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Disassociation of verbal learning and hippocampal volume in type 2 diabetes and major depression

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Abstract

Objective—The purpose of this study was to examine the relationship between verbal learning and memory performance and hippocampal volume in subjects with co-morbid type 2 diabetes and major depression compared to healthy control subjects and subjects with type 2 diabetes alone.

Methods—24 subjects with type 2 diabetes and 20 subjects with type 2 diabetes and major depression were recruited from endocrinology clinics and were compared to 32 healthy control subjects recruited from the community. Subjects were scanned on a 1.5 T GE scanner and hippocampal volumes were measured using Freesurfer. The California Verbal Learning Test assessed learning and memory. Significant predictors of verbal learning performance (e.g., age, gender, education, blood pressure, stroke risk, hemoglobin A1c, and hippocampal volume) were determined using a stepwise linear regression.

Results—Subjects with diabetes and depression had significantly worse performance on verbal list learning compared to healthy control subjects. Hippocampal volume was a strong predictor of performance in healthy control subjects and age and hippocampal volume were strong predictors in subjects with type 2 diabetes alone. Age alone was a significant predictor of verbal learning performance in subjects with diabetes and depression.

Conclusions—The relationship between hippocampal volume and performance on the CVLT is decoupled in subjects with type 2 diabetes and major depression and this decoupling may contribute to poor verbal learning and memory performance in this study population.

Keywords

Diabetes; depression; medical co-morbidities; hippocampus; cognition

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Introduction

Type 2 diabetes and major depression have been associated in a number of epidemiological studies (Rustad et al., 2011). One manifestation of this association is that patients with type 2 diabetes are at increased risk of developing major depression (Aarts et al., 2009). Importantly, this increased risk is also associated with negative outcomes such as increased rates of diabetic complications (Katon et al., 2005) and greater mortality rates, particularly in women (Pan et al., 2011).

As associated disorders, there is growing evidence to suggest that they also may share similar underlying neurobiological substrates. For example, previous work from our group has demonstrated neuroanatomical, neurochemical and biophysical alterations in subjects with both type 2 diabetes and major depression. We have demonstrated subjects with diabetes and depression have elevated frontal white matter myo-inositol and decreased subcortical glutamate/glutamine compared to healthy control subjects (Ajilore et al., 2007). Subjects with diabetes and depression also showed regional cortical thinning in the medial prefrontal cortex (Ajilore et al., 2010). In addition, we have shown that specific cognitive functions correlated with findings from structural imaging and magnetic resonance spectroscopy imaging studies are altered in subjects with type 2 diabetes and major depression. For example, executive function has been correlated with right orbitofrontal gray matter volume in subjects with diabetes and depression, but not in healthy controls subjects (Watari et al., 2008). Conversely, frontal white matter myo-inositol levels negatively correlated with visuospatial function in healthy controls subjects, but not in subjects with both diabetes and depression (Haroon et al., 2009).

While the studies from our group focused on frontal-subcortical regions and their relationship to executive function, many studies have examined hippocampal alterations in type 2 diabetes and major depression separately as related to learning and memory function. It has been shown that older subjects with type 2 diabetes demonstrate significant hippocampal atrophy (den Heijer et al., 2003) compared to healthy controls. Hippocampal volume reductions associated with type 2 diabetes have been shown to be related to impaired memory performance and glycemic control (Gold et al., 2007). Additionally, in type 2 diabetes, memory impairment has been associated with clinical variables such as hemoglobin A1c (Hgb A1c) levels (Bruehl et al., 2010) and stroke risk (Elias et al., 2004). In addition, structural and functional alterations associated with the hippocampus have been seen in major depression. Decreased hippocampal volumes have been shown in a number of depressed populations (Sheline et al., 2002) and hippocampal shape deformations have been correlated with memory function in late-life depression (Ballmaier et al., 2008). While hippocampal volume and memory function have been studied in diabetic populations and depressed populations separately, to our knowledge, this relationship has not been examined in subjects with both disorders.

