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Neuropsychological Outcomes at Mid-Life Following Moderate to Severe Malnutrition in Infancy

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Abstract

Objective—To compare neuropsychological profiles of adults who had experienced an episode of moderate to severe protein-energy malnutrition confined to the first year of life with that of a healthy community comparison group.

Method—We assessed neuropsychological functioning in a cohort of Barbadian adults, all of whom had birth weight >2500g. The previously malnourished group (N=77, Mean age = 38 years, 53% male) had been hospitalized during the first year of life for moderate to severe protein energy malnutrition and subsequently enrolled in a program providing nutrition education, home visits, and subsidized foods to 12 years of age. They also had documented, adequate nutrition throughout childhood and complete catch-up in growth by the end of adolescence. The healthy comparison group (N=59, Mean age = 38 years, 54% male) were recruited as children from the same classrooms and neighborhoods.

Results—Adjusted for effects of standard of living during childhood and adolescence and current intellectual ability level, there were nutrition group differences on measures of cognitive

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flexibility and concept formation, as well as initiation, verbal fluency, working memory, processing speed, and visuospatial integration. Behavioral and cognitive regulation were not affected.

Conclusions—Postnatal malnutrition confined to the first year of life is associated with neurocognitive compromise persisting into mid-life. Early malnutrition may have a specific neuropsychological signature, affecting response initiation to a somewhat greater extent than response inhibition.

Keywords

infant; adult; lifespan; executive function

Neuropsychological Outcomes at Mid-Life Following Moderate to Severe Malnutrition in Infancy

Malnutrition in infancy and early childhood presents a major public health challenge in many parts of the developing world. In 2010, an estimated 167.2 million preschool children worldwide had growth stunting (that is, height more than 2 standard deviations below the expected population mean). The World Health Organization estimates that by 2015, 17.6% of preschool aged children worldwide will have experienced malnutrition, most of whom (an estimated 112.8 million) live in developing countries (Shashidhar, 2009).

Adequate nutrition in the early years of life is crucial for brain development. Experimental studies in animals provide ample documentation of the adverse neurodevelopmental effects of malnutrition during critical periods of brain development (Galler, Shumsky, & Morgane, 1996). Pre- and postnatal nutritional deprivation can result in longer-term alteration of brain structural and functional development (Bedi, 2003; Bronzino, Austin-LaFrance, Mokler, & Morgane, 1997; Galler, et al., 1996; Lister, et al., 2005; Lister, et al., 2006; Lukoyanov & Andrade, 2000). These changes are correlated with later compromise of learning and memory in affected animals (Almeida, Tonkiss, & Galler, 1996; Durán, Cintra, Galler, & Tonkiss, 2005; Lukoyanov & Andrade, 2000; Tonkiss, Galler, Shukitt-Hale, & Rocco, 1991; Valadares, Fukuda, Françolin-Silva, Hernandez, & Almeida, 2010).

The development of the hippocampus, for example, as well as its connectivity to other brain structures, can be substantially altered by prenatal malnutrition, and subregions of prefrontal cortex are especially vulnerable (Galler, et al., 1996; Morgane, et al., 1993; Morgane, Mokler, & Galler, 2002; Rosene, et al., 2004). Although these effects can be partially mitigated by nutritional rehabilitation, the brains of rehabilitated animals show persistent structural, microstructural, and neurochemical changes (Feoli, et al., 2008; Levitsky & Strupp, 1995; Mokler, Galler, & Morgane, 2003; Mokler, Torres, Galler, & Morgane, 2007; Morgane, et al., 1993; Morgane, et al., 2002). Previously malnourished animals also demonstrate long-term changes in cognition and emotionality, with behavioral rigidity a key outcome (Levitsky & Strupp, 1995; McGaughy, et al., 2013; Strupp & Levitsky, 1995; Tonkiss & Galler, 1990).

Human studies provide ample documentation of functional compromise, both cognitive and behavioral, during childhood and adolescence in children who were previously malnourished or growth stunted during the postnatal period, presumed to reflect the impact of the malnutrition on the developing brain (Berkman, Lescano, Gilman, Lopez, & Black, 2002; Galler & Ramsey, 1989; Galler, Ramsey, Solimano, Lowell, & Mason, 1983; Grantham-McGregor, 1995; Ivanovic, et al., 2000; Kar, Rao, & Chandramouli, 2008; Liu, Raine, Venables, Dalais, & Mednick, 2003). These studies generally find not only impaired IQ and educational attainment, but also behavioral problems in affected children and adolescents.

Given the worldwide prevalence of infantile malnutrition, its persisting effects on brain and behavioral development in experimental studies, and the well-documented cognitive and behavioral impacts of early malnutrition on child and adolescent development, the functioning of these children when they become adults is of major social concern. Individuals who suffered malnutrition early in life may well harbor life-long impairments, affecting their cognitive functioning, physical health, psychosocial adjustment, and economic productivity (Victoria, et al., 2008); however, the specific nature of their neurocognitive deficits is not yet well appreciated.

