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Cognitive Functioning and Insulin Regulation in Obese Youth

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ABSTRACT

Background: There are data that suggest adiposity is associated with diminished cognitive functioning in adults and youth, independent of related co-morbidities. Little is known about the pathophysiological mechanisms associated with cognitive function in obese youth. The objective of the present study was to assess the associations among cognitive functioning and insulin regulation in a sample of obese youth. Methods: The sample consisted of 30 obese, non-diabetic youth (BMI > 95th percentile) ages 6 - 16 years (mean age = 12.60 years) referred to an outpatient pediatric endocrinology clinic. Youth were administered the Wechsler Abbreviated Scale of Intelligence (WASI) and Wide Range Assessment of Memory and Learning (WRAML-2). Results: Verbal memory, attention/concentration, and intelligence scores were similar across obese youth with elevated insulin levels and normal insulin levels. Obese youth with elevated insulin levels had lower scores in visual memory, with a medium effect (effect size = 0.51). Fasting insulin levels were not associated with any of the four cognitive domains in the multiple linear regression analysis (P > 0.05). Conclusions: These data provide preliminary evidence that visual memory may be impacted in obese youth with insulin resistance. Longitudinal studies examining insulin regulation, cognitive functioning, and weight status over time are needed.

KEYWORDS

Pediatric Obesity; Cognitive Functioning; Insulin

1. Introduction

Cognitive functioning refers to the mechanisms by which information is processed, integrated, stored, and retrieved by the brain. Six broad, but related, cognitive domains are generally recognized including intelligence, learning/memory, speed of information processing, attention/executive function, academic achievement, and visual motor integration [1,2]. There is growing evidence that adiposity is associated with diminished cognitive functioning in adults and youth, independent of related co-morbidities [3,4]. In their systematic review on obesity and cognitive functioning, Smith and colleagues (2011) identified 24 studies in youth and adults ages 4 - 65 years and found that across the lifespan adiposity was independently associated with deficits in cognitive function, particularly in the domain of executive function (e.g., attention, impulsivity, mental flexibility, inhibition, problem solving, decision making) [5].

While the mechanisms underlying obesity-related cognitive impairment are not well understood, insulin resistance is one pathophysiological mechanism that has been proposed to affect cognition in the obese. Insulin resistance can lead to lower levels of plasma insulin in the brain and in turn disrupt the regulation of brain functions [6]. Abnormal insulin regulation has been associated with *poorer* cognitive functioning in elderly adults [7,8] and impairments in neuronal activity in obese youth [9]. To the best of our knowledge, this pathophysiological mechanism has not been previously investigated in relation to cognitive function in obese youth using well-validated, standardized psychological measures.

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Elucidating the associations among cognitive functioning and insulin regulation in obese youth may have important implications for the management of childhood obesity. Current obesity treatments and preventative strategies have demonstrated limited long-term success with youth [10-13]. The effectiveness of these programs is in part related to the youth and family's ability to perform tasks that require higher order cognitive functions (e.g., associating food selections with weight, adhering to a diet and exercise regime, planning meals, measuring portion sizes) [14]. Identifying modifiable factors associated with cognitive impairment in obese youth may result in the development of targeted interventions that increase levels of cognitive functioning in this population. Such interventions could translate into improved long-term obesity outcomes for youth.

Consequently, the objective of the present study was to examine the associations among cognitive functioning (verbal/visual memory, attention/concentration, intelligence) and insulin regulation in a clinical sample of obese youth. We hypothesized that 1) obese youth with normal fasting insulin levels would demonstrate higher scores than obese youth with elevated fasting insulin levels on a standardized measure of attention/concentration, with a small to medium effect and 2) insulin resistance would be associated with poorer performance in attention/concentration.