The purpose of this study was to examine the relationship between verbal learning and memory performance and hippocampal volume in subjects with type 2 diabetes and major depression compared to healthy control subjects and subjects with type 2 diabetes alone. Given our own work demonstrating abnormal correlations between cognition and

biomarkers in this population and previous studies that have shown alterations in hippocampal structure and memory impairment associated with both type 2 diabetes and major depression separately, we hypothesized that 1) subjects with co-morbid depression and diabetes would have poorer list learning than both healthy control and type 2 diabetes subjects while subjects with type 2 diabetes alone would display intermediate performance between that of their diabetic depressed and healthy control counterparts; and 2) in healthy controls, hippocampal volume would be a strong predictor of list learning performance, while in subjects with diabetes both with and without depression, predictors related to diabetic complications (e.g., HgbA1c, blood pressure, stroke risk) would also be strong predictors of performance.

Methods

Subject Selection

All subjects were recruited at the University of California, Los Angeles between September 2002 and March 2007. Subjects were given a structured clinical interview (Structured Clinical Interview for DSM-IV) (Spitzer et al., 1992) by a trained research associate. 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. All subjects participated with written informed consent in accordance with UCLA's Institutional Review Board requirements and the Declaration of Helsinki.

We recruited 61 subjects between the ages of 30 and 85, diagnosed with type 2 diabetes by their endocrinologist or primary care clinician. Type 2 diabetes was diagnosed using established clinical criteria (Mayfield, 1998). 44 of the 61 subjects had both complete neuropsychological and neuroimaging data. Of the 44 subjects with type 2 diabetes, 20 met DSM-IV criteria for major depressive disorder (DD), and 24 subjects denied a history of past or current depression and were enrolled as diabetic controls (DC). Subjects with diabetes were on varying combinations of oral hypoglycemic agents and insulin for blood sugar control. There was no difference in antidiabetic medications between diabetic groups (oral hypoglycemics only: $\chi^2 = 1.35$, $p = .246$; insulin only: $\chi^2 = .068$, $p = .795$; combination: $\chi^2 = 1.92$, $p = .165$). Stroke risk was assessed using the modified Framingham stroke risk profile (American Heart Association, 1990) and glycemic control was measured by Hgb A1c levels.

Subjects screened for depression were assessed by a board-certified or board-eligible psychiatrist. Inclusion criteria for depressed subjects consisted of a score of 15 or higher on the Hamilton Rating Scale for Depression (Hamilton, 1960) and no clinically relevant psychotic features. Depression severity was also assessed using the Beck Depression Inventory-II (Beck et al., 1996). Subjects diagnosed with major depression were drug-naïve or free of antidepressant medications for at least 2 weeks prior to the study to remove medication effects as a possible confound. Mean age of onset for major depressive disorder was 49.3 years old (s.d. = 10.12).

Thirty-eight healthy control subjects (HC) were recruited from the community using local advertising, of which 32 had complete neuropsychological and neuroimaging data. These subjects represent a sample selection that overlap with subjects whose recruitment details and characteristics have been described in previously published studies from our group (Ajilore et al., 2007).

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 ms; echo time = 6 ms; 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).

Hippocampal volume measurements were obtained using automated segmentation by the Freesurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). Details of the procedure used by the Freesurfer program have previously published (Fischl et al., 2002; Fischl et al., 2004). Briefly, this processing includes motion correction of volumetric T1 weighted images, removal of non-brain tissue, automated Talairach transformation, and segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002; Fischl et al., 2004). Automated segmentation results were manually reviewed for any gross abnormalities or processing errors. There was no significant difference between left and right hippocampal volumes (repeated measures ANCOVA, $p=.833$) thus they were averaged and normalized using intracranial volume.

