Original Article

Neuro-developmental outcome and brain-derived neurotrophic factor level in relation to feeding practice in early infancy

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Abstract

This study was designed to assess brain-derived neurotrophic factor (BDNF) as a possible candidate for enhanced cognition in breastfed infants. The study was conducted on 42 infants, 4–6 months old, who were classified according to their feeding pattern into breastfed group, formula-fed group and mixed-feeding group. Each infant was subjected to history taking, clinical examination, estimation of the level of BDNF by Enzyme-Linked Immunosorbent Assay (ELISA) technique and assessment by Bayley scale of infant development-second edition (BSID-II). The current study revealed that breastfed group had higher BSID-II scores followed by mixed-fed group then formula-fed one, yet these results reached statistical significance only in total behaviour rating scale (TBRS) and Motor Quality Percentile rank values. Additionally, breastfed infants had significantly higher values of BDNF when compared to those receiving formula milk. Negative correlations between BDNF and both weight for age and weight for length scores were detected. Furthermore, significant positive correlation was detected between BDNF and TBRS. Regression analysis studies revealed that breastfeeding is the most determinant factor for BDNF, TBRS and Motor Quality Percentile rank values. Serum BDNF levels are significantly higher in breastfed infants and shows positive correlations with the results of BSID-II. Given that simultaneous increase in brain BDNF occurs due to onsite production, transport from the periphery or both, it is prudent to hypothesize that BDNF could be one of the factors responsible for the enhanced cognition detected in breastfed infants.

Keywords: brain-derived neurotrophic factor, brain function, breastfeeding, cognition, development, formula.

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Introduction

Infants must be provided with food containing all the necessary nutrients for proper growth and development (Gong *et al*. 2008). The human brain growth spurt begins during the third trimester of pregnancy and continues throughout the first 2 years of life, coinciding with the lactation period (Viberg *et al*. 2008).

The World Health Organization (WHO) and the American Dietetic Association suggest that infants should be exclusively breastfed until 6 months, which is expected to be the ideal feeding mode for infants (Gong *et al*. 2008). Breastfeeding, as numerous investigators have reported, might impart many advantages for the development of infants, including reduced risk of necrotizing enterocolitis, gastroenteritis, respiratory infection and immunologically based diseases, in addition to improved cognitive development (Schack-Nielsen & Michaelsen 2007).

Brain-derived neurotrophic factor (BDNF), a vital trophic protein for neuronal survival and differentiation in the developing nervous system, has been implicated in synaptic plasticity. Additionally, BDNF is involved in different aspects of learning and memory processing, in particular, in memory persistence and storage (Bekinschtein *et al.* 2008a).

There is experimental evidence that BDNF can cross the blood–brain barrier (Poduslo & Curran 1996; Pan *et al.* 1998). According to these results, BDNF changes within the central nervous system and cerebrospinal fluid might be paralleled by changes of BDNF serum levels. Additionally, Song *et al.* (2008) suggested that BDNF is anterogradely transported by axons; thus, peripherally derived and/or applied BDNF may act on the regeneration of central axons of ascending sensory neurons. Hypothetically, this may also apply centrally as well as peripherally.

To explore one of the possible candidates behind the enhanced cognition in breastfed infants and in line with the previous hypotheses, we designed the current study to measure the serum BDNF together with neuro-developmental assessment in relation to pattern of feeding in the first 6 months of life.

Subjects and methods

Subjects

The present cross-sectional study was conducted on 42 clinically healthy infants whose ages ranged between 4 and 6 months, recruited from the outpatient clinic, Children's Hospital, Faculty of Medicine, Ain Shams University in the period from April 2008 to December 2008. They were 28 males and 14 females recruited at random among those presenting for dietetic advice, vaccination or circumcision (in males). Preterm infants and those with any neurological disorder or those with history of perinatal prob-

lems such as pre-eclampsia, obstructed labour or cyanosis at birth were excluded. We started with a randomly chosen number; sampling started with number 4 in the list of patients attending the clinic and fulfilling the inclusion criteria then every 5th subsequent child and this was done for the assigned period. The enrolled infants were divided into three groups according to their feeding patterns. The first group comprised 14 breastfed infants; the second group comprised 14 artificially fed infants, while the third group comprised 14 infants on mixed feeding.

Methodology

After the approval of the study procedures by the Children's Hospital Board, an informed consent was obtained from the parents or care givers. All infants were then subjected to full history taking laying stress on the perinatal history, developmental history and socio-economic standard scoring according to Park & Park (1979). Dietetic history was taken especially type of feeding, age of weaning and type of weaning foods.

