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Regional cortical gray matter thickness differences associated with type 2 diabetes and major depression

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Abstract

Objective—The purpose of this study was to examine the effect of type 2 diabetes with major depression on cortical gray matter using magnetic resonance imaging and cortical pattern matching techniques. We hypothesized that diabetic subjects and depressed diabetic subjects would demonstrate decreased cortical gray matter thickness in prefrontal areas as compared to healthy control subjects.

Methods—Patients with type 2 diabetes (n=26) and patients diabetes and major depression (n=26) were compared with healthy controls (n=20). Gray matter thickness across the entire cortex was measured using cortical pattern matching methods.

Results—All subjects with diabetes demonstrated decreased cortical gray matter thickness in the left anterior cingulate region. Additionally, depressed diabetic subjects showed significant cortical gray matter decreases in bilateral prefrontal areas compared with healthy controls. Correlations between clinical variables and cortical gray matter thickness revealed a significant negative relationship with cerebrovascular risk factors across all three groups, most consistently in the left dorsomedial prefrontal cortex. A significant positive relationship between performance on attention and executive function tasks and cortical gray matter thickness predominately in left hemisphere regions was also seen across all subjects.

Conclusion—Depression and diabetes are associated with significant cortical gray matter thinning in medial prefrontal areas.

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Disclosure/Conflict of Interest

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Keywords

MRI; neurocognition; neuroanatomy; mood; diabetes

1. Introduction

Type 2 diabetes is a significant public health problem associated with a number of devastating sequelae including renal disease, retinal disease and peripheral neuropathy. Due to the microvascular compromise associated with these complications, type 2 diabetes is likely to have deleterious effects on the brain as well. Several studies have probed this idea by examining structural alterations in the brain associated with type 2 diabetes. In a recent review of neuroimaging in diabetes, the authors note several studies demonstrating significant atrophy in cortical and subcortical regions (van Harten et al. 2006). One study cited showed that type 2 diabetes was associated with hippocampal and amygdalar atrophy (den Heijer et al. 2003). A more recent study has demonstrated increased white matter lesions and gray matter atrophy associated with type 2 diabetic subjects when compared to control subjects (Jongen et al. 2007).

In addition to neuroanatomical alterations, major depression can be seen as an associated neuropsychiatric sequela of diabetes. This is evidenced by the notion that major depression and type 2 diabetes are mutual risk factors. There is a large literature examining the relationship between major depression and type 2 diabetes. Prevalence of major depression in a sample diabetic population ranged from 8.5% to 27% according to one study (Gavard et al. 1993). A more recent study reported an age-adjusted prevalence of depression in diabetic patients of 8.3% (95% confidence interval, 7.3% to 9.3%) (Li et al. 2007). Depressed patients have 2.2 times the risk of developing diabetes as compared to non-depressed subjects (Eaton et al. 1996). This bidirectional association was confirmed in a recent analysis using a large, ethnically diverse sample. The presence of major depression has consequences for diabetes in terms of increased rates of hyperglycemia, reduced compliance, diabetic complications, and increased mortality (de Groot et al. 2001; Lustman and Clouse 2005; Katon et al. 2005).

We have examined the relationship between type 2 diabetes and major depression in a number of domains. Previous work from our group has shown that diabetic subjects (both depressed and non-depressed) had poorer performance on executive functioning tasks compared to healthy control subjects. In addition, compared to healthy control subjects, depressed diabetic subjects had significantly poorer performance on attention processing tasks (Watari et al. 2006). We have also looked at biochemical differences associated with type 2 diabetes and major depression using magnetic resonance spectroscopy. Diabetic subjects (depressed and non-depressed) had higher myo-inositol concentrations in frontal white matter while depressed diabetic subjects demonstrated lower glutamate/glutamine concentrations in subcortical regions compared to healthy control subjects (Ajilore et al. 2007). Our group has shown that diabetic subjects both with and without depression had lower overall total gray matter volumes and smaller gray matter volumes in anterior cingulate and orbitofrontal regions after controlling for total gray matter (Kumar et al. 2008). Given the deleterious effects of major depression and type 2 diabetes on neurochemistry and cognitive functioning, we wanted to investigate whether these differences were related to structural alterations in the brain focusing on cortical gray matter thickness in the same subject population.

