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

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Abstract

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

Study design—Prepubertal children (7–9-year-olds, $n = 126$), classified as non-overweight ($<85^{\text{th}}$ %tile BMI-for-age [$n = 73$]) or overweight/obese ($\geq 85^{\text{th}}$ %tile BMI-for-age [$n = 53$]), completed relational (hippocampal-dependent) and item (hippocampal-independent) memory tasks, and performance was assessed with both direct (behavioral accuracy) and indirect (preferential disproportionate viewing [PDV]) measures. Adiposity (%whole body fat mass, subcutaneous abdominal adipose tissue, visceral adipose tissue, and total abdominal adipose tissue) was assessed using DXA. Backward regressions identified significant ($P < 0.05$) predictive models of memory performance. Covariates included age, sex, pubertal timing, socioeconomic status, IQ, oxygen consumption ($\text{VO}_{2\text{max}}$), and body mass index (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 socioeconomic status jointly predicted the PDV measure of relational memory. In contrast, among non-overweight children, male sex predicted item memory behavioral accuracy, and a model

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consisting of socioeconomic status and BMI z-score jointly predicted the PDV measure of relational memory.

Conclusions—Regional, and not whole body, fat deposition was selectively and negatively associated with hippocampal-dependent relational memory among overweight/obese prepubertal children.

Keywords

Cognition; associative memory; subcutaneous fat; visceral fat; DXA

Converging evidence now suggests that poor cognitive function may be yet another complication of obesity¹. Obesity is an independent risk factor for developing dementia and Alzheimer disease later in life². In addition, the complications of obesity are becoming evident in obese children.³ However, there has been only limited research connecting obesity to cognitive function in childhood. Central adiposity, in particular, is implicated in the progression of insulin resistance⁴. Yet fat around the abdominal viscera in 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 unknown⁵. Furthermore, as in adults, different fat compartments in children may have differential functional effects based on weight status⁶.

Increased waist-to-hip ratio is negatively correlated with memory and hippocampal volume among adults^{7,8}. The hippocampus is critical for relational (associative) memory, which supports representations of the relations between items, such as the relations among the constituent elements of events and their subsequent flexible expression⁹. It is likely that acquisition of relational knowledge provides a foundation for scholastic achievement, and its flexible expression enables success in handling novel challenges. Therefore, changes in the development of this system in childhood would have wide-ranging impact. In contrast, memory for individual items (item memory) relies on perirhinal cortex, the anterior region of the parahippocampal gyrus⁹. The dependence of these two memory processes on distinct neural substrates provides an opportunity to study their differential sensitivity to adiposity.

Consequently, this study examined whether relational and/or item memory were related to whole body and central adiposity in prepubertal children and whether these associations varied by weight status. We hypothesized that central adiposity would be selectively and negatively associated with relational memory and this association would vary based on weight status.

Methods

Prepubertal children between 7 and 9 years ($n = 126$) provided written assent and legal guardians provided written informed consent in accordance with the regulations of the University of Illinois Institutional Review Board. Children were screened for neurological disorders, physical disabilities, psychoactive medication status, and normal or corrected-to-normal vision. Data were also collected on 1) IQ, using the Kaufman Brief Intelligence

Test¹⁰ or the Woodcock-Johnson Tests of Cognitive Abilities¹¹, 2) socioeconomic status (SES) as estimated based on household income, participation in a school meal-assistance program, maternal and paternal education levels, and how many parents work full-time, and 3) pubertal status¹².

Anthropometrics and Body Composition

Height and weight were measured using a stadiometer (Seca; model 240) and a Tanita WB-300 Plus digital scale, respectively. The Centers for Disease Control (CDC, 2000) growth charts were used to determine body mass index (BMI)-for-age percentile and BMI z-scores¹³. Non-overweight or overweight/obese categorization was based on the 85th percentile BMI-forage cutoff¹³.

Adiposity was assessed by dual energy x-ray absorptiometry (DXA) using a Hologic QDR 4500A bone densitometer (software version 13.4.2, Bedford, MA). Percent whole body fat mass (%WBFM) was expressed using the standard software measure. The estimation of central adiposity variables has been previously described¹⁴. In summary, the abdominal region of interest was a 5 cm wide section placed across the entire abdomen just above the iliac crest at a level that approximately coincides with the 4th lumbar vertebrae on the whole body DXA scan. Total abdominal adiposity (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 the estimate of subcutaneous fat overlying the abdominal cavity. This estimated SAAT was subtracted from the TAAT to determine visceral adipose tissue (VAT). This estimated VAT has been shown in previous work to correlate ($r = 0.92$, $P < .01$) with computed tomography (CT) values of VAT¹⁴.