All infants underwent complete clinical examination with special emphasis on the anthropometric measurements and neurological examination. The weight was measured using an electronic scale with subject wearing light clothes and approximated to the nearest 0.5 kg. The length was measured on a wooden scale with subject barefooted and approximated to the nearest 0.5 cm. The skull circumference was measured with a measuring tape and approximated to the nearest 0.5 cm. The weight, length for age and weight for length Z-scores were calculated based on the growth charts supplied by the WHO (2006). The mid-arm circumference was measured at the mid-arm point, midway between the tip of acromial process and the epicondyle of the humerus and approximated to the nearest 0.5 cm.

Key messages

- Brain derived neurotrophic factor (BDNF) levels were significantly higher in breastfed infants compared to those artificially fed.
- Serum BDNF levels were positively correlated with Bayley Scale of Infant Development scores (BSID-II).
- BDNF could be one of the factors responsible for the enhanced cognition detected in breastfed infants.

Two millilitres of venous blood were withdrawn from each infant under complete aseptic technique in one test tube and left to clot at room temperature for 30 min then centrifuged at 3000 rpm for 15 min. The separated serum was stored at –20°C until time of assay of BDNF by Enzyme-Linked Immunosorbent Assay (ELISA) technique using the Quantikine Human BDNF Immunoassay supplied by R&D Systems, Inc. Minneapolis, USA.

Neurodevelopment assessment was carried out using Bayley scale of infant development-second edition (BSID-II) (Bayley 1993). The examiners were blinded to the subject groups and their BDNF levels.

Statistical analysis

The data were coded, entered and processed on an IBM-PC compatible computer using SPSS 15.0 (SPSS Inc, Chicago, IL, USA). Data were tested for skewness and kurtosis to assess normality using Kolmogorov–Smirnov test.

Data are presented as median and range for continuous variables and as count and percentage for categorical variables. Groups of patients were compared using Fisher's exact test for categorized variables and using analysis of variance (ANOVA) test for continuous variables. To control for multiple comparisons, a Bonferroni adjustment was used. Pearson correlation coefficient was used to evaluate associations for continuous variables. Multiple regression was used to adjust the difference between variables for significant factors; results are presented as regression coefficients and 95% confidence intervals. All *P*-values represented were two-sided, and statistical significance was declared at $P < 0.05$.

Results

There were no statistical differences in age (F = 0.92 and $P > 0.05$), sex [$\chi^2 = 1.50$ and $P > 0.05$ (Table 1)] or socioeconomic standard ($\chi^2 = 0.57$ and $P > 0.05$) between the breastfed, artificially fed and mixed-feeding groups.

There were no statistical differences in the anthropometric measurements among the three studied groups ($P > 0.05$, respectively) as shown in Table 2.

Table 1. Comparison between the three groups as regards the sex distribution

Sex	Breastfed group		Formula-fed group		Mixed-fed group		χ^2	P
	N	%	N	%	N	%		
Male	11	78.6%	9	64.3%	8	57.1%	1.50	0.47
Female	3	21.4%	5	35.7%	6	42.9%		

Table 2. Comparison between the three studied groups as regards Anthropometric measurements:

	Breastfed group		Formula-fed group		Mixed-fed group		F^*	P
	Mean	SD	Mean	SD	Mean	SD		
Weight at birth	3.24	0.25	3.45	0.31	3.21	0.28	3.05	0.06
Weight (Kg)	7.51	0.64	7.88	0.85	7.92	0.67	1.33	0.28
Weight for age (Z-score)	0.20	0.58	0.57	0.92	0.57	0.61	1.21	0.31
Length (cm)	64.29	1.94	65.69	1.32	65.37	2.21	2.20	0.12
Length for age (Z-score)	–0.47	0.48	0.02	0.46	–0.31	0.65	3.08	0.06
Weight for length (Z-score)	0.69	0.73	0.85	1.19	1.06	0.75	0.58	0.56
Skull circumference (cm)	43.86	1.41	43.64	1.28	43.60	1.07	0.17	0.85
Mid arm circumference(cm)	14.27	1.16	13.85	0.70	14.37	0.85	1.26	0.30

*Analysis of variance test. SD, standard deviation.

