

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 Helleman, 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 con-

trols), 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.

Arch Gen Psychiatry. 2009;66(3):324-330

Author Affiliations:

Departments of Psychiatry and Radiology and the Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles (UCLA) (Drs Kumar, Thomas, Ajilore, and Helleman); and the Sanjay Gandhi Institute of Post Graduate Medical Education and Research, Lucknow, India (Dr Gupta).

TYPE 2 DIABETES IS A COMMON metabolic disorder associated with multiple organ system dysfunction and considerable mortality and morbidity.¹ 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.² 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.³⁻⁵ Depression in patients with diabetes is associated with poor treatment compliance, compromised quality of life, in-

creased rates of hyperglycemia, other complications of diabetes, and mortality.⁶⁻⁹ 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.^{10,11} Cortical-subcortical circuits in particular, with their distinctive components, have been consistently implicated in the underlying neurobiology of mood disorders.¹²⁻¹⁵ 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.¹⁶

Table 1. Clinical and Demographic Characteristics of the 3 Groups

Characteristic	Mean (SD) by Group			Statistical Test	P Value
	HC (n=30)	DC (n=22)	DD (n=16)		
Age, y	54.9 (11.04)	60.7 (9.79)	58.1 (10.71)	$F_{2,65} = 1.9$.15
Male:female ratio	7:23	6:16	2:14	$\chi^2 = 1.33$.52
Education, y	16.7 (3.30)	13.9 (4.14)	13.6 (3.56)	$F_{2,65} = 5.4$.007 ^a
CIRS	2.8 (2.46)	6.5 (3.70)	7.2 (2.66)	$F_{2,65} = 14.6$	<.001 ^a
CVRF	4.7 (4.64)	12.0 (4.55)	12.6 (4.86)	$F_{2,65} = 21.9$	<.001 ^a
MMSE	29.1 (1.12)	28.2 (2.01)	27.6 (2.4)	$F_{2,65} = 4.1$.02 ^a
HbA _{1c}	5.4 (0.41)	6.9 (1.14)	7.8 (1.74)	$F_{2,62} = 26.1$	<.001 ^a

Abbreviations: CIRS, total Cumulative Illness Rating Scale scores; CVRF, Cerebrovascular Risk Factor score; DC, diabetic control; DD, diabetes with major depression; HbA_{1c}, hemoglobin A_{1c} levels; HC, healthy control; MMSE, Mini-Mental State Examination scores.

^aValues are statistically significant.

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.¹⁷ 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.¹⁸⁻²⁰ 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 etio-pathogenesis 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.^{21,22} 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.^{23,24} Based on prior studies demonstrating that depression and diabetes independently affect neuroanatomy and physiology,^{17,18,25} 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 con-

trols), patients diagnosed with diabetes and MDD, and controls without diabetes or MDD (healthy controls).²⁶ 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.²⁷ 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.²⁸ 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.²⁹ 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 A_{1c} (HbA_{1c}) levels. In addition, cerebrovascular risk factors were assessed using the American Heart Association's Stroke Risk Prediction Chart³⁰ 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.³¹ 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).

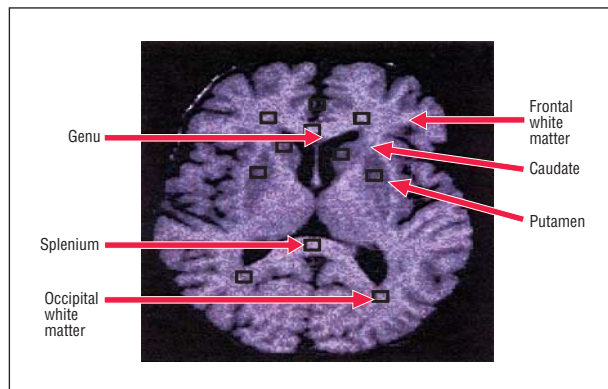


Figure 1. Magnetic resonance image of a patient with major depression shows the voxels (boxes) at different locations from where the magnetization transfer ratio was extracted.

