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Exploring Effects of Type 2 Diabetes on Cognitive Functioning in Older Adults

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Type 2 diabetes may be associated with exacerbated aging-related declines in cognitive neuropsychological performance. The authors examined whether such effects are systematic (i.e., broadly distributed across domains or domain-specific) or moderated by age (i.e., varying across age within older adults). The authors assembled recent cross-sectional data from the Victoria Longitudinal Study (VLS) Sample 3 (Wave 1; initial $n = 570$; initial age = 53–90 years). Using a comprehensive, multidimensional spectrum of cognitive neuropsychological tests, the authors examined performance differences by diabetes status (diabetes group vs. healthy controls) and age (young-old vs. old-old). Our results showed that healthy controls significantly outperformed the diabetes group only on markers of executive functioning and speed. Notably, the diabetes-related effects were robust across the two late-life age groups. Future research examining longitudinal changes is recommended.

Keywords: Type 2 diabetes, cognitive aging, executive function, speed

Type 2 diabetes is a chronic metabolic condition characterized by abnormally high blood glucose levels as a result of insufficient usage of insulin. Formerly known as Non-Insulin Dependent Diabetes Mellitus or adult-onset diabetes, its prevalence significantly increases across adulthood, typically affecting individuals over the age of 40 years (Votey & Peters, 2005). Recent estimates on the prevalence of diabetes (Type 1 and Type 2) have indicated diagnosis rates for adults over age 60 at about 12% in Canada (Health Canada, 2002) and 20% in the United States (National Institute of Health, 2005). Approximately 90% of these cases are Type 2. Associated with Type 2 diabetes are increased risk of hypertension, stroke, and cerebrovascular disease (e.g., Awad, Gagnon, & Messier, 2004; Messier, 2005; Reunanen, Kangas, Martikainen, & Klaukka, 2000). These potential comorbidities have been shown to affect neural integrity and cognition, especially when coexistent with diabetes (Hassing, Hofer, et al., 2004). Recent literature has reported a relationship between diabetes and an earlier or accelerated decline in cognition (e.g., Awad et al., 2004; Hassing, Grant, et al., 2004; Hassing et al., 2003), including a twofold increase in the risk of dementia (Nilsson, 2006).

Few studies have examined whether adverse cognitive effects of diabetes are broad or selective across domains, or whether such effects differ across a broad age band of older adults. We explore these issues with a relatively healthy and generally cognitively intact sample of 53–90 year-old adults tested on multiple domains of cognitive neuropsychological performance. Specifically, our database includes multiple indicators of the key domains represented (often separately) in the literature: episodic and semantic memory, neurocognitive speed, executive functioning, fluency, and global cognitive competence. This comprehensive approach is designed to contribute to resolving some of the mixed patterns of results across studies varying in cognitive domains, measures, and age groups represented.

Although the general trend is for diabetes-related deficits in performance, discrepant results are common (Nilsson, 2006). First, verbal episodic memory is typically (but not uniformly) affected in diabetes patients (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004; Messier, 2005; Ryan & Geckle, 2000; Wahlin, Nilsson, & Fastbom, 2002), extending well-known patterns of normal aging-related decline (e.g., Dixon et al., 2004). These deficits have been seen predominantly in adults over the age of 70 (Messier, 2005), and for measures of immediate verbal memory (e.g., word list recall; Awad et al., 2004). Notably, Hassing, Grant, et al. (2004) found no diabetes-related cognitive performance deficits at baseline but observed accelerated longitudinal decline in episodic memory (and speed) for the diabetes group. Second, diabetes-related slowing has been observed with a variety of speeded tasks, especially those measuring basic reaction time or perceptual speed (e.g., Arvanitakis, Wilson, & Bennett, 2006; Awad et al., 2004; Fontbonne, Berr, Ducimetière, & Alpérovitch, 2001; Messier, 2005). However, Messier's (2005) review indicated that less than half the included studies actually reported diabetes-related slowing. We include indicators of three main domains of neurocognitive speed: reaction time, perceptual speed, and a unique set of semantic speed measures. Third, selected measures of executive functioning have produced diabetes-related performance deficits in some (but not all) studies (Awad et al., 2004; Messier, 2005; Ryan & Geckle, 2000; Stewart & Liolitsa, 1999). Because executive functioning may involve multiple underlying processes or dimensions (de Frias, Dixon, & Strauss, 2006; Miyake, Freidman,

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Emerson, Witzki, & Howerter, 2000), it may be especially susceptible to task-related selection effects in special population research (Nilsson, 2006). Our database taps multiple aspects of executive functioning (i.e., inhibition, shifting, speed). Fourth, some studies have focused on general measures of global cognition with diabetes-related deficits both observed (e.g., Hassing et al., 2003) and not found (e.g., Arvanitakis, Wilson, & Bennett, 2006; Fontbonne et al., 2001). We use and report global cognition results descriptively only.