Table 3. Comparison between the three groups as regards mean values of BSID-II

	Breastfed group		Formula-fed group		Mixed-fed group		$F*$	P
	Mean	SD	Mean	SD	Mean	SD		
Mental developmental index	103.29	12.24	98.71	11.08	100.36	6.80	0.71	0.50
Psychomotor developmental index	108.64	13.19	105.21	10.08	106.07	10.90	0.34	0.71
Total behaviour rating scale	34.86	9.96	24.93	7.42	29.07	7.69	4.90	0.01
Motor quality percentile rank	48.07	10.22	37.14	11.82	45.07	11.63	3.53	0.04
Attention/arousal percentile rank	46.38	16.95	30.33	14.45	35.00	17.15	1.82	0.19
Orientation engagement percentile rank	36.83	16.58	31.50	9.93	32.50	15.46	0.27	0.77
Emotion regulation percentile rank	43.33	14.72	36.13	16.52	36.13	16.52	0.44	0.65

*Analysis of variance test. SD, standard deviation.

Table 4. Multiple comparisons between the three studied groups regarding total behaviour rating scale and motor quality percentile rank tests

Dependent variable			Mean* difference	P
Total behaviour rating scale	Breastfed group	Formula-fed group	9.93	0.01
		Mixed-fed group	5.79	0.23
	Formula-fed group	Mixed-fed group	−4.14	0.60
Motor quality percentile rank	Breastfed group	Formula-fed group	10.93	0.04
		Mixed-fed group	3.00	1.00
	Formula-fed group	Mixed-fed group	−7.93	0.21

*Bonferroni.

Table 3 shows a trend of higher Bayley scale scores in the breastfed group than in the mixed-fed group, which was also higher than those for the formula-fed group, yet these results reach statistical significance only in total behaviour rating scale (TBRS) and motor quality percentile rank values. Furthermore, in Table 4, the multiple comparisons show a significant difference only between breastfed and formula-fed groups regarding TBRS and motor quality percentile rank.

On applying the ANOVA test, the current study revealed statistical differences in the serum BDNF among the three studied groups (Fig. 1). Table 5 shows that it is the breastfed group that demonstrates significantly higher BDNF level compared to the formula-fed group.

In a trial to correlate the BDNF levels to the anthropometric measurements; significant negative correlations were detected between both weight-for-age Z-score (WAZ) and weight-for-length Z-score (WLZ) and BDNF (Figs 2,3, respectively). Addition-
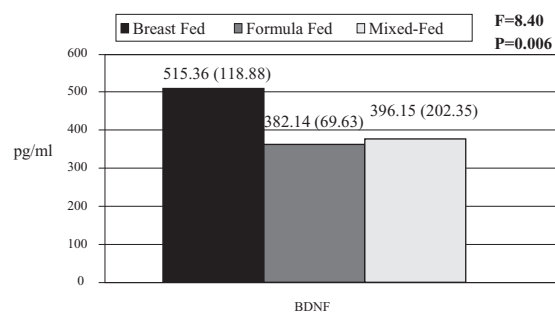
Fig. 1. Mean values of brain-derived neurotrophic factor (BDNF) serum levels in the three studied groups. N.B. Values are presented as mean (standard deviation).

ally, Fig. 4 demonstrates a significant positive correlation between TBRS and BDNF.

Multiple regression analysis studies show that after adjustment, there is a closely significant increase in mean adjusted BNDF in breastfed children compared to the two other groups. Additionally, there was a significant increase in mean adjusted TBRS and

Table 5. Multiple comparisons of BDNF levels between the three studied groups

		Mean* difference	P
Breastfed group	Formula-fed group	133.21	0.04
	Mixed-fed group	119.20	0.09
Formula-fed group	Mixed-fed group	−14.01	1.00

*Bonferroni. BDNF, brain-derived neurotrophic factor.

motor quality percentile rank in breastfed children compared to the two other groups (Tables 6–8).

Discussion

The present study revealed that breastfed group had higher Bayley Scale scores followed by the mixed-fed group then the formula-fed one, yet these results reached statistical significance only in TBRS and motor quality percentile rank values.

These results are concurrent with the meta-analysis done by Anderson *et al.* (1999) which indicated that, after adjustment for appropriate key cofactors, breastfeeding was associated with significantly higher scores for cognitive development than was formula feeding. Moreover, Angelsen *et al.* (2001) found that the correlation between breastfeeding and cognitive ability increases with longer duration of breastfeeding. It was found that there is a mean difference of 2.4 points on cognitive test at the age of 6 months between children breastfed for less than 5 months, compared to children breastfed for at least 5 months.

