Measuring the Impact of Nutrition on Cognitive Development

Carol L. Cheatham, PhD

Human brain development begins at conception. However, the influence of nutrition on brain development begins *before* conception and continues for many years. Certain nutrients are needed before a child is conceived if fetal development is to proceed in a typical manner. After a brief overview of a few of these nutrients, this summary focuses on the effects of nutrition on cognitive development. The rationale for studying the effects of nutrition on two specific cognitive abilities—memory and speed of processing—are outlined. The importance of nutrition to cognition in general cannot be overstated as memory is central to learning, and speed of processing underlies all cognitive abilities. Also, this summary illustrates behavioral and electrophysiological methods of measuring the effects of nutrition on infant memory (behavioral) and speed of processing (electrophysiological).

Nutrition and Fetal Development

The best way to ensure a healthy pregnancy and good outcomes for the infant is to start with a healthy well-nourished mother. There is evidence that when mothers are underweight at conception they are at risk of having a baby who suffers from intrauterine growth restriction, even if they gain sufficient weight during pregnancy.[1] However, the opposite—overweight at conception—puts the mother at risk of gestational diabetes and preeclampsia and of having an overly large baby that requires a caesarian section.[2,3] However, there is no empirically derived recommendation for maternal weight for height at conception.

Malnourished women may experience difficulty getting pregnant as the body senses that the host is not prepared for gestation.[4] Those malnourished women who do get pregnant have increased risk of miscarriage or of giving birth to infants with developmental issues. One nutrient that has long been known to be important before conception is folate, which is related to neural tube closure. However, after 30 years of fortifying the food supply with folate, related birth defects are still occurring. New evidence indicates that choline, methionine, and betaine may also be important for neural tube development.[5] Ensuring that all these nutrients are in sufficient supply at conception may decrease the incidence of neural tube disorders.

Iodine is another nutrient important enough to ensure preconception sufficiency by fortifying the daily food supply (ie, salt). Iodine deficiency can result in cretinism. The sequelae of cretinism are due to the inability of the mother to produce enough thyroid hormone in those crucial first few months when the fetal thyroid is not yet functioning. Because thyroid hormones are involved in neurogenesis and neuronal migration, as well as in several other neuronal processes, the effects of iodine deficiency can be globally pervasive in the brain. Evidence indicates that sufficient iodine is important preconceptionally. In a study in Ecuador, one village was treated with iodine every 4 years and another was left alone. Intelligence quotients (IQs) of the children at 11 years of age were compared. Mean IQs were higher in the treated village, but interestingly, if the treatment occurred before pregnancy or in the 1st trimester, the difference in IQ was a full 11 points.[6] If treatment was administered later in pregnancy, there was little effect.[7,8]

Malnourished women who become pregnant are also at risk for preterm delivery due to iron deficiency.[9] In addition, iron deficiency is the leading cause of mental deficiencies worldwide. A fetus can become iron deficient in many different ways. If the fetus is experiencing intrauterine growth restriction, is small for gestational age, or if the mother develops gestational diabetes or preeclampsia, the fetus will suffer from iron deficiency.[10,11] Iron deficiency has been studied extensively, and we know that low iron in the last few months of pregnancy and just after birth is related to a disruption in recognition memory. If the deficiency happens later—around 9-10 months of age—it will disrupt myelination and speed of processing. Thus, timing of a deficiency is important.

Nutrition and Cognitive Development

From midgestation to 2 years after birth, the brain is developing rapidly. It triples in weight, and the 100 billion neurons that are present at birth each form 15,000 synapses (Figure).

- Brain growth spurt—midgestation to 2 years of age
- Triples in weight; forms 100 billion neurons each with 15,000 synapses

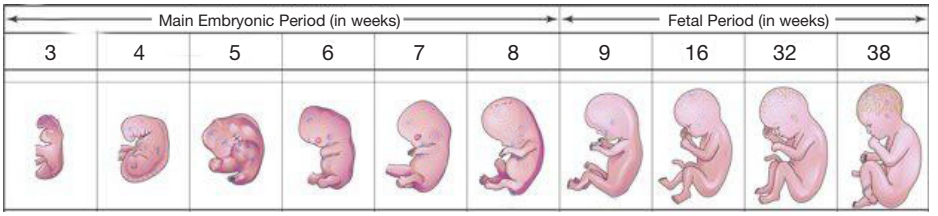

Figure. Critical periods in fetal and infant brain development.