The purpose of this study was to examine the regional neuroanatomical differences associated with both type 2 diabetes and major depression using magnetic resonance

imaging. Specifically, since laminar thickness may index pathophysiological processes within the neuropil, we used cortical pattern matching methods to compare cortical thickness at high spatial resolution across the cortex between diagnostic groups. Cortical thickness is considered to be a more reliable measure of gray matter differences compared to volumetric analyses due to decreased structural variability in the cytoarchitecture (Singh et al. 2006). We hypothesized that diabetic subjects and depressed diabetic subjects would demonstrate decreased cortical gray matter thickness in prefrontal areas as compared to healthy control subjects. We also examined the correlations between cortical gray matter thickness and clinical variables (stroke risk, medical co-morbidities, hemoglobin A1c, and diabetes duration). We hypothesized that there would be inverse relationship between cortical gray matter thickness and these clinical variables. Finally, we examined the correlations between cortical gray matter thickness and two cognitive domains (attention processing and executive function) with the hypothesis that there would be a positive relationship between thickness and performance on tasks related to these two domains.

2. Methods

2.1 Subject Selection

We investigated 52 subjects between the ages of 30–80, diagnosed with type 2 diabetes by their primary care physicians. Type 2 diabetes was diagnosed using established clinical criteria (Mayfield 1998). Of the 52 subjects with type 2 diabetes, 26 met DSM-IV criteria for major depressive disorder, and 26 subjects denied a history of or current depression and were enrolled as diabetic controls. Subjects were recruited from three outpatient clinical sites: Gonda Diabetes Center at UCLA, UCLA Division of Endocrinology (Santa Monica, CA), and a satellite diabetes clinic (Alhambra, CA). Twenty control participants were recruited through newspaper advertisements circulating in Los Angeles, California. These subjects represent a sample selection whose recruitment details and characteristics have been described in previously published studies from our group (Kumar et al. 2008; Watari et al. 2006; Kumar et al. 2009). All subjects were given a structured clinical interview (Structured Clinical Interview for DSM-IV) (Spitzer MB 1992) by a trained research associate. Depressed patients received a score of 15 or higher on the Hamilton Rating Scale for Depression (Hamilton 1960) and none of them had any clinically relevant psychotic features. All patients screened for depression were assessed by a board-certified or board-eligible psychiatrist. All patients diagnosed with major depression were drug-naïve or free of antidepressant medications for at least 2 weeks prior to the study. Diabetic patients were on varying combinations of oral hypoglycemic agents and insulin for blood sugar control. Exclusion criteria for the present study included the following: dementia, central nervous system diseases, unstable medical illnesses, other Axis I disorders (including bipolar disorder), drug or alcohol dependence, or head trauma. Health status and medical co-morbidities were assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS; (Linn et al. 1968)) and the Cerebrovascular Risk Factor Scale developed by the American Heart Association (CVRF), respectively. To determine glycemic control, hemoglobin A1c (Hgb A1c) levels were measured for all subjects. Subjects also received a neuropsychological battery described in Watari et al, 2006 that included tasks that assessed the cognitive domains of attention and executive function (Watari et al. 2006). The scores were aggregated according to an *a priori* conceptual design into two composite variables: 1) simple attention included visuomotor tracking (Trail Making A) and sustained attention (Stroop, Part A and B) and 2) executive function included working memory manipulation (Letter-Number Sequences), nonverbal inductive reasoning (Matrix Reasoning), reverse learning (Wisconsin Card Sorting Test), response inhibition (Stroop, Part C), dual attention (Trail Making B), phonetic fluency (Controlled Oral Word Association), and nonverbal design fluency (Ruff Figural Fluency). The aggregated variables showed acceptable internal

validity: Cronbach alphas were 0.80 for executive and 0.78 for attention. All subjects participated with informed consent in accordance with UCLA's Institutional Review Board requirements.

2.2 Image Processing

Subjects were scanned with a 1.5-T Signa magnet (GE Medical Systems, Milwaukee). Images were obtained with the following protocol as a whole-brain, gradient-echo (spoiled gradient recall acquisition) T1-weighted series acquired coronally with section thickness of 1.4 mm, no gaps (repetition time=20 msec; echo time=6 msec; flip angle=45°; field of view=22 cm; number of excitations=1.5; matrix size= 256×192 mm; in-plane resolution=0.86×0.86 mm).

