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Are Neurocognitive Speed and Inconsistency Similarly Affected in Type 2 Diabetes?

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Abstract

Type 2 diabetes (T2D) is a disease of aging with indirect but detectable and cumulative neurological implications. We systematically tested whether neurocognitive speed (mean rate) or inconsistency (intraindividual variability) was the more sensitive clinical marker of T2D. Three of four research questions used a cross-sectional wave of the Victoria Longitudinal Study (VLS) divided into T2D (age 55-81 years) and control (age = 53-91 years) groups. The fourth question addressed relative two-wave longitudinal changes. Each of four speeded tasks produced intraindividual mean rate (IM) and intraindividual standard deviation (ISD) scores. First, the T2D group performed more slowly than the controls. Second, this deficit extended to inconsistency, but less uniformly. Third, based on logistic regression analyses, IM was the more effective predictor of T2D status. Fourth, we observed similar longitudinal change patterns for IM and ISD. Results are linked to the theoretical location of T2D on an adjusted neural vulnerability continuum.

Keywords

Aging; Intraindividual Variability; Logistic Regression Analyses; Neurocognitive Speed; Type 2 Diabetes; Victoria Longitudinal Study

Type 2 diabetes (T2D) is a disease engendered by pathological variability (e.g., in glycemic control) and treated with best practices designed to reduce variability around a target level (e.g., HbA1c level less than 7%; Ford, Li, Little, & Mokdad, 2008). However, a recent report indicates that about 43% of American adults diagnosed with T2D were unsuccessful in meeting this American Diabetes Association recommended target for glycemic control (Ford et al., 2008). Older adults with T2D face several formidable challenges to achieving the goal of optimal glycemic control. The challenges include potential sources of variability from the (a) biological factors of T2D (i.e., vacillation in proximal determinants of T2D severity, glucose and insulin control) and (b) behavioral or disease management realm (i.e., cross- or within-person variations in self-care behaviors may contribute to difficulties in achieving regularity in glycemic control). Moreover, variations in glycemic control may be among the mechanisms leading to T2D-related cognitive deficits among older adults

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(Nilsson, 2006). Notably, Nilsson and Wahlin (2009) linked deleterious neurobiological changes associated with T2D to T2D-related cognitive decrements among older adults.

Although the growing number of reports are somewhat varied in details of their methods and results, T2D-related cognitive deficits have been observed in the fundamental domains of executive functioning and neurocognitive speed (Gregg et al., 2000; Naor, Steingruber, Westhoff, Schottenfeld-Naor, & Gries, 1997; van den Berg et al., 2008; Vanhanen et al., 1997; Yeung, Fischer, & Dixon, 2009), as well as in episodic memory (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001; McFall, Geall, Dolcos, & Dixon, 2010; Nilsson, 2006; Nilsson & Wahlin, 2009). Neurobiological factors associated with these and other T2D-related cognitive deficits are being actively explored. One view is that the cognitive changes in T2D may phenotypically present as accelerated aging-related decline (Roriz-Filho et al., 2009; Wahlin, Nilsson, & Fastbom, 2002). Such changes are thought to be driven by multiple mechanisms, likely involving the cumulative effects of oxidative stress, inflammation, advanced glycation end-products and other factors (Gispen & Biessels, 2000). In addition, brain imaging studies have demonstrated T2D-related changes in hippocampus and cerebral cortex (Gispen & Biessels, 2000; Messier, 2005), temporal lobe atrophy (Wrighten, Piroli, Grillo, & Reagan, 2009), and an increased prevalence of white matter hyperintensities (Gispen & Biessels, 2000) and micro-infarcts (Manschot et al., 2006, 2007).

Not yet examined in T2D-cognition research is whether the deficits observed in mean level of cognitive performance extend or relate to intraindividual variability (IIV) in speeded performance. The following logic establishes briefly why both the investigation of mean-level and IIV-based indicators of neurocognitive speed may be worthy of attention in the case of T2D: (a) IIV is measured by the same tasks that evaluate overall speeded (mean rate) performance, (b) recent research has shown that mean rate speeded performance is affected in T2D patients, (c) mean rate of speeded performance and mean IIV are correlated, (d) available neurobiological evidence in T2D suggests that IIV (at the cognitive level) may be expected, and (e) available neuropsychological evidence suggests that elevated neurocognitive IIV is associated with various neurological conditions (e.g., Gorus, De Raedt, Lambert, Lemper, & Mets, 2010; MacDonald, Nyberg, & Backman, 2006). For example, elevated IIV in neurocognitive speed performance has been demonstrated with neurologically based conditions such as Parkinson's (de Frias, Dixon, Fisher, & Camicioli, 2007), mild cognitive impairment (Dixon et al., 2007; Strauss et al., 2007), and incident dementia (Duchek et al., 2009; Holtzer, Verghese, Wang, Hall, & Lipton, 2008). In contrast, reports of IIV assessments in populations of neurologically typical older adults with somatic illnesses (such as arthritis) have shown no significant elevation in neurocognitive inconsistency (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000).

What might be expected for older adults with T2D? We suggest that along an etiologically-based continuum spanning proximal neurological-centered diseases (e.g., Alzheimer's) to distal non-neurological/somatic diseases (e.g., arthritis), T2D may be conceptualized as intermediate, in that it originates non-neurologically but projects influence to the cerebral cortex due to its vascular and glucose involvement. Consolidating the foregoing review, we arrive at the following conjecture. Despite the fact that T2D is not principally a neuropathic disease, it has some characteristics that could implicate neurocognitive inconsistency: (a) it is a disease with biological-systemic variability as a key pathological phenotype, (b) it is associated with deficits in neurocognitive speed (often related to IIV), and (c) it is associated with dopaminergic dysregulation, which is thought to be the primary facilitator of IIV in cognitive performance in neurological conditions (MacDonald, Cervenka, Farde, Nyberg, & Bäckman, 2009). This fact may have clinical significance. Specifically, although not uniformly documented, in some instances for some neurological conditions, IIV has been tested as a candidate to be a more effective indicator of neurocognitive deficits than is mean

rate (speed) (e.g., Dixon et al., 2007; MacDonald, Hultsch, & Dixon, 2008). Finding early behavioral markers of both neurologically-centered and neurologically-related disease transitions is a clinically important pursuit.

