Effects of Acute Hypoglycemia on Working Memory and Language Processing in Adults With and Without Type 1 Diabetes

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PATHOPHYSIOLOGY/COMPLICATIONS

OBJECTIVE

To examine the effects of hypoglycemia on language processing in adults with and without type 1 diabetes.

RESEARCH DESIGN AND METHODS

Forty adults were studied (20 with type 1 diabetes and 20 healthy volunteers) using a hyperinsulinemic glucose clamp to lower blood glucose to 2.5 mmol/L (45 mg/dL) (hypoglycemia) for 60 min, or to maintain blood glucose at 4.5 mmol/L (81 mg/dL) (euglycemia), on separate occasions. Language tests were applied to assess the effects of hypoglycemia on the relationship between working memory and language (reading span), grammatical decoding (self-paced reading), and grammatical encoding (subject-verb agreement).

RESULTS

Hypoglycemia caused a significant deterioration in reading span ($P < 0.001$; $\eta^2 = 0.37$; Cohen $d = 0.65$) and a fall in correct responses ($P = 0.005$; $\eta^2 = 0.19$; Cohen $d = 0.41$). On the self-paced reading test, the reading time for the first sentence fragment increased during hypoglycemia ($P = 0.039$; $\eta^2 = 0.11$; Cohen $d = 0.25$). For the reading of the next fragment, hypoglycemia affected the healthy volunteer group more than the adults with type 1 diabetes ($P = 0.03$; $\eta^2 = 0.12$; Cohen $d = 0.25$). However, hypoglycemia did not significantly affect the number of errors in sentence comprehension or the time taken to answer questions. Hypoglycemia caused a deterioration of subject-verb agreement (correct responses: $P = 0.011$; $\eta^2 = 0.159$; Cohen $d = 0.31$).

CONCLUSIONS

Hypoglycemia caused a significant deterioration in reading span and in the accuracy of subject-verb agreement, both of which are practical aspects of language involved in its everyday use. Language processing is therefore impaired during moderate hypoglycemia.

Cognitive function is impaired during acute hypoglycemia and frequently affects people with type 1 diabetes (1,2); elucidation of which cognitive domains are affected and by how much is of practical importance. Although cognitive domains do not function independently of each other, it is pertinent to design studies that investigate how everyday activities are affected by hypoglycemia as this has direct relevance to people with diabetes. Previous studies have demonstrated the effects

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A slide set summarizing this article is available online.

of hypoglycemia on specific cognitive domains, including memory, attention, nonverbal intelligence, visual and auditory information processing, psychomotor function, spatial awareness, and executive functioning (3–14). However, the effects of hypoglycemia on language processing have seldom been explored.

In adults, language processing involves numerous pathways to ensure the rapid comprehension and production of speech and text. These skills are an integral part of everyday life and appear to be effortless. However, speech fluency and speed deteriorate if an individual is distracted by a second task, such as walking or finger tapping (15). Similarly, sentence comprehension is impaired when people also have an extrinsic memory load (16). Moreover, brain-damaged adults with acquired dyslexias experience difficulty with basic language use. Several different patterns of impairment have been described, suggesting that numerous components are involved (17). During hypoglycemia, people with type 1 diabetes may temporarily be deprived of these skills and could potentially be disadvantaged during everyday activities.

Language production can be broadly subdivided into conceptualization (conceiving an intention to express, selecting, and ordering relevant information), formulation (lexical retrieval and syntactic and phonological planning), articulation, and self-monitoring. Conceptualization and self-monitoring appear to require working memory (18). However, the effects of working memory on other stages of language production, such as syntactic (grammatical) planning, are less clear (18,19). Similarly, language comprehension can be divided into sublexical and lexical processing, syntactic analysis (determining word categories and syntactic structure), and semantic integration. The stages of comprehension that require working memory and the extent to which such working memory is domain general or domain specific remain open to debate (16,20).

Slurred speech and language difficulties are recognized features of hypoglycemia, but to our knowledge, the effects of hypoglycemia on linguistic processing have not been studied systematically. The current study used transient insulin-induced hypoglycemia in adults with and without type 1 diabetes to examine its effects on three aspects of language: the relationship between working memory and language (reading span), grammatical decoding (self-paced reading), and grammatical encoding (producing subject-verb agreement). Tests of these issues have been used extensively to understand the nature of language processing and its relationship to other cognitive abilities, specifically working memory (17).

RESEARCH DESIGN AND METHODS

Forty adults (19 male [48%]) participated in the study, 20 of whom had type 1 diabetes and were recruited from the diabetes clinic at the Royal Infirmary of Edinburgh. Twenty volunteers without diabetes were recruited by advertising locally. These control participants were studied to distinguish between the acute effects of hypoglycemia on language processing (which should be apparent in both groups) and any potential effects of glycemic control on cognitive function, which would be evident only in the group with diabetes. Participant characteristics are shown in Table 1. The median age was 30 years (range 19–44). No differences in age, BMI, or sex distribution were observed between the two groups. In participants with type 1 diabetes, median duration of diabetes was 5 years (range 2–27), and mean HbA_{1c} was 7.5% (SD 0.08) (58 mmol/mol [SD 0.83]).

Exclusion criteria included a history of intercurrent illness, hypertension, previous head injury, seizure or blackouts, alcohol or drug abuse, or psychiatric disorder. Individuals with type 1 diabetes who had a history of impaired awareness of hypoglycemia were excluded. None of the participants was taking medication other than insulin or the oral contraceptive pill. Patients reported that they had normal hearing, normal/corrected vision, and English as their native language, all of which were prerequisite for the cognitive test battery.