In addition, Rao *et al.* (2002) found that infants who were exclusively breastfed >12 weeks had mean performance IQ 5 points higher at 5 years of age than children exclusively breastfed <12 weeks. Their study predicted that exclusively breastfed for 24 weeks would give small for gestational age children an advantage of 11 IQ points over those breastfed for ≤12 weeks.

Also, Mortensen *et al.* (2002) studied a cohort of 9125 individuals in Denmark born between 1959 and 1961, whose early feeding was recorded at 12 months of age. After adjusting for numerous socio-demographic and birth characteristics, the authors

suggested that there is a dose–response of duration of breastfeeding up to 9 months of age and higher adult intelligence. They concluded that human breast milk enhances brain development and improves cognitive development in ways that formula cannot.

Additionally, Morley *et al.* (2004) measured Mental Development Index (MDI) scores in a cohort of infants and found that at 18 months, breastfed infants had MDI scores 11.7 points higher. After adjusting for two sets of potential confounding variables, the association was ~8 points higher among breastfed infants. However, the authors did not find a clear dose–response relation with either partial or exclusive breastfeeding. Furthermore, data from a non-verbal intelligence test at 8.5 years of age in the Cebu Longitudinal Health and Nutrition survey in the Philippines indicated that there were 1.6- and 9.8-point advantages in cognitive abilities for breastfeeding compared with no breastfeeding in normal birthweight and low-birthweight infants, respectively (Daniels & Adair 2005).

From another perspective, Daniels & Adair (2005) stated that nearly all studies done previously have been conducted in developed countries in which women who breastfeed also exhibit other positive health-related characteristics that may facilitate cognitive development (e.g. better socio-economic standard, education, intelligence, responsiveness or home environment). The authors added that disentangling the positive effects of these other characteristics from those of breastfeeding has been a tremendous challenge. However, the current study, although performed in a developing country, still detected better cognitive values in breastfed infants.

In the present study, infants who received human milk showed statistically significant higher serum BDNF values when compared to those who received formula milk.

