Relationships Between Hyperglycemia and Cognitive Performance Among Adults With Type 1 and Type 2 Diabetes

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OBJECTIVE — Hyperglycemia is a common event among patients with type 1 and type 2 diabetes. While the cognitive-motor slowing associated with hypoglycemia is well documented, the acute effects of hyperglycemia have not been studied extensively, despite patients' reports of negative effects. This study prospectively and objectively assessed the effects of hyperglycemia on cognitive-motor functioning in subjects' natural environment.

RESEARCH DESIGN AND METHODS — Study 1 investigated 105 adults with type 1 diabetes (mean age 37 years and mean duration of diabetes 20 years), study 2 investigated 36 adults with type 2 diabetes (mean age 50 years and mean duration of diabetes 10 years), and study 3 investigated 91 adults with type 1 diabetes (mean age 39 years and mean duration of diabetes 20 years). Subjects used a hand-held computer for 70 trials over 4 weeks, which required them to complete various cognitive-motor tasks and then measure and enter their current blood glucose reading.

RESULTS — Hyperglycemia (blood glucose >15 mmol/l) was associated with slowing of all cognitive performance tests ($P < 0.02$) and an increased number of mental subtraction errors for both type 1 and type 2 diabetic subjects. The effects of hyperglycemia were highly individualized, impacting ~50% of the subjects.

CONCLUSIONS — Acute hyperglycemia is not a benign event for many individuals with diabetes, but it is associated with mild cognitive dysfunction.

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Patients with diabetes often report acute and transient cognitive disruptions associated with hyperglycemia. The impact of such effects could influence quality of life and daily functioning, as well as indicate cues to aid patients in better recognizing the presence of hyperglycemia. Holmes et al. (1) reported significant slowing of visual reaction time during a hospital clamp study at a blood glucose level of 16.7 mmol/l but were unable to replicate this subsequently using an auditory reaction-time task (2). Davis et al. (3) reported that blood glucose in the 20- to 30-mmol/l range was associated with a 9.5% reduction in type 1 diabetic children's performance IQ. Performance IQ was worsened in 67% of the children studied. Summerfield et al. (4) used a hyperinsulinic glucose clamp to test cognitive functioning at 14.5 and 16 mmol/l in adults with type 2 diabetes. During hyperglycemia, significant disruptions occurred in the performance of complex tests of cognitive functioning, such as four-choice reaction time. However, other investigators (5,6) were unable to detect decay in cognitive-motor performance on selected neuropsychological tests during hyperglycemia.

Contrary to hypoglycemia and its associated neuroglycopenia, a major barrier to the investigation of the effects of hyperglycemia on cognitive-motor performance is the absence of a clear physiological mechanism that explains how hyperglycemia negatively influences brain functioning. However, research suggests several possible mechanisms (6). Blood-brain barrier microvascular dysfunction may occur as a result of transient hyperglycemia (7). Altered synthesis or reuptake of monoamine neurotransmitters as a result of altered precursor availability to the brain or changes in insulin availability to the brain are other possible explanations (8,9). Complex effects on peptide neurotransmitters may be produced by uncontrolled diabetes (10,11). Any one of these mechanisms alone may be insufficient, and several of these mechanisms could be additive. At this point, no conclusion can be drawn about any specific mechanism(s) responsible for possible short-term cognitive dysfunction. However, hyperglycemia's disruptive effects on cognitive-motor functioning must first be verified, and then exploring possible physiological mechanisms will be justified.

The specific hypotheses tested in this study are *1*) hyperglycemia is associated with cognitive-motor dysfunctions, *2*) hyperglycemia disrupts cognitive-motor functioning in adults with either type 1 or type 2 diabetes, and *3*) cognitive-motor disruptions associated with hyperglycemia are individualized. The last hypothesis is based on our previous findings that symptoms, as well as cognitive motor disruptions, associated with hypoglycemia

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Abbreviations: HHC, hand-held computer; PSAT, Paced Serial Addition Test; SMBG, self-monitoring of blood glucose.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic variables for the three study groups*

