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Emotional and neutral declarative memory impairments and associated white matter microstructural abnormalities in adults with type 2 diabetes

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ABSTRACT

Declarative memory impairment is frequently reported among adults with type 2 diabetes mellitus (T2DM), who also demonstrate hippocampal volume reduction. Our goals were to ascertain whether emotional memory, which is mediated by neural circuits overlapping those of declarative memory, is also affected. In addition we wanted to characterize cerebral white matter (WM) involvement in T2DM. We studied 24 middle-aged and elderly patients with T2DM who were free of obvious vascular pathology or a psychiatric disorder, and 17 age- and education-matched healthy individuals with no evidence of insulin resistance. We examined emotional and neutral memory and performed a whole-brain voxelwise WM assessment utilizing diffusion tensor imaging (DTI). We found clear evidence of impairment in declarative memory among diabetic subjects and in addition found some preliminary support to suggest a possible blunting of the memory facilitation by emotional material among female but not male diabetics. This report is also the first DTI assessment among individuals with T2DM, which after accounting for overt WM damage, revealed diffuse but predominantly frontal and temporal WM microstructural abnormalities, with extensive involvement of the temporal stem. Hierarchical regression analyses demonstrated that immediate, but not delayed, emotional memory performance was explained by temporal stem FA, independent of age, poor metabolic regulation, and systolic blood pressure. Given that the temporal lobe memory networks appear to be particularly vulnerable to the deleterious effects of T2DM, this may help explain the observed memory impairments among diabetics. Future efforts should better clarify, with a larger sample, whether emotional memory is affected in adults with T2DM and whether there are clear gender effects.

1. Introduction

Type 2 diabetes mellitus (T2DM), in addition to its recognized associated complications such as stroke, retinopathy, microvascular abnormalities, and neuropathy (e.g., Stumvoll et al., 2005), is also linked to cognitive dysfunction (e.g., Strachan et al., 1997; Ryan and Geckle, 2000), with recent or declarative memory being the cognitive domain most frequently affected (e.g., Grodstein et al., 2001; Gold et al., 2007). We have reported declarative memory impairments (Bruehl et al., 2007) and associated hippocampal volume reduction in late middle-aged and elderly patients with T2DM (Gold et al., 2007). To date, no studies have examined whether emotional declarative memory is also affected in patients with T2DM.

Emotional arousal is known to enhance memory processing via interactions between amygdala and various memory systems such as working memory (dorsolateral prefrontal region) and declarative memory system (medial temporal lobe (MTL); McGaugh, 2002). Volume reductions of MTL structures, including the hippocampus and amygdala, have been reported in T2DM independent of atherosclerosis (den Heijer et al., 2003), hypertension and dyslipidemia (Gold et al., 2007) even in individuals with well controlled diabetes of relatively short duration (Gold et al., 2007). The MTL structures, and in particular the hippocampus, have been shown to be highly vulnerable to damage (e.g., Cervos-Navarro and Diemer, 1991; Convit et al., 2003), and although the number of reports remains relatively small, it appears that they are affected by the metabolic dysregulation present in T2DM (Convit et al., 2003). This report represents a first attempt to ascertain whether emotional declarative memory, which is highly dependent on the MTL, is also affected in T2DM.

The reports of MTL abnormalities in T2DM have primarily come from gray matter (GM) volumetric assessments; however, the status

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of the MTL white matter (WM) remains unclear. WM assessment in T2DM has predominantly focused on gross overt structural changes (i.e. whole-brain WM lesion volume), which is often accomplished using semi-quantitative methods (van Harten et al., 2006; Manschot et al., 2007). Thus, in the present study, we concentrated on WM assessment utilizing a more sensitive MR technique, diffusion tensor imaging (DTI). To quantify WM microstructural integrity, we used fractional anisotropy (FA; Basser and Pierpaoli, 1996). Given the inherent limitations in DTI, namely the spatial distortions inherent in an echo-planar acquisition, this technique would not be adequate to assess the integrity of relatively small fiber tracts that are relevant to recent memory functions such as the angular bundle, hippocampal-amygdala-transitional area (HATA), and the mamillothalamic tract. Consequently, in this first effort, we concentrated on characterizing the extent of brain microstructural integrity involvement and in particular the involvement of the temporal stem, a relatively large and dense fiber tract that mediates information between the temporal lobe and other parts of the brain, including the frontal lobe, thalamus, and the limbic system (Kier et al., 2004).

We hypothesized that relative to age-matched non-diabetic controls, diabetics would perform worse on both neutral and emotional declarative memory. Given that the existing literature supports memory enhancement for emotional stimuli (e.g., Berrin-Wasserman et al., 2003), we anticipated that both diabetics and controls would have better memory performance for emotional than for neutral material, but that individuals with diabetes may show a blunting of the difference between emotional and neutral memory. In addition, given the extensive literature demonstrating stronger memory facilitation by emotional material among females (review in Hamann, 2005), we conducted exploratory analyses to ascertain whether females with diabetes were more affected than males with diabetes. Furthermore, we hypothesized that relative to non-insulin resistant controls, individuals with T2DM would have reduced fractional anisotropy (FA) values in the fronto-temporal regions known to be central to memory processing, with the temporal stem particularly affected. After controlling for the variables that could influence memory performance (age, peripheral glucose control, and hypertension), we assessed the strength of the associations between temporal stem FA and both emotional and neutral memory performance.