No previous studies have searched for the presence of BDNF in breast milk or breastfed infants. Breast milk contains many growth factors and although BDNF was not recovered from the breast milk, other growth factors were (Kverka *et al.* 2007 and Woo *et al.* 2009). Additionally, breastfeeding process itself may trigger the secretion of BDNF because it is the best pleasurable peaceful situation for the infant and the
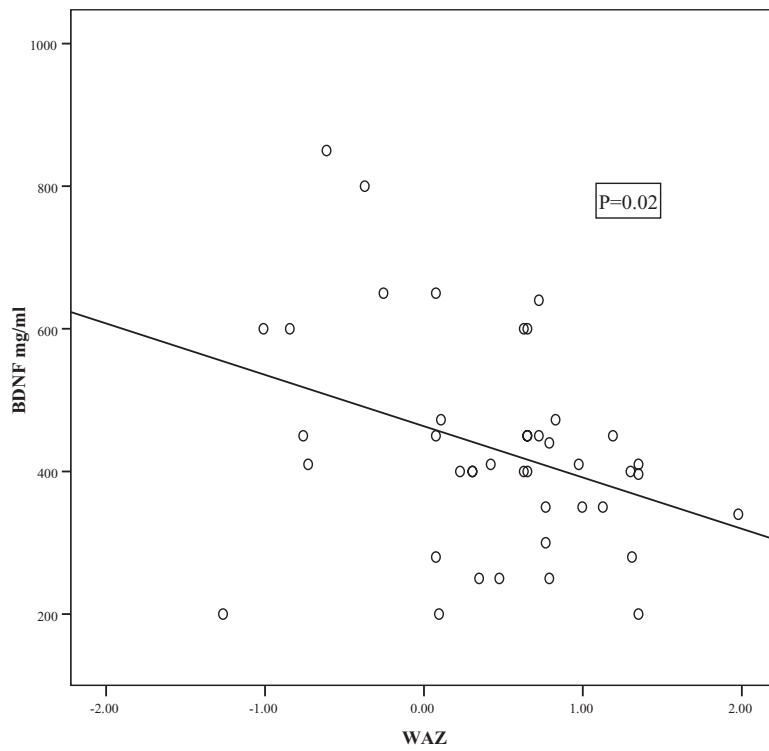
Fig. 2. Scatter diagram showing correlation between weight-for-age Z-score (WAZ) and brain-derived neurotrophic factor (BDNF).
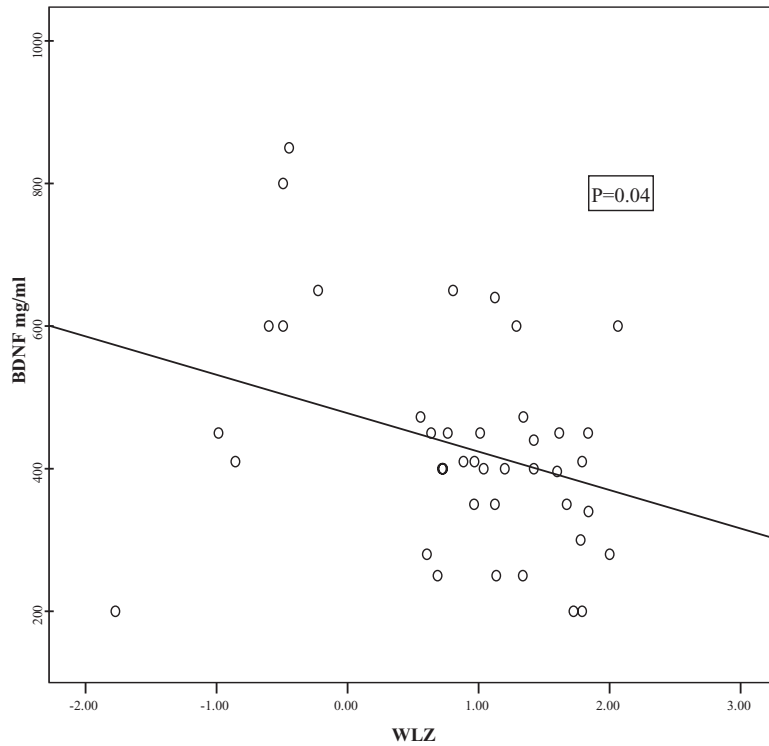
Fig. 3. Scatter diagram showing correlation between weight-for-length Z-score (WLZ) and brain-derived neurotrophic factor (BDNF).
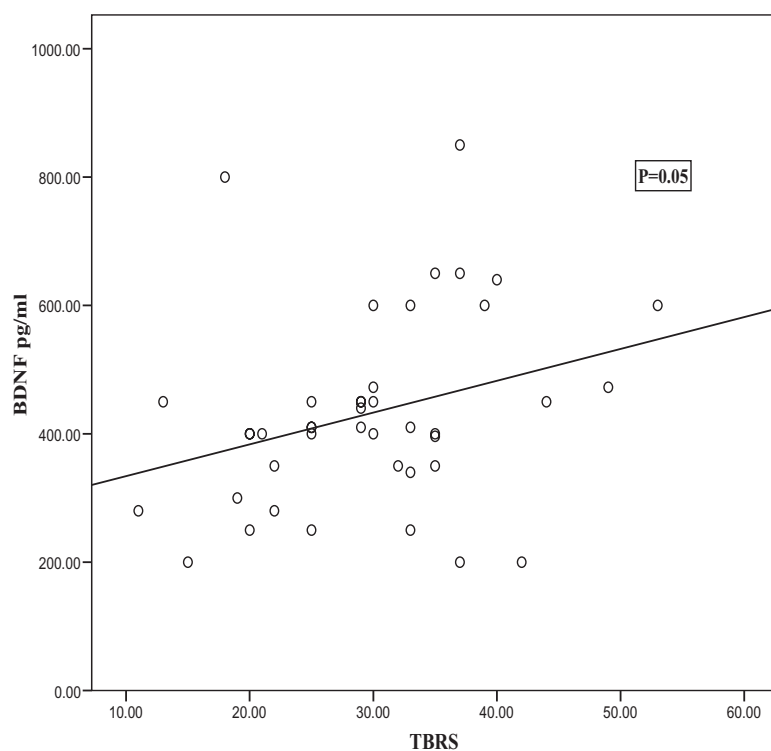
Fig. 4. Scatter diagram showing correlation between total behaviour rating scale (TBRS) score and brain-derived neurotrophic factor (BDNF).

Table 6. Effect of type of feeding and sex on BDNF

	Coefficient	95% CI	P
Breastfed group			
Formula fed*	−122.0	−228.0,−16.0	0.05
Mixed fed*	−102.6	−210.2,5.0	
Male			0.10
Female†	−77.5	−171.0,16.0	

*Compared with breastfed group (reference group). †Compared to male. BDNF, brain-derived neurotrophic factor.

