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Differential Effects of Insulin Resistance on Frontal Lobe Related Cognitive Function in Adolescents and Adults

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Abstract: The aim of this study was to determine whether effects of insulin resistance (IR) on frontal lobe mediated abilities differ between adolescents and middle-aged adults. These analyses included 118 adolescents aged 16-21 and 118 adults aged 45-60. IR was defined as having a homeostasis model assessment of insulin resistance (HOMA-IR) > 3.99. These analyses focused on higher-order frontal lobe-mediated function and assessed the differential effects of IR by age group on eight targeted cognitive/functional measures. There were significant differences between adolescents who were insulin sensitive (IS) and those with IR on the Stroop interference score (Cohen's d = 0.61) and Frontal Systems Behavior Scale (FrSBe) executive dysfunction (Cohen's d = -1.00). Adults with and without IR did not differ on any of the selected measures. There were significant interactions between age group and IR status for the Stroop interference score (partial eta^2 = 0.029) and FrSBe executive dysfunction scale (partial eta^2 = 0.045). Compared to their IS peers, adolescents with IR performed significantly worse on 2/8 indices of frontal lobe function, while no frontal lobe related cognitive differences existed in the adult population. As anticipated, there was a significant age group by IR status interaction for these higher-order frontal abilities. Poor performance in these measures indicates difficulties in planning, organization and self-regulation, skills that are crucial for life-long learning and achievement of future goals. These data suggest that the still-developing brains of adolescents may render them more vulnerable to the negative effects of metabolic dysregulation than do equivalent metabolic abnormalities in adults.

Keywords: Insulin Resistance, Metabolic Syndrome, Diabetes, Executive Function, Adolescents

1. Introduction

Childhood obesity is a growing epidemic, with a dramatic rise in prevalence over the last 50 years [1]. Nationally, over 25% of all children are considered obese, while the prevalence among adolescent-aged children is nearly 35% [2]. Although genetics can influence metabolic disease independent of obesity, this is rare, and individuals with obesity generally have higher rates of metabolic dysregulation, including insulin resistance (IR), a precursor to type 2 diabetes (T2DM). Diabetes is associated with many comorbidities, such as cardiovascular disease, kidney failure and blindness. Less widely known are the effects of diabetes on cognition; adults with diabetes are consistently found to have deficits in learning, memory and frontal-lobe mediated executive function (EF) [3, 4]. These cognitive decrements correlate with data from imaging studies that show hippocampal atrophy and frontal lobe white matter alterations in those with diabetes, and suggest that these regions may be particularly susceptible to damage from metabolic insult [5, 6].

Neurocognitive changes also have been noted in adults with IR in the absence of frank glycemic dysregulation. Specifically, IR has been associated with deficits in memory, attention and EF [7, 8] as well as with gray matter reductions and medial temporal atrophy in the elderly [9]. Several

biological mechanisms connecting IR and brain health have been considered in the literature. For one, insulin has downstream stimulatory effects on endothelial production of nitric oxide (NO), a potent vasodilator. Therefore, reduced insulin signaling secondary to IR may lead to impaired neurovascular reactivity and reduced blood flow during periods of high metabolic demand [10]. Other studies have explored insulin's role in glucose metabolism and found that those with greater insulin resistance had reduced brain glucose uptake, as seen by ^{18}F-deoxyglucose positron emission tomography (PET) imaging, in key regions such as the prefrontal and temporal cortices, which are known to be involved in learning and memory [11].

Although less is known about the neurocognitive effects of obesity-related metabolic disease among adolescents, research to date suggests youth are at risk for impairments in more cognitive domains than adults. Studies have shown that compared to normal weight peers, adolescents with obesity exhibit cognitive impairments in processing speed [12], attention, EF, visuospatial reasoning and abstraction [13, 14], and have poorer academic performance and lower scores on measures of intellectual function [15]. Additionally, adolescents with metabolic syndrome (MetS), including IR, were found to have decrements in EF and cognitive flexibility [16].