The image pre-processing has been described in more detail in previous publications (Ballmaier et al. 2004a; Shattuck and Leahy 2002). In brief, image pre-processing involved whole brain extraction, radiofrequency bias field correction, and automated tissue classification into gray matter, white matter, and CSF using a partial volume correction method (Shattuck et al. 2001). Brain volumes were then transformed into standard stereotaxic space without scaling. From these volumes, the cortical surface was extracted using automated software resulting in a three-dimensional (3D) model of each hemispheric surface. On the 3D cortical surface model from each subject, 29 sulcal landmarks located throughout the brain were traced for each hemisphere. Interrater variability of manual outlining was measured as the three-dimensional root mean square difference in millimeters between 100 equidistant points from each sulcal landmark traced in six test brains relative to a gold standard arrived at by a consensus of raters. Intrarater reliability was computed by comparing the three-dimensional root mean square distance between equidistant surface points from sulcal landmarks from one test brain traced six times by the same rater. Three-dimensional root mean square disparities were <2 mm, and on average <1 mm, between points for all landmarks within and between raters (Ballmaier et al. 2004a).

Cortical pattern matching methods have been detailed previously (Thompson et al. 2001; Sowell et al. 2004; Narr et al. 2005). Briefly, to align cortical anatomy and allow the measurement of cortical thickness at homologous cortical regions across subjects at high spatial density, the manually-derived sulcal landmarks were used as anchors to drive surface warping algorithms. These cortical pattern matching algorithms create three-dimensional deformation fields that translate each subject's anatomy to the average anatomical pattern from the entire study group. Although the surface anatomy of each subject is not made conform to the average anatomical pattern of the group, the cortical pattern matching algorithms serve to impose a spatial correspondence between the same anatomical points or co-ordinate locations across all individuals at high density (Thompson et al. 2001; Sowell et al. 2004; Narr et al. 2005). Thus gray matter cortical thickness can be measured in each subject at anatomically and spatially equivalent points on the cortical surface. Cortical thickness estimations were determined by measuring the shortest 3D distance between the cortical gray-white matter boundary to the hemispheric surface without crossing CSF voxels as previously described (Thompson et al. 2001; Sowell et al. 2004; Narr et al. 2005).

2.3 Statistical analysis

Chi-squared analysis and t-tests were used to analyze demographic and clinical variables. All image-based statistics were implemented using the statistical package "R" (<http://www.r-project.org>). For subject group comparisons, cortical thickness was modeled as a function of diagnosis (healthy control versus diabetic control, healthy control versus depressed diabetic and diabetic control versus depressed diabetic) with age, gender, education, and brain volume as covariates. Pairwise comparisons were analyzed to examine

the specific effects of diabetes alone, in addition to diabetes with co-morbid major depression. Exploratory analyses using partial correlations (with age, gender, education and brain volume as covariates) between cortical thickness and performance on cognitive tests, as well cortical thickness and clinical variables (with age, gender, and brain volume as covariates) were also measured using “R”.

Permutation testing was used to rule out Type I error from performing multiple spatially-correlated comparisons between groups. The permutation testing methods have been employed in several of our prior publications to confirm the significance of the statistical maps and correct for multiple spatially correlated comparisons conducted at thousands of surface points to minimize Type I error (Anderson and Braak CJ 2003). The number of surface points across the hemisphere (or within a specific region of interest) that were significant at a threshold of $p < .05$ using the reduced model (i.e. correcting for age, gender, and brain volume) were compared to the number of significant surface points that occurred by chance when subjects (or residuals for the reduced model) were randomly assigned to groups across 1,000 new randomized analyses. The regions of interest used in the permutation analyses were based on the *a priori* hypothesis that cortical thickness differences would occur in the prefrontal cortex. For our exploratory correlational analyses where there were no *a priori* regions of interest, we used false discovery rate (FDR) estimations to correct for Type I errors (Storey 2002). With $\alpha = 0.05$, FDR results under 5% were considered to be statistically significant.