Source (illustration only):
http://sara1hays.files.wordpress.com/2008/02/criticalperiodshumandevelopment1.jpg.

The brain is most susceptible to insult when it is developing most rapidly and thus, as illustrated above, timing of the deficiency is central.[12] It follows, then, that during the prenatal months and the first 2 years of life, any nutrient deficiencies will have an enormous effect on the developing brain. Research with animals has shown that nutrient deficiencies rarely (except in the case of iodine) cause issues with the entire brain.[13] Some structures are affected permanently, and the hippocampus and cerebellum are the most vulnerable.[13] We would expect the behaviors subserved by the hippocampus, and the cerebellum to be affected; in the case of the hippocampus that would be memory functions, and in the case of the cerebellum, motor coordination and procedural learning. In the individual, malnutrition has been shown to have an acute effect on the actions of neurotransmitters and the functions of receptors.[13] At this cellular level, the link to receptors and neurotransmitters indicates that we would want to test speed of processing. Thus, from animal research of nutrient deficiencies, we see that memory and speed of processing are good candidate cognitive abilities to assess the effects of nutrition on human cognition.

Speed of processing can be implied from many behavioral assessments. However, by using an electrophysiology paradigm known as event-related potentials (ERPs), it is possible to document processing speed directly. ERPs are recordings of electroencephalograms (EEGs) that are time-locked to stimuli. The EEG is recorded and the differences in activity between the recording and a reference are extracted. The stimuli can be auditory or visual, and the number of recording electrodes varies from just a few to as many as 128 for an infant assessment. In the simplest of descriptions, the random background noise, which includes interference from

ambient electrical noise, is identified at the reference and is subtracted from the other leads, leaving the electrical potential of the brain that is related to the stimulus event. ERP has great temporal resolution, but we cannot assess individual trials. The segments of each condition within a participant are averaged together, and then data from the participants are averaged together to arrive at a grand mean. The resulting waveform includes information about latency to processing and processing time for each experimental condition (Table).

Table. Extracting the Signal Using the Electrophysiology Paradigm Known as Event-Related Potentials (ERPs)

- ERP generation is based on differences in voltage between electrodes and a reference
  - — EEG background noise should average to zero
  - — The residual activity represents brain activity to the event
  - — Limitation: cannot access individual trials
- Compare grand means of conditions

The hippocampus-based cognitive ability known as declarative memory is supported by the temporal cortices and cortical areas, specifically the association areas and the frontal and prefrontal lobes.[14] The hippocampus and the surrounding cortices serve as a clearinghouse for memories, effectively interconnecting and consolidating information. In humans, hippocampal development starts around 16 weeks gestation and continues at least into the 3rd year of life,[15] not reaching adult morphology until the child is 5 years of age.[16] Hippocampal neurons change substantially in size and shape across the first year of life.[15] Also during the 1st year of life, there is evidence of the development of dentate connectivity[16] and neocortical connectivity.[17] The ability to differentiate familiar and novel stimuli (recognition memory) is evidenced in the first 6 months of life and is dependent on the integrity of the parietal lobe (attention) and the parahippocampal structures in the temporal lobes (recognition memory).[18,19] At 6 months, the hippocampus uses the same levels of glucose as an adult hippocampus.[16] The hippocampus proper and, more specifically, the dentate gyrus are crucial for encoding, storing, and recalling sequences of actions.[20] The hippocampus becomes functionally mature when it reaches peak synaptic density between 12 and 15 months of age.[16]

In the months prior to this (7-12 months of age), we would expect, and do indeed

find, wide variation in longer-term declarative memory (ie, memory that is acquired rapidly, is subject to forgetting, is flexible, and can be articulated). A developmental shift occurs between the ages of 9 and 10 months in declarative memory abilities,[21] which coincides with the maturation of the dentate gyrus and the coalescing of the temporal-frontal circuit. Thus, cognitive development maps onto the development and functionality of the temporal lobes (hippocampus and surrounding cortices), parietal lobes, and frontal lobes, thereby supporting the structure-function relation.