Extant literature supports the theory that damage to the brain during childhood and adolescence can have significant long term effects, particularly on the still developing frontal lobe [17-19], which continues to undergo morphologic changes through adolescence and myelination into the twenties [20]. Specifically, adolescents with T2DM and MetS have been found to have measurable changes in brain architecture, despite a presumed relatively short duration of metabolic dysregulation. In a study comparing adolescents with T2DM to controls with obesity but without diabetes, those with diabetes had significantly lower white matter volume as well as increased whole brain and frontal lobe cerebrospinal fluid (CSF), an indicator of cerebral atrophy [21]. Changes in hippocampal size, CSF volume and white matter integrity were also noted in non-diabetic adolescents with MetS, which includes IR as its central criterion [22].

Importantly, cognitive abilities do not always obey anatomic boundaries, and normal cognitive function depends on the integrity of multiple associated brain regions. Understanding of the connections between brain anatomy and cognition is rooted in neuropsychological assessments of people with known focal brain lesions as well as functional magnetic resonance imaging (fMRI) studies. From this body of research, the frontal lobe has been associated with a constellation of complementary but distinct abilities, some of which are categorized under the umbrella domain of executive functioning, and include anticipation, strategic planning, impulse control, mental flexibility and affect regulation [23]. Other commonly tested cognitive abilities such as phonemic verbal fluency have also been associated with the frontal lobe [24]. Performance on these functions parallels frontal lobe development, and as such, adolescents who are still undergoing frontal lobe white matter maturation may have more difficulty with these and related tasks and behaviors.

This study aims to explore whether the effect of IR on higher-order frontal lobe-mediated cognitive function differs between adolescents and middle-aged adults. We hypothesize that both adolescents and adults with IR will perform more poorly on frontal lobe-related measures, but that the effects will be more pronounced among adolescents.

2. Methods

A total of 118 adolescents aged 16 to 21 and 118 adults aged 45 to 60 were included in this analysis. Participants in both age groups were primarily recruited from online advertisements. Additional adolescent participants were recruited from a local high school, while additional adult participants were recruited from the Center for Brain Health, which is a National Institute of Health (NIH) funded laboratory at NYU studying normal and abnormal aging.

Exclusion criteria common to both age groups included lack of English proficiency, significant head trauma (e.g., concussion or with loss of consciousness), or history of neurological or psychiatric disorders. Significant medical conditions, with the exception of dyslipidemia, hypertension and polycystic ovarian syndrome (PCOS), were also exclusionary. Adolescents with T2DM were excluded from this study, while adults with T2DM were permitted if they were not being treated with insulin or insulin secretagogues.

2.1. Biochemical Assessment

All participants underwent a comprehensive medical and neurological evaluation. Morning blood draws were obtained after an overnight fast and were assayed for glucose, insulin and cholesterol profile. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula: fasting glucose (mg/dL) x fasting insulin (mU/L)/405. In the presence of significant deficits in pancreatic beta cell function, the HOMA-IR score is not a valid measure of IR. Thus, individuals with T2DM, who by definition have some degree of beta cell dysfunction, were considered to have IR regardless of HOMA-IR score, as IR is central in the pathogenesis of this disease. There is currently no consensus in the literature on appropriate HOMA-IR cutoff scores in non-diabetic individuals to designate insulin sensitivity or resistance for either adolescents or adults [25]. In these analyses, those with HOMA-IR scores of less than 2.16 were considered to be insulin sensitive (IS), while those with scores above 3.99 were considered to have IR. These values were chosen as they approximate the extreme values of previously cited cutoffs [26] thus representing reasonably conservative definitions of IS and IR. Those with intermediary HOMA-IR values were excluded from these analyses in order to maximize uncovering an effect, if one exists, by using only the extreme groups. The median HOMA-IR score for all subjects (prior to exclusion of the intermediary group) was between the cutoffs of IS and IR

(2.27). This left 118 adolescents and 118 adults for these analyses.