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 African 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 episode of depression was 16.4 (18.2) months and the duration of diabetes was 112.4 (97.4) months in the diabetic control group and 156 (119) months in the depressed diabetic group. Details of our recruitment and other sample characteristics have been previously published.^{17,32} All subjects also received a structural magnetic resonance scan and a comprehensive neuropsychological 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 Protection Guidelines.

IMAGING

Magnetic resonance imaging was performed using a 1.5-T scanner (Signa Lx Echospeed Plus 9.1; General Electric Medical System, Milwaukee, Wisconsin) using transmit/receive quadrature head coil. Imaging was performed in axial plane using fast spin echo T2 (repetition time, 4900 milliseconds; echo time, 85 milliseconds; number of excitations, 2; echo train length, 16), T1 (repetition time, 1000 milliseconds; echo time, 20 milliseconds; number of excitations, 2), and MT-T1 weighted sequences. The parameters for the MT T1 were exactly the same as for T1 except for the off-resonance pulse applied 1.2-kHz off resonance for a duration of 16 milliseconds. All imaging was performed in axial plane with a slice thickness of 3 mm, with no interslice gap, a 240-mm field of view, and a matrix size of 192 × 256.

The matrix interpolated to 256 × 256 after the transferring the images to the workstation. The MTR was computed voxel by voxel using the formula $MTR = (M_0 - M_s) / M_0 \times 100\%$, where M_s and M_0 are the voxel signal intensities with and without the off-resonance MT-saturation pulse, respectively. The computation was done only in those voxels in which both M_0 and $(M_0 - M_s)$ exceed a predefined lower threshold. The software used was developed in house, along with the region-of-interest (ROI) analysis interface.

For quantification of the MTR, the slice displaying the most anterior margin of the genu of the corpus callosum was chosen as the reference slice. This slice was selected because its landmarks are more consistently identifiable across scans and in the regions we were interested in; the anterior cingulate gray matter, head of the caudate nucleus, putamen, periventricular frontal and occipital white matter, and genu and splenium of

the corpus callosum are clearly visible at this level. In cases where the putamen was not clearly seen in the same slice that clearly displayed the other structures, the next contiguous slice was used for quantification of the MTR. The T2-weighted images were closely examined for hyperintensities in these regions to avoid these lesions while placing our voxel in the ROI. The ROIs were placed in all of the above-defined regions with a voxel volume varying from 0.12 to 0.34 mL (**Figure 1**). The size of the voxel was guided by the size of the region to be quantified; hence, it showed variation.

The voxel of interest was placed so that it was devoid of any partial volume effect from adjoining tissues that may contaminate the results of MTR quantification. The different regions were selected using the in-house-developed software program and the mean signal intensity on the MTR image was quantified as the MTR for the different regions. One of the authors (R.G.), a neuroradiologist responsible for voxel placement and quantification, was blind to the clinical status of all subjects. Regions of interest were selected based on earlier reports of lower MTRs in patients with late-life depression.

STATISTICAL ANALYSIS

The differences between patients and controls on their scores for the ROIs were compared using the general linear model. Age, sex, ethnicity, education, HbA_{1c} levels, and Cumulative Illness Rating Scale scores were identified as potential confounding variables and controlled for by including them as covariates in the model. To control the false discovery rate due to multiple testing, the Benjamini-Hochberg approach was used to determine the significance of the results.³³ If a ROI shows a significant difference in the omnibus test, post hoc *t* tests with Tukey adjustment were used to establish the pattern of differences.³⁴ Additionally a general linear model was used to examine associations between MTR in the caudate nucleus (bilateral) and the duration of the current episode of depression and the duration of diabetes after controlling for the aforementioned variables.