Neuropsychological Battery

All study subjects completed a comprehensive neuropsychological battery originally described in Watari et al. (Watari et al., 2006). Briefly, the battery included tasks that assessed the cognitive domains of language, visuospatial processing, verbal and non-verbal learning and memory, attention and executive function. For this study, we focused on the California Verbal Learning Tests (CVLT; (Delis et al., 2000)), a measure of learning and memory. The CVLT is a 16-item 5-trial list learning task with free and cued recall assessed immediately and after a 15-20 minute delay. The variable of interest for this study was the total number of recalled words across the five learning trials (CVLT total score; max score=80).

Statistical Analysis

Demographic and clinical variables were analyzed using a one-way analysis of variance for continuous variables and chi-squared test for categorical variables. Between-group performance differences on the CVLT were investigated using an analysis of covariance (ANCOVA) adjusting for age, gender, and education. Likewise, between-group differences for hippocampal volume, normalized using intracranial volume, were assessed by ANCOVA using age and gender as covariates. To assess whether hippocampal volume predicted verbal list learning performance, we used a stepwise linear regression with CVLT Trial1-5 total

learning score as the dependent variable and age, gender, education, systolic blood pressure, stroke risk (minus age), Hgb A1C and normalized hippocampal volume as independent variables. Given that executive functioning and white matter volume have been known to be altered in diabetes and depression (Watari et al., 2006) and may underlie learning and memory impairment (Elderkin-Thompson et al., 2007), a secondary analysis was performed to examine if executive function and total cerebral white matter volume influenced memory performance. Executive function was measured using a composite score (z-score) from the following cognitive tests chosen on a conceptual basis with a Cronbach α of 0.80: the WAIS-III Letter-Number Sequencing, Matrix Reasoning, Wisconsin Card Sorting Test, Stroop Test, Trail Making Test B, Verbal Fluency Task, and the Ruff Figural Fluency Task (Watari et al., 2006). Total cerebral white matter was normalized using intracranial volume.

Results

Clinical and demographic measures

DD subjects performed significantly worse than healthy control subjects on the CVLT (Fig. 1). Cohen's d for differences between HC and DC subjects was .71 and .81 for differences between HC and DD subjects, suggesting a robust effect size despite relatively small sample sizes. While subjects with type 2 diabetes also did poorly compared to healthy controls, the difference was not statistically significant. All subjects with diabetes (regardless of co-morbid depression) had significantly higher HgbA1c values and stroke risk profiles compared to healthy control subjects (Table 1). Systolic blood pressure was significantly higher in DD subjects compared to healthy controls. There was no significant difference in age, gender, education, or hippocampal volume between the three subject groups.

Regression analysis

Hippocampal volume was a significant predictor of performance on the CVLT in healthy control subjects, while hippocampal volume and age were significant predictors in subjects with type 2 diabetes alone. In DD subjects, only age was a significant predictor of performance on the CVLT (Table 2). A secondary analysis revealed that entering executive function z-scores or total normalized cerebral white matter volume into the linear regression model did not alter the pattern of results in any of the three subject groups.

Discussion

This is the first study to assess the combined impact of type 2 diabetes and major depression on hippocampal structure and function. In our study sample, the combination of type 2 diabetes and major depression significantly impaired learning and memory on the CVLT when compared to the absence of both disorders. In healthy control subjects and subjects with type 2 diabetes alone, hippocampal volume predicted performance, with larger hippocampal volumes associated with better verbal list recall. In the diabetic depressed group, only age was a significant predictor of performance with younger age associated with better verbal list recall demonstrated by a standardized beta of $-.578$. The findings of the present study extend previous studies examining the relationship between the hippocampus

and memory in major depressive disorder into a combined depression and diabetes population.

It has been shown that subjects with major depression fail to activate the hippocampus during a verbal memory encoding task in comparison to healthy control subjects (Bremner et al., 2004). In addition, recent work published by Fairhall and colleagues demonstrate that the relationship between hippocampal activation and successful memory encoding was dysregulated in subjects with major depressive disorder using functional magnetic resonance imaging (Fairhall et al., 2010). The extent to which these findings would be exacerbated in type 2 diabetes and depression has been unclear; however, results of our current study suggests that learning and memory is differentially impaired when these disorders are combined.