Hypertension was defined as a systolic value greater or equal to 130 mm Hg, a diastolic value greater or equal to 85 mm Hg or the use of antihypertensive medication. For participants under 19 years of age, hypertension was assigned for those with a systolic or diastolic blood pressure exceeding the 90th percentile adjusted for age, sex and height [27].

2.2. Neuropsychological Assessment

Participants in both age cohorts were administered the same comprehensive battery of neuropsychological tests to assess a range of cognitive domains. Tests were administered under standardized conditions by trained psychometrists and supervised by a licensed neuropsychologist. The following cognitive tasks were utilized to assess frontal lobe function: Controlled Oral Word Association Test (COWAT), Stroop Task, Trail Making Test, Category Test and Tower of London (TOL). Frontal lobe function was also assessed using the Frontal Systems Behavior Scale (FrSBe), a self-reported questionnaire that includes separate scores for apathy, disinhibition and executive dysfunction. To test the specificity of the hypothesized differences in frontal lobe, the effect of insulin resistance on one measure of learning/recent memory and one of working memory were also included. The California Verbal Learning Test (CVLT) was used to assess learning and memory and is primarily temporal lobe-mediated. Letter/Number Sequencing assessed working memory, a lower order cognitive function that is frontal-mediated but not considered an EF ability. Full Scale IQ (FSIQ), indicative of global brain functioning, was included as a descriptive participant characteristic. Each cognitive test varied by which demographic variables, if any, they were adjusted for in calculation of the test score (i.e., age, education, sex).

2.3. Statistical Analyses

All analyses were conducted using SPSS Version 20. Tests that did not include T score or other standardized conversions were normalized into Z scores (Trail Making B - A difference, Category Test errors, TOL excess moves, Letter/Number Sequencing). Given that adolescents and adults differed significantly in extent of education, tests that were not already education-adjusted (Stroop Interference score, Trail Making B - A difference, TOL excess moves, FSIQ, CVLT-II, Letter/Number Sequencing) were adjusted for education. Insulin resistance is associated with age [28], and thus unsurprisingly there were significant differences in age between IR and IS adults. Given these differences for the adults, linear regression analyses between age and the cognitive tests for the adults were utilized. Only estimated FSIQ, shown as a descriptive value, was significantly correlated to age in the adult cohort, thus difference in FSIQ between IS and IR adults was age adjusted.

Two-way analysis of variance (ANOVA) tests, a type of analysis considered robust for both parametric and non-parametric data, were utilized to examine between and within group differences. For this reason, non-parametric analyses for variables not passing test of normality were not used. This also allowed us to keep the output of the analyses consistent and report all effect sizes in the same units. Chi-square tests were used for categorical variables (e.g., Sex, Hypertension Yes/No).

3. Results

Individuals with IR in both age groups had significantly higher BMI, cholesterol/HDL ratios, triglyceride levels, percent body fat, and systolic and diastolic blood pressure than their IS counterparts. Although adults with IR were significantly older than IS adults (53.07 +/- 4.63 v. 51.01 +/- 4.09), it is unlikely that a two year mean difference between the groups contributed to these results as demonstrated by the lack of difference in any of the cognitive outcomes after adjusting for age. No significant age difference existed between IR and IS adolescents. Education-adjusted values of CVLT and Letter/Number sequencing (control variables) did not differ within age groups.

Adolescents and adults did not differ significantly in sex distribution (percent female), BMI, or percent body fat. There were also no significant differences in education-adjusted scores of CVLT-II and Letter/Number sequencing. As expected, adults had significantly more years of education than adolescents (15.54 +/- 2.23 v. 12.88 +/- 1.37). Age cohorts also differed significantly in prevalence of metabolic dysfunction; adults had significantly higher blood pressure, cholesterol/HDL ratios and triglyceride levels than adolescents and significantly higher prevalence of hypertension (Table 1). These results are consistent with epidemiological data demonstrating a higher prevalence of metabolic abnormalities in adults [29-32].