Adult Outcomes after Childhood Malnutrition

Data on longer-term outcomes of pre- and postnatally malnourished children are only recently becoming available. Effects of prenatal malnutrition have been investigated in the context of epidemiologic studies of outcomes for children born during times of severe famine, where prenatal nutrition was compromised. For example, the Dutch Famine Study followed individuals whose mothers had been pregnant during a famine in Holland during World War II and who were thus presumed to have been exposed to nutritional deprivation prenatally. At age 59, no long-term impact on cognition was detected, based on a battery of information processing measures, although there was indication that exposure to malnutrition early in the pregnancy could have a long-term impact on stress associated with cognitive performance (de Groot, et al., 2011; Ginty, Phillips, Rosebloom, Carroll, & Derooij, 2012).

In terms of postnatal malnutrition, a recent compilation of data from five epidemiologic cohorts (Martorell, Melgar, Maluccio, Stein, & Rivera, 2010) found that weight gain in the first two years of life predicted school attainment in adulthood. Intervention studies further corroborate an impact of malnutrition early in life. A Guatemalan study found that a protein supplement (versus a calorie supplement) extending from the prenatal period through the first two years of life resulted in long-term benefit in terms of cognitive outcomes and schooling at age 40 (Pollitt, Gorman, Engle, Rivera, & Martorell, 1995; Stein, et al., 2008) and improved educational attainment (Li, Barnhart, Stein, & Martorell, 2003). Although stunting in the first few years of life is generally associated with long-term intellectual compromise (Dewey & Begum, 2011), one study in Peru reported that those children who recovered their physical growth did not differ in cognitive functioning from a control group of children who had never experienced stunting (Crookston, et al., 2011), suggesting that physical rehabilitation can lead to neurocognitive recovery. Infectious diseases in childhood,

in particular parasitic infections, have also been linked to reduced IQ, and may play a role in the associations between early malnutrition and longer term cognitive outcomes (Eppig, Fincher, & Thornhill, 2010; Guerrant, DeBoer, Moore, Scharf, & Lima, 2013; Scrimshaw & Gordon, 1967).

Although these reports generally suggest long-term developmental impacts of early malnutrition occurring in early postnatal development, none utilized a controlled design, and the outcome metrics were quite general. Findings relevant to the malnutrition and its potential impacts, therefore, are in many cases inferential rather than controlled, and the outcomes measures are limited and non-specific. Moreover, the developmental timing of the malnutrition was not well specified; malnutrition or undernutrition could have begun prenatally and/or persisted during childhood.

Barbados Nutrition Study

The Barbados Nutrition Study (BNS) is a lifespan longitudinal study that has followed over a forty-year period a cohort who had been hospitalized for moderate to severe malnutrition during the first year of life. The BNS was designed originally as a case-control study, with a matched healthy control group recruited from the same classrooms and neighborhoods as the previously malnourished children. It therefore provides the opportunity for direct assessment of the potential developmental impacts of an episode of moderate to severe malnutrition in the first year of life. A key feature of the study is that all children were of normal birth weight (>2500g) and the malnourished group was enrolled in a government program after their initial rehabilitation. This program provided nutrition education, subsidized foods, health monitoring, and medical care until 12 years of age. Thus, interpretation of findings is not complicated by the potential effects of prenatal malnutrition or of chronic postnatal undernutrition or growth stunting. Indeed, by adolescence, the previously malnourished children had achieved complete catch-up in physical growth and no evidence of anemia, parasites, or other nutritional compromise (Galler, Ramsey, Salt, & Archer, 1987). Therefore, outcomes observed in these individuals can be more confidently attributed to *moderate to severe malnutrition that was limited to the first year of life*.

As children and adolescents, the previously malnourished individuals displayed significant compromise in their cognitive development, which would predict longer term impact. They exhibited lower IQ, more attention problems, and poorer school achievement than the control group when assessed longitudinally on multiple occasions (Galler, Ramsey, Forde, Salt, & Archer, 1987; Galler, Ramsey, & Solimano, 1984; Galler, Ramsey, Solimano, & Lowell, 1983; Galler, et al., 1983). Their performance on the Common Entrance Examination, a standard academic competency test administered to all Barbadian children at 11 years of age, was also poorer, referable largely to their impaired IQ and attention as measured throughout the primary grades (Galler, Ramsey, Morley, Archer, & Salt, 1990; Waber, et al., 2011).

