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Title

Acute hypoglycemia impairs executive cognitive function in adults with and without type 1 diabetes

Running title

Hypoglycemia and executive function

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Abstract

Objective: Acute hypoglycemia impairs cognitive function in several domains. Executive cognitive function governs organization of thoughts, prioritization of tasks and time management. This study examined the effect of acute hypoglycemia on executive function in adults with and without diabetes.

Research design and methods: Thirty-two adults with and without type 1 diabetes with no vascular complications or impaired awareness of hypoglycemia were studied. Two hyperinsulinemic glucose clamps were performed, at least two weeks apart, in single-blind, counterbalanced order, maintaining blood glucose at 4.5 mmol/l (euglycemia) or 2.5 mmol/l (hypoglycemia). Executive functions were assessed using a validated test suite (Delis-Kaplan Executive Function). A general linear model (repeated-measures ANOVA) was used. Glycemic condition (euglycemia or hypoglycemia) was the within-participant factor. Between-participant factors included order of session (euglycemia-hypoglycemia or hypoglycemia-euglycemia), test battery used and diabetes status (with or without diabetes).

Results: In comparison with euglycemia, executive functions (with one exception) were significantly impaired during hypoglycemia; lower test scores were recorded with more time required for completion. Large Cohen's *d* values (>0.8) suggests that hypoglycemia induces decrements in aspects of executive function with large effect sizes. In some tests the performance of participants with diabetes was more impaired than those without diabetes.

Conclusions: Executive cognitive function, which is necessary to carry out many everyday activities, is impaired during hypoglycemia in adults with, and without, type 1 diabetes. This

important aspect of cognition has not previously received systematic study with respect to hypoglycemia; the effect size is large, both in terms of accuracy and speed.

Introduction

The human brain is dependent on glucose as its energy source; acute hypoglycemia results in neuroglycopenia with subsequent cognitive impairment. Individuals with type 1 diabetes are exposed to an average of two episodes of self-treated hypoglycemia per week (1). In general, performance on complex cognitive tasks deteriorates when blood glucose declines below 3.0 mmol/L (54mg/dL) (2; 3). Previous studies have demonstrated that, for complex tasks, accuracy is often preserved at the expense of speed (4). The impairment of cognitive function is reversible, although full recovery requires between 20 to 75 minutes after the restoration of euglycemia (5; 6). Acute hypoglycemia has been shown to impair various cognitive domains including memory, attention, information processing, psychomotor function, and spatial ability (7-10). However, the effect of hypoglycemia on executive cognitive function, which is important for everyday functioning, has received little systematic study.

Executive function incorporates a number of complex, interdependent cognitive processes that allow an individual to plan, initiate, sequence, monitor and inhibit complex behavior (11). This allows a person to organize thoughts, prioritize tasks, manage time efficiently and make decisions. Executive function is therefore vital for the performance of many everyday activities, and in children inadequate executive functioning has been linked to poorer adherence to treatment (12). Executive function is not localized to one particular area of the brain (13), although evidence from neuroimaging studies suggests that the frontal lobes of the brain (and their connections to other regions) are closely associated with this cognitive domain (14).

The present study examined the effects of acute hypoglycemia on executive function in adult humans with and without type 1 diabetes, using a well validated test battery (15-18). Performance was examined, in a counterbalanced design, under euglycemic and hypoglycemic

conditions.

Research design and methods

Participants

Sixteen adults with type 1 diabetes and 16 non-diabetic adults were studied. Baseline demographics are shown in table 1. The groups were matched for age and body mass index. Participants with diabetes were recruited from the diabetes clinic at the Royal Infirmary of Edinburgh and had no history of macrovascular or microvascular disease. Digital retinal screening was used to exclude diabetic eye disease, peripheral neuropathy was excluded using clinical examination and nephropathy was excluded by the absence of microalbuminuria. Participants without diabetes were recruited by e-mail and paper advertisements within the local hospital and university. None of the participants had a history of seizures, head injury, psychiatric disorder, or alcohol or drug abuse. Participants were on no medication other than insulin or the oral contraceptive pill. Other exclusion criteria included impaired awareness of hypoglycemia (19), pregnancy, a co-existing systemic disease or malignancy.

HbA1c was measured by high performance liquid chromatography (non-diabetic reference range 5.0-6.05% (31-43 mmol/mol); Bio-Rad Laboratories, Munich, Germany) and was Diabetes Control and Complications Trial-aligned. All participants gave written consent before participating in the study, which had been approved by the local medical ethics advisory committee.