RESULTS

The MTRs in the right and left caudate nuclei are significantly different between the diagnostic groups (right caudate $F_{2,40} = 23.4$, $P < .001$; left caudate $F_{2,40} = 32.56$, $P < .001$; *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 pattern of differences. For the right caudate, the estimated marginal mean (standard error of the mean [SEM]) values after controlling for the covariates are healthy controls, 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 $\alpha = .05$ after Tukey correction. For the left caudate, the estimated marginal mean (SEM) values after controlling for the covariates 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 $\alpha = .05$ after Tukey correction. Note that the effect size for the left caudate is somewhat larger, and that the mean

Table 2. Magnetization Transfer Ratios in the 3 Groups

Region	Mean (SD) Ratio by Group			$F_{2,40}$	Unadjusted <i>P</i> Value
	HC	DC	DD		
RC	35.13 (1.23)	31.90 (2.34)	29.93 (2.07)	12.48	<.001 ^a
LC	35.11 (1.28)	32.14 (2.47)	28.75 (3.14)	19.14	<.001 ^a
RP	34.72 (1.05)	34.09 (1.93)	33.22 (2.59)	2.56	.09
LP	35.41 (1.57)	33.97 (2.25)	34.26 (2.14)	1.95	.16
RF	43.90 (2.05)	43.55 (1.90)	43.57 (1.35)	0.02	.95
LF	44.77 (1.54)	44.50 (1.88)	44.18 (1.80)	0.27	.76
RO	43.27 (3.01)	43.35 (2.58)	42.62 (1.63)	0.19	.83
LO	42.75 (2.43)	42.05 (1.90)	41.96 (1.70)	2.05	.15
Genu	46.04 (3.01)	46.18 (1.67)	45.74 (2.07)	0.06	.95
Splenium	45.52 (2.65)	45.86 (2.20)	44.73 (2.00)	0.28	.75
AC	27.99 (3.58)	26.63 (3.87)	25.06 (5.01)	1.00	.38

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.

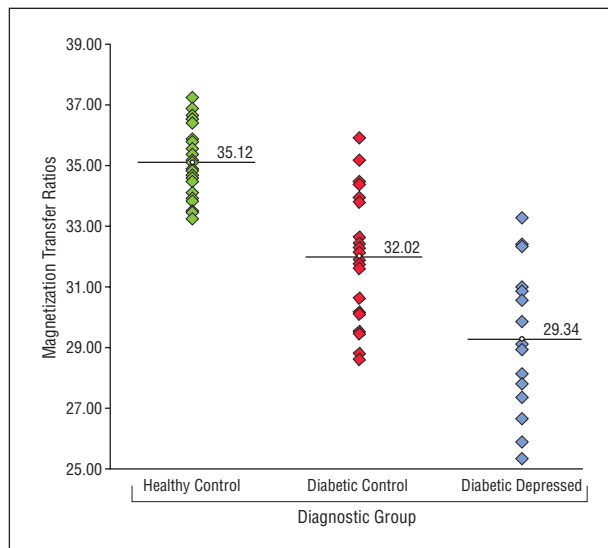


Figure 2. Scatterplot of the magnetization transfer ratios from the caudate nucleus, bilaterally, of the 3 groups.

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, HbA_{1c} 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.

COMMENT

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 re-

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

Region	HC vs DC	HC vs DD	DC vs DD
RC	1.24	2.12	0.87
LC	1.02	2.19	1.18
RP	0.39	0.52	0.91
LP	1.13	1.04	0.09
RF	0.18	0.05	0.12
LF	0.24	0.31	0.07
RO	0.21	0.33	0.12
LO	0.28	0.48	0.19
Genu	0.45	0.39	0.06
Splenium	0.05	0.38	0.44
AC	0.38	0.28	0.67

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.

gions 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 later 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 rostrocaudally 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

sulcus close the loop. The lateral orbitofrontal circuit originates in Brodmann area 10 and projects to the ventromedial section of the caudate nucleus. This portion of the caudate then projects to the globus pallidus interna and the substantia nigra. Projections from these sites to the thalamic nuclei and back to the orbitofrontal cortex complete the circuit.³⁶

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.^{10,11,38} Subcortical structures have been consistently implicated in behavioral and emotional states.^{12-15,41} Injury to the caudate and lenticular nuclei has been associated with MDD, subcortical dementia, and aphasia.^{13,39,42} Starkstein et al⁴³ 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.^{42,45} While these aforementioned circuits are anatomically distinct, there is considerable anatomical and functional overlap between the regions involved.^{35,36} 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.^{48,52} In 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.²³ 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.³³ In a sample of patients diagnosed with chronic schizophrenia, Foong et al⁴⁸ 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.^{52,54} 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 is 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.^{51,54}

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 aberrations 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.

