Published in final edited form as:

Neuroimage. 2014 October 15; 100: 703–705. doi:10.1016/j.neuroimage.2014.07.016.

Nutritional influences on early white matter development: Response to Anderson and Burggren

Sean C.L. Deoni[a,*], **Douglas C. Dean III**[a], **Lindsay Walker**[a], **Holly Dirks**[a], and **Jonathan O'Muircheartaigh**[a,b]

[a]Advanced Baby Imaging Lab, School of Engineering, Brown University, Providence, RI 02912, USA

[b]Department of Neuroimaging, King's College London, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK

Abstract

Does breastfeeding alter early brain development? In a recent retrospective study, our group examined the cross-sectional relationship between early infant feeding practice and white matter maturation and cognitive development. In groups matched for child and mother age, gestation duration, birth weight, gender distribution, and socio-economic status; we observed that children who were breastfed exclusively for at least 3 months showed, on average, increased white matter myelin development compared to children who either were exclusively formula-fed, or received a mixture of breast milk and formula. In secondary analysis on sub-sets of these children, again matched for important confounding variables, we found improved cognitive test scores of receptive language in the exclusively breast-fed children compared to formula or formula + breast-fed children; and that prolonged breastfeeding was associated with increased motor, language, and visual functioning in exclusively breast-fed children. In response to this work, Anderson and Burggren have questioned our methodology and, by association, our findings. Further, they use their critique as a platform for advancing an alternative interpretation of our findings: that observed results were not associated with prolonged breast-feeding, but rather delayed the introduction of cow's milk. In this response, we address and clarify some of the misconceptions presented by Anderson and Burggren.

Keywords

Brain development; Breastfeeding; Myelin maturation; White matter development; Infant imaging; Myelin; Infant nutrition

Introduction

Does breastfeeding influence early brain and cognitive maturation? Recently, we sought to investigate this question in a retrospective and cross-sectional study (Deoni et al., 2013). As

*Corresponding author at: Advanced Baby Imaging Lab, School of Engineering, Brown University, Providence, RI 02912, USA. sdeonii@brown.edu (S.C.L. Deoni).

☆Manuscript prepared for submission to NeuroImage (*Comments and Controversies*).

summary, in a relatively large cohort of infants, toddlers, and young children between 10 months and 4 years of age, we examined the relationship between infant feeding practice to measures of brain development and cognitive ability. Based on medical history information and parental interview, children were grouped as: exclusively breastfed for a minimum of 90 days; exclusively formula-fed; or combined breast and formula-fed. Groups were matched for important confounding factors that influence brain development, including: child and mother age, gestation duration, birth weight, gender distribution, and socio-economic status (SES). Using a myelin water fraction (MWF) imaging method that reports a surrogate measure of myelin content (termed mcDESPOT) (Deoni et al., 2008; 2011), our primary analysis examined group differences in rate of myelin development between these three groups. We found that, on average, children who were exclusively breastfed showed increased white matter myelin development compared to children who either were exclusively formula-fed, or received a mixture of breast milk and formula. Building on these results, we performed two secondary analyses: 1. On an older subset of children, 2.2 to 4 years of age, we examined group differences in myelin content and cognitive ability; and 2. In the exclusively breastfed children, we examined the correlation between myelin content and breastfeeding duration. For both of these secondary analyses, groups were again matched for child and mother age, gestation duration, birth weight, gender distribution, and SES.

In a recent review of this study, Anderson and Burggren raised important questions regarding our methodology, findings, and conclusions (Anderson and Burggren, 2014). While recognizing that no scientific study is without fault, not at least retrospective investigations on populations of convenience, we wish to address and clarify some of their comments, specifically: 1. That we prematurely claim a causal relationship between infant feeding practice, white matter development, and cognitive outcomes; 2. That we did not control for important confounding variables in our analysis; and 3. That our cognitive comparisons based on raw test scores did not properly account for age and, thus, over-emphasized differences. We then briefly comment on a proffered alternative interpretation of our findings, that observed results were not associated with prolonged breast-feeding, but rather delayed introduction of cow’s milk.

Point 1

In any analysis based on correlation, it is not possible to make causative claims regarding observed relationships. We agree with Anderson and Burggren’s assertion that “a strictly causal relationship among breastfeeding, white matter development, and cognitive ability is un-substantiated”. Indeed, we underscore this not only in the title of our paper, specifying its cross-sectional nature, but also state explicitly in the discussion that “the cross-sectional nature of our study precludes us from performing the predictive analysis (necessary) to more conclusively demonstrate a causal link between breastfeeding, structural development, and cognitive outcome”.