3. Results

Table 1 describes the demographic data in our different subjects groups: healthy control subjects, diabetes only group, and subjects with type 2 diabetes and major depression. There was no significant difference in age, education, or gender between our three subject groups. While the depressed diabetic subjects had a longer duration of diabetes, higher Hgb A1c, CIRS, and CVRF results, they did not differ significantly from the diabetes only subjects. When examining general neuroanatomical characteristics in the three subject groups, there was no significant difference in total brain volume and overall cortical gray matter thickness in both hemispheres (Table 2). We first examined pairwise regional differences in cortical gray matter thickness among our three subject groups covaried for age, gender, and brain volume. Uncorrected statistical maps of significant cortical thickness differences for the comparison between healthy control subjects and diabetic subjects are shown in Figure 1. Diabetic subjects demonstrated decreased cortical gray matter thickness in the left anterior cingulate and adjacent to the left parietal-occipital sulcus. However, these regional differences did not survive permutation testing. Significant decreases in cortical gray matter thickness that did survive permutation testing included cortical gray matter thinning anterior to the paracentral sulcus and in bilateral dorsomedial prefrontal cortices in depressed diabetic subjects compared to healthy controls ($p < 0.05$). There were no regional differences in cortical thickness for comparisons of diabetic subjects with depressed diabetic subjects (data not shown).

In an exploratory analysis, we then examined the relationship between selected clinical variables and cortical gray matter thickness. While there was no significant correlation associated with duration of diabetes, Hgb A1c, CIRS, or HAM-D scores, there was significant cortical gray matter thinning ($FDR = .009$) correlated with cerebrovascular stroke risk (CVRF) predominately in the left hemisphere across all three groups (Figure 2). Regions of significant cortical thinning included the orbitofrontal cortex, temporal pole, and the medial superior frontal gyrus. When examining individual subject groups, no subject group had a significant correlation that survived FDR correction despite diabetic control

subjects having a similar pattern of cortical thickness correlations as the total study population.

We also examined whether performance on tasks of attention and executive function are associated with differences in cortical gray matter thickness. In Watari et al, diabetic subjects (both with and without depression) had poorer performance on tasks of attention, while depressed diabetic subjects did worse on executive function tasks (Watari et al. 2006). Across all subject groups, there were significant areas where cortical gray matter thickness was correlated with better performance on both tasks of attention processing (Figure 3A) and executive function (Figure 3B). Areas correlated with attention processing were predominately in the left hemisphere located in the vicinity of the temporal pole, occipital pole and adjacent to the post-central sulcus. Similar patterns of results were observed for executive function, but relationships were present within the left frontopolar cortex, in addition to the temporal pole and occipital pole. In comparing subject groups, healthy control subjects were the only group to have significant positive associations between cortical thickness and attention processing (FDR=0.014) and executive function (FDR=0.0265).

4. Discussion

In summary, there were significant regional differences in cortical thickness between depressed diabetic subjects and healthy controls. The regional thinning in subjects with diabetes only was noted to a lesser degree compared to healthy subjects. The less extensive cortical thinning in diabetic subjects without depression was suggestive of a greater influence of major depression over type 2 diabetes in subjects with both diseases. Clinical variables representing stroke risk (CVRF) were significantly correlated with cortical gray matter thinning across all subjects in our study population. Performance on attention and executive function tasks were significantly correlated with cortical gray matter thickness across all subjects.

In our study, the regions of significant cortical thinning associated with major depression and type 2 diabetes included the medial superior frontal gyrus and the anterior cingulate. Our previous volumetric study also identified gray matter decreases in the anterior cingulate of diabetic subjects (Kumar et al. 2008). This study used more conventional techniques measuring gray matter volumes, in contrast to the cortical thickness measurement employed in the present study. Cortical thickness measures have been used in a number of morphometric studies and it represents the combination of neurons, glial cells, axons and dendritic arborization. Reductions in any of these elements may account for the decreases in cortical thickness observed. In the existing literature, the anterior cingulate has been implicated in a number of studies examining neuroanatomical differences associated with major depression. Gray matter volume losses in the anterior cingulate have been shown to occur in late-life depression and depression in adults (Ballmaier et al. 2004b; Caetano et al. 2006; Tang et al. 2007). The anterior cingulate is also the locus of neurochemical differences associated with depression such as lower glutamate/glutamine as measured by magnetic resonance spectroscopy (Auer et al. 2000). While there is less data on the importance of the superior frontal gyrus in mood regulation, a recent intriguing functional MRI study included this region as a part of cortical network associated with the feeling of regret (Chandrasekhar et al. 2007). In another functional study, decreased perfusion was noted in the left superior frontal gyrus in depressed patients performing the Tower of London task (Goethals et al. 2005).