The exact neuroanatomical or neurochemical effects of Type 2 diabetes on cognitive performance are relatively unknown. One study suggests that frontal structures may be affected by diabetes sequelae and may therefore be associated with occasionally observed deficits in episodic memory recall, verbal fluency, and executive functioning (Wahlin et al., 2002). Additionally, reduced volumes of the amygdala and the hippocampus in diabetes patients may underlie deficits associated with learning and memory (den Heijer et al., 2003). A recent report on MRI abnormalities and cognitive changes found substantial white matter lesions and subcortical atrophies in Type 2 diabetes patients, suggesting an accelerated rate of age-related structural changes (Manschot et al., 2006). In addition to possible diabetes-related neurological mechanisms, several comorbid health conditions may confound (or exacerbate) cognitive sequelae of diabetes. Prominent among these comorbidities are neurological and psychiatric conditions, hypertension, cardiovascular and cerebrovascular disease, and drug use (e.g., Arvanitakis, Wilson, Li, Aggarwal, & Bennett, 2006; Jacobson et al., 2007; Robertson-Tchabo, Arenberg, Tobin, & Plotz, 1986; Vanhanen et al., 1998; van Harten et al., 2007; Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004). Accordingly, we applied a series of cognitive and physical health-related exclusionary criteria to our group selections. Furthermore, because hypertension is associated with brain and cognition changes in older adults (Elias, Elias, Robbins, & Budge, 2004; Raz, Rodrigue, Kennedy, & Acker, 2007) and especially among diabetes patients (Hassing, Hofer, et al., 2004), systolic blood pressure was considered as a covariate.

Given the considerable extent of conflicting results across most neuropsychological domains, the general trends and precise effects of Type 2 diabetes on cognitive aging are not firmly delineated. The cross-study variability in results could stem from several methodological differences, including (a) few and selective cognitive measures and (b) restricted or uncontrolled age-related sampling of older adults. As recommended elsewhere (Brands et al., 2007), this study presents a comprehensive range of neuropsychological indicators, thus promoting both cross-study and within-sample comparisons. Specifically, we use recent cross-sectional data derived from the Victoria Longitudinal Study (VLS), a Canadian sample comprised of relatively healthy and non-demented individuals. We explore these issues in two conventional age groups, young-old adults (YO, 53–70 years old) and old-old adults (OO, 71–90 years old), in order to test whether diabetes exerts its cognitive effects in earlier or later late life (Wahlin et al., 2002). After accounting for recommended health confounds, we examine two research questions. First, are there group differences between those with Type 2 diabetes and healthy controls in performance across a range of cognitive neuropsychological measures? Second, are observed group differences affected by age differences within this older adult sample?

Two additional methodological features should be noted. First, our diabetes patients report that their cases are relatively mild or moderate (97.56%), and that their conditions are controlled by oral medication (39.02%), insulin (7.32%), diet and exercise (24.39%), or a variety of other combinations (19.53%). Accordingly, this diabetes group supplements those in the literature comprised of relatively severe patients from nursing homes or health clinics (e.g., Arvanitakis et al., 2004). By examining community-dwelling volunteers to a large-scale project, the present sample may be more representative of current early or well-controlled Type 2 diabetes populations in North America. Arguably, for more severe cases, cognitive deficits may be attributed to disease severity, neurological sequelae, or multiple comorbid conditions (Nilsson, 2006). Second, because previous studies are each characterized by relatively few (and nonoverlapping) cognitive measures, our analyses are conducted at the level of each measure, but clustered within cognitive domains. Regarding the first research question, we expected significant diabetes-related differences in performance on episodic memory, verbal fluency, and neurocognitive speed, but not semantic memory. The mixed results in research on executive functioning in diabetes and normal aging do not support a strong hypothesis. Regarding age differences, we hypothesized (in the absence of previous research) that the group differences in cognitive performance will be more pronounced in the old-old adults.

Method

The Victoria Longitudinal Study (VLS) is a multicohort epidemiological study of biomedical, health, cognitive, and neurocognitive aspects of aging. Three independent samples of initially healthy older adults are followed at 3-year intervals (see Dixon & de Frias, 2004).

Participants

The base participants were from the first wave (2002–03) of VLS Sample 3 ($n = 570$, age range = 53–90 years; M age = 68.29 years, $SD = 8.60$). Data from an in-progress second wave are unavailable. A strict sequential procedure for selection and exclusion of participants in two groups (Type 2 diabetes and control) was adopted. Inclusion into the diabetes group was based on a three-step diagnosis flowchart, including required confirmatory information from all three sequential sources. First, all diabetes patients self-reported (a) a formal diabetes diagnosis, (b) an adult onset age (over 31), and (c) treatment or control practices (i.e., diet, exercise, oral medication, insulin, or a combination). Second, the actual objective medications of the diabetes patients were checked concurrently for the presence of relevant drugs (e.g., metformin, glyburide, tolbutamide, gliclazide, and pioglitazone hydrochloride). Third, all surviving diabetes patients were contacted three years after the present testing for confirmation of self-reported diabetes diagnoses. Although the VLS does not have access to additional diabetes-confirming medical information (i.e., blood glucose level above 6.0mmol/L at baseline, or elevated HbA1c level), our three-step diagnostic procedure goes beyond the frequently used and validated self-report classifications (e.g., Arvanitakis, Wilson, Li, et al., 2006; Connolly, Unwin, Sherriff, Bilous, & Kelly, 2000; Kriegsman, Penninx, van Eijk, Boeke, & Deeg, 1996; McNeely & Boyko, 2004; Midthjell, Holmen, Bjørndal,

