Preliminary Evidence of Cognitive and Brain Abnormalities in Uncomplicated Adolescent Obesity

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Objective: To ascertain whether pediatric obesity without clinically significant insulin resistance (IR) impacts brain structure and function.

Methods: Thirty obese and 30 matched lean adolescents, all without clinically significant IR or a diagnosis of metabolic syndrome (MetS), received comprehensive endocrine, neuropsychological, and MRI evaluations.

Results: Relative to lean adolescents, obese non-IR adolescents had significantly lower academic achievement (i.e., arithmetic and spelling) and tended to score lower on working memory, attention, psychomotor efficiency, and mental flexibility. In line with our prior work on adolescent MetS, memory was unaffected in uncomplicated obesity. Reductions in the thickness of the orbitofrontal and anterior cingulate cortices as well as reductions of microstructural integrity in major white matter tracts without gross volume changes were also uncovered.

Conclusions: It was documented, for the first time, that adolescents with uncomplicated obesity already have subtle brain alterations and lower performance in selective cognitive domains. When interpreting these preliminary data in the context of our prior reports of similar, but more extensive brain findings in obese adolescents with MetS and T2DM, it was concluded that “uncomplicated” obesity may also result in subtle brain alterations, suggesting a possible dose effect with more severe metabolic dysregulation giving rise to greater abnormalities.

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Introduction

With the rise of sedentary lifestyles and ready access to inexpensive high caloric density foods, the prevalence of obesity is rising at an alarming rate and is a major risk factor for type 2 diabetes mellitus (T2DM), cardiovascular disease as well as other adverse health conditions (1). Currently in the United States, 17% of children are obese and an additional 18% are overweight (2) and 6% of them are morbidly obese with a body mass index (BMI) above 40 kg/m². Obese youths are likely to become obese adults and are at risk for the same diseases faced by obese adults, but regrettably, at much younger ages and demonstrating more severe and harder to treat forms of disease (3).

There is a sizable literature documenting the negative brain consequences of obesity in adults (e.g., see ref. 4), with frontal lobe-based functions being particularly vulnerable (5). In contrast, the pediatric literature is less well developed and the cognitive findings are much less consistent. Some reports demonstrated lower general intellectual functioning (6) and academic achievement (7), lower mental flexibility (8), and difficulty with attention and set shifting (9) in obese children. However, better powered studies focusing on less severe forms of obesity failed to identify such associations (e.g., see ref. 10).

There are also a handful of reports documenting brain circuits that may be involved in obesity (e.g., see refs. 11,12). These reports very likely included obese individuals with clinically significant insulin resistance (IR), a common co-morbidity. We have previously described frontal and temporal lobe abnormalities in obese adolescents with T2DM relative to obesity-matched adolescents without IR (13,14). More recently, we demonstrated that non-diabetic obese adolescents with Metabolic Syndrome (MetS) also have poorer academic
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normalization, skull-stripping, and an affine transformation to Talairach space. A tissue segmentation algorithm was used to separate WM from non-WM, and the results were further optimized using a tessellation process followed by topological correction and smoothing (29). The cortex was inflated, flattened and registered to a spherical atlas using individual cortical folding patterns point-to-point (30). A cortical parceling algorithm assigns an anatomical label to each vertex on the cortical sheet (31). We computed GM volumes for the OFC (lateral and medial combined) and ACC (rostral and caudal combined). To account for interhemispheric differences in surface area, we averaged the cortical thickness of the OFC and ACC subregions between hemispheres weighted by their corresponding surface areas.

DTI processing
FA maps were corrected for spatial distortion inherent in echo planar acquisitions and normalized to standard (Talairach) space using the published Automatic Registration Toolbox software (32). Please refer to Yau et al. (2009) for detailed methods (33). In brief, the MPRAGE image was manually skull-stripped using the method described above and was then spatially normalized to a standard MNI template using a 3D non-linear algorithm. The T2-weighted image was then skull-stripped and registered to the MPRAGE image through an iterative process. A 2D nonlinear algorithm was used to correct for spatial distortions on the non-diffusion-weighted b0 image. Finally, all the transformations were applied to spatially correct and normalize the FA maps.