As noted above, however, in clinical studies of the long-term effects of malnutrition, environmental influences remain a significant consideration, potentially accounting for adverse outcomes associated with the malnutrition. Indeed, even though the healthy control group in the BNS had been recruited from the same classrooms and neighborhoods as the

previously malnourished group, there were statistically significant differences in their socioeconomic circumstances as measured during childhood and adolescence. For example, relative to the comparison group, families of the malnourished children had somewhat lower incomes and more children in the home (Galler & Ramsey, 1985). In addition, their mothers were less well-educated and had their first child at a younger age, while the malnourished children were born later in the birth order (Galler, et al., 2010). Although these environmental influences were themselves systematically associated with cognition and academic achievement as would be expected, they nevertheless did not mediate the association between malnutrition and cognitive compromise (Galler, Ramsey, & Forde, 1986; Galler, et al., 1983; Waber, et al., 2011).

In 2006, the BNS undertook to assess outcomes in its participants in mid-adulthood, including neuropsychological, psychiatric, and social functioning, as well as physical health. There was an estimated 9-fold increase in the prevalence of IQ in the range of intellectual disability (< 70) in the previously malnourished group, and basic academic skills were significantly depressed, even after adjusting for the effects of standard of living throughout childhood and adolescence (Waber, et al., 2013). Adult IQ was highly correlated with childhood IQ, indicative of the continuity of cognitive effects over time. The previously malnourished group also self-reported more attention problems and performed more poorly on a continuous performance test (Galler, Bryce, Zichlin, et al., 2012). Inattention symptoms were more prevalent than impulsivity, and omission errors differentiated the groups better than commission errors. Finally, the educational and occupational attainment of the previously malnourished group was significantly reduced, as was their household income, with the disparity increasing over time, indicative of the long-term economic implications of the developmental impairment (Galler, Bryce, Waber, et al., 2012). Although not completely eliminated, the group difference in social position was attenuated with childhood IQ in the model, attesting to the functional and adaptive implications of the cognitive impairment.

The present report further expands the characterization of these individuals by documenting their *neuropsychological profiles*. Based on the childhood data, we hypothesized that the neuropsychological differences would be most prominent in measures of executive functioning. Findings of behavioral rigidity from the animal studies, as well as the profile of attention deficits in these individuals (Galler, Bryce, Zichlin, et al., 2012), further led us to hypothesize that within the broad umbrella of executive functioning, *response initiation* would be more affected than *response inhibition* (Burgess & Shallice, 1996).

Methods

Site

The study was conducted in Barbados, a Caribbean country whose current population is approximately 260,000 persons. The composition of the population is 92% African/Caribbean origin, 4% Caucasian; the remaining population is mainly of Asian, Lebanese, and Syrian descent. In 1970, the infant mortality rate was 46 per 1,000 live births. That rate has now fallen to 7.8, and Barbados is ranked forty-second on the Human Development Index (United Nations Development Programme, 2011). Thus, whereas moderate-severe cases of infant malnutrition were of significant concern when this study was undertaken in

the 1970's, infant malnutrition is now virtually eliminated from the island due to its improved economy and the impact of island-wide nutrition-related education (Ramsey, Demas, & Trotter, 1984).

Design and Participants

Figure 1 illustrates the design and specifies the source of the 136 individuals on whom the present report was based. Participants were evaluated comprehensively at three time points spanning childhood and adolescence and subsequently as adults. In 1977, 129 children with histories of marasmus (deficiency of protein and calories) and 129 healthy comparison children, all of whom were between the ages of 5 and 11 at that time, were evaluated. The same children were re-evaluated in 1982 (not shown in the Figure). In 1984 and again in 1991 (not shown), an additional group of children who had been hospitalized for kwashiorkor (N=62, insufficient protein in the diet) during the same period as the children with marasmus was recruited for comparison purposes. At that time, 123 (marasmus, N=61; healthy comparison, N=62) of the original 258 children were selected for evaluation because they were the best matches for age, sex and grade in school to the kwashiorkor group. Note that the reduction in sample size at that point was not due to attrition, but to the focus of the study design at the third time point on potential differences in outcome between marasmus and kwashiorkor.

Data collection for the present study was carried out between 2006 and 2010, when these individuals were in the latter part of their fourth decade of life. Anyone who had participated at any point in the study was eligible for this long-term follow-up. Since the kwashiorkor and marasmus groups did not differ on outcomes measured in adolescence (Waber, et al., 2011), or in preliminary analyses of the adult outcomes, their data were combined for the present study. The sample thus included 80 previously malnourished (MAL) and 63 control (CON) participants. Median age of hospital admission (for the MAL group) was 7.37 months (range 1-13 months). Of these, neuropsychological data were obtained from 77 individuals from the MAL group and 59 from the CON group.

