Central Adiposity Is Negatively Associated with Hippocampal-Dependent Relational Memory among Overweight and Obese Children

Naiman A. Khan, PhD, RD[1], Carol L. Baym, PhD[2], Jim M. Monti, PhD[2], Lauren B. Raine, BS[1], Eric S. Drollette, BS[1], Mark R. Scudder, BS[1], R. Davis Moore, PhD[1], Arthur F. Kramer, PhD[2,3,4,5], Charles H. Hillman, PhD[1,2,3,4,5], and Neal J. Cohen, PhD[2,3,4,5]

Objective To assess associations between adiposity and hippocampal-dependent and hippocampal-independent memory forms among prepubertal children.

Study design Prepubertal children (age 7-9 years; n = 126), classified as non-overweight (<85th percentile body mass index [BMI]-for-age [n = 73]) or overweight/obese (≥85th percentile BMI-for-age [n = 53]), completed relational (hippocampal-dependent) and item (hippocampal-independent) memory tasks. Performance was assessed with both direct (behavioral accuracy) and indirect (preferential disproportionate viewing [PDV]) measures. Adiposity (ie, percent whole-body fat mass, subcutaneous abdominal adipose tissue, visceral adipose tissue, and total abdominal adipose tissue) was assessed by dual-energy X-ray absorptiometry. Backward regression identified significant ($P < .05$) predictive models of memory performance. Covariates included age, sex, pubertal timing, socioeconomic status (SES), IQ, oxygen consumption, and BMI *z*-score.

Results Among overweight/obese children, total abdominal adipose tissue was a significant negative predictor of relational memory behavioral accuracy, and pubertal timing together with SES jointly predicted the PDV measure of relational memory. In contrast, among non-overweight children, male sex predicted item memory behavioral accuracy, and a model consisting of SES and BMI *z*-score jointly predicted the PDV measure of relational memory.

Conclusion Regional, but not whole-body, fat deposition was selectively and negatively associated with hippocampal-dependent relational memory among overweight/obese prepubertal children. *(J Pediatr 2015;166:302-8)*.

Converging evidence now suggests that poor cognitive function may be yet another complication of obesity.[1] Obesity is an independent risk factor for developing dementia and Alzheimer disease later in life.[2] In addition, the complications of obesity are becoming evident in obese children.[3] Nonetheless, there has been only limited research connecting obesity to cognitive function in childhood. Central adiposity in particular is implicated in the progression of insulin resistance.[4] Fat around the abdominal viscera in the mesentery and omentum, known as visceral fat, is functionally different from fat in the abdominal subcutaneous areas (subcutaneous fat); however, the implications of these fat depositions or their sum (total abdominal adiposity) on pediatric cognitive function remain unknown.[5] Furthermore, as in adults, different fat compartments in children may have differential functional effects based on weight status.[6] Increased waist-to-hip ratio is negatively correlated with memory and hippocampal volume in adults.[7,8]

The hippocampus is critical for relational (associative) memory, which supports representation of the relationships between items, such as the relationships among the constituent elements of events and their subsequent flexible expression.[9] It is likely that acquisition of relational knowledge provides a foundation for scholastic achievement, and its flexible expression enables successful handling of novel challenges. Therefore, changes in the development of this system in childhood would have wide-ranging impacts. In contrast, memory for individual items (item memory) relies on the perirhinal cortex, the anterior region of the parahippocampal gyrus.[9] The dependence of these 2 memory processes on distinct neural substrates provides an opportunity to study their differential sensitivity to adiposity.

Consequently, in the present study, we examined whether relational and/or item memory are related to whole-body and central adiposity in prepubertal

BMI	Body mass index
CT	Computed tomography
DXA	Dual-energy X-ray absorptiometry
PDV	Preferential disproportionate viewing
SAAT	Subcutaneous abdominal adipose tissue
SES	Socioeconomic status
TAAT	Total abdominal adipose tissue
VAT	Visceral adipose tissue
VO_{2max}	Maximal oxygen consumption

From the [1]Department of Kinesiology and Community Health, [2]Beckman Institute for Advanced Science and Technology, [3]Department of Psychology, [4]Neuroscience Program, and [5]Center for Nutrition, Learning, and Memory, University of Illinois, Urbana, IL

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children, and whether these associations varied by weight status. We hypothesized that central adiposity would be selectively and negatively associated with relational memory, and that this association would vary based on weight status.