In much of the discussion concerning potential linkages between white matter and microstructure and cognitive ability, Anderson and Burggren reference work based on diffusion tensor imaging based metrics, specifically fractional anisotropy. It is worth pointing out that FA and MWF are not similar metrics (Mädler et al., 2008). Rather FA is pre-dominately a measure of microarchitecture and fiber coherence (Beaulieu, 2002; Wheeler-Kingshott and Cercignani, 2009), while MWF is believed to more sensitively reflect myelin content (MacKay et al., 1994; Laule et al., 2008). Our group has provided some of the earliest investigations of the relationships between developing MWF and maturing behavioral and cognitive abilities (Dean et al., 2014; O'Muircheartaigh et al., 2014) in healthy and typically-developing infants and young children.

Point 2

It is clear that infant and childhood neurodevelopment is influenced by numerous environmental and genetic factors (Winick, 1969; Thompson et al., 2001; Lidsky, 2003; Peirano and Algarín, 2007; Peper et al., 2007; Hackman and Farah, 2009; Winner et al., 2009), and that infant nutrition represents only one of these important factors. As pointed out, maternal health and age, child age, prematurity, gender, and SES have each been shown to be associated with brain development, cognitive ability, and intelligence. Hence, contrary to assertions by Anderson and Burggren that we did not control for these influences, i.e., "When comparing both white matter and test scores, mothers were not controlled for age and socio-economic status (SES) and their children were not controlled for gender", we state plainly throughout the manuscript, and summarize in Table 1 (Deoni et al., 2013), that groups where either matched for these effects (through pair-wise *t*-tests), or were included as co-variates in each stage of analysis. This included each set of analysis, including our comparison of white matter and test scores. A multivariate or causal modeling approach, such as the authors suggest, could indeed be performed to examine the influence of each of these measures, and their combination, on measures of brain MWF development more fully. We did not undertake such an approach.

Point 3

Anderson and Burggren next comment on our use of raw cognitive scores, rather than age-adjusted T-scores, for group comparisons. It is undeniable that the Mullen scales of early learning scale linearly with age (Mullen, 1995). Thus, we took care not only to match groups for mean age, but also age distribution to mitigate the effects illustrated in Anderson and Burggren's Figure 1. Unfortunately, as Anderson and Burggren did not request the raw data used in our study, it is difficult to comment on how their figure was constructed, how they recovered appropriate age-corrected scores, or how they arrived at their conclusion that there were "no statistically significant differences between any of the five domains tested using a 2-sample *t*-test" using their recovered age-adjusted scores. To address this more directly, we re-analyzed our data using the corresponding age-adjusted T-scores. Using these, we show (Table 1) similar results as presented in our original paper. To address the prior comment that we did not control for mother's age, SES and child's gender, we include these variables in Table 1 also. In this older subset of participants, there were no significant differences in mother's SES ($p = 0.72$), child's age ($p = 0.91$), maternal age ($p = 0.31$), or gender composition ($p = 0.63$). This analysis did reveal, however, that in addition to significant differences in receptive language ($p = 0.006$), visual reception also differed significantly between the exclusively breastfed and formula-fed groups ($p = 0.01$).

Following their comments on our methodology and results, Anderson and Burggren offer an alternative interpretation of our findings: that observed results are not associated with prolonged breast-feeding, but rather delayed introduction of cow's milk. While this is an interesting topic, we do not feel that our data can be used to support or oppose this hypothesis. Unlike information related to breastfeeding practice and percentage, duration, and formula brand, we have little information regarding the introduction or use of cow's milk in our participants. One could readily speculate on numerous other dietary or environmental contributors that are introduced at the same time as cow's milk that may also have deleterious effects (Winick, 1969; Lidsky, 2003; Peirano and Algarín, 2007; Winner et al., 2009). Only through further research, particularly those employing prospective longitudinal and randomized designs, will we gain a more complete appreciation of early nutrition and brain development. This, we believe, is a goal we can all agree on.

Acknowledgments

This work was supported by the National Institutes of Mental Health (R01 MH087510). JOM is supported by a Sir Henry Wellcome Postdoctoral Fellowship awarded by the Wellcome Trust (No. 096195).

References

Anderson A, Burggren A, 2014 Cognitive and neurodevelopmental benefits of extended formula-feeding in infants: re: Deoni et al. 2013. Neuroimage (5).