Although we were able to account for 98% of the original participants through preliminary interviewing of community contacts, fewer were studied. A number of factors contributed to this reduction in numbers. Some individuals were deceased or incarcerated, and a number had moved off the island and were lost or inaccessible to follow-up. A further source of attrition was a limitation in funding resources to support the data collection effort. A total of 248 (149 MAL, 99 CON) individuals were available (i.e., alive, residing on the island, not incarcerated) to recruit, of whom we successfully evaluated 136 (77 MAL, 59 CON). Preliminary analysis confirmed that there were no statistically significant differences between participants and non-participants from the original cohort in terms of age, gender, group membership, childhood IQ, or childhood standard of living (Waber, et al., 2013). The participants in this study could therefore validly be assumed to be representative of the original cohort. Written informed consent was provided by all participants under the oversight of the Judge Baker Children's Center Human Research Review Committee (Assurance No. FWA 00001811).

Measures

Childhood Standard of Living—Childhood standard of living was measured at all 3 measurement points in childhood and adolescence using a Socioeconomic Status and Ecology Questionnaire, which assessed conditions in the home, as well as educational level and employment history of the parents. The questionnaire contained 50 items assessing environmental conditions that were most relevant to the social context at the time (Galler, Bryce, Waber, et al., 2012; Galler, et al., 1983). Factor analysis, based on data combined across all three time points, identified a first principal component (Galler, et al., 2010) that appeared to represent standard of living, including possession of a refrigerator, bath, television, electricity, running water, closet, and gas or electric cooking fuel; number of bedrooms/rooms; household food expenditure; type of toilet; and weekly household income. Scores based on this factor were standardized to have zero mean and unit variance.

Neuropsychological Battery—The neuropsychological test battery was intended to be comprehensive, with an emphasis on executive functioning, including both laboratory and questionnaire measures of response inhibition and response initiation (cognitive flexibility). The battery included well-standardized neuropsychological tests, with minor modifications for the Barbados setting. Because of dialect differences between Barbadian and Standard American English, formal measurement of more complex language functioning was not undertaken. Also, because the tests are not normed in Barbados, U.S. norms were applied. Although these standardized scores are valid for group comparison, they are not necessarily representative of performance relative to the Barbadian population and should be interpreted accordingly.

The Wechsler Abbreviated Scale of Intelligence – Vocabulary and Matrix Reasoning subtests (Wechsler, 1999) were administered to provide a general estimate of IQ. Since the control group had a mean estimated IQ of 100 (Table 1), the U.S. norms are likely a reasonably good approximation of the performance of the general Barbadian population on many measures.

The neuropsychological battery included the following: Wechsler Adult Intelligence Scale – Third Edition – Digit Symbol and Letter-Number Sequencing (Wechsler, 1997); Purdue Pegboard (Tiffin & Asher, 1948); Wide Range Assessment of Memory and Learning – II – Sentence Memory (Sheslow & Adams, 2004); Delis-Kaplan Executive Function System – Trails, Color-Word Interference, and Verbal Fluency (Delis, Kaplan, & Kramer, 2001); Rey-Osterrieth Complex Figure, Boston Qualitative Scoring System (Stern, et al., 1999); Wisconsin Card Sorting Test (Heaton, 2005); and Behavioral Rating Inventory of Executive Functioning – Adult (Roth, Isquith, & Gioia, 2007). The latter two measures were introduced mid-way into the study, and so there were fewer participants for those variables (64 MAL, 45 CON). Within the context of this battery, measures of executive function were designated on an *a priori* basis to assess *response inhibition* (D-KEFS Color-Word Interference, BRIEF Inhibit, Emotional Control, and Self-Monitor scales) or *response initiation* (D-KEFS Verbal Fluency, Wisconsin Card Sort, and BRIEF Shift and Initiate scales).

Testing was carried out in a single session at the BNS laboratory in Bridgetown, Barbados by a trained local psychologist or psychometrician, both of whom were blind to the nutritional history of the participants. Each tester completed pilot testing on at least 5 individuals prior to the start of the study to assure valid and reliable administration, and the protocols were monitored by the neuropsychologist (DPW) and her staff throughout the study to assure reliability. The session lasted approximately 3 hours, including a brief break.

Statistical Methods

Data were analyzed using SAS statistical software, version 9.2. (SAS Institute, 2010). Means, standard deviations, and ranges were calculated for all outcomes. Group differences in demographic characteristics were evaluated by t-tests.

Because of the known impact of socioeconomic circumstances on cognitive outcome and the documented differences between the nutrition groups on this variable, we adjusted for its effects in all analyses. We adjusted for childhood socioeconomic status but not current socioeconomic status since the latter was viewed as a potential outcome of longstanding functional compromise associated with the early malnutrition.

Since we were more interested in neuropsychological profiles than in overall level of intellectual functioning, we needed to adjust for group differences in current IQ, which were substantial (Waber, et al., 2013). Since most of the neuropsychological measures were highly correlated with IQ, simply adjusting for IQ could run the risk of attenuating potentially interesting profiles (Dennis, et al., 2009); yet, failing to adjust for IQ could yield so many statistically significant differences that profiles would be obscured. As a middle ground, we chose to adjust for IQ as a categorical variable (IQ $\leq$ 70 versus IQ $>$ 70), thereby adjusting for more severe cognitive impairment while allowing potential patterns to emerge.