Table 1. Descriptive characteristics and control variables by insulin sensitive (IS)/insulin resistance (IR) status and age group.

	Adolescents			Adults		
	IS (*n* = 80) Mean (SD)	IR (*n* = 38) Mean (SD)	*p*	IS (*n* =72) Mean (SD)	IR (*n*=46) Mean (SD)	*p*
Age	19.83 (1.47)	19.36 (1.13)	0.086	51.01 (4.09)	53.07 (4.63)	0.013*
Education (years)	13.04 (1.48)	12.55 (1.06)	0.073	15.70 (2.26)	15.28 (2.19)	0.32
Sex (% female)	48.80	63.20	0.14	52.8	45.7	0.45
Estimated FSIQ[a]	107.27 (11.78)	101.61 (10.52)	0.059	111.19 (10.23)	109.81 (10.03)	0.66
BMI (kg/m^2)	25.42 (5.73)	37.46 (5.72)	<0.001***	26.87 (6.16)	34.61 (6.96)	<0.001***
Body fat (%)	29.15 (10.15)	41.39 (8.68)	<0.001***	29.35 (9.71)	35.36 (8.03)	0.002**
Cholesterol/HDL	2.97 (0.80)	3.83 (0.76)	<0.001***	3.43 (0.87)	4.20 (1.22)	<0.001***
Triglycerides	71.08 (35.16)	105.26 (43.25)	<0.001***	84.75 (36.87)	159.70 (71.20)	<0.001***

	Adolescents			Adults		
	IS (n = 80) Mean (SD)	IR (n = 38) Mean (SD)	p	IS (n = 72) Mean (SD)	IR (n=46) Mean (SD)	p
SBP (mm Hg)	109.44 (10.46)	114.30 (9.32)	0.016*	116.00 (11.09)	127.97 (12.06)	<0.001***
DBP (mm Hg)	64.77 (8.44)	68.84 (7.73)	0.013*	71.48 (7.99)	77.31 (9.06)	<0.001***
Hypertension (yes)	2	1	0.97	12	30	<0.001***
CVLT (T Score)[b]	48.94 (10.15)	47.97 (9.41)	0.66	54.64 (10.17)	52.64 (11.77)	0.47
Letter/Number sequencing (Z-score)	-0.013 (0.98)	0.032 (0.97)	0.64	0.015 (0.98)	-0.21 (0.96)	0.99

***Table 1.** Continued.*

	Adolescents	Adults	
	(n = 118) Mean (SD)	(n = 118) Mean (SD)	p
Age	19.68 (1.39)	51.81 (4.40)	<0.001***
Education (years)	12.88 (1.37)	15.54 (2.23)	<0.001***
Sex (% female)	53.40	50.00	0.60
Estimated FSIQ[a]	105.51 (11.66)	110.67 (10.13)	0.84
BMI (kg/m^2)	29.29 (8.02)	29.89 (7.49)	0.55
Body fat (%)	33.04 (11.24)	31.71 (9.52)	0.36
Cholesterol/HDL	3.24 (0.89)	3.73 (1.08)	<0.001***
Triglycerides	82.08 (41.03)	113.97 (64.21)	<0.001***
SBP (mm Hg)	111.01 (10.32)	120.60 (12.83)	<0.001***
DBP (mm Hg)	66.08 (8.40)	73.72 (8.85)	<0.001***
Hypertension (yes)	3	42	<0.001***
CVLT (T Score)[b]	48.63 (9.89)	53.86 (10.82)	0.062
Letter/Number sequencing (Z-score)	0.0012 (0.97)	0.0010 (0.97)	0.14

IS = insulin sensitive; IR = insulin resistant; BMI = body mass index; HDL = high-density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; FSIQ = full scale intelligence quotient; CVLT = California Verbal Learning Test. [a]age adjusted; [b]sex and age adjusted; * p < 0.05; ** p < 0.01; ***p < 0.001.

