Circumscribed Cognitive Dysfunction in Middle-Aged Adults With Type 2 Diabetes

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OBJECTIVE — To examine the extent to which type 2 diabetes is associated with poorer performance on measures of learning, memory, psychomotor speed, and problem-solving in middle-aged adults.

RESEARCH DESIGN AND METHODS — This cross-sectional study evaluated 50 adults (age range 34–65 years, mean 50.8) with type 2 diabetes and 50 demographically similar community control subjects without diabetes. Each subject received a thorough physical examination and a detailed neuropsychological assessment. Factor analysis was used to assign specific tests to 1 of 4 cognitive domains (learning, memory for stories, problem-solving, and psychomotor speed). Hierarchical regression analysis was used to identify demographic and biomedical variables associated with cognitive dysfunction.

RESULTS — Learning, memory, and problem-solving skills were unaffected by type 2 diabetes. In contrast, psychomotor slowing was predicted by a diagnosis of diabetes (r^2 change = 0.075, $P <$ 0.002) with additional variance in psychomotor efficiency explained independently by HbA_1 (r^2 = 0.064, $P < 0.003$) and vibratory threshold (r^2 = 0.112, $P < 0.0001$). The magnitude of psychomotor slowing on specific tests ranged from 12% (Digit Vigilance) to 23% (Grooved Pegboard).

CONCLUSIONS — Middle-aged adults with type 2 diabetes manifest psychomotor slowing that is associated with poorer metabolic control, whereas learning, memory, and problem-solving skills appear to be largely intact. The development of psychomotor slowing may be a manifestation of a "central neuropathy" induced by chronic hyperglycemia.

Diabetes Care 23:1486–1493, 2000

Learning and memory dysfunction is widely believed to be a consequence of type 2 diabetes, particularly in adults ≥65 years of age (1). Case-control studies have demonstrated repeatedly that, as a group, older adults with type 2 diabetes remember word lists and stories less efficiently than their nondiabetic peers (2–8), and large community-based epidemiological studies have identified type 2 diabetes as a strong independent predictor of poorer performance on learning and memory tasks (9,10). Diabetes-associated dysfunction has also been reported but somewhat less consistently in other cognitive domains, including attention (2,4,7), abstract reasoning and problem-solving (6,10,11), and psychomotor efficiency (6,9,12–14). Given the increased prevalence of cortical atrophy in older adults with type 2 diabetes (15,16), this cognitive dysfunction likely reflects diabetes-associated changes within the central nervous system.

Virtually all research demonstrating a link between type 2 diabetes and cognitive dysfunction has focused on adults >65 years of age. Data on the relationship between type 2 diabetes and cognitive function in middle-aged adults are far more controversial. Neurophysiological measures of brain activity during the performance of cognitive tasks have demonstrated consistently that middle-aged adults with type 2 diabetes have longer P300 latencies, which are indicative of abnormal brain function (17,18). On the other hand, the relatively few studies of cognitive function in adults <65 years of age have, with few exceptions (4,18), failed to find evidence of diabetes-associated cognitive dysfunction (19–21). Possible reasons for these negative findings include the use of an extremely limited neuropsychological assessment battery (21), very different patient populations (e.g., Native Americans with a relatively more brief duration of diabetes [19]), and small homogeneous samples of very healthy subjects (20).

To evaluate the nature and extent of diabetes-associated cognitive dysfunction in middle-aged adults, we recruited subjects with and without type 2 diabetes from the community, evaluated their medical status systematically, and administered a comprehensive battery of standardized cognitive tests. Our study has 2 features that differentiate it from previous research. First, our analyses focused on cognitive domains (e.g., learning, memory, problem-solving, and psychomotor efficiency) rather than individual test variables as primary outcome measures. Second, we developed statistical models that incorporated demographic, intraindividual, and biomedical variables common to both diabetic and nondiabetic subjects to determine the extent to which each of these variables contributed to subjects' performance on each cognitive domain. By drawing on previous studies of older adults (1), we hypothesized that learning and memory skills would be particularly vulnerable to dysfunction in our sample of middle-aged diabetic adults.