Methods

A total of 126 prepubertal children aged 7-9 years provided written assent, and each child's legal guardian provided written informed consent in accordance with the regulations of the University of Illinois Institutional Review Board. Children were screened for neurologic disorders, physical disabilities, psychoactive medication status, and normal or corrected-to-normal vision. Data were also collected on IQ, using the Kaufman Brief Intelligence Test[10] or the Woodcock-Johnson Tests of Cognitive Abilities[11]; socioeconomic status (SES), estimated based on household income, participation in a school meal-assistance program, maternal and paternal education levels, and number of parents working full-time; and pubertal status.[12]

Anthropometrics and Body Composition

Height and weight were measured using a stadiometer (model 240; Seca, Hamburg, Germany) and a digital scale (WB-300 Plus; Tanita, Tokyo, Japan). The Centers for Disease Control and Prevention's 2000 growth charts were used to determine body mass index (BMI)-for-age percentile and BMI *z*-score.[13] Classification of children as non-overweight or overweight/obese was based on the 85th percentile BMI-for-age cutoff.[13]

Adiposity was assessed by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR 4500A bone densitometer (software version 13.4.2; Hologic, Bedford, Massachusetts). Percent whole-body fat mass was expressed using the standard software measure. The estimation of central adiposity variables has been described previously.[14] In brief, the abdominal region of interest was a 5-cm-wide section placed across the entire abdomen just above the iliac crest at a level approximately coinciding with the fourth lumbar vertebrae on the whole-body DXA scan. Total abdominal adipose tissue (TAAT) was defined as the total adipose tissue area within this region. Subcutaneous abdominal adipose tissue (SAAT) was determined using an algorithm that composites the adipose tissue on the sides of the abdominal cavity and estimated amount of subcutaneous fat overlying the abdominal cavity. This estimated SAAT was subtracted from the TAAT to determine the visceral adipose tissue (VAT) value. This estimated VAT has been shown to correlate ($r = 0.92$; $P < .01$) with computed tomography (CT)-determined VAT values.[14]

Cardiorespiratory Fitness Assessment

Maximal oxygen consumption (VO_{2max}) was measured using a modified Balke treadmill protocol.[15] Oxygen consumption was measured with a computerized indirect calorimetry system (True Max 2400; ParvoMedics, Sandy, Utah) with averages for oxygen consumption and respiratory exchange ratio assessed every 20 seconds. VO_{2max} was based on maximal effort, as evidenced by: (1) a peak heart rate ≥185 bpm[15] and a heart rate plateau[16]; (2) a respiratory exchange ratio >1.0[17]; (3) a score of >8 on the children's OMNI rating of perceived exertion scale[18]; and/or (4) a plateau in oxygen consumption corresponding to an increase of <2 mL/kg/min despite an increase in workload.[15] The absolute VO_{2max} was then adjusted for fat-free mass (derived by DXA) to calculate the measure of fat-free VO_{2max}.[19]

Memory Tasks

Children completed a task adapted from Monti et al,[20] but with child-friendly creatures (Electronic Arts, XXX, California) rather than faces (**Figure 1**; available at www.jpeds.com).[21] In separate study test blocks, children studied individual creatures (item condition) or uniquely paired associations between creatures and backgrounds ("habitats"; relational condition). During the test, participants were instructed to find the creature originally studied with that scene from an array of 3 creatures. One of the creatures had been studied with that scene (target), and the other 2 had been studied with other scenes (foils). Thus, familiarity across the 3 creatures was matched, necessitating the use of hippocampal-dependent relational memory.[22] In the item condition, the background scene was the same for all creature–scene pairings within each block. During the test, participants were instructed to find the previously viewed creature. In each test display, 2 creatures were novel and 1 creature had been studied, allowing for discrimination on the basis of familiarity, an ability independent of the hippocampus.[23] Lists of stimuli were counterbalanced across conditions between participants, and target locations on test trials were counterbalanced within participant such that the target was equally likely to appear in any of the 3 possible locations. The order of study test blocks was counterbalanced across participants such that one-half of the participants began with the relational condition and the other one-half began with the item condition.

