Published in final edited form as:

Psychiatry Res. 2009 December 30; 174(3): 223–230. doi:10.1016/j.psychres.2009.04.016.

Emotional and Neutral Declarative Memory Impairments and Associated White Matter Microstructural Abnormalities in Adults with Type 2 Diabetes

Po Lai Yau^{a,b}, David Javier^a, Wai Tsui^{a,c}, Victoria Sweat^a, Hannah Bruehl^a, Joan C. Borod^b, and Antonio Convit^{a,c,*}

^a Department of Psychiatry, New York University School of Medicine, New York, NY 10016

^b Neuropsychology Doctoral Subprogram, Department of Psychology, Queens College and The Graduate Center, City University of New York, New York, NY, 10016

^c Nathan Kline Institute for Psychiatric Research, Orangeburg, NY 10962

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.

Keywords

T2DM; Emotional Memory; Diffusion Tensor Imaging (DTI); Temporal Stem; Fractional Anisotropy (FA)

*Corresponding Author: Antonio Convit, M.D., Millhauser Laboratories, HN-400, New York University School of Medicine, 550 First Avenue, New York, NY 10016, 212 263-7565 (phone), 212 263-3270 (fax), Email: antonio.convit@med.nyu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Type 2 diabetes mellitus (T2DM), in addition to its recognized associated complications such as stroke, retinopathy, microvascular abnormalities, and neuropathy (e.g., , is also linked to cognitive dysfunction (e.g., , with recent or declarative memory being the cognitive domain most frequently affected (e.g., . We have reported declarative memory impairments and associated hippocampal volume reduction in late middle-aged and elderly patients with T2DM. 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, hypertension and dyslipidemia even in individuals with well controlled diabetes of relatively short duration. The MTL structures, and in particular the hippocampus, have been shown to be highly vulnerable to damage (e.g., , and although the number of reports remains relatively small, it appears that they are affected by the metabolic dysregulation present in T2DM. 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 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. 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.

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., , 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. 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; 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.

2.2 Hypertension Diagnosis

Sitting blood pressure (BP) was determined by averaging two readings obtained during the second visit: 30 minutes 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 cutoff (a systolic BP ≥ 130 mmHg or a diastolic BP ≥ 85 mmHg).

2.3 Neuropsychological Evaluations

For the Emotional Memory Test (EMT; 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 minutes after the administration. Additional tests used for assessing neutral declarative memory were the California Verbal Learning Test (CVLT; and the logical memory subtest of the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987). The Shipley Institute of Living Scale 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.

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°) was utilized for structural imaging and acquired in the coronal plane. A T2-weighted sequence (TR 9000 ms, TE 94 ms; TI 2000 ms; FOV $210 \times$

210; 50 slices; slice thickness 3 mm) was used for correcting the DTI images and was collected axially. To rule out primary neurological disease and to quantify WM disease utilizing the modified Fazekas Scale, fast fluid-attenuated inversion recovery (FLAIR; TR 9000 ms; TE 97 ms; FOV 210×210 ; 1 average and 2 concatenations; Flip angle 145°) image was used together with the MPRAGE. A DTI echo planar sequence (TR 6100 ms; TE 75 ms; delay in TR = 0; b values 0, 1000; 6 directions; FOV 210×210 ; 4 averages and 1 concatenation; 50 axial slices; voxel size $1.64 \times 1.64 \times 3 \text{ mm}^3$) was acquired, which was standardized at a scan angle parallel to a line drawn between anterior and posterior commissure (AC-PC line). To optimize image co-registration, the DTI, T2-weighted, and FLAIR images were acquired in the same orientation, slice number, and thickness.

2.5 Analyses of the Diffusion Tensor Imaging Data

2.5.1 DTI Voxelwise Image Processing and Analysis (VANCOVA)—The goal of these analyses was to correct for spatial distortions in the FA maps, register to a target MPRAGE image (voxel size $1 \times 1 \times 1 \text{ mm}^3$) reformatted in the axial plane in Talairach space, and create group maps for whole brain voxelwise comparisons. Intrasubject and intersubject registrations were performed utilizing an in-house software Multi-modal Imaging Data Analysis System (MIDAS) and the Automated Registration Toolkit 2 (ART2) software developed at the Nathan Kline Institute (NKI).