Study procedure

Experimental sessions were performed in the Wellcome Trust Clinical Research Facility at the Royal Infirmary of Edinburgh. Participants attended for two experimental sessions at least two weeks apart. Participants with type 1 diabetes were required to monitor their blood glucose frequently for the 48 hours preceding each experimental session, which was postponed if they

had recorded a blood glucose level $<3.5\text{mmol/L}$ ($<63\text{mg/dL}$) or had experienced symptoms suggestive of hypoglycemia. Sessions commenced at 08:00h and all patients fasted overnight. Participants with type 1 diabetes omitted their morning fast-acting insulin or switched off their insulin pump.

During each session a modified hyperinsulinemic glucose clamp was performed (20). To arterialize any blood samples, the non-dominant arm was wrapped in a warmed blanket with a retrograde intravenous cannula inserted into the forearm. An additional cannula was inserted into the non-dominant antecubital fossa to infuse insulin (Human Actrapid, Novo Nordisk Pharmaceuticals, Crawley, UK) and 20% dextrose. Insulin was infused at a constant rate of 1.5mUnit/kg/min using a Gemini PCI pump (Alaris Medical Systems, San Diego, California). Blood samples were taken at 5 minute intervals and analyzed using a glucose oxidase method (2300 Stat, YSI, Yellow Springs, OH). The dextrose infusion rate was adjusted to maintain the appropriate arterialized blood glucose concentration.

Two experimental conditions (hypoglycemia and euglycemia) were studied in a single blind, random counterbalanced order. During each experimental session, arterialized blood glucose was maintained at 4.5mmol/L (81mg/dL) for 30 minutes. It was then either maintained at 4.5mmol/L throughout (the euglycemia condition), or lowered over 20 minutes to 2.5mmol/L (45mg/dL) (the hypoglycemia condition). The experimental condition lasted for 60 minutes, after which euglycemia was restored. Participants consumed a meal on completion of the study.

Hypoglycemia Scores

Participants scored their symptoms at baseline and during the experimental period using a subjective, validated questionnaire, the *Edinburgh Hypoglycaemia Symptom Scale*. This measures the intensity of commonly experienced hypoglycemic symptoms graded on a 7 point

Likert scale (1 = not present, 7= very intense); these symptoms have been grouped previously into autonomic, neuroglycopenic and malaise sub-groupings (21).

Baseline intelligence & Educational Achievement

The National Adult Reading Test (NART) tests the pronunciation of 50 phonologically irregular English words and is widely used as an estimate of peak intellectual ability (22). Educational achievement was determined by whether a participant had high school, degree or doctoral level qualifications.

Cognitive function tests

Tests of executive function were performed during both experimental conditions. All tests were from the Delis-Kaplan Executive Function (D-KEFS) test suite and are described below. The D-KEFS is a well validated series of tests which comprehensively assess the domain of executive functions and is suitable for adults with a range of ability levels (15; 16). Practice effect was controlled for by counterbalancing the order of the experimental conditions (euglycemia before hypoglycemia and *vice versa*) and counterbalancing the parallel forms of the tests (battery A before battery B and *vice versa*) using a Latin Square. This study design was chosen to minimize many of the previous criticisms of cognitive function testing during hypoglycemia (23). Order effects were sought but, from prior experience in cognitive testing in hypoglycemic clamp studies, none are usually found.

The Digit Symbol Substitution Test (DSST) (from the Wechsler Adult Intelligence Scale III-UK) and “Trail Making B” (from the Delis-Kaplan Executive Function System) tests were used as ‘marker’ cognitive tests that are reliably affected by moderate hypoglycemia (18; 24). The DSST is a test of coding performed at speed, and for each mistake five points were subtracted from the score achieved to give an overall score. “Trail Making B”, also a test of executive

function, tests a wide range of cognitive processes including complex attention, visual scanning, psychomotor speed and mental flexibility (17). The test requires the participant to switch back and forth between connecting numbers and letters in sequence (e.g. 1-A-2-B-3-C); it covers two pages which increases spatial scanning demands. Time taken (in seconds) was subtracted from 200; for each mistake five additional points were subtracted to give a total score.

Executive function tests

Verbal fluency (category switching): This test requires both rapid retrieval from semantic knowledge and cognitive flexibility to allow switching between categories. Participants were required to generate words, alternating between two different semantic categories (e.g. fruit and furniture). The outcome variable was the total score with one point awarded for each correct pair named during the time limit.