An Eyelink 1000 eye-tracker (SR Research, XXX, Ontario, Canada) was used remotely to record eye-movements at 500 Hz. Time courses were quantified using preferential disproportionate viewing (PDV), defined as the difference in proportion of time spent viewing correctly selected matching creatures relative to proportion of time spent viewing incorrectly selected creatures before a behavioral response. This measure corrects for the fact that individuals look longer at the stimulus that they will behaviorally select, independent of previous experience. In this way, the magnitude of PDV provides a measure of memory for previous experience, with greater PDV indicating a greater degree of memory accuracy, an effect that has been shown to manifest even before the viewer's behavioral awareness.[24]

Statistical Analyses

Differences between the non-overweight and overweight/obese participants in memory measures were assessed using an independent-samples *t* test. Initially, Pearson correlations were used to assess bivariate relationships between adiposity

and memory measures in all participants. Subsequently, bivariate correlations within weight category were performed. Finally, stepwise multiple regression within each weight status group was applied using the backward method of predictor entry (demographics, fitness, and adiposity) to determine predictors of memory performance. This method initially includes all variables, followed by a step-by-step elimination until no omitted variable would have contributed to the model. Each predictor's contribution was assessed by studying its significance (α-level, 0.05). Statistical analyses were performed with SPSS 19 (IBM, Armonk, New York).

Results

A total of 126 children aged 7-9 years (71 females) participated in this study. SES categorization of the participants was 35% low, 35% medium, and 30% high. According to the Tanner pubertal staging questionnaire, 85% of participants were stage 1 and 15% were stage 2. BMI-for-age categorization revealed that 5% of the participants were underweight, 53% were normal weight, 14% were overweight, and 28% were obese. The non-overweight and overweight/obese groups are compared in Table I. As expected, the overweight/obese participants had greater percent whole-body fat mass (10.9%; 95% CI, 9.1%-12.6%), TAAT (190.3 cm^2; 95% CI, 153.5-227.2 cm^2), SAAT (156.9 cm^2; 95% CI, 123.8-190.0 cm^2), and VAT (33.5 cm^2; 95% CI, 27.3-39.7 cm^2) ($P < .01$ for all). Although overweight/obese children had lower VO_{2max} relative to total body weight (−7.3 kg/mL/min; 95% CI, −9.4 to −5.2 kg/mL/min; $P < .01$), the 2 groups did not differ in VO_{2max} relative to fat-free mass (−1.13 kg/mL/min; 95% CI, −3.7 to 1.5 kg/mL/min; $P = .41$).

There were no differences in accuracy or PDV for either form of memory between non-overweight and overweight/obese participants (Table II); however, relational memory accuracy was positively correlated with age ($r = 0.15$; $P = .04$) and male sex ($r = 0.23$; $P < .01$), but negatively correlated with SAAT ($r = −0.28$; $P = < .01$) and TAAT ($r = −0.21$; $P = .01$). Item memory was positively correlated with male sex ($r = 0.21$; $P < .01$) and IQ ($r = 0.16$; $P = .04$), but negatively correlated with SAAT ($r = −0.18$; $P = .02$) and TAAT ($r = −0.15$; $P = .04$). No significant correlates of relational or item memory PDV were identified.

Results of the bivariate correlations by weight status category are presented in Table II. Among non-overweight children, no adiposity measure was related to relational memory; however, relational memory accuracy was positively correlated with fat-free VO_{2max} ($r = 0.20$; $P = .04$). Item memory accuracy was positively correlated with male sex ($r = 0.30$; $P = .01$) and VAT ($r = 0.30$; $P = .01$); however, when correlations were stratified by sex, VAT was not correlated with item memory performance for males ($r = 0.10$; $P = .29$) or females ($r = 0.16$; $P = .29$). Relational memory PDV was positively correlated with SES ($r = 0.23$; $P = .02$) and IQ ($r = 0.13$; $P = .14$). No significant correlations for PDV in the item memory condition were observed.