The finding that age significantly contributed to performance only in the presence of diabetes and was the sole predictor of performance in the depressed diabetic sample when compared to same-aged healthy controls suggests the possibility of exaggerated cognitive aging in the presences of diabetes and accelerated decline when diabetes is combined with depression. This may be due in part to possible neuropathological contributors of each disorder including white matter damage, not assessed in the study. For example, a recent review suggests that depression might represent accelerated cellular aging, reflected in abnormalities in cortisol, neurotrophic factors, oxidative damage, and telomere length (Wolkowitz et al., 2010). Diabetes may play a role in brain aging as well. Although insulin receptors are present throughout the central nervous system, they predominate in such regions as the hippocampus and the prefrontal cortex (Craft, 2009); two regions known to show relatively greater change with age that may be further exacerbated by alterations in insulin signaling and receptor function (Raz, 2011). For example, insulin and insulin signaling pathways also inhibit the phosphorylation of tau (Craft, 2009), the main constituent of neurofibrillary tangles which correlate best with cognition in pathological aging. Future studies are needed to assess these links more closely.

Despite our sample's relatively young age, their diabetic status combined with their depression may be negatively impacting hippocampal functioning through increased age-related deposition of A β and increased levels of stress hormones such as cortisol. Preliminary work related to the presence of the ϵ 4 allele in diabetes (Peila et al., 2002) provides initial support for this possibility; however, future studies are needed that incorporate these various genetic, neuropathologic and endocrine markers into studies designed to understand the structural and functional alterations associated with type 2 diabetes and major depression in isolation as well as in combination.

One of the main limitations of the study is the relatively small sample size for the three subject groups. The sample size may not have been large enough to detect statistically significant differences between subjects with type 2 diabetes alone and the other two subject groups. However, despite the sample size issues, the effect sizes for CVLT performance differences were quite large, .71 and .81 for DC and DD subjects, respectively. Sample size issues may also contribute to insufficient power to detect the relationship between predictor variables and CVLT performance. For example, in our regression model, executive function

was not a significant predictor of CVLT performance despite being significantly correlated with CVLT performance ($r = .49$, $p < .001$). An additional limitation of the current study is the lack of a depression only subject group. While the addition of this group which would have helped to have elucidate whether DD subjects simply reflected the effect of depression or an additive effect of depression and diabetes, we feel the results of the present study adds to our understanding of the synergistic (and negative) impact of combined diabetes and major depression on cognition.

Unlike previous studies, subjects with diabetes (either with or without depression) did not demonstrate hippocampal atrophy when compared to healthy controls; furthermore the combination of diabetes and depression did not impact hippocampal volume when compared to diabetes alone. This non-significant finding may be due in part to age and/or severity of diabetes. Previous studies demonstrating hippocampal atrophy associated with type 2 diabetes predominately featured older subjects aged 60 and older; our subjects ranged in age from 36 to 84 (mean age = 55.5). Thus, differences in the present findings when compared to previous reports of hippocampal atrophy associated with diabetes regardless of depression may be attributable to the younger age of our study population and the fact that potential structural changes have not had time to evolve in our sample. In addition, subjects with diabetes for the present study were recruited from an endocrinology clinic and had relatively well-controlled diabetes which may have mitigated its impact (Ajilore et al., 2007). However, despite this, we still observed a modulation of hippocampal involvement in memory performance as a function of disease status.

Conclusions

In summary, subjects with type 2 diabetes and major depression had significantly poorer performance on the CVLT compared to healthy controls. Subjects with type 2 diabetes alone also did poorly but did not differ significantly from healthy controls or DD subjects. In addition, the relationship between hippocampal volume and performance on the CVLT is decoupled in subjects with type 2 diabetes and major depression. Future studies are planned to address to what degree is this effect attributable to major depression alone or a synergistic relationship between depression and diabetes as it relates to neuropathologic, endocrine, or genetic components of both disorders. Additionally, capitalizing on recent advances in functional connectivity and network analysis will be helpful to ascertain how functional alterations in hippocampally mediated cognitive processes may (or may not) be explained by hippocampal connections to other key neuroanatomical structures, such as the prefrontal cortex and the parietal lobe, when type 2 diabetes and major depression are combined.