If T2D-related deficits in cognitive performance (rate of speed) have neurobiological underpinnings, what might be the corresponding neurobiological correlates of possible T2D-IIV relationships? Some aspects of phenotypic T2D presentation have implicated variability in biological systems, and converge on a common theme of pathological inconsistency. These include irregular oscillations of plasma insulin (Schmitz, Rungby, Edge, & Juhl, 2008), deleterious effects of glucose excursions (Monnier et al., 2006; Zaccardi, Pitocco, & Ghirlanda, 2009), and behavioral variations in treatment adherence. In the first example, for both prodromal T2D and overt T2D, abnormal insulin fluctuations represent a pathological loss of systemic control, as well as reduced responsiveness to changes in blood glucose concentrations. In the second example, clinical T2D research has for decades focussed on effects of mean glucose control (HbA1c), but recent reports have uncovered an independent role for glucose variability in vascular complications (Ceriello, 2005) and streamlined mechanisms of oxidative stress (Monnier et al., 2006). In the third example, clinical research has demonstrated treatment adherence issues are especially problematic in T2D groups, with intervention outcomes directly related to consistent, long-term management of factors such as weight (Krause et al., 2007), eating behavior (e.g., binge eating; Ryan, Gallanagh, Livingstone, Gaillard, & Ritz, 2008), glucose control (Gallegos, Ovalle-Berumen, & Gomez-Meza, 2006), and medication taking (Kuo et al., 2003). Arguably, barriers to achieving long-term, successful management of T2D are often mediated by both independent and interacting factors of behavioral inconsistency. For example, disordered eating (which occurs in up to 27% of T2D patients; Ryan et al., 2008) may have a direct effect on weight control, and elevated BMI is related to overall glucose control. Medication taking behavior has also been shown to exhibit significant within-person variability in some T2D populations and has been associated with deleterious effects on kidney health and overall mortality (Kuo et al., 2003).

The present study occurs in the context of the Victoria Longitudinal Study (VLS). Previous reports on T2D-related cognitive deficits and decrements from the VLS (Fischer et al., 2009; Yeung et al., 2009) have demonstrated robust performance decrements in a variety of speeded tasks. Correspondingly, previous VLS reports have also linked elevated intraindividual variability in speeded performance to neuropsychological conditions and aging (e.g., Dixon et al., 2007; MacDonald, Hultsch, & Dixon, 2003). We use four source speed tasks: lexical decision (LEX), semantic verification (SEM), choice reaction time (CRT; 2 choice, 4 choice, and 8 choice), and simple reaction time (SRT). Four research goals are investigated in this study. First, cross-sectional differences in neurocognitive speed performance (mean rate) will be compared across diagnostic older adult groups (T2D group vs. Control). Second, intraindividual standard deviations (ISDs) will be calculated for both T2D and control groups, and will be used to assess cross-sectional differences in intraindividual variability. Third, logistic regression analyses will be employed to determine the extent to which mean rate or ISDs (or both) successfully identified T2D individuals from the larger sample. The fourth research goal will incorporate initial two-wave longitudinal data to test the effects of T2D status on speeded mean rate and inconsistency over a 3-4-year period.

Method

The VLS is a multi-cohort study of biomedical, health, cognitive, and neurocognitive aspects of aging. Three independent samples of initially healthy older adults are followed at

about three-year intervals (see Dixon & de Frias, 2004). The VLS is in full compliance with all prevailing research ethics guidelines.

Participants

The present participants were from VLS Sample 3 and completed baseline testing in 2002-03 and a second wave of testing in 2005-06, yielding cross-sectional and 3-4-year longitudinal data.

Cross-sectional sample: Two diagnostic groups—Participants from the first wave of VLS Sample 3 consisted of 577 community dwelling adults (age range = 53-90 years; *M* age = 68.29 years, *SD* = 8.60). A total of 7 participants were removed from the baseline sample (6 with missing information on diabetes status, 1 with type 1 diabetes), for an initial Wave 1 (W1) sample of *n* = 570. Participants were further examined and were selected into appropriate T2D and control groups based on defined diagnosis information and exclusionary criteria.

The presence of T2D was determined by a multiple-stage diagnostic procedure involving a series of self-report, objective medication information, and validity checks at both W1 and Wave 2 (W2). We utilized a sequence of strict diagnostic criteria for selection into the T2D or the control group (e.g., McFall et al., 2010; Yeung et al., 2009). Specifically, inclusion into the T2D group required that all of the following five conditions be met: (a) self-report of formal diabetes diagnosis (by a physician) and severity rating at W1; (b) W1 report of onset age of about 30; (c) W1 report of method of treatment (i.e., oral medication, insulin, diet and exercise, no control, or any combination); (d) W1 presence of objective prescription and nonprescription medications for those T2D participants who reported this form of treatment; and (e) three-year (W2) follow-up validity check confirming T2D-related diagnosis, severity rating, and treatment method. Although the VLS does not have access to additional T2D-confirming medical information (i.e., blood glucose level above 6.0mmol/L at baseline, or elevated HbA1c level), our multi-step diagnostic procedure goes well beyond the frequently used and documented self-report classifications (e.g., Arvanitakis, Wilson, Li, Aggarwal, & Bennett, 2006; Connolly, Unwin, Sherriff, Bilous, & Kelly, 2000), and is consistent with diagnostic criteria currently used in the literature (Arvanitakis et al., 2006; Gregg et al., 2000; Luchsinger, Tang, Stern, Shea, & Mayeux, 2001; Yeung et al., 2009). Of the original 570 adults, 48 were identified as potential T2D patients based on initial self-reports (condition 1 above). Of these, 44 met the full and strict criteria of our multistage diagnostic procedure.