Table I. Body composition and memory performance of participants by weight status

Variables	Non-overweight (n = 73)	Overweight/obese (n = 53)
IQ	111.1 ± 14.1	108.7 ± 11.8
BMI *z*-score*	−0.07 ± 0.81	1.82 ± 0.54
VO_{2max}, kg/mL/min*	44.0 ± 6.1	36.7 ± 5.8
Fat-free VO_{2max}, kg/mL/min	60.7 ± 7.4	59.6 ± 7.3
WBFM, %*	28.5 ± 4.7	39.4 ± 5.1
TAAT, cm^2*	135.4 ± 45.3	325.7 ± 128.5
SAAT, cm^2*	109.4 ± 47.2	266.2 ± 113.8
VAT, cm^2*	26.0 ± 11.2	59.5 ± 20.6
Relational memory accuracy, %	64.1 ± 13.6	64.1 ± 15.1
Item memory accuracy, %	86.6 ± 9.5	85.5 ± 8.9
Relational memory PDV, %	8.4 ± 8.9	8.4 ± 9.9
Item memory PDV, %†	9.6 ± 13.9	11.2 ± 12.3

WBFM, whole-body fat mass.
Data are presented as mean ± SD.
*Significant difference between groups ($P < .05$).
†Data available for only 114 participants (48 overweight/obese).

Among overweight/obese children, relational memory accuracy was positively associated with male sex ($r = 0.29$; $P = .02$) and negatively correlated with all DXA measures of adiposity ($P < .05$ for all). Item memory accuracy was positively correlated with SES ($r = 0.25$; $P = .03$) and negatively correlated with SAAT ($r = -0.24$; $P = .04$). Pubertal timing was negatively correlated with relational memory PDV ($r = −0.25$; $P = .04$).

The backward regression analyses identified no significant predictors of relational memory accuracy and item memory PDV among non-overweight children. However, a model comprising SES ($\beta = 0.25$; $P = .03$) and BMI *z*-score ($\beta = −0.20$; $P = .09$) achieved significance ($P = .03$) while explaining 9% of the variance in relational memory PDV. Although sex alone significantly predicted item memory accuracy ($\beta = 0.30$; $R^2 = 0.09$; $P = .01$), male sex was not an independent predictor, because sex was not a significant predictor of item memory accuracy once VAT and IQ were included in the model. Among overweight/obese participants, no independent predictors or significant predictive models of item memory accuracy or PDV were observed. A model consisting of pubertal timing ($\beta = −0.30$; $P = .03$) and SES ($\beta = −0.25$; $P = .08$) achieved significance ($P = .04$) and explained 12% of the variance in relational memory PDV; however, TAAT was identified as an independent negative predictor of relational memory accuracy ($\beta = −0.45$; $P < .01$) and explained 20% of the variance in relational memory accuracy scores. Figure 2 illustrates the correlation between TAAT and accuracy in both memory forms among non-overweight and overweight/obese children.

Discussion

The hippocampus is critical for learning and memory throughout the lifespan. In this report, we document an inverse

Table II. Correlations between memory indices and participant characteristics by weight status

	Non-overweight (n = 73)				Overweight/obese (n = 53)			
	Relational memory		Item memory		Relational memory		Item memory	
Variables	Accuracy	PDV	Accuracy	PDV	Accuracy	PDV	Accuracy	PDV*
Age	0.16	0.03	0.06	−0.05	0.14	0.05	0.10	0.13
Sex†	0.18	0.18	0.30‡	0.19	0.29§	0.10	0.09	−0.07
Pubertal timing	−0.12	0.07	−0.01	0.02	−0.20	−0.251§	−0.10	−0.08
SES	−0.05	0.23§	0.03	0.06	0.22	−0.19	0.25§	0.01
IQ	0.08	0.20§	0.13	0.12	0.14	−0.15	0.21	0.14
BMI *z*-score	−0.05	−0.18	0.09	0.13	−0.19	−0.10	−0.14	0.03
Fat-free VO_{2max}	0.20§	−0.05	−0.06	−0.03	0.05	−0.12	0.15	0.15
%WBFM	−0.05	−0.12	−0.08	0.06	−0.36‡	−0.07	−0.20	0.15
SAAT	−0.10	−0.11	−0.16	−0.01	−0.46‡	−0.15	−0.24§	0.07
VAT	0.15	0.10	0.30‡	0.17	−0.23§	−0.03	−0.11	0.12
TAAT	−0.07	−0.09	−0.09	0.03	−0.45‡	−0.14	−0.23	0.08

*Data available for only 116 participants (67 not overweight, 49 overweight/obese).
†Females coded as 0, and males coded as 1.
‡Correlation is significant at the 0.01 level (1-tailed).
§Correlation is significant at the 0.05 level (1-tailed).

relationship between central adiposity and hippocampal-dependent relational memory among overweight/obese prepubertal children. On regression analyses, this relationship did not extend to item memory, which relies on the perirhinal cortex, demonstrating a selective association of central adiposity with hippocampal-dependent memory processes.