& Lund-Larsen, 1992; Reunanen et al., 2000), and it is consistent with diagnostic criteria currently used in the literature (Arvanitakis, Wilson, Li, et al., 2006; Gregg et al., 2000; Luchsinger, Tang, Stern, Shea, & Mayeux, 2001). Of the original 570 adults, 48 were identified as potential Type 2 diabetes patients. As a result of diagnosis procedures, we selected a provisional diabetes group ($n = 44$; $M = 69.33$ years, $SD = 7.64$) and a pool of nondiabetes control participants ($n = 522$; $M = 68.13$ years, $SD = 8.68$).

Next, we implemented four sets of standard exclusionary criteria. First, we confirmed that no participants had been previously diagnosed with Alzheimer's disease or vascular dementia. Second, participants scoring less than 26 on the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975) were removed (diabetes $n = 0$, control $n = 12$). Third, based on the VLS intake health inventory, we inspected the following clusters of potential comorbid diseases: (a) neurological conditions (i.e., stroke, Parkinson's disease, epilepsy, and head injury), (b) cardiovascular disease (i.e., heart trouble, hypertension, hypotension, and atherosclerosis), (c) other related health conditions (i.e., spinal condition and thyroid complications), and (d) psychiatric conditions (i.e., depression, alcohol dependence, drug dependence, use of antidepressant or antipsychotic medication). Participants from the diabetes group ($n = 18$) who self-rated that they had moderately serious or very serious cases of any of these four clusters of conditions were selected for follow-up and examined individually for potential adverse cognitive effects. We reasoned that comorbidities in aging are common, so we ensured that the present diabetes patients would be removed only if they had both a potentially cognitively impairing health condition and a demonstrated cognitive deficit. If any of the 18 selected diabetes patients scored 1 *SD* (or more) below the diabetes group mean on any of the cognitive reference tests (word recall, story memory, vocabulary, simple reaction time) they were removed from the sample. Accordingly, an additional $n = 3$ diabetes participants (two with severe heart trouble and one with a severe spinal condition, and all with cognitive impairment) were excluded. One moderate Parkinson's disease participant performed outside the acceptable range only on reaction time, so we excluded this individual for the speeded tasks. Fourth, because of relatively plentiful control group members, our procedures were simpler. Control participants ($n = 86$) were excluded if they met at least one of the following criteria: (a) indication of very serious case on any of the above exclusion health conditions, or (b) indication of a moderately serious history of stroke or Parkinson's disease, whether or not their behavioral performances were adversely affected.

For the final sample ($n = 465$), the diabetes group ($n = 41$; 23 women, 18 men) ranged from 55 to 81 years old ($M = 68.59$ years, $SD = 7.16$) and the control group ($n = 424$; 294 women, 130 men) ranged from 53 to 90 years old ($M = 67.84$ years, $SD = 8.50$). The two groups were very similar in general age proportions and specifically so in the oldest decade (80–90 years, with similar proportions of diabetes (4.95%) and control (4.87%) participants). An ANOVA (*n*.s.) on years of education showed that the diabetes group ($M = 15.12$ years, $SD = 3.44$) and the control group ($M = 15.33$ years, $SD = 2.92$) were high and similar. Participants' ratings of their health on 5-point scales (1 = *very good* health, 5 = *very poor* health) were generally within the very good to fair range. However, as compared to controls, diabetes participants perceived poorer health relative to a perfect state, $F(1, 461) = 34.13$, $p < .000$, partial $\eta^2 = 0.069$ ($M_D = 2.39$, $SD_D = 0.86$; $M_C = 1.69$, $SD_C = 0.71$), and relative to others their own age, $F(1, 461) = 17.33$, $p < .000$, partial $\eta^2 = 0.036$ ($M_D = 2.00$, $SD_D = 0.78$; $M_C = 1.50$, $SD_C = 0.68$). Given the chronic illness for which they were selected into this study, these perceptions accurately reflect their different overall health status.

We further characterized the groups using VLS physiological tasks (see MacDonald, Dixon, Cohen, & Hazlitt, 2004). Body mass index (BMI; kg/m^2) was significantly higher in diabetes participants, $F(1, 459) = 29.99$, $p < .000$, partial $\eta^2 = 0.061$ ($M_D = 30.20$, $SD_D = 4.65$; $M_C = 26.46$, $SD_C = 3.97$). Eight readings of blood pressure (mmHg) were averaged across four testing sessions. Whereas no group differences were observed for diastolic blood pressure ($M_D = 77.35$, $SD_D = 9.20$; $M_C = 75.06$, $SD_C = 8.89$), mean systolic blood pressure in the diabetes group was significantly higher than controls, $F(1, 444) = 14.38$, $p < .000$, partial $\eta^2 = 0.031$ ($M_D = 134.14$, $SD_D = 15.27$; $M_C = 125.21$, $SD_C = 13.69$). Potential diabetes-related visual acuity complications were assessed using the Close Vision task (Snellen fractions), but no significant differences were observed. Comparisons of audition (using a test of audio acuity, dB) also showed no significant group differences. As noted earlier, we assessed global cognitive competence using the standard 18-item MMSE (Folstein et al., 1975). Scores were generally high and clinically insignificant for both groups. Overall, the diabetes participants were aware of their chronic condition and calibrated their personal health evaluation accordingly, but they were not substantially inferior in other health, sensory, and physiological characteristics. Final demographic and physiological characteristics of the age (YO, 53–70 years; old-old, OO, 71–90 years) X diabetes status (diabetes and controls) groups are reported in Table 1.