Table 7. Effect of type of feeding and social class on TBRS

	Coefficient	95% CI	P
Breastfed group			
Formula fed*	−11.0	−17.0,−5.0	0.004
Mixed fed*	−7.0	−13.2,−0.7	
Low			0.54
Middle†	−2.78	−9.9,4.4	
High†	−3.77	−12.1,4.6	

*Compared with breastfed group (reference group). †Compared with low class. TBRS, total behaviour rating scale.

secretion of BDNF is known to be decreased by stress and increased by intellectual stimulation which is well documented among breastfed infants. Furthermore, infants feeding from the breast suckle strongly and this voluntary exercise also stimulates BDNF secretion (Russo-Neustadt *et al.* 2000 and Gomez-Pinilla *et al.* 2008).

Although this study did not measure brain BDNF levels, it seems plausible that brain BDNF is increased because of simultaneous onsite production, transport from the periphery or both. We hypothesize that

BDNF may be one of the causative factors of higher cognitive functions in breastfed group especially that the regression analysis favours breastfeeding as a determinant factor for BDNF level.

Regarding the correlation studies in this work, negative correlations between BDNF and both WAZ and WLZ scores were detected. As the anthropometric measurements did not differ significantly with the pattern of feeding of the studied infants, the detected correlations could be explained by the studies in animal models which suggest that BDNF plays a key

Table 8. Effect of type of feeding, sex and order of birth on motor quality percentile rank

		Coefficient	95% CI	P
	Breast fed			
Groups	Formula fed*	−11.2	−19.2,−3.1	0.02
	Mixed fed*	−3.0	−11.3,5.3	
Sex	Male			0.03
	Female†	7.6	0.6,15.0	
Order of birth	1			0.11
	2‡	2.24	−5.3,9.8	
	3‡	9.24	0.5,18.0	

*Compared with breast fed group (reference group). †Compared to male. ‡Compared to 1.

role in energy homeostasis; it is believed to act primarily within the ventromedial hypothalamus to regulate energy intake (Unger *et al*. 2007).

Although studies in animals provide support for a role of BDNF in energy homeostasis, data in humans are relatively limited. Some studies have shown an inverse association between the peripheral BDNF concentration and the body mass index in children and adults (El-Gharbawy *et al*. 2006). Furthermore, Krabbe *et al*. (2007) added that a common BDNF polymorphism, Val66Met, has been inconclusively associated with altered body weight. Moreover, Yeo *et al*. (2004) described an obese child with hyperphagia and a heterozygous missense substitution resulting in impaired signalling of the cognate receptor of BDNF, TrkB.

In this study, distinct positive correlation was detected between BDNF values and all studied BSID-II parameters, yet only the correlation with the TBRS reached statistical significance.

This could be explained by the work of Yamada & Nabeshima (2003) who reported that in the brain, BDNF is active in the hippocampus, cortex and basal forebrain, areas vital to learning, memory and higher thinking. Moreover, BDNF itself is important for long-term memory (Bekinschtein *et al*. 2008b).

It is worth noting that in the current study, breast-feeding was a determinant factor for TBRS and motor quality percentile rank by regression analysis.

BDNF potentiates excitatory synaptic transmission in hippocampal neurons. It has been shown to play a critical role in learning outcome in a large number of studies and to have a role in hippocampal-dependent cognitive performance. Thus, spatial memory was found to be superior in rats housed in enriched rather than in impoverished environments and after training. Disruption of BDNF expression by use of anti-sense oligonucleotides, in heterozygous BDNF knockout animals or by use of anti-BDNF antibodies caused severe impairment in spatial memory and learning. Similarly, impaired learning was evident in the conditional TrkB knockout and in mice overexpressing the truncated form of TrkB (Allen & Dawbarn 2006).

Finally, the results of the current study show that girls have non-significantly less BDNF values than boys. This difference is not enough for the different sex composition of the three groups to explain the evident difference in BDNF; however, it does show that sex differences exist and that future studies need to balance the number of girls and boys in each group to avoid confounding of sex with the feeding pattern.

In conclusion, serum BDNF levels are significantly higher in breastfed infants and shows positive correlations with the results of BSID-II. Given that simultaneous increase in brain BDNF occurs due to onsite production, transport from the periphery or both, it is prudent to hypothesize that BDNF could be one of the factors responsible for the better cognition detected in breastfed infants. Larger-scale studies are recommended to further prove this finding as well as other studies to measure the BDNF in breast milk and to explore other candidate factors for better cognition in breastfed infants.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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