	Study 1	Study 2	Study 3
Age (years)	37.5 ± 0.9 (23–59)	50 ± 11 (28–75)	39.4 ± 10.4 (25–61)
Disease duration (years)	19.7 ± 9.9 (2–46)	10 ± 9 (1–35)	20.2 ± 10.7 (1–52)
Mean blood glucose (mmol/l)	9.6 ± 1.8 (4.7–16.9)	9.7 ± 3.7 (5.9–23.9)	9.3 ± 5.1 (1.1–33.3)
HbA_{1c} (%)	8.6 ± 2.3 (6.3–16.9)*	6.9 ± 1 (7–14)	7.6 ± 1.2 (4.0–12.6)
BMI (kg/m^2)	NA	34 ± 10 (19–65)	25.4 ± 4.4 (17.7–41.2)
% female	62	42	57
% using insulin	100	58	100

Data are means ± SD (range) unless otherwise noted. *HbA_{1c} estimate based on HbA1 assay.

are individualized (12–14) in terms of glycemic threshold for occurrence and individual vulnerability.

RESEARCH DESIGN AND METHODS

Study 1 subjects

A total of 105 adults with type 1 diabetes were recruited through three different sites: the University of Virginia (n = 33), Vanderbilt University (n = 39), and the Joslin Diabetes Center (n = 33). Because subjects were recruited to participate in the Blood Glucose Awareness Training study (15), and not for the expressed purpose of investigating the acute effects of hyperglycemia, subjects and research assistants collecting the data were blind to the hypotheses. The subject group consisted of 65 women and 40 men with a mean (± SD) age of 37.5 ± 9.0 years, a diabetes duration of 19.7 ± 9.9 years, and an HbA1 of 10.4 ± 2.3% (equivalent to an HbA_{1c} of 8.6%) (Table 1).

In groups of four to eight subjects, the study was described, informed consent was secured, and subjects were taught to use and demonstrated competency in the use of One Touch memory meters (Lifescan, Milpitas, CA) and the Psion 250 hand-held computer (HHC). During the subsequent month, subjects were instructed to use their HHC immediately before routine self-monitoring of blood glucose (SMBG), three to four times each day, for a total of 50 trials. On each HHC trial, data were collected on cognitive-motor performance and then blood glucose level. First, the HHC presented and recorded the subject's performance on three cognitive-motor tests. In a psychomotor task, the subject was instructed to think of as many words as possible that start with the letter "A" in 30 s and to tap the "enter" key each time an "A" word came to mind. Then, the subject was presented with 10 mental subtraction problems that involved subtracting a randomly generated single-digit number from a three-digit number with answers entered on the HHC number pad. Finally, 15 four-choice reaction-time trials occurred in which the number 1, 3, 7, or 9 was randomly presented on the screen and the subject pressed the corresponding number on the keypad as quickly as possible. The dependent variables were the number of "A" words recalled, time to complete 10 mental subtractions, as well as the number of errors, and time to complete the 15 reaction-time trials.

Next, the HHC prompted the subject to measure and enter his/her blood glucose reading from the One Touch meter after completing the cognitive-motor tests. To assess reliability, the 1-month HHC data collection was repeated 5 months later, generating an average of 82.5 valid HHC trials per subject.

Three precautions were taken to encourage and monitor valid data entry, i.e., cognitive-motor testing before SMBG and thus blind to actual blood glucose level. First, the HHC prompted subjects with the message "No blood sample yet" as soon as it was turned on. Second, the HHC tracked elapsed time between the prompt "Measure your blood glucose" and the entry of that SMBG reading. Since at least 45 s were required for a subject to lance a finger, collect a blood sample, and analyze blood glucose level with the One Touch meter, any readings entered in <45 s were considered invalid. Third, the blood glucose readings entered into the HHC were compared with memory meter data to ensure accuracy of the SMBG results. We have used these procedures extensively in our investigations of hypoglycemia (12,16,17).

Study 2 subjects

Thirty-four adults with type 2 diabetes were recruited through newspaper and television announcements in Central Virginia. The subject group consisted of 15 women and 19 men, with a mean (± SD) age of 50 ± 11 years and a mean diabetes duration of 10 ± 9 years (Table 1).