First, we manually skull-stripped the structural native MPRAGE image, which was then spatially normalized to the target image using a 3D non-linear warping algorithm. This step yielded a 3D warp field containing transformation parameters necessary for spatial normalization of the FA maps. *Second*, a rigid-body linear transformation was used to optimize the T2-to-MPRAGE registration. We re-sliced the native MPRAGE image to match the T2 image in orientation, number of slices, FOV, and voxel size, which yielded the first 4×4 transformation matrix. A second transformation matrix was produced by iteratively correcting for registration errors due to subject motion. We multiplied the two matrices and the product was then inverted to produce the final T2-to-MPRAGE transformation matrix. *Third*, with a non-linear 2D warping algorithm developed by Ardekani, the *b0* image was iteratively warped to correct for spatial distortions using the skull-stripped T2 image as a guide, which produced a 2D warp field containing distortion correction and spatial transformation information. *Fourth*, the FA values were computed, and overlay maps were generated from the native DTI images using algorithms described in Basser and Pierpaoli (1998) and Basser (1995). *Finally*, to reduce interpolation errors, we combined the three transformations from the previous steps into one single transformation, which was applied to spatially correct and normalize the FA maps.

Group images created from the spatially corrected and normalized FA maps were subjected to a two-tailed voxelwise analysis of covariance (VANCOVA), with age as a covariate. To control for WM hyperintensities, we used the FLAIR image as a covariate, which was normalized to the target template by applying the same transformation parameters that had been applied to the FA maps. A white matter mask created from the average MPRAGE image of all subjects was used to confine FA analysis within WM regions. There were 3 cases (1 control and 2 diabetics) with extensive spatial distortions on a few of the lowest brain sections but with good quality data for sections through and above the gyrus rectus. To ensure that our results were not driven by data contamination from miscoregistration due to the distortion on those three cases, we conducted one analysis using all cases but restricting the data to slices at or above the gyrus rectus and a second analysis excluding those 3 cases but utilizing the complete brain, namely also including those below the gyrus rectus.

2.5.2 Region of Interest (ROI) Placement—To examine associations between memory and WM integrity of the temporal stem, an *a priori* region of interest, we derived the FA values for the temporal stem using an ROI-based method, which is operationally standardized, anatomically based, and done at the case level. FA maps were generated from the distortion corrected *b0* image (see algorithms described above in steps 3 and 4 of the voxelwise analysis). So as to avoid placement bias inherent in placing the ROIs directly on the FA maps, ROIs were drawn using MIDAS on the *b0* image with the co-registered T2 and FLAIR images as anatomical guides. To standardize the ROI placement, the raters, blind to diabetes diagnosis, first identified the section where the cerebral peduncle first merges with the internal capsule (See Figures 1a). *Second*, the ROIs were placed 2 and 3 slices inferior to this plane, namely 6 and 9 mm inferior (see Figure 1b and 1c). *Third*, on the two sections chosen, square-shaped ROIs, nine voxels in size, were drawn bilaterally, and placed laterally and just posterior to the interpeduncular fossa (see green squares in Figures 1b & 1c). *Fourth*, to minimize contamination, in addition to placing the ROI in the middle of the in-plane WM region, we checked the ROI in the orthogonal planes and also the sections immediately above and below to ensure that the ROI was not abutting a CSF space or GM. We then averaged the left and right temporal stem ROIs across the two sections, which yielded an ROI with an overall volume of 0.29 cc.

2.6 Statistical Analysis

Two-tailed independent samples *t*-tests were conducted to examine group differences in demographics, endocrine data, cognitive data, and white matter FA (ROI-based analysis). Chi-square tests were used for nominal variables, including gender and ratings of periventricular and deep WM hyperintensities. To ascertain whether the anticipated blunting of the facilitative effect of emotional material on declarative memory was stronger among female diabetics, we performed an exploratory analysis using two-way mixed ANOVAs to examine interaction effects by gender with group (diabetics vs. controls) and memory condition (emotional vs. neutral) as the factors, for immediate and delayed recall, respectively.