Our current observation of biophysical abnormalities in the head of the caudate nucleus is consistent with an earlier study demonstrating lower glutamate/glutamine in the left subcortical region (a subcortical voxel that included the head of the caudate nucleus) in patients with diabetes and depression.¹⁶ Collectively, these findings indicate a strong subcortical neurobiological component to depression in patients diagnosed with type 2 diabetes. Our neuroanatomic 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

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.

Submitted for Publication: April 10, 2008; final revision received August 4, 2008; accepted September 18, 2008.

Correspondence: Anand Kumar, MD, UCLA Neuropsychiatric Institute, 760 Westwood Plaza, Room C9-938 A, Los Angeles, CA 90095 (akumar@mednet.ucla.edu).

Author Contributions: Dr Kumar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants MH 074545:01, MH 063764:04, and MH 065695 from the National Institutes of Health.

Additional Contributions: The authors would like to acknowledge the assistance of Christine Darwin, MD, of the Department of Endocrinology at the UCLA Medical Center and Anel Dzmura and Genevieve Rodriguez at the UCLA Semel Institute for Neuroscience and Human Behavior.

REFERENCES

1. Harati Y. Diabetes and the nervous system. *Endocrinol Metab Clin North Am*. 1996;25(2):325-359.
2. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol*. 2006;5(1):64-74.
3. Gavard JA, Lustman PJ, Clouse RE. Prevalence of depression in adults with diabetes: an epidemiological evaluation. *Diabetes Care*. 1993;16(8):1167-1178.
4. Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type II diabetes: a prospective population-based study. *Diabetes Care*. 1996; 19(10):1097-1102.
5. Li C, Ford ES, Strine TW, Mokdad AH. Prevalence of depression among US adults with diabetes: findings from the 2006 behavioral risk factor surveillance system. *Diabetes Care*. 2008;31(1):105-107.
6. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med*. 2000; 160(21):3278-3285.
7. Lin EH, Katon W, Von Korff M, Rutter C, Simon GE, Oliver M, Ciechanowski P, Ludman EJ, Bush T, Young B. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care*. 2004;27(9): 2154-2160.
8. Lustman PJ, Clouse RE. Depression in diabetic patients: the relationship between mood and glycemic control. *J Diabetes Complications*. 2005;19(2):113-122.
9. Katon WJ, Rutter C, Simon G, Lin EH, Ludman E, Ciechanowski P, Kinder L, Young B, Von Korff M. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care*. 2005;28(11):2668-2672.
10. Fuster JM. The prefrontal cortex: an update: time is of the essence. *Neuron*. 2001; 30(2):319-333.
11. Kumar A, Cook IA. White matter injury, neural connectivity and the pathophysiology of psychiatric disorders. *Dev Neurosci*. 2002;24(4):255-261.
12. Cummings JL. Frontal-subcortical circuits and human behavior. *Arch Neurol*. 1993; 50(8):873-880.
13. Cummings JL. The neuroanatomy of depression. *J Clin Psychiatry*. 1993;54(suppl):14-20.
14. Alexopoulos GS. Frontostriatal and limbic dysfunction in late-life depression. *Am J Geriatr Psychiatry*. 2002;10(6):687-695.
15. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nat Neurosci*. 2007;10(9):1116-1124.
16. Ajilore O, Haroon E, Kumaran S, Darwin C, Binesh N, Mintz J, Miller J, Thomas MA, Kumar A. Measurement of brain metabolites in patients with type 2 diabetes and major depression using proton magnetic resonance spectroscopy. *Neuropsychopharmacology*. 2007;32(6):1224-1231.
17. Kumar A, Haroon E, Darwin C, Pham D, Ajilore O, Rodriguez G, Mintz J. Gray matter prefrontal changes in type 2 diabetes detected using MRI. *J Magn Reson Imaging*. 2008;27(1):14-19.
18. Soininen H, Puranen M, Helkala EL, Laakso M, Riekkinen PJ. Diabetes mellitus and brain atrophy: a computed tomography study in an elderly population. *Neurobiol Aging*. 1992;13(6):717-721.
19. den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, Breteler MM. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia*. 2003;46(12):1604-1610.
20. Akisaki T, Sakurai T, Takata T, Umegaki H, Araki A, Mizuno S, Tanaka S, Ohashi Y, Iguchi A, Yokono K, Ito H. Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT). *Diabetes Metab Res Rev*. 2006;22(5):376-384.
21. Eng J, Ceckler TL, Balaban RS. Quantitative 1H magnetization transfer imaging in vivo. *Magn Reson Med*. 1991;17(2):304-314.
22. Balaban RS, Ceckler TL. Magnetization transfer contrast in magnetic resonance imaging. *Magn Reson Q*. 1992;8(2):116-137.
23. Kumar A, Gupta RC, Albert TM, Alger J, Wyckoff N, Hwang S. Biophysical changes in normal-appearing white matter and subcortical nuclei in late-life major depression detected using magnetization transfer. *Psychiatry Res*. 2004;130(2): 131-140.
24. Ballmaier M, Kumar A, Elderkin-Thompson V, Narr KL, Luders E, Thompson PM, Hojatkashani C, Pham D, Heinz A, Toga AW. Mapping callosal morphology in early- and late-onset elderly depression: an index of distinct changes in cortical connectivity [published online ahead of print August 22, 2007]. *Neuropsychopharmacology*. 2008;33(7):1528-1536.
25. Ballmaier M, Sowell ER, Thompson PM, Kumar A, Narr KL, Lavretsky H, Welcome SE, DeLuca H, Toga AW. Mapping brain size and cortical gray matter changes in elderly depression. *Biol Psychiatry*. 2004;55(4):382-389.
26. Mayfield J. Diagnosis and classification of diabetes mellitus: new criteria. *Am Fam Physician*. 1998;58(6):1355-1370.
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
28. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278-296.
29. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189-198.