RESEARCH DESIGN AND METHODS

Participants

Adults with type 2 diabetes were recruited from a diabetes research subject registry maintained by the Pittsburgh Obesity/Nutri-

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Received for publication 21 February 2000 and accepted in revised form 14 June 2000.
Abbreviations: WAIS-R, Wechsler Adult Intelligence Scale–Revised.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic characteristics of the sample*

	Type 2 diabetic subjects	Control subjects	*P*
n	50	50	—
Age (years)	50.8 ± 7.7	50.5 ± 7.4	>0.75
Female (%)	70	76	>0.50
African-American (%)	28	4	0.001
Years of education	14.4 ± 3.1	14.0 ± 2.2	>0.25
WAIS-R information scaled score	10.7 ± 1.9	10.7 ± 2.3	>0.75
Symptom checklist 90-R depression T score	56.4 ± 10.9	56.8 ± 11.7	>0.75
Subjects consuming any alcohol in the past month (%)	36	54	>0.25
Drinks per week in drinkers	2.0 ± 1.9	2.0 ± 1.6	>0.75
HbA_1 (%)	10.2 ± 2.4	6.7 ± 0.5	0.001
Systolic blood pressure (mmHg)	127.2 ± 16.8	116.4 ± 19.0	0.004
Diastolic blood pressure (mmHg)	76.7 ± 10.6	73.8 ± 10.5	>0.15
Triglycerides (mg/dl)	188.1 ± 88.5	134.9 ± 73.3	0.004
Vibratory threshold (arbitrary vibration units)	3.85 ± 2.7	3.06 ± 1.3	0.078
Peripheral vascular disease (%)	6	2	—
Diabetic peripheral neuropathy (%)	28	—	—
Advanced background retinopathy (%)	10	—	—
Proliferative retinopathy (%)	6	—	—

Data are means ± SD or %.

tion Research Center (Pittsburgh, PA). Nondiabetic comparison subjects were recruited by asking participants in this and other diabetes research projects to bring a nondiabetic friend or family member with them. Individuals were excluded if they had a current or past history of chronic alcohol or drug abuse, a head injury with a loss of consciousness that exceeded 10 min, or a current psychiatric disorder. A total of 50 type 2 diabetic adults 34–65 years of age were compared with 50 nondiabetic adults who were selected for study inclusion on the basis of age and sex. Type 2 diabetic subjects completed a detailed medical examination with appropriate laboratory tests to assess the presence of diabetes-associated micro- and macrovascular complications and comorbid disorders. All had been diagnosed at least 2 years before this evaluation (means ± SD duration of diabetes 8.1 ± 5.9 years). Nondiabetic comparison subjects completed a similar but abbreviated medical examination to ensure that none met the criteria for type 2 diabetes (22). This study was approved by the University of Pittsburgh Institutional Review Board, and all subjects were paid for participating.

Demographic characteristics of the 2 groups are summarized in Table 1. Both diabetic and nondiabetic samples were comparable in that they were moderately well educated, without symptoms of depression, of average intelligence, likely to be female, and middle-aged. A significantly higher proportion of African-American subjects was evident in the type 2 diabetes group. As expected, type 2 diabetic subjects have significantly higher HbA_1 values, higher systolic blood pressure readings, higher triglyceride levels, and higher great-toe vibratory thresholds. Insulin-treated subjects comprised 26% of the type 2 diabetes group (HbA_1 11.0 ± 1.8%); the remainder were treated with oral antidiabetic agents (56%, HbA_1 10.71 ± 2.2%) or diet (18%, HbA_1 7.47 ± 2.1%). The latter group was in better control than the other 2 groups ($P < 0.05$), who did not differ from each another regarding HbA_1.