To minimize the chance of making Type I errors in the DTI VANOVA analysis, we reduced the number of multiple comparisons by restricting the accepted cluster size to those having at least 100 contiguous voxels (equivalent to at least 0.1 cc in volume) and then by choosing a false discovery rate (FDR) less than 0.01. Using the algorithm previously described in Benjamini and Hochberg (1995), we chose a *p*-value threshold of 0.005 to ensure that the FDR would be kept below 0.01.

Bivariate correlation analyses were conducted to examine relationships among EMT measures that separated the groups, age, systolic and diastolic blood pressure, QUICKI, and temporal stem FA. We conducted a hierarchical regression analysis for each of these EMT measures. In each model, we examined the unique effect of temporal stem FA on memory performance (Step 3) after accounting for age in Step 1 and the QUICKI score and systolic BP as a block in Step 2.

Any subject with a value of 3 or more standard deviations from the group mean was considered an outlier and excluded in the analysis of that particular variable.

3. Results

3.1 Descriptive and Endocrine Data

The groups were comparable in age, years of education, and gender (Table 1). Diabetics varied widely in the length of time from diagnosis, ranging from weeks to decades. Relative to controls, diabetics had significant elevations in fasting glucose ($t[24] = -5.58, P < 0.0001$),

fasting insulin ($t[26] = -4.38, P < 0.0005$), glycated hemoglobin (HbA_{1c}; $t[26] = -6.18, P < 0.0001$), and reductions in HDL ($t[39] = 2.50, P = 0.02$; see Table 1). Diabetics had higher levels of triglyceride and fibrinogen but lower LDL and total cholesterol levels than controls (likely due to the higher use of statins among diabetics), none of which reached statistical significance. Relative to controls, individuals with T2DM had significantly higher body-mass-index (BMI; $t[38] = -5.33, P < 0.0001$) and systolic blood pressure ($t[39] = -2.45, P = 0.02$), but not diastolic blood pressure. Sixteen diabetics (8 females and 8 males) and two controls (both females) were hypertensive; all but one control subject were treated pharmacologically for their hypertension.

3.2 Neuropsychological Results

The groups had comparable IQ scores within the normal range. Congruent with our predictions, diabetic subjects performed consistently worse than controls on all measures of declarative memory, with effect sizes mostly being medium to medium large and group differences at least marginally significant in four of the ten measures (Table 2). Significantly lower scores were observed among diabetics in both immediate ($t[39] = 2.13, P = 0.04$) and delayed ($t[38] = 2.12, P = 0.04$) recall of the emotional paragraph, and a non-significant trend was observed in delayed recall of the neutral paragraph ($t[38] = 1.90, P = 0.06$) (Figure 2). Group differences also approached statistical significance on the CVLT short delay free recall ($t[38] = 1.94, P = 0.06$).

Consistent with our expectations, the two-way mixed ANOVAs revealed weak to moderate interaction effects between group and memory type among women (immediate, ($F[1, 18] = 0.81, P = 0.38$; delayed $F[1, 18] = 1.91, P = 0.18$). Although these interaction effects were non-significant, the results descriptively suggest that female diabetics when compared with female controls showed no discernible memory enhancement for emotional materials in both recall conditions. As expected, the interaction effects were less strong among the male subjects. To provide graphic support for the hypothesized gender effect on emotional memory among diabetics, we have included below Figures 3a and 3b, which showed no discernible difference between emotional and neutral memory among female diabetics, whereas male diabetics did show some enhancement in both recall conditions.

The groups were comparable in working memory, attention as measured with the DSST, and verbal fluency (see Table 2). On the Digit Vigilance Test, however, diabetics had a significantly slower response time than controls ($t[33] = 2.02, P = 0.05$). Given the differences in sustained attention between the groups, we repeated the group comparisons on the memory measures, controlling for the response time on the Digit Vigilance test, and the results remained unchanged.

3.3 DTI Analysis Results

The chi-square tests yielded no group differences on ratings of periventricular or deep WM hyperintensities. However, the DTI results from both VANOVA and ROI-based analyses revealed significant cerebral WM microstructural alterations among diabetics.

