Recent Advances in Infant Cognition: Implications for Long-Chain Polyunsaturated Fatty Acid Supplementation Studies

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ABSTRACT: The assessment of cognitive function in early life has recently become an issue for consideration in long-chain polyunsaturated fatty acid (LC-PUFA) supplementation studies. This article reviews the various means by which such assessment has been done in past LC-PUFA supplementation studies and provides some background on recent advances in the measurement of infant cognition that may need to be considered when planning or designing future supplementation studies. These include (i) consideration of the specificity of LC-PUFA effects on cognition, (ii) inclusion of multiple tasks or levels of measurement as outcome measures, and (iii) a stronger emphasis on developmental processes in the design of such studies.

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Given the putative importance of some long-chain polyunsaturated fatty acids (LC-PUFA) to central nervous system (CNS) integrity and function, it has long been suspected that LC-PUFA play some role in mammalian behavior and behavioral development. The contribution of LC-PUFA to learning and cognition has been investigated in both animals (1–3) and humans (4,5). In addition, LC-PUFA deficiencies have been theoretically linked with a range of behavioral disorders from sudden infant death (6), to dyslexia (7), to schizophrenia (8).

For some time now, an understanding of the science of infant behavior and development has been relevant to scientists investigating the effects of LC-PUFA on behavioral development. There is an intriguing and plausible theoretical case to be made for the importance of LC-PUFA for the development of the CNS and retina during the pre- and postnatal periods (9–16). Thus, it has been hypothesized that early manipulations (either supplemented or deprived diets) of LC-PUFA should affect visual and cognitive development. Rather than wait until subjects reach maturity, many of these investigators have chosen to assess the effects of such manipulations with measures of visual and cognitive function in infant participants. As such, the period of infancy has served as a preliminary "proving ground" for such early nutritional manipulations.

INFANT COGNITION AND LONG-CHAIN POLYUNSATURATED FATTY ACIDS (LC-PUFA)

A critical point in studies of this sort is the choice of the dependent measure. Studies of infant visual function have been widely conducted in this area for some time (e.g., Ref. 17), showing both positive (18–26) and null (27–31) effects for LC-PUFA supplementation. The choice of dependent variable within this realm is perhaps facilitated by the fact that there is a finite set of such measures for visual function (e.g., acuity or contrast sensitivity), and that the standardized measures that do exist (e.g., Ref. 32) possess good validity and reliability. However, other investigators have chosen to examine whether manipulations of LC-PUFA early in life affect broader cognitive functions. In choosing dependent measures designed to reflect early manifestations of cognition in infancy and toddlerhood, these investigators face a number of difficult issues (see Ref. 33), many of which remain unresolved among those in the field of early cognitive development. The purpose of this article is to try to address some of these fundamental issues on this topic for the audience that may be interested in the effect of LC-PUFA on cognition and behavioral development in early infancy. Although some data on standardized tests will be reviewed briefly, the primary focus of the paper is on recent advances in laboratory tasks of infant cognition. The aim is to provide a current description of this field and to explicate the implications of recent advances in this area for researchers interested in applying these tasks as outcomes in studies of early nutrition. Although the article will make reference to the extant data from clinical studies of LC-PUFA and behavior in infancy, methodological differences among those studies that may have given rise to differential outcomes on such measures will not be addressed here.

MEASURES OF INFANT COGNITIVE/INTELLECTUAL FUNCTION

The first issue facing investigators interested in this topic of research is that there is no one widely accepted measure for assessing cognition or cognitive development in the infant/toddler age range. There are two broad classes of assessment tools. One class is comprised of normative, standardized tests of general behavioral or developmental function. The second class is comprised of laboratory tasks that have been designed to tap a specific cognitive process. In the sections that follow,

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Abbreviations: AA, arachidonic acid; CNS, central nervous system; DHA, docosahexaenoic acid; ERP, evoked response potentials; HR, heart rate; LC-PUFA, long-chain polyunsaturated fatty acids; MDI, Mental Development Index.

these two classes of assessment are generally described, along with a brief review of studies of LC-PUFA manipulations that have employed them.