Neuropsychological assessment

Learning ability and memory ability were assessed with 3 clinical tests previously found to be sensitive to subtle mnemic deficits in middle-aged adults (23,24). More detailed descriptions of each measure can be found elsewhere (25,26). Verbal learning efficiency was assessed with the Verbal Paired-Associate Learning Test in which 10 pairs of unrelated words were presented at a rate of 1 pair every 2 s. Subjects were then tested by presenting the first word of each pair as a retrieval cue for the other word (27). Four such study test trials were administered with a delayed recall test 30 min later. Nonverbal learning ability was measured by the Symbol-Digit Paired-Associate Learning Test. Subjects studied 7 pairs of items to remember, each was presented for 3 s of study, and subjects were then tested for the number by cueing with the symbol alone (27). Four study test trials were administered with delayed recall 30 min later. Working memory was assessed with the Four-Word Short-Term Memory Test, a task in which subjects heard 4 words read at a rate of 1/s followed by a 3-digit number from which they counted backwards for 5, 15, or 30 s and then recalled the words. A total of 5 trials at each of the 3 retention intervals were administered (23).

Memory for meaningful highly organized information was assessed by asking subjects to recall 2 brief stories from the Logical Memory subtest of the Wechsler Memory Scale–Revised (28). Two stories were read to subjects who were asked to repeat them immediately after hearing them and after a 30-min delay.

Problem-solving and mental flexibility were evaluated with 4 clinical tests. The Category test is a challenging deductive reasoning task in which the subject was presented with a series of stimuli and had to discover the underlying organizing principle (e.g., oddity) by making a response and using feedback to guide subsequent responses (29). The Tactual Performance test required the blindfolded subject to place a series of geometric shapes into a form board as quickly as possible—first with the dominant hand, then with the nondominant hand, then with both hands together. It requires the integration of spatial and kinesthetic skills as well as good memory and problem-solving skills (29). Visuospatial organization and problem-solving skills were assessed with the Object Assembly subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (30). Subjects were presented with 4 jigsaw-like puzzles and were required to put them together as rapidly as possible. Mental flexibility was measured with the Trail Making test part B (29). Subjects were presented with a page of numbers and letters arranged randomly and were told to connect them by alternating sequentially (e.g., 1-A-2-B...) as quickly as possible.

Psychomotor efficiency was measured with 5 tests. The Digit Vigilance test (31) assessed the ability to sustain attention by requiring subjects to rapidly scan 2 pages of numbers for a specific target. The Stroop Interference test (32) evaluated the ability to inhibit a highly overlearned response by presenting subjects with color names

printed in incompatible colors (the word "red" is printed in green ink) and having them name the color of the ink as quickly as possible. The Embedded Figures test assessed visuospatial analysis but required no motor response (27). On each of 10 trials, subjects were told to quickly identify which of 4 complex patterns contained a simple geometric design. The Digit Symbol Substitution test (30) required attention, rapid responding, visual scanning, and associative learning because subjects substituted numbers for symbols according to a preestablished code. The Grooved Pegboard (33) measured eye–hand coordination and fine motor dexterity by having subjects insert 25 key-shaped pegs into a pegboard as quickly as possible—first with the dominant hand and then with the nondominant hand. Mean time for both hands is reported.

Intelligence was estimated with the Information subtest from the WAIS-R. Symptoms of depression were ascertained from the Symptom Checklist 90-R (34). To ensure that neuropsychological test results were not influenced by ambient hypoglycemia, a fingerstick blood glucose reading was obtained before cognitive assessment; subjects with values <70 mg/dl received a snack and were retested. The entire cognitive assessment required ~3 h, and tests were administered in the same order for all subjects.

Medical variables

All physical examinations were conducted by medical staff members at the Epidemiology of Diabetes Complications Research Center; a detailed description of the methodology can be found elsewhere (35). Stable HbA_1 was measured with automatic high-performance liquid chromatography (Diamat; BioRad, Hercules, CA). Blood pressure was measured with a random-zero sphygmomanometer according to the Hypertension Detection and Follow-Up Program protocol after a 5-min rest. Triglycerides were measured enzymatically. Vibratory thresholds were measured on the plantar surface of the great toe on the dominant side of the body using the Vibratron II device (Physitemp Instruments, Clifton, NJ). A forced-choice procedure with 20 trials was used to assess large sensory nerve fibers. Peripheral vascular disease was defined as an ankle-to-arm blood pressure ratio <0.9. Clinically significant diabetic peripheral neuropathy was assessed during a neurological examination performed by a trained internist. Distal symmetrical polyneuropathy was defined according to the Diabetes Control and Complications Trial criteria (36) as the presence of 2 or more of the following: symptoms consistent with distal symmetrical polyneuropathy, decreased or absent tendon reflexes, and signs of sensory loss. Retinopathy was assessed in diabetic subjects with stereoscopic color fundus photographs in 3 (1, 2, and 4) standardized fields. Photographs were graded at the Wisconsin Reading Center using the Wisconsin Epidemiologic Study of Diabetic Retinopathy Classification and Grading System (37).