How do we test the declarative memory abilities in infants who cannot offer verbal reports? Elicited and deferred imitation have become accepted as nonverbal assessments of declarative memory. That these paradigms measure declarative memory has been shown empirically. The definition of declarative memory is basically a memory that was acquired quickly, is subject to forgetting, and is flexible. A memory of an imitated event can be acquired in one trial.[22] Memories for the events fall out in a typical forgetting curve,[23] and they are flexible.[24] Finally, McDonough and colleagues have shown that adults with amnesia that affects declarative memory processes do, in fact, fail an age-appropriate analog.[25] So, we are confident that this behavioral measure actually is testing hippocampal function.

In an imitation protocol, 3-dimensional props are used to produce novel multistep sequences comprising multiple actions. Participants are tested for recall of specific sequences immediately (a measure of initial encoding), after a delay of a few minutes (a measure of the ability to successfully transfer information to long-term memory stores), and/or after a delay of weeks or months (a measure of the ability to maintain and retrieve a long-term mnemonic trace). The number of steps and the length of delays depend on the age of the participants[26]: the older the child, the longer the delay, and the higher the number of steps that can be tolerated. Administration of the task begins by offering the child the props that comprise one event to get a baseline measure of activity. This is followed by the demonstration of the target actions by the researcher and an opportunity for the child to imitate either immediately, after the prescribed delay, or both. Two dependent variables are determined from offline coding of the session video, the number of actions produced and the number of pairs of actions produced in the correct order. Recall of the proper ordering of the steps is the most challenging for the children.

ERP paradigms and imitation paradigms have been used in research with infants of mothers with diabetes who are inherently iron deficient and whose infants have received varying levels of the fatty acid docosahexaenoic acid (22:6n-3; DHA). ERP paradigms have proven to be sensitive to small fluctuations in nutrients

and subsequent cognitive development as early as the 1st week of life.[27-30] Imitation paradigms also differentiate between infants with different nutritional backgrounds.[31-33] Thus, nutrition researchers should work with developmental cognitive neuroscientists to use these methodologies to determine the effects of nutrition on brain development. Proper nutrition for fetuses, infants, and children can help ensure that children have a chance to achieve their cognitive potential.

References

1. Kramer MS. The epidemiology of adverse pregnancy outcomes: an overview. *J Nutr.* 2003 May;133(5)(suppl 2):1592S-1596S.
2. Abrams B, Parker J. Overweight and pregnancy complications. *Int J Obes.* 1988;12(4):293-303.
3. Seligman LC, Duncan BB, Branchtein L, Gaio DS, Mengue SS, Schmidt MI. Obesity and gestational weight gain: cesarean delivery and labor complications. *Rev Saude Publica.* 2006 Jun;40(3):457-465.
4. Susser M, Stein Z. Timing in prenatal nutrition: a reprise of the Dutch Famine Study. *Nutr Rev.* 1994 Mar;52(3):84-94.
5. Shaw GM, Carmichael SL, Yang W, Selvin S, Schaffer DM. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. *Am J Epidemiol*. 2004 July 15;160(2):102-109.
6. Greene LS. A retrospective view of iodine deficiency, brain development, and behavior from studies in Ecuador. In: Stanbury JB, ed. *The Damaged Brain of Iodine Deficiency.* New York, NY: Cognizant Communication; 2004:173-185.
7. Pharoah PO, Connolly KJ. A controlled trial of iodinated oil for the prevention of endemic cretinism: a long-term follow-up. *Int J Epidemiol.* 1987 Mar;16(1):68-73.
8. Pharoah PO, Connolly KJ. Effects of maternal iodine supplementation during pregnancy. *Arch Dis Child.* 1991 Jan;66(1):145-147.
9. Scanlon KS, Yip R, Schieve LA, Cogswell ME. High and low hemoglobin levels during pregnancy: differential risks for preterm birth and small for gestational age. *Obstet Gynecol.* 2000 Nov;96(5, pt 1):741-748.
10. Georgieff MK, Landon MB, Mills MM, et al. Abnormal iron distribution in infants of diabetic mothers: spectrum and maternal antecedents. *J Pediatr.* 1990 Sep;117(3):455-461.
11. Lozoff B, Georgieff MK. Iron deficiency and brain development. *Semin Pediatr Neurol.* 2006 Sep;13(3):158-165.
12. Cheatham CL, Sesma HW, Georgieff MK. The development of declarative memory in infants born preterm. In: Bauer PJ, ed. *Advances in Child Development and Behavior*. London, England: Elsevier; 2010:111-135. *Varieties of Early Experience: Implications for the Development of Declarative Memory in Infancy*; vol 38.