Of the eight measures of higher-order frontal lobe function included in this study, the adolescent IR group performed significantly worse than the adolescent IS group on two out of eight measures or 25% (Stroop interference score and FrSBe executive dysfunction) with moderate to large effect sizes (Cohen's ds 0.56 and 1.00, respectively). Predicted differences also were noted for the COWAT and FrSBe apathy scale, although they did not reach significance (COWAT: p = 0.076, Cohen's d = 0.37; FrSBe apathy p = 0.089, Cohen's d = -0.73). The groups did not differ in scores on Trails B – A difference, Category test errors, TOL excess moves and FrSBe disinhibition. Adults with IR were not found to have any significant differences in frontal lobe abilities compared to the adult IS group (Table 2).

***Table 2.** Cognitive and behavioral scores by insulin sensitive (IS)/insulin resistance (IR) status and age group.*

	Adolescents				Adults				Interaction (Age group by IR status)	
	IS (n = 80) Mean (SD)	IR (n = 38) Mean (SD)	p	Cohen's d	IS (n =72) Mean (SD)	IR (n=46) Mean (SD)	p	Cohen's d	p	Partial eta^2
COWAT (T Score)[b]	44.93 (11.51)	41.18 (8.37)	0.076	0.37	44.42 (12.42)	46.00 (10.30)	0.49	-0.14	0.086	0.013
Stroop interference score (T score)	57.26 (8.02)	52.14 (8.72)	0.003**	0.61	52.47 (6.54)	52.80 (7.61)	0.80	-0.05	0.010*	0.029
Trail Making B-A (Z-score)	-0.029 (0.98)	0.088 (0.97)	0.78	-0.12	-0.027 (1.04)	0.020 (0.99)	0.89	-0.05	0.75	<0.001
Category Test Errors (Z Score)[c]	-0.40 (0.79)	-0.45 (0.95)	0.78	0.06	0.46 (0.96)	0.39 (0.95)	0.73	0.07	0.95	<0.001
TOL excess moves (Z score)[a]	0.017 (0.99)	-0.0077 (0.98)	0.67	0.03	-0.053 (0.98)	0.097 (0.95)	0.57	-0.16	0.56	0.002
FrSBe Apathy (T Score)[c]	55.46 (14.38)	64.22 (8.84)	0.089	-0.73	51.28 (12.42)	52.29 (11.66)	0.79	-0.08	0.21	0.017
FrSBe Disinhibition (T Score)[c]	51.57 (14.18)	57.22 (10.02)	0.27	-0.46	49.48 (9.55)	54.88 (18.14)	0.19	-0.37	0.97	<0.001
FrSBe Executive Dysfunction (T Score)[c]	53.03 (12.10)	64.67 (11.20)	0.012*	-1.00	51.03 (11.69)	51.00 (11.94)	0.99	<0.001	0.044*	0.045

IS = insulin sensitive; IR = insulin resistant; COWAT = Controlled Oral Word Association Test; TOL = Tower of London; FrSBe = Frontal Systems Behaviors Scale; [a]age adjusted; [b]sex and age adjusted; [c]sex, age and education adjusted; * p < 0.05; ** p < 0.01.