Sorting test: Based on the Wisconsin Card Sorting Test (25), this test is designed for isolating and measuring multiple components of concept-formation and problem-solving abilities. Each participant was shown two groups of three cards each and was then required to state how the two groups were sorted (e.g. one card set shows singular words and the other displays plural words). Outcome variables were the total score, with four points awarded for each correct description, and time taken.

Twenty questions test: The participant is presented with a stimulus page depicting pictures of 30 common objects (e.g. banana, airplane or bowl). The participant must ask the fewest number of yes/no questions possible in order to identify the unknown target object. The ideal response would eliminate half of the remaining objects. This test assesses the participant's ability to perceive the various subcategories (e.g. land-based objects and those that fly). By incorporating feedback from previous answers, participants can formulate a yes/no question to eliminate the

maximum number of objects. One point was awarded for each correctly phrased question with a lower score denoting better performance. Participants performed this test twice, outcome variables included combined score and total time taken. Analysis of the quality of responses was then made in a quantitative manner to give the third outcome variable. Subjects scored five points for an answer which eliminated half of the remaining objects, four points for a response that eliminated ± 1 of half the remaining objects, three points for ± 2 , two points for ± 3 , 1 point for ± 4 and 0 points for ± 5 . So if there were 8 remaining objects and a response eliminated 3 objects then that question would score 4 points. This score was then divided by the number of questions taken to answer to give the third outcome variable.

Tower test: The Tower test assesses several key executive functions including spatial planning and maintaining an instructional set (26). Participants must build the designated tower in the fewest number of moves possible by moving differently-sized disks across three pegs. Four towers of increasing difficulty were constructed during each experimental session; to avoid a practice effect a parallel version of equivalent difficulty was created by shifting each piece to the right. One point was awarded for each move taken; therefore a lower score denoted better performance. Outcome variables were the combined score for all four towers and the total time taken.

Color-Word Interference Test (Stroop): Based on the classic Stroop procedure, these four tests assess the participant's ability to inhibit an overlearned verbal response (i.e. name the ink color of the word instead of reading the printed word) (27). The first two (baseline) tasks require the participant to name blocks of color (Stroop 1) and read color words printed in black ink (Stroop 2). The third task prints color words in a different color (Stroop 3), e.g. the word "red" printed in blue ink (inhibiting). The fourth task involves asking the participant to switch back and forth between naming ink colors and inhibiting (Stroop 4); testing both inhibition and cognitive

flexibility. Time required for completion became the score for that task; four seconds were added for an uncorrected error and two seconds for a corrected error. Five combined task scores were calculated (Table 2). Stroop A is the sum of all four tasks, Stroop B is the sum of the first two tasks and an indication of performance in key lower level skills (i.e. reading and naming). Stroop C and D demonstrate any effect on executive functioning while attenuating the impact of any deficit in more basic cognitive functioning (i.e. reading printed words). The “Stroop Interference Effect” (Stroop C) indicates the increase in time taken to perform the task requiring an inhibited response compared with simply reading or naming the ink color (28). Stroop E demonstrates the additional time required to switch between tasks (cognitive flexibility) while attenuating the effect of inhibition. Many of the Stroop tests rely on color discrimination, this has been shown previously to be unaffected by moderate hypoglycemia although may become impaired with more profound hypoglycemia (29).

Statistical Analysis

A general linear model (repeated measures ANOVA) was used. Glycemic condition (euglycemia or hypoglycemia) was the within-participant factor (repeated measure). Order of session (euglycemia followed by hypoglycemia or *vice-versa*), order of test battery (test battery A followed by battery B or *vice versa*) and diabetes status (participants with or without diabetes) were between-participants’ factors with the NART score as a covariate. Effect sizes were calculated using Cohen’s *d* to assess the extent of any cognitive decrement caused by hypoglycemia ($d=0.2$ small, $d=0.5$ medium, $d=0.8$ large) (30). All analyses were performed using Microsoft Excel 2010 (Redmond, Washington, USA) and SPSS version 18.0 (SPSS, Chicago, USA) both for Windows. Unless otherwise stated, data are expressed as mean \pm SD and $p<0.05$ was considered to be significant.

Results

Blood glucose: Target blood glucose levels were achieved for both the hypoglycemic (2.45 ± 0.11 mmol/L) and euglycemic (4.54 ± 0.09 mmol/L) conditions; glucose levels were similar in participants with or without diabetes ($p=0.23$ and $p=0.11$ respectively, t-test).