Measures

Episodic memory. First, the VLS *word list recall* task consisted of the immediate free recall of two standardized lists of 30 words, each including six words from each of five taxonomic categories (e.g., Dixon et al., 2004; Hultsch, Hertzog, Dixon, & Small, 1998). The score was the average of the number of words recalled from the two lists. Second, the *Rey Auditory Verbal Learning Test* (RAVLT; see Vakil & Blachstein, 1993) required that a word list (15 nouns; List A) was read to the participant, followed by free recall, in each of five trials (Trial A1-A5). Next, for Trial B, an interference list of 15 different nouns was followed by free recall. Next, the words from List A (Trial A6) were recalled. Raw scores from Trial B (acquisition) and Trial A6 (retention) were used. Third, we administered six standardized structurally equivalent *story memory* tests (with approximately 300 words and 60 propositions within 24 sentences), used in the VLS (e.g., Dixon, Hertzog, Friesen, & Hultsch, 1993; Dixon et al., 2004). Average gist recall was computed and converted to proportions.

Semantic memory. First, the *vocabulary test* consisted of 54 multiple-choice questions from the Educational Testing Service kit of factor-referenced cognitive tests (Ekstrom, French, Harman, & Dermen, 1976). The score was the total number of correct items. Second, *fact recall* was measured with two different 40-item tests of general information (e.g., from history, arts, sports) derived

Table 1
Characteristics of Participants in Diabetes and Control Groups According to Age Group

Variables	Diabetes		Controls	
	Young-old $n = 24$	Old-old $n = 17$	Young-old $n = 273$	Old-old $n = 151$
Age	63.64 (4.57)	75.59 (3.07)	62.45 (4.46)	77.59 (4.36)
Range	55 – 69	71 – 80	53 – 70	71 – 90
Gender (% female)	66.7	41.2	72.5	63.6
Age at diagnosis	55.26 (10.09)	66.75 (5.88)		
Duration of condition	8.12 (8.13)	8.54 (6.07)		
Education	14.63 (3.55)	15.82 (3.24)	15.60 (2.84)	14.83 (3.00)
Perfect health	2.29 (0.91)	2.53 (0.80)	1.62 (0.70)	1.81 (0.70)
Relative health	2.08 (0.78)	1.88 (0.78)	1.50 (0.70)	1.50 (0.66)
BMI (kg/m^2)	30.72 (4.05)	29.51 (5.41)	26.61 (4.10)	26.19 (3.73)
Systolic blood pressure (mmHg)	131.33 (15.19)	137.95 (14.98)	123.24 (13.55)	128.70 (13.27)
Diastolic blood pressure (mmHg)	77.76 (8.92)	76.80 (9.82)	75.97 (8.84)	73.44 (8.78)
Close vision (right eye; Snellen)	11.95 (0.21)	11.19 (2.99)	11.77 (1.63)	11.55 (2.11)
Close vision (left eye; Snellen)	10.96 (0.21)	10.25 (2.75)	10.80 (1.34)	10.61 (1.98)
Smoking status (%)				
Never	41.7	41.2	47.6	32.5
Previously	50.0	58.8	49.1	59.6
Currently	8.3	0.0	3.3	7.9
Alcohol use (%)	54.2	70.6	89.0	91.4
Antihypertensive drugs (% use)	54.2	47.1	12.8	25.8

Note. Means and standard deviations are presented as *M (SD).* Age, age at diagnosis, duration of condition and education are presented in years. Age is calculated from the participant's initial testing session. Perfect health represents participant self-rating relative to a perfect state, whereas relative health reflects self-rating relative to peers of a similar age based on a scale from 1–5 (1 = *very good*, 5 = *very poor*).

from a normed battery (Nelson & Narens, 1980). The two scores were averaged and converted to a percentage of correct (see Hultsch et al., 1998).

Verbal fluency. The VLS fluency tests have three standard parts (Hultsch et al., 1998), including subtests of *opposites*, *figures of speech*, and *similarities*. Participants used a limited time to write as many correct words as possible. Raw scores for each subtest were recorded.