Procedures were identical to those of study 1, except for the following differences. The Handspring Visor Platinum served as the HHC. Because the reaction-time test did not have a significant hyperglycemic group effect in study 1, in study 2 it was replaced with two levels of the Paced Serial Addition Test (PSAT). The PSAT presented a sequence of single-digit numbers, and the subject entered the sum of each pair of sequential numbers. Levels 1 and 2 presented the numbers at 4- and 2-s intervals, respectively. The dependent variables were the number of correct additions on the faster and slower PSAT.

Study 3 subjects

Ninety-one adults with type 1 diabetes were recruited through newspaper and television announcements in Central Virginia to participate in a study investigating bio-behavioral precursors to hypoglycemia. The subject group consisted of 52 women and 39 men, with a mean (± SD) age of 39.4 ± 10.4 years and a mean diabetes duration of 20.2 ± 10.7 years (Table 1).

Procedures were identical to those in study 2, except only the subtraction test was used in order to reduce subject burden.

Data analysis. The data were analyzed at two levels: across subject at a group level and within subject for individual subjects. To evaluate group effects, blood glucose readings were categorized into five different ranges that contained a similar number of readings across all subjects (Table

Table 2—*BG categories used in group data analysis*

Blood glucose category	Blood glucose range (mmol/l)	BG events/category		
		Study 1	Study 2	Study 3
1	6.1 < 8	1,456	599	968
2	8 < 10	1,017	472	865
3	10 < 12.2	1,237	322	803
4	12.2 < 15	1,178	221	777
5	>15	1,238	284	864

2). This allowed assessment of cognitive-motor performance in discrete blood glucose ranges at a group level. Subjects' responses were analyzed using ANOVA. Since each subject contributed several entries in each blood glucose range, the assumption of independence of the observations may be violated, resulting in an artificially higher number of degrees of freedom in the *F* tests. To avoid potential exaggeration of the group effects and to account for parallel tests, the significance level was lowered to $P < 0.01$.

Each subject's individual data were analyzed to determine how many of the cognitive-motor tasks were significantly impaired with elevated blood glucoses. To evaluate an individual subject's performance/blood glucose relationships, ANOVAs were inappropriate because of too few samples in each blood glucose category and correlation analysis was inappropriate because of its assumption of linearity. Consequently, we designed an individual test for cognitive dysfunction (see APPENDIX). For each subject and for each test, we first computed the performance mean score and SD during euglycemia (blood glucose 6–8 mmol/l) and then computed its deviation for each hyperglycemic trial (blood glucose >15 mmol/l) as the number of SDs from euglycemic performance. In other words, the deviation of each test at hyperglycemia was presented as a *Z* score using normative euglycemic data. For each subject a cognitive test was considered significantly disrupted during hyperglycemia if these *Z* scores were significantly higher than zero at $P < 0.05$. The statistical reasoning behind this test is presented in the APPENDIX.

RESULTS

Test-retest reliability

In study 1 the average blood glucose, the percentage of readings >8.9 mmol/l and >11.1 mmol/l, respectively, were compared between the two datasets collected at months 1 and 6. The test-retest correlation of each of these variables was $r = 0.60–0.63$ ($P < 0.001$), and there were no significant differences in test-retest means. Similarly, test-retest HbA1s were highly correlated ($r = 0.85$, $P < 0.001$). The test-retest performance of cognitive-motor tests was highly correlated, ($r = 0.80–0.96$, $P < 0.001$ in each case). Therefore, the data were considered reliable over time and collapsed across the two time samples.

Group effects of hyperglycemia

In study 1, hyperglycemia (blood glucose >15 mmol/l) was associated with slower performance on the psychomotor task, as reflected by fewer A words retrieved in 30-s intervals ($F = 5.08$, $P = 0.0004$) (Fig. 1). Similarly, hyperglycemia slowed mental subtraction speed ($F = 3.71$, $P = 0.005$) and increased subtraction errors ($F = 2.72$, $P = 0.02$). However, hyperglycemia did not significantly slow choice reaction time ($F = 2.08$, $P = 0.09$).

