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THE COGNITIVE AND NEURODEVELOPMENTAL BENEFITS OF BREASTFEEDING:

Nutrition or parent-infant interaction

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The cognitive and neurodevelopmental benefits of breastfeeding: Nutrition or parent-infant interaction

Submitted by Kristina Boström to the University of Skövde as a final year project towards the degree of B.Sc. in the School of Bioscience. The project has been supervised by Judith Annett.

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I hereby certify that all material in this final year project which is not my own work has been identified and that no work is included for which a degree has already been conferred on me.

Signature: ____

Abstract

Breastfeeding is encouraged exclusively until the infant is 6 months and then continuing up until the age of two years and further, as a supplement to solid food. Few infants get this opportunity even though positive effects have been seen. In recent days brain imaging techniques has begun to study the differences in brain development between breastfed and formula fed infants. In this essay methods for assessing the cognitive and neurodevelopmental aspect of breastfeeding aspects will be reviewed. The results found in this review suggest that breastfeeding has a benefit in the development of the brain and in addition a beneficial impact on the parents. This can be seen in faster development of crucial brain areas, better cognitive functions and better maternal sensitivity which in turn relates to a child’s better adjustment. However, it is not clear how these benefits develop, if it is due to breastfeeding or parental characteristics related to breastfeeding.

Keywords: breastfeeding, brain, development, cognitive, formula

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Introduction

The breastfeeding rate in Sweden is below the suggested optimal level. According to guidelines by WHO, breast milk should be an infant's only food source the first 6 months of life (WHO Baby-friendly Hospital Initiative, n.d.). An exception is supplementation of vitamin D, which is promoted in Sweden (Socialstyrelsen, 2013). In, with a supplement of vitamin D. In the 2011 only 13,5 percent of the infants were fed exclusively with breast milk and 63 percent were partly breastfed, despite the recommendations not to introduce other food sources before 6 months of age (Socialstyrelsen, 2013).

Baby-Friendly-Hospital-Initiative (BFHI)

BFHI is developed by the World Health Organization (WHO) and The United Nations Children's Fund (UNICEF) in 1991 (WHO Baby-friendly Hospital Initiative, n.d.). This initiative was developed with the purpose that all mothers shall get help with the initiation of breastfeeding (UNICEF, n.d.). The BFHI consists of ten steps, that the hospital has to implement as a standard in order to get the label of BFHI. The ten steps are developed in order to protect, promote and support breastfeeding. These steps are: [1] a written routine at the hospital on how to protect, promote and support breastfeeding, [2] train all personal to implement the written routine from the previous step, [3] to inform all pregnant women about benefits and management of breastfeeding, [4] help mothers to initiate breastfeeding within 30 minutes after birth, [5] tell mothers how to maintain breastfeeding even if separated from the child, [6] only give the infants formula if it is medically needed, [7] let mother and child be together 24 hours a day(rooming-in), [8] encourage that the infant breastfeed on demand, [9] not give artificial teats or pacifiers to the infants, [10] create support groups which mothers can attend after leaving the hospital (UNICEF, n.d.). Research comparing hospitals pre and post certifying as Baby-friendly has suggested that BFHI has increased the number of exclusively breastfeed infants both at 4 and 6 months after birth. This applies to both rural and urban countries (Labbok, Wardlaw, Blanc, Clark , & terreri, 2006; Kramer, et al., 2001; Abrahams & Labbok, 2009).

A study performed in Norway also suggests that the BFHI is effective in increasing breastfeeding rates (Andreassen, Bale, Kaaresen, & Dahl, 2001). This study found that the duration of breastfeeding increased with a mean between 0,2-1,1 months after the hospitals integrated BFHI into their practice. The prolongation of breastfeeding is also supported in a study by Hansen et al. (2012).Another study examined if bed-sharing between mother and infant were related to breastfeeding rates (Galler, Harrison, & Ramsey, 2006).

They found that that bed-sharing was negatively correlated to the mothers rating of both anxiety and depression. The infants who were sharing bed with their mothers were also more likely to be breastfed than those not bed-sharing (Galler, Harrison, & Ramsey, 2006).

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Is breastfeeding the best way to promote the child’s long-term development?

Breastfeeding has been suggested to be the best way to nurture an infant (WHO Baby-friendly Hospital Initiative, n.d.). Benefits of breastfeeding have been observed on the mother’s ability to read the cues of her infant, called maternal sensitivity (Bystrova, et al., 2009). It has also been suggested to protects against child mortality (Boccolini, de Carvalho, de Oliveira, & Pérez-Escamilla, 2013). Breast milk is seen to be rich in nutrients (Gordon, 1997) that are easy for the body to take up (Deoni, et al., 2013) and the importance of nutrition in an infant’s development has been suggested by some research (Morse, 2012; Gordon, 1997).

However, the research findings are not consistent. In a review by Jansen, de Weerth, and Riksen-Walraven (2008) they did not find support for that the effects seen on development are caused by breastfeeding alone. For example, oxytocin is suggested to be an important hormone for maternal bonding but can be seen in management of stress related to social situations (Kubzansky, Mendes, Appleton, Block, & Adler, 2012). Further, Swain, Lorberbaum, Kose, and Strathearn (2007) discus that brain areas involved in parent-infant bonding and interaction are involved in other social situations such as love and attachment as well. Skin-to-skin contact is suggested to play a major role in maternal sensitivity (Bystrova, et al., 2009), which has been related to better cognitive development of the child (Narvaez, et al., 2013).

If it is the breast milk itself or other factors included in breastfeeding that gives the advantages is not clear and the relationship tends to be complex and hard to test empirically (Agostoni, Baselli, & Mazzoni, 2013). The benefits of breastfeeding are hard to test due to the ethical aspects of doing clinical trials of breastfeeding, environmental factors and individual confounding factors. Factors like pollution and personality (Agostoni, et al., 2013). This makes it hard to draw definitive conclusions about the link between aspects of breastfeeding and developmental benefits without thorough longitudinal research.

Factors such as self-efficacy, postpartum depression, anxiety, social support, intention to breastfeed and the mothers attitude (de Jager, Skouteris, Broadbent, Amir, & Mellor, 2013) has been seen to affect breastfeeding duration, which add to the complexity of studying benefits of breastfeeding.

Brain development proceeds from the more primitive areas, such as the brainstem, and follows a specific pattern ending with the more advanced areas such as frontal brain areas. The frontal areas are responsible for functions including reasoning, perception and motor control (Billiards, Pierson, Haynes, Folkerth, & Kinney, 2006). The more advanced areas continues developing after birth (Hallowell & Spatz, 2012) and the prefrontal cortex reaches its developmental rate peak at around the age of 13 (Tsujimoto, 2008). It is due to the rapid pace in which the brain develops that it is important to provide the infant with accurate nurturance at specific ages. If the infant receive what is needed for the best development it may affect the functioning in years to follow. Today it is unclear what exactly optimal development is, cause the difference in normal difference (Evans, 2006)

In recent years the development of research equipment has progressed rapidly. We are today able to examine the biological bases of how breastfeeding affect the development in early childhood. This gives new possible ways to establish what factors might link development and breastfeeding. The aim of this essay is to give an overview of currently published articles examining the biological base of breastfeeding benefits. Further also the benefits of parenting and parent-infant interaction for the cognitive development will be addressed in order to establish what the current field of breastfeeding has found about where the developmental benefits stem from.

This essay consists of four parts. Beginning with a short overview on why a mother may choose to breastfeed, and some characteristics of who is more likely to initiate breastfeeding. Further some factors that may decrease the likelihood of initiating breastfeeding is discussed, as is factors that may prolong the breastfeeding.

The second part of the essay covers an overview of pregnancy, pregnancy hormones, and diet in the infants first postpartum months. This includes a discussion about the content of breast milk, fatty acids and why this may be important for the infant's development.

The third part is a summary of what benefits that may come from breastfeeding, nutrition, skin-to-skin contact and maternal sensitivity. Studies will be presented based on what outcome measure is used, starting with Bayley scale of infant development (BSID) and continuing with EEG and visual evoked potential (VEP), Wechsler's IQ scale and last measures including specific brain regions will be review. Studies not controlling for maternal factors will be reviewed alongside with studies comparing supplementation with long-chain polyunsaturated fatty acids (LCPUFAS), as it is not possible to separate these effects from the results. After this a link between maternal sensitivity and cognitive development will be reviewed and followed by other aspects such as oxytocins' importance for the development of maternal sensitivity. This part also includes a brief discussion about maternal depression due to its impact on the development of maternal sensitivity and initiation of breastfeeding.

The last part is about what the results imply and what conclusions can be drawn upon the results. Limitations of the studies and implications for further research will be discussed.