Executive functioning. Four tests of executive functioning have been validated, normed, and analyzed in the VLS and elsewhere (see Bielak, Mansueti, Strauss, & Dixon, 2006; de Frias et al., 2006). First, for the *Hayling sentence completion test*, initiation speed and response inhibition were tested (Burgess & Shallice, 1997). In two sections requiring speeded responses, participants were read 15 sentences, each with the last word missing. Whereas the goal of the first section was to respond with a word that swiftly completed the sentence, the goal of the second section was to suppress an initial response by providing a word disconnected to the sentence. Recorded were response latencies (ms) and overall standard scores based on correct responses from the two sections. Second, the *Brixton spatial anticipation test* measured abstraction of logical rules (Andrés & Van der Linden, 2000). Each page of a 56-page booklet contained two rows of five circles, with one of the 10 circles filled in blue. Participants selected which circle they anticipated would be filled on the next page based on the pattern they deduced. A standard score out of 10 (ranging from 1 = *impaired* to 10 = v*ery superior*) was derived. Third, for the three-part *Stroop test*, participants were required to inhibit their automatic verbal responses in reading printed words and instead name the color in which each word was printed. A standard interference index calculated the difference in response latency between Part A (name the color of the printed dots) and Part C (read the color name when printed in incongruent ink), divided by the initial response latency in Part A alone ([Part C – Part A]/Part A). Fourth, the *Color Trails 2* (CT-2) task measured response inhibition without the influence of language. Numbers from 1–25 were randomly arranged twice on a page, once in pink-colored and once in yellow-colored circles. Participants were instructed to connect the numbers from 1–25 in proper sequence, during which they must alternate from one color to the next. The time to complete the task was measured in seconds.

Neurocognitive speed. Five standard speed tests have been used in previous VLS research in aging and special populations (e.g., Dixon et al., 2007; Hultsch et al., 1998). Four were computerized tests presented using a 386 IBM-compatible computer that controlled stimulus timing and presentation. Participants responded by pressing designated keys on a response console, and performance was recorded in milliseconds (ms). Two of these were semantic speed tests (lexical decision, sentence verification) and two were reaction time tests. The fifth test measured perceptual speed (digit symbol substitution). First, for *lexical decision*, participants read a string of five to seven letters and indicated whether the letters produced an English word (e.g., *island* vs. *nabion*). The scores were the mean latencies across the 60 trials (composed of 30 words and 30 nonwords). Second, for *sentence verification*, participants read 50 individually presented sentences and indicated whether each sentence was plausible or nonsensical (e.g., "the tree fell to the ground with a loud crash" vs. "the pig gave birth to a litter of kittens this morning"). Two outcome measures were used: the average latency (correct responses) of the 50 trials and the percentage of errors. Outlier latency values greater or less than three standard deviations from the mean were removed. Third, for the *simple reaction time* (SRT) test, a warning stimulus was presented in the middle of a screen, followed by a signal stimulus

to which participants pressed a key. Ten practice trials were followed by 50 test trials. Ten trials were presented at a time, with randomly alternating intervals separating the warning and signal stimuli (500, 625, 750, 875, and 1000 ms). Each interval was presented five times across the trials. The score was the average latency of the 50 trials. Fourth, for the *choice reaction time* (CRT4) test, a 2 × 2 grid corresponding with the key arrangement on a response console was presented. Each block had 10 trials, wherein the participant attended to four plus signs, one of which transformed into a square, to which the matching key was pressed. Following 10 practice trials, the average latency across 20 test trials was calculated. Fifth, the *Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution* task (DSS; Wechsler, 1991) has been used widely to measure perceptual speed (Hassing, Grant, et al., 2004; MacDonald, Hultsch, Strauss, & Dixon, 2003). In a 90-s period, participants used a coding key of nine numbers paired with specific symbols to fill rows of empty numbered test boxes. The score was the number of correctly transcribed items.

Procedure and Analyses

VLS protocol requires that all measures are administered in the same sequence to all participants. For each wave, actual testing occurs across four sessions about one week apart (for participant comfort and testing efficiency). Detailed VLS procedural information has been previously documented (Dixon & de Frias, 2004; Hultsch et al., 1998). In order to optimize comparison with previous reports of specific cognitive effects, a series of two-way univariate analyses of covariance (ANCOVA) was conducted. The covariate was systolic blood pressure, given (a) observed group differences as noted above, and (b) recent research showing effects of hypertension on diabetes-cognition relationships (Hassing, Hofer, et al., 2004). Diabetes status (diabetes or control) and age group (YO or OO) were the fixed factors, with each cognitive measure as the dependent variable. Regarding statistical significance, to partially adjust for multiple ANCOVAs, we focused on alpha levels of $p \leq .01$. For limited archival, exploratory, and comparative purposes, we also note statistical trends up to $p \leq .05$ (Nilsson, 2006). Analyses were conducted using SPSS Version 15.0 statistical software.

Results

See Table 2 for basic age and diabetes status group results. No significant interaction effects were found, indicating that the cognitive effects of Type 2 diabetes are not moderated by late-life age differences. Significant main effects are described below, emphasizing the diabetes status factor.