Standardized Normative Measures of Infant Development

There are a number of traditional standardized measures of infant cognitive or "mental" development. These include tests such as the Bayley Scales of Infant Development (34), the Kaufman Assessment Battery for Children (e.g., Ref. 35), the Battelle Developmental Inventory (e.g., Ref. 36), and the Denver Developmental Screening Test (e.g., Ref. 37). Many of these tests are derived from infant scales constructed during the 1920s or 1930s; their construction is based on the assumption that developmental outcome can be characterized as some aggregate of the infant's attainment of normative developmental milestones across a number of domains (motor, imitation, language). The summing of items across domains to achieve a single score is perhaps attributable to an implicit assumption that a construct of "general intelligence" exists in infancy (38–40).

Other more recent normative tests for the infant/toddler age ranges are constrained to a particular domain. Most prominent among these are tests of language or communicative development. These include the Sequenced Inventory of Communicative Development (41), the Reynell Developmental Language Scales (42), and the MacArthur Communicative Development Inventory (43). These tests avoid the pitfalls associated with the assumption of a general intelligence factor, but still calculate the optimality of outcome based on the comparison of the infant's performance against some standardized norms.

LC-PUFA effects on laboratory-based tasks. Standardized tests have been used in a number of follow-up studies of infant LC-PUFA supplementation. These include both positive and null findings. Carlson *et al.* (44) reported an advantage on the Bayley Mental Development Index (MDI) for preterm infants who were fed a LC-PUFA-supplemented formula. In a series of follow-up reports, Agostoni *et al.* (45,46) reported a strong correlation between LC-PUFA composition of the red cell membrane and improved neurodevelopmental performance on a standardized psychomotor developmental test (Brunet-Lexine Scale) at 4 mon of age. In a large-scale clinical trial, Scott *et al.* (47) reported no effects of LC-PUFA supplementation on Bayley MDI scores at 12 mon of age in a clinical trial, and in fact reported negative effects for LC-PUFA supplementation on some standardized language measures. Birch *et al.* (48) report an advantage of nearly half a standard deviation on the new Bayley scale at 18 mon for infants supplemented with docosahexaeonic acid (DHA) and DHA plus arachidonic acid (AA) until 17 wk of age. In contrast, Makrides *et al.* (49) found no differences among infants assigned to placebo, DHA supplementation, and DHA + AA supplementation groups at 12 and 24 mon on the Bayley Scales. In the last-mentioned study, however, it may be worth noting that breast-fed infants outperformed all three of the formula-fed groups on the Bayley at 24 mon of age. Clearly, the results of these studies are mixed; although positive outcomes were observed in a majority of the studies, these are tempered by null findings in larger-scale clinical trials.

Laboratory Measures of Infant Cognition

Along with the standardized tests, some researchers have adapted a number of specific laboratory tasks as cognitive outcome variables in experiments and clinical trials of LC-PUFA. In general, such tasks were developed initially for purposes of conducting basic research on early cognitive development, and were designed explicitly to assess specific components of information processing or CNS function in infancy. As such, they are advantageous relative to the standardized tests because they presumably tap more specific cognitive domains with greater depth and accuracy, and their interpretation does not rest on assumptions about the structure of the intellect in infancy. Their disadvantage, however, is that they are not standardized in either their administration or interpretation (39,40). As a result, the outcomes of different studies may vary as a function of how the tasks are conducted. Furthermore, some ambiguity may exist in the interpretation of results. Let us first consider those tasks and/or measures that have been used in prior research with LC-PUFA research.

Visual habituation. In this task, a visual stimulus is repetitively presented to the infant, and the duration of the infant's looking is measured over the course of these presentations. The presentations may proceed on the basis of parameters chosen by the investigator ("fixed trial" habituation procedures), or may be provisional upon the infant's looking ("infant-controlled" procedures; see Ref. 38 for a procedural review). The duration of infants' looking declines across such repeated presentations, and this decline (or "habituation curve") is generally taken to reflect the infant's visual learning. The procedure is appropriate for infants from birth through ~10 mon of age. Many variables have been culled from this habituation curve that are thought to represent some index of the efficiency or rapidity of this learning. These variables include the slope or magnitude of the decline, trials to some criterion of decrement, or some measure of the infant's duration of looking (50).