There were no differences in memory performance between groups based solely on weight, however; that is, non-overweight and overweight/obese children did not differ in accuracy or PDV in either condition. Therefore, weight status alone might not be the key determinant of memory function among prepubertal children, and it is possible that differences in memory performance across the BMI-for-age cutoff for overweight emerge later in development. Separating subsequent analyses by weight status allowed us to examine whether the degree of central adiposity is differentially correlated with distinct types of memory among normal and overweight/obese children. The discovery that TAAT, both independently and selectively, correlated with relational memory among overweight/obese children raises important questions for future research. Previous studies have demonstrated differences in several lifestyle factors (eg, diet, physical activity, sleep patterns),[25-27] as well as metabolic outcomes (eg, lipid profiles, inflammatory markers)[28,29] between normal and overweight children. It is plausible that these factors could possibly account for the differential associations observed across groups in the present study.

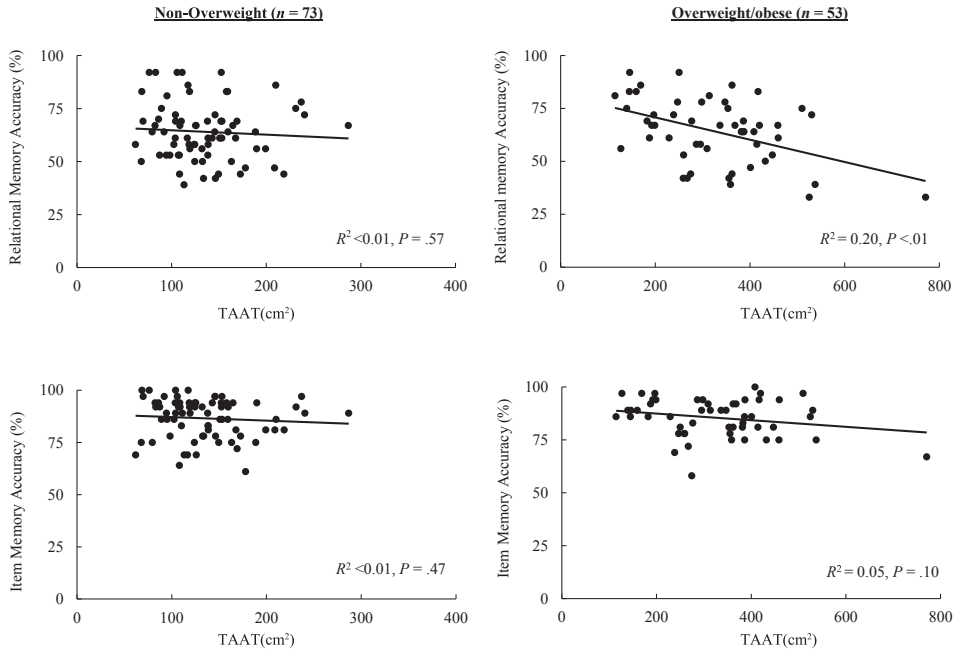

Figure 2. Scatterplots illustrating the correlation between TAAT and relational and item memory accuracy.

Centralized fat deposition appears to play a greater role in metabolic diseases than whole-body adiposity or BMI.[30] VAT, relative to SAAT, has been shown to be particularly pathogenic owing to its higher lipolytic activity and closer proximity to hepatic portal vasculature.[31] Thus, the finding that VAT did not predict memory performance after adjustment for covariates was surprising. Among non-overweight participants, VAT was positively correlated with item memory accuracy in an uncorrected bivariate correlation; however, this association was not significant after inclusion of sex in the regression models. Thus, the initial correlation observed between VAT and item memory may be a function of males (higher in VAT) outperforming females on the item memory task. Furthermore, VAT was not related to item memory in non-overweight males or females. In contrast, the influence of TAAT on relational memory accuracy appeared to be mediated by SAAT, which also has been shown to correlate with hyperinsulinemia in prepubertal children.[32] Nevertheless, the present study provides evidence that in prepubertal children, cumulative abdominal adipose tissue is a more significant correlate of hippocampal function than its individual components.