Episodic memory. In contrast to several previous findings, no significant differences were observed between diabetes and control

Table 2
Mean Cognitive Performance for Main Effects of Diabetes Status and Age Group

	Diabetes status group			Age group		
Cognitive measure	Diabetes *n = 41*	Controls *n = 424*	*p*	Young-old *n = 297*	Old-old *n = 168*	*p*
Global cognition						
MMSE	28.75 (1.08)	28.87 (1.04)	.701	29.06 (0.91)	28.52 (1.18)	.002
Episodic memory						
Word recall	16.01 (5.37)	17.63 (4.32)	.055	18.50 (3.79)	15.72 (4.92)	.000
RAVLT acquisition	5.70 (2.26)	6.31 (4.46)	.531	6.77 (5.19)	5.38 (1.76)	.063
RAVLT retention	9.93 (3.42)	10.25 (4.92)	.871	10.94 (5.38)	8.98 (3.23)	.031
Story memory	35.27 (9.72)	39.10 (10.21)	.071	41.07 (9.61)	34.75 (10.01)	.001
Semantic memory						
Vocabulary	41.70 (6.48)	42.45 (6.62)	.500	42.12 (6.15)	42.82 (7.33)	.365
Fact recall	50.25 (16.52)	51.43 (15.36)	.456	52.31 (15.32)	49.63 (15.51)	.273
Verbal fluency						
Opposites	12.98 (5.20)	13.66 (4.49)	.390	13.96 (4.44)	12.97 (4.70)	.143
Figures of speech	9.33 (3.12)	9.81 (3.16)	.271	10.18 (3.16)	9.05 (3.02)	.060
Similarities	14.70 (6.22)	15.79 (6.04)	.302	16.25 (6.07)	14.73 (5.92)	.036
Executive functioning						
Hayling	5.16 (1.44)	5.84 (1.21)	.003	6.03 (1.05)	5.34 (1.42)	.002
Brixton	4.43 (1.88)	5.11 (2.12)	.110	5.49 (1.95)	4.29 (2.16)	.005
Color Trails 2 (s)	106.09 (36.05)	91.08 (29.10)	.013	83.05 (22.61)	108.65 (34.21)	.000
Stroop Test	1.39 (0.88)	1.17 (0.61)	.072	1.10 (0.60)	1.36 (0.69)	.030
Semantic speed						
Lexical dec. (ms)	1550.26 (606.68)	1315.34 (494.66)	.015	1257.10 (397.21)	1474.46 (639.08)	.029
S.V. (% error)	5.25 (4.48)	3.99 (3.25)	.038	3.76 (3.16)	4.70 (3.70)	.047
S.V. (ms)	4074.65 (1071.75)	3451.27 (1207.54)	.008	3290.98 (1021.15)	3883.52 (1404.35)	.040
Reaction time						
SRT (ms)	370.59 (76.80)	343.90 (79.06)	.097	328.83 (68.18)	376.36 (87.54)	.001
CRT4 (ms)	951.34 (168.56)	886.14 (171.53)	.114	825.90 (123.94)	1004.48 (184.38)	.000
Perceptual speed						
DSS raw score	46.25 (12.42)	50.43 (10.84)	.093	53.69 (9.98)	43.77 (9.92)	.000

Note. Means and standard deviations are presented as *M (SD)*. SRT, CRT4, Lexical dec., S.V., and DSS represent simple reaction time, choice reaction time, lexical decision, sentence verification, and Digit Symbol Substitution, respectively. Actual *n*s vary across cognitive tasks due to missing data. All *p*s are for main group effects.

groups on any outcome measure of episodic memory. However, in concordance with normal aging patterns, YO groups performed significantly better than OO groups on two episodic measures, including word list recall, $F(1, 443) = 18.32$, $p < .000$, partial $\eta^2 = 0.040$, and story memory recall, $F(1, 443) = 11.49$, $p < .001$, partial $\eta^2 = 0.025$, with a trend for RAVLT retention, $F(1, 443) = 4.69$, $p < .031$, partial $\eta^2 = 0.010$.

Semantic memory. No significant group differences were observed on either measure.

Verbal fluency. No significant diabetes-related group differences were observed.

Executive functioning. The control group performed significantly better than the diabetes group on the Hayling task, $F(1, 434) = 8.86$, $p < .003$, partial $\eta^2 = 0.020$, with a trend for Color Trails 2, $F(1, 440) = 6.26$, $p < .013$, partial $\eta^2 = 0.014$. No diabetes-related group differences were evident on the Brixton or the Stroop test. Significant age group differences were observed for all four measures of executive functioning, including the Hayling, $F(1, 434) = 9.32$, $p < .002$, partial $\eta^2 = 0.021$; Color Trails 2, $F(1, 440) = 21.73$, $p < .000$, partial $\eta^2 = 0.047$; and the Brixton, $F(1, 438) = 7.98$, $p < .005$, partial $\eta^2 = 0.018$.

Semantic speed. Healthy controls performed significantly faster than participants with diabetes on the sentence verification task, $F(1, 442) = 7.17$, $p < .008$, partial $\eta^2 = 0.016$, with a trend for a lower error rate, $F(1, 442) = 4.32$, $p < .038$, partial $\eta^2 = 0.010$. Healthy controls also displayed a trend for faster performance on the lexical-decision task, $F(1, 442) = 5.96$, $p < .015$, partial $\eta^2 = 0.013$. Regarding age, the YO group tended to outperform the OO group on the lexical-decision task, $F(1, 442) = 4.83$, $p < .029$, partial $\eta^2 = 0.011$, and the percent error, $F(1, 442) = 3.98$, $p < .047$, partial $\eta^2 = 0.009$, and latency measure, $F(1, 442) = 4.25$, $p < .040$, partial $\eta^2 = 0.010$, of the sentence verification task.