Factors that affect the choice to breastfeed

Research has identified several factors that appear to be important in the choice to breastfeed or not. In Sweden 96 percent of all infants are breastfed at one week of age (Socialstyrelsen, 2013). Factors such as low education, tobacco use before birth or neonatal intensive care are negatively related with breastfeeding initiation (Sjöström, Welander, Haines, Andersson, & Hildingsson, 2013). Early weaning of breastfeeding can be due to physical challenges such as pain related to breastfeeding or the physical demand of needing to breastfeed. Anxiety of breastfeeding is in some cases present and can cause early weaning (Kelleher, 2006). A study examining psychological stress has seen that the stress can be a factor that postpone the initiation of breastfeeding with healthy vaginal delivered term infants (Doulougeri, Panagopoulou, & Montgomery, 2013). It is further suggested that the maternal perception of the child affects whether or not the mother continues to breastfeed. The mothers with more confidence may have an easier time breastfeeding (Wojnar, 2004).

Cesarean section is one other factor that may affect the initiation of breastfeeding. Rowe-Murray and Fisher (2002) found that in hospitals not baby-friendly certified, most infants delivered with cesarean section did not get skin-to-skin contact direct after birth. Neither did the infants start to breastfed in the first hour after birth. However, baby-friendly hospitals did manage to introduce breastfeeding to most infants within an hour after cesarean section births. The goal set by UNICEF (UNICEF, n.d.) and WHO (WHO Baby-friendly Hospital Initiative, n.d.) is to establish breastfeeding within half an hour after birth, which is difficult to establish if cesarean section is used (Rowe-Murray & Fisher, 2002). Another aspect of cesarean section is that initiation of breastfeeding on the operating table may cause discomfort. The discomfort can lead to breast- and nipple-pain, and a hard time for the mothers to establish breastfeeding. However, the discomfort can also be connected to the characteristics of the mother (Hsien, Fu, Long, & Lin, 2011). The effect by cesarean section on oxytocin release is one other important factor related to the initiation of breastfeeding and mother infant interaction (Kendrick, et al., 2000).

It is suggested that the attitude and promotion of breastfeeding to mothers with middle socioeconomic status (SES) is important for their choice of breastfeeding. Birthing mothers were less likely to initiate breastfeeding after birth if they knew or belived that a nurse, her partner or her mother did not have an opinion about breastfeeding. The same results were found if the nurse, the partner or the mother were not promoting breastfeeding (Odom, Li, Scanlon, Perrine, & Grummer-Strawn, in press). It is also suggested that the way nurses explain breastfeeding is important for the mothers' choice to breastfeed (Burns, Schmied, Fenwick, & Sheehan, 2012). However in Norway only 63 % of the asked mothers received help from the nurses, while many also reported hands-on help, which may feel uncomfortable or upsetting for the mother (Kelleher, 2006). Mothers that received help with their smoking during pregnancy were more likely to breastfeed (Mejdoubi, et al., in press), which support the importance of support from health care professions. Beyond social support, the employment status is an impacting factor on initiation and duration of breastfeeding. Attanasio, Kozhimannil, McGovern, Gjerdingen, and Johnson (2013) found that work status did not affect intention to breastfeed. However, the full-time working mothers were as likely to breastfeed partly as the non-employed mothers but less likely to exclusively breastfeed their infant even if they intended to before birth (Attanasio, et al., 2013 ; Mandal, Roe, & Fein, 2010).

In USA, it has been found that adolescent mothers are less likely than adult mothers to initiate breastfeeding. Some of the reasons for this may be that adolescent mother more often are of black race, are unmarried, has less education and low income (Apostolakis-Kyrus, Valentine, & DeFranco, 2013). Several of these reasons was seen to be related to lower breastfeeding rates also for adult mothers in a study performed in Sweden and Australia (Sjöström, et al., 2013). Moreover, the duration of breastfeeding among adolescent mothers are related to participation in childbirth classes, exclusive breastfeeding, depressive symptoms and intimate partner violence (Sipsma, et al., 2013). As mentioned, social support, both from family, partner, nurses and school personal, were related to initiation of breastfeeding. However, problems with breastfeeding were related to early weaning (Wambach & Cohen, 2009). Reasons for adolescent mothers to stop breastfeeding their infant includes factors such as pain, the infant did not like to breastfeed or the mothers got back to work or school (Sipsma, et al., 2013).

The infant's physiological status is in some cases one factor that contributes to not initiating breastfeeding. In Sweden about one out of twenty children are born before week 37 of pregnancy (preterm), as seen in adult mothers those with infants born preterm are less likely to start breastfeeding (Apostolakis-Kyrus, et al., 2013). These children are born immature and this may be a complication for initiation of breastfeeding. However, Nyqvist (2008) found that the preterm infant could initiate breastfeeding in mean 7 days after birth, and had full physiology for feeding after a mean of 42.5 days after birth. This short time to reach the physical ability to exclusive breastfeeding, suggests that the preterm infant has an early development of oral motor control.

Disabilities and chronic illnesses among the infants are other factors that may complicate the breastfeeding. One such disability is tongue-tie, were the infant are not able to stretch out the tongue enough to create vacuum. If the tongue-tie is released it improves breastfeeding, even though it may be related to pain in the nipple (Miranda & Milroy, 2010). Ransjö-Arvidson et al. (2001) found that infants to mothers that got analgesia did not initiate breastfeeding as often as infants with mothers not receiving analgesia. Infants also had worse temperature regulation and were crying more if the mothers received analgesia.

A feeding-cup is an alternative to feed preterm infants with instead of a bottle, and when the infant can eat from the breast, the cup is weaned. The infants who receive milk in a cup instead of a bottle have significantly longer breastfeeding duration (Yilmaz, Caylan, Karacan, Bodur, & Gokcay, 2014). In one study they found that a higher intake of fruit and vegetables were related to longer breastfeeding duration (Amir & Donath, 2012). However, the intake of fruit and vegetables has also been linked to more optimism and higher concentrations of serum antioxidants (Boehm, Williams, Rimm, Ryff, & Kubzansky, 2013). Which may explain some of the personal characteristics that can affect breastfeeding duration more than the breastfeeding per se. Maternal eating patterns are another factor that may prolong the breastfeeding duration. In contrast restraint eating, external eating behavior (Brown, in press), higher preferences for salt (Verd, Nadal-Amat, Gich, & Leshem, 2010), obesity and smoking (Amir & Donath, 2012) are examples of factors that are related to shorter duration of breastfeeding.

Pregnancy and infant Brain development during pregnancy

During pregnancy the mothers production of the hormones progesterone, prolactin, estrogen and oxytocin increase and reach its stop at birth. Involved fathers can also show altered hormonal levels, which includes higher levels of prolactin and cortisol and lower levels of sex hormones (testosterone and estradiol; Swain, et al., 2007). The breast physiology in the mother changes during pregnancy and the mammary glands develop the ability to secrete milk (Kent, 2007), which is called lactogenesis 1. The different components of breastmilk travels via diffusion to the basement membrane of the leucocytes, in which milk are composed (Kent, 2007). Breast milk is composed by glucose, amino acids, minerals and vitamins. The lipids found in the breast milk are most of the energy intake that the breastfeeding infant needs (Koletzko, et al., 2001).

Difference in breast milk content may be due to different intake of food. However differences are only found in the amount of micronutrients (Kent, 2007) and fatty acids (Moltó-Puigmartí, Castellote, Carbonell-Estrany, & López-Sabater, 2011). There are also different amount of fatty acids in the milk of mothers who have given birth to very preterm, preterm and term infants (Moltó-Puigmartí, et al., 2011). In contrast, the milk is similar in amount of lactose, proteins and total fats independent of the mother's nutrition status (Kent, 2007). The proteins found in milk are caseins, alpha-lactalbumin, immunoglobulins, albumin, lactoferrin, nonprotein nitrogen, enzymes, hormones, growth factor and nucleotides (Kent, 2007). The fats include triglycerides and fatty acids (Kent, 2007), which according to Guesnet and Alessandri (2011) and McCann and Ames (2005) are important for myelination of the axons. The amount of fatty acids may not differ as much between mothers because it is derived from sources in the body (Koletzko, et al., 2001), which point to the importance of long-term nutritional intake. The breast milk also contains carbohydrates such as lactose, glucose, galactose and oligosaccharides. The oligosaccharides are thought to play a protective role in the digestive systems where it acts as a protection against intestinal infections and triggers the immune system (Boehm & Stahl, 2007). Milk also contains water, minerals, vitamin trace-elements and electrolytes (Kent, 2007).

The colostrum and the mature milk show differences in content. Mature milk contains more lipids and higher concentrations of casein, lactose, potassium, citrate, calcium and phosphates, while it decreases in concentrations of protein, sodium and chloride. Overall the content of fat, protein and calcium decrease over time while the lactose is similar (Kent, 2007). The content of AA (omega 6) and DHA (omega 3) in colostrum and mature milk are different between mothers giving birth to very preterm (less than 30 weeks), preterm (30-37 weeks) and term born (38-42 weeks) infants (Moltó-Puigmartí, et al., 2011).