When the adolescent and adult cohort data were combined, there were significant age group by IR status interactions for the Stroop interference score (p = 0.010, partial eta^2 = 0.029) (Figure 1) and FrSBe executive dysfunction scale (p = 0.044, partial eta^2 = 0.045) (Figure 2). In addition, an interaction in the predicted direction, albeit short of statistical significance, was present for the COWAT (p = 0.086, partial eta^2 = 0.013). Neither BMI nor hypertension modified these reported

associations, and effect sizes remained essentially the same after controlling for these variables. There were no significant interactions between age group and IR status on any of the remaining frontal lobe measures (Table 2).
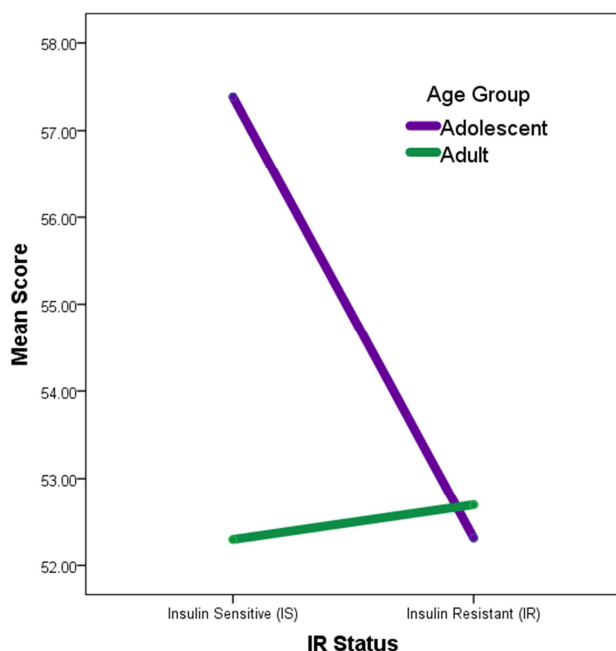

Figure 1. *Insulin sensitive (IS)/insulin resistance (IR) status versus mean Stroop interference score in adolescents and adults.*
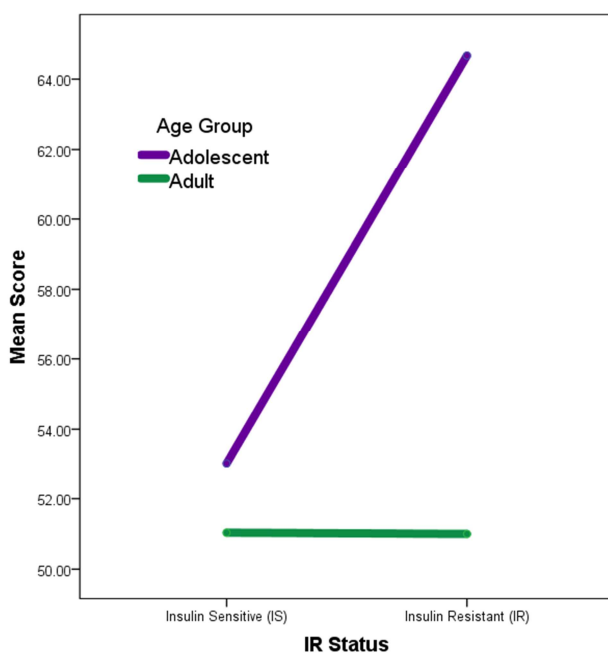

Figure 2. *Insulin sensitive (IS)/insulin resistance (IR) status versus mean FrSBe Executive Dysfunction score in adolescents and adults.*

To place the frontal lobe-related decrements among adolescents with IR into a more global context, the measures with significant differences between IS and IR groups were contrasted with cognitive tasks that are directly related to academic (school) performance. The COWAT and Stroop

interference task were both found to be significantly correlated to reading, numerical and spelling scores on the Wechsler Individual Achievement Test (WIAT) (Pearson coefficients = 0.176 to 0.287). The FrSBe executive dysfunction score was significantly correlated to the WIAT numerical score only (Pearson coefficient = 0.194).

4. Discussion

Adolescents with IR performed substantially worse than their IS peers on several measures of frontal lobe function, while adults with IR did not differ from IS adults, leading to significant interactions between age group and IR status in these measures. This demonstrates that the impact of IR on these cognitive or behavioral outcomes is more pronounced in adolescents than middle-aged adults. Of note, there were no significant between- or within-group differences for CVLT and Letter/Number sequencing (the "control" variables), suggesting that the effect of IR and age group on frontal lobe-related measures is not driven by differences in memory or working memory.