In the VANOVA analysis, we identified a total of 12 clusters, eleven of which showed significant FA reductions among diabetics, independent of age and signs of WM hyperintensities. Although these 11 clusters were found in all four lobes, the majority of them were concentrated in the frontal and temporal regions, and the largest was located in the left temporal stem (see Table 3 and Figure 4 for the top six clusters by size). The single cluster showing significant FA elevations in the diabetic group had substantial partial volume contamination from neighboring ventricular CSF. After excluding the three cases with extensive distortions, the second analysis produced no additional clusters on the image slices below the gyrus rectus.

Consistent with the results from our voxelwise analysis, ROI-based analysis revealed that relative to controls, diabetics had significant reductions in temporal stem FA ($t[36] = 2.16$, $P = 0.04$).

3.4 Regression Models Predicting Memory Performance

Bivariate correlation results demonstrated that the measures of declarative emotional and neutral memory that separated the groups correlated positively with the QUICKI (higher QUICKI score indicates better insulin function) score and temporal stem FA (see Figure 5 for scatterplots depicting associations between emotional memory and temporal stem FA) and negatively with systolic BP (Table 4). Please note that age was not associated with any of the measures included in the regression analyses, and that temporal stem FA had no discernible correlation with age, QUICKI score, or systolic BP. Additionally, diastolic BP only correlated weakly with the memory measures and was therefore excluded from the regression analyses.

When the immediate recall of the emotional paragraph was used as the dependent variable, the hierarchical regression model accounted for 33.4% of the variance in memory performance ($F[4, 31] = 3.87$, $P = 0.01$; see Table 5). Age alone explained only 0.6% of the variance ($P = 0.66$). After controlling for age, QUICKI score and systolic BP together accounted for an additional 22.2% of the variance ($P = 0.02$). Temporal stem FA explained an additional and significant 10.5% of the variance in memory performance above and beyond the effects of age, QUICKI score, and systolic BP ($P = 0.04$; see Table 5). The hierarchical regression models accounted for an overall 25.1% ($F[4, 31] = 2.60$, $P = 0.06$) and 21.5% ($F[4, 31] = 2.12$, $P = 0.10$) of the variance in delayed emotional and neutral memory performance, respectively, but temporal stem FA measures did not contribute to the variance in either of these two memory measures (Table 5).

4. Conclusion

To the best of our knowledge, this is the first report on emotional memory functioning in middle-aged and elderly patients with T2DM. A strength of this report is that our subjects have no obvious signs of vascular pathology or psychiatric disorder. We found clear evidence of emotional memory impairment in T2DM as well as descriptive (albeit non-significant and therefore only tentative) preliminary data suggesting a possible blunting of the facilitative effect of emotional material on both immediate and delayed memory among female diabetics. This possible gender effect remains to be clearly demonstrated in a larger set of subjects.

This report is also the first DTI-based report of subtle WM abnormalities and their associations with declarative memory impairment among adults with T2DM. Consistent with our hypotheses, WM microstructural abnormalities were present among individuals with T2DM and were predominantly located in the frontal and temporal regions, with the left temporal stem being extensively affected. One of the strengths of this report is that the results of our VANCOVA analysis revealed microstructural WM abnormalities even after accounting for overt WM pathology. Secondly, our findings suggest that these microstructural abnormalities in the temporal stem may explain the lower emotional memory performance present among diabetics, even after accounting for age, metabolic dysregulation, and hypertension. Moreover, the fact that our robust findings of temporal stem WM abnormalities were replicated utilizing two independent analysis methods adds some face validity to these findings.

Emotional stimuli, particularly those of negative valence, are known to promote memory processing by, among other mechanisms, heightened arousal and attention (e.g. Kensinger, 2007). Our results showed that after we accounted for the attentional differences, the group differences in emotional and neutral memory remained. Consistent with the literature (e.g., both groups had higher retention for emotional than for neutral verbal materials, but when

examining female diabetics alone, we found no discernible differences between emotional and neutral memory performance. It is therefore possible that our diabetic subjects, particularly the female patients, were less responsive to the arousing effects of the negative emotional content, and this may explain why the group differences were more prominent on emotional than on neutral memory measures. It has been shown that among women, brain activation associated with emotional arousal tends to be left lateralized and that stronger associations are found between emotional memory and activation of the left amygdala (Canli et al., 2002). Whether the observed blunted memory enhancing effects are related to amygdalal dysfunction among these patients remains to be explored.