Cardiorespiratory Fitness Assessment

VO_{2max} was measured using a modified Balke treadmill protocol¹⁵. Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400, Sandy, UT) with averages for VO₂ and respiratory exchange ratio assessed every 20s. VO_{2max} was based upon maximal effort as evidenced by (1) a peak heart rate 185 bpm¹⁵ and a heart rate plateau¹⁶; (2) respiratory exchange ratio >1.0 ¹⁷; (3) a score on the children's OMNI ratings of perceived exertion scale >8 ¹⁸; and/or (4) a plateau in oxygen consumption corresponding to an increase of less than 2 ml/kg/min despite an increase in workload¹⁵. 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 al²⁰, however the current version used child-friendly creatures (Electronic Arts Inc., 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). At test, participants were instructed to find the creature originally studied with that scene from an array of three creatures. One of the creatures had been studied with that scene (target) and two had been studied with other

scenes (foils). Familiarity across the three creatures was thus matched, necessitating the employment of hippocampal-dependent relational memory²². In the item condition, the background scene was the same for all creature-scene pairings within each block. At test, participants were instructed to find the previously viewed creature. In each test display two creatures were novel and one studied, allowing the discrimination to be made on the basis of familiarity, an ability that is independent of the hippocampus²³. Lists of stimuli were counterbalanced across conditions between participants, and target location on test trials was counterbalanced within participant such that the target was equally likely to appear in any of the three possible locations. Order of study-test blocks was counterbalanced across participants such that half the participants began with the relational condition and half with the item condition.

An Eyelink 1000 eye-tracker (SR Research, 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 – prior to behavioral response. This measure corrects for the fact that individuals look more 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 prior to the viewer's behavioral awareness²⁴.

Statistical Analyses

Differences between non-overweight and overweight/obese in memory measures were assessed using an independent samples *t*-test. Initial Pearson's correlations assessed bivariate relationships between adiposity and memory measures among all participants. Subsequently, bivariate correlations within weight category were performed. Finally, step-wise 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 first 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 at .05). Statistics were performed using SPSS 19 (IBM, Somers, NY).

Results

A total of 126 (71 females) 7–9-year-olds 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% were stage 1 and 15% belonged to 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. Comparisons between non-overweight and overweight/obese groups are presented in Table I. As expected, overweight/obese participants had greater (all *P*s < .01) %WBFM (10.9%; 95% confidence interval [CI], 9.1 to 12.6), TAAT (190.3cm²; 95% CI, 153.5 to 227.2), SAAT (156.9cm²; 95% CI, 123.8 to 190.0), and VAT (33.5cm²; 95% CI, 27.3 to 39.7). Although overweight/obese children had

lower $\text{VO}_{2\text{max}}$ relative to total body weight (-7.3kg/ml/min ; 95% CI, -9.4 to -5.2 , $P < .01$), the groups did not differ in $\text{VO}_{2\text{max}}$ relative to fat-free mass (-1.13kg/ml/min ; 95% CI, -3.7 to 1.5 , $P = .41$).

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 being male ($r = 0.23$, $P < .01$), but negatively correlated with SAAT ($r = -0.28$, $P < .01$), and TAAT ($r = -0.21$, $P = .01$). Item memory was positively correlated with being male ($r = 0.21$, $P < .01$) 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 separated 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 $\text{VO}_{2\text{max}}$ ($r = 0.20$, $P = .04$). Item memory accuracy was positively related to male sex ($r = 0.30$, $P = .01$) and VAT ($r = 0.30$, $P = .01$). However, stratifying the correlations by sex revealed that 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 ($r = 0.13$, $P = .14$), and no significant correlations were observed for PDV in the item memory condition.

Among overweight/obese children, relational memory accuracy was positively associated with male sex ($r = 0.29$, $P = .02$) and negatively related to all DXA measures of adiposity (all P s $< .05$). 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 ($r = -0.25$, $P = .04$) was negatively correlated with relational memory PDV among overweight/obese children.

According to the backward regression analyses, there were no significant predictors of relational memory accuracy and item memory PDV among non-overweight children. However, a model consisting of 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 ($\beta = 0.30$, $R^2 = 0.09$, $P = .01$), being male was not an independent predictor because sex was not a significant predictor of item memory accuracy following the inclusion of VAT and IQ 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 relationship between central adiposity and hippocampal-dependent relational memory among overweight/obese prepubertal children. Following 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.

However, there were no differences in memory performance between groups, when considered solely according to weight. That is, non-overweight and overweight/obese children did not differ in accuracy or PDV in either condition. Therefore, weight status alone may 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 differentially correlates with distinct types of memory among normal and overweight/obese children. The discovery that TAAT, 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 (e.g., diet, physical activity, sleep patterns)^{25–27} as well as metabolic outcomes (e.g., lipid profiles and inflammatory markers)^{28,29} between normal and overweight children. It is plausible that these factors may account for the differential associations observed across groups in the current study.