In study 2, hyperglycemia (blood glucose >15 mmol/l) was associated with slower performance on the psychomotor task, as reflected by fewer A words retrieved in 30-s intervals ($F = 6.38$, $P = 0.001$). Similarly, hyperglycemia slowed mental subtraction speed ($F = 4.82$, $P < 0.001$) and increased subtraction errors ($F = 3.62$, $P < 0.01$). Performance on PSAT-1 ($F = 3.74$, $P = 0.02$) and PSAT-2

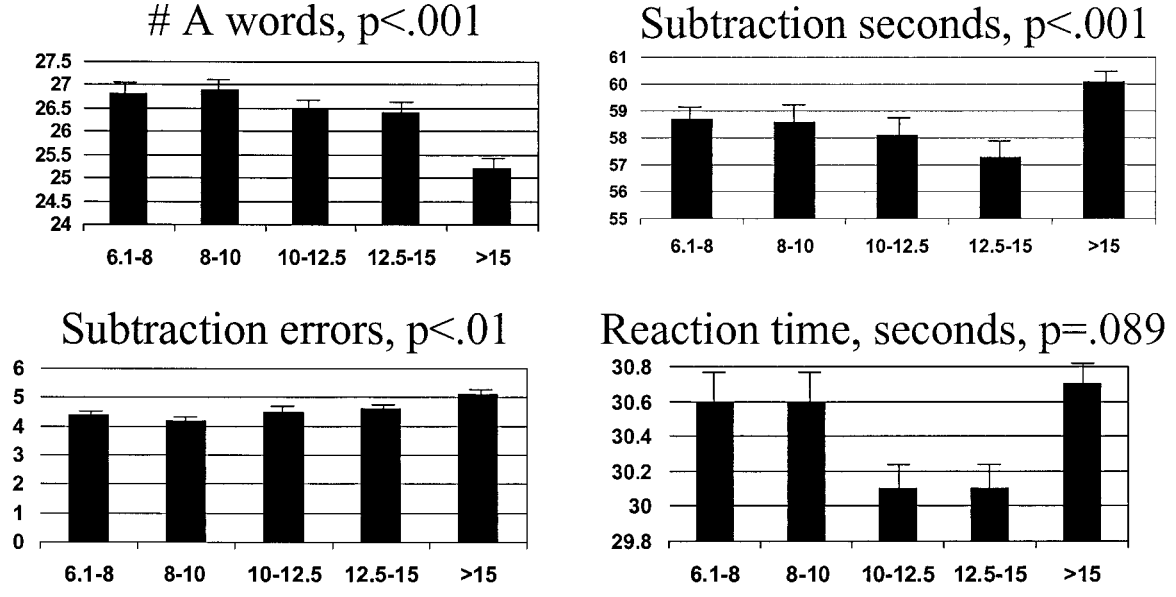

Figure 1—*Study 1 mean ± SEM error bars for performance variables for different blood glucose categories (mmol/l) and ANOVA* P *levels for type 1 diabetic subjects.*

