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Insulin Resistance is Associated with Smaller Brain Volumes in a Preliminary Study of Depressed and Obese Children

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Abstract

Objective—During childhood, the brain can consume up to 65% of total calories and a steady supply of the brain's main fuel glucose needs to be maintained. Though the brain itself is not dependent on insulin for the uptake of glucose, insulin plays an important role in energy homeostasis. Thus, risk for insulin resistance during brain development may negatively impact whole brain volume.

Methods—We investigated the link between insulin resistance and whole brain volume as measured by structural MRI in 46 unmedicated depressed and overweight youth between the ages of 9 to 17 years.

Results—Smaller whole brain volumes were associated with insulin resistance independent of age, sex, depression severity, body mass index, socioeconomic status, Tanner Stage, and IQ ($r=0.427$, $p=0.008$).

Conclusions—There may be a significant cost of insulin resistance on the developing brain. Disentangling the precise relation between insulin resistance and the developing brain is critical.

Keywords

brain; insulin; obesity; metabolism; depression

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O.P. and M.S. contributed with the literature search, study design, data collection, data analysis, data interpretation and writing. A.O. and Y.Z. contributed on the data collection, analysis and writing. O.P. and M.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest:

Dr. Singh receives research support from Stanford's Child Health Research Institute, National Institute of Mental Health, National Institute of Aging, Neuronetics, Johnson and Johnson, and the Brain and Behavior Foundation. She has been on the advisory board for Sunovion. No other authors report any conflicts of interest.

Introduction

The adult brain consumes ~20–25% of total calories even though it only accounts for ~2% of the total body weight (1). Caloric needs are even more important in childhood when total energy consumed can reach heights of ~65% (2). The brain's main energy source is glucose, which needs to be actively transported through the blood brain barrier in a continuous and steady manner. Importantly, though the brain itself is not dependent on the hormone insulin in order to take up glucose, insulin is critical in regulating the supply of glucose in the peripheral blood stream. In the periphery, insulin signals cells to increase glucose uptake (3). Beyond regulating peripheral glucose, insulin also functions at the blood brain barrier where insulin is both brought into the brain via a saturable transport system and acts on embedded receptors (4,5). Finally, insulin receptors within the brain make the brain itself an insulin sensitive organ (6).

In adults, an association between insulin resistance and reduced brain volume has been shown in a number of studies (7–9). In children, type 1 diabetes has shown widespread deleterious effects on the growth of gray and white matter (10). In the present research, we sought to identify if a similar pattern could be identified in youth with insulin resistance. Our research was driven by the hypothesis that because the brain is so energetically expensive, abnormalities in metabolism during childhood could have widespread implications. Here, insulin resistance, based on relatively high versus low levels of insulin in overweight and depressed youth, was used as a proxy for metabolic impairment. Importantly, this research was focused on a general association between insulin resistance and the brain in childhood, and therefore did not focus on a particular region of the brain. Rather than focus on a particular region, we chose the broadest and simplest structural measure obtainable with MRI: whole brain volume. We hypothesized that higher levels of insulin would be associated with smaller whole brain volumes. In order to test this hypothesis, we investigated the relation between insulin resistance, as measured before, during, and after an oral glucose tolerance test (OGTT), and whole brain volume.

Research Design and Methods

Subjects

We recruited 46 unmedicated and overweight youth with depression between the ages of 9 to 17 years. All adolescent participants provided written assent, and at least one parent or legal guardian provided written informed consent prior to all study procedures. This study was approved by Stanford University's Institutional Review Board and all protocols were implemented in accordance with their guidelines and regulations. Inclusion Criteria were: 1) girls and boys ages 9–17 years; 2) at least one parent or guardian willing to participate; 3) participants are able and willing to give written informed assent/consent; 4) youth meeting criteria for at least moderate symptoms of depression as defined by a CDRS-R score of >35. Exclusion Criteria: 1) currently taking medication or receiving psychotherapy for a mood disorder; 2) a DSM-5 diagnosis of attention-deficit with hyperactivity, pervasive developmental disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD) or Tourette's disorder; 3) a diagnosis of type 1 or type 2 diabetes, 4) currently taking medications that impair insulin action (e.g. glucocorticoids for asthma); 5)

IQ<70 by the Weschler Abbreviated Scale of Intelligence (WASI); 6) neurologic disorders (e.g. seizures); 7) drug or alcohol abuse or dependence 6 months prior to study; 8) unstable medical or psychiatric disorder requiring immediate hospitalization or emergency medical treatment; 9) a positive pregnancy test; 10) contraindication for MRI, including weight greater than 550 lbs or anterior-posterior diameter greater than 46 cm. Participants were ascertained transdiagnostically, and evaluated for dimensional levels of depression symptoms severity using the clinician administered Children's Depression Rating Scale-Revised (CDRS-R). We calculated each participant's BMI Z score as a standardized measure for overweight and obese status, defined by a Z score of greater than the 85th percentile, that takes into account sex and age norms in children. Tanner Stage (11) was assessed via a clinical physical exam by a trained Pediatrician to determine pubertal status. IQ was assessed by trained raters using the Weschler Abbreviated Scale of Intelligence (WASI) (12). This 30–45 minute assessment consists of multiple questions that screen for verbal, nonverbal, and general cognitive ability and generates verbal, performance, and full-scale IQ scores. Socioeconomic status (SES) was determined using the Hollingshead Four Factor Index of Socioeconomic Status (13), which measures SES using four domains: marital status, educational attainment, employment status, and occupational prestige.