Left temporal stem FA values were more strongly associated with immediate emotional memory than with the other memory measures. Extrapolating from our DTI findings, it is possible that the suggested microstructural damage in the left temporal stem may hinder the signal transduction that is necessary for mediating the immediate effect of emotion during learning. Alternatively, this lack of consistency may be the result of the sample that we evaluated, where one third of our diabetics had been diagnosed with T2DM of less than 5 years duration, and the relatively young age (below 50) of a subset of these patients. There was also a great deal of variability in the degree of glucose control. Future studies should focus on well controlled patients who have had diabetes for a consistent period of time.

Our results highlight the vulnerability of temporal lobe memory systems to the deleterious effects of T2DM. Although there is a small but growing literature demonstrating brain complications in T2DM, the underlying mechanisms remain poorly understood. MR spectroscopy studies in T2DM have examined the association between elevated HbA1C and reduced metabolism in cerebral WM but the results are inconsistent, with one study showing association and another not. Another possible mechanism may be due to impaired cerebral perfusion and vasomotor reactivity, which has been demonstrated in diabetes and which may result in diminished metabolic substrate delivery, particularly during periods of brain activation, thus contributing to the damage in T2DM (Convit, 2005).

Our results also showed a cluster demonstrating significant FA reductions in the superior temporal WM among individuals with T2DM, and this was located in close proximity to the temporal stem cluster. Whether these two clusters of WM abnormality originate from the same fronto-temporal fiber bundle cannot be established without further investigation. Given that these superior temporal WM fibers may be involved in auditory processing, which is an essential component of our declarative memory tests, this may in part explain the observed memory impairments in our diabetic subjects.

There are a few limitations in the present report. Due to the preliminary nature of the present proof of concept study, we did not control for multiple comparisons. With a larger sample, we hope to better clarify the extent of emotional memory impairment and better characterize whether there are gender effects among individuals with T2DM. Furthermore, it will be important to ascertain whether the possible blunting of emotional valence-mediated memory enhancement is associated with the amygdala volume reductions that have been reported in diabetes. Also of note are the inherent limitations of DTI, namely the spatial distortions inherent in an echo-planar acquisition such as this, which limits the ability to ascertain the integrity of relatively small fiber tracts that are relevant to memory functions and evaluate brain regions that are adjoining CSF (e.g., the fornix and cingulum, both of which play important roles mediating memory functions). Future work should also employ refinements in the imaging methods such as DTI tractography, which would improve the accuracy of sampling and perhaps lead to improved comparability across subjects.

Are the identified abnormalities present during pre-clinical stages of diabetes? Future efforts should include longitudinal evaluations aimed at tracking pathological changes as they transition from the pre-clinical stages into diabetes as well as ascertaining whether these brain and memory abnormalities are reversible with significant improvements in peripheral glucose control.

Acknowledgments

This study was supported by grants DK 064087, P30-AG-08051 and NCRR M01 RR00096.