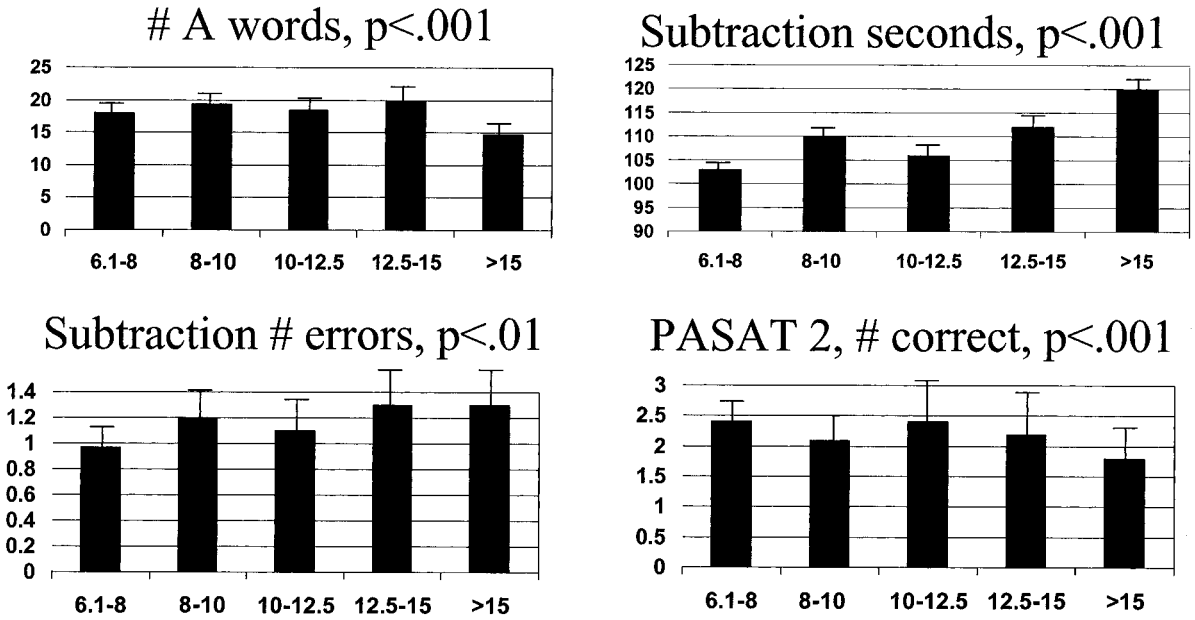

Figure 2—*Study 2 mean ± SEM error bars for performance variables for different blood glucose categories (mmol/l) and ANOVA* P *levels for type 2 diabetic subjects.*

($F = 4.83$, $P < 0.001$) was disrupted, with more addition errors (Fig. 2).

In study 3, hyperglycemia (blood glucose >15) was associated with slower mental subtraction time ($F = 7.73$, $P < 0.0001$) and increased number of errors ($F = 3.87$, $P = 0.003$).

Individual effects of hyperglycemia

In study 1 (Table 3) the percentage of type 1 diabetic subjects who demonstrated significant ($P < 0.01$) disruptions in 0, 1, 2, and 3 of any of the cognitive-motor tasks with hyperglycemia (blood glucose >15) was 45, 24, 16, and 11%, respectively. Concerning specific tests and mental subtraction time and errors, psychomotor task and choice reaction time were significantly affected for 21, 20, 20, and 28%, respectively, of the individual subjects (Table 3). The standardized effect size (APPENDIX) for those type 1 diabetes subjects significantly affected was 3.2, 2.7, 2.4, and 3.0, respectively, for subtraction time, subtraction errors, A words, and reaction time.

A series of exploratory correlations and *t* tests were conducted between potential predictor variables and the number of cognitive-motor dysfunctions per subject to investigate possible factors contributing to individual differences in sensitivity to hyperglycemia (Table 3). The predictor variables were duration of disease, sex, glycosylated hemoglobin, percentage of SMBG readings >15 mmol/l, and mean cognitive-motor performance during euglycemia and depression, as defined by the Beck Depression Inventory. Greater routine exposure to hyperglycemia was only mildly related to number of cognitive tests impaired during hyperglycemia, as reflected by both higher HbA1c readings and greater percentage of SMBG readings >15 mmol/l. Similarly, there was a small relationship indicating that

Table 3 —*Individual effects and correlates of cognitive disruptions during hyperglycemia*

	Study 1	Study 2	Study 3
Mean no. of SMBGs >15 mmol/l	17.8	19.4	17.9
Number of tests significantly impaired: % subjects with impaired performance			
0	45%	46%	41%
1	24%	33%	48%
2	16%	8%	12%
3	11%	13%	
% subjects with specific tests significantly affected by hyperglycemia			
Subtractions, speed	21%	38%	19%
Subtractions, errors	20%	21%	52%
A words	20%	21%	
Reaction time	28%		
PSAT 1		4%	
PSAT 2		4%	
Relationship with no. of cognitive tests impaired			
Duration		$r = -0.36$*	
HbA_{1c}	$r = 0.20$†	$r = -0.30$*	$r = 0.34$‡
% SMBGs >15 mmol/l	$r = 0.20$*	$r = -0.29$†	$r = 0.39$‡
Mean euglycemic performance	$r = -0.18$†	$r = -0.38$*	$r = -0.19$*

*$P < 0.05$, †$P < 0.1$, ‡$P < 0.01$.

worse performance during euglycemia was associated with greater decay during hyperglycemia.

