Focal Subcortical Biophysical Abnormalities in Patients Diagnosed With Type 2 Diabetes and Depression

Anand Kumar, MD; Rakesh Gupta, MD; Albert Thomas, PhD; Olusola Ajilore, MD, PhD; Gerhard Hellemann, PhD

Context: Major depressive disorder has been consistently identified in patients with type 2 diabetes. Despite its high prevalence and clinical effect, the neurobiological substrates underlying depression in patients with diabetes remain largely unknown.

Objective: To examine the biophysical integrity of proteins in critical white and gray matter regions in patients with type 2 diabetes and major depression to understand the pathophysiology of depression in diabetes.

Design: A cross-sectional magnetization transfer study using magnetic resonance imaging. Regions examined included the anterior cingulate, corpus callosum, frontal and occipital white matter, and the caudate and lenticular nuclei.

Setting: A tertiary care university hospital.

Participants: We studied 16 patients diagnosed with type 2 diabetes and major depression, 22 patients diagnosed with diabetes without depression (diabetic controls), and 30 controls without diabetes or major depression (healthy controls).

Main Outcome Measures: Magnetization transfer ratios, a measure of the biophysical structure of proteins in the gray and white matter.

Results: Magnetization transfer ratios were significantly lower bilaterally in the head of the caudate nucleus in the group with diabetes and depression compared with the other 2 groups (P < .001). Diabetic controls had values between the depressed diabetic and healthy control groups. There were no significant differences in magnetization transfer ratios between groups in the other regions examined.

Conclusions: These data indicate that there is an important subcortical biophysical component to depression in patients with type 2 diabetes. This finding has broad implications for the neuronal circuitry underlying mood disorders.

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Type 2 diabetes is a common metabolic disorder associated with multiple organ system dysfunction and considerable mortality and morbidity. While the vascular and metabolic complications of type 2 diabetes are well recognized, the behavioral correlates of diabetes are also getting increased recognition. Disorders of mood and cognition are consistently associated with type 2 diabetes, which is now recognized as a risk factor for the development of Alzheimer disease. The relationship between diabetes and mood is complex and possibly bidirectional; prevalence estimates of clinically significant major depressive disorder (MDD) in patients with type 2 diabetes range from 8.5% to 28%, and patients diagnosed with MDD have 2.2 times the risk of developing diabetes. Depression in patients with diabetes is associated with poor treatment compliance, compromised quality of life, increased rates of hyperglycemia, other complications of diabetes, and mortality. While the clinical correlates of depression in patients with type 2 diabetes are well characterized, the neurobiological underpinnings of depression in these patients remain largely unknown.

Neuronal circuits are responsible for the regulation of emotional states and play an important role in the pathophysiology of psychiatric disorders. Cortical-subcortical circuits in particular, with their distinctive components, have been consistently implicated in the underlying neurobiology of mood disorders. Earlier work from our laboratory demonstrated that patients with type 2 diabetes and major depression had lower concentrations of glutamate/glutamine in the subcortical region, detected using magnetic resonance spectroscopy, when compared with both patients with diabetes without depression and controls without diabetes or depression.
Our morphometric studies demonstrated that patients with type 2 diabetes with and without depression had volumetric reductions in the prefrontal gray matter regions when compared with healthy controls. In that study, patients with diabetes and depression did not demonstrate any additional neuroanatomic changes other than those induced by diabetes. Smaller volumes in the mesial temporal region, together with qualitative evidence of global atrophy and neuroimaging evidence of stroke, have also been reported in patients with type 2 diabetes when compared with controls. A combination of physiological and anatomical perturbations in distinct gray and white matter regions that comprise a neuronal circuit may underlie mood and related behavioral changes frequently observed in patients with type 2 diabetes.