Statistical analyses

The large number of neuropsychological variables was first reduced to 4 factors using principal components factor analysis with varimax rotation. Factor scores were calculated and converted into T scores (50 ± 10); these were used as dependent variables in subsequent analyses. To examine the independent contribution of relevant demographic and biomedical variables to neuropsychological test performance, hierarchical multiple regression was used. Separate regression models were evaluated for each of the 4 cognitive domain factor scores. Demographic and biomedical variables were selected as possible predictors if univariate between-group differences were significant or if previous work demonstrated a relationship between the variable and cognitive performance. Predictor variables were entered in 4 blocks: *1*) demographic characteristics (age, sex, and race), *2*) estimated intelligence (WAIS-R information), *3*) diagnostic group (diabetic or nondiabetic), and *4*) metabolic control (HbA_1). If block 3 or 4 significantly predicted the cognitive factor score, then systolic blood pressure and serum triglyceride levels were entered on block 5, and vibratory threshold (in arbitrary vibration units) was entered on block 6. Final β values (unstandardized regression coefficients) are reported, as is the proportion of variance explained by each block (r^2 change). Descriptive univariate between-group comparisons were assessed with Student's 2-tailed *t* test or the χ^2 test as appropriate. Magnitude of effect size (*d*) for each cognitive test score was calculated as the mean group difference divided by the pooled SD (38); a "small" effect is operationally defined as $d = 0.2$; a "medium" effect is operationally defined as $d = 0.5$. All statistical analyses were performed using SPSS Version 9.0.1 for Windows (SPSS, Chicago).

RESULTS

Factor analysis

Principal components factor analysis was used to reduce the 16 test scores to a more manageable number. The resulting 4-factor solution accounted for 65.5% of the total variance. Individually, the verbal learning factor accounted for 18.1% of the variance, story memory for 13.1%, problem-solving for 18.8%, and psychomotor speed for 15.5%. All factor loadings were >0.60. In all but 2 instances, individual tests loaded on a single factor. Scores from the Short-Term Memory test loaded equally on the learning, story memory, and psychomotor efficiency factors, whereas Grooved Pegboard scores loaded on both psychomotor efficiency and problem-solving factors. Consistent with standard neuropsychological practice (33), a clinical decision was made to assign the Short-Term Memory test to the learning factor and to assign the Grooved Pegboard test to the psychomotor efficiency factor. To calculate homogeneous factor scores, separate factor analyses were next run that were limited to the 5 test variables that loaded on psychomotor speed, the 4 variables that loaded on abstract reasoning, and the 7 variables that loaded on verbal learning and memory. The latter analysis yielded separate verbal learning and story memory factor scores. Summary factor scores for each of the 4 domains are presented as T scores (Table 2).

The degree to which each of the 4 domains yielded an accurate representation of its composite test scores was assessed by using reliability analysis techniques to calculate Cronbach's α. Standardized item α values were all acceptable and ranged from 0.76 (psychomotor efficiency) to 0.94 (story memory).