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Key Points

- This study combines neuroimaging with cognitive performance in patients with type 2 diabetes
- This is the first study to show an alerted relationship between hippocampal volume and learning/memory performance in patients with type 2 diabetes with and without major depression.
- This work has implications for the impact of depression on older patients with diabetes who are at higher risk of developing cognitive dysfunction.

Figure 1.

CVLT performance by group: Diabetic depressed subjects had significantly poorer performance compared to healthy control subjects ($F = 5.16$, $p = .008$; pairwise comparisons are indicated in the figure). Diabetic non-depressed subjects also did poorly compared to healthy control subjects, but they did not significantly differ with either healthy control subjects or diabetic depressed subjects.

Figure 2. Hippocampal volume by group. There was no significant difference in hippocampal volumes ($F = 1.613$, $p = .205$)

Table 1

Subject Characteristics

		Healthy Control (HC)	Diabetic Controls (DC)	Diabetic Depressed (DD)		
		n = 32	n = 24	n = 20	χ^2	p
Gender	Male	9	9	4	1.643	0.44
	Female	23	15	16	F (df = 2)	p
Age (years)		53.47 (10.34) [36 - 80]	58.88 (8.32) [43 - 71]	54.8 (10.71) [38 - 84]	2.14	0.125
Education (years)		15.81 (3.04) [12 - 25]	14.54 (2.96) [6 - 21]	14.4 (3.07) [6 - 20]	1.81	0.171
HgbA1c (% ,mmol/mol)		5.45 (.42) 36 (5)	7.09 (1.1) 54 (12)	7.52 (1.6) 59 (17)	24.91	<.0001
		[4.5 – 6.5] [26 – 48]	[5.2 – 9.4] [33 – 79]	[5.5 – 11.4] [37 – 101]		
Diabetes Duration (years)			9.75 (7.8) [1 – 29]	8.80 (7.6) [1 – 30]	.166	.686
Systolic Blood Pressure		123.91 (16.02) [99 – 172]	131.92 (16.95) [103 – 164]	138.60 (19.21) [104 – 177]	4.636	.013
Stroke Risk P		3.16 (2.6) [0 – 10]	8.83 (3.2) [3 – 18]	9.90 (4.1) [4 – 22]	33.69	<.0001
Beck Depression Score		1.34 (1.6) [0 – 6]	2.75 (2.6) [0 – 8]	24.4 (10.9) [7 – 51]	106.68	<.0001
Hippocampal Volume (mm ³ /cm ³)		2.79 (.30) [2.06 - 3.36]	2.83 (.37) [2.26 – 3.41]	2.94 (.33) [2.26 – 3.57]	1.613	0.205
CVLT Total Score		54.88 (10.99) [34 – 73]	47.46 (9.93) [27 – 64]	46.95 (8.32) [30 – 64]	5.156	0.008
Executive Function z-score		0 (.44) [–1.09 – .85]	–.26 (.45) [–1.06 – .66]	–.51 (.66) [–1.61 – .54]	5.89	.004
Total Cerebral White Matter Volume (mm ³ /cm ³)		145.43 (9.99) [119 – 165]	147.49 (12.16) [122 – 166]	146.95 (11.68) [124 – 169]	.257	.774

Table 2

Linear regression analysis

Group	Predictor Variable	R ²	Standardized β	<i>t</i>	<i>p</i> value
Healthy Control	Step 1	.310			
	- Hippocampal volume		.557	3.419	.002
Diabetic Control	Step 1	.428			
	-Age		-.654	-4.06	.001
	Step 2	.588			
	-Age		-.518	-3.50	.002
	- Hippocampal volume		.423	2.86	.009
Diabetic	Step 1	.334			
Depressed	-Age		-.578	-2.918	.01