During lactogenesis 2 the onset of milk secretion occurs. This onset is triggered by adequate levels of prolactin, insulin, adrenal cortisol and the withdrawal of circulating progesterone in the mother (Kent, 2007). The prolactin and oxytocin also shows elevated levels during breastfeeding (Riordan & Wambach, 2010). When the infant is suckling prolactin, released by the anterior pituitary, reaches its peak about 45 minutes after onset (Kent, 2007). As mentioned, oxytocin are released when the infant are suckling (Kent, 2007), but the release of oxytocin also occurs when the infants is touching the breast (Matthiesen, Ransjö-Arvidson, Nissen, & Uvnäs-Moberg, 2001).

Oxytocin is important for the contraction of the milk ducts that starts the expulsion of the milk in the breast (Kent, 2007). Oxytocin receptors have been found in both humans and animals and besides secretion of milk it has been seen to play a role in attachment (Swain, et al., 2007). Oxytocin receptors has been found in pre-optic area/hypothalamic area, mid brain and upper pons, and in areas such as basal nucleus of Meynert, diagonal band of Broca, lower pons, medulla and upper spinal cord sites (Swain, et al., 2007). Regulation of oxytocin receptors are seen to stem from bed nucleus of the stria terminalis, hypothalamic paraventricular nucleus, central nucleus of the amygdala, ventral tegmental area and lateral septum. In animal studies it has also been found that an electric stimulation in the anterior cingulate cortex stimulates oxytocin release and milk ejection (uterine contractions) (Swain, et al., 2007).

Another factor that is important for the secretion of milk is the vacuum created by the child when suckling. Geddes et al. (2012) found that infants can feed from an experimental teat and get the same amount of milk as is documented in breastfed infants. This is with ultrasound seen to be due to vacuum only (Geddes, et al., 2012).

Widström et al. (2011) discuss in their observational study that the odor, secreted from the areolar glands on the breast, may help the infant to locate the breast and nipple. It was found that both the number of areolar glands and the mother’s experience of breastfeeding are related to lactation onset. They also found that the weight gain of the infant was positively related to the number of areolar glands of the mother. However, it has been found that some women are missing areolar glands (Doucet, Soussignan, Sagot, & Schaal, 2012).

The behavior of infants placed skin-to-skin after birth is similar between infants. This indicates that there are inborn reflexes in newborns that are activated if the child is optimally positioned, on the mothers chest. (Widström, et al., 2011). To place the child properly and with undisrupted skin-to-skin contact has been seen to relate to effective suckling (Cantrill, Creedy, Cooke, & Dykes, 2014), which support the findings that newborns benefits from skin-to-skin contact in order to establish breastfeeding.

Importance of fatty acids on brain development

Fatty acids (including but not limited to omega 3 and 6) are transferred to the fetus via the placenta, and are accumulated in the infant through pregnancy in the membrane of the retina and the gray matter (Innis, 2005). Most of the accumulation of DHA and AA takes place in the third trimester of pregnancy (Reynolds, 2001) and the white matter increase with about five times between gestational age (GA) 35 and 41 (Kinney, 2006). This leaves preterm born infants at risk for a less mature central nervous system CNS. The concentrations of fatty acids seen in the infant are closely related to the serum concentration of the same fatty acid seen in the mother (Innis, 2005). Higher concentration of DHA (omega 3) and AA (omega 6) in infants at birth gives advantages in several weeks after birth. Nevertheless, there are contrary findings who do not confirm this advantage of fatty acid intake (van Goor, Dijck-Brouwer, Erwich, Schaafsma, & Hadders-Algra, 2011). Supplementation with DHA and AA during pregnancy showed no significant effect compared to placebo when following up on the neurological development in infants at18 months of age (van Goor, et al. 2011). Reduced accumulation of DHA has been seen to change the metabolism of dopamine and serotonin, and is related to less response from the brainstem to audio. The EEG pattern of infants with more serum DHA is more developed at day 2 postpartum, suggesting a more mature CNS (Innis, 2005).

Cognitive- and neuro-development

The study of how breastfeeding affect brain development can be done in different ways. It can for example be studied as only nutrition (food), only closeness (skin contact and parent-infant interaction) or as both nutrition and closeness. This section focuses on measures of breastfeeding and LCPUFAS and how it affects the course of brain development in term and preterm infants. This is followed by studies looking at the effect of skin contact and parent-infant interaction on development, both neurological and behavioral.

Bayley scale of infant development (BSID) is a scale measuring the psychomotor and mental development of infants and young toddlers up till the age of three years. This scale is supposed to measure the infant's cognitive ability and is also used as an assessment for neurological development. The scale consists of two sub scales, the Psychomotor Development Index (PDI) and the Mental Development Index (MDI). The PDI covers the gross and fine motor skills of the infant and the MDI looks at language and visual-motor problem solving ability of the infant (Jensen, et al., 2005). The assessment consists of play tasks which the infant shall perform, and scores are then given depending on how difficult tasks the infant manage.

Narvaez et al. (2013) did a longitudinal study with 682 mothers and their infants over the first three years of the infant's life. The recruited mother-and-child dyads were in community groups at risk for child neglect. The sample consisted of 396 adolescent mothers (mean 17.5 years), 169 mothers with education limited to high school diploma (mean 25.5 years) and 117 comparison mothers not at risk for child neglect (mean age 27.9 years). They looked at several different outcomes such as maternal responsivity and touch, maternal social support, BSID and behavioral problems. Also breastfeeding initiation was measured in a larger interview at the age of six months, so they could analyze the relation between breastfeeding initiation and the outcome measures. Of all the mothers, 531 answered this breastfeeding question when the infants were six months of age.

The results related to BSID in the study by Narvaez et al. (2013) was that maternal responsivity, as measured by an home observation based on a protocol by Caldwell and Bradly (1984, 2001), were positively related to the scores on BSID even when controlling for background variables. Narvaez et al. (2013) also found that the 221 infants who received some breast milk had better scores on BSID than those not receiving any breastmilk at all. Also maternal touch was related to the BSID scores, and was assessed by protocol developed by Caldwell and Bradly (1984, 2001) in the home observation. Greater maternal touch at four months predicted better outcomes on the BSID at 36 months, and this prediction remained when maternal responsivity was controlled for. Maternal support was measured using the social support inventory, and the greater social support the better scores on the BSID measured at the age of 24 months. However, this relation was no longer significant at the age of 36 months (Narvaez, et al., 2013).

van Goor, et al. (2011) used the BSID as outcome measure in their study where they supplemented mothers during pregnancy with either AA or both DHA and AA. van Goor et al. (2011) analyzed the fatty acid content in the umbilical cord (vein wall and artery wall).

The analysis of the umbilical cord showed differences in fatty acid content between the three groups (AA-supplement, AA+DHA-supplement and control group; all enrolled between week 14-20 in pregnancy), but the only correlation to the BSID at 18 months was seen in a weak positive correlation to the total amount of omega-6 fatty acids and the scores on the MDI subscale. The participants were similar in birth weight, GA and breastfeeding duration (van Goor, et al. 2011).

In a study supplementations of mothers were made with a total of 227 mothers and 230 newborn infants (Jensen, et al., 2005). In this study they started supplementation with DHA within five days after giving birth. The DHA-group consisted of 114 mothers and 115 infants, whereas the control group contained 113 women and 115 infants. The mothers in both groups received an identical capsule each day from start and then continually for four months. The characteristics of the infants were similar in both groups with a mean GA of 39 weeks and a mean birth weight of 3470 gram. Additionally all of the recruited mothers planned to breastfeed exclusively for at least four months. Jensen et al. (2005) analyzed the fatty acid content in breast milk and blood from both mothers and infants. Analyses of the mothers in the DHA-supplemented group showed that they had significantly more DHA in their breast milk. Analyses of the infant's plasma in the supplemented group showed that it contained more DHA on a significant level compared to the unsupplemented group. The results on the BSID showed that the PDI scores measured at 30 months of age where significantly higher in the infants to the DHA-supplemented mothers compaired to the other groups. This significance also remained after controlling for confoundings (Jensen, et al., 2005).

Feldman and Eidelman (2003) examined the relation between the amount of breast milk and the BSID at the age of six months. The 86 enrolled infants were born before a GA of 33 weeks (mean 30.45) and had a birth weight less than 1750 gram (mean 1298 gram). Each infant's feeding pattern were recorded in ml (cc) and then divided into three groups based on the percentage of breast milk received. The first group contained 31 infants which received less than 25 percent breast milk (minimal group), the second group (n=21) received between 25 and 75 percent breast milk (intermediate group) and the third group of 34 infants received more than 75 percent breast milk (substantial group). None of the infants were breastfed more than 5 percent of the total feedings. All infants were fed with nasogastric tube until they had a GA of 35 weeks and were then gradually bottle-fed. The outcome measures were mother-infant interaction using the mother-newborn coding system (Feldman, 1998) at 27 weeks GA, maternal depression using the Beck depression inventory (Beck, 1978), neurodevelopmental status using the Neonatal Behavioral Assessment Scale (Brazelton, 1973) at 37-38 weeks GA and BSID (Bayley, 1993) at six month corrected age.