30. American Heart Association. *Stroke Risk Factor Prediction Chart*. Dallas, TX: American Heart Association; 1990.
31. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc*. 1968;16(5):622-626.
32. Watari K, Letamendi A, Elderkin-Thompson V, Haroon E, Miller J, Darwin C, Kumar A. Cognitive function in adults with type 2 diabetes and major depression. *Arch Clin Neuropsychol*. 2006;21(8):787-796.
33. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Roy Statist Soc B*. 1995;57:289-300.
34. Tukey JW. Components in regression. *Biometrics*. 1951;7(1):33-69.
35. Selemon LD, Goldman-Rakic PS. Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J Neurosci*. 1985;5(3):776-794.
36. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci*. 1986; 9:357-381.
37. Chow TW, Cummings JL. Frontal-subcortical circuits. In: Miller BL, Cummings JL, eds. *The Human Frontal Lobes*. New York, NY: The Guilford Press; 1999:3-26.
38. Roberts AC, Tomic DL, Parkinson CH, Roeling TA, Cutter DJ, Robbins TW, Everitt BJ. Forebrain connectivity of the prefrontal cortex in the marmoset monkey (*Callithrix jacchus*): an anterograde and retrograde tract-tracing study. *J Comp Neurol*. 2007;502(1):86-112.
39. Taylor WD, Steffens DC, McQuoid DR, Payne ME, Lee SH, Lai TJ, Krishnan KR. Smaller orbital frontal cortex volumes associated with functional disability in depressed elders. *Biol Psychiatry*. 2003;53(2):144-149.
40. Ballmaier M, Narr KL, Toga AW, Elderkin-Thompson V, Thompson PM, Hamilton L, Haroon E, Pham D, Heinz A, Kumar A. Hippocampal morphology and distinguishing late-onset from early-onset elderly depression. *Am J Psychiatry*. 2008; 165(2):229-237.
41. Alexander MP, Naeser MA, Palumbo CL. Correlations of subcortical CT lesion sites and aphasia profiles. *Brain*. 1987;110(pt 4):961-991.
42. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci*. 1989;12(10):366-375.
43. Starkstein SE, Robinson RG, Berthier ML, Parikh RM, Price TR. Differential mood changes following basal ganglia vs thalamic lesions. *Arch Neurol*. 1988;45 (7):725-730.
44. Moorhouse P, Rockwood K. Vascular cognitive impairment: current concepts and clinical developments. *Lancet Neurol*. 2008;7(3):246-255.
45. Weintraub D, Hurtig HI. Presentation and management of psychosis in Parkinson's disease and dementia with Lewy bodies. *Am J Psychiatry*. 2007;164(10): 1491-1498.
46. Grossman RI. Magnetization transfer in multiple sclerosis. *Ann Neurol*. 1994;36 (suppl):S97-S99.
47. Bjartmar C, Yin X, Trapp BD. Axonal pathology in myelin disorders. *J Neurocytol*. 1999;28(4-5):383-395.