2. Methods

2.1. Participants

Participants were 30 obese children and adolescents (BMI > 95th percentile) ages 6 - 16 years referred to an outpatient pediatric endocrinology clinic for weight-related concerns. The sample was originally comprised of 35 obese youth; however, complete data was not available for 5 participants. Consequently, these participants were excluded from the final analyses. It should be noted that the 5 excluded participants did not differ systematically from the final sample on any of the demographic variables, BMI percentile, or cognitive measures. The 30 participants all had a BMI percentile greater than the 95th percentile adjusted for age and gender, with 56.7% of the sample at or above the 99th BMI percentile adjusted for age and gender. **Table 1** contains demographic information for the sample. The sample was predominantly female (70%) and their mean age was 12.60 years (SD = 2.67). With regard to race/ethnicity, 11 children were Caucasian/Hispanic (36.7%), 10 were Black (30.0%), and 9 were Caucasian (30.0%). Approximately 90% of participating parents had less than a college degree while 10% had a college degree or greater.

Table 1. Sample demographics.

	Total Sample (n = 30)	Normal Insulin Sample (n = 19)	Elevated Insulin Sample (n = 11)
Characteristics			
Age (years)			
Mean (SD)	12.60 (2.67)	12.47 (2.88)	12.73 (1.90)
Range	6 - 16	6 - 16	10 - 16
Gender			
Boys (%)	9 (30.0%)	5 (26.3%)	3 (27.3%)
Girls (%)	21 (70.0%)	14 (73.7%)	8 (72.7%)
Race/Ethnicity			
Caucasian/Hispanic (%)	11 (36.7%)	6 (31.6%)	5 (45.5%)
Black (%)	10 (30.0%)	7 (36.8%)	3 (27.3%)
Caucasian (%)	9 (30.0%)	6 (31.6%)	3 (27.3%)
Parent Education			
Some college/vocational school (%)	12 (40.0%)	7 (36.8%)	5 (45.5%)
High school diploma or GED (%)	11 (36.7%)	5 (26.3%)	6 (54.5%)
College degree (%)	2 (6.7%)	2 (10.5%)	0 (0.0%)
Some high school or less (%)	2 (6.7%)	2 (10.5%)	0 (0.0%)
Professional/graduate degree (%)	1 (3.3%)	1 (5.3%)	0 (0.0%)
No information provided (%)	2 (6.7%)	2 (10.5%)	0 (0.0%)
Child BMI Percentile			
96th percentile (%)	3 (10.0%)	3 (15.8%)	0 (0.0%)
98th percentile (%)	10 (33.3%)	9 (47.4%)	2 (18.2%)
99th percentile (%)	17 (56.7%)	7 (36.8%)	9 (81.8%)
Mean (SD)	98.37 (1.09)	97.95 (1.31)	98.81 (0.40)

Note: SD equals standard deviation.

2.2. Measures

Intelligence. The Wechsler Abbreviated Scale of Intelligence (WASI) is a brief measure of intellectual functioning for individuals ages 6 to 89 years [15]. In the current study, we used the two-subtest full scale intelligence quotient (FSIQ-2) to measure general cognitive functioning [16]. The FSIQ-2 is comprised of the Vocabulary (a measure of Comprehension Knowledge) and Matrix Reasoning (a measure of Fluid Reasoning) subtests. The FSIQ-2 has a mean of 100 and standard deviation of 15 meaning that scores falling between 85 and 115 represent the Average range [15]. The technical manual reports reliability estimates for the FSIQ-2 in youth ranging from 0.85 (test-retest) to 0.93 (internal consistency) [15]. The correlation between the WASI FSIQ-2 and the Wechsler Intelligence Scale for Children-III (WISC-III) FSIQ scores among youth was 0.82 [15].

Memory and Attention/Concentration. Memory and attention/concentration were evaluated using the Wide Range Assessment of Memory and Learning, Second Edition (WRAML-2) [17]. The WRAML-2 is a measure of memory and learning functioning for individuals ages 5 through 90 years [17]. The 6 core subtests that comprise the Verbal Memory, Visual Memory, and Attention/Concentration index scores were administered to children and adolescents in the present study [17]. For example, the Story Memory subtest (part of the Verbal Memory domain) asks the child to immediately retell two short stories after listening to them verbally. Each WRAML-2 index score has a mean of 100 and standard deviation of 15 meaning that scores falling between 85 and 115 represent the Average range. The technical manual reports internal consistency reliability coefficients for the WRAML-2 core indices ranging from 0.82 to 0.96 [17].