References

- 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* 2006;32:1224–1231. [PubMed: 17180124]
- Ardekani BA, Braun M, Hutton BF, Kanno I, Iida H. A fully automatic multimodality image registration algorithm. *Journal of Computer Assisted Tomography* 1995;19:615–623. [PubMed: 7622696]
- Ardekani BA, Guckemus S, Bachman A, Hoptman MJ, Wojtaszek M, Nierenberg J. Quantitative comparison of algorithms for inter-subject registration of 3D volumetric brain MRI scans. *Journal of Neuroscience Methods* 2005;142:67–76. [PubMed: 15652618]
- Basser PJ. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR in Biomedicine* 1995;8:333–344. [PubMed: 8739270]
- Basser PJ, Pierpaoli C. A simplified method to measure the diffusion tensor from seven MR images. *Magnetic Resonance in Medicine* 1998;39:928–934. [PubMed: 9621916]
- Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance Series B* 1996;111:209–219. [PubMed: 8661285]
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B (Methodological)* 1995;57:289–300.
- Benton, AL.; Hamsher, K.; Varney, NR.; Spreen, O. *Contributions to Neuropsychological Assessment: A Clinical Manual*. Vol. 1. Oxford University Press; New York: 1983.
- Berrin-Wasserman S, Winnick WA, Borod JC. Effects of stimulus emotionality and sentence generation on memory for words in adults with unilateral brain damage. *Neuropsychology* 2003;17:429–438. [PubMed: 12959509]
- Boller F, El Massioui F, Devouche E, Traykov L, Pomati S, Starkstein SE. Processing emotional information in Alzheimer's Disease: effects on memory performance and neurophysiological correlates. *Dementia & Geriatric. Cognitive. Disorders* 2002;14:104–112.
- Bruehl H, Rueger M, Dziobek I, Sweat V, Tirsi A, Javier E, Arentoft A, Wolf OT, Convit A. Hypothalamic-Pituitary-Adrenal axis dysregulation and memory impairments in type 2 diabetes. *Journal of Clinical Endocrinology Metabolism* 2007;92:2439–2445. [PubMed: 17426095]
- Canli T, Desmond JE, Zhao Z, Gabrieli JDE. Sex differences in the neural basis of emotional memories. *Proceedings of the National Academy of Sciences* 2002;99:10789–10794.
- Cervos-Navarro J, Diemer NH. Selective vulnerability in brain hypoxia. *Critical Reviews in Neurobiology* 1991;6:149–182. [PubMed: 1773451]
- Convit A, Wolf OT, Tarshish C, de Leon MJ. Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. *Proceedings of the National Academy of Sciences, USA* 2003;100:2019–2022.
- Convit A. Links between cognitive impairment in insulin resistance: An explanatory model. *Neurobiology of Aging* 2005;26:31–35. [PubMed: 16246463]
- Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. *California Verbal Learning Test - Research Edition*. The Psychological Corporation; New York: 1987.

- den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, Breteler MMB. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia* 2003;46:1604–1610. [PubMed: 14595538]
- Gold S, Dziobek I, Sweat V, Tirsi A, Rogers K, Bruehl H, Tsui W, Richardson S, Javier E, Convit A. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia* 2007;50:711–719. [PubMed: 17334649]
- Grodstein F, Chen J, Wilson RS, Manson JE. Type 2 diabetes and cognitive function in community-dwelling elderly women. *Diabetes Care* 2001;24:1060–1065. [PubMed: 11375371]
- Hachinski, VC. Differential Diagnosis of Alzheimer's Dementia: Multi-Infarct Dementia. In: Reisberg, B., editor. *Alzheimer's Disease* Free Press. New York: 1983. p. 188-192.
- Hamann S. Sex Differences in the Responses of the Human Amygdala. *The Neuroscientist* 2005;11:288–293. [PubMed: 16061516]
- Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *The Journal of Clinical Endocrinology and Metabolism* 2000;85:2402–2410. [PubMed: 10902785]
- Kensinger EA. Negative emotion enhances memory accuracy: behavioral and neuroimaging evidence. *Current Directions in Psychological Science* 2007;16:213–218.
- Kier EL, Staib LH, Davis LM, Bronen RA. MR imaging of the temporal stem: anatomic dissection tractography of the uncinate fasciculus, inferior occipitofrontal fasciculus, and meyer's loop of the optic radiation. *American Journal of Neuroradiology* 2004;25:677–691. [PubMed: 15140705]
- Lewis, R.; Rennick, PM. *Manual for the Repeatable Cognitive-Perceptual-Motor Battery*. Axon; Grosse Pointe, MI: 1979.
- Manschot S, Biessels G, de Valk H, Algra A, Rutten G, van der Grond J, Kappelle L. on behalf of the Utrecht Diabetic Encephalopathy Study Group. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. *Diabetologia* 2007;50:2388–2397. [PubMed: 17764005]
- McGaugh JL. Memory consolidation and the amygdala: a systems perspective. *Trends in Neurosciences* 2002;25:456–461. [PubMed: 12183206]
- Novak V, Last D, Alsop DC, Abduljalil AM, Hu K, Lepicovsky L, Cavallerano J, Lipsitz LA. Cerebral blood flow velocity and periventricular white matter hyperintensities in type 2 diabetes. *Diabetes Care* 2006;29:1529–1534. [PubMed: 16801574]
- Ryan CM, Geckle MO. Circumscribed cognitive dysfunction in middle-aged adults with Type 2 diabetes. *Diabetes Care* 2000;23:1486–1493. [PubMed: 11023141]
- Sahin I, Alkan A, Keskin L, Cikim A, Karakas HM, Firat AK, Sigirci A. Evaluation of in vivo cerebral metabolism on proton magnetic resonance spectroscopy in patients with impaired glucose tolerance and type 2 diabetes mellitus. *Journal Of Diabetes And Its Complications* 2007;22:254–260. [PubMed: 18413166]
- Scheltens P, Barkhof F, Leys D, Pruvo JP, Nauta JJ, Vermersch P, Steinling M, Valk J. A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *Journal of the Neurological Sciences* 1993;114:7–12. [PubMed: 8433101]
- Strachan MW, Deary IJ, Ewing FM, Frier BM. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care* 1997;20:438–445. [PubMed: 9051402]
- Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *The Lancet* 2005;365:1333–1346.
- van Harten B, de Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ. Brain imaging in patients with diabetes: A systematic review. *Diabetes Care* 2006;29:2539–2548. [PubMed: 17065699]
- Wechsler, D. *WAIS-R manual*. Psychological Corporation; New York, NY: 1981.
- Wechsler, D. *Wechsler Memory Scale-Revised*. Psychological Corporation/Harcourt Brace Javanovich; San Antonio, NY: 1987.
- Zachary RA, Paulson MJ, Gorsuch RL. Estimating WAIS IQ from the Shipley Institute of Living Scale using continuously adjusted age norms. *Journal of Clinical Psychology* 1985;41:820–831. [PubMed: 4078008]