Symptom scores: Autonomic symptom scores increased from 10.6 ± 4.1 during euglycemia to 22.6 ± 9.3 during hypoglycemia ($p<0.001$, Cohen's d 1.68). Neuroglycopenic symptom scores increased from 10.8 ± 5.5 to 19.6 ± 8.7 ($p<0.001$, Cohen's d 1.22). Malaise symptom scores increased from 2.5 ± 1.3 to 3.4 ± 1.8 ($p=0.004$, Cohen's d 0.63).

Educational achievement & baseline intelligence: Nine (56.3%) healthy volunteers had doctorate level qualifications compared with four (25.0%) participants with diabetes ($p=0.20$, Pearson Chi Square). Mean NART scores were significantly lower in participants with diabetes than those without (36.3 ± 3.8 and 40.5 ± 5.4 respectively, $p<0.02$, t-test). As expected, National Adult Reading Test (NART) scores (taken at baseline) did not differ significantly between the two experimental sessions ($p=0.18$, t-test).

General cognitive function tests: Performance during hypoglycemia was significantly impaired in both the Trail Making and DSST ($p<0.001$ for both, Cohen's d 1.16 for trail making and 0.84 for DSST). No significant difference on these tests was observed between people with, and without, diabetes (result not shown).

Executive function tests: No significant effects were found for order of session (hypoglycemia followed by euglycemia or *vice versa*). The only significant effects for diabetes status were for the Stroop A ($p<0.05$), Stroop B ($p<0.05$) and verbal fluency ($p<0.03$) tasks; performance

during both euglycemia and hypoglycemia of participants with diabetes was worse than those without diabetes.

Performance during hypoglycemia was significantly impaired on every measure of executive function examined other than Stroop E, both in terms of scores achieved and time taken (Tables 2 & 3). Hypoglycemia significantly prolonged the time to completion in all of the tests where time was not fixed. The high Cohen's *d* values (>0.8) indicate that hypoglycemia induced decrements with large effect sizes (see tables for Cohen's *d* values).

The lower performance scores achieved during hypoglycemia in the Stroop test were not simply due to slower information processing, participants made a significantly greater number of errors during hypoglycemia compared with euglycemia (5.81 ± 3.93 and 1.91 ± 1.96 respectively, $p < 0.001$, unpaired t test). Both self-corrected and uncorrected errors were significantly increased during hypoglycemia compared with euglycemia (data not shown, $p < 0.001$ & $p = 0.002$ respectively).

In the Twenty questions test, responses given during hypoglycemia are often of a poorer quality, e.g. asking very specific questions that would only eliminate one or two of the remaining objects (i.e. does it fly? is it a bowl? is it orange?). Analysis of the quality of responses showed that scores during hypoglycemia were significantly lower than during euglycemia (see methods for scoring system) (5.11 ± 1.40 and 6.24 ± 1.48 respectively, $p = 0.003$, unpaired t test).

Significant glycemic condition by diabetes status interactions were observed for Stroop A, Stroop B and the sorting test (time taken) ($p = 0.02$, $p = 0.002$ and $p = 0.004$ respectively). This suggests that the effects of hypoglycemia differ significantly between participants with, and without, diabetes. Figure 1 shows that in all three tests, participants with diabetes were affected

by hypoglycemia to a greater degree than those without diabetes. When the NART scores are entered as a covariate, participants with diabetes continued to experience a greater detrimental effect of hypoglycemia than those without diabetes in the sorting test ($p=0.02$) and Stroop B ($p=0.01$), but not for Stroop A ($p=0.12$).

Conclusions

The present study has demonstrated that acute hypoglycemia markedly impairs performance in almost all the aspects of executive function that were tested in adults with, and without, type 1 diabetes. All domains of executive function were significantly impaired except for Stroop E. Where the time taken was a variable rather than a constant, in all tests the time to completion was significantly longer. The generally large Cohen's d values (>0.8) indicate that hypoglycemia accounted for a large part of the variation in results.

It is debatable as to whether the decrement in processing speed is solely responsible for the observed impairment in executive function (31). However, the present study has demonstrated more specific decrements; the quality of the responses was poorer during hypoglycemia in the Twenty questions test with subjects more likely to ask closed questions that failed to eliminate many of the remaining objects. In the Stroop test the number of errors, both uncorrected and self-corrected, was greater during hypoglycemia. This suggests that during hypoglycemia, subjects were less aware of an error being made and so were less likely to correct the error; this has been shown previously in driving simulator studies in which participants were less likely to correct any driving errors when hypoglycemic (32).