The purpose of our current study was to examine the biophysical characteristics of proteins in specific neocortical, subcortical, and white matter regions implicated in the etiopathogenesis of depression using magnetization transfer (MT). Magnetization transfer is a validated magnetic resonance imaging technique that provides estimates of myelin and axonal density in white matter and protein and cell membrane composition in gray matter regions and subcortical nuclei. We hypothesized that MT ratios (MTRs), a measure of abnormalities in the macromolecular protein compartment, would be lower in critical gray and white matter regions in patients with diabetes and MDD when compared with control subjects without depression. Choices of specific regions of interest were based on the existing literature on the neurobiology of mood and our earlier studies that demonstrated biophysical and structural abnormalities in several gray and white matter regions in patients diagnosed with late-life MDD. Based on prior studies demonstrating that depression and diabetes independently affect neuroanatomy and physiology, we additionally hypothesized that patients with type 2 diabetes without depression will have MT values that fall between the depressed diabetic and healthy control groups.

### METHODS

#### CLINICAL

Our study sample consisted of 3 groups: patients diagnosed with type 2 diabetes using established clinical criteria (diabetic controls), patients diagnosed with diabetes and MDD, and controls without diabetes or MDD (healthy controls). Diabetic patients with and without depression were recruited from 3 sites: the clinics associated with the department of internal medicine and endocrinology at the main UCLA campus, the general internal medicine clinics located at Santa Monica UCLA (an affiliated site), and the community satellite clinical site at Alhambra, which is an ethnically enriched site. Controls were recruited from the community by advertising in local newspapers and community newsletters. The salient clinical and demographic characteristics of our study samples are presented in Table 1.

All depressed patients met established DSM-IV criteria for MDD. Patients with MDD were screened using structured clinical psychiatric interviews and had Hamilton Depression Rating Scale Scores of 15 or greater on the 17-item scale. All patients were free of significant clinical brain disorders other than MDD in the depressed diabetic group. None of the depressed patients had any other major psychiatric disorder such as dementia, bipolar disorder, or substance abuse. All subjects had Folstein Mini-Mental State Examination scores of 24 or higher. Depressed patients had not taken psychotropic medication for at least 2 weeks prior to the study. Laboratory testing for all subjects included complete and differential blood counts, hepatic, renal, and thyroid screens, electrolyte levels, and hemoglobin A1C (HbA1C) levels. In addition, cerebrovascular risk factors were assessed using the American Heart Association’s Stroke Risk Prediction Chart and overall medical comorbidity was ascertained using the Cumulative Illness Rating Scale, which provides an assessment of the degree of organ system dysfunction and overall medical burden.

Three of the 16 subjects diagnosed with MDD reported the index (current) episode as their first. Seven patients reported 1 prior depressive episode, 1 patient reported 2, and 1 reported 3. In 4 cases, the information on prior episodes was considered unreliable. Twenty-one patients with diabetes (those with and without depression) were taking oral hypoglycemic agents alone for diabetes control. Two patients were taking insulin only and 13 patients were taking a combination of insulin and oral hypoglycemics for blood glucose control. Patients with diabetes were taking different forms of insulin (Humulin N [Eli Lilly & Co, Indianapolis, Indiana], Humalog [Eli Lilly & Co], Lantus [Sanofi Aventis, Bridgewater, New Jersey], Novolog [Novo Nordisk Pharmaceuticals Inc, Princeton, New Jersey], Insulin R &N [synonymous with Humulin R or N]), and oral hypoglycemic drugs including Glucovance combination (Bristol-Myers Squibb, New York, New York), Glucophage only (Bristol-Myers Squibb), glyburide, Prandin (Novo Nordisk), glipizide, Actos (Takeda Pharmaceuticals, Deerfield, Illinois), and Avandia (Glaxo SmithKline, Philadelphia, Pennsylvania).