The percentage of type 2 diabetic subjects in study 2 (Table 3) who had zero to four cognitive-motor disruptions significantly associated with hyperglycemia was 46, 33, 8, and 13%, respectively. Mental subtraction time and errors, psychomotor task, PSAT-1, and PSAT-2 were significantly slowed for 38, 21, 21, 4, and 4% of the subjects, respectively (Table 3). The standardized effect size for those type 1 diabetic subjects significantly affected was 2.9, 2.3, 2.7, 1.6, and 1.8, respectively, for subtraction time, subtraction errors, A words, PSAT-1, and PSAT-2.

A similar series of exploratory correlations and *t* tests were conducted as in study 1 (with the addition of BMI) to identify factors contributing to individual differences in sensitivity to hyperglycemia. Subjects with a shorter duration of disease, less exposure to hyperglycemia, and worse performance during euglycemia were more likely to have more cognitive tests impaired during hyperglycemia (Table 3).

The percentage of type 1 diabetic subjects in study 3 (Table 3) who had zero to two disruptions significantly associated with hyperglycemia was 41, 48, and 12%, respectively. Subtraction speed and/or errors were significantly affected for 19 and 52% of the subjects (Table 3). The standardized effect size for those type 1 diabetic subjects significantly affected was 3.8 and 2.3, respectively, for subtraction time and subtraction errors.

A comparable series of exploratory correlations and *t* tests were conducted as in studies 1 and 2 to determine what factors might predict individual sensitivity to hyperglycemia. Similar to study 1, more routine exposure to hyperglycemia and poorer performance during euglycemia was associated with greater effects of hyperglycemia on cognitive functioning (Table 3).

An overall logistic regression was preformed combining subjects from all three studies to predict those who did and did not demonstrate cognitive sensitivity to hyperglycemia. This correctly classified 66% of the cases ($\chi^2 = 16.83$, $P = 0.002$) incorporating only two predictor variables: percentage of blood glucoses >15 mmol/l and baseline performance of subtraction errors

CONCLUSIONS — Consistent with some other investigations using laboratory methodologies (1,3,4), this field study assessing both type 1 and type 2 diabetic subjects' cognitive-motor functioning during daily routines found significant cognitive dysfunction during hyperglycemia among some subjects. Inspection of the figures suggests that this is not a linear relationship but that there may be a threshold around 15 mmol/l, when cognitive-motor function begins to be affected. The generalizability of these findings is enhanced by the use of three different subject samples with both type 1 and type 2 diabetes, multiple cognitive tasks assessing both verbal and mathematical skills, and repeated samples per subject, with subjects from multiple centers and blind to the hypotheses being tested. An interesting observation is that while hypoglycemia has been consistently associated with initial cognitive slowing, but not typically an increase in errors (1,2), hyperglycemia appears to be related to either cognitive slowing or increased errors (of the affected subjects, only ~25% demonstrated both a significant slowing and errors). This was confirmed in the group data analyses of all three studies, where subtraction errors increased when blood glucose exceeded 15 mmol/l.

While the group results demonstrate that hyperglycemia can have a negative impact on cognitive performance, these effects were highly individualized. Approximately 55% of the subjects across all three studies demonstrated such effects, similar to the 67% reported by Davis et al. (3). Exploratory analyses of individual differences for both type 1 diabetes studies indicated a mild relationship between greater routine exposures to hyperglycemia, as reflected by the percentage of SMBG readings >15 mmol/l, HbA_{1c}, and more cognitive tests affected by hyperglycemia. This is consistent with the results of studies demonstrating that greater exposure to hypoglycemia is associated with greater cognitive impairments during hypoglycemia (16) and is inconsistent with adaptive theories speculating that individuals may accommodate to extreme blood glucose levels.

These findings, along with a consistent literature demonstrating cognitive deficits with hypoglycemia (3,14,18,19), suggest that there is a homeostatic neuroglycemic range within which optimal cognitive-motor functioning occurs. This range would appear to be between 4 and 15 mmol/l. This might be considered an intuitive finding, since other physiological parameters, such as blood pressure, body temperature, water concentration, and body weight all have a range within which the body functions optimally.