In addition to the diagnostic criteria, all W1 participants were evaluated on three sets of standard exclusionary criteria, as previously applied in VLS T2D research: (a) no previously diagnosed Alzheimer's disease or vascular dementia; (b) no participants scoring less than 26 on the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975); (c) no pre-existing neurological conditions (e.g., stroke, Parkinson's disease), cardiovascular disease (e.g., hypertension), or psychiatric conditions (e.g., depression, antipsychotic medication). After following documented and standardized procedures (e.g., McFall et al., 2010), 3 T2D and 98 control participants were excluded from the present sample.

For the final cross-sectional sample (*n* = 465), the T2D 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 T2D (4.95%) and control (4.87%) participants). Full background information is presented in Table 1. ANOVAs showed key group similarities, with only several exceptions. 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, T2D participants perceived their health to be poorer relative to a perfect state, F (1, 461) = 34.13, $p < 0.000$, partial $\eta^2 = 0.069$, and relative to others their own age, F (1, 461) = 17.33, $p < 0.000$, partial $\eta^2 = 0.036$. 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. Only two significant differences were detected. Body mass index (BMI; kg/m^2) was significantly higher in T2D participants, F (1, 459) = 29.99, $p < 0.000$, partial $\eta^2 = 0.061$. Eight readings of blood pressure (mmHg) were averaged across four testing sessions. Whereas no group differences were observed for diastolic blood pressure, mean systolic blood pressure in the T2D group was significantly higher than controls, F (1, 444) = 14.38, $p < 0.000$, partial $\eta^2 = 0.031$. No differences were observed for vision, audition, MMSE, grip strength, or peak expiratory flow. Overall, the T2D 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.

Longitudinal sample—A total of 330 participants (T2D: $n = 28$; controls: $n = 302$) of the 465 participants used for the cross-sectional sample returned 3-4 years later and completed the second wave of testing. The overall retention rate was 71.0%, with notably similar rates for T2D participants (68.3%) and control participants (71.2%). Primary reasons for attrition were death and re-location or unavailability.

The same exclusion criteria used in W1 were applied at W2 with the exception that we modified the MMSE criteria in two minor ways consistent with the literature (e.g., Gorus et al., 2010): The cutoff score was shifted to 24 from 26 and we checked for a 3-point drop from W1 to W2. Overall, we removed n=30 control participants from the longitudinal sample (0 T2D participants) as a result of applying the continuing and the modified MMSE exclusion criteria. The final longitudinal sample comprised a T2D group ($n = 28$; 18 female, 10 male) and a control group ($n = 272$; 188 female, 84 men). All participants met our sample criteria, including participation in both waves. The average interval was M = 4.2 years (SD = .64 years). Background information is presented in Table 2. Similarities and differences between the groups on self-rated health and physiological measures mirrored those observed at W1. The T2D participants perceived themselves as having poorer health (relative to a perfect state) than the controls, $F(1, 297) = 33.14$, $p < .001$, partial $\eta^2 = .10$. Similarly, T2D participants’ self-perceptions of health in comparison to their peers were significantly lower than those of controls at W2, $F(1, 297) = 21.30$, $p < .001$, partial $\eta^2 = .07$. Body mass index (BMI; kg/m2) was significantly greater for the T2D group at W2, $F(1, 297) = 11.11$, $p < .001$, partial $\eta^2 = .04$. As well, systolic blood pressure was significantly higher in T2D participants at W2, $F(1, 297) = 14.09$, $p < .001$, partial $\eta^2 = .05$, whereas no difference was observed for diastolic blood pressure.

Measures

Four standard measures of neurocognitive speed used in previous VLS research with older adults and special populations (e.g., Dixon et al., 2007) were available. All were computerized tests that controlled stimulus timing and recorded response latencies to an accuracy of +/− 1 msec. Missing data were rare, so we computed analyses on all available data rather than using listwise deletion.

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*). A total of 60 trials were presented (30 words and 30 non-words).

Semantic 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). A total of 50 trials were presented (24 plausible and 26 nonsensical).

Simple reaction time (SRT)—A mid-screen warning stimulus was followed by a signal stimulus to which participants pressed a key. A total of 50 trials were presented in blocks of 10 trials, with five randomly alternating intervals separating the warning and signal stimuli (500, 625, 750, 875, and 1000 ms).

***Choice reaction time 2, 4, and 8* (CRT2, CRT4, CRT8)—**A 3 × 3 grid corresponding with the key arrangement on a response console was presented. For each block of ten trials, participants were required to attended to a two, four, or eight block matrix (CRT2, CRT4, and CRT8, respectively) containing plus signs. A warning tone was presented followed by a 1000ms delay and then the appropriate 2-, 4-, or 8-square matrix was presented. In this matrix one of the plus signs in the first matrix was transformed into a square: participants were required to press the key corresponding to this position on the matrix. A total of 20 trials were presented in two blocks of 10 trials for each task. Scores were calculated independently for each level of choice.