Statistical analyses
The Shapiro-Wilk Test evaluated data normality. For cognitive variables, values >3 SDs from the respective group mean were excluded. Two-tailed independent samples t-tests (effect size Cohen’s d) examined group differences for normally distributed variables; otherwise, the Mann-Whitney U test (effect size r) was used. Univariate ANOVA analyses confirmed whether the observed cognitive differences were not confounded by sleep apnea, subclinical depression, or level of physical activity. The chi square test evaluated categorical variables. Overall CSF volume and all brain measures were residualized to the ICV volume using linear regression to adjust for individual brain size differences. A two-tailed voxelwise ANCOVA (VANCOVA) analysis examined group differences in WM FA with age as a covariate and a WM mask to restrict the analysis to WM regions. We minimized Type I error by restricting the accepted cluster size to at least 100 contiguous voxels (volume >100 mm3) and by choosing a P-value threshold of 0.005 to keep the false discover rate below 1%. To ensure the validity of our DTI results, we mapped each significant cluster onto the individual normalized FA maps to check for contamination.

Results
The groups were well matched demographically (Table 1). Obese adolescents had higher BMI and larger waist circumference. All participants had normal fasting glucose levels and all except one obese participant (who had 22.20 μU/ml but a HOMA of 3.91) had normal insulin levels (< 20.00 μU/ml), thus as per our definition, no participant had clear evidence of IR, although obese adolescents had significantly higher insulin levels. Obese adolescents had significantly elevated systolic and tended toward higher diastolic BP. Two obese adolescents had been previously diagnosed with hypertension and one of them was on medication, and additionally, one obese and two lean adolescents, all males, met thresholds for hypertension when evaluated in our laboratory. Obese adolescents also had significantly lower HDL (15 obese/7 lean) and higher LDL levels as well as non-significantly higher triglycerides (4 obese/3 lean had elevated triglycerides). Obese adolescents had significantly elevated plasma C-reactive protein (CRP) levels, even after excluding those with values ≥10 mg/dl, who we argue could have an infection or acute inflammation. The groups did not differ on ratings of obstructive sleep apnea, subclinical depressive symptoms, or level of physical activity.

Neuropsychological results
Obese adolescents had lower academic achievement, with statistically significant reductions in arithmetic and spelling skills (Table 2). Working memory was the only memory measure that trended lower in the obese group. Mental flexibility measured by Trails B total time was the only executive function that also trended lower. Obese adolescents tended to perform worse on WRAML Attention-Concentration Index and Trails A Test but the groups did not differ on DVT total time. Obese adolescents also tended to score lower on psychomotor efficiency. These cognitive differences remained largely unchanged after controlling for age, sex, self-ratings of sleep apnea, BDI scores, or level of physical activity.

Imaging results
One obese adolescent with an ICV volume 3 SDs larger than the group mean was excluded from brain volumetric analysis but was retained in the voxelwise DTI analyses, which are independent of brain size. As expected, the groups had comparable ICV volume and whole brain cortical thickness and did not differ for any of the ICV-adjusted volumes (Table 3). Although there were no significant differences in prefrontal lobe volumes, obese adolescents had reductions in the ICV-adjusted cortical thickness of OFC (P < 0.05) and ACC (P < 0.10), both with medium effect sizes.

In the absence of gross brain volume differences or clinically significant WM hyperintensities on the FLAIR image, the VANCOVA analysis of the FA maps identified seven significant clusters (1,651 voxels or 1.65 cc in volume), six of which showed age-adjusted WM FA reductions among obese adolescents (P < 0.005). The clusters showing FA reduction were located, by order of size, in the left temporal stem, right optic radiation, left internal capsule, left splenium, left external capsule, and left optic radiation (see Figure 1 for the largest six clusters). The single cluster showing FA elevation was located in the right prefrontal region and had partial GM contamination. The temporal stem cluster, the largest identified (790 voxels), also had some GM contamination, but given its prominent size, the cluster would have remained the largest and substantial in size even after excluding those potentially contaminated voxels. At a more conservative P-value threshold of 0.001, only the left temporal stem cluster remained significant (373 voxels). These results remained the same even after controlling for sex or hypertension status.