Paired-comparison tasks. In novelty preference tasks, the infant is presented ("familiarized") with a visual stimulus to study for some amount of time, and then tested for whether s/he is able to recognize the stimulus by simultaneously pairing the familiarized stimulus with a novel one and allowing the infant to compare between the two. Recognition is generally indicated by some systematic preference for looking at one of the stimuli during this "paired-comparison" phase. Most typically, this is a preference for the novel stimulus, but under conditions of insufficient familiarization or increased cognitive demands, this preference may be expressed in terms of a preference for the familiarized stimulus (see Ref. 38). The initial familiarization period may be conducted using a habituation procedure. More commonly, however, the familiarization is conducted by allowing the infant to study the stimulus for some fixed amount of time. A set of paired-comparison tasks (in which stimuli, familiarization times, and tasks protocols were standardized) comprised the Fagan Test of Infant Intelligence (FTII; 51). The FTII was a popular instrument through most of the 1990s in followup studies of various sorts, including some studies manipulating dietary LC-PUFA. This procedure is appropriate for infants from 2 to ~12 mon of age.

It is worth noting that some of the variables that can be culled from the habituation curve (most notably measures of look duration) are also available from an analysis of infant looking during the familiarization phase (52).

Problem-solving tasks. A number of tasks that tap higher-order cognitive functions have also been used in evaluating the effects of LC-PUFA supplementation. One is the "A-not-B" task (e.g., Ref. 53). Here, the infant is shown an object (e.g., a toy) being hidden under a cup or in a well at some location ("A"), and is then allowed to search and retrieve the object from the location. A brief delay (e.g., 5–15 s) may be imposed between the hiding and search. After several successful retrievals, the object is then hidden at a second location ("B"). Between 8 and 12 mon of age, infants will generally search at the first location rather than the second, that is, the infant searches at location A, not at B, thus giving rise to the name of the task. This perseverative error is generally attributed to the infant's inability to inhibit the previously successful response of searching at location A, and it has been taken to reflect immaturity of the dorsolateral frontal cortex.

Other problem-solving tasks have been used as well. These typically involve having the infant pull a string to retrieve an object or move one object out of the way to get to another. Thus, the infant must engage in some goal-directed behavior ("means") to attain a satisfactory outcome ("ends").

LC-PUFA effects on laboratory-based tasks. Several studies have documented significant differences between infants whose diets were supplemented with LC-PUFA (particularly DHA) in performance of such tasks. In general, the most consistent finding has been demonstrated for infant look duration culled from paired-comparison tasks. This finding has been generally interpreted as reflecting more rapid or more efficient visual learning. Werkman and Carlson (54) first observed this effect in preterm infants fed a DHA-supplemented diet through 9 mo of age. Assessment points were at 6.5, 9, and 12 mo of age. Carlson and Werkman (55) subsequently reported the same effect in 12-mon-old infants whose supplementation ended at 2 mon of age. Reisbick *et al.* (56) experimentally deprived infant monkeys of DHA and observed the opposite effect; the DHA-deprived infants looked for significantly longer durations. It is worth noting that, in each case, dietary supplementation affected look duration, but did not affect subjects' novelty preference performance.

Willatts *et al.* (57) also observed briefer duration looks during habituation in DHA-supplemented infants, but only in infants whose attentional patterns were characterized as more "disorganized" (i.e., with nonlinear/nonmonotonic declines). Willatts *et al.* (58) subsequently reported that DHA-supplemented infants performed better on means-ends tasks at 10 mon of age (see also Ref. 59).

RECENT ADVANCES IN THE MEASUREMENT OF INFANT COGNITION

These findings are provocative and intriguing, and are generally in line with other results that suggest that cognitive function is affected positively by dietary LC-PUFA. These results have been obtained with procedures that might have been considered advanced or experimental in the early 1990s. However, infants' performance in each of the procedures outlined above may be interpreted in various ways (38,39). Indeed, there have been significant advances in the field of infant cognition since the mid-1990s to which researchers interested in using these tasks may profitably attend.