Feldman and Eidelman (2003) found that the substantial group had significantly better scores on both the PDI and MDI subscales than the groups with less breast milk amounts. The intermediate and minimal group showed no significant difference in BSID scores. They also found that maternal depression were significantly negative related to scores on the MDI subscale, but not related to the PDI scores. However, the PDI scores were positively related to more affectionate touch. Affectionate touch was in itself seen to relate to better neurological development measured by the Neonatal Behavioral Assessment Scale (NBAS). The NBAS subscale Range of States was positively related to MDI scores.

Another study on 42 preterm born infants found no significant difference on the BSID scores between formula fed infants receiving DHA and AA and those not receiving any supplement (van Wezel-Meijler, et al., 2002). In this study they enrolled mothers who had choose not to breastfeed their infants, and had given birth to a infants with a GA of less than 34 weeks and a birth weight of less than 1750 gram. The infants were then randomized into supplemented or unsupplemented formula group. The group receiving supplemented formula showed significantly higher amounts of DHA, but not AA, compared to the unsupplemented group. However they found a significant trend with the unsupplemented infants showing higher PDI scores through the measured year.

Deoni et al. (2013) did an analysis on development using the Mullen scales of early learning (Mullen, 1992) and found that breastfed children showed better receptive language score when compared to formula fed children. However, even infants fed with formula complemented with breast milk showed better language scores.

Visual Evoked Potential and Electroencephalography

Electroencephalography (EEG) measures the electrical activity in the brain, which is recorded by electrodes placed on the scalp. EEG records different behavioral states, categorized by different amplitudes (mV).The EEG records both activation created by the stimulus and various unrelated brain activation (noise). To create a more interpretable result free from noise, the stimulus is repeated. Every time the stimulus has its onset the EEG starts from the beginning and from these recordings an average is calculated. The stimulus and following activation is repeating which make the more random background noise average out and a more clear result without artifacts will be present. This evoked response makes it possible to detect the activation that is specific to only the stimulus processing in the brain (Gazzaniga, Ivry, & Mangun, 2009).

Jing, Gilchrist, Badger, and Pivik (2010) did a study where they compared EEG spectral power in 120 healthy full term infants. The infants were divided into three feeding groups (breast fed, milk based formula fed and soy based formula fed) with a mean GA of 39.1 weeks and birth weight 3.5 kg. At the age of three months the infants weighted at least 5 kg. Each of the feeding groups consisted of 20 male and 20 female infants. The resting EEG activity was measured at the age of three, six, nine and twelve months, and included 124 electrode sites. The analysis of the readings was based on both individual electrodes and on eight groups of electrodes divided into anterior and posterior sites. The anterior sites included prefrontal, frontal, lateral frontal and central regions and the posterior sites included parietal, occipital, anterior temporal and posterior temporal regions. In the results 3066 artifact free segments were used.

The EEG spectral power differed significantly through age with an increase in anterior areas and decreased in posterior areas between three and twelve months. The highest power in anterior areas occurred at six months for formula fed infants while the highest power in breast fed infants were seen at nine months. At nine months, there was a significantly higher spectral power in the breastfed infants compared to the formula fed infants. All those result were seen in the 0.1-3 Hz band.

The mean spectral power in the 3-6 Hz band differed significantly over brain areas. The formula fed infants had higher spectral power than the breast fed infants in anterior areas reaching significance at six months and continued to be highest until twelve months. However, the breast fed infants showed highest anterior spectral power at three months.

In the 6-9 Hz band there was significantly higher increase in spectral power in the anterior regions compared to the posterior brain regions, seen between the ages of three to six months between the breast fed and the formula fed groups. However, the significant spectral power differences between age six and nine months were seen between the milk based formula fed and the soy based formula fed infants, in the left frontal areas (Jing, et al., 2010).

The 9-12 Hz band showed a mean power increase with age in all groups. In the breast fed group it was higher spectral power than in the soy based formula fed group, when looking at both anterior and posterior regions at nine months. In this band the spectral power were higher in breastfeed boys than breast fed girls, whereas the spectral power was greater in formula fed girls than formula fed boys (both milk and soy based formula). In formula fed boys the spectral power was lower than that of breast fed boys at three and nine months. For breast fed boys the maximum spectral power was observed at nine months, but in both formula fed groups of boys this peak occurred at twelve months. At three month the soy formula fed girls had significantly higher spectral power than both the milk based formula fed and the breastfed girls, with the last two showing similar spectral power. At nine months, milk based formula fed girls had significantly higher spectral power than the soy based formula fed girls. In girls at twelve months, the breast fed and milk based formula fed has similar spectral power (Jing, et al., 2010).

In the 12-30 Hz band, breast fed boys showed highest spectral power at all ages. At three months there was a significant difference between the breast fed and the soy based formula fed boys, at nine months there was significant differences between breast fed and both formula fed infant groups. At the age of twelve months the significance between the breast fed and the soy based formula fed boys remained. The pattern seen in girls in the 12-30 Hz band is slightly different. Among girls, the highest spectral power are seen in milk based formula fed infants at the ages of six, nine and twelve months. Whereas, the soy based formula fed infants had the highest spectral power at three months. At three months the breast fed girls has significantly lower spectral power than the soy based formula fed girls. At six months, the breast fed girls had significantly lower spectral power than the milk based formula fed girls, and a trend towards significance were seen between the milk based and the soy based formula fed girls. At the age of nine month, the milk based formula fed infants had significantly higher spectral power than those fed with soy based formula. Breastfed boys has higher mean spectral power than the breastfed girls in all areas regardless of hemisphere, but this significant difference did not occur in any of the formula fed groups (Jing, et al., 2010).

Visual evoked potential (VEP) measures the amplitude (millivolt) and latency (milliseconds between stimulus onset and recorded brain activation) from the averaged EEG of the neural activity, as a response to a stimulus. This stimulus is often created by light, including sweep, transient and flash stimulus. Jensen et al. (2005) studied 227 breastfeeding mothers and their 230 newborn children for four months starting within five days after birth. The mothers were divided into two groups, one receiving DHA as a supplement to their ordinary food and the other receiving an identical capsule of placebo. Each group took one capsule a day for four months. Both of these groups consisted of 115 infants, all of which were born term (mean 39 weeks) and had a normal birth weight (mean 3470 gram) (Jensen, et al., 2005).

Jensen et al. (2005) assessed visual function using the Teller acuity card procedure, and did VEP using both sweep VEP and transient VEP. Their result indicated that visual acuity and sweep VEP did not show a significant difference between the infants of supplemented and unsupplemented mothers, even though the DHA in the breast milk and infant plasma of the supplemented group was significantly higher. Though, the transient VEP showed a significant difference between the groups with lower amplitude in the supplemented group at the ages of four and eight months. VEP was also measured by van Wezel-Meijler, et al. (2002), whose results indicated no significant difference in sweep VEP between infants that were fed breast milk with supplemented DHA and those receiving unsupplemented breast milk via breastfeeding.

Morale et al. (2005) did a study where they found that those infants receiving breast milk or formula with DHA and AA had better Sweep VEP acuity than those fed formula without LCPUFAS, breastfed infants had also significantly better visual acuity than those receiving formula with LCPUFAS. The articly by Morale et al. (2005) is a summary of four studies made by the same researchers (Birch, et al., 2005; Birch, et al., 2002; Birch, Hoffman, Uauy, Birch, & Prestidge, 1998; Hoffman, et al., 2003). In these studies there were a total of 243 infants (measures have been carried out between the years of 1993 and 2000). All the infants were born with a GA of between 37 and 40 weeks and considered full term and normal weight at birth. These four studies contained a total of twelve different groups. The first and second group received unsupplemented formula only, the first group for 4 months and the second group for twelve months. The groups contained 20 and 44 infants respectively. The third and fourth groups received formula supplemented with DHA and AA for four and twelve months, these groups consisted of 38 infants in the four months trial and 42 infants in the twelve months trial. The fifth group consisted of 30 infants who received breast milk for six weeks and then was weaned to unsupplemented formula. The sixth group consisted of 28 infants who were initially breastfed and weaned to supplemented formula at the age of 6, 17 or 26 weeks of age, and received this formula until the age of 52 weeks. The seventh and eighth groups were initially breastfed and were weaned to unsupplemented formula at the age of 17 and 26 weeks respectively. The seventh group consisted of 16 infants and the eighth group consisted of 15 infants. The ninth and tenth groups were both breastfed for 17 and 26 weeks respectively and when weaned received supplemented formula until the age of 52 weeks. The group weaned at 17 weeks consisted of 23 infants and the group weaned at the age of 26 weeks contained 7 infants. The two additional groups were reference groups receiving breast milk, the first consisted of 19 infants that were breastfed for an average of 37 weeks whereas the second reference group consisted of 14 infants breastfed for at least 52 weeks. This resulted in a total of 100 infants who were breastfed and when weaned fed with supplemented formula until the age of 52 weeks. In addition to a total of 163 infants breastfed or formula fed with supplement for a maximum of 26 weeks. The sweep VEP acuity were measured at the age of 52 weeks, and analyses of the 94 exclusively breastfed infants showed a positive correlation between the duration of breastfeeding and the sweep VEP acuity.

