Relationships of real-time glucose levels on cognitive-linguistic performance in adults with and without diabetes

Introduction
Diabetes mellitus (DM) is a chronic disorder of carbohydrate metabolism caused by abnormal insulin function or insulin deficiency, resulting in elevated blood sugars. The influence of DM on human health is enormous and is increasing steadily worldwide, in terms of overall health, mortality and economic impacts. Diabetes is highly relevant to aphasiologists. People with diabetes have significantly higher incidence than others of numerous conditions likely to affect cognition and language (e.g., stroke, brain atrophy, atherosclerosis, peripheral and autonomic neuropathies, and dementia). Numerous studies demonstrate associations between diabetes and problems of cognition and language (An extensive reference list will be provided as a handout). Despite robust evidence of diabetes-associated cognitive and linguistic deficits identified through surveys and psychometric testing, little is known about the degree to which performance of adults with diabetes differs from those without diabetes when general variations in glucose values and real-time moment-by-moment glucose values are taken into consideration.

Purpose
We engaged in a carefully controlled study of the potential differential impact of acute fluctuations in glucose levels on cognitive and linguistic abilities. Measuring interstitial glucose levels every five minutes via controlled glucose monitoring sensors (CGMS) allows the documentation of glucose levels and symptomatic and asymptomatic hypoglycemia over a span of several days. We examined empirical evidence of the specific effects of fluctuations in glucose levels among persons with diabetes on linguistic and cognitive abilities. We explored the relationship of moment-by moment and longer-term blood glucose levels and cognitive and linguistic performance in people with and without diabetes. No previous study has specifically addressed two key areas examined here: 1) the relationship between actual glucose levels using continuous glucose measurement during assessment of cognitive and linguistic performance and 2) patterns of variation in glucose levels in individuals. Furthermore, we contextualize results in terms of the self-report of cognitive and linguistic symptoms in adults with and without diabetes.

Method
Participants included 15 adults without diabetes (confirmed via fasting glucose and HbA1C levels) and 16 adults with Type 1 DM (T1DM), with diagnosis confirmed by an endocrinologist. T1DM is characterized by a lack of insulin production (in contrast to Type 2 DM, which is characterized by gradual insulin resistance) and requires multiple injections of insulin per day. Inclusion in the diabetic group was limited to T1DM because it affects individuals at a young age, thus allowing for a young sample in a controlled age range. Inclusion for both groups was limited to ages 20 to 40.

The experimental protocol spanned three days. Prior to an initial visit (Day 1), participants completed a survey, which included questions regarding health, current diabetes management, and problematic symptoms related to cognition and language. On Day 1, they were given a glucose test to confirm diagnosis of DM versus control group status. Then a CGMS electrode sensor was inserted under the skin in the abdominal area. CGMS measures subcutaneous interstitial glucose levels. Measured continuously, values are averaged and reported every five minutes. CGMS is accurate within a range of 40-400 mg/dL. All participants were given a

journal and instructed to note events known to influence blood glucose levels. On Days 2 and 3 each participant engaged in extensive cognitive-linguistic testing. Objective repeated (Day 1 and Day 2) measures were obtained to assess each of the following constructs purportedly associated with diabetes: verbal memory, nonverbal memory, attention/concentration, psychomotor skills (including reaction time), visuospatial abilities, orientation, verbal fluency, and problem-solving (See Table 1. Details, including justification in terms of repeated-measures reliability and other psychometric properties, will be provided.) Extensive hearing evaluations were administered; those results are not addressed here. Depression inventory, intelligence screening, and hearing test results allowed consideration of potential confounds.

Results
Detailed statistical results are not included for brevity here. There were no significant differences between the control and diabetic groups in terms of age or education. The severity of self-reported problems with retrieval of proper names, verbal expression, reading comprehension, clarity of thought, and concentration was greater in control participants than participants with diabetes. Severity of auditory comprehension problems reported was greater among those with diabetes.

According to mean amplitude glycemic excursion (MAGE) scores calculated over a standardized 36-hour segment of the three-day monitoring period, participants with diabetes had significantly greater variability in glucose regulation; their self-report of glucose fluctuation problems in terms of severity and frequency were not correlated with actual measures of variability. MAGE scores were not significantly correlated with any of their self-reported symptoms of cognition or language.