### Table 1. Clinical and Demographic Characteristics of the 3 Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HC (n=30)</th>
<th>DC (n=22)</th>
<th>DD (n=16)</th>
<th>Statistical Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.9 (11.04)</td>
<td>60.7 (9.79)</td>
<td>58.1 (10.71)</td>
<td>F&lt;sub&gt;2,65&lt;/sub&gt; = 1.9</td>
<td>.15</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>7.23</td>
<td>6.16</td>
<td>2.14</td>
<td>x&lt;sup&gt;2&lt;/sup&gt; = 1.33</td>
<td>.52</td>
</tr>
<tr>
<td>Education, y</td>
<td>16.7 (3.30)</td>
<td>13.9 (4.14)</td>
<td>13.6 (3.56)</td>
<td>F&lt;sub&gt;2,65&lt;/sub&gt; = 5.4</td>
<td>.007&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CIRS</td>
<td>2.8 (2.46)</td>
<td>6.5 (3.70)</td>
<td>7.2 (2.66)</td>
<td>F&lt;sub&gt;2,65&lt;/sub&gt; = 14.6</td>
<td>&lt;.001&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>CVRF</td>
<td>4.7 (4.64)</td>
<td>12.0 (4.55)</td>
<td>12.6 (4.86)</td>
<td>F&lt;sub&gt;2,65&lt;/sub&gt; = 21.9</td>
<td>&lt;.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.1 (1.12)</td>
<td>28.2 (2.01)</td>
<td>27.6 (2.4)</td>
<td>F&lt;sub&gt;2,65&lt;/sub&gt; = 4.1</td>
<td>.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HbA1C</td>
<td>5.4 (0.41)</td>
<td>6.9 (1.14)</td>
<td>7.8 (1.74)</td>
<td>F&lt;sub&gt;2,65&lt;/sub&gt; = 26.1</td>
<td>&lt;.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: CIRS, total Cumulative Illness Rating Scale scores; CVRF, Cerebrovascular Risk Factor score; DC, diabetic control; DD, diabetes with major depression; HbA1C, hemoglobin A1C levels; HC, healthy control; MMSE, Mini-Mental State Examination scores.

<sup>a</sup>Values are statistically significant.
Ms and M0 are the voxel signal intensities with and without the
(M0−Ms) exceed a predefined lower threshold. The software used
detection Guidelines.

informed consent was obtained from all study participants in
the University of California's Human Subject Prote-
ction Guidelines.

The ethnic composition of the 3 groups was as follows: healthy
controls, 21 white, 5 Asian, 1 Latino, and 3 African
American; depressed diabetic, 5 white, 3 Asian, 5 Latino, 2 Afri-
can American, and 1 self-described as other; diabetic controls,
7 white, 3 Asian, 6 Latino, 4 African American, and 2 self-
described as other. The mean (SD) duration of the current epi-
dose of diabetes was 112.4 (97.4) months in the diabetic control group
and 156 (119) months in the depressed diabetic group. De-
tails of our recruitment and other sample characteristics have
been previously published. All subjects also received a struc-
tural magnetic resonance scan and a comprehensive neuropsy-
chological assessment as part of our research study. Written
informed consent was obtained from all study participants in
keeping with the University of California's Human Subject Pro-
tection Guidelines.

IMAGING

Magnetic resonance imaging was performed using a 1.5-T scan-
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The MTRs in the right and left caudate nuclei are sign-
ificantly different between the diagnostic groups (right
caudate F[4,45] = 23.4, P < .001; left caudate F[4,45] = 32.56,
P < .001; P values are adjusted for multiple testing using
the Benjamini-Hochberg approach33). The MTRs in the
other regions examined did not differ between groups
(Table 2, Figure 2).

For the 2 ROIs that showed a significant difference in the
omnibus test—left caudate and right caudate—post hoc t
tests with Tukey adjustment were used to establish the pat-
tern of differences. For the right caudate, the estimated
marginal mean (standard error of the mean [SEM]) values
after controlling for the covariates are healthy con-
trols, 35.4 (0.67); diabetic controls, 31.9 (0.56); and
depressed diabetic patients, 29.4 (0.67). These 3 mean values
are significantly different from each other at α = .05 after
Tukey correction. For the left caudate, the estimated
marginal mean (SEM) values after controlling for the covari-
ates are healthy controls, 35.2 (0.64); diabetic controls, 31.8
(0.64); and depressed diabetic patients, 27.8 (0.75). These 3
mean values are significantly different from each other at
α = .05 after Tukey correction. Note that the effect size
for the left caudate is somewhat larger, and that the mean

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for the diabetic controls is roughly halfway between the mean values of the healthy controls and the depressed diabetic patients (Table 3). There were no statistically significant associations between the duration of diabetes (in both groups with diabetes) and the duration of the current episode of depression (in the MDD group) and MTR values in the caudate after controlling for age, sex, education, ethnicity, HbA1c level, and Cumulative Illness Rating Scale scores (as above), using a general linear model. Table 2 presents the uncorrected raw data obtained from all subjects.