48. Foong J, Symms MR, Barker GJ, Maier M, Woermann FG, Miller DH, Ron MA. Neuropathological abnormalities in schizophrenia: evidence from magnetization transfer imaging. *Brain*. 2001;124(pt 5):882-892.
49. Kumar R, Gupta RK, Rathore RK, Rao SB, Chawla S, Pradhan S. Multiparametric quantitation of the perilesional region in patients with healed or healing solitary cysticercus granuloma. *Neuroimage*. 2002;15(4):1015-1020.
50. Chen JT, Kuhlmann T, Jansen GH, Collins DL, Atkins HL, Freedman MS, O'Connor PW, Arnold DL; Canadian MS/BMT Study Group. Voxel-based analysis of the evolution of magnetization transfer ratio to quantify remyelination and demyelination with histopathological validation in a multiple sclerosis lesion. *Neuroimage*. 2007;36(4):1152-1158.
51. Bruno SD, Barker GJ, Cercignani M, Symms M, Ron MA. A study of bipolar disorder using magnetization transfer imaging and voxel-based morphometry [published online ahead of print October 6, 2004]. *Brain*. 2004;127(pt 11):2433-2440.
52. Hanyu H, Asano T, Sakurai H, Takasaki M, Shindo H, Abe K. Magnetization transfer measurements of the hippocampus in the early diagnosis of Alzheimer's disease. *J Neurol Sci*. 2001;188(1-2):79-84.
53. Gunning-Dixon FM, Hoptman MJ, Lim KO, Murphy CF, Klimstra S, Latoussakis V, Majcher-Tascio M, Hrabe J, Ardekani BA, Alexopoulos GS. Macromolecular white matter abnormalities in geriatric depression: a magnetization transfer imaging study. *Am J Geriatr Psychiatry*. 2008;16(4):255-262.
54. Hanyu H, Shimizu S, Tanaka Y, Kanetaka H, Iwamoto T, Abe K. Differences in magnetization transfer ratios of the hippocampus between dementia with Lewy bodies and Alzheimer's disease. *Neurosci Lett*. 2005;380(1-2):166-169.
55. van Waesberghe JH, Kamphorst W, De Groot CJ, van Walderveen MA, Castelijns JA, Ravid R, Lycklama à Nijeholt GJ, van der Valk P, Polman CH, Thompson AJ, Barkhof F. Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. *Ann Neurol*. 1999;46(5):747-754.
56. Schmierer K, Tozer DJ, Scaravilli F, Altmann DR, Barker GJ, Tofts PS, Miller DH. Quantitative magnetization transfer imaging in postmortem multiple sclerosis brain. *J Magn Reson Imaging*. 2007;26(1):41-51.
57. Hickman SJ, Toosy AT, Jones SJ, Altmann DR, Miszkiel KA, MacManus DG, Barker GJ, Plant GT, Thompson AJ, Miller DH. Serial magnetization transfer imaging in acute optic neuritis. *Brain*. 2004;127(pt 3):692-700.
58. Emmer BJ, Steens SC, Steup-Beekman GM, van der Grond J, Admiraal-Behloul F, Olofsen H, Bosma GP, Ouwendijk WJ, Huizinga TW, van Buchem MA. Detection of change in CNS involvement in neuropsychiatric SLE: a magnetization transfer study. *J Magn Reson Imaging*. 2006;24(4):812-816.