Participants with diabetes performed significantly more poorly on one measure of selective attention (TEA telephone search) and two measures of verbal fluency (D-KEFS naming in categories and category switching). For all other measures, there were no differences between groups.

For both groups, differences between Day 2 and Day 3 measures of cognitive and linguistic performance correlated significantly with differences in actual glucose values.

Discussion

Of the constructs assessed, participants with diabetes reported greater severity only for auditory comprehension in conversation. Otherwise, participants without diabetes reported greater severity in challenges with everyday cognitive and linguistic problems than did those with diabetes. This is surprising in light of previous research demonstrating association of diabetes with several areas of cognition and language. Self-report data are also inconsistent with actual test results. That is, despite the fact that participants with diabetes reported less severity of cognitive and linguistics problems, they demonstrated worse performance on each of the three measures for which performance differed significantly between the two groups.

In those with diabetes, self-reporting of glucose fluctuations in terms of severity and frequency of hypoglycemic episodes was also not consistent with actual measures of glucose variability.

This may suggest a lack of awareness of patterns of glucose regulation, or it may be due to the fact that MAGE scores reflected only a small window (36 hours) of glucose monitoring that may not have been representative of typical daily patterns.

For both groups, differences between repeated measures of cognitive and linguistic performance (Day 2 versus Day 3 scores) on most tasks correlated significantly with differences in actual glucose values recorded while participants were engaged in those specific tasks. This highlights the association between moment-by-moment glucose levels and cognitive and linguistic task performance regardless of diagnosis of diabetes. Further exploration of this association is warranted given the analyses now afforded through new CGMS technology.

Further research is needed to examine the degree to which specific difficulties in cognition and language are due to acute changes in glucose levels or, rather, to more chronic etiologies associated with the long-term metabolic effects of erratic glucose control, hyperglycemia or hypoglycemia. The cumulative effects of mild and more significant hypoglycemia throughout a lifetime are poorly understood. There is great concern that, with more aggressive attempts to reduce the long-term complications of diabetes (such as retinopathy or kidney disease) through intensive glucose control, the risk of hypoglycemia-induced neurological damage may be increased as well. Repetitive episodes of asymptomatic hypoglycemia could lead to permanent brain damage and may be a causative factor underlying a long-term decline in cognitive and linguistics functions. A great deal remains to be learned about connections between underlying etiologies of DM and its macrovascular, microvascular, and neuropathic influences on cognition and language.

References

An extensive reference list supporting the introduction, literature review, and discussion will be provided. Only sources cited in this brief proposal are listed here.

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TASK	Description	Construct/Domain
Center for Epidemiologic Studies Depression Scale (CES) (Radloff, 1977) CES_D	Measure of depression	Depression
Rivermead Behavioral Memory Test-Extended (RBMT-E) (Wilson, Clare, Baddeley,et al, 1998) Subtest 10	Assesses temporal and reality orientation	Orientation/Cognition
Weschler Abbreviated Scale of Intelligence III (WAIS-III) (Weschler, 1997) 1. WASI_VOC 2. WASI_MAT 3. WASI_FSIQ	1. Provide word meanings 2. Complete matrix grid patterns 3. Combined verbal/nonverbal scores	1. Vocabulary knowledge 2. Nonverbal reasoning
California Verbal Learning Test, 2nd ed (CVLT) (Delis, Kramer, Kaplan, & Ober, 2000) 1. CVLT_1 - CVLT_5 2. CVLT_List B 3. CVLT_short_delay 4. CVLT_short_delay_cued 5. CVLT_long_delay 6. CVLT_long_delay cued	1. Standard score of list recall after initial presentation for trials 1 to 5 (List A) 2. Standard score of list recall from List B 3. Recall of List A (immediately after recall of List B) 4. Recall of List A-semantic cues provided 5. Recall of List A after at least 20 min delay 6. Recall of List A after 20 min delay-semantic cues provided	1-6. Immediate recall, auditory attention, verbal learning
Test of Everyday Attention (TEA) (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994) 1. TEA_M1; TEA_M2 (Map Search – 60, 120 sec) 2. TEA_TS (Telephone search) 3. TEA_TSC (Telephone search with counting) 4. TEA_L (Lottery)	1. Search for images in a map of Philadelphia in 1 and 2 minutes 2. Search for names in the yellow pages 3. Search for names in the yellow pages while counting tones presented aloud 4. Listen to alpha and 10-digit string; write down the two letters that precede the target numbers	1. Selective attention 2. Selective attention 3. Sustained attention 4. Sustained attention
Delis Kaplan Executive Function System (DKEFS) (Delis, Kaplan, & Kramer, 2001)		