Learning

Results from the hierarchical multiple regression analyses are summarized in Table 3. In taking this analytic approach, we found no association between having type 2 diabetes and learning ability after first controlling for demographic characteristics and intelligence. Demographic variables accounted for 31% of the variance of the learning factor score (block 1), and estimated premorbid intelligence accounted for an additional 17% of the variance (block 2, r^2 change; Table 3). Together, both blocks

Table 2—*Raw scores, 95% CIs and effect size estimate (*d*) for each test variable*

	Type 2 diabetic subjects	Control subjects	*d*
Learning			
Learning factor score	48.9 ± 9.7 (43.1–51.6)	51.1 ± 10.3 (48.2–54.0)	0.23
Verbal Learning	26.8 ± 8.9 (24.3–29.4)	30.3 ± 8.0 (28.0–32.6)	0.41
Delayed Verbal Recall	8.3 ± 2.5 (7.6–9.0)	8.8 ± 2.0 (8.2–9.4)	0.20
Symbol-Digit Learning	20.1 ± 5.6 (18.5–21.7)	20.8 ± 6.3 (19.0–22.6)	0.12
Delayed Symbol-Digit Recall	6.2 ± 1.4 (5.8–6.6)	5.9 ± 1.5 (5.4–6.4)	0.18
Short-Term Memory	34.0 ± 10.4 (31.1–36.9)	37.4 ± 9.7 (34.7–40.2)	0.34
Memory for stories			
Memory Factor Score	51.8 ± 9.7 (49.0–54.5)	48.2 ± 10.1 (45.4–51.1)	0.34
Logical Memory, immediate	27.9 ± 6.6 (26.0–29.8)	25.6 ± 6.3 (23.8–27.4)	0.36
Logical Memory, delay	23.7 ± 6.6 (21.9–25.6)	21.4 ± 7.5 (19.3–23.6)	0.33
Problem-solving			
Problem-solving factor score	47.8 ± 9.7 (45.0–50.5)	52.2 ± 9.9 (49.4–55.0)	0.45
Category Test errors	42.5 ± 16.2 (37.9–47.2)	37.7 ± 18.7 (32.4–43.0)	0.27
Tactual Performance time	935.5 ± 356.8 (834.1–1,036.9)	795.9 ± 327.6 (702.9–889.1)	0.41
Object Assembly score	9.9 ± 3.3 (8.9–10.9)	11.1 ± 2.9 (10.3–11.9)	0.39
Trail Making Part B time	71.2 ± 28.2 (63.1–79.2)	62.5 ± 27.1 (54.8–70.2)	0.31
Psychomotor efficiency			
Psychomotor factor score	46.5 ± 10.5 (43.5–49.4)	53.5 ± 8.1 (51.2–55.9)	0.50
Digit Vigilance time	407.7 ± 94.5 (380.8–434.5)	363.8 ± 79.9 (341.1–386.5)	0.50
Stroop Interference T score	42.8 ± 6.4 (40.9–44.6)	48.0 ± 8.0 (45.8–50.3)	0.73
Embedded Figures time	8.8 ± 5.3 (7.3–10.3)	7.5 ± 3.6 (6.5–8.5)	0.34
Digit Symbol scaled score	10.7 ± 1.8 (9.5–10.9)	11.5 ± 1.9 (10.5–12.0)	0.41
Grooved Pegboard time	91.1 ± 25.9 (83.7–98.5)	74.1 ± 13.7 (70.2–78.0)	0.86

Data are means ± SD (95% CIs).

explained ~48% of the total variance in the learning factor score ($P < 0.0001$). Neither diagnostic group (r^2 change = 0) nor HbA_1 (r^2 change = 0.005) accounted for additional variance in the learning factor score.

Memory for stories

Hierarchical regression analysis indicated that the memory factor score was not influenced by demographic variables (r^2 change = 0.05, $P > 0.15$) but was associated with premorbid intelligence (r^2 change = 0.18). Importantly, after accounting for demographic and intelligence variables, diagnostic group category independently explained a small but statistically significant amount of variance (3.4%, $P = 0.04$, $\beta = -0.185$), with type 2 diabetes predicting somewhat better performance on the story memory factor, which was contrary to our expectation. No other biomedical variables increased the explanatory power of this regression model. The entire model explained ~26% of the variance in the story memory factor score ($P < 0.0001$).

Problem-solving

Regression analysis showed that the ability to solve cognitively demanding problems rapidly and accurately was strongly influenced independently by demographic characteristics (r^2 change = 0.266) and to a lesser extent by intelligence (r^2 change = 0.086). After controlling statistically for those variables, neither diagnostic group nor HbA_1 accounted for additional variance in the problem-solving factor score (total variance explained 35.2%, $P < 0.0001$).