These findings have potential clinical meaning for individuals living with diabetes. In this study, hyperglycemia resulted in increased errors and slower responses when performing basic verbal and mathematical tasks, which are important in numerous daily functions, such as balancing checkbooks, calculating insulin dosing, and school and work performance. Further research is needed to determine the impact of hyperglycemia-related cognitive disruption on the daily lives and functioning of individuals with type 1 and type 2 diabetes. Also implicit is that excessive carbohydrate loading before exams or other cognitive-sensitive tasks intended to avoid the negative consequences of hypoglycemia may in fact be counter productive, if such actions lead to hyperglycemia. Instead, optimal cognitive functioning would be anticipated with optimal blood glucose control. The immediate negative consequences of hypoglycemia inherently encourage some individuals to keep their blood glucose >4 mmol/l. The possibility that cognitive dysfunction may occur when blood glucoses exceed 15 mmol/l could be similarly motivating for some patients to avoid hyperglycemia and to achieve tighter blood glucose control. Further, if patients could be trained to both recognize and accurately interpret these disruptions in cognitive performance, they may better recognize hyperglycemia and more quickly take action to treat it (15).

These findings are inconsistent with some laboratory studies (2,5,6,20) that did not find effects of hyperglycemia on cognitive functioning. The differences may be attributed to differences in methodologies. The negative laboratory studies performed one neuropsychological test during a single artificially induced episode of hyperglycemia and typically with a small subject sample. The current studies had larger subject samples and multiple testing per subject during hyperglycemia within naturalistic conditions. Since only approximately half of the subjects are anticipated to demonstrate cog-

nitive affect during hyperglycemia, future studies might benefit from large sample sizes, with multiple testing during hyperglycemia and a selected subject sample of individuals who perform poorly during euglycemia.

A limitation of these data are that, although they were replicated across tasks, diseases, and sites, they still represent observational findings and not experimental manipulations. These findings also do not help to understand the physiological mechanisms underlying such hyperglycemic effects on brain function. However, some laboratory manipulations of hyperglycemia have confirmed these findings (1,4). As detailed in the introduction, there are several proposed underlying physiological mechanisms, but these will require laboratory studies to determine which are responsible for the observed cognitive disruptions during hyperglycemia. In addition, since these studies only assessed adults with diabetes, further naturalistic studies are needed to determine whether hyperglycemia similarly affects routine cognitive-motor performance in pediatric populations.

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Appendix

Individual test for cognitive dysfunction

We propose the following procedure as a within-subject test for significance of a cognitive-motor dysfunction (or symptoms) with respect to a certain glycemic condition such as hypoglycemia or hyperglycemia. The test is based on a set of cognitive-motor performance scores taken during that condition and a set of cognitive-motor performance scores during a control condition, such as euglycemia. In the example below we will elaborate the procedure for screening of hyperglycemic cognitive-motor performance scores with a control performance during euglycemia defined as blood glucose between 5 and 8.3 mmol/l (90–150 mg/dl).

1) For each subject and each cognitive test, mean and SD are computed from the performance scores during euglycemia.

2) For each subject, each cognitive test, and each hyperglycemic reading (e.g., when blood glucose is >15 mmol/l), the *Z* score of that cognitive test is computed as the number of SDs away from the test's mean euglycemic performance.

3) For each subject and each cognitive test (CT) the average hyperglycemic *Z* score (Z_{CT}) is computed together with the number of hyperglycemic readings (n_h).

4) Criterion for significance: the CT is considered significant for hyperglycemia if the product $\zeta_{CT} = n_h^{1/2} \cdot Z_{CT}$ is >1.28.

Statistical background of the test. Under the null hypothesis that a cognitive test is not elevated during hyperglycemia, the *Z* score Z_{CT} would have a central normal distribution (with a mean of 0 and SD of 1). Thus, the average *Z* score of n_h observations would have a normal distribution of 0 and an SD of $1/(n_h^{1/2})$. It follows that $\zeta_{CT} = n_h^{1/2} \cdot Z_{CT}$ would have a normal distribution with a mean of 0 and an SD of 1. Therefore, if ζ_{CT} is >1.28 (central normal distribution quintile corresponding to a probability of 0.9), the null hypothesis must be rejected at a significance level of 0.1.

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