Statistical Procedure

Intraindividual means and standard deviations were computed using RT latencies from each multi-trial neurocognitive speed task. Distributions of raw latency scores for each task were examined for outliers. Extremely fast or slow responses may represent various sources of measurement error (e.g., accidental key press, distraction). Lower bounds for legitimate responses were suggested by prior research (150 ms for SRT and CRT 2, 4, 8; 400 ms for lexical; 1000 ms for semantic; Dixon et al., 2007). Upper bounds for outliers were determined for each task and individual; RTs for trials that exceeded 3 SD above a given individual's mean were excluded. Missing RT trial values were imputed using a regression substitution procedure that forms individual equations of response times across all trials. The procedures for eliminating outlying trials and imputing missing values decrease within-subject variation, thus representing a conservative approach to examining inconsistency.

Computation of intraindividual means—For each task, the average rate across trials was calculated in terms of *intraindividual means* (IM). IMs were computed as the average of each individual's raw RT latencies across all trials.

Computation of intraindividual variability—Variability estimates were computed as the across-trial intraindividual standard deviation (ISD) about each individual's mean RT. Numerous approaches for computing ISD estimates, and associated criticisms, have been well documented (see Hultsch, Strauss, Hunter, & MacDonald, 2008 for the logic and justification of our approach). In creating the ISD scores, we controlled for various confounding influences including age group differences in mean RT, T2D status, practice effects across trials, and their higher-order interactions. These effects were residualized using a split-plot regression approach:

$$Y = a + b(\text{age group}) + c(\text{T2D status}) + d(\text{trial}) + e(\text{age group X T2D status}) + f(\text{age group X trial}) + g(\text{age group X T2D status X trial}) + e$$

ISD scores were subsequently computed using the standardized residuals derived from the above equation. This residualizing approach removes any systematic within-subject (i.e., trial) and between-subject (i.e., age group) sources of variance in mean RT, with the remaining sources of variance reflecting each individual's unsystematic portion (i.e.,

inconsistency). To facilitate the presentation across tasks we adopted an easily interpretable metric; namely, the residuals were converted to standardized *T*-scores ($M = 50$, $SD = 10$) prior to computing ISDs for each task. In the case of longitudinal data, ISDs were also computed for each wave.

Statistical Analyses—For all measures of neurocognitive speed, group differences (T2D vs. controls) in mean performance (IMs) and performance variability (ISDs) were evaluated using multivariate analyses of variance (MANOVA). T2D Status (2), and Age group (Young Old (YO; 51-70 years) vs. Old Old (OO; 71-85 years)) were assessed as fixed factors in the initial multivariate model for both IM and ISD. In order to determine the presence T2D and age group differences in IM performance, follow-up univariate ANOVAs for mean SRT, SEM, and LEX performance were conducted. CRT 2, 4 and 8 ISD task performances were analyzed concurrently using a follow-up MANOVA with T2D Status and Age as fixed factors. Subsequently, a series of logistic regression analyses evaluated whether the identification of T2D individuals is improved by adding ISDs to the predictive models. Given concerns with multicollinearity among predictors, we computed not only simultaneous entry logistic models (including both IM and ISD in the same model), but also models where IM and ISD were entered separately with subsequent fit comparisons made between these models. For the longitudinal analyses, repeated measures ANOVAs were used in order to assess main effects of Wave and T2D Status as well as the presence of any Wave x T2D Status interactions across the follow-up study period. Separate analyses were computed for each neurocognitive speed task.

Results

The results are summarized in two sections: we first present the cross-sectional findings, followed by the longitudinal results. Within each section, results corresponding to the four primary research goals are summarized. One-tailed p-values are reported based on our a priori hypotheses regarding the direction of the effect.

Cross-Sectional Models

Our first three research questions were evaluated with W1 cross-sectional data. We used a MANOVA to assess T2D status group (T2D, controls) and age (YO, OO) effects in concurrent neurocognitive speed performance for both IMs and ISDs. Regarding mean rate (IMs), the multivariate F test was significant for both T2D group status, $F(6, 445) = 2.16$, $p < .05$, $\eta^2 = .03$, and age group, $F(6, 445) = 8.17$, $p < .01$, $\eta^2 = .10$. The interaction term was not significant. The univariate ANOVA results were consistent with expectations (see Table 3). The T2D group exhibited significantly slower mean RT performance for all tasks: SRT, $F(1, 450) = 6.22$, $p < .05$, $\eta^2 = .01$; CRT2, $F(1, 450) = 4.72$, $p < .05$, $\eta^2 = .01$; CRT4, $F(1, 450) = 5.21$, $p < .05$, $\eta^2 = .01$; CRT8, $F(1, 450) = 5.40$, $p < .05$, $\eta^2 = .01$; Lexical, $F(1, 450) = 7.66$, $p < .01$, $\eta^2 = .02$; and Semantic, $F(1, 450) = 8.34$, $p < .01$, $\eta^2 = .02$. Similarly, the Old-Old age group exhibited uniformly slower response latencies than did the Young-Old group: SRT, $F(1, 450) = 7.77$, $p < .01$, $\eta^2 = .02$; CRT2, $F(1, 450) = 32.07$, $p < .01$, $\eta^2 = .07$; CRT4, $F(1, 450) = 47.64$, $p < .01$, $\eta^2 = .10$; CRT8, $F(1, 450) = 39.62$, $p < .01$, $\eta^2 = .08$; Lexical, $F(1, 450) = 4.53$, $p < .05$, $\eta^2 = .01$; and Semantic, $F(1, 450) = 4.32$, $p < .05$, $\eta^2 = .01$.