Psychomotor efficiency

Results of the regression analysis demonstrated that, although demographic characteristics explained an appreciable amount of variance (24%) in psychomotor performance, an additional 7.5% ($P = 0.002$) of variance could be explained independently by diagnostic group. Premorbid intelligence was unrelated to performance ($r^2 = 0.015$, $P > 0.15$). Of particular interest is the finding that, after controlling statistically for all other variables, including group membership, HbA_1 explained an additional 6.4% of the variance ($\beta = -0.213$), and vibratory threshold accounted for an additional 11.2% of the variance ($\beta = -0.374$). Neither systolic blood pressure nor triglyceride levels contributed significantly to this model. Together, the 5 blocks of variables explained 51% of the variance in psychomotor efficiency ($P < 0.0001$).

Because HbA_1 values are correlated with both blood pressure ($r = 0.272$, $P < 0.01$) and triglyceride levels ($r = 0.267$, $P < 0.01$), one could argue that our strategy of entering HbA_1 first could mask the possible effects of blood pressure and triglyceride levels on psychomotor efficiency. For that reason, a second regression model was evaluated in which diagnostic group was entered on block 3 (as in model 1), triglycerides and blood pressure were entered on block 4, HbA_1 was entered on block 5, and vibratory threshold was entered on block 6. No appreciable change in results was noted. Blood pressure and triglycerides failed to explain significant variance (r^2 change = 0.01, $P > 0.50$, $\beta = -0.114$ for blood pressure and -0.029 for triglycerides), whereas HbA_1 continued to explain significant variance (r^2 change = 0.061, $P < 0.005$, $\beta = -0.213$), as did vibratory thresholds ($r^2 = 0.112$).

Individual predictor variables

Within each of the 4 regression models, better performance was consistently associated with younger age and with higher scores on the WAIS-R Information subtest

(data not shown). Sex (being female) was significantly associated with better performance on measures of learning. Race (being Caucasian) was associated significantly with better performance on learning and problem-solving summary scores. Higher HbA_1 levels and decreased sensitivity to vibration were intercorrelated to some extent (Pearson's $r = 0.301$, $P < 0.002$), yet each was independently associated with poorer performance on measures of psychomotor efficiency in the regression model. The magnitude of these effects is relatively small, especially when the statistical relationships obtained from the composite psychomotor factor score are translated into units that are specific to individual cognitive tests. For example, given the unstandardized regression coefficient for HbA_1 (-0.857), for each 1% change in HbA_1, a 7.7-s change would occur in Digit Vigilance time, a 0.5-point change would occur in Stroop Interference T score, a 0.4-s change would occur in Embedded Figures time, a 0.1-U change would occur in the Digit Symbol scaled score, and a 2.1-s change would occur in time to complete the Grooved Pegboard.

Depressive symptomatology was not incorporated into these regression analyses because our preliminary analyses revealed no meaningful zero-order correlation coefficients between any factor score and the Symptom Checklist 90-R Depression T score (Pearson's *r* ranged between 0.025 and 0.122, $P > 0.10$). Alcohol intake was also excluded from regression analyses for the same reason (Spearman's ρ ranged between 0 and 0.16, $P > 0.10$). Despite the strong relationship recently reported between peripheral vascular disease and cognitive deterioration (39), our low rates of peripheral vascular disease (6%) precluded inclusion of that variable into the regression analyses.

Univariate test results

To identify individual tests that may prove to be particularly useful clinically in assessing cognitive function in middle-aged diabetic adults, we have provided a summary listing of unadjusted scores in Table 2. Although diabetic and nondiabetic subjects appear to differ on several tests, as indexed by the unadjusted test scores (e.g., verbal learning score), multivariate adjustment for variables known to affect test scores (e.g., age, sex, race, and estimated intelligence) renders many of those differences nonsignificant. Indeed, after such adjustments are made, the only tests that reliably differentiate diabetic from nondiabetic subjects are Logical Memory immediate recall ($P < 0.05$) (on which individuals with diabetes perform somewhat better) and 3 psychomotor tests, Digit Vigilance ($P < 0.01$), Stroop Interference ($P < 0.005$), and Grooved Pegboard ($P < 0.003$), on which diabetic subjects perform more poorly.