Support for the detrimental effects of fat mass on memory can be found in rodent studies showing that obesity induced by diet or leptin receptor deficiency was related to compromised hippocampal function[33] and impaired long-term potentiation of neurons in the hippocampus.[34] Compared with their lean counterparts, obese rats (classified based on their greater weight gain and larger epididymal fat pads) took significantly more time to find a hidden platform during a Morris water maze task designed to access spatial learning and memory, processes known to depend on the hippocampus.[33] Moreover, compared with lean rats, obese Zucker rats exhibited impaired long-term potentiation in the CA1 region of the hippocampus.[34] Whether obesity has a selectively negative effect on the hippocampus or a generalized effect on a wider brain network merits further study. To our knowledge, no previous study has directly investigated the relationship between measures of adiposity and relational memory among humans. Structural magnetic resonance imaging studies indicate that both SAAT and VAT are negatively related to total brain volume, independent of cardiovascular risk factors.[35] Specific to central adiposity, a 1-SD increase in waist-to-hip ratio is related to a 0.2-SD decrease in hippocampal volume.[8] The aforementioned studies did not assess cognitive function, however, and thus future studies are needed to assess the effects of obesity on hippocampal memory. Nevertheless, our results add to the evidence provided by rodent models and neuroimaging results in adult humans indicating adiposity-related perturbations in hippocampal function and structure.

Several possible mechanisms may underlie the link between central adiposity and impaired hippocampal function.[36] First, central adiposity–induced changes in glucose homeostasis may affect hippocampal-dependent memory processes. In rodents, delivery of insulin to the hippocampus strengthens spatial memory, whereas blocking of insulin signaling impairs memory function.[37] Second, abdominal adipose tissue secretes proinflammatory markers known to be neurotoxic.[38,39] Systemic inflammation is known to increase central inflammation, predicting cognitive decline.[40] Finally, prolonged cortisol release caused by chronic stimulation of the hypothalamic-pituitary-adrenal axis may preferentially affect central fat mass owing to an increased number of glucocorticoid receptors in abdominal fat mass. Abdominal fat has been shown to release cytokines that stimulate the hypothalamic-pituitary-adrenal axis to release even more glucocorticoids.[41] Activation of this cycle results in increased central adiposity, insulin resistance, and, critically, hippocampal atrophy.[42]

Alternatively, central adiposity perhaps could have served as a surrogate marker of physical inactivity, and our results may demonstrate the adverse effects of a sedentary lifestyle on hippocampal function. The hippocampus is known to undergo neurogenesis into adulthood[43] and to exhibit susceptibility to the negative effects of aging and positive effects of environmental enrichment and exercise.[44-46] Environmental enrichment or the combination of inanimate and social stimulation induces experience-dependent neuroplasticity in the rodent brain[44,47]; however, activity is a key component of environmental enrichment, and voluntary exercise in a running wheel enhances survival of newborn neurons in the dentate gyrus.[48] In addition to neurogenesis, exercise has broader effects on the brain, including enhanced gliogenesis, synaptogenesis, and angiogenesis, as well as increases in growth factors, including brain-derived neurotrophic factor.[49] Low levels of physical activity play an important role in the development of an excess central adiposity in children and adolescents.[50] Given that overweight children are less likely be physically active compared with their lean counterparts,[50] our present results may reflect the negative effects of physical inactivity on hippocampal memory.

This study has several limitations. DXA-generated values for VAT and SAAT were estimated by modeling and are not equivalent to those generated by direct imaging with CT or magnetic resonance imaging. However, DXA has been shown recently to provide accurate estimates of abdominal fat compartmentalization while using only a fraction of the radiation of CT, making DXA a suitable alternative for use in pediatric populations. In addition, although our analyses accounted for key demographic and fitness covariates, future studies should assess biomedical markers of metabolic health and inflammation, such as those noted above.