Regarding the second research question, corresponding MANOVAs for intraindividual variability (ISD) in neurocognitive speed also revealed a significant multivariate effect for both T2D group status, $F(6, 445) = 2.12$, $p = .05$, $\eta^2 = .03$, and age group, $F(6, 445) = 2.82$, $p < .05$, $\eta^2 = .04$. The interaction term was not significant. Univariate ANOVAs demonstrated significant (one tailed) increases in ISDs for the T2D group for Lexical, F(1,

450) = 7.72, $p < .01$, $\eta^2 = .02$, and Semantic, $F(1, 450) = 3.56$, $p < .05$, $\eta^2 = .01$) speed, but no diagnostic group differences in variability were observed for the remaining speed measures (SRT, CRT2, CRT4, CRT8) (see Table 3). Significant age group differences in IIV were observed for select reaction time measures (SRT, $F(1, 450) = 4.64$, $p < .05$, $\eta^2 = .01$; CRT2, $F(1, 450) = 12.60$, $p < .01$, $\eta^2 = .03$; CRT4, $F(1, 450) = 4.97$, $p < .05$, $\eta^2 = .01$), but not for the measures of Lexical and Semantic speed.

Our third research question focused on the T2D status effect, observed uniformly for IM (mean rate) and selectively for ISD (intraindividual variability). Logistic regression analyses were employed to determine whether ISDs, over and above IMs, can differentially improve the identification of those with T2D. The dichotomous group outcome variable was coded as 0 = controls and 1 = T2D, with odds ratios greater than 1 indicating an increased risk of T2D. In light of our a priori directional hypotheses, 1-tailed probability values are reported. Accordingly, we computed two separate sets of logistic regression models for each speeded measure, with one model focusing on IM as a predictor and the other model focusing on ISD. Moderate to high multicollinearity was observed between markers of IM and ISD for the same cognitive indicator: SRT (r = 0.55), CRT2 (r = 0.52), CRT4 (r = 0.52), CRT8 (r = 0.58), LEX (r =0.90), and SEM (r = 0.82). Thus, acknowledging potential differential reliability (Schmiedek, Lövdén, & Lindenberger, 2009), we computed separate-entry models to test the extent to which IM or ISD differentiated diagnostic group status (control vs.T2D), with simultaneous-entry models used to demonstrate whether either IM or ISD confers unique predictivity.

IM estimates of response latency significantly distinguished between the control and T2D groups for all cognitive predictors (see Table 4). In general, results indicated that for every 100 ms increase in mean response latency, the likelihood of being in the T2D group compared to the control group increased by 50% for SRT, 20% for CRT2, CRT4, and CRT8, and 10% respectively for lexical decision and semantic verification. Correspondingly, when ISD was entered as the sole predictor, T2D could be differentiated from controls for three of the speed tasks (Table 4). For every 0.1 SD increase in performance variability (ISDs), the risk of being in the T2D group increased by 8% for CRT2, 8% for Lexical, and 7% for Semantic speed. Informal fit comparisons based on the single-predictor (i.e., IM-only and ISD-only) logistic models suggest that the mean rate models may be more effective at predicting T2D group status than the variability (IIV) prediction models. This was tested in the next set of analyses.

Overall, results from the simultaneous entry of both mean performance (IM) and intraindividual variability (ISD) revealed the following pattern. When entered simultaneously, neither IM nor ISD uniquely predicted T2D status for two of the six neurocognitive speed measures: CRT2 and lexical decision. Both contributed in combination to the prediction of T2D status. However, for the remaining four measures, slower mean rate (IM) was linked to an increased likelihood of being in the T2D group. Specifically, for SRT, IM and ISD together significantly differentiated adults with T2D from controls, χ^2 (2, N = 454) = 6.42, p <.05, Nagelkerke's R^2 = .03. Mean latency significantly predicted T2D status independent of ISD: β = 0.004, SE = .002, Wald (1) = 4.43, p <.05, Exp(β) = 1.004. A similar pattern was observed for CRT4 and CRT8, with the simultaneous entry of IM and ISD resulting in a significant omnibus test of model coefficients: CRT4, χ^2 (2, N = 454) = 7.98, p <.05, Nagelkerke's R^2 = .04, and CRT8, χ^2 (2, N = 454) = 6.57, p <.05, Nagelkerke's R^2 = .03. For both measures, mean latency differentiated T2D status from controls independent of ISD: CRT4, β = 0.003, SE = .001, Wald (1) = 7.94, p <.05, Exp(β) = 1.003, and CRT8, β = 0.003, SE = .001, Wald (1) = 5.72, p <.05, Exp(β) = 1.003. Finally, the simultaneous entry of IM and ISD for semantic verification also yielded a significant omnibus test of model coefficients, χ^2 (2, N = 454) = 8.34, p <.05, Nagelkerke's R^2 = .04.

Mean latency significantly distinguished T2D from controls independent of ISD: $\beta = 0.000$, SE = .000, Wald (1) = 5.13, $p < .05$, Exp(β) = 1.001. In all instances, the significant odds ratio indicated that slower individuals, independent of how variable they are, were at greater risk of being in the T2D group. Notably, for all speeded measures, intraindividual variability did not uniquely distinguish T2D risk independent of the mean rate variable.

Longitudinal Models

Repeated measures ANOVAs were used to model speeded (IM and ISD) change over time, specifically examining the main effects of T2D status, longitudinal wave (2), and T2D Status x Wave interactions.