Tasks for More Specific Processes and Underlying Substrates

The first advance is attributable to the growing influence of cognitive neuroscience in the field of developmental psychology. The scope of cognitive neuroscience is to identify and understand the neural substrates to which cognitive/behavioral processes may be attributed. The elucidation of such substrates is complicated by developmental processes (60), but substantial progress has been made in many areas, such as the development of the ability to plan and execute motor responses in infancy (53) and in the development of visual attention in infancy (61).

A by-product of this progress is a proliferation of tasks that tap specific processes and that presumably represent the function of specific underlying neural substrates. For example, in the area of visual attention, research has identified two separate neural substrates (see Fig. 1). One of these mediates the broadband detection of visual objects, the direction of attention to (and disengagement from) the location of such objects. The other mediates analysis of visual features and object recognition. These are sometimes referred to, respectively, as the "where" and "what" systems of visual attention. There is some crosstalk between the systems, but a primary pathway through which the systems interact is located in the frontal lobe. This frontal input may be thought of as providing "top-down" control over the two systems. For example, frontal areas probably provide the voluntary "holding" or maintenance of attention that is colloquially referred to as "attention span." A number of different functions have been identified for each of these systems, and for many of these functions, tasks have been adapted for use with human infants (see Table 1).

This point has several implications for follow-up research, such as LC-PUFA supplementation studies, that seeks to employ measures of infant cognition. First, some of the results of previous studies may be open to reinterpretation. For example, look duration in infants (which has been linked to DHA manipulations) has been interpreted as an index of rapidity or efficiency of learning. Recent work (62,63),

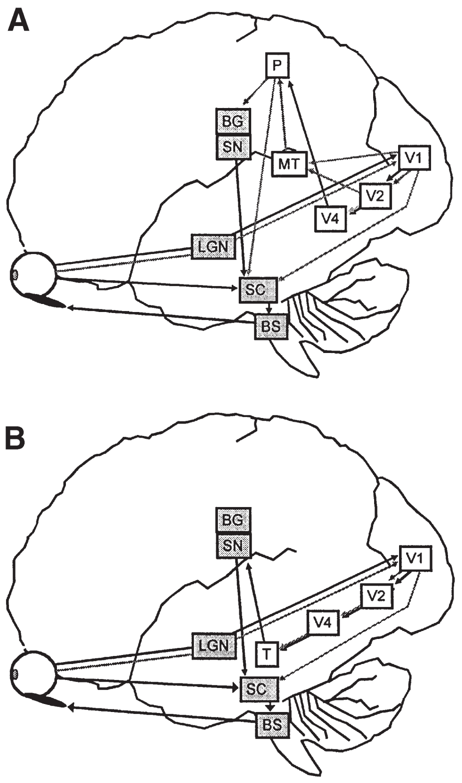

FIG. 1. Attention systems in the brain: (A) the dorsal or "where" pathway; (B) the ventral or "what" pathway. The figures represent schematics redrawn from various sources (78–81). Unshaded structures are cortical structures; shaded structures are subcortical. Legend: BG, basal ganglia; BS, brain stem; LGN, lateral geniculate nucleus; MT, medial temporal lobe; P, parietal lobe; SC, superior colliculus; SN, substantia nigra; T, temporal lobe; V1, V2, V4, areas of visual cortex.

however, suggests that look duration (at least during the middle portions of the first year) may reflect the infant's ability to disengage attention from visuospatial loci (a function of the dorsal, or "where" system). Interestingly, it has been argued that the paired-comparison task is mediated by the ventral attentional system (60). The finding that LC-PUFA affect look duration but do not improve paired-comparison performance (e.g., Ref. 56) supports the dissociability of the tasks, and also the possible specificity of the LC-PUFA effect.