Insulin Regulation. Insulin regulation was measured in the present study using fasting insulin. Normal fasting insulin was considered 0 - 23 mcUnit/ml. Hemoglobin A1c was also utilized to assure exclusion of any participants with existing diagnosis of diabetes mellitus. Normal hemoglobin A1c values were considered 4% - 6.8%.

Body Mass Index. Body mass index (BMI) was obtained from the child's medical record. BMI is calculated as weight in kilograms divided by height in meters squared.

Since BMI norms are age- and sex-specific for children and adolescents, we calculated participants' BMI percentiles based on the Centers for Disease Control and Prevention (CDC) norms [18]. A BMI percentile $\geq 95^{th}$ percentile is classified as obese.

Demographics. Parents completed a demographic questionnaire that asked about their child's sex, age, race/ethnicity, as well as the parent's highest educational attainment.

2.3. Procedures

Data collection took place between November 2011 and January 2013. Participants were recruited from a patient population seeking evaluation and treatment for weight-related concerns at an outpatient pediatric endocrinology clinic. Participant inclusion criteria included: primary caregivers with target child/adolescent ages 6 - 16 years; patient with a primary diagnosis of obesity or referral for initial evaluation due to weight-related concerns; fluency in English for patient and parent. Exclusion criteria included: diagnosis of diabetes mellitus; patients with neurological disorder or injury, moderate or severe head injury, or other major medical conditions known to affect cognitive function; current diagnosis of developmental disability or mental retardation; past or current diagnosis of cortisol excess; and multiple anti-psychotic use. Data collection procedures took place directly after the patient's scheduled office visit. Primary caregivers of patients received a flyer from their physician soliciting their participation in the study. Two trained clinical psychology doctoral students obtained parent consent and child assent. Participating parents were asked to complete a paper-and-pencil version of the demographic form in the waiting room of the pediatric endocrinology clinic. Youth were administered the WASI and WRAML-2 by a trained clinical psychology doctoral student in a separate exam room in the pediatric endocrinology clinic. The study took approximately one hour to complete. Biochemical and demographic data were transcribed from the patient's medical record. Demographic data was collected on date of enrollment. Each caregiver/patient dyad received a $30 gift card upon completion of the study. This study was approved by the Institutional Review Boards (IRBs) at Scott & White Clinics and Baylor University; all procedures followed the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.4. Statistical Analyses

Descriptive statistics were computed for the WASI, WRAML-2, and fasting insulin levels. Independent samples *t* tests were used to compare obese youth with elevated fasting insulin levels and those with fasting insulin levels in the normative range on verbal memory, visual memory, attention/concentration, and intelligence. To determine the magnitude of the differences between obese youth with elevated verses normal fasting insulin levels, effect sizes were calculated [19]. Effect sizes were calculated by taking the difference between the elevated insulin sample mean and the normal insulin sample mean, divided by the pooled standard deviation. Effect sizes for differences in means were categorized as small (0.20), medium (0.50), and large (0.80) [19].

Multiple linear regression analysis was conducted with 4 separate models in which each cognitive domain represented a different outcome (e.g., verbal memory, visual memory, attention/concentration, and intelligence). Each model used hierarchical entry with demographics (e.g., gender, age, race/ethnicity, parental education) entered in the first block as control variables. Fasting insulin was added in the second block of each model in order to assess the increment in variance accounted for by insulin regulation. The increment in variance accounted for by the variable added in the second block was tested for statistical significance ($P < 0.05$). Statistical analyses were conducted in SPSS Version 19 for Windows [20].