Group differences were evaluated by longitudinal multiple regression analyses (SAS PROC MIXED) with infant malnutrition the independent variable and childhood standard of living (measured at T1, T2, and T3 as available) and categorical IQ included as covariates in the model. These analyses involved simultaneously fitting separate multiple regression equations at T1, T2, and T3, thereby allowing the effects of the childhood standard of living to vary over time. Since the sex distributions were nearly identical, sex was not included in the final models

Finally, in order to directly assess the hypothesis that response initiation would be affected to a greater extent than response inhibition, we created composite variables by normalizing to z-scores the four measures in each group (Response Initiation: Wisconsin Card Sorting Test Total Errors, D-KEFS Verbal Fluency Letters, BRIEF Shift, Initiate; Response Inhibition: D-KEFS Interference Errors, BRIEF Inhibit, Emotional Control, and Self-Monitor) and calculating the mean. These were submitted to a mixed effects analysis (PROC MIXED), with malnutrition group the between factor and response type the within factor, adjusting for the effects of sex and intellectual disability. The malnutrition by response type interaction was examined as a test of the hypothesis. The number of participants was somewhat reduced for this analysis because fewer had completed the BRIEF and the Wisconsin Card Sorting Test.

Results

Demographic Characteristics

Table 1 displays the demographic characteristics of the study sample. The nutrition groups did not differ in age or sex, but standard of living in childhood and adolescence was higher in the control group. There was an estimated group difference of 16 points in IQ.

Since sample attrition raised concerns about bias, we compared the demographic characteristics, as documented at the time of their entry to the study as children or adolescents, of individuals who did and did not participate as adults. Participants and non-participants did not differ in terms of representation from the malnourished and control groups, childhood IQ, or childhood standard of living. Borderline range differences ($p=0.10$) were detected for age (participants older) and sex (proportionally fewer males among participants).

Neuropsychological Outcomes

Table 2 displays the unadjusted group means, as well as parameter estimates for models that included malnutrition status and childhood standard of living as predictors, with and without IQ in the model. The parameter estimates for malnutrition can be interpreted as adjusted mean differences (comparing MAL to CON group).

As expected, in models adjusted only for childhood standard of living, the MAL group performed more poorly on nearly all measures, the only exceptions being the D-KEFS Color-Word Interference and the Purdue Pegboard. In the IQ-adjusted models, significant differences persisted for the WAIS Digit Symbol and Letter-Number, D-KEFS Trails (Numbers) and Verbal Fluency (Letters), Rey-Osterrieth Complex Figure, and Wisconsin Card Sorting Test.

Group differences on the Wisconsin Card Sorting Test were particularly robust, with effect sizes in the medium range, even after adjusting for childhood standard of living and IQ level. We further explored this group difference by adjusting for IQ as a continuous variable. Significant differences persisted for Total Errors ($B=-5.42$, $p<0.05$), Categories ($B=0.82$, $p<0.05$), and Learning to Learn ($B=7.86$, $p<0.05$), with a marginally significant difference for Concept ($B=7.25$, $p<0.10$). Figure 2 shows the distribution of categories achieved (unadjusted for covariates) for the two groups. The Control group achieved a median of 3 categories, whereas the previously malnourished group achieved a median of only 1 category and a number of participants were unable to achieve even one category.

Table 3 shows outcomes for the BRIEF Self-Report. Again, there were significant group differences for most subscales and for all the composite indices. With IQ level in the model, however, the effect sizes were again substantially reduced, but several scales remained statistically significant (Shift, Initiate, Planning/Organization), as did all the index scores.

Finally, the mixed effects analysis documented main effects for nutrition group ($p<0.0001$) and response type ($p<.0001$), with overall performance better on tasks of response inhibition than response initiation for both nutrition groups. Although the nutrition group differences,

adjusted for covariates, were larger for response initiation (0.55) than for response inhibition (0.32), as predicted, the interaction failed to achieve statistical significance, $F(1, 76)=1.71$, $p<0.2$).

Discussion

The present findings further document the life-span neurocognitive and neurobehavioral burden of infantile malnutrition in a well-characterized sample that has been followed in a controlled study over four decades from infancy to mid-life. Although the overwhelming finding is one of global cognitive compromise, specific neuropsychological deficits emerged against this backdrop. Measures of response initiation appeared to be more affected by nutrition group than measures of response inhibition, as predicted, but the difference did not achieve statistical significance in this setting. Additional deficits were documented in visuospatial integration (Rey-Osterrieth Complex Figure), processing speed, and working memory (Letter-Number Sequencing).