The complications associated with diabetes are primarily due to vascular compromise which can lead to renal disease, retinal disease, and stroke. Therefore, we wanted to examine the

relationship of medical co-morbidities and vascular risk to cortical gray matter thickness. There was no *a priori* hypothesis as to which regions would be affected by our measure of medical co-morbidities or stroke risk; however it is notable that regions of cortical thinning in depressed diabetic subjects overlapped with areas of correlative significance. Numerous previous studies have examined the correlation of white matter changes to vascular risk factors and medical co-morbidities (Jeerakathil et al. 2004; Hickie et al. 2005). These correlations have also demonstrated implications for the progression of mood disorders. For example, vascular risk has also been associated with cognitive decline and dementia in elderly depressed patients (Steffens et al. 2007). While we have recently reported gray matter volumetric differences associated with vascular risk factors (Kumar et al. 2008), to our knowledge, this is the first report of cortical gray matter thickness associations with clinical variables such as stroke risk.

Previous studies from our group have shown that diabetic subjects (both with and without depression) had performance deficits in executive function compared with healthy control subjects and depressed diabetic subjects perform significantly worse on tasks of attention processing compared to healthy control subjects (Watari et al. 2006; Watari et al. 2007). When correlating cortical gray matter thickness with cognitive performance in tasks of attention processing and executive function, significant regional differences were noted predominately in the left hemisphere. The strong correlation between simple attention and left parietal tissue around the post-central sulcus, particularly the posterior bank, suggests a relationship between the attentional network and cortical thinning. Mesulam identified three regions that, if compromised by lesions, would lead to attentional neglect, and one region was the dorsolateral parietal cortex just below the intraparietal sulcus (Mesulam 1990). Functional MRI has shown the areas within this region to be involved in attention to explicit speech (Sabri et al. 2008), implicit speech (Geiser et al. 2008), and even the relationship between verbal and nonverbal stimuli (Noordzij et al. 2008). The cortical thickness differences that correlated with executive function expanded to include the more of the occipital cortex. Some of the executive tests were nonverbal tests that required spatial analysis, so different areas within the inferior parietal may be dedicated to different types of stimuli.

The frontopolar region exhibited significant cortical thickness differences associated with performance on executive function. This highly developed area is well-known to coordinate executive functions involved in complex decision-making (Koechlin and Hyafil 2007). Another area of correlation between cortical thickness differences and cognitive function occurred in the temporal pole. A recent theory posits that the temporal pole is critical in the binding of highly processed perceptual inputs to visceral emotional responses (Olson et al. 2007). Intuitively, it seems appropriate that the temporal pole would be associated with cognitive testing. However, until more definitive evidence is available, the possibility must be considered that the correlations with temporal pole and parietal cortex are more associated with general testing ability and confidence in a testing situation than with the specific types of tests administered.

The results discussed in this study are presented within the context of a few limitations. For example, the lack of a significant difference between subjects with diabetes only and healthy control subjects may reflect a limitation of our study involving the recruitment of diabetic subjects from outpatient clinics. These patients were well-monitored as outpatients and subsequently represented a “healthier” population of diabetic subjects than would be found in a more general community sample. This is reflected in the relatively low Hgb A1c values seen in our population. In addition, we did not obtain lifetime hypoglycemic episodes in our diabetic subjects. A recent review suggests that recurrent hypoglycemic episodes have an unclear relationship to cognitive function (McNay and Cotero 2010), thus exploring the role

of hypoglycemia with our neuroanatomical analysis may contribute to our understanding of this controversial issue.

The significant cortical thinning seen in depressed diabetic subjects compared to controls may reflect a synergistic relationship between major depression and type 2 diabetes. The lack of a significant effect of type 2 diabetes alone suggests that the effect of cortical thinning may be due solely to major depression. A limitation of the study involved the lack of a depression only subject group to address this particular issue. However, the focus of the present study was to investigate the impact of depression in the context of type 2 diabetes. The inclusion of a depressed, non-diabetic comparator group, as well as lifetime hypoglycemic episodes, will be addressed in future studies.

In conclusion, microvascular compromise from diabetes may contribute as a risk factor for significant cognitive and behavioral sequelae. The results from our study contributes to the notion that medical co-morbidities such as stroke risk associated with type 2 diabetes are related to structural gray matter alterations reflected in pathophysiology of major depression.