In conclusion, we provide evidence in children connecting central adiposity, a clinically significant fat deposition in the human body, to the hippocampus and relational memory. The finding that obesity-related impairment is already manifest during the school years has considerable implications for pediatric cognitive health. In light of the currently elevated prevalence of childhood obesity, these findings raise troubling public health concerns by contributing yet another

piece of evidence regarding the negative influence of adiposity even early in life. ■

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Reprint requests: Naiman A. Khan, PhD, RD, Neurocognitive Kinesiology Laboratory, Department of Kinesiology and Community Health, University of Illinois, 313 Louise Freer Hall, MC-052, 906 S Goodwin Ave, Urbana, IL 61801. E-mail: nakhan2@illinois.edu

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Trypsinogen Deficiency Disease

Townes PL. J Pediatr 1965;66:275-85

As Townes points out in this article, the evaluation of malnutrition or failure to thrive in infancy covers a broad spectrum of etiologies, from social or environmental causes of inadequate caloric intake to specific inborn errors of metabolism, with a myriad of factors between the extremes. The approach to these patients has not changed significantly over the last 50 years, although our testing has become more sophisticated and more readily obtained. Townes' patient was hospitalized at 8 weeks of age with poor weight gain, diarrhea, and edema despite adequate caloric intake. The family history of a sibling who also failed to grow well and died at 6 months of age suggested an inherited disease. Ongoing deterioration despite trials of multiple enteral therapies and a failure to identify a cause of his severe hypoproteinemia during the first 6 weeks of admission necessitated the "desperate measure" to start intravenous infusion of protein hydrolysate and lipid emulsion. The marked improvement with this intervention directed Townes to hypothesize the defect in either proteolysis or amino acid absorption. Through systematic comparison of nitrogen balance on either standard or hydrolysate formula and subsequent direct testing of pancreatic fluid for enzymatic activity, they identified the specific enzyme defect leading to the patient's failure to thrive and likely the cause of his sibling's death. The patient went on to develop normally on protein hydrolysate formula and eventual use of porcine pancreatic enzyme replacement with an age-appropriate diet.

This patient was the first to be diagnosed with isolated trypsinogen deficiency with secondary lack of activation of chymotrypsin and procarboxypeptidase. Over the last 50 years, additional, albeit exceedingly rare, isolated pancreatic enzyme deficiencies (including lipase, amylase, and colipase) resulting in failure to thrive have been identified. However, their exact molecular defects have not yet been determined. The cumbersome direct pancreatic exocrine function testing utilized by Townes required collaboration with numerous research labs but is now commercially available and performed on samples obtained with direct visualization using standard endoscopic techniques. The pioneering efforts of Townes is an elegant example of how the practice of medicine combining a thorough history, physical examination, observation, and systematic testing can ascertain a rare cause of a common condition resulting in a life-saving therapy.

Joseph J. Palermo, MD, PhD
Division of Gastroenterology,
Hepatology, and Nutrition
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
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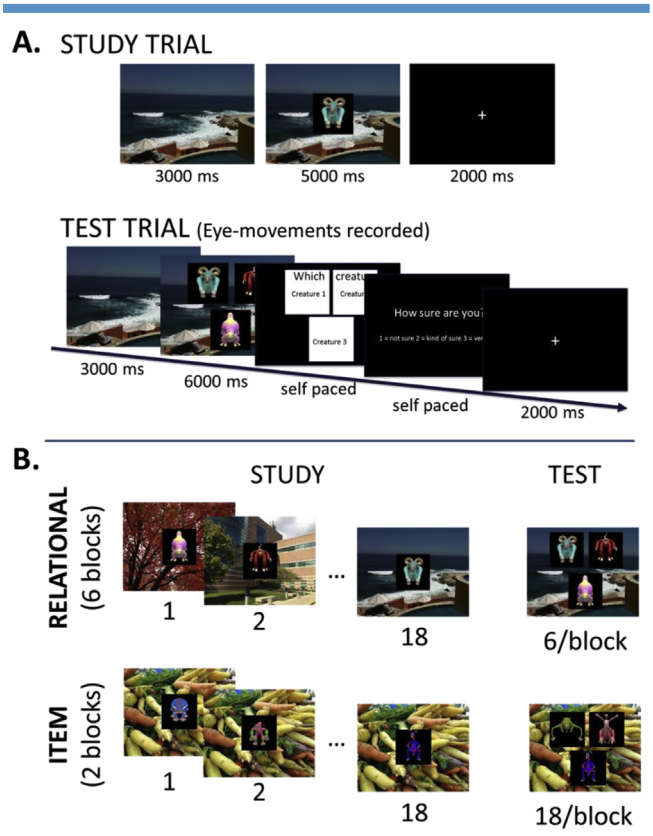

Figure 1. **A,** Single trial progression in the study (*top*) and test (*bottom*) phases. Durations of each trial component are specified in milliseconds. **B,** Example study and test trials from the Relational condition (*top*) and Item condition (*bottom*).