Separate, one-tailed between-subjects tests were computed for both performance indices (i.e., IM and ISD) for all speed tasks in order to investigate their individual predictivity for diagnostic group differences. Using IM as the performance index, significant diagnostic group differences were observed for SEM ($F(1, 295) = 14.93$, $p < .001$, $\eta^2 = .048$) and LEX ($F(1, 295) = 3.69$, $p < .05$, $\eta^2 = .012$). Using ISD as the performance index, significant diagnostic group differences were observed for SEM ($F(1,295) = 3.37$, $p < .05$, $\eta^2 = .011$); LEX ($F(1, 295) = 5.14$, $p < .05$, $\eta^2 = .017$), CRT 2 ($F(1, 294) = 23.10$, $p < .001$, $\eta^2 = .073$), CRT 4 ($F(1, 294) = 3.33$, $p < .05$, $\eta^2 = .011$), and CRT 8 ($F(1, 294) = 9.09$, $p < .01$, $\eta^2 = .010$).

Significant main effects for Wave were observed for several neurocognitive speed tasks across both performance indices. Tasks showing significant main effects for Wave (one tailed) for both IM and ISD were: LEX (IM: $F(1, 295) = 14.12$, $p < .001$, $\eta^2 = .05$; ISD: $F(1, 295) = 5.09$, $p < .05$, $\eta^2 = .02$), SEM (IM: $F(1, 295) = 11.31$, $p < .001$, $\eta^2 = .04$; ISD: $F(1, 295) = 2.93$, $p < .05$, $\eta^2 = .01$), and CRT 2 (IM: $F(1, 294) = 21.33$, $p < .001$, $\eta^2 = .07$; ISD: $F(1, 294) = 11.41$, $p < .001$, $\eta^2 = .04$). For CRT 4 only IM was associated with a significant wave effect (IM: $F(1, 294) = 4.35$, $p < .04$, $\eta^2 = .02$; ISD: n.s.). No significant wave effects were observed for SRT and CRT8. In general, similar wave effects were produced by IM and ISD. As these univariate wave effects are collapsed across the T2D status groups, we next examined the interactions.

Results for the Wave x Status interactions across all measures revealed that the 2-wave trajectories for the two groups varied significantly only for CRT2 performance. Differences in the two diagnostic groups' trajectories for CRT2 performance across waves are shown for both indices (ISD, $F(1) = 5.39$, $p < .05$, $\eta^2 = .018$; IM, $F(1) = 5.56$, $p < .05$, $\eta^2 = .019$). Mean CRT2 IM performance for the T2D group was 774.27 ms (S.D. = 179.00) at Wave 1, and 849.53 ms (SD = 239.02) at Wave 2. In comparison, mean CRT2 IM performance for the control group was 708.71 ms (SD = 147.94) at Wave 1, and 732.10 ms (SD = 162.81) at Wave 2. On average, the T2D group slowed by about 75 ms, whereas the control group slowed by about 24 ms. With regard to variability, mean CRT2 ISD performance for the T2D group was 8.10 (SD = 4.01) at Wave 1, and 10.15 (SD = 6.74) at Wave 2. In comparison, mean CRT2 ISD performance for the control group was 6.62 (SD = 2.92) at Wave 1, and 6.96 (SD = 3.07) at Wave 2. On average, the increase in inconsistency for the T2D group was substantial (about 2 ISDs), whereas the increase for the controls was modest (about .3 ISD).

Discussion

In recent years, a breadth of literature has emerged demonstrating the potential significance of speed and inconsistency as indices of neurocognitive vitality and vulnerability. Related to aging, conditions diverse in origin, typicality, and depth of neurological compromise have been assessed in the literature. The research has revealed an apparent pattern of diagnostic

"clustering." On the one hand, substantial neurocognitive slowing and inconsistency has been shown for normal aging and for conditions that have neurological foci of disease pathogenesis (e.g., MCI, Alzheimer's). On the other hand, primarily somatic aging-related conditions (e.g., arthritis) do not show elevated levels of intraindividual variability (e.g., MacDonald et al., 2009). The present research fills a gap in this literature by targeting an aging-related disease that is intermediate along a continuum of neuropathic involvement. Specifically, T2D is a potent test case of the clinical reach of the speed-inconsistency phenomenon, as it is not principally neurological in nature but it has been described as a disease of intraindividual variability (in glycemic control). In addition, T2D disease processes and comorbidities (e.g., high blood pressure, increased oxidative load) are involved in aging-related neuropathy, and T2D has been linked to neurocognitive decline. We examined whether neurocognitive speed or inconsistency were similarly affected by T2D status.

Four sets of T2D-related results are discussed. First, as expected, mean rate decrements in speeded performance across all tasks were confirmed for the T2D group. Although not well-established, selected recent studies have demonstrated that speed decrements may be an important element of the T2D profile of cognitive deficits (e.g., Fischer et al., 2009; Yeung et al., 2009). Second, not previously investigated was the next research question, whether T2D patients would also display deficits in inconsistency. The results revealed a general trend toward moderately elevated intraindividual variability in the T2D group, as compared with the control group. However, close inspection revealed that only two of six tasks produced statistically significant differences (Lexical Decision and Semantic Verification). Although not contrary to theoretically derived expectations, this result was not supportive of the contention that neurocognitive inconsistency would be more affected by T2D than mean rate. Notably, IM effects were detected across the four tasks, but ISD effects were isolated to the two tasks requiring more cognitive load, a result observed elsewhere (e.g., Dixon et al., 2007; Gorus et al., 2010) and possibly linked to effects in prefrontal cortical underpinnings (e.g., West, Murphy, Armelio, Craik, & Stuss, 2002). In addition, as all present T2D participants had access to national health care and were in relatively managed phases of the disease, the precursor mechanisms (e.g., variability in glucose control) were relatively controlled. Subsequent research might investigate more advanced or less managed T2D cases, but it must be acknowledged that such groups may also produce equivalently affected (lowered) performance on traditional speed measures (rate).