The primary finding of the present study is that the biophysical abnormalities in patients with type 2 diabetes and MDD are focal and restricted to the head of the caudate nucleus. Additionally, patients with type 2 diabetes who didn’t have depression had abnormalities that were between the depressed diabetic and healthy control groups. Magnetization transfer values in the other regions examined in both groups with diabetes were comparable with values in the healthy control subjects.

The head of the caudate nucleus is extensively connected with neocortical and other subcortical structures in anatomically distinct well-integrated circuits.35-38 Cortical-subcortical circuits (prefrontal, striatal, pallidal, thalamic, and prefrontal circuits) are well characterized anatomically and have motor and behavioral functions.36 Three of the 5 primary cortical subcortical circuits, the oculomotor, dorsolateral prefrontal, and lateral orbitofrontal circuit have direct connections from the prefrontal region to the caudate nucleus.36 The dorsolateral and lateral orbitofrontal circuits have a more readily identifiable link to behavior and have been implicated in several behavioral syndromes.36,39,40 The dorsolateral circuit originates around the principal sulcus and on the dorsal prefrontal convexity, projects to the dorsolateral head of the caudate nucleus, and extends rostro-caudally to the tail of the caudate nucleus. Rostral projections of the caudate then extend to the globus pallidus and the substantia nigra and from these sites to thalamic nuclei. Projections from the thalamic nuclei to the dorsolateral prefrontal cortex around the principal

**Table 2. Magnetization Transfer Ratios in the 3 Groups**

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean (SD) Ratio by Group</th>
<th>F_{2,40}</th>
<th>Unadjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC</td>
<td>35.13 (1.23)</td>
<td>12.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LC</td>
<td>35.11 (1.28)</td>
<td>19.14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RP</td>
<td>34.72 (1.05)</td>
<td>2.56</td>
<td>.09</td>
</tr>
<tr>
<td>LP</td>
<td>35.41 (1.57)</td>
<td>1.95</td>
<td>.09</td>
</tr>
<tr>
<td>RF</td>
<td>43.90 (2.05)</td>
<td>0.02</td>
<td>.95</td>
</tr>
<tr>
<td>LF</td>
<td>44.77 (1.54)</td>
<td>0.27</td>
<td>.76</td>
</tr>
<tr>
<td>RO</td>
<td>43.27 (3.01)</td>
<td>0.19</td>
<td>.83</td>
</tr>
<tr>
<td>LO</td>
<td>42.75 (2.43)</td>
<td>2.05</td>
<td>.15</td>
</tr>
<tr>
<td>Genu</td>
<td>46.04 (3.01)</td>
<td>0.06</td>
<td>.95</td>
</tr>
<tr>
<td>Splenium</td>
<td>45.52 (2.65)</td>
<td>0.28</td>
<td>.75</td>
</tr>
<tr>
<td>AC</td>
<td>27.99 (3.58)</td>
<td>1.00</td>
<td>.38</td>
</tr>
</tbody>
</table>

Abbreviations: AC, anterior cingulate; C, caudate; DC, diabetic control; DD, diabetes with major depression; F, frontal white matter; HC, healthy control; L, left; O, occipital white matter; P, putamen; R, right.

aValues are statistically significant.