Indices of insulin sensitivity

Participants were assessed on serum markers of insulin resistance after a glucose challenge using the oral glucose tolerance test (OGTT). After an overnight fast of at least ten hours, youth participants had blood drawn for glucose and insulin at the following time-points: fasting at t-10 minutes before glucose challenge, fasting at t=0 just prior to glucose challenge, and then t+30 minutes, t+60 minutes, t+90 minutes, and t+120 minutes after glucose challenge with 75 grams of a glucola oral solution. Insulin values were measured by immunoassay. Insulin sensitivity was determined by fasting insulin measures and with the Matsuda Index, calculated with the following formula: $\text{Matsuda} = 10000 / (G_0 \times I_0 \times G_{\text{mean}} \times I_{\text{mean}})^{1/2}$ where G_0 is fasting glucose, I_0 is fasting insulin, G_{mean} is average serum glucose across entire OGTT period, and I_{mean} is mean insulin across entire OGTT period (14). A higher Matsuda index denotes more insulin sensitivity.

MRI Acquisition

Brain images were acquired on a 3T GE Signa Excite scanner equipped with an 8-channel head coil. Structural images were collected using a fast spoiled gradient (3D FSPGR) recalled pulse sequence: TR = 8.5 ms, TE = 3.32 ms (TE = 3.17), TI = 400 ms, flip angle = 15°, field of view(x) = 25.6 cm, matrix of 256 × 256, 186 slices in the axial plane, and a slice thickness of 1 mm.

MRI Pre-Processing

Scans were processed using FreeSurfer to produce a measure of whole brain volume, (<http://surfer.nmr.mgh.harvard.edu>) (15,16). Briefly, processing streams included removing non-brain tissue, intensity normalization, segmenting gray/white matter, and aligning each image volume to a standardized space. To ensure the accuracy of gray/white matter segmentation, exclusion of scalp and other non-brain tissue, and the inclusion of brain tissue and cortical surfaces were visually inspected by an expert rater (YVZ). Manual corrections were

performed by this rater where appropriate, in accordance with previously established procedures (10,17). Finally, the whole brain volume (specifically, BrainSegNotVent - <http://www.freesurfer.net/fswiki/MorphometryStats>) was extracted.

MRI Analysis

We used the Statistical Package for Social Sciences (SPSS) version 22 to conduct a partial correlation between the whole brain volume and the Matsuda Index. Age, sex, BMI Z score, and CDRS scores were included as covariates. We then reran the analysis with the addition of socio-economic status (SES), Tanner stage and IQ also included as covariates.

Results

Participant details are summarized in Table 1. To isolate the effects of risk for insulin resistance on total brain volume, we performed a partial correlation to control for age, sex, depression severity, BMI Z score, SES, Tanner Stage and IQ included as covariates. The effects of these covariates (as measured via multiple regression) on the two primary variables of interest are summarized in Table 2 and Table 3. After controlling for the age, sex, depression severity, BMI Z score, SES, Tanner Stage, IQ via partial correlation, whole brain volume and the Matsuda Index were significantly associated with each other ($r=0.427$, $p=0.008$) Figure 1.

Discussion

This study demonstrated that smaller whole brain volumes are associated with insulin resistance in childhood. The relation between the brain and insulin is complex and there is still much we do not know (6), however, we do know that the brain requires a large portion of the body's glucose (1) and needs even more in childhood (2). This research was conducted with the hypothesis that because insulin is intricately linked to the peripheral glucose supply that powers the brain, and because the brain consumes a large portion of glucose, insulin resistance in childhood may be negatively associated with whole brain volume. Our results support this hypothesis.

This research was done within obese children with depressive symptoms, who are at high risk for developing insulin resistance. This is because insulin resistance is closely tied to obesity in developing populations; obesity in turn has been linked to metabolic, cardiovascular, gastrointestinal, pulmonary, orthopedic and psychiatric disorders (18,19). In addition, recent evidence in adults (20–23) and youth (24) suggest fundamental neural and behavioral disruptions that link depression to insulin resistance through a shared underlying mechanism that (25,26) mediates the progressive worsening of depressive symptoms (27–30).