During euglycemia glucose is the main source of energy for the brain. During hypoglycemia alternative substrates may be utilized as energy sources, although in general they ameliorate, but do not reverse, the effects of neuroglycopenia (33). Administration of some of these alternative fuels (e.g. amino acids or lactate) has been shown to reduce the decrement in cognitive performance observed during hypoglycemia (34; 35). In these studies insufficient information was given to determine whether there had been a significant improvement in the quality of the answers given.

Glycemic targets were maintained and symptom scores incremented appropriately during hypoglycemia. The expected decrement in performance during hypoglycemia in the cognitive 'marker' tests was consistent with the results of other similar studies (4; 7; 10). Previous studies have shown that several domains of cognitive function are impaired during acute hypoglycemia, including memory and spatial awareness (9; 36). Previous research also demonstrated that performance of complex cognitive tasks is preferentially impaired by hypoglycemia, while simpler tasks such as finger tapping or reaction time are less affected (4; 10).

The executive function tests that were used in the present study examined a series of diverse yet interdependent complex cognitive processes. The category switching part of the verbal fluency test examined cognitive switching abilities similar to those examined by Trail making B. The sorting test examined concept-formation and problem solving abilities. The Twenty questions test assessed the ability to perceive sub-categories within the list of objects presented. The Tower test assessed spatial planning and the ability to maintain an instruction set. All of these cognitive tests were impaired during hypoglycemia.

The Stroop test uses a series of combined scores to give an indication of performance in both lower and higher level cognitive functioning (table 2); all but Stroop E were significantly impaired during hypoglycemia. Stroop E is the additional time taken to switch between tasks and is thus a measure of cognitive flexibility; it is noteworthy that other measures of cognitive flexibility such as the verbal fluency test and Trail making B *were* impaired by hypoglycemia.

The cognitive processes affected will impinge on performance of everyday activities. Impaired ability to switch between semantic categories and retrieval from semantic knowledge would interfere with planning and make it difficult to construct a list of items suitable for a specific

purpose (e.g. for a camping trip). In such a scenario, impaired spatial planning and failure to maintain an instructional set would make loading an automobile or erecting a tent more difficult to undertake.

Compared with their performance during euglycemia, participants with diabetes experienced a greater detrimental effect of hypoglycemia than those without diabetes in the sorting test (time taken), Stroop A and Stroop B. Higher baseline intelligence is known to improve performance during the Stroop test, the effect of higher intelligence scores (in adults) on performance during the sorting test is less clear cut (28; 37). Whereas the groups with and without diabetes were otherwise well matched (table 1), the significantly lower NART scores (a measure of crystallized intelligence) that were documented in the participants with diabetes may have been a confounding factor. However, when the NART scores are entered as a covariate, participants with diabetes continued to experience a greater detrimental effect of hypoglycemia compared to those without diabetes in the sorting test (time taken) and for Stroop B, but not for Stroop A. Differential effects of hypoglycemia between people with and without diabetes were found in a study of a different cognitive domain, psychomotor function. However, in that study, the detrimental effect of hypoglycemia was greater in participants *without* diabetes (10). The mechanism underlying this differing effect of diabetes status of performance during hypoglycemia is unknown.

A possible weakness of the present study is that time constraints allowed each test of cognitive function to be performed only once during each experimental session. Tests to assess several cognitive domains take time to perform and it has been suggested that cognitive adaptation may occur when exposure to hypoglycemia is relatively prolonged (5; 38), although this premise has been disputed (39). Cerebral adaptation to hypoglycemia, which results in a lesser magnitude of impairment of cognitive function, is a feature of people with type 1 diabetes who have impaired

awareness of hypoglycemia (40); individuals with this acquired syndrome were excluded from the study.

The present study provides further evidence of a global impairment of most high level cognitive functions during hypoglycemia. Both speed of information processing and the quality of answers given were adversely affected by hypoglycemia. Executive function is essential for many everyday activities (such as driving, analyzing data or planning events); its disruption during hypoglycemia will have a profound effect on the functioning of a person with diabetes.

Author contributions

AJG researched data, performed statistical analysis in discussion with IJD, wrote the manuscript and is the guarantor of this work. IJD and BMF helped with the study design, contributed to the discussion and reviewed/edited the manuscript.

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Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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