Beaulieu C, 2002 The basis of anisotropic water diffusion in the nervous system — a technical review. NMR Biomed 15 (7–8), 435–455 (11). [PubMed: 12489094]

Dean DC, O'Muircheartaigh J, Dirks H, Waskiewicz N, Walker L, Doernberg E, et al., 2014 Characterizing longitudinal white matter development during early childhood. Brain Struct. Funct (4 8.).

Deoni SCL,Rutt BK,Arun T,Pierpaoli C,Jones DK, 2008 Gleaning multicomponent T1 and T2 information from steady-state imaging data. Magn. Reson. Med 60 (6), 1372–1387 (12). [PubMed: 19025904]

Deoni SCL, Mercure E, Blasi A, Gasston D, Thomson A, Johnson M, et al., 2011 Mapping infant brain myelination with magnetic resonance imaging. J. Neurosci 31 (2), 784–791 (1 12). [PubMed: 21228187]

Deoni SCL, Dean DC, Piryatinsky I, O'Muircheartaigh J, Waskiewicz N, Lehman K, et al., 2013 Breastfeeding and early white matter development: a cross-sectional study. Neuroimage 82, 77–86 (11 15). [PubMed: 23721722]

Hackman DA, Farah MJ, 2009 Socioeconomic status and the developing brain. Trends Cogn. Sci 12 (2), 65–73.

Laule C,Kozlowski P,Leung E,Li DKB,MacKay AL,Moore GRW, 2008 Myelin water imaging of multiple sclerosis at 7T: correlations with histopathology. Neuroimage 40 (4), 1575–1580 (5 1). [PubMed: 18321730]

Lidsky TI, 2003 Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain 126 (1), 5–19 (1 1). [PubMed: 12477693]

MacKay A, Whittall K, Adler J, Li D, Paty D, Graeb D, 1994 In vivo visualization of myelin water in brain by magnetic resonance. Magn. Reson. Med 31 (6), 673–677 (6). [PubMed: 8057820]

Mädler B, Drabycz SA, Kolind SH, Whittall KP, MacKay AL, 2008 Is diffusion anisotropy an accurate monitor of myelination? Correlation of multicomponent T2 relaxation and diffusion tensor anisotropy in human brain. Magn. Reson. Imaging 26 (7), 874–888 (9). [PubMed: 18524521]

Mullen EM, 1995 Mullen Scales of Early Learning

O'Muircheartaigh J, Dean DC, Ginestet CE, Walker L, Waskiewicz N, Lehman K, et al., 2014 White matter development and early cognition in babies and toddlers. Hum. Brain Mapp (2 27).

Peirano PD, Algarín CR, 2007 Sleep in brain development. Biol. Res 40 (4), 471–478. [PubMed: 18575679]

Peper JS, Brouwer RM, Boomsma DI, 2007 Genetic influences on human brain structure: a review of brain imaging studies in twins. Hum. Brain Mapp 28 (6), 464–473. [PubMed: 17415783]

Thompson PM, Cannon TD, Narr KL, Van Erp T, 2001 Genetic influences on brain structure. Nature 4 (12), 1253–1258.

Wheeler-Kingshott CAM, Cercignani M, 2009 About “axial” and “radial” diffusivities. Magn. Reson. Med 61 (5), 1255–1260 (5). [PubMed: 19253405]

Winick M, 1969 Malnutrition and brain development. J. Pediatr 74 (5), 667–679. [PubMed: 4888313]

Winner E,Evans AC,Schlaug G, 2009 Musical training shapes structural brain development. J. Neurosci 29 (10), 3019–3025. [PubMed: 19279238]

Table 1

Child demographic information.

	Group #1: exclusively breastfed	Group #2: exclusively formula-fed	p-Values
Participants (n)	21	12	
Age (days)	1287 ± 153	1281 ± 118	0.91
Male:Female	7:14	5:7	0.63[a]
Maternal age (years)	32 ± 4.8	29.4 ± 6.7	0.31
Maternal SES	6.3 ± 0.6	6.4 ± 0.7	0.72
Mullen fine motor T-score	64.8 ± 10.9	56 ± 7.7	**0.01**
Mullen expressive language T-score	50.5 ± 13	43.3 ± 13.3	0.14
Mullen receptive language T-score	61.9 ± 7.7	49.3 ± 12.5	**0.006**
Mullen visual reception T-score	56.2 ± 8.7	51.3 ± 10.8	0.2

Bold values indicate significant differences ($p < 0.05$) corrected for multiple comparisons.

[a] Chi-square statistic = 0.23.