3. Results

On the WRAML-2 Verbal Memory Index, 13.2% of the total sample scored below the Average range, 70.1% scored within the Average range, and 16.7% scored above the Average range. Approximately 13.3% of the total sample scored below the Average range on the WRAML-2 Visual Memory Index, 76.7% scored within the Average range, and 10.0% scored above the Average range. On the WRAML-2 Attention/Concentration Index, 50.0% of the total sample scored below the Average range and 50.0% scored within the Average range. Approximately 3.3% of the total sample scored below the Average range on the WASI FSIQ-2, 86.7% scored within the Average range, and 10% scored above the Average range.

Elevated fasting insulin levels (>23 mcUnit/ml) were found in 36.7% of the total obesity sample. There were no statistically significant differences between obese pediatric patients with elevated insulin levels and normal insulin levels on gender, age, race/ethnicity, and parental education (**Table 1**).

Means and standard deviations for the WRAML-2 Verbal Memory, Visual Memory, and Attention/Concentration indices and the WASI FSIQ-2 are presented in **Table 2**. Obese youth with elevated insulin levels scored similarly to obese youth with normal insulin levels on verbal memory, attention/concentration, and intelligence. None of these differences were statistically significant and effect sizes were in the small range. Obese youth with normal insulin levels scored higher than obese youth with elevated insulin levels on visual memory, with a medium effect (effect size = 0.51); however, this mean difference was not statistically significant.

Table 3 presents both significant and non significant standardized beta coefficients (e.g., the value of the beta when all predictors were included) for the four models for which the primary outcomes were verbal memory, visual memory, attention/concentration, and intelligence. Fasting insulin was not significantly associated with any of the 4 cognitive domains. Gender was significantly associated with verbal memory and attention/concentration ($P < 0.05$) in that being a girl was associated with higher scores in these domains. Age was significantly associated with attention/concentration and intelligence ($P < 0.05$) in that younger age was associated with higher scores in these domains.

Table 2. WRAML-2 Verbal Memory, Visual Memory, and Attention/Concentration and WASI FSIQ-2 scores across obese youth with elevated and normal fasting insulin levels.

	Normal Insulin (N = 19)		Elevated Insulin (N = 11)		Effect Sizes
Scale	Mean	SD	Mean	SD	
WRAML-Verbal Memory	98.47	12.96	99.45	15.85	0.07
WRAML-Visual Memory	102.05	15.33	95.09	9.42	0.51
WRAML-Attention/ Concentration	86.42	10.69	87.45	10.38	0.10
WASI FSIQ-2	99.47	15.39	99.64	9.17	0.01

Note: None of the mean differences between the two groups were statistically significant. SD equals standard deviation.

Table 3. Multiple linear regression analyses of insulin regulation and cognitive function in obese youth.

Variables	Verbal Memory	Visual Memory	Attention/ Concentration	Intelligence
Block 1				
R^2	0.21	0.11	0.43	0.28
Gender	0.42^{*}	0.21	0.56^{**}	0.30
Age	−0.21	0.09	-0.36^{*}	-0.47^{*}
Race/Ethnicity	0.02	0.22	0.19	0.09
Parental Education	0.20	0.09	−0.23	−0.12
Block 2				
R^2 change	0.01	0.00	0.00	0.00
Fasting Insulin	0.12	−0.04	0.02	0.04
Cumulative R^2	0.22	0.11	0.43	0.28

Note: Betas presented are standardized betas for the full model. Both significant and non significant betas are presented. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

4. Discussion

The objective of the present study was to investigate the associations among cognitive functioning and insulin regulation in a clinical sample of obese youth. Consistent with previous literature [21,22], the greatest difficulties in our overall sample were observed in an area of executive function. Half of the obese youth in our sample scored below the range expected of same-aged peers on the WRAML-2 Attention/Concentration Index. This index is an estimate of brief attentional demands and immediate rote recall abilities. Performance on the Attention/Concentration Index in the present study contrasted greatly from performance on the other cognitive domains (e.g., verbal memory visual memory, intelligence) in which at least 85% of the sample scored at or above the range expected of same-aged peers.