Reaction time. There were no observed diabetes group differences on SRT or CRT4. As expected, YO participants were faster than OO participants on both the SRT, $F(1, 440) = 12.11$, $p < .001$, partial $\eta^2 = 0.027$, and CRT4, $F(1, 440) = 47.25$, $p < .000$, partial $\eta^2 = 0.097$.

Perceptual speed. No significant diabetes-related effect was observed between the diabetes group and the healthy controls on the DSS task. YO participants performed significantly faster than OO participants, $F(1, 442) = 30.42$, $p < .000$, partial $\eta^2 = 0.064$.

Discussion

A growing literature has examined the extent and depth of potential cognitive effects of Type 2 diabetes in older adults. We contribute to this literature by examining simultaneously a broad range of cognitive neuropsychological measures as performed by both YO and OO healthy controls and relatively mild diabetes patients. Our findings revealed significant group differences within select domains, most consistently in speed-intensive measures of executive functioning and semantic speed. As suggested by Nilsson (2006), not all aspects of cognition may be equally or coincidentally affected by Type 2 diabetes, at least in relatively mild-to-moderate cases.

Two results are briefly noted and not further discussed. First, performance on global cognition (i.e., MMSE) for both groups was high and virtually identical. We excluded low performers from a relatively well-educated volunteer sample and reported MMSE results for descriptive purposes only. Second, previous studies have employed older adults from different and mixed age bands (e.g., under age 70, Fontebonne et al., 2001; over age 70, Hassing, Grant, et al., 2004). Examining whether systematically sampling along the age index would affect diabetes-related cognitive effects, we found commonly observed late-life cross-sectional age effects but no interactions of age group with diabetes status. Diabetes-related cognitive effects may be generally constant across age, at least for the current ranges of duration and severity.

Regarding the executive functioning results, two measures produced significant performance differences in favor of the controls: that is, the Hayling (involving speed and inhibition) and Color Trails 2 (involving speed and shifting). In addition, the group means were nonsignificant but in the same direction for the other two executive tests: that is, the Brixton (involving rule attainment and planning) and Stroop interference index (involving inhibition of responses). The fact that executive functioning tests are associated with inconsistent patterns of diabetes-related deficits (Messier, 2005) is not unexpected given the broad and sometimes multidimensional nature of the construct and the variable tasks used to measure associated processes in different populations (e.g., de Frias et al., 2006; Zhang, Han, Verhaeghen, & Nilsson, 2007). Because studies on diabetes and aging may produce executive functioning results that are in part a function of the tests used, a theoretically convergent pattern has been elusive. The present results contribute to potential consolidation of the executive functioning deficit associated with milder forms of diabetes in that the tasks for which we found group differences required a contribution of speed. Conceivably, simpler tasks measuring less speed-intensive aspects may be less sensitive to milder diabetes-related effects. Some of the inconsistency in the literature may be due to the fact that multiple aspects of executive functioning are differentially represented in neuropsychological test batteries and perhaps even applied unsystematically across age and disease severity continua. The notion that earlier effects may be observed in tasks requiring rapid performance of executive-demanding processes may be tested in future research using samples of broader clinical severity and with longitudinal follow-ups. Such deficits may cascade throughout the executive functioning domain as diabetes progresses and the rates of aging- and disease-related structural changes in the brain accelerate (Manschot et al., 2006).

The results were selective also within the neurocognitive speed domain. Of the three sets of speed measures, no group performance differences were found for either traditional reaction time (SRT and CRT4) or perceptual speed tasks (e.g., Cosway, Strachan, Dougall, Frier, & Dreary, 2001; Fontbonne et al., 2001; Hassing, Grant, et al., 2004). Instead, the diabetes group performed most prominently and significantly slower than the control group on the sentence verification task, with a consistent trend for lexical decision. Perhaps tasks requiring quick and precise processing of new verbal information may be sensitive markers for detecting cognitive deficits in relatively milder diabetes patients (Arvanitakis, Wilson, & Bennett, 2006; Nilsson, Fastbom, & Wahlin, 2002), a conclusion not available without the presence of semantic speed tasks (as well as the Hayling). Normal aging-related slowing of performance is well known, and accelerated (or inconsistent) slowing may signal early cognitive impairment or Alzheimer's disease (Dixon et al., 2007; Rapp & Reischies, 2005). Future

clinical and longitudinal research may test the possibility that speed-intensive tasks involving semantic operations may be differentially sensitive markers in older diabetes patients. However, given the novelty of semantic speed assessments in diabetes literature, replication studies would be useful.