TABLE 1
List of Visual Attention Components Tested in Infancy[a]

- Spatial orienting
  - Smooth pursuit
  - Fast (involuntary/express) saccades
  - Disengagement of attention
  - Inhibition of return
- Attention to visual object features
  - Sensitivity to color/form
  - Attention to color/form compounds
  - Intrastimulus shifting
  - Object cue dominance
- Endogenous (voluntary) control of attention
  - Interstimulus shifting
  - Inhibition of saccades
  - Sustained attention

[a] Adapted from Ref. 61.

A side implication of such a high degree of "modularity" of cognitive measures in infancy is that it is entirely possible to obtain effects that are not readily reconcilable. For example, how could Carlson and colleagues (54,55) and Reisbick *et al.* (56) observe improvements in look duration as a function of DHA status, but Scott *et al.* (47) observe significantly lower language outcome at 14 mon of age in DHA-supplemented infants? If one holds to a unitary approach to intellectual function, these findings make no sense at all. If, however, one considers the possibilities that the substrates reflected in attention are different from the one reflected in language, and may thus be differentially affected, then the findings appear far less anomalous.

A final implication to be discussed here arises from the fact that the number of dependent variables now available to researchers interested in conducting follow-up studies is indeed quite large. Unlike the standardized normative tests, whose construction and scoring rest on the assumption that the infant's performance can be reduced to a single score that reflects general intelligence or overall cognitive function, research suggests that these different functions are dissociable in terms of their underlying neural substrates and developmental course (61). As such, the choices that followup researchers make in evaluating the effects of LC-PUFA with such new tasks should be based on a strong theoretical position as to what function LC-PUFA might be expected to affect, and at what age point this effect might be expected to be manifest (39).

Multilevel Measurement

A second major change in the field of measuring infant cognition that has occurred at the cutting edge of the field is that researchers no longer rely solely on behavioral measures, i.e., 5–10 yr ago, it would have sufficed to measure infant looking in the habituation or paired-comparison paradigms. However, it has become more common to see such behavioral paradigms bolstered with convergent measures (64). Such convergent measures can be psychophysiologic (e.g., heart rate; HR) or electrophysiologic (e.g., evoked response potentials; ERP) in nature. The increasing availability of high-density ERP systems (with measurement from as many as 128 electrodes on the scalp) nearly approximates neuroimaging (65,66), although the choice of paradigms is constrained to some degree with such increasingly sophisticated measurement systems.

The addition of such multilevel measurement allows for two things. First, it is possible to observe internal reactions to events within paradigms that heretofore have not yielded data. For example, in a recent study (67), 4-mon-olds were observed in a fixed-trial habituation procedure; measurement of looking was augmented by simultaneous recording of HR. It was observed that infants routinely showed brief but significant accelerations to stimulus presentations; that is, upon illumination of the stimulus, infants' HR increased. One striking finding was that infants who looked for long durations had significantly greater HR accelerations than infants who looked for brief durations. Thus, the simultaneous measurement of HR provided a finding that would not have been available with only behavioral measures of attention.

Second, the addition of measures allows for a much finer and more precise analysis of cognitive components during attention. In particular, Richards and Casey (e.g., Refs. 64,68,69) have taken the characteristic HR deceleration that occurs during infant looking and have parsed the looking into three distinct phases, each of which putatively reflects different types of information processing (see Fig. 1). "Orienting," which is the initial portion of the deceleration, reflects a simple reaction to the detection of the stimulus. "Sustained Attention," which is the asymptotic portion of the decelerative response, is presumed to reflect the voluntary maintenance of attention to the stimulus. Finally, "Attention Termination" is a period during which HR begins to increase from its decelerative asymptote, and reflects the end of processing. The hypothesized characteristics of the latter two phases have been supported by research over the 1990s (64,68,69). Such a framework has been useful in studying individual differences in infant cognition; indeed, one of the defining characteristics of infants exhibiting prolonged durations during an infant-controlled habituation, relative to their shorter-looking counterparts, was increased amounts of attention termination (70). That is, longer-looking infants spent more time looking when their HR patterns suggested that they were probably not processing very much information.

It goes without saying that access to new measures and the ability to conduct finer-grained analyses in familiar paradigms has great potential for followup work of the type that LC-PUFA supplementation studies might take.