In tandem with the previously reported elevation of inattention symptoms with only a trend effect for impulsivity symptoms (Galler, Bryce, Zichlin, et al., 2012), the present findings suggest an emerging profile or behavioral signature of early nutritional deprivation. Limitations of cognitive aspects of executive functioning were demonstrated, but evidence for impairment of the more regulatory functions was somewhat weaker. Collectively, these findings add substantially to existing reports of adult cognitive outcomes, which have previously been restricted to general indicators such as educational attainment or IQ.

The primary hypothesis of the study was that the previously malnourished individuals would exhibit compromise of executive functioning, in particular cognitive flexibility. In fact, performance on the Wisconsin Card Sorting Test was prominently impaired in the previously malnourished individuals, with effect sizes in the moderate range even after adjusting for IQ level and with a somewhat reduced sample size. Indeed, the effects generally remained statistically significant even after adjusting for IQ as a continuous rather than a categorical variable. The previously malnourished group made more errors and achieved fewer categories, including but not limited to the perseverative errors that would reflect lack of flexibility. Self-report on the BRIEF, moreover, further confirmed cognitive flexibility as a problem area.

Cultural influences are also relevant to these neuropsychological outcomes. Even though the IQ of the control group was estimated in the Average range (mean=99, SD=15), their performance on some of the neuropsychological measures was notably discrepant. Their mean scores on processing speed as well as many of the D-KEFS outcomes were only in the Low Average range, and they achieved a median of only three categories on the WCST, well below normative expectation for a US population. Scores on the D-KEFS are primarily based on response times, which may be influenced by cultural norms. Indeed, many participants were observed to approach the tasks in a slow and careful manner rather than appearing hurried or rushed. In addition, cross-cultural studies report that the number of categories achieved on the WCST can vary normatively across cultures and can also be related to acculturation (Coelho, do Rosário, Mastroso, Miranda, & Amodeo Bueno, 2012;

Coffey, Marmol, Schock, & Adams, 2005; Shan, Chen, Lee, & Su, 2008; Shu, Tien, Lung, & Chang, 2000). This variability in performance levels across measures within the control group emphasizes the importance of including a control group in cross-cultural studies such as this one.

Potential Neural Substrates

The neural substrates affected by early malnutrition in humans are not well understood. Magnetic resonance imaging studies have documented structural changes in the brains of children during the acute phases of protein-energy malnutrition, the most consistent being cerebral atrophy (Atalabi, Lagunju, Tongo, & Akinyinka, 2010; Hazin, Alves, & Falbo, 2007; Odabas, et al., 2005). One longitudinal study reported, however, that by 90 days after admission for rehabilitation, the cerebral “shrinkage” was largely reversed, suggesting recovery (Gunston, Burkimsher, Malan, & Sive, 1992). In the rodent models, however, malnutrition can lead to microstructural and neurochemical changes that are not reversed by nutritional rehabilitation (Galler, et al., 1996; Levitsky & Strupp, 1995; McGaughy, et al., 2013; Mokler, et al., 2003; Morgane, et al., 1993), thought to signal impaired synaptic plasticity and responsiveness. Although such changes would not be detected by clinical MRI, neuropathological analysis of the brains of infants who died of malnutrition has in fact documented alterations in dendritic structure (Benítez-Bribiesca, De la Rosa-Alvarez, & Mansilla-Olivares, 1999).

The prominent differences in performance on the Wisconsin Card Sorting Test, with moderate to large effect sizes even after adjusting for intellectual disability, are of particular interest in this regard. These outcomes align nicely with recent experimental evidence in prenatally malnourished rats, who demonstrated deficits in set shifting on an intradimensional/extradimensional set shifting paradigm; the cognitive demands of this task are well-aligned with those of the WCST. Although the previously malnourished rats did not differ from control animals in establishing an attentional set, they required more trials to achieve the extradimensional set shift, indicative of cognitive rigidity (McGaughy, et al., 2013). In a related study, prenatally malnourished rats assessed in a sustained attention paradigm were less susceptible than control animals to the detrimental effects of an auditory distractor. This type of cognitive rigidity can result from damage to the prelimbic cortex of rodents (Birrell & Brown, 2000; McGaughy, Ross, & Eichenbaum, 2008), or to the dorsolateral prefrontal cortex of primates (Dias, Robbins, & Roberts, 1996a, 1996b, 1997) and humans (Owen, Roberts, Polkey, Sahakian, & Robbins, 1991).

The neural substrates for the WCST have been systematically explored by functional neuroimaging. Although the WCST was at one time viewed as an indicator of prefrontal functioning, contemporary neuroimaging studies implicate a distributed network, involving primarily prefrontal cortex, but also inferior parietal lobe, temporo-parietal association cortex and visual cortex, as well as the basal ganglia (Nyhus & Barceló, 2009). Monchi and colleagues (Monchi, Petrides, Petre, Worsley, & Dagher, 2001) identified two distinct circuits underlying performance: a distributed network involving mid-dorsolateral prefrontal cortex was associated with receiving positive or negative feedback, and a network involving mid-ventrolateral prefrontal cortex associated with negative feedback and hence the need to

shift. Although these findings obviously cannot be directly applied to our observations, they reinforce the notion that infant malnutrition can have long-term impact on the development of frontal cortex and associated functional networks. Neuroimaging studies using positron emission tomography (PET) have revealed associations between WCST performance and dopamine receptors (D1) in prefrontal cortex (Takahashi, Yamada, & Suhara, 2012) and D2 receptors in the hippocampus (Takahashi, et al., 2008), further suggesting potential mechanisms.