In order to isolate the effects of insulin resistance, we controlled for depressive symptoms, BMI Z score, SES, Tanner Stage and IQ in our analysis. We found that insulin resistance is associated with reduced brain volume independent of depressive symptoms, BMI Z score, SES, Tanner Stage or IQ. These variables as well as many other genetic and environmental variables not available could potentially interact with the complex developmental trajectory

of the brain. However, our finding suggests that there may be a significant cost of developing insulin resistance on the developing brain. Alternative explanations associated with metabolic abnormalities also need to be investigated. For example, dehydration associated with elevations in plasma glucose and/or shared underlying metabolic profiles that itself are associated with a propensity toward smaller brain volume and insulin resistance may also play a role. Regardless, this finding is especially worrying when viewed in a global context because the prevalence of insulin resistance, metabolic syndrome, and depression (31) are increasing (32), particularly in younger populations with prevalence estimates of insulin resistance ranging from 20 to 40 % in different populations (33–37). Furthermore, since this study was focused on the general association between insulin and the whole brain, it is possible that particularly sensitive target regions of insulin such as the hypothalamus, striatum, and other limbic (e.g. hippocampus), and prefrontal regions may be even more adversely impacted (38–40).

Although the purpose of this research was to examine the association between risk for insulin resistance and whole brain volume in childhood, the question remains of how exactly peripheral insulin resistance is associated with smaller brain volumes. In adults, peripheral insulin resistance has been linked to brain atrophy (6,41) and in children it has been linked to abnormal brain growth (42). Though we cannot currently answer whether the association between brain volume and insulin resistance in this study is related to atrophy or abnormal brain growth, it is becoming increasingly clear that insulin resistance is associated with brain abnormalities. For example, research in adults has also found a negative relation between insulin resistance and the brain, including reduced hippocampal and cortical gray matter volumes (43,44), widespread white matter alterations (45), and functional connectivity abnormalities (46). In addition, like these previous studies, we also used the OGTT in order to measure peripheral insulin resistance, which is limited compared to the “gold standard” hyperinsulinemic euglycemic clamp (47). In order to maximize our own quantification of insulin resistance, we chose a commonly used measure (Matsuda Index) derived from the OGTT that has been previously shown to be highly correlated with the gold standard clamp in children (48). Finally, the OGTT measurements are based on peripheral insulin levels. There is evidence that the concentration of insulin in the brain is higher than in the periphery (49,50). Interestingly, though this fact means our use of insulin levels in the peripheral blood leaves a lot to be desired, because central concentrations of insulin are high, it hints at the relative importance of insulin’s role in the brain. Future research that takes advantage of improved brain insulin biomarkers (51) will be better positioned to unravel the precise role of insulin insensitivity in the developing brain. In addition, beyond insulin, other obesity related endocrine changes (52) may also be associated with brain development.

We have provided evidence that a risk for insulin resistance in childhood is associated with smaller whole brain volumes. This finding needs to be reproduced in a larger independent sample, and tracked longitudinally and in transitions to adulthood. As obesity (32), depression (53,54), and diabetes (55,56) are reaching epidemic proportions, disentangling the precise relation between insulin and the developing brain should be viewed as a priority.

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Figure 1. Correlation between Whole Brain Volume and the Matsuda Index

Scatterplot shows the significant correlation between the Matsuda Index and whole brain volume controlled for sex, age, CDRS and BMI Z score. A lower Matsuda index indicates greater insulin resistance. Brain volume units are mm^3 .

Table 1**Participant Demographics**

	Mean	Standard Deviation	Minimum	Maximum
Gender (male/female)	18/28			
Age (years $\pm$ SD)	14.82	1.95	9.91	17.96
Brain Volume (mm ^{^3})	1167421.93	124970.03	884470	1446520
Matsuda Index	3.358	1.762	0.759	7.104
BMI Z Score	1.746	0.4861	0.9475	2.6836
CDRS Score	53.61	11.258	36	82
Tanner Stage	3.89	0.924	1	5
Socio-economic Status (SES)	46.696	12.439	15.5	61.0
WAIS-IV ¹	102.67	17.230	55	134
Fasting Glucose	92.755	9.023	70.25	112.50
Fasting Insulin	15.446	9.807	4.0	45.0
Time 30 Glucose	151.815	26.314	99.5	248.0
Time 30 Insulin	107.04	74.154	5	300
Time 60 Glucose	150.867	40.080	79.5	294.0
Time 60 Insulin	107.17	76.897	3	300
Time 90 Glucose	133.484	39.203	75.55	300
Time 90 Insulin	103.07	79.468	9	300
Time 120 Glucose	122.77	33.858	63	264
Time 120 Insulin	86.22	71.402	8	400

Glucose unites are mg/dl. Insulin unites are mIU/L.

Table 2

Multiple Regression Coefficients of Matsuda Index

Variable	Regression coefficient	p-value
Constant	−5.725	0.257
Brain Volume	6.805E-006	0.008
Age	−0.119	0.603
Sex (F)	1.549	0.019
BMI Z-score	−1.101	0.052
CDRS t-score	0.004	0.863
Tanner Stage	0.452	0.339
SES Score	0.028	0.172
IQ	0−.010	0.519

Table 3

Multiple Regression Coefficients of Brain Volume

Variable	Regression coefficient	p-value
Constant	1225505.503	0.000
Matsuda Index	26735.518	0.008
Age	758.445	0.958
Sex (F)	-148687.347	0.000
BMI Z-score	48303.174	0.180
CDRS t-score	-1847.355	0.187
Tanner Stage	-11108.281	0.710
SES Score	-129.569	0.919
IQ	1454.094	0.136