**Table 3. Effect Sizes (d) a**

<table>
<thead>
<tr>
<th>Region</th>
<th>HC vs DC</th>
<th>HC vs DD</th>
<th>DC vs DD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC</td>
<td>1.24</td>
<td>2.12</td>
<td>0.87</td>
</tr>
<tr>
<td>LC</td>
<td>1.02</td>
<td>2.19</td>
<td>1.18</td>
</tr>
<tr>
<td>RP</td>
<td>0.39</td>
<td>0.52</td>
<td>0.91</td>
</tr>
<tr>
<td>LP</td>
<td>1.13</td>
<td>1.04</td>
<td>0.09</td>
</tr>
<tr>
<td>RF</td>
<td>0.18</td>
<td>0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>LF</td>
<td>0.24</td>
<td>0.31</td>
<td>0.07</td>
</tr>
<tr>
<td>RO</td>
<td>0.21</td>
<td>0.33</td>
<td>0.12</td>
</tr>
<tr>
<td>LO</td>
<td>0.28</td>
<td>0.48</td>
<td>0.19</td>
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<tr>
<td>Genu</td>
<td>0.46</td>
<td>0.39</td>
<td>0.06</td>
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<tr>
<td>Splenium</td>
<td>0.05</td>
<td>0.38</td>
<td>0.44</td>
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<tr>
<td>AC</td>
<td>0.38</td>
<td>0.28</td>
<td>0.67</td>
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Abbreviations: AC, anterior cingulate; C, caudate; DC, diabetic control; DD, diabetes with major depression; HC, healthy control; F, frontal white matter; L, left; O, occipital white matter; P, putamen; R, right.

aBased on the empirical standard deviation of the variables and the marginal means after adjusting for all covariates.
Lewy body dementia. Our finding of lower MTRs in lesional gray and white matter regions in patients with diabetes when compared with controls.53 More recently, Gunning-Dixon expanded on those findings and reported lower MTRs in several cortical and subcortical white matter regions when compared with controls.54–56 This finding resulted from postmortem MT imaging of the white matter of tissue obtained from patients with multiple sclerosis. The extent to which this observation can be generalized to other disease states remains unknown. Low MTRs in the parenchyma are on occasion associated with edema, gliosis, Wallerian degeneration, and inflammation, and is potentially reversible with treatment.56–58 The biochemical correlates of low MTRs in the gray matter are less clear, though physiological impairments to cell membranes and proteins together with neuronal and synaptic loss are offered as plausible explanations.33,35,36

Our data demonstrate that diabetes is associated with biophysical compromise to the head of the caudate nucleus that is significantly different from our healthy controls. These data are consistent with our prior article indicating that patients with type 2 diabetes with and without depression had smaller prefrontal gray matter volumes when compared with controls without diabetes.17 In an earlier study we reported that executive functions and processing speed in patients with diabetes without depression were between those of the depressed diabetic and healthy control groups.32 These findings suggest that certain neurobiological and cognitive changes are intrinsic to type 2 diabetes independent of clinical depression. Additional neurobiological abnormalities in critical regions such as the subcortical nuclei may lead to major mood disturbances and additional cognitive impairments in these patients. The lack of a relationship between certain primary clinical measures of diabetes and our neuroimaging indices in our sample suggests that the subcortical biophysical abnormalities may be related to the metabolic abnormalities in more subtle ways than can be clinically ascertained at the present time. The present finding of smaller prefrontal lobe volumes in patients with type 2 diabetes with and without depression indicate an additional structural prefrontal component to the abnormal prefrontal subcortical circuitry in patients with depression.17 The anatomical abnormality in the prefrontal region and the biophysical abnormality in the head of the caudate nucleus could additionally impair the downstream components of the circuit that extends through the globus pallidus and the thalamus and back to the prefrontal cortex. Neurobiological aberrations in the dorsolateral and orbitofrontal circuits could plausibly contribute to the

Neuronal circuits are highly interconnected, and the anatomical and functional connectivity provide the substrates for integrated higher cognitive functions that are largely behavioral in nature.10,11,30 Subcortical structures have been consistently implicated in behavioral and emotional states.12–15 Injury to the caudate and lenticular nuclei has been associated with MDD, subcortical dementia, and aphasias.13,39,52 Starkstein et al39 reported that vascular injury to the head of the caudate nucleus on the left side was selectively associated with MDD in a sample of African American patients with stroke. Dementia has been identified with both subcortical strokes and subcortical ischemic vascular disease.44 In addition, degenerative disorders such as Huntington and Parkinson disease in which the caudate nucleus and cortical subcortical circuits are compromised are associated with a broad spectrum of behavioral aberrations such as depression, anxiety, psychosis, and disinhibition.52,53 While these aforementioned circuits are anatomically distinct, there is considerable anatomical and functional overlap between the regions involved.53,54 The overall circuitry is therefore not isolated either anatomically or functionally and is sensitive to input from diverse brain regions. Anatomical or physiological compromise to one portion of the circuit could affect other components of the circuit, thereby resulting in diverse motor and behavioral manifestations.