Centralized fat deposition, rather than whole body adiposity or BMI, appears to play a greater role in metabolic diseases³⁰. VAT, relative to SAAT, has been shown to be particularly pathogenic due to its higher lipolytic activity and closer proximity to hepatic portal vasculature³¹. Therefore, the finding that VAT did not predict memory performance following adjustment for covariates was surprising. Among non-overweight participants, VAT was positively related to item memory accuracy in an uncorrected bivariate correlation, however, this association was not significant following inclusion of sex in the regression models. Hence, 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. Further, VAT was not related to item memory among neither non-overweight males nor females. In contrast, the influence of TAAT on relational memory accuracy appeared to be mediated by SAAT which has also been shown to correlate with hyperinsulinemia among prepubertal children³². Nevertheless, the current study provides evidence that, among 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 – is related to compromised hippocampal function³³ and impaired long-term potentiation of neurons in the hippocampus³⁴. 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 hippocampus³³. In addition, Gerges et al (33) observed that, relative to lean rats, the CA1 region of the hippocampus of obese Zucker rats exhibited impairment in long-term potentiation. However, whether obesity has a selectively negative effect on the hippocampus or a generalized effect on a wider brain network warrants 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 (MRI) studies indicate that both SAAT and VAT are negatively related to total brain volume, independent of cardiovascular risk factors³⁵. Specific to central adiposity, a 1-SD increase in waist-hip ratio is related to a 0.2-SD decrease in hippocampal volume⁸. However, these aforementioned studies did not assess cognitive function and thus future studies are needed to assess the effects of the obesity on hippocampal memory. Nevertheless, our results add to the evidence from 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 function³⁶. First, central adiposity-induced changes in glucose homeostasis may affect hippocampal-dependent memory processes. Among rodents, delivering insulin to the hippocampus strengthens spatial memory, while blocking insulin signaling impairs memory function³⁷. Secondly, abdominal adipose tissue secretes proinflammatory markers known to be neurotoxic^{38,39}. Systemic inflammation is known to increase central inflammation, predicting cognitive decline⁴⁰. Finally, prolonged cortisol release caused by chronic stimulation of the hypothalamic-pituitary-adrenal (HPA) axis may preferentially affect central fat mass due to increased number of glucocorticoid receptors in abdominal fat mass. Abdominal fat has been shown to release cytokines that stimulate the HPA axis to release even more glucocorticoids⁴¹. Activation of this cycle results in increased central adiposity, insulin resistance and, critically, hippocampal atrophy⁴².

Alternatively, central adiposity could have served as a surrogate marker of physical inactivity and our results perhaps reveal the adverse effects of a sedentary lifestyle on hippocampal function. The hippocampus is known to undergo neurogenesis⁴³ into adulthood 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^{47,48}. However, activity is a key component of environmental enrichment and voluntary exercise in a running wheel enhances survival of newborn neurons in the dentate gyrus⁴⁹. 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 (BDNF)⁵⁰. Low levels of physical activity play an important role in the development of excess of central adiposity in children and adolescents⁵¹. Given that overweight children are less likely to be physically active, compared with their lean counterparts⁵¹, the current results may reflect the negative effects of physical inactivity on hippocampal memory.

The current study has several limitations. DXA generated values for VAT and SAAT are estimated by modeling and are not equivalent to those generated by direct imaging using

computed tomography (CT) or MRI. 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. 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 on the negative influence of adiposity even early in life.

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Abbreviations

VAT	visceral adipose tissue
SAAT	subcutaneous abdominal adipose tissue
TAAT	total abdominal adipose tissue
IQ	intelligence quotient
DXA	dual energy x-ray absorptiometry
%WBFM	percent fat mass
PDV	preferential disproportionate viewing
BDNF	brain-derived neurotrophic factor

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Figure 1.

Scatterplots illustrating the correlation between total abdominal adipose tissue and relational and item memory accuracy.

A. STUDY TRIAL **TEST TRIAL (Eye-movements recorded)** **B.** **Figure 2.**

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).

Table 1

Body composition memory performance of participants by weight status

	Non-Overweight (<i>n</i> = 73)	Overweight/obese (<i>n</i> = 53)
Intelligence Quotient	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)
% Whole Body Fat Mass *	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)
^a Item Memory PDV (%)	9.6 (13.9)	11.2 (12.3)

Data presented as mean ± SD

^aData only available for 114 participants (48 overweight/obese)* Significant difference between groups (*P* < 0.05)

BMI, body mass index; VO_{2max}, maximal oxygen consumption; TAAT, total abdominal adipose tissue; SAAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; PDV, preferential disproportionate viewing

Table 2

Correlations between memory indices and participant characteristics by weight status

	Non-Overweight (<i>n</i> = 73)				Overweight/obese (<i>n</i> = 53)			
	Relational Memory		Item Memory		Relational Memory		Item Memory	
	Accuracy	PDV	Accuracy	PDV	Accuracy	PDV	Accuracy	^a PDV
Age	0.16	0.03	0.06	-0.05	0.14	0.05	0.10	0.13
^b 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	-.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

^aData only available for 116 participants (67 non-overweight, 49 overweight/obese)^bFemales 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).

PDV, preferential disproportionate viewing; SES, socioeconomic status; IQ, intelligence quotient; SAAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; TAAT, total fat in abdominal region of interest