Experiential Influences

Potential experiential influences are also relevant. Even though the healthy control children were selected from the same classrooms and neighborhoods as the index children, the groups still differed in their standard of living. Although we adjusted statistically for these effects in all our models, our indicators could have failed to fully capture significant but unknown experiential adversities or other influences that could account to some extent for the differences.

Another consideration is maternal depression, which is known to predispose to infant malnutrition in fragile economic circumstances (Galler, Harrison, Biggs, Ramsey, & Forde, 1999; Rahman, Iqbal, Bunn, Lovel, & Harrington, 2004). The BNS did not obtain data on maternal-infant interactions, but it did assess maternal depression during childhood and adolescence. Although maternal depression was associated with childhood cognitive and behavioral outcomes, its effect was independent of the malnutrition and thus did not mediate the malnutrition effect (Waber, et al., 2011).

Finally, although group differences in IQ in the Barbados sample are relatively stable over time (Waber, et al., 2013), the observed profiles are not necessarily direct sequelae of brain alterations associated with the episode of malnutrition. They may also reflect the developmental interactions of the neurologically compromised child with the physical and social environment, and in particular with an impoverished environment (Gottlieb & Halpern, 2002; Wachs, 2009). To some extent, therefore, the adult outcomes may be epiphenomena, reflecting the ongoing developmental impact of the child's neurological impairment on these interactions, and the further impact of the interactions themselves on subsequent neural and behavioral development. We cannot infer from these data, therefore, what the effects of early malnutrition might be in an environment that provided greater support for child development.

Limitations

This study has several limitations. First, as discussed, although we used the best available data to control experimentally for experiential differences between the nutrition groups, we cannot be certain that the group differences observed are fully attributable to the history of early malnutrition and that there were not undetected but salient experiential or genetic differences between the groups. Second, because of dialect variants, we had limited ability to measure language and we thus cannot comment on language functioning, an important neuropsychological outcome. Nor did we include direct measures of learning efficiency, which could have been informative. Third, the current report includes 44% of the original

sample and 55% of potentially available participants. Although we found no evidence of bias (in terms of age, gender, group membership, childhood IQ, or childhood standard of living), suggesting that our participants are representative of the cohort, there could have been some unknown source of bias that we did not detect, potentially compromising generalizability.

Conclusion

The findings of the present study suggest that the lifetime neuropsychological morbidity ensuing from an episode of moderate to severe malnutrition confined to the first year of life is considerable. This morbidity was detected even among individuals who had been of normal birth weight, nutritionally rehabilitated, achieved complete catch-up in their physical growth and remained in good health throughout childhood. These neuropsychological burdens can carry substantial social, economic, and health risks.

Given the prevalence of both malnutrition and undernutrition among young children worldwide, our findings suggest that this condition can lead to lifelong functional impairment, with associated loss of human capital and increased social burden. Since the participants in the BNS were fully rehabilitated nutritionally, with complete catch-up in physical growth, the prospects for mitigating these significant neurodevelopmental insults once they have occurred are uncertain at best. Prevention of early childhood malnutrition as well as early life interventions must therefore remain a major public health goal, especially in the developing world.

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Figure 1.
Source of adult participants from Barbados Nutrition Study for neuropsychological follow-up study.

Figure 2. Percent of participants in previously malnourished (MAL) and Control (CON) groups by number of categories achieved on the Wisconsin Card Sorting Test (unadjusted for covariates).

Table 1
Demographic characteristics by group

	Malnutrition Group(N=77)		Control Group(N=59)	
	Mean	S.D.	Mean	S.D.
Age (years)	38.36	1.86	38.13	1.93
Sex N(%) male	41 (53.2)		32 (54.2)	
Childhood Standard of Living at T1 ***	-0.91	0.93 (n=53)	-0.27	0.80 (n=59)
Childhood Standard of Living at T2 *	0.31	0.81 (n=47)	0.66	0.74 (n=52)
Childhood Standard of Living at T3 *	0.16	0.73 (n=58)	0.53	0.62 (n=28)
WASI Estimated IQ (Adult) ***	82.83	16.62	99.03	15.43

*
p<0.05,

**
p<0.01,

p<0.001

Table 2
Unadjusted Means and Parameter Estimates (mean differences) for Effect of Malnutrition History on Neuropsychological Test Battery Adjusted for Childhood Standard of Living with and without Adjusting for IQ (<70 versus > 70)