Lower MTRs have been demonstrated in multiple psychiatric and neurological disorders including MDD, schizophrenia, multiple sclerosis, degenerative disorders, bipolar disorder, and parasitic infections of the brain.23,46–51 Lower MTRs have been demonstrated in both gray and white matter regions and in several clinical brain disorders.52 When an earlier study of a sample of patients with late-life MDD, we detected lower MTRs in several white and gray matter regions including the genu and splenium of the corpus callosum, occipital white matter, and head of the caudate nucleus and the putamen when compared with controls.25 More recently, Gunning-Dixon expanded on those findings and reported lower MTRs in several cortical and subcortical regions including the anterior cingulate, prefrontal subregions, and insula in the left hemisphere in patients with late-life MDD when compared with controls.37 In a sample of patients diagnosed with chronic schizophrenia, Foong et al56 identified lower MTRs in the parietooccipital cortex bilaterally and in the genu of the corpus callosum when compared with controls. These findings were interpreted as evidence of impaired connectivity in the brain that is predisposed to behavioral disturbances. Lower MTRs have been identified in both gray and white matter regions in patients with Alzheimer disease and Lewy body dementia. Lower MT in the hippocampus also helped distinguish patients with Alzheimer disease from those with Lewy body dementia.52,53 Our finding of lower MTRs in a focal, circumscribed, subcortical nucleus stands in marked contrast to earlier studies describing diffuse changes in the brains of patients with depression and schizophrenia. This does not necessarily indicate a discrepancy in findings, but may suggest a more focal selective compromise of circuits in depression secondary to type 2 diabetes when compared with the more classic idiopathic forms of the disorder.

Postmortem MT and biochemical studies demonstrate that in the white matter, lower MTRs are associated with demyelination and low axonal density.55,56 This finding resulted from postmortem MT imaging of the white matter of tissue obtained from patients with multiple sclerosis. The extent to which this observation can be generalized to other disease states remains unknown. Low MTRs in the parenchyma are on occasion associated with edema, gliosis, Wallerian degeneration, and inflammation, and is potentially reversible with treatment.56–58 The biochemical correlates of low MTRs in the gray matter are less clear, though physiological impairments to cell membranes and proteins together with neuronal and synaptic loss are offered as plausible explanations.33,35

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mood changes observed in our sample of patients with type 2 diabetes.

We would like to acknowledge a few limitations of our study. First, our relatively small sample sizes may have precluded the expected correlations between some of our clinical and neuroimaging measures from reaching statistical significance. Nonetheless, we remain confident about our finding in the head of the caudate nucleus given its robust nature and the effect size associated with it. Second, we used a more traditional ROI approach to our MT image analysis than the more automated voxel-based analytic method. This was based on our a priori hypotheses regarding regions that would show biophysical abnormalities in the depressed group based on our earlier studies of MDD. Consequently, we are unable to comment on the biophysical status of other prefrontal regions involved in prefrontal-subcortical circuitry. Finally, the absence of a group with depression but without diabetes to some degree limits our ability to make more definitive statements on the contributions of mood vs diabetes to our findings. However, the observation that patients with diabetes without depression have MT changes that fall between the other groups does indicate that both depression and diabetes play a role in the biophysical abnormalities that were detected.

In summary, our findings demonstrate biophysical abnormalities in the head of the caudate nucleus in patients with type 2 diabetes and MDD. This may provide the subcortical component to abnormalities in prefrontal-subcortical circuits that mediate abnormalities in mood, cognition, and behavior. Preclinical models that target the caudate and other components of the circuit may help in further clarifying the anatomical and physiological correlates of depression in patients with type 2 diabetes.

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