Discussion
To our knowledge, this is the first preliminary report of reduced brain structural integrity and lower cognitive performance among
adolescents with uncomplicated obesity. Notably, none of our participants had IR or met criteria for MetS, thus allowing us to examine the brain effects in obesity alone. We found that relative to demographically matched lean adolescents, obese adolescents with no clear evidence of IR had significantly lower academic achievement (i.e., arithmetic and spelling) and trended toward lower scores for selective frontal lobe-based cognitive tests. Similar to prior reports in adolescents with obesity co-morbidities (13,15), adolescents with uncomplicated obesity also had significantly lower academic achievement (i.e., arithmetic and spelling). They also tended to score lower on some frontal lobe functions involved in working memory, attention, and psychomotor efficiency. Mental flexibility was the only type of executive function that trended toward significance. In agreement with our report on obese non-diabetic adolescents with MetS (15), memory functions were unaffected in obese adolescents without IR. It is likely that actual metabolic disturbance, such as IR, is needed to compromise memory.

Obese adolescents without IR, unlike obese adolescents with MetS (15) or T2DM (13), did not have gross brain volume changes. Here, we demonstrated for the first time that non-IR obese adolescents had reduced cortical thickness in the OFC and ACC but contrary to prior reports that did not exclude adolescents with clear IR (e.g., see Ref. 34), we did not find volume changes in those regions. Studies of other disease conditions in adolescents have suggested that cortical thickness is a more sensitive measure of cortical integrity than volume (e.g., see Ref. 35) as it is more related to GM density. Despite the modest sample size, the DTI results are consistent with our prior reports of obese adolescents with IR (15), and demonstrate FA reduction in major fiber tracts involved in cortico-subcortical as well as interhemispheric signal transmission, and importantly, these observations were independent of hypertension. Notably, our most prominent FA finding was in the left temporal stem, which is consistent with our previous report in adolescent T2DM (13). This cluster may contain the uncinate fasciculus, a major component of the temporal stem connecting between the frontal lobe and the limbic system, which may in part contribute to deficits in reward processing in obesity (36). DTI tractography using a more sophisticated DTI protocol with at least