13. Levitsky DA, Strupp BJ. Malnutrition and the brain: changing concepts, changing concerns. *J Nutr.* 1995 Aug;125(suppl 8):2212S-2220S.

14. Eichenbaum HB, Cohen NJ. *From Conditioning to Conscious Recollection: Memory Systems of the Brain.* New York: Oxford University Press; 2001.

15. Zaidel DW. Quantitative morphology of human hippocampus early neuron development. *Anat Rec.* 1999 Jan;254(1):87-91.

16. Seress L. Morphological changes of the human hippocampal formation from midgestation to early childhood. In: Nelson CA, Luciana M, eds. *Handbook of Developmental Cognitive Neuroscience.* Cambridge, MA: The MIT Press; 2001:45-58.

17. Lavenex P, Banta Lavenex P, Amaral DG. Postnatal development of the primate hippocampal formation. *Dev Neurosci.* 2007;29(1-2):179-192.

18. Fortin NJ, Wright SP, Eichenbaum HB. Recollection-like memory retrieval in rats is dependent on the hippocampus. *Nature.* 2004 Sep 9;431(7005):188-191.

19. Snyder KA, Blank MP, Marsolek CJ. What form of memory underlies novelty preferences? *Psychon Bull Rev.* 2008 Apr;15(2):315-321.

20. Fortin NJ, Agster KL, Eichenbaum HB. Critical role of the hippocampus in memory for sequences of events. *Nat Neurosci.* 2002 May;5(5):458-462.

21. Carver LJ, Bauer PJ. The dawning of a past: the emergence of long-term explicit memory in infancy. *J Exp Psychol Gen.* 2001 Dec;130(4):726-745.

22. Bauer PJ. Holding it all together: how enabling relations facilitate young children's event recall. *Cognitive Dev.* 1992;7(1):1-28.

23. Bauer PJ, Cheatham CL, Strand Cary M, Van Abbema DL. Short-term forgetting: charting its course and implications for long-term remembering. In: Shohov SP, ed. *Advances in Psychology Research*, vol 9. New York: Nova Science Publishers Inc; 2002:53-74.

24. Bauer PJ, Dow GA. Episodic memory in 16- and 20-month-old children: specifics are generalized but not forgotten. *Dev Psychol.* 1994;30(3):403-417.

25. McDonough L, Mandler JM, McKee RD, Squire LR. The deferred imitation task as a nonverbal measure of declarative memory. *Proc Nat Acad Sci U S A.* 1995 Aug 1;92:7580-7584.

26. Bauer PJ, Wenner JA, Dropik PL, Wewerka SS. Parameters of remembering and forgetting in the transition from infancy to early childhood. *Monogr Soc Res Child Dev.* 2000;65(4):i-vi, 1-204.

27. Cheatham CL. Electrophysiological evidence of the influence of maternal FADS2 genotype on the memory abilities of breastfed 6-month-olds. Paper presented at: International Conference on Infant Studies; June 9, 2012; Minneapolis, MN.

28. deRegnier RA, Long JD, Georgieff MK, Nelson CA. Using event-related potentials to study perinatal nutrition and brain development in infants of diabetic mothers. *Dev Neuropsychol*. 2007;31(3):379-396.

29. Henriksen C, Haugholt K, Lindgren M, et al. Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid. *Pediatrics*. 2008 Jun;121: 1137-1145.

30. Siddappa AJ, Georgieff MK, Wewerka S, Worwa C, Nelson CA, deRegnier RA. Iron deficiency alters auditory recognition memory in newborn infants of diabetic mothers. *Pediatr Res*. 2004 Jun;55(6):1034-1041.

31. Cheatham CL. Effects of flaxseed oil supplementation and FADS genotype on declarative memory abilities in toddlers. *FASEB J.* 2012 March 29;26:266.8.

32. Cheatham CL, Colombo J, Carlson SE. The effect of feeding formula enriched with docosahexaenoic acid on the declarative memory abilities of 10-month-olds. Paper presented at: 8th Biennial Meeting of the International Society for the Study of Fatty Acids and Lipids; May 17-22, 2008; Kansas City, KS.

33. Riggins T, Miller NC, Bauer PJ, Georgieff MK, Nelson CA. Consequences of low neonatal iron status due to maternal diabetes mellitus on explicit memory performance in childhood. *Dev Neuropsychol.* 2009;34(6):762-779.