2. Methods

2.1. Subjects

We examined 24 middle-aged and elderly patients with T2DM (11F/13M) and 17 non-insulin resistant controls (9F/8M) comparable in age and education (see Table 1). All subjects had a minimum of a high-school education and no functional deficits. Diabetic subjects fulfilled criteria for T2DM and were referred by collaborating endocrinologists, responded to advertisements on the web and in local periodicals, or were participating in our longitudinal aging studies. Control subjects were selected so as not to have significant insulin resistance, as demonstrated by a Quantitative Insulin Sensitivity Check Index (QUICKI) score of 0.35 or above (Katz et al., 2000). Data included medical, endocrine, psychiatric, neuropsychological, and brain MRI assessments during a comprehensive 8-hour evaluation completed over 3 visits. All participants were free of psychiatric illness, such as depression, significant vascular disease (Hachinski score less than 3; Hachinski, 1983), or significant WM disease (score of 2 or below on the modified Fazekas Scale; Scheltens et al., 1993), and to avoid the possible confounding effects of hypoglycemic episodes, we selected individuals with T2DM with no history of insulin treatment. The protocol was approved by the NYU School of Medicine IRB, and written informed consent was obtained from all participants.

Table 1
Demographics and endocrine data.

	T2DM ($n=24$)	Controls ($n=17$)			
	Mean ± SD	Mean ± SD	t	P	Effect size
Age (years)	57.21 ± 8.05	56.44 ± 6.94	−0.32	0.75	−0.10
[a]Education (years)	15.29 ± 2.76	16.06 ± 1.75	1.09	0.28	0.32
Diabetes duration (years)	7.94 ± 5.64				
[a,b]BMI (kg/m^2)	32.13 ± 5.96	24.09 ± 3.69	−5.33	<0.0001	−1.56
[b]Systolic BP (mm Hg)	120.38 ± 12.46	111.00 ± 11.48	−2.45	0.02	−0.78
Diastolic BP (mm Hg)	70.96 ± 6.80	68.24 ± 6.16	−1.31	0.20	−0.42
QUICKI score	0.31 ± 0.03	0.39 ± 0.04	7.68	<0.0001	2.46
[a,b]Insulin (pmol/l)	15.35 ± 10.48	5.65 ± 2.35	−4.38	<0.0005	−1.18
[a,b]Glucose (mmol/l)	142.46 ± 55.28	78.71 ± 7.23	−5.58	<0.0001	−1.49
[a,b]HbA$_{1C}$ (%)	7.83 ± 1.88	5.37 ± 0.42	−6.18	0.00	−1.67
Cholesterol	177.92 ± 39.68	193.24 ± 34.45	1.28	0.21	0.41
[b]HDL (mmol/l)	42.54 ± 13.26	52.71 ± 12.15	2.50	0.02	0.79
LDL (mmol/l)	110.04 ± 33.71	120.35 ± 31.54	0.98	0.33	0.31
[a]Triglycerides (mg/dl)	146.54 ± 109.86	101.06 ± 44.37	−1.61	0.12	−0.51
Fibrinogen (mg/dl)	339.00 ± 46.76	328.71 ± 58.30	−0.63	0.53	−0.20

[a] Adjusted for unequal group variances.
[b] $P<0.05$.

2.2. Hypertension diagnosis

Sitting blood pressure (BP) was determined by averaging two readings obtained during the second visit: 30 min after arrival and at the end of that evaluation. Subjects were classified as hypertensive if they received anti-hypertensive treatment, or had a sitting BP above the NCEP cut-off (a systolic BP ≥ 130 mm Hg or a diastolic BP ≥ 85 mm Hg).

2.3. Neuropsychological evaluations

For the Emotional Memory Test (EMT; Boller et al., 2002), the subject was read one emotional (a woman in a park who attempted to help a man before he committed suicide) and one neutral paragraph (a woman who was waiting for her sister at a restaurant), each containing 48 embedded facts. Recall of the paragraphs was tested immediately and 15 min after the administration. Additional tests used for assessing neutral declarative memory were the California Verbal Learning Test (CVLT; Delis et al., 1987) and the logical memory subtest of the Wechsler Memory Scale — Revised (WMS-R; Wechsler, 1987). The Shipley Institute of Living Scale (Zachary et al., 1985) was used to estimate overall intellectual functioning.

Given that memory performance may be confounded by the presence of frontal lobe abnormalities, we also administered tests targeting frontal lobe functions such as working memory, sustained attention, and verbal fluency. Working memory was tested with the Digit Span Backwards subtest from the WMS-R. The WAIS-R Digit Symbol Substitution Test (DSST; Wechsler, 1981) and the Digit Vigilance Test (Lewis and Rennick, 1979) were used to assess complex attention. Verbal fluency was tested with the Controlled Oral Word Association Test (Benton et al., 1983).

2.4. MR image acquisition

All subjects were studied on the same 1.5 T Siemens Avanto MRI System. One control and one diabetic subject had missing MR scans, and the DTI image of one diabetic subject was excluded from the analysis due to extensive spatial distortions secondary to movement during the acquisition. T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR 1300 ms; TE 4.38 ms; TI 800 ms; FOV 250 × 250; 196 slices; slice thickness 1.2 mm; NEX 1; Flip angle 15°)