### TABLE 1 Demographic and Endocrine Data

| Measures                        | Obese (n = 30)     | Lean (n = 30)    | Effect size | P      |
|---------------------------------|-------------------|-----------------|-------------|--------|
| Age (year)                      | 17.64 ± 1.62 (14.89-20.76) | 17.22 ± 1.55 (14.28-20.21) | 0.27         | 0.30   |
| Gendera                         | 17 F/13 M         | 19 F/11 M       | −0.13       | 0.61   |
| Socioeconomic statusb           | 1.96 ± 1.12       | 2.20 ± 1.15     | −0.28       | 0.40   |
| School gradeb                   | 11.87 ± 1.67      | 11.47 ± 1.84    | −0.10       | 0.42   |
| Ethnicity (White, Hispanic, African American, Asian)b | 6/15/6/3         | 5/13/8/4       |             |        |
| BMI (kg/m²)d                    | 35.47 ± 5.88      | 21.12 ± 2.18    | −0.86       | <0.001 |
| Waist measurement (cm)c         | 106.82 ± 13.33    | 75.93 ± 6.19    | 2.97        | <0.001 |
| HOMA-IR indexc                  | 1.95 ± 0.86       | 1.40 ± 0.69     | −0.30       | 0.02   |
| Glucose (mg/dl)b                | 74.93 ± 6.37      | 75.83 ± 6.85    | −0.06       | 0.64   |
| Insulin (µIU/ml)                | 10.56 ± 4.71      | 7.49 ± 3.53     | 0.74        | 0.01   |
| HbA1C (%)b                      | 5.33 ± 0.33       | 5.24 ± 0.25     | −0.18       | 0.17   |
| HDL (mg/dl)                     | 45.90 ± 9.31      | 54.93 ± 11.64   | −0.86       | 0.002  |
| LDL (mg/dl)                     | 102.97 ± 25.47    | 90.50 ± 22.80   | 0.52        | 0.05   |
| Triglycerides (mg/dl)c          | 79.13 ± 32.53     | 69.03 ± 28.61   | −0.20       | 0.11   |
| Systolic BP (mm Hg)c            | 113.27 ± 12.80    | 100.93 ± 9.17   | −0.51       | <0.001 |
| Diastolic BP (mm Hg)c           | 67.40 ± 9.93      | 63.07 ± 7.33    | −0.23       | 0.08   |
| CRP (mg/l)c                     | 3.06 ± 2.46       | 0.88 ± 1.69     | −0.59       | <0.001 |
| Self-rating of sleep apnea¹     | 0.20 ± 0.16       | 0.15 ± 0.11     | −0.14       | 0.27   |
| Beck Depression Inventory scoreb | 9.45 ± 7.17       | 7.28 ± 7.06     | −0.18       | 0.18   |
| IPAQ total score (MET-min/week)³ | 4,873.14 ± 3,563.48 | 4,233.54 ± 2,384.29 | −0.05       | 0.71   |

Normally distributed continuous variables were evaluated with the t-test (effect size Cohen’s d) unless indicated otherwise.

¹The chi-square test was used for categorical variables.

²The Mann-Whitney U test was used (effect size r: 0.1, small; 0.3, medium; 0.5, large).

Note: Clinical cutoffs for abnormal values—HOMA-IR > 3.99; fasting glucose > 100 mg/dl; fasting insulin > 22 µIU/ml; HbA1C > 5.7%; HDL < 40 mg/dl (males) and <50 mg/dl (females); LDL > 130/110 mg/dl; triglycerides > 110 mg/dl; systolic/diastolic BP, for those 18 years of age > 90th percentile for age, gender, and height; for those over 18 years of age, systolic BP > 130 mm Hg or diastolic BP > 85 mm Hg; CRP > 3 mg/l.
Obesity and functional damage. Our obese adolescents had no clear IR or fasting hyperglycemia but their HOMA-Index or fasting insulin values were significantly higher than lean controls, but these elevations were not associated with our cognitive and brain observations. A more sensitive measure of insulin sensitivity measured using the intravenous glucose tolerance test may shed light on the possible effects of subclinical IR on cognition and brain. Future work should better characterize these associations in an expanded set of adolescents and ascertain for the presence of possible sex effects.

Contrary to expectation, we did not find reduced WM microstructural integrity in the frontal lobes similar to those reported in adults. It is likely that more metabolic dysregulation, such as clinically significant IR, is necessary to impact WM maturation in the frontal lobe of the adolescent brain. Unlike our prior findings in adolescent with MetS (15) and T2DM (13) where we saw no clear lateralization, the current WM findings are mostly left-lateralized. These findings may not be directly comparable to prior data on adults and children since here the obese adolescents have no significant co-morbidities.

Both groups had individuals with obesity co-morbidities (only 4 obese/3 lean with hypertriglyceridemia, 3 obese/2 lean with hypertension, and 15 obese/7 lean with low HDL); however, their links with brain abnormalities are less well-established, particularly in the pediatric literature. We conducted exploratory correlation analyses (data not presented) but did not uncover any robust associations with the cognitive or brain measures. Although marked fasting hyperinsulinemia, or fasting hyperglycemia may be needed to cause gross brain structural damage and functional disturbances, it is possible that sub-threshold IR can contribute to subtle brain structural

30 diffusion directions would help clarify the involvement of the temporal stem.