The third research goal compared the predictivity of mean rate and ISD for concurrent T2D classification. The two single-predictor sets of logistic regression models revealed patterns that closely tracked the group difference results reported for the first two research questions. Specifically, when entered in sole-predictor models, increased slowing consistently predicted probability of T2D classification, whereas increased inconsistency did so more selectively. Correspondingly, the simultaneous entry models (with both IM and ISD entered together) suggested that the traditional speed measure (mean rate) was relatively more effective at T2D classification (based on results from four of the speed measures). In part, the moderate extent of unique predictivity by either the IM or ISD predictors, and their overall combined importance to model prediction, underscores (a) the relationship between the two markers (correlated), (b) the nature of the sample (with T2D patients with relatively well-managed severity and conditions), and (c) the fact that T2D is indirectly linked to neurological effects (e.g., Dixon et al., 2007; Hultsch et al., 2008). Overall, the results pertaining to the first three research questions suggest that, theoretically, both mean and variability in performance are complementary and potentially useful indices of cognitive vitality in T2D patients. However, clinically, the more promising single indicator might be mean rate (slowing). Not tested yet, but available for future research, is how these two markers would fare in distinguishing group performance and predicting group membership

in the context of other known neuropsychological (e.g., executive functioning, episodic memory) or biological diagnostic (e.g., HbA1c levels) and co-morbidity (e.g., systolic blood pressure) markers and modulators of T2D deficits (e.g., McFall et al., 2010; Nilsson & Wahlin, 2009). Additional research with a broader range of T2D severity is also recommended.

Fourth, longitudinal analyses of speed and inconsistency in T2D are relatively novel in this literature (Fischer et al., 2009). Across the present study period two central findings were revealed. We observed group effects (favoring the control participants) across the two waves for both IM and ISD (LEX, SEM, CRT2) and for IM only (CRT 4). Similar (and null) wave effects were observed for the remaining speeded tasks. The key targeted elements of the analysis plan were the two-way interactions. Significant wave x T2D status effects emerged only for choice reaction time (CRT2). Moreover, the CRT2 interaction was shown for both performance indices, and displayed very similar patterns. Specifically, for IM, the longitudinal interval was associated with greater slowing for the T2D group than for the healthy control group. Similarly, for ISD, the interval was associated with greater longitudinal increases in inconsistency for the T2D group than for the control group. Overall, the results of the longitudinal analyses indicated that the two speed indicators behave similarly with respect to short-term longitudinal changes associated with T2D. Relatively few differential changes were observed over this relatively short interval, suggesting that future research could benefit from (a) more waves of measurement, (b) longer intervals of tracking neuropsychological changes for T2D patients, or (c) more severe or less-managed cases of T2D being followed. In addition, the present sample did not include enough T2D patients to support prospective regression models predicting T2D status at a longitudinal interval. Future research on this complementary aspect is recommended.

Several limitations and associated future directions should be noted. First, our theoretical continuum of neurological vulnerability (ranging from AD [more] to arthritis [less]) appears to be confirmed. However, this continuum may also apply within the spectrum of T2D (as well as other conditions with indirect neurological projections). As alluded to above, relatively well-controlled cases—expected to predominate in VLS participants—may be at the lower range of neural vulnerability (although higher than arthritis patients and typically aging older adults) than would be less effectively controlled cases (who may lie closer on this continuum to mildly impaired older adults). Poorly controlled cases of T2D are associated with increases in pathological variability in disease management and characteristics (e.g., poor treatment adherence: Awad & Gagnon, 2004; increases in glycemic variability: Zaccardi, Pitocco, & Ghirlanda, 2009; irregular insulin release; Schmitz, Rungby, Edge, & Juhl, 2008). Patients with more poorly controlled T2D may be more predisposed to both negative biological outcomes and increases in bio-behavioral variability. For example, abnormal variability in blood pressure has been observed in T2D patients with relatively uncontrolled conditions (Mazze et al., 2004), and increased blood pressure variability is associated with cognitive and life quality dysfunction in older adults (Sakakura, Ishikawa, Okuno, Shimada, & Kario, 2008). Future research could investigate the application of the neural vulnerability continuum within the context of T2D. This would include increased sampling of less-controlled (i.e., more severe and more neurologically vulnerable) T2D patients than were available in the present study. Conceivably, to the extent to which study samples contain well-controlled cases, the neurocognitive speed-inconsistency ramifications of T2D may be underestimated. However, it is important to underscore that the present results do reflect the T2D-neurocognition effects likely to be evident for generally mixed, moderately, or well-controlled cases, a common profile in western societies.

Second, the issue of T2D management implies that future research should consider the role, effectiveness, and steadiness of everyday interventions, especially to the extent that they might affect the location of an individual in terms of neurological vulnerability. T2D patients may display different patterns of change as a function of long-term adherence to treatment regimens designed to modify or control proximal and distal factors that reduce the risk of neurological compromise. Therefore, individual differences among T2D patients in medications, lifestyle adjustments, personality characteristics, nutrition, and self-maintenance behaviors merit more active consideration. From this perspective, T2D may eventually be viewed as also a mid- and late-life prodromal phase of very late-life frailty. Third, the present study featured a novel longitudinal component, but further longitudinal factors could be valuable in future research. For example, additional waves of measurement and a more extended follow-up period could more definitively test the speed-inconsistency theory for T2D.

In sum, we investigated a novel aspect of the neuropsychology of T2D and aging. We explored whether the two prominent speed indicators—mean rate or intraindividual variability—were affected similarly by T2D. Subsequently, we focused on which of these two might be more affected by, and more predictive of, T2D status and T2D-related neural vulnerability. We framed the study by locating T2D conceptually in an intermediate location of a continuum from greater (Alzheimer's) to lesser (arthritis) neural vulnerability. This invited the conjecture that the effects of intraindividual variability—so prominent in neurological conditions, detectable in normal aging, but not so elevated in somatic aging conditions—might be moderate in T2D. Indeed, the main result is that both facets of speed are affected by T2D—even among patients with relatively available health care—although present evidence indicates that mean rate may be more theoretically and clinically implicated.