The data brought together in this analysis included two separate studies with overlapping cognitive and medical evaluations. An important exception is that adults with T2DM were included while adolescents with T2DM were excluded. Of note, T2DM is uncommon in adolescence [33], and may be difficult to distinguish from non-IR mediated forms of this disease such as Type 1 or maturity onset diabetes of the young (MODY). Nevertheless, adults with diabetes included in this analysis differ from adolescents with IR in that in addition to impaired glucose control they likely have a longer duration of IR, which should increase their potential cognitive deficits. If so, this would attenuate the age group by IR status interaction, which highlights the strength of these findings.

As expected, age cohorts differed significantly in prevalence of comorbidities associated with IR, namely hypertension and obesity. There is some evidence that these metabolic abnormalities are independently associated with cognitive deficits. For example, our group has previously shown that adolescents with obesity but without IR fare more poorly on tests of memory, attention, mental flexibility and academic subject tests than normal weight peers [13]. Studies of hypertension and cognition have reported inconsistent results, but have suggested that elevated blood pressure in middle age may increase risk for Alzheimer's and vascular dementia [34], and may be independently associated with increased risk of executive and visuospatial deficits [35]. Results remain the same after controlling for BMI and hypertension, suggesting the effect IR exerts on the measured frontal lobe abilities is likely independent of these other variables.

Adolescents with IR performed more poorly on the COWAT and Stroop interference score, while no such pattern existed among adults. The COWAT is a measure of phonemic verbal fluency and is highly correlated with frontal lobe function [24, 36]. Stroop interference reflects cognitive

flexibility and capacity to overcome habitual response and is a measure of EF [24, 37]. Although other brain regions are involved in these tasks, both are considered sensitive markers of frontal lobe integrity [36].

Adolescents with IR also scored significantly more poorly than their IS peers on the FrSBe executive dysfunction scale. The structured setting in which neuropsychological tests are administered is not always optimal for detecting deficits in EF and thus inclusion of this self-reported measure complements the neurocognitive battery. Moreover, this scale directly reflects functional deficits in planning, problem solving and self-regulation that are noticeable to the participant. Though not significantly different, adolescents with IR also had substantially higher FrSBe apathy scores than IS adolescents, which is important as it reflects a lack of drive, persistence and interest, all of which could help explain the cognitive findings.

Frontal lobe-related cognitive function, particularly executive abilities, are crucial for anticipation of future events and achievement of long-term goals. While important at any age, executive dysfunction is especially worrisome in adolescence when it can affect school performance and subsequent academic and professional opportunities. When the frontal lobe measures were compared to a set of academic performance markers also included in this study, the COWAT and Stroop interference score were both found to be significantly correlated to reading, numerical and spelling scores. Studies examining associations between EF and academic success have consistently found that poor EF negatively impacts school performance in children [38], with similar effect sizes in both reading and math scores [39]. While the impact of executive dysfunction on academic performance is strongest in younger children, there is evidence to suggest that this association continues into the high school years [39].

Due to the cross-sectional nature of this study, it is impossible to determine if adolescents with IR will face continued frontal lobe related cognitive declines or if these differences merely reflect delayed cognitive development. Prior evidence that MetS is associated with structural brain changes such as cerebral atrophy and white matter alterations in adolescents [22, 40] suggests that these effects may be lasting. Even if these differences reflect only a lag in development, the detrimental impact on school performance and professional trajectory may have effects well into adulthood.

Deficits in executive dysfunction may have an exaggerated health impact on those with metabolic disease, especially if sustained into middle age. Adolescents with IR are more likely to develop diabetes and cardiovascular disease in their lifetime than their metabolically normal peers, yet EF deficits may make it more difficult for them to adhere to diet and exercise and even more so to complex insulin or oral medication regimens.