TABLE 2 Cognitive Data

| Measures                                      | Obese (n = 30) Mean ± SD | Lean (n = 30) Mean ± SD | Effect size  | P     |
|----------------------------------------------|--------------------------|-------------------------|--------------|-------|
| Intellectual functioning and academic achievement |                          |                         |              |       |
| Estimated full-scale IQ                      | 102.56 ± 11.49           | 107.44 ± 13.18          | -0.40        | 0.15  |
| WRAT arithmetic standard score               | 96.04 ± 11.02            | 103.52 ± 13.82          | -0.60        | 0.03  |
| WRAT spelling standard score<sup>a</sup>    | 101.71 ± 12.10           | 106.81 ± 11.46          | -0.28        | 0.04  |
| WRAT reading standard score<sup>b</sup>     | 106.61 ± 12.13           | 107.85 ± 9.44           | -0.11        | 0.68  |
| Memory function                              |                          |                         |              |       |
| WRAML general index                          | 103.30 ± 12.79           | 106.61 ± 12.52          | -0.26        | 0.32  |
| WRAML verbal index score                     | 105.37 ± 12.14           | 104.29 ± 11.57          | 0.09         | 0.73  |
| WRAML visual index score<sup>c</sup>        | 102.52 ± 10.32           | 100.31 ± 12.98          | 0.19         | 0.48  |
| WRAML working memory index                   | 100.17 ± 15.57           | 107.69 ± 13.96          | -0.51        | 0.06  |
| Executive function                           |                          |                         |              |       |
| Trails B time (s)<sup>d</sup>               | 64.56 ± 21.17            | 55.31 ± 15.68           | 0.50         | 0.08  |
| TOL excess moves<sup>e</sup>                | 16.77 ± 13.15            | 12.32 ± 7.01            | -0.13        | 0.33  |
| WCST perseverative errors<sup>f</sup>       | 10.85 ± 8.39             | 9.96 ± 5.56             | -0.01        | 0.92  |
| Stroop interference score                    | 0.07 ± 7.32              | -2.00 ± 6.02            | 0.31         | 0.24  |
| COWAT total score<sup>g</sup>               | 34.39 ± 8.27             | 39.97 ± 14.71           | -0.38        | 0.15  |
| Attention and psychomotor efficiency         |                          |                         |              |       |
| WRAML attention-concentration index          | 101.40 ± 13.65           | 108.86 ± 15.94          | -0.50        | 0.06  |
| Trails A time (s)<sup>j</sup>               | 28.14 ± 8.91             | 24.04 ± 7.27            | -0.23        | 0.08  |
| DVT total time<sup>i</sup>                  | 396.43 ± 128.12          | 358.52 ± 72.33          | -0.17        | 0.22  |
| DSST total score                             | 60.19 ± 10.57            | 65.89 ± 12.20           | -0.50        | 0.07  |

Normally distributed continuous variables were evaluated with the t-test (effect size Cohen’s d) unless indicated otherwise.

COWAT, Controlled Oral Word Association Test; DVT, Digit Vigilance Test; DSST, Digit Symbol Substitution Test; TOL, Tower of London Test; WCST, Wisconsin Card Sorting Test; WRAML, Wide Range Assessment of Memory and Learning; WRAT, Wide Range Achievement Test.

<sup>a/b</sup>The Mann–Whitney U test was used (effect size Cohen’s d).<sup>c</sup>Scores more than 3 SDs within the group mean were excluded.<sup>d</sup>Adjusted for unequal variances (t-test).

30 diffusion directions would help clarify the involvement of the temporal stem.
integrity and function (please see theoretical model presented in Convit [2005]) (40).

This study has several strengths. The groups were well-matched to minimize socio-economic and education bias. We used reliable, validated, and sensitive brain assessment methods so as to detect the anticipated subtle changes. The fact that our obese adolescents are free of clinically significant IR allows us to explore possible associations between uncomplicated obesity and brain structure and function. Furthermore, our controls are not a sanitized group of individuals without any abnormality, but a real world sample: seven had low HDL, three high triglycerides, two high BP, and one with abdominal obesity (but a normal BMI of 21.7 kg/m²). Had our lean adolescents been all metabolically healthy, or the sample size been larger, the group differences would likely have been more prominent. These data are in line with our prior report of progressive reductions of brain structural and functional integrity with increasing MetS factors met (15).