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Table 1

Cross-sectional (Wave 1) sample demographic characteristics of T2D and control groups

Group	T2D	Controls
	n **= 41**	***n*** **= 424**
Age (Years)	68.59 (7.16)	67.84 (8.50)
Gender (% female)	56.1	69.6
Education (years)	15.12 (3.44)	15.32 (2.92)
Subjective Health (absolute rating)	2.39 (.86)	1.69 (.71)
Subjective Health (relative rating)	2.0 (0.78)	1.5 (0.68)
BMI	30.20 (4.65)	26.46 (3.97)
Tobacco use (%)		
Yes	4.9	5.0
Previously	53.7	52.8
Never	41.5	42.2
Alcohol consumption (%)		
Yes	61.0	89.9
Previously	24.4	4.7
Never	14.6	5.4
Disease duration (years)	8.3 (7.3)	
Diabetes medication use (%)		
Insulin	22.0	
Oral hypoglycemics	39.0	
Diet/ exercise	36.6	
No treatment used	4.9	
Diabetes severity (%)		
Mild	53.7	
Moderate	43.9	
Severe	2.4	

Note. BMI = body mass index. Standard deviations are represented in parentheses.

Table 2

Longitudinal sample demographic characteristics of T2D and control groups by wave

	Wave 1	Wave 2
Group	**Mean (SD)**	**Mean (SD)**
Age (Years)		
T2D	68.45 (7.82)	72.80 (7.67)
Control	66.74 (7.97)	71.08 (7.85)
Gender (% female)		
T2D	64.3	64.3
Control	69.1	69.1
Education (years)		
T2D	15.21 (3.40)	14.96 (3.63)
Control	15.79 (2.79)	15.79 (2.86)
Systolic Blood Pressure		
T2D	134.99 (13.09)	136.89 (18.91)
Control	123.93(13.70)	125.00(15.62)
Subjective Health (absolute rating)		
T2D	2.29 (0.85)	2.50 (0.84)
Control	1.62 (0.66)	1.72 (0.66)
Subjective Health (relative rating)		
T2D	1.86 (0.76)	2.07 (0.86)
Control	1.45 (0.65)	1.52 (0.57)
BMI		
T2D	30.12 (4.14)	28.91 (5.16)
Control	26.50 (3.86)	26.25 (3.89)
MMSE		
T2D	28.86 (1.04)	28.79 (1.07)
Control	28.98 (0.98)	28.81 (1.02)
Tobacco use (%; T2D (controls))		
Yes	3.6 (4.40)	0.0 (3.30)
Previously	50.0 (48.20)	53.6 (52.60)
Never	46.4 (47.40)	46.4 (44.10)
Alcohol		
consumption (%; T2D (controls))		
Yes	60.7 (91.2)	78.6 (92.60)
Previously	21.4 (4.00)	21.4 (5.10)
Never	17.9 (4.80)	0.0 (2.20)
Disease duration (years)	8.31 (7.68)	12.69 (7.65)

	Wave 1	Wave 2
Group	**Mean (SD)**	**Mean (SD)**
Diabetes medication use (%)		
Insulin	10.71	21.43
Oral hypoglycemics	50.00	60.71
Diet/ exercise	21.43	14.29
No treatment used	17.86	3.57
Diabetes severity (%)		
Mild	53.57	46.43
Moderate	42.86	50.00
Severe	3.57	3.57

Note. T2D group: $n = 28$. Control group: $n = 272$. BMI = body mass index. MMSE = Mini-Mental State Examination. Standard deviations are represented in parentheses.

Table 3

Cross-sectional (Wave 1) IM and ISD performance for T2D and control groups

	T2D		Control	
Task	**Mean**	**SD**	**Mean**	**SD**
SEM				
IM	4232.51**	1157.07	3560.04**	1257.76
ISD	6.84*	3.20	5.69*	3.51
LEX				
IM	1304.26**	505.00	1094.01**	408.64
ISD	7.37**	5.66	5.39**	3.81
SRT				
IM	383.28**	96.72	345.35*	78.66
ISD	8.14	4.76	6.89	4.54
CRT2				
IM	800.67*	177.54	731.22*	162.96
ISD	8.07	4.10	7.02	3.32
CRT4				
IM	957.84*	171.35	886.61*	169.49
ISD	6.94	2.90	6.92	3.19
CRT8				
IM	982.15*	174.22	909.29*	165.82
ISD	7.33	2.65	6.82	3.36

Note. Mean IM performance measured in milliseconds. Significance is based on one-tailed tests.

* $p < .05$

** $p < .01$

Table 4

Logistic regression (separate entry) results for cross-sectional sample

	Separate-Entry Models				
	β	**SE**	**Wald(1)**	***p***	**Exp(β)**
SEM					
IM	0.000	.000	8.46	<.01	1.001
ISD	0.064	.034	3.53	<.05	1.07
LEX					
IM	0.001	.000	5.95	<.05	1.001
ISD	0.078	.029	7.25	<.01	1.08
SRT					
IM	0.005	.002	6.98	<.01	1.005
ISD	-	-	-	-	-
CRT2					
IM	0.002	.001	5.99	<.05	1.002
ISD	0.075	.042	3.29	<.05	1.08
CRT4					
IM	0.002	.001	5.87	<.05	1.002
ISD	-	-	-	-	-
CRT8					
IM	0.002	.001	6.12	<.05	1.002
ISD	-	-	-	-	-

Note. Significant simultaneous entry model results presented in the text.