upon optimal delivery of nutrients (e.g., lipids and long-chain fatty acids) that comprise its structure; as well as energy sources (e.g., iron) for the myelin-producing oligodendrocytes. Nutrient deficiencies, therefore, can result in sub-optimal myelination (in extent and/or timing), that can have long-lasting neurocognitive effects. Of interest, therefore, is the influence of breastmilk vs. infant formula, on early brain development and later cognitive outcomes. The prevailing consensus from large epidemiological studies is that exclusive early breastfeeding is associated with improved measures of intelligence (IQ)<sup>3-8</sup>. Prior morphometric brain imaging studies support these findings, revealing increased white and gray matter volume, associated with IQ, in adolescents who were breastfed as infants<sup>9-11</sup>.

While the specific mechanism by which breastfeeding or breastmilk may influence myelination and consequently, cognitive development, remains poorly understood, interest has long focused on the importance of long-chain polyunsaturated fatty acids, in particular arachidonic and docosahexaenoic acid, or AA and DHA, that, until recently, were present only in breastmilk. Together, DHA and AA comprise approximately 20% of the fatty acid content of the brain, and are involved in a number of aspects of early neurodevelopment. These include regulating membrane function; modulating cell growth, inter- and intra-cellular communication, and protein function; involvement in membrane lipid biosynthesis and myelination<sup>12</sup>; and are integral components of brain gray and white matter<sup>13, 14</sup>. Deficiencies in DHA during the rapid period of myelination (birth to 6 months of age) can severely and permanently reduce myelination<sup>15</sup>. However, beyond fatty acids, breastmilk also contains an ever-changing menu of myelin-important nutrients, including zinc, choline, and vitamin B12.

To explore the affect of infant feeding practice (i.e., breastfeeding vs. formula feeding) on early brain myelination and cognitive development we used quiet magnetic resonance imaging (MRI) scans<sup>16</sup> to compare measures of white matter microstructure (specifically, myelin water fraction, MWF<sup>17</sup>) in a large cohort (n=316) of healthy and typically developing children from 4 months to 6 years of age. Children were either exclusively breastfed a minimum of 3 months; exclusively formula-fed a minimum of 3 months; or received a mixture of breast milk and infant formula. Using a longitudinal design we examined differences in developmental trajectories and associations between development and cognitive outcomes, across the 3 groups.

Breastfed children were found to exhibit increased white matter development and myelination in later maturing frontal and association brain regions. Results were significant even when controlling for known and common confounders, including child age, gender, racial composition, gestation, birth weight, and maternal age, education and socioeconomic status

(SES). Positive relationships between white matter microstructure and breastfeeding duration were also found in several brain regions that are anatomically consistent with observed improvements in cognitive and behavioral performance measures, specifically expressive language, visual reception, and fine motor skills. Contrasting the longitudinal trajectories showed that breastfed children had protracted periods of myelination and development between birth and 18 months of age that, ultimately, resulted in significantly greater myelin by 2 years of age.

Associated with these differential trajectories of brain development, we also found differences in cognitive maturation trends, though all children were considered within the normal developmental range.

Cumulatively, our results associate early exclusive breastfeeding with increased development in late maturing white matter regions, including the frontal and temporal white matter, peripheral aspects of the internal capsule and corticospinal tracts, superior longitudinal fasciculus and superior occipital-frontal fasciculus. These regions and pathways are commonly associated with higher-order cognition, such as executive functioning, planning, social-emotional functioning and language, domains in which breastfed infants were also found to have improved cognitive performance. While the exact mechanism (s) that underlie these observed myelination differences remain unclear, our results add to the consensus that breastfeeding has a positive impact of brain development.

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