There were no statistically significant differences between obese youth in our sample with normal fasting insulin levels and elevated fasting insulin levels on the four cognitive domains measured. However, we found a medium effect between obese youth with normal insulin levels and obese youth with elevated insulin levels on visual memory, with the normal insulin sample manifesting better overall visual memory. Normal plasma insulin levels are thought to promote optimal functioning of the hippocampus, the region of the brain primarily responsible for memory function. A number of studies have documented that increasing plasma insulin levels in adults with cognitive impairment improves memory function [23]. In one study with middle aged obese adults, insulin sensitivity mediated the relationship between BMI and working memory-related brain activation in the right parietal cortex [24]. As such, it is possible that altering insulin sensitivity through proper diet and exercise in obese youth with insulin resistance may result in improvements in visual memory. Future studies are needed to replicate our findings and elucidate whether interventions that modify insulin sensitivity in obese youth with insulin resistance result in gains in visual memory.

We found no associations between fasting insulin levels and the cognitive domains measured in the multiple linear regression analysis. This finding is not consistent with previous literature conducted with nonobese elderly adults [7,8] and obese middle-aged and elderly women [6]. Although it is likely that our small sample size atenuated the probability of detecting statistically significant differences in the multiple linear regression analysis, another possible explanation for our findings is that the negative impact of insulin resistance on verbal memory, attention/concentration, and intelligence takes place over time and is affected by a person's obesity status across the lifespan. A recent study that found impairment in neural activity among obese youth with insulin resistance does not support this explanation [9]. However, this study did not use norm-referenced measures of cognitive function, but latencies and amplitudes of P300 waves which measure brain processes involved with the evaluation and categorization of stimuli. Taken together, the data suggest longitudinal studies examining insulin regulation, cognitive functioning, and weight status over time are needed using well validated, standardized cognitive measures.

Our finding that being a girl was associated with better attention/concentration is consistent with previous literature that suggests boys generally demonstrate greater deficits in attention [25]. The finding that younger age was significantly associated with better attention/concentration and intelligence in our sample underscores the importance of obesity prevention and early intervention. This finding is consistent with the idea that there may be prolonged effects of obesity on cognitive functioning. Childhood represents a critical period to initiate positive lifestyle changes and influence a youth's metabolic programming [26]. There are data that suggest early identification and referral for treatment in youth is associated with better obesity treatment outcomes [27]. Our data indicate that early obesity intervention may also be associated with better cognitive outcomes in youth, particularly in the areas of attention/concentration and intelligence.

The present study has a number of limitations. We were not able to infer causation between insulin regulation and cognitive domains measured due to the cross-sectional design of this study. Given data that suggest neurological deficits may also serve as a risk factor for obesity [28], future prospective studies are needed in obese youth examining these variables. Our sample was also small limiting the generalizability of the findings and our ability to detect statistically significant differences. However, it should be noted that administration of standardized cognitive measures is time consuming, costly, and requires extensive psychological assessment expertise; these factors generally limit the ability to administer these measures to large samples in clinical research. Our study did not utilize functional neuroimaging and only assessed one pathophysiological mechanism in relation to cognitive functioning in obese youth. It has been suggested that other pathophysiological mechanisms, including systemic inflammation and triglycerides, may impact cognitive functioning in the obese [5]. Future research is needed that uses functional neuroimaging and assesses other possible pathophysiological mechanisms associated with cognitive impairment in obese youth. Finally, we did not assess physical activity, aerobic fitness, diet intake, or parental intelligence.

To the best of our knowledge, this is the first study to report on the associations among insulin regulation and cognitive function in a clinical sample of obese youth using well validated, standardized cognitive measures. The present study has a number of strengths including diversity in sample race/ethnicity and exclusion of youth with other major medical conditions that would be expected to impact cognitive functioning.

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