Khedr, Farghaly, Amry, and Osman (2004) used flash VEP, Brainstem auditory evoked potential (BAEP; measures the hearing function) and somatosensory evoked potential (SSEP; measures neural firing of the peripheral nerves) to assess a relatively small group of 52 infants. All the 52 infants were born full term with a normal birth weight. The participant consisted of 30 breastfed infants and 22 formula fed infants. The SSEP showed that the formula fed infants had longer latency. Additionally, the BAEP showed a significantly prolongation of wave one and subsequent prolongation of wave two, three, four and five. Also the inter-peak latency of the cortical/erb's component was significantly prolonged, however the absolute latency of neither cortical nor erb's components was significantly different between the groups. The results of the flash VEP showed that the formula-fed infants had a significantly longer latency between stimulus onset and the peak of the P100 wave than the breastfed group, indicating a slower neuronal response.

On the other hand, van Wezel-Meijler, et al. (2002) examined the flash VEP in preterm born infants without finding any significance. A total of 42 infants born before a GA of 34 weeks weighing less than 1750 gram at birth, with mothers who chose not to breastfeed their infants were selected and randomly assigned into two groups. The first group was receiving unsupplemented formula, while the second group received formula supplemented with both DHA and AA (with twice as much AA as DHA). Every infant was fed with preterm formula until they reached a weight of 3000 gram, after which they received term formula. Both the preterm and term formula were supplemented in the supplemented formula group. In this study they did not find any significant differences between the groups in flash VEP at neither three nor at twelve months corrected age (van Wezel-Meijler, et al., 2002).

Wechsler intelligence scale

A study that gathered breastfeeding status in retrospect when the children were at the ages between 12 and 18 years was performed by Kafouri et al. (2013), and at the same time MRI and an intelligence test were performed. All the 571 adolescences were born full term with a mean of 39,2 weeks, a mean birth weight of 3434,6 g and had a similar parental income and education. The outcome measures of breastfeeding were divided into four groups; not breastfed, breastfed less that 4 weeks, breastfed between 4 and 16 weeks, and breastfed more than 16 weeks. The intelligence test was performed using Wechsler intelligence scale

(WISC) for children III (Wechsler, 1991), consisting of verbal IQ and performance IQ. MRI was assessed at follow up in adolescence. In the group of adolescences breastfeed more than 16 weeks as infants it was seen significantly higher scores on the subscale on performance IQ and on total IQ, but the pattern was not significant for verbal IQ (Kafouri, et al., 2013).

Breastfeeding and its relation to IQ outcomes have been examined by Isaacs et al. (2010). The study looked at 50 preterm born infants born before a GA of 30 weeks which then were followed up to the age of 15 years and 9 months. All infants were fed with own mothers milk and in addition a supplement of either term formula, nutrient enriched preterm formula or banked breast milk. All infants were considered normally developed when the first study finished at 7-8 years of age, when they did a cognitive and neurological assessment Wechsler IQ test and MRI-scan were assessed at follow up for this study (at adolescent). Wechsler IQ test includes three components: fullscale IQ, verbal IQ and performance IQ. MRI analyses included white matter, cortical gray matter and total brain volume. Isaacs et al. (2010) found that there were significant differences between boys and girls, with a significant correlation between percentage of breast milk and all IQ subscales in boys. Boys also showed a significant correlation between all subscales of IQ and white matter.

Brain activation and brain structure

Kafouri et al. (2013) did a study on adolescents where they asked mothers in retrospect for how long they breastfed their child, and at follow up they did MRI scans. All the participants were born full-term and with normal weight for GA and had similar parental income and education. The breastfeeding duration were divided into four different groups (not breastfed, breastfed less than 4 weeks, breastfed between 4 and 16 weeks, and breastfed more than 16 weeks). The MRI scans were compared in seven intelligence related areas including bilateral frontal eye field, left medial prefrontal cortex, bilateral ventro lateral prefrontal cortex, left mid dorsolateral frontal cortex, left and right superior and inferior parietal lobule, left angular gyrus and right lateral occipital cortex. All of these areas were selected from meta-analysis.

Kafouri et al. (2013) found that those breastfed more than 16 weeks had thicker cortex in superior and inferior parietal lobules. This significance was not seen in any other group of breastfeeding duration, even though an indication for thicker cortex was seen to be related to increasing amounts of breast milk. However, they did not find any correlation between cortical thickness and scores on the WISC in any breastfeeding group, or with all participants. This study also observed age and sex differences, with girls having thicker cortex than boys and a general decrease in cortical thickness with age (Kafouri, et al., 2013).

A study on preterm born infants found a relation between breast milk intake and white matter volume measured by MRI scans taken in adolescent (Isaacs, et al., 2010). MRI analyses included white matter, cortical gray matter and total brain volume. Boys showed significant correlation between all subscales of IQ and white matter volume. However, it was not found any significant correlations between gray matter and any of the measures. Boys and whole group showed a positive correlation between total brain volume and percentage of breast milk intake, while girls alone did not show this correlation. The only significant correlation seen in girls was between white matter volume and the percentage of breast milk intake, this correlation was also present if looked at the whole group or boys only (Isaacs, et al., 2010).

Deoni et al. (2013) did a study where they examined white matter and myelin water fraction using mcDESPOT (multicomponent Driven Equilibrium Single Pulse Observation of T1 and T2).The mcDESPOT is imaging the water content of the myelin so that the microstructure can be analyzed. This is due to the different relaxation time of the water that is trapped between lipid bilayers and the intra and extra-axonal water. This method has been seen to correlate with histological analyzes of the content of myelin. 133 toddlers between ten months and four years were divided into three groups. One group was exclusively breast fed, with 85 infants and a mean age of 775 days. The second group was exclusively formula fed and contained 38 infants with a mean age of 807 days. The last group received both formula and breast milk, in this group there were 51 infants with a mean age of 773 days. There was no significant difference in mean age, birth weight, maternal age, education or socioeconomic status (SES). The exclusively breast fed group had a mean breast feeding duration of 413 days whereas the mixed fed group had a mean breast feeding duration of 149 days (Deoni, et al., 2013). All children were assessed within seven days of the scanning using the Mullen scales of early learning (Mullen, 1992). These scales assess a broad range of behavioral development in domains of fine and gross motor-control, recepetive and expressive language and visual reception.

Compared to the formula and mixed fed groups, the breast fed infants showed increased rate of brain development including frontal brain, left temporal lobe, corpus callosum, internal capsule and corticospinal tract, cerebellum and left optic radiation. In contrast, formula and mixed fed infants had increased rate of brain development in areas such as right optic radiation, right occipital and right internal capsule (Deoni, et al., 2013). As myelin water fraction development was similar in all three groups for children younger than

800 days, an additional analysis on behavioral differences was performed in children older than 800 days (2.2 to 4 years). This examination showed that breast fed infants had significant higher myelin water fraction values, when compared to the formula fed infants in areas like right hemisphere inferior frontal white matter, right cortical spinal tract and premotor cortex. Breast fed children had significantly more myelin water fraction than the mixed fed group in left optic radiation adjacent to the angular gyrus, right inferior parietal lobe, bilateral premotor cortex and right prefrontal cortex. The breast feeding duration and myelin water fraction were significantly correlated in areas such as bilateral internal capsule, corticospinal tract, superior occipito-frontal fasciculus, left cerebellar white matter, left superior parietal lobe, right auditory cortex and right somatosensory cortex.

Analysis between children breast fed less than 12 month and longer than 15 month showed that there were significant differences in bilateral brocas area, parietal lobes, secondary somatosensory cortex, right auditory cortex, right frontal lobe, left optic radiation, premotor cortex and primary somatosensory cortex (Deoni, et al., 2013). These developmental differences gave an explanation of the differences seen in the Mullen scales of early learning, with breastfed children showing better receptive language score when compared to formula fed children. No significant difference in the Mullen scales of early learning was found between mixed fed and exclusively breast fed infants. Bilateral brocas area is associated with language, whereas primary and secondary somatosensory cortex and premotor cortex is associated with motor control (Deoni, et al., 2013).