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Figure 1. Effect of Diagnosis on Cortical Gray Matter Thickness

Top row: Diabetic subjects demonstrated cortical gray matter thinning particularly in the left anterior cingulate compared to healthy controls, but this result did not hold up after permutation testing. Bottom row: Depressed diabetic subjects show cortical thinning in the medial superior frontal regions. HC: Healthy control subjects, DC: Diabetic control subjects, DD: Depressed diabetic subjects (uncorrected images shown)

Figure 2. Correlation between Cortical Gray Matter Thickness and CVRF

Uncorrected partial correlation map of cortical gray matter differences associated with stroke risk (CVRF). HC: Healthy control subjects (FDR=.247), DC: Diabetic control subjects (FDR=.11), DD: Depressed diabetic subjects (FDR=.078), Total: All subjects (FDR=.0093).

Figure 3.

Figure 3A. Correlation of Cortical Gray Matter Thickness with Attention Processing.

Uncorrected partial correlation maps showing cortical gray matter thickness associated with performance on attention processing tasks. HC: Healthy control subjects (FDR=.0145), DC: Diabetic control subjects (FDR=.993), DD: Depressed diabetic subjects (FDR=.139), Total: All subjects (FDR = 0.021)

Figure 3B. Correlation of Cortical Gray Matter Thickness with Executive Function:

Uncorrected partial correlation maps showing cortical gray matter thickness associated with performance on executive function tasks. HC: Healthy control subjects (FDR=.0265), DC: Diabetic control subjects (FDR=.999), DD: Depressed diabetic subjects (FDR=.103), Total: All subjects (FDR=.0182)

Subject Characteristics

There were no significant differences between the three groups in age, gender distribution, and education. Diabetic subjects (with and without depression) were significantly different from healthy control subjects with Hgb A1c levels, CIRS and CVRF scores. While depressed diabetic subjects had a longer diabetes duration, higher Hgb A1c values, and higher CIRS and CVRF scores than diabetic control subjects, the two groups were not statistically distinct.

Table 1

	Healthy Control	Diabetic Control	Depressed Diabetic	χ^2	P
	n=20	n=26	n=26		
Gender	N (%)	N (%)	N (%)	0.82	0.66
Male	5 (25)	8 (31)	6 (23)		
Female	15 (75)	18 (69)	20 (77)		
	Mean (S.D.)			F	P
				(df=2)	
Age	55.15 (8.23)	57.81 (8.49)	55.50 (9.66)	0.65	0.53
Education	15.20 (2.67)	14.58 (4.04)	12.69 (3.77)	3.13	0.05
Diabetes Duration	--	9.85 (8.24)	10.50 (8.82)	--	0.78
Hgb A ₁ C*	5.55 (1.13)	7.10 (1.11)	7.64 (1.68)	14.16	<.0001
CIRS*	2.75 (2.43)	5.73 (3.57)	6.69 (2.96)	9.82	<.005
CVRF*	5.00 (4.45)	10.69 (3.79)	11.04 (4.92)	14.75	<.0001
HAM-D	--	--	21.5 (4.12)	--	--
Attention Processing*	.404 (.53)	.111 (.67)	-.446 (.90)	7.207	.002
Executive Function*	.380 (.54)	.034 (.55)	-.390 (.86)	6.310	.003

Hgb A1c – Hemoglobin A1c, CIRS – Cumulative Illness Rating Scale, CVRF – Cerebrovascular Risk Factor Scale, HAM-D – Hamilton Rating Scale for Depression. Attention processing and executive function are represented by average z-scores.

Neuroanatomical Characteristics

Table 2

The three subject groups did not differ in total brain volume or overall bilateral cortical thickness.

	Healthy Controls n=20		Diabetic Control n=26		Depressed Diabetic n=26		F (df=2)	P
	Mean	(SD)	Mean	(SD)	Mean	(SD)		
Total Brain Volume (cc)	1289.82	(128.90)	1232.71	(119.54)	1231.37	(122.64)	1.59	0.21
Left Cortical Gray Matter Thickness (mm)	4.83	(0.28)	4.75	(0.34)	4.74	(0.29)	0.64	0.53
Right Cortical Gray Matter Thickness (mm)	4.80	(0.27)	4.71	(0.34)	4.75	(0.30)	0.49	0.62