Table 3—*Hierarchical regression results for each cognitive domain*

	r^2	r^2 change	*P* for r^2 change
Learning			
Demographics	0.308	0.308	0.000
Intelligence	0.480	0.172	0.000
Group	0.480	0.000	0.794
HbA_1	0.485	0.005	0.358
Memory for stories			
Demographics	0.048	0.048	0.187
Intelligence	0.227	0.179	0.000
Group	0.261	0.034	0.041
HbA_1	0.261	0.000	0.902
Problem-solving			
Demographics	0.266	0.266	0.000
Intelligence	0.352	0.086	0.001
Group	0.366	0.014	0.158
HbA_1	0.384	0.018	0.102
Psychomotor efficiency			
Demographics	0.240	0.240	0.000
Intelligence	0.255	0.015	0.189
Group	0.330	0.075	0.002
HbA_1	0.394	0.064	0.003
Systolic blood pressure/triglycerides	0.402	0.008	0.587
Vibratory threshold	0.514	0.112	0.000

CONCLUSIONS — One major aim of this study was to test the hypothesis that type 2 diabetes is associated with learning and memory deficits in middle-aged adults. In general, we found little compelling support for that position. Multivariate analyses indicated that diabetic adults 34–65 years of age performed at least as well as their nondiabetic peers on all of our learning and memory measures after taking into account demographic factors that are known to affect cognitive test performance. We have no good explanation for our unexpected finding that subjects with diabetes recalled somewhat more information than nondiabetic subjects when asked to remember several brief stories, but given the modest magnitude of that effect, and the multiple variables examined, we cannot rule out the possibility that this result is because of chance. Indeed, in an effort to better understand this unanticipated result, we subsequently performed the analysis again using a somewhat different strategy (i.e., multivariate analysis of variance techniques with actual test scores rather than factor scores and age, race, and sex as covariates). Consistent with the possibility that our prior results may be a statistical or measurement artifact, the omnibus F for diagnostic group was no longer significant for the 2 story memory measures but remained significant for the psychomotor efficiency measures (data not shown).

Our finding of essentially normal memory function is consistent with several other reports of intact learning and memory skills in middle-aged adults with type 2 diabetes (19–21). To date, only 2 groups have reported memory dysfunction in middle-aged subjects (4,18). Differences in patient (or control) samples and/or test selection could account for discrepant results across studies. For example, Dey et al. (18) used a single very limited screening measure of memory that was administered to a heterogeneous group of English and Hindi native speakers, whereas Meuter and colleagues (4,40) evaluated subjects' performance on an overly inclusive memory/concentration factor.

On the other hand, our findings are inconsistent with the vast majority of studies conducted on adults >65 years of age,

which indicate that verbal learning and memory problems are commonly associated with type 2 diabetes (1). Although the literature seems to indicate that being >65 years of age greatly increases the risk that adults with diabetes will manifest learning and memory deficits relative to their nondiabetic friends, we are not in a position to determine how or to what extent glycemic status and age interact to induce learning and memory deficits because we did not include a control group of adults >65 years of age in this study. This issue deserves further investigation.

Results from our comprehensive assessment also indicated that problem-solving skills were intact in our diabetic sample, but psychomotor slowing was quite pronounced. Middle-aged adults with type 2 diabetes consistently performed more poorly than nondiabetic peers on tasks that required rapid visual scanning while searching for specific targets (Digit Vigilance), inhibition of highly overlearned responses while rapidly performing a color-naming test (Stroop Interference), and eye–hand coordination (Grooved Pegboard). Diabetes-associated reductions in psychomotor efficiency ranged from 12% (Digit Vigilance) to 23% (Grooved Pegboard). Using hierarchical regression modeling techniques, we were able to explain >50% of the variance in the psychomotor efficiency summary score with a diagnosis of diabetes, HbA_1 level, and vibratory threshold values each independently predicting between 6 and 11% of the variance.