An Emphasis on Developmental Process

One last advance that is relevant to the use of measures of infant cognition in short-term outcome research is not the direct result of improvements in technology or the influence of other sciences. It is, rather, an advance that may be attributed to a growing theoretical shift in the field of developmental psychology.

The study of development is, by definition, the study of change. Over the past 20 yr, there has been a growing emphasis on the consideration of developmental processes, rather than a simple focus on behavioral products at particular points in time (71–73). In the 1990s, researchers working with LC-PUFA dietary manipulations were attracted to measures of infant cognition largely because those measures had been observed to be correlated to some degree with performance on standard tests of intelligence (i.e., IQ) and language during childhood and adolescence (38). Thus, habituation and novelty preference measures were used primarily as substitutes for, or facsimiles of, a cognitive product (i.e., IQ); the attraction, however, was that these measures could be taken during infancy.

This mind-set reflects a focus on static cognitive "products" that might simply be "tapped" in some emergent or precursor form early in the lifespan. In this way of thinking, it should be possible to implement an intervention (here, some dietary manipulation of LC-PUFA), choose a measure of early cognition, and then take a "snapshot" at one point during infancy to see whether the intervention makes a difference. This approach is inspired by a "psychometric approach" to infancy that was encouraged in some earlier publications (e.g., 38,50). The psychometric approach is attractive in its parsimony and simplicity, in that it leans heavily on the assumption that there will be a putatively direct causal relationship between early and mature cognitive function. A major drawback to this approach, however, is that it essentially ignores the processes by which cognitive functions develop and evolve over the lifespan. Indeed, one particular study of the paths through which the continuity of cognitive function travels from infancy to childhood has revealed that the significant relationships between early and later measures are not direct, but are rather mediated through a series of complex variables across age (74).

The consideration of such complex and cascading causal effects in development is generally within the realm of developmental systems theory (e.g., Ref. 75). The growing importance of this approach in understanding behavioral development has several implications for research in the area of LC-PUFA supplementation.

First, there will be an emphasis on measuring the developmental course of cognitive function in infancy, rather than simply taking such measures in a "snapshot" or "slice" at one particular age point. Indeed, researchers will have to conduct more extensive longitudinal measurements and use measures of the developmental course of variables in assessing whether nutritional supplementation affects cognitive outcome. Our own recent work on the development of look duration (76) suggests that the developmental course of look duration is complex, and that different phases of the course may reflect the functional onset of different neural substrates. As such, an LC-PUFA supplementation follow-up study that assesses look duration at one (or perhaps even two or three) particular age points will not provide an adequate means to evaluate the effects of the supplementation over all of these phases. It should be noted, however, that relatively intensive longitudinal measurement is more the norm than the exception in the literature on early manipulation of dietary LC-PUFA. Most of the studies on infant visual function and infant visual attention have collected data at three or more age points.

A second methodological implication of adopting a broader, developmental systems approach is that researchers should consider whether variables other than LC-PUFA manipulations interact with the manipulations themselves. For example, it is possible that LC-PUFA supplementation has larger effects in populations in which environmental quality (e.g., socioeconomic status or caregiver responsiveness) is poor, compared with populations in which environmental conditions are more optimal. Many other examples of such variables can be proposed (e.g., individual differences in metabolism or reactivity), all of which might interact with nutritional supplementation.

A third and final implication is that small or transient effects observed at one age point may not be unimportant. For example, in a recent meta-analysis, SanGiovanni *et al.* (77) concluded that DHA supplementation produces an early but transient improvement in visual acuity. Such transience has caused some to dismiss the finding. However, the fact that a control group will show the same visual acuity as a supplemented groups at 10 mon of age ignores the possibility that the acceleration of the visual acuity curve experienced by the supplemented group may have a longer-term effect. For example, the improvement in visual acuity in DHA-supplemented infants appears during a time period in which it has been shown that the visual substrates of the CNS can be greatly affected by environmental input. The maintained focus upon the acuity variable misses the possibility that even a small early advantage in lower-order function may serve to affect higher-order functions at some later point.

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