VERBAL FLUENCY 1a. D_KEFS_letter_flu (Letter Fluency) 2a. D_KEFS_category_flu (Category Fluency) 3a. D_KEFS_category_correct (Category Switching-correct) 4a. D_KEFS_switch_acc (Category Switching - accuracy) 5a. D_KEFS_int1-int 4(Fluency interval 1 - 4) 6a. D_KEFS_setloss (Fluency set loss) 7a. D_KEFS_rep (Fluency repetition)	1a. Name words that begin with F A S 2a. Category-based generative naming 3a. Number of correct names in 2 categories 4a. Naming accuracy while switching categories 5a. Total correct names in 4, 15-sec intervals 6a. Score of words that violate criterion rules 7a. Number of words repeated during naming	1a. Verbal fluency 2a. Verbal fluency 3a. Verbal fluency 4a. Cognitive flexibility 5a-7a. Verbal fluency
SORTING 1b. D_KEFS_correct_sort (Free sort) 2b. D_KEFS_descript (Free sort description) 3b. D_KEFS_recog 4b. D_KEFS_comb_descr 5b. D_KEFS_contrast 6b. D_KEFS_freesort_1 7b. D_KEFS_freesort_2 8b. D_KEFS_freesort_3 9b. D_KEFS_freesort_4 10b. D_KEFS_sortrec_1 11b. D_KEFS_sortrec_2 12b. D_KEFS_combined_1 13b. D_KEFS_cominbed_2 14b. D_KEFS_abstractions 15b. D_KEFS_questions 16b. D_KEFS_weights	1b. Correct number of cards sorted using personalized rationale in target groups 2b. Scored ability to describe sorting rationale 3b. Total number of correct descriptions in both card sets 4b. Description performance in Free Sort and Sort Recognition conditions 5b. Performance difference b/t Sort Recognition and Free Sort 6b. Score for repeated free sorts 7b. Score for attempted free sorts 8b. Score for incorrect free sort descriptions 9b. Score for repeated free sort descriptions 10b. Score for incorrect sort recog descriptions 11b. Score for repeated sort recog descriptions 12b. Combined score for free sort & sort recog incorrect descriptions 13b. Combined score for free sort & sort recog repeated descriptions 14b. Measure degree of abstract thinking in 20 question task 15b. Number of questions asked 16b. Weighted achievement score for 20 questions	1b- 4b. Initiated problem solving (verbal/nonverbal) 5b. Can reveal deficits in concept-formation and initiation 8b, 10 b, 12b. Elevated # reflects impaired concept formation 9b, 11b, 13b. Elevated # reflects concept perseveration 14b. Abstract thinking
Hillis Verbal Assessment Tasks (Hillis, 2002) 1. LEX_oral 2. LEX_written 3. LEX_aud_comp 4. LEX_reading_comp 5. LEX_lex_dec 6. LEX_oral_reading	1. Verbal picture naming 2. Written picture naming 3. Picture ID using spoken yes/no questions 4. Written word to picture matching 5. Classify letter string as a word or nonword 6. Read words/nonwords aloud	1-6. Expressive/Receptive skills of spoken and written language
Multilingual Aphasia Exam (MAE) (1989) 1. MAE_oral 2. MAE_written 3. MAE_block	1. Spelling words aloud 2. Writing words 3. Spelling words with the use of letter blocks	1-3. Spelling ability in oral expressive speech, handwriting, and object manipulation