Figure 1. Placement of Manual ROIs in the Temporal Stem

(a) The section where the cerebral peduncle, visible in the midbrain section, first merges with the internal capsule

(b) & (c) ROIs are drawn on the second and third sections inferior to the section shown in (a)

Figure 2. Emotional and Neutral Memory Performance by Disease Group

Diabetics performed consistently worse than controls on both neutral and emotional memory.

Figure 3. Descriptive Interaction between Gender and Memory Type among Diabetics
Female but not male diabetics showed a possible blunting of memory facilitation by emotional material in both (a) immediate and (b) delayed recall conditions.

Figure 4. Clusters Demonstrating Significant White Matter FA Reductions among Diabetics (VANCOVA Analysis Controlling for Age; Minimum Cluster Size of 100 voxels; $p < 0.005$)
 Each column illustrates a significant cluster in 3 orthogonal orientations (axial, coronal, and sagittal) on an average normalized structural image with the axes passing through the centroid of the cluster (the Talairach space coordinates for the clusters are listed on Table 3).

(a) Immediate Recall

(b) Delayed Recall

Figure 5.
Scatterplots of Associations between Emotional Memory Performance and Temporal Stem FA for (a) Immediate and (b) Delayed Recall Conditions

Table 1

Demographics and Endocrine Data

	T2DM (<i>n</i> = 24)		Controls (<i>n</i> = 17)		<i>t</i>	<i>P</i>	Effect Size
	Mean ± SD		Mean ± SD				
Age (yrs)	57.21 ± 8.05		56.44 ± 6.94		-0.32	0.75	-0.10
/ Education (yrs)	15.29 ± 2.76		16.06 ± 1.75		1.09	0.28	0.32
Diabetes Duration (yrs)	7.94 ± 5.64		--		--	--	--
/ * BMI (kg/m ²)	32.13 ± 5.96		24.09 ± 3.69		-5.33	< 0.0001	-1.56
* 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
/ * Insulin (pmol/L)	15.35 ± 10.48		5.65 ± 2.35		-4.38	< 0.0005	-1.18
/ * Glucose (mmol/L)	142.46 ± 55.28		78.71 ± 7.23		-5.58	< 0.0001	-1.49
/ * HbA1C (%)	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
/ * 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
/ 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