Analyses of the frontal lobe in 21 infants who died of sudden infant death syndrome (SIDS) were made by Wang, McVeagh, Petocz and Brand-Miller (2003). They analyzed a piece of the frontal lobe (including cortex and underlying white matter) and compared the amount of ganglioside bound sialic acid, protein bound sialic acid and the amount of fatty acids in the ganglioside ceramide with the amount of breast milk. The samples were from nine formula fed infants and twelve breastfed infants. They found that more protein bound sialic acid was related to longer lives in the breast fed group, but there were no such significant difference in the formula fed group. The breast fed infants had more DHA and omega-3 fatty acids in frontal cortex gangleosides compared to the formula fed infants. Further, gangleoside bound sialic acid was significant correlated with gangleocide ceramide DHA and omega-3 fatty acids, but not for AA. The correlation was stronger for the breast fed infants and protein bound sialic acid was more strongly correlated with DHA than AA. The total amount of sialic acid was significantly correlated with DHA, AA and total omega-3 fatty acids (Wang, et al., 2003).

Parent-infant interaction

The second important factor that may contribute to cognitive and neurodevelopmental benefits is the interaction between parent and child. Cognitive ability measured by the BSID and its relation to mothers touch, responsivity and social support, alongside with measures of prosociality and behavioral problems of the child were examined with 682 mothers (Narvaez, et al., 2013). The participants were recruited because they fell in the risk group for child neglect. The participants consisted of 396 adolescent mothers with a mean age of 17.5 years, 169 mothers with an education limited to high school diploma and a mean age of 25.5 years and the remaining 117 mothers were in a comparison group with an educational level of at least 2 years collage education (mean age 27.9 years). The results by Narvaez et al. (2013) indicates that maternal responsivity was related to all the child outcome variables mentioned above, even when controlling for background variables. Breastfeeding initiation was assessed at six months after given birth and 531 mothers answered, these answers were then compared with the outcome measures. Of the 531 mothers, 221 had initiated breastfeed their children.

Breastfeeding initiation was related to better infant prosociality scores at 18 months and related to less behavioral problems at 24 months. These results were still significant when controlling for responsivity. However, the results did not remain significant at 36 months. The breastfeeding initiation was also positively correlated with all subscales of the BSID, but the effect was not further assessed in this study. Maternal touch at four months was related to less behavioral problems at 24 and 36 months, but only the significance at 36 month remained when controlling for maternal responsivity. Maternal touch at four month also predicted better outcomes on the BSID at 36 months, and this remained when controlling for maternal responsivity. Maternal social support predicted prosociality at 24 and 36 months, this relation remained significant when controlling for maternal responsivity. Also, less behavioral problems and better BSID scores were related to maternal social support at 24 months, but not at 36 months (Narvaez, et al., 2013).

Preterm born infants and their mothers were assessed when they interact (Feldman & Eidelman, 2003). They found that the substantial group (more than 75 percent of nutrition was breast milk) showed significant more affectionate touch than the other two groups, and there was also significant differences between the intermediate (between 25 and 75 percent of nutrition were breast milk) and minimal group (less than 25 percent of nutrition were breast milk), indicating a dose response. Though, maternal talk showed the opposite pattern, as the minimal group showed most maternal talk, and the substantial group had least maternal talk. The infants in the substantial group were more alert than both groups receiving less breast milk, but there were no significant difference between the intermediate and minimal groups. Also for the neurological development a dose response was found, where the substantial group showed the highest scores on the NBAS subscale motor maturity. Further, there was also significant difference between the intermediate and minimal groups. The NBAS subscale range of states showed a significant difference between the substantial group and the other two groups. The substantial group had significantly better scores on both MDI and PDI subscales, while the two lower groups did not show the same significance (Feldman & Eidelman, 2003).

The interaction between parent-child and its relation to breastfeeding or skin-to-skin contact were assessed by Bystrova et al. (2009). In this study they videotaped 124 mother-infant dyads which then were coded for characteristics of the interaction with the coding system Pcera (Clark, 1985) when the infants were one year old. The participants were recruited at birth and randomly assigned to one of four conditions. In the first group, skin-to-skin, the mother got to have their newborn on the chest for between 25 and 120 minutes directly after birth and the infants were then swaddled or dressed in clothes and transferred to the maternity ward for rooming-in, these infants also got to breastfeed on demand. In the second group, mothers arms, the infants were swaddled or dressed in clothes directly after birth and then placed on mothers chest for between 25 and 120 minutes before transferred to the maternity ward for rooming-in. These infants also got to breastfed on demand. In the third group, nursery, the infants were swaddled or dressed in clothes and then kept in a cot 25-120 minutes after birth and then got to stay in the cot when transferred to the maternity ward. The only contact the infants had with their mothers where when breastfeeding seven times a day. In the last group, reunion, the infants were swaddled or dressed in clothes direct after birth and then kept in a cot 25-120 minutes after birth. They were then transferred for rooming-in with the mother at the maternity ward (Bystrova, et al., 2007). Breastfeeding were assessed independent of group. They found that the mother-infant interaction at the age of one year were significantly better if the infant was placed skin-to-skin right after birth or had started suckling in the birthing room, compared to those who did not have a chance to suckle or were not assigned to the skin-to-skin group (Bystrova, et al., 2009).

Abdallah, Badr and Hawwari (2013) examined the effect of infant massage near birth and the effects on later cognitive development and pain perception measured at one year of age. In this study they examined 66 preterm infants at birth and 50 of these were examined at follow-up after one year. At birth they were neurologically assessed and at follow up they were assessed with BSID and Premature Infants Pain Profile (PIPP) scale (Stevens, Johnston, Petryshen, & Taddio, 1996). The results by ten minutes massage after feeding sessions as long as the infant were in neonatal intensive care unit (NICU) were better BSID scores than those not receiving massage. They also found that the infants receiving massage showed less pain (Abdallah, et al., 2013).

An fMRI study on the relation between maternal sensitivity and BOLD signal found that breastfeeding mothers showed greater activation in right superior frontal gyrus and the amygdala compared to those formula feeding their infants (Kim, et al., 2011). A total of 17 mothers were assessed in the fMRI at between two and four weeks postpartum and the maternal sensitivity were assessed between three and four months postpartum. Maternal sensitivity were assessed using a video recording and were coded using the coding interaction behavior manual (Feldman, 1998).

Examination of mothers has further been made by Aghdas, Talat and Sepideh (in press), who showed that mothers who got their infants skin-to-skin immediately after birth rated higher on breastfeeding self-efficacy at 28 days postpartum. They also initiated breastfeeding earlier than those who did not have their infant skin-to-skin (Aghdas, et al., in press). Because the ethical issues with separating infants from their mothers, a study with rats has found that separation has effects on the pups (Ohta, et al., 2013). In this study they separated the mothers and the pups for three hour twice a day, and found that the serotonin concentrations in the pups got significantly altered in dorsal raphe nuclei, in the median raphe nuclei, in the amygdala the hippocampus and in medial prefrontal cortex. This indicates that the serotonin (5HT) metabolism is altered if pups are separated from their mothers (Ohta, et al., 2013).

Kim et al. (2011) did fMRI analyses on 17 mothers to term born healthy infants between the second and fourth week postpartum. Nine of the mothers were breastfeeding their infants and eight were formula-feeding their infants. The stimuli was recorded crying from both own and other infants. They found increased maternal brain activation in areas such as right lateral globus pallidus/putamen, right putamen, left inferior frontal gyrus, right superior prefrontal gyrus. When controlling for education , bilateral insular, right fusiform gyrus, right precuneus, right cuneus, left superior and middle temporal gyrus showed greater BOLD signal to own infant cry if the mother were breastfeeding (Kim, et al., 2011).

Pearson, Lightman and Evans (2011) found a similar result when they measured attentional bias (time looking at pictures) towards distressed infants, were the breastfeeding mothers showed greater attentional bias. In this study they examined the attention bias in 51 women both before birth (GA between 34-39 weeks) and 9-33 weeks after birth. They compared the attentional bias index within each subject and then added feeding method and confounding variables to the analysis. The breastfeeding mothers showed an increase in response time with 37 ms, which resulted in greater attentional bias index (Pearson, et al., 2011).

Maternal depression. Maternal depression has been seen to reduce the duration of breastfeeding (Nishioka, et al., 2011; Feldman & Eidelman, 2003), to be related to lower maternal sensitivity, and further to lower scores on the BSID scales (Feldman & Eidelman, 2003). The importance of the mothers health has therefore a vital role for the development of the infants. Feldman and Eidelman (2003) found that mothers to preterm infants receiving substantial amount of breast milk had lower maternal depressive symptoms. They also linked higher depressive scores to less maternal sensitivity, lower MDI scores in the infant, longer until the first feeding of breast milk to the infant and also less amount of received breast milk (Feldman & Eidelman, 2003).