Whether these cognitive deficits are reversible with improvement in insulin sensitivity and whether it differs by age is not well understood. In animal models, insulin-sensitizing agents were found to improve cognition in adults with IR [41], though no equivalent studies were done in younger animals. Several longitudinal studies measuring cognitive variables pre- and post-bariatric surgery found improvements in memory, attention and EF with follow-up periods ranging from three months to three years after surgery [42, 43]. This is especially noteworthy as bariatric surgery is known to have positive effects on insulin sensitivity, leading to total remission of diabetes in a significant portion of cases [44, 45]. Again, these studies were in adults, and thus it is unclear whether the same beneficial effects would have been achieved in adolescents, or in adults known to have IR beginning in childhood.

The primary limitation of this study is its cross-sectional design, which precluded the evaluation of the longitudinal impact of IR on cognition. As the duration of IR could not be ascertained, the potential role of chronicity on frontal lobe-related cognitive dysfunction could not be determined. Further, the impact of the severity of IR on cognition could not be analyzed, given that calculation of HOMA-IR assumes normal beta cell insulin production and release and is not valid in those with T2DM, a substantial subset of this adult IR sample. Despite these limitations, this study is intended to be a proof of concept that adolescents with IR face greater deficits in frontal lobe mediated function than do adults. Future studies would ideally use more dynamic methods to measure insulin resistance and sensitivity such as the hyperinsulinemic/euglycemic clamp or frequently sampled, insulin modified, intravenous glucose tolerance test, methods that are also valid in those with beta cell dysfunction. This would allow the findings reported here to be characterized in the context of a continuous measure of IR that would be valid in those with T2DM as well as lesser forms of metabolic dysregulation.

This study is unique in that it compares the impact of IR on cognition between adolescents and adults using standardized biochemical and neuropsychological measures. Further strengths include a moderately sized and diverse cohort with high prevalence of obesity and insulin resistance. Our comprehensive neuropsychological battery allowed us to detect differences in frontal lobe related cognitive functions, which may not have been evident from a single test.

5. Conclusion

As obesity becomes more prevalent in childhood, so too does IR and diabetes. These data yielded significant differences between IR and IS adolescents in 25% of the frontal lobe mediated functions and differences nearly reaching significance in an additional 25% of tested measures, while no such differences were present in middle-aged adults. Given that adolescents had more substantial cognitive differences from their non-IR peers than did IR adults, despite a likely shorter period of metabolic dysfunction, these findings suggest that the still-developing brain of adolescents may be more vulnerable to possible neurotoxic effects of IR.

The importance of frontal lobe-mediated tasks such as EF, especially in youth, cannot be over emphasized. Impairments in cognitive abilities and behaviors in adolescence can impact decision-making and school performance during a critical period, potentially altering an individual's trajectory towards life-long learning. As such, these results, in tandem with what is known about the deleterious cardiovascular effects of obesity and diabetes, should encourage and inform preventive health measures and screening practices in youth. For example, screening for metabolic dysfunction should be a routine component of annual exams for all youth, but especially for those carrying excess weight. If found to be insulin resistant, the child and caregiver should be provided with an explanation of what this means and should be offered extensive nutrition and weight loss counseling. Moreover, although somewhat controversial, pediatricians may want to consider prescribing these patients insulin-sensitizing medications, such as Metformin, to slow or halt progression from IR to diabetes, perhaps protecting the brain from further insult. Future longitudinal studies are still needed to evaluate how adolescents with IR fare later in life and to assess the utility of weight loss or insulin sensitization in preventing and reversing these cognitive deficits.

Funding and Disclosure

Abbreviations

BMI = Body Mass Index, IS = Insulin Sensitive, IR = Insulin Resistance, EF = Executive Function, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, T2DM = Type 2 Diabetes

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