* *P* < 0.05

/ Adjusted for unequal group variances

Table 2

Cognitive Data

	T2DM (<i>n</i> = 24) Mean ± SD	Controls (<i>n</i> = 17) Mean ± SD	<i>t</i>	<i>P</i>	Effect Size
Full Scale IQ	106.74 ± 13.00	112.78 ± 12.28	1.50	0.14	0.47
* Emotional Paragraph – Immed.	25.56 ± 5.75	29.53 ± 6.08	2.13	0.04	0.67
Neutral Paragraph – Immed.	23.25 ± 7.27	25.29 ± 7.00	0.90	0.37	0.29
* Emotional Paragraph – Delayed	22.43 ± 5.48	26.59 ± 6.89	2.12	0.04	0.68
† Neutral Paragraph – Delayed	19.35 ± 7.12	23.72 ± 7.09	1.90	0.06	0.61
† CVLT Short Delay Free Recall	11.04 ± 3.26	13.00 ± 2.92	1.94	0.06	0.64
CVLT Short Delay Cued Recall	11.83 ± 2.28	12.94 ± 2.70	1.42	0.16	0.45
CVLT Long Delay Free Recall	11.79 ± 2.64	12.71 ± 3.27	0.99	0.33	0.31
CVLT Long Delay Cued Recall	12.46 ± 2.19	13.24 ± 2.59	1.04	0.31	0.33
WMSR Logical Memory – Immed.	27.29 ± 6.33	29.65 ± 6.71	1.14	0.26	0.36
WMSR Logical Memory – Delayed	22.25 ± 7.70	26.24 ± 7.87	1.62	0.11	0.51
WMSR - Digit Span Backward	7.39 ± 2.29	8.41 ± 2.60	1.32	0.20	0.42
COWA Verbal Fluency - Mean	16.35 ± 4.13	16.01 ± 4.82	0.23	0.82	-0.08
Score (Letters F, S, A)					
Digit Symbol Substitution Test	55.30 ± 12.04	60.41 ± 10.40	1.40	0.17	0.45
† Digit Vigilance Total Time	436.17 ± 56.70	391.92 ± 70.01	-2.02	0.05	-0.72

* $P < 0.05$

† $P < 0.10$

Table 3

Significant Clusters Demonstrating FA Reductions in T2DM ($P < 0.005$)

FA White Matter Clusters	Size (#voxels)	Mean <i>t</i> value (<i>df</i> = 34)	Talairach Coordinates		
			X	Y	Z
Left Temporal Stem	417	-3.33	45	34	-32
Right Prefrontal Region	229	-3.54	-38	-21	-14
Left frontal Temporal Region	216	-3.27	37	43	-13
*Right External capsule	176	-3.86	-30	3	-16
Left Parietal Region	173	-3.69	49	58	12
Left Middle Temporal Region	159	-3.34	54	53	-28

* remained significant at $P < 0.001$

Table 4

Results of Bivariate Correlation

	Age	QUICKI Score	Systolic BP	Temporal Stem FA
Emotional Paragraph - Immediate	-0.14	0.35 [*]	-0.44 [*]	0.39 [*]
Emotional Paragraph – Delayed	0.02	0.45 [*]	-0.13	0.29 [†]
Neutral Paragraph – Delayed	-0.13	0.40 [*]	-0.21	0.28 [†]
Age	--	-0.05	0.10	0.04
QUICKI Score	--	--	-0.36 [*]	0.17
Systolic BP	--	--	--	-0.12

Note: Values displayed are Pearson's r

* P < 0.05

† P < 0.10

Table 5

Predicting Emotional and Neutral Memory by Temporal Stem FA

DV	Age			QUICKI Score & Systolic BP				Temporal Stem FA			
	β	ΔR^2	P	β (QUICKI Score)	β (Systolic BP)	ΔR^2	P	B	ΔR^2	P	
Emotional Paragraph	-0.04	0.01	0.66	19.43	-0.14	0.22	0.02 [*]	49.55	0.11	0.04 [*]	
- Immediate Emotional Paragraph	0.08	0.01	0.60	52.78	-0.01	0.22	0.02 [*]	27.22	0.02	0.33	
- Delayed Neutral Paragraph	-0.03	0.00	0.85	50.86	0.00	0.17	0.05 [*]	41.13	0.05	0.19	
- Delayed											

* $P < 0.05$