This study is limited by its modest sample size and the relatively large number of comparisons. We minimized the chance of obtaining any abnormality, but a real world sample: seven had low HDL, three high triglycerides, two high BP, and one with abdominal obesity (but a normal BMI of 21.7 kg/m²).

### Table 3: Brain Data

| Measures                        | Obese (n = 26) | Lean (n = 27) | Effect size | P   |
|---------------------------------|----------------|---------------|-------------|-----|
| ICV volume (cc)                 | 1,198.98 ± 99.31 | 1,209.62 ± 118.91 | -0.10       | 0.73|
| Overall CSF volume              | 31.83 ± 19.22  | 30.39 ± 10.82 | -0.06       | 0.64|
| Hippocampal volume              | 2.96 ± 0.36    | 2.94 ± 0.38   | 0.11        | 0.71|
| PFC volume                      | 313.73 ± 45.96 | 305.61 ± 42.32 | 0.43        | 0.14|
| OFC gray matter volume          | 27.52 ± 2.73   | 28.34 ± 2.64  | -0.39       | 0.17|
| ACC gray matter volume          | 8.28 ± 1.47    | 8.53 ± 1.21   | -0.18       | 0.52|
| Whole brain cortical thickness  | 2.46 ± 0.08    | 2.47 ± 0.07   | -0.13       | 0.64|
| Total OFC cortical thickness    | 2.76 ± 0.14    | 2.83 ± 0.10   | -0.55       | 0.06|
| Total ACC cortical thickness    | 2.83 ± 0.15    | 2.90 ± 0.16   | -0.52       | 0.07|

All brain data are residualized to the ICV volume. For ease of interpretation, raw values for the descriptive data are presented (volumes are expressed in cc and cortical thickness in mm³).

Normally distributed continuous variables were evaluated with the t-test (effect size Cohen’s d).

**The Mann-Whitney U test was used (effect size r: 0.1, small; 0.3, medium; 0.5, large).**

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**Figure 1** Six of the seven clusters demonstrating significant FA group differences are displayed in order of cluster size (VANCOVA analysis controlling for age; minimum cluster size of 100 voxels; P < 0.005; clusters in blue represent FA reductions in obese adolescents whereas positive associations in yellow represent FA elevation). Each column shows three orthogonal orientations of the average normalized structural image illustrating a significant cluster with the axes passing through the centroid of the cluster. The largest cluster, found in the left temporal stem, was the only one that remained significant at a more conservative P-value threshold of 0.001. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
spurious significant results by removing extreme cognitive outliers and using conservative thresholds in our brain microstructural assessments. Although many of the cognitive differences were subtle and may not be clinically relevant, which we had anticipated in this group of adolescents with “uncomplicated” obesity, these data provide some unique insights into the possible early negative consequences of childhood obesity on brain and cognition, along with indication of future areas of exploration. Thus, we felt justified in not controlling for multiple comparisons in this preliminary report. Lastly, to better understand brain involvement, future studies should include a more comprehensive brain evaluation including direct assessments of the components of the neural networks thought to be involved in obesity.

Conclusions

We conclude that uncomplicated obesity may be sufficient to induce subtle brain structural alterations prior to clinically significant obesity co-morbidities being present. However, to cause gross structural damage, further metabolic dysregulation, such as marked fasting hyperinsulinemia, or fasting hyperglycemia may be necessary. The present findings are a significant contribution to the small pediatric literature on brain and obesity, particularly among obese adolescents without clear evidence of IR or MetS. These data suggest that early interventions are warranted to protect the brain. Future work should also clarify whether these cognitive and brain alterations are reversible with lifestyle intervention and weight loss.

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