Changes in psychomotor efficiency have been discussed only infrequently as a correlate or consequence of type 2 diabetes (1), despite the fact that at least 5 other reports have shown psychomotor slowing in this patient population (4,6,9,13,14). Significant reductions in psychomotor efficiency are not restricted to adults with type 2 diabetes but can be found in both children (41,42) and adults (4,43–45) with type 1 diabetes. Because our previous work demonstrated a strong association between peripheral neuropathy and psychomotor slowing in adults with type 1 diabetes (43), we suggested that mental slowing may be a common manifestation of a "central neuropathy" induced by chronic hyperglycemia. According to that interpretation, metabolic changes associated with peripheral neuropathy (e.g., alterations in Na^+-K^+-ATPase activity and the ensuing reduction in *myo*-inositol and sorbitol metabolism [46,47]) may trigger similar biochemical abnormalities at the neuronal level. The resultant structural and functional changes, primarily in white matter, would eventuate in slowed rates of neural transmission and longer response times.

Consistent with that prediction are reports indicating that young or middle-aged adults with a history of poor metabolic control or diabetes-associated biomedical complications are more likely to show longer brainstem auditory-evoked potential or P300 latencies (17,48) as well as white matter abnormalities on magnetic resonance imaging (49–52). Children with type 1 diabetes duration of at least 2 years also show longer brainstem auditory-evoked potential latencies, which are correlated with disease duration, long-term HbA_1, and hypoglycemic events (53). This constellation of neuroimaging, electrophysiological, and neuropsychological findings suggests to us that chronic hyperglycemia may contribute to the development of detectable brain dysfunction that is manifested behaviorally as an overall reduction in mental efficiency. That interpretation is consistent with results from our regression model of the psychomotor efficiency domain, which demonstrate that slower performance was associated independently with higher HbA_1 values and with higher vibratory thresholds. The latter measure has been used to provide a reliable estimate of both diabetes-associated and age-related peripheral neuropathy (54,55).

Whether diabetes-associated psychomotor slowing is a permanent sequela of poor metabolic control or whether it is reversible is an issue that remains unresolved. If, however, chronic hyperglycemia affects the brain at the cellular level, then any intervention that improves metabolic control and reduces HbA_1 levels ought to induce a corresponding improvement in psychomotor efficiency. Preliminary support for that possibility comes from a recent study in which older adults (55–75 years of age) with type 2 diabetes were randomized to either treatment as usual or to 2 weeks of intensive inpatient treatment (i.e., individually adapted diet, daily blood glucose monitoring) (56). A brief battery of psychomotor measures was administered before treatment, immediately after treatment, and again 6 weeks later. Intensive treatment was associated with a significant improvement in blood glucose levels as well as an improvement in psychomotor efficiency, with faster psychomotor test performance being significantly associated with improved (i.e., lower) HbA_1 levels. These intriguing findings need to be replicated with a larger sample of subjects and with a more comprehensive battery of cognitive tests.

In summary, middle-aged adults with type 2 diabetes manifest psychomotor slowing that is associated with poorer metabolic control, whereas learning, memory, and problem-solving skills appear to be similar to those of demographically similar adults who do not have diabetes. These findings may have limited generalizability because the study design was not epidemiological, and subjects were predominantly female and relatively healthy. Nevertheless, our data agree with the anecdotal reports from many of our diabetic research subjects and their family members who expressed concerns about declining mental efficiency and self-perceptions that they are no longer as "sharp" as they used to be. In our view, mental slowing is a very common correlate of chronic hyperglycemia and may contribute in part to the development of the mild cognitive impairment reported in many older adults (57).

Acknowledgments — This work was supported in part by a grant from the National Institutes of Health (RO1-DK-39629).

The authors acknowledge the assistance of the Epidemiology of Diabetes Program under the direction of Trevor Orchard for conducting physical examinations and laboratory assays, the assistance of the Obesity/Nutrition Research Center under the direction of Rena Wing for subject recruitment, and the support of the Data Analysis Core of the Center for Research on Chronic Disorders under the direction of Susan Sereika.

The results of this study were presented in part at the 59th Scientific Sessions of the American Diabetes Association, San Diego, California, June 1999.

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