Nishioka et al. (2011) further examined the effect of breastfeeding in 568 Japanese mothers. They found a link between higher maternal depressive symptoms and formula feeding, and also better parent-infant bonding in the breastfeeding mothers as measured at one and five months postpartum (Nishioka, et al., 2011). Field et al. (2010) found the same effect with 28 depressed mothers and 28 non depressed mothers, were the depressed mothers who breastfed had better interaction with their infants than the depressed mothers who were not breastfeeding. In both the depressed and non-depressed group there were equal numbers breastfeeding dyads and bottle-fed dyads. In Iceland it was found that lower depressive score were related to exclusive breastfeeding (Thome, Alder, & Ramel, 2006).

One theory to why maternal depression occurs is the presence of retinoids that have accumulated during pregnancy (Mawson & Wang, 2013). In the colostrum it is a high dose of retinoids that are ejected during breastfeeding. If these retinoids are not ejected, they may cause poisoning in the maternal body which then causes the depressive symptoms. The high dose of these retinoid's then decrease over time as do the depressive symptoms. This may be a reason why breastfeeding are important for not developing maternal depression after birth.

Discussion

Breastfeeding and human milk has been seen to relate to several benefits for the developing child. Breastfed children has better scores on BSID measured at an age of 36 months, than formula fed infants (Narvaez, et al., 2013), as did preterm born infants at corrected age of 6 months receiving substantial amount of mothers breast milk (Feldman & Eidelman, 2003). This indicates that the breast milk given by breastfeeding or by nasogastric tube had an effect on the cognitive development in early life, even when demographics are controlled for and similar between the groups. This may suggest that the breast milk itself is the key factor for the developmental benefits found in these studies.

Morale et al. (2005) found that those supplemented with DHA in formula had a similar development to those only breastfed and therefore studies looking at the supplementation with DHA are of interest. van Goor et al. (2011) found that those infants with more omega-6 fatty acids in the umbilical cord had better MDI scores at the age of 18 months (van Goor, et al., 2011). In addition to this finding, the breast milk of DHA-supplemented mothers contained more DHA and the infants had higher amount of DHA in their plasma. The infants had better PDI scores at the age of 30 months (Jensen, et al., 2005), whereas Wezel-Meijler (2002) did not find any significances between DHA-supplemented infants and BSID scores.

These benefits may be linked to findings by Deoni et al. (2013), where the Mullen scales of early learning scores showed that breastfed children had better receptive and expressive language scores, better gross and fine motor scores and better visual reception, which the researchers linked to more developed myelination in bilateral brocas area, which is associated with language. They also found better myelin structure in primary and secondary somatosensory cortex and premotor cortex which is associated with motor control (Deoni, et al., 2013). The improved BSID scores seen in breastfed infants or infants fed with human milk may then be due to a more mature brain development. No difference between myelination was measured by MRI or seen in the visual evoked potential between DHA supplemented and unsupplemented groups, which may suggest that there is no importance of the DHA supplementation in later brain development, but rather in early infancy.

IQ is a measure of cognitive ability, and breastfeeding is related to better performance on IQ measures. As found in the article by Kafouri et al. (2013), the exclusively breastfed group of adolescent had thicker cortex and better scores on the WISC. They discuss that areas such as the parietal cortex are important for visuospatial skills and perceptual organizations which is measured by performance IQ, indicating that the thicker cortex and higher IQ scores are correlated. In their study they found that the superior and inferior parietal lobules were thicker in the exclusively breastfed group, but did not find any significant correlation between breastfeeding duration and cortical thickness per se, which may have been due to correcting for all seven areas. Additionally they found that exclusively breastfed infants showed better scores on the performance and full IQ scale, but not for verbal IQ (Kafouri, et al., 2013).

The results by Kafouri et al. (2013) were previously found by Isaacs et al. (2010), also examining adolescents and the IQ performance based on the feeding pattern in infancy. Additionally Isaacs et al. (2010) found a gender difference, with boys having a correlation between the amount of breast milk and all IQ subscales, which were not as evident in girls. As found in Kaufori et al. (2013) there were no correlation between breast milk and cortical thickness but separate correlations with both IQ and cortical thickness which may suggest an independent development or a lack of a proven significant correlation. A gender difference has been found in other studies, suggesting different development in boys and girls. A difference in brain size and volume has been reported by Ruigrok et al. (2014) in their meta-analyze, with males having greater overall volume, which is opposite to findings by Kaufori et al. (2013). Ruigrok et al. (2014) argue that the observed gender differences may be due to gene expression, hormones or other gender specific aspects, and linked the structural differences to neurological disorders such as depression and autism. However Kaufori et al. (2013) found that breastfed infants had thicker cortex and higher IQ scores. This is suggesting that the breast milk may have a beneficial effect on cortical thickness and later on brain functions. Ruigrok et al. (2014) did only analyze normal brain development and not breastfeeding which may be why they did not found the same pattern as Kaufori et al. (2013) and Isaacs et al. (2010) did.

Studies of VEP have found that both breast feeding and supplementation give an advantage in visual acuity measured by different VEP measures. The flash VEP has been seen to yield results that indicate a developmental benefit for breastfeeding infants. Khedr, et al. (2004) found a longer P100 latency which may suggest delayed brain messaging in formula fed infants. This can be linked to an improved structural foundation, which may help in later functional performance. The prolonged evoked potential peak latency may indicate a slowed neural conduction, which may be due to incomplete myelination of the cortex between the retina and the occipital cortex.

As suggested by Guesnet and Alessandri (2011) the LCPUFAS in at least the first six months of life are crucial for proper development of the cortex and should be a supplement both during pregnancy, lactation and added to formula in order to support the development of the cortex and increase visual acuity. As the breast milk contain much LCPUFAS it may be the best choice for infant feeding. Differences is found between infants supplemented and not supplemented with DHA in the transient VEP and the sweep VEP, with DHA supplemented infants showing better acuity (Jensen, et al., 2005; Morale, et al., 2005). The infants received DHA supplement via formula or milk also showed increased DHA levels in plasma, but Jensen (2005) were unable to link the increased levels of DHA to the lower amplitude in the transient VEP. This may be due to lack of control for confounding variables such as the mothers DHA levels during pregnancy and the amounts of meals containing fish. Morale et al. (2005), however, found that the breastfed infants showed the best visual acuity compared to both the DHA supplemented and unsupplemented groups. The difference in development between DHA supplemented and unsupplemented infants may be a key to nutritional aspects of the maturing visual system. Mortensen, Michaelsen, Sanders and Reinisch (2002) suggest that breastfeeding beyond six months is related to higher adult intelligence, but may have confounding factors because of the long span between infancy and intelligence measure in adulthood.

However, van Wezel-Meijler et al. (2002) did not found any significant difference when comparing DHA supplemented and unsupplemented formula. But this study contained only 42 infants and may lack power to reach significance, even though they have ruled out potential confounding variables.

Other benefits on the developing cortex were found in SSEP and BAEP suggesting a benefit of breastfeeding. The BAEP is supposed to measure the hearing ability in infants and children were the first wave of the BAEP is representing auditory nerve action potential. The breastfed infants showed a prolongation of BAEP waves one to five in the formula fed group (Khedr, et al., 2004). The prolongation of this wave may be due to lower levels of myelination of the auditory nerve in the formula fed infants. This may indicate a better hearing in breastfed infants, and a more developed myelination in the auditory nerve. Also the SSEP are benefited from breastfeeding, with the breastfed infants showing a shorter time between stimulus onset and inter-peak latency. No differences in the absolute wave latency of the erb´s or cortical components were seen, but there were a difference in the cortical/erb´s inter-peak latency between formula and breastfed infants. This results may reflect that the peripheral nerve is almost completely myelinated at birth and the feeding method does not matter. However, the significant prolongation of the inter-peak latency of the cortical/erb´s components suggest that the nervous system reaches near adult values of central and peripheral conduction earlier in breastfed infants than formula fed ones.

Breastfeeding has been associated with greater development in later developing regions associated with social-emotional functions and executive functions, including the frontal and temporal white matter, internal capsule, corticospinal tract and parts of the fasciculus (Deoni, et al., 2013). Also areas such as primary and secondary somatosensory cortex, the brocas area and right auditory cortex, left optic radiation and the premotor cortex were more developed in breastfed infants (Deoni, et al., 2013). These areas can be linked to better hearing as is suggested by the results on BAEP (Khedr, et al., 2004), better motor control which is suggested by the BSID scores on PDI (Feldman & Eidelman, 2003) and better visual function as is suggested by more mature development on VEP (Khedr, et al., 2004). These findings may support the hypothesis that LCPUFAS have a key role in the development of the brain, which is also suggested by Isaacs et al. (2010) who found a correlation between breast milk intake and both IQ-scores and total brain volume.