Two conspicuous null findings require brief comment, as they are relevant to previous literature and complement the two observed deficits described above. First, although verbal episodic memory tends to be more frequently impaired in both healthy older adults (e.g., Dixon et al., 2004) and older diabetes patients (see Nilsson, 2006), we observed no significant diabetes-related differences for any of our three verbal episodic tasks. The provisional importance of this null result is weakened by the informal observation that the group means are generally in the expected direction (see Table 2). This implies both methodological (e.g., role of covariates, statistical power) and clinical directions for future research. We were able to check one of these issues, namely, the role of a comorbidity covariate. Post hoc ANOVAs (without systolic BP as covariate) revealed a tendency for two memory tasks (and the two additional speeded tasks) to produce trends ($p \leq .05$) in the expected direction. Therefore, active diabetes-related comorbidities (e.g., hypertension) may be a contributing factor to whether domain-specific cognitive deficits are observed (Saxby, Harrington, McKeith, Wesnes, & Ford, 2003; Hassing, Hofer, et al., 2004; Waldstein, 1995). Future clinical research may examine whether episodic memory deficits are not leading indicators of early diabetes-related cognitive effects, but markers of further progression of the disease and expanded neurological involvement.

A second set of null findings merits brief comment. In contrast to some previous research (see Nilsson, 2006), we did not find significant group differences in performance on any measure of verbal fluency. As with executive functioning, the fluency tests used in various studies differ considerably in procedure and cognitive demands. For example, whereas our measures required relatively abstract thinking in finding opposites, figures of speech, and similarities between words, the fluency tasks used by Wahlin et al. (2002) required more basic letter-word fluency. Future research comparing more levels of complexity and demand in fluency could be helpful in delineating the extent of the deficit, its relationship to severity of the disease, and the possibility of some early preserved fluency skill. Similarly, expected null findings for semantic memory were observed for the typical vocabulary measure and this pattern was extended to include the previously untested fact memory task. Broadening the range of diabetes severity, exploring further comorbidities, and conducting longitudinal follow-ups will begin to clarify the timing of and extent to which fluency and semantic memory may be affected by diabetes (Arvanitakis et al., 2004; Hassing, Grant, et al., 2004).

Overall, our interpretation has emphasized three important themes: (a) classification and diagnosis clarity (e.g., disease identification and severity, comorbidities, exclusionary criteria), (b) possible temporal ordering of diabetes-related cognitive neuropsychological outcomes as the disease progresses, and (c) potential theoretical and clinical value of comprehensive cross-sectional and follow-up longitudinal assessments. If executive resources and speed may be most prominently compromised relatively early in Type 2 diabetes, confirmatory and complementary evidence should be observed across studies with various combinations of the elements of the three themes. Among the strengths of this study is the unusually broad age range of older adults, with which we confirmed that aging-related diabetes effects may be invariant across young-old and old-old age groups. Second, we accessed VLS Sample 3 archives for self-report and objective diagnostic information, background and comorbid health indicators, and an extensive battery of cognitive neuropsychological domains. Third, with the broad cognitive neuropsychological battery, we were able to detect a profile of robust effects in select domains, most notably executive functioning and speed. Given the current comprehensive cross-sectional baseline, future longitudinal research—with the VLS and other studies—can examine potentially differential decline patterns. Fourth, we covaried systolic blood pressure in our analyses, as there is evidence to suggest that elevated blood pressure increases cognitive decline independent of diabetes (Elias, D'Agostino, Elias, & Wolf, 1995; Waldstein, 2003). The importance of considering hypertensive effects is highlighted, as it may differentially contribute to cognitive decline and inflate the differences attributed to diabetes.

A first limitation reflects several unmodifiable characteristics of our sample: It is volunteer-based, from a smaller urban population in Canada, predominantly Caucasian, relatively well-educated, initially selected on global cognitive intactness, and with generally available health care. Thus, results are not necessarily representative of the entire Canadian or western population, but they may generalize to a large and growing population of relatively healthy aging preboom and boomer populations. Future studies of greater diversity are encouraged. Second, although provisional diagnoses of Type 2 diabetes were based on a combination of commonly used self-report, follow-ups, and objective medication data, more precise biological information (e.g., HbA1c levels, Fasting Blood Glucose levels) is currently unavailable in the VLS. Conceivably, some nondiagnosed cases may be present in the control group, but their unlikely presence would have rendered a more conservative test of the hypotheses. Third, although well characterized, a larger diabetes group would have been preferable. We noted earlier, however, that our diabetes group ($n = 41$) is well within the range of comparable neuropsychological studies (with *n*s of 20–41). Moreover, as a proportion of the VLS parent sample, it is similar to Canadian population expectations.

Overall, this study contributes to the literature with a comprehensive neuropsychological battery and a broad age range with which to explore deficits associated with relatively mild Type 2 diabetes in older adults The results both qualify and extend those of previous reports, particularly (but differentially) in the domains of speed, executive functioning, and episodic memory. Given the modern western lifestyle, associated health risks, and growing populations of older adults, Type 2 diabetes will likely increase as a common aging-related challenge to neurobiological and cognitive health. Future studies examining longitudinal trends in neuropsychological sequelae of diabetes will help determine whether different patterns of cognitive decline occur across both health condition (diabetes group vs. healthy controls) and neuropsychological domain (executive functioning, cognitive speed, episodic memory).

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