	Unadjusted Means			Parameter Estimates		
	Malnutrition Group		Control Group	Malnutrition		Malnutrition with IQ in model
	Mean	S.D.		Beta	Beta	
WAIS-III (Scaled Score)						
Digit Symbol	6.31	2.39	8.25	2.43	-1.79****	-1.21**
Letter-Number	6.63	3.09	8.69	2.90	-1.90****	-1.23*
D-KEFS Trails (Scaled Score)						
Visual	8.05	3.22	9.54	2.70	-1.21*	-0.47
Letter	6.06	3.77	8.19	2.84	-1.98**	-0.79
Number	6.71	3.31	9.10	3.36	-2.14****	-1.28*
Alternating	5.52	3.55	6.88	3.76	-1.35*	-0.34
D-KEFS Color-Word Interference (Scaled Score)						
Color	6.88	3.97	8.27	3.13	-0.91	0.01
Word	7.48	3.76	8.51	3.35	-1.08	-0.11
Interference	6.12	3.77	7.36	3.46	-0.45	-0.13
Interference-Switch	5.82	3.99	7.01	3.60	-1.09	-0.49
Interference Errors	5.97	3.53	7.57	3.60	-1.14	-1.14
Interference-Switch Errors	7.22	3.88	9.23	2.75	-1.97**	-1.02
D-KEFS Verbal Fluency (Scaled Score)						
Letters	6.70	3.54	9.49	3.54	-2.88****	-1.84**
Category	6.32	3.00	7.89	3.37	-1.40*	-0.68
Letter-Category Switch	7.22	3.39	8.14	2.97	-0.66	0.09
Rey-Osterrith Complex Figure (T-Score)						
Copy Presence and Accuracy	41.31	13.86	47.7	11.32	-7.14**	-5.55*
Immediate Presence and Accuracy	41.33	9.95	46.7	9.63	-5.33**	-3.61
Delayed Presence and Accuracy	39.32	10.46	45.2	8.75	-6.09**	-4.66*

	<i>Unadjusted Means</i>		<i>Parameter Estimates</i>			
	Malnutrition Group		Control Group		Malnutrition with IQ in model	
	Mean	S.D.	Mean	S.D.	Beta	Beta
Organization	45.13	14.00	51.0	12.90	-7.00**	-5.88*
Purdue Pegboard (# pegs)						
Right	13.92	2.22	14.09	1.96	-0.09	0.11
Left	13.03	2.29	13.72	1.62	-0.51	-0.27
Both	10.66	2.05	11.20	1.77	-0.33	-0.07
WRAML-2 Sentence Memory (Scaled Score)	7.45	2.28	8.49	1.81	-1.08**	-0.42
Wisconsin Card Sorting Test^a (Standard Score)						
Total Errors	80.67	12.53	94.56	12.70	-12.40***	-9.74***
Perseveration Errors	87.74	13.02	97.63	14.36	-9.29***	-6.92*
Concept	81.46	11.83	95.14	15.18	-12.08***	-9.34***
Categories (raw)	1.60	4.60	2.90	1.50	-1.32***	-1.09***
Learning to Learn	-10.19	8.11	-1.38	4.74	7.85***	7.71**

* p<0.05

** p<0.01

*** p<0.001

**** p<0.0001

^a MAL, N=54; CON, N=43

Table 3
Unadjusted Means and Parameter Estimates (mean differences) for Effect of Malnutrition History on Behavioral Rating Inventory of Executive Functioning Scores Adjusted for Childhood Standard of Living with and without Adjusting for IQ (≤ 70 versus > 70)

	Malnutrition		Control		Malnutrition		Malnutrition with IQ in model	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Behavioral Regulation Index	49.51	11.21	43.34	7.52	5.49**		3.40*	
Inhibit	45.71	7.75	42.74	4.25	2.64**		1.32	
Shift	52.84	11.01	45.88	9.17	6.59**		3.83*	
Emotional Control	50.65	12.42	44.64	9.04	5.13*		3.53	
Self-Monitor	48.80	9.81	44.48	6.80	4.11*		2.63	
Metacognitive Index	46.25	7.53	42.00	5.74	4.54***		3.31*	
Initiate	45.69	7.48	43.36	7.52	4.16**		3.27*	
Working Memory	50.11	10.67	45.24	6.27	5.06**		3.01	
Planning/Organization	49.53	6.94	44.50	6.39	4.96***		3.70**	
Task Monitoring	46.85	7.59	44.00	7.14	3.06		2.31	
Organization of Materials	42.73	7.62	40.57	5.10	2.33		2.22	
General Executive Composite	47.36	9.33	41.81	6.05	5.39***		3.70*	

Note. Higher score indicates more problems.

* $p < 0.05$
 ** $p < 0.01$
 *** $p < 0.001$