The different spectral power between groups of feeding is suggesting a benefit in myelination. The increased activity in the 0.1-9 Hz band seen in formula fed infants may reflect greater neuronal circuit development, which also would increase the myelination of the activated axons. The activation of neurons and the difference in the time when a peak in spectral power is reached may reflect a benefit for breastfed infants were the number of oligodendrocytes may be reduced in later development for formula fed infants. As such the breast milk may provide an aspect of optimal CNS maturation, the patterns observed in this study (Jing, et al., 2010) may also be a process that helps this maturation.

Wang et al. (2003) found differences in brain sialic acid between formula fed and breastfed infants. This add to the suggested conclusion that breast milk provide a structural benefit, which in the longer run provides better brain development and further cognition. The cognitive benefits may be due to the correlation between the amount of DHA and ganglioside sialic acid content. The percentage of DHA in the total amount of LCPUFAS may indicate that sialic acid and LCPUFAS are important building blocks for neural tissue.

The gender differences observed in EEG spectral power (Jing, et al., 2010) may involve different underlying structural aspects. A gender difference is also suggested by Kafouri et al. (2013) with MRI, suggesting different developmental needs for girls and boys. Kafouri et al. (2013) found thicker cortex in girls than boys whereas Jing et al. (2010) found greater spectral power in breastfed boys compared to breastfed girls. Additionally, Isaacs et al. (2010) found greater total brain volume and white matter in breastfed boys that in formula fed boys, but this was not seen in girls. Greater brain volume is also seen in a meta-analyze by Ruigrok et al. (2014). It was also seen that in preterm boys the percentage of exclusive breast milk is accounted for about 25 percent of the variance in boys and only 5 percent in girls

(Isaacs, et al., 2010). These results further add to the suggested difference in gender development.

Parent-infant interaction

The effect of parenting on child outcomes may be important, as it increases the child's adjustment and the cognitive ability measured by BSID. However, the effects on cognitive ability were limited to two years of age suggesting that parenting or feeding does not affect cognitive development more than the first two years of life. Also social support had a protective effect on child behavioral outcomes, suggesting the importance of social support in parenting. Breast milk is one important aspect of more effective parenting, with the breastfeeding mothers showing better interaction with the child. This may be important to note, thought breastfeeding may be the key in both nutritional and parenting aspects of development. It is hard to separate the effects noted by only parenting factors, only nutrition and what breastfeeding per se is contributing.

As Bystrova et al. (2009) found, the interaction between mother and child is better if the infants were skin-to-skin or breastfed within the first two hour after birth. This adds to the theory that it may not be the breastfeeding itself but rather the skin-to-skin contact or hormonal changes due to skin contact that contribute to maternal sensitivity and thus increase the behavioral outcomes of the child. This is also supported by Abdallah et al. (2013) showing a relation between massage (skin-contact), decreased pain perception and better BSID scores.

Brain imaging studies of maternal sensitivity, attentional bias and animal studies further adds to the importance of parent infant interaction benefits in breastfeeding dyads. The greater activation seen in amygdala, putamen, globus pallidus and superior frontal gyrus has been linked to caregiving behavior and empathy in both human and animals (for a review see Swain, et al., 2007), which may explain the higher maternal sensitivity. This may be due to the temperament of the mothers who chose to breastfed, whereas the temperament of mothers has been seen to be different in interaction. This were, however, not supported by Pearson et al. (2011) who found that the greater attentional bias index seen in breastfeeding mothers were not present before birth. This is suggesting that it is the act of breastfeeding that is important for later maternal sensitivity, and may be due to hormonal changes in the mother.

This is also supported by Swain et al. (2007) who found greater BOLD signal in mothers who delivered vaginally than those who delivered by cesarean section, when they listened to own infant's cry. This greater activation to infant cry was also found by Kim et al.

(2011) who linked this to greater maternal responsivity. The link between oxytocin and childbirth has been done in a review by Kendrick (2000). Oxytocin, the hormone expressed in milk ejection (Kent, 2007), may be one explanation to the increased maternal sensitivity due to its involvement in bonding (Feldman, Weller, Zagoory-Sharon, & Levine, 2007). Skin-to-skin contact was also seen to increase the breastfeeding self-efficacy (Aghdas, et al., in press), which also may be due to the hormonal changes in parent-infant interaction. It has been seen that the oxytocin change the cortisol release in both fathers and infants, dependent of interaction quality (Weisman, et al., 2013).

Serotonin is another hormone involved in pregnancy which is also important for the development of the infant’s brain. This is due to the changed serotonin metabolism, as has been seen in animal trials where pups has been separated from their mothers (Ohta, et al., 2013). The importance of touch has been seen in humans, mostly if deprived of touch by depressed mothers or institutional care (see review by Field, 2010). The effects of touch may be due to oxytocin release, which has been seen to have elevated levels after touch (Field , 2010).

Although the benefits in breastfed infants are seen, the underlying mechanisms are not fully understood. More research on the neurodevelopmental aspects of feeding method needs to be done and so is more research examining the underlying mechanisms of nutritional uptake. That there is a clear advantage for the infants fed with DHA enriched supplementation has been seen, but not why and how the DHA works in the brain. Also the amount of oligosaccharides is higher in breast milk than in formula which may be an additional aspect of the advantage seen in breastfed or infants fed with breast milk. Further, the DHA in formula is only the precursors to DHA and must be synthesized by the infants, whereas the DHA in human milk does not need to be synthesized. Another aspect is that the breast milk contains cholesterol which has been seen to improve myelination (Deoni, et al., 2013), whereas the formula lack cholesterol in sufficient amounts. The underlying mechanisms in brain development are not fully understood and more research need to examine why there is gender differences and why the brain develops as it does.

Maternal depression

The importance of breastfeeding on maternal sensitivity is not clear but it is suggested that breastfeeding may prevent the presence of maternal depression. Neighter the causality is clear as it may be those in less risk for maternal depression that start to breastfeed and not the other way around. It is however found that the ejection of breast milk is related to less maternal depression (Feldman & Eidelman, 2003) as due to the fact that the infants studied did not breastfeed but only received the milk via nasogastric tube. The mental ability are linked to the maternal depressive scores as well (Feldman & Eidelman, 2003), which may be due to the maternal sensitivity as has been seen by Narvaez et al. (2013).

The presence of maternal depression can also be due to the characteristics of the mother, one such example is that pre-birth and post-birth measures of depression were more related than the feeding group (Skrundz, Bolten, Nast, Hellhammer, & Meinlschmidt, 2011). They examined 73 women and found a relation between the plasma oxytocin and maternal depression. The higher concentration of the plasma oxytocin was related to the non-depressed group (Skrundz, et al., 2011). This suggests that the oxytocin may have an important part in the development of postpartum depression and are adding to the benefits from higher concentrations of oxytocin on maternal sensitivity. The intake of fruit and vegetables were seen to be related to longer breastfeeding duration. This is important because more optimistic mother may be more resilient to breastfed, and therefore encounter less subjective challenges while breastfed.

Many factors may contribute to the initiation and the duration of breastfeeding. The importance of breastfeeding has been established by WHO by the promotion of BFHI (WHO Baby-friendly Hospital Initiative, n.d.), and it has increased the number of breastfeeding mothers since the BFHI start 1991. The research on this topic has found several factors that may be important such as the midwife’s attitude and the social support of the mother. The promotion of breastfeeding and positive attitudes from the public are therefore important factors to improve. Breastfeeding may be the best feeding for the infant, however, the result yield from studying breastfeeding needs to be taken with some caution due to the complex relationship between nutrition and interaction between the parent and child. One cannot separate the effects from one variable from the other and therefore not make any definitive conclusions. Also the included studies have its limitations. Deoni et al. (2013) discusses that the mcDESPOT may not be a proper measure of myelin water fraction, which further studies need to tell. The findings from Wang et al. (2003) should be taken with caution as they are from infants who died of sudden infant death and may not be generalized to other infants. The results of most studies need to be taken with caution due to its narrow characteristics of the participants.

Conclusion

The cognitive and neurodevelopmental aspects that has been reviewed in this essay concludes that there cannot be any definitive conclusions of whether breastfeeding increase brain development or not, this because very few articles has been made on the topic assessing brain images. Even though most of the articles on the correlation between breastfeeding and later development suggest that breastfeeding has an beneficial effect, it is hard to tell if it is nursing, nutrition or the closeness between parent and child that gives this advantages. It may be all of these in synchrony or maybe there is a factor that is not yet found that have the most importance for optimal development. The conclusion of this essay is therefore that we shall promote breastfeeding due to the fact that it has benefits even though we do not know exactly what they may be. We do not know what mechanism that underlies these benefits either. This conclusion raises some further questions that should be addressed in research to come. What are the mechanisms of breastfeeding? And what in the breastfeeding is important for the infants and its development?

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