Study Design

Each participant was studied on two occasions, separated by at least 2 weeks, with cognitive testing being conducted during controlled hypoglycemia on one occasion and during euglycemia on the other. Ethical approval for the study was granted by the local medical ethics committee. All participants gave written informed consent. The participants with type 1 diabetes were required to have not experienced hypoglycemia in the 48 h before each study session. If a blood glucose of <4.0 mmol/L was identified within the 24 h preceding the study session, the session was deferred for at least 1 week.

A modified hyperinsulinemic glucose clamp (21) was used to manipulate blood glucose. A repeated-measures, counterbalanced design was used, with half the participants undergoing a euglycemia (blood glucose 4.5.mmol/L) clamp first, followed by a hypoglycemia (blood glucose 2.5 mmol/L) clamp, and vice versa for the other half. A cognitive test battery was administered during the two study conditions (euglycemia and hypoglycemia). Participants were blinded as to the study order and their prevailing blood glucose concentration.

Procedure

Each session commenced at 0800 h after an overnight fast and the omission of morning insulin for the participants with diabetes. Two intravenous cannulae were

Table 1—Characteristics of participants

	Control subjects without diabetes	Participants with type 1 diabetes	All participants
Sex (% male:female)	40:60	55:45	48:52
Age (years)	32 (22–44)	30 (19–39)	30 (19–44)
BMI (kg/m^2)	24.6 (18.9–31.5)	24.6 (19.7–27.9)	24.9 (6.66)
NART error score	8 (3–21)	14 (3–24)	12 (3–24)
Predicted IQ	121 (126–111)	116 (108–126)	118 (108–126)
HbA_{1c}, mean (SD) (mmol/mol [%])	N/A	58 (0.83) [7.5 (0.09)]	N/A
Duration of diabetes (years)	N/A	5 (2–27)	N/A

Data are given as median (range) unless otherwise stated. Predicted IQ was calculated using the following formula: 128 − 0.83 × NART error score.

placed in the nondominant arm. One was inserted in a retrograde manner in a distal hand vein. A warm blanket was used to arterialize venous blood, which was sampled every 5 min. A second cannula was placed in the antecubital fossa for a variable infusion of 20% dextrose and human soluble insulin (Humulin S; Eli Lilly and Company, Indianapolis, IN). After a priming regimen, insulin was infused at 60 mU/m^2/min. During each study condition, blood glucose was lowered to 4.5 mmol/L (baseline) for 20 min and then either maintained at 4.5 mmol/L (euglycemia) or lowered to 2.5 mmol/L (hypoglycemia) over a period of 20–30 min. Blood glucose was stabilized at this level for a further 20 min before cognitive testing.

General Cognitive Function Tests

General intellectual ability was estimated at baseline using the National Adult Reading Test (NART), a test of pronunciation of vocabulary (22). The mean number of errors recorded was significantly less in the group without diabetes compared with the group with diabetes (9 [SD 5] vs. 14 [SD 4]; Student *t* test, P = 0.002). As a total group, participants had above average intelligence according to the NART conversion tables in the manual. IQ scores are given in Table 1 and were calculated using the following formula: predicted full-scale IQ = 128 − (0.83 × NART error score).

Tests of language processing and working memory were administered along with Trail Making B (TMB) (5–7,10–12, 23,24) and Digit Symbol Test (DST) (5–7, 10–12,24,25), which are known to be consistently affected by hypoglycemia. The order of tests was identical during each study condition. Every participant practiced all tests (except the NART) before each experiment. For the DST, all participants converted the same short sequence of numbers to symbols, with every digit from 1 to 9 being represented in the test sequence. On the TMB, participants all completed the same practice trail, with each test trail differing from the previous one in order to ensure that the practice attempt would not invalidate subsequent tests.

Language Processing Tests

Reading Span

This test, adapted from Daneman and Carpenter (26), assesses language processing ability in relation to working memory. Such tests have been applied very widely in the psychology of language and memory (17). Participants were shown a sentence on a computer screen followed by an unrelated word on the next screen. They read both of these aloud before they saw a new screen with another sentence. Having read a set of sentences and unrelated words, each participant wrote down the isolated words in the correct order. Initially, groups of two sentences were presented before the participant was allowed to record the isolated words. As the test proceeded, the participant was presented with groups of three, four, five, and six sentences, representing a reading span of three, four, five, or six, respectively. Each participant was allowed three attempts at each span length. A score was awarded for the total number of correct words recalled. A second score was given for the reading span. This was scored as 1 if all three attempts were correct in each span, or 0.5 if two out of three attempts were correct for each span. If a mistake was made at any given span, no further scores were given for higher spans (see example in Table 2).

Self-Paced Reading

This test examined the interaction between syntactic organization of a sentence and working memory. To do this, contrasts were considered between less and more complex types of sentences. Both the use of self-paced reading and its application to the study of processing complexity are central to psycholinguistic theory (17). First, sentences containing subject-relative (SR) and object-relative (OR) clauses (e.g., 1a and 1b, respectively) have the same words in different orders:

1a. SR: The banker that/irritated the lawyer/played tennis every Saturday.
1b. OR: The banker that/the lawyer irritated/played tennis every Saturday.

In SR clauses, the main clause subject (banker) is also the subject of the verb of the embedded clause, whereas in OR clauses, the main clause subject is the object of the verb of the embedded clause. OR clauses are generally harder to understand than SR, as demonstrated in studies involving reading time (27), comprehension by aphasic subjects (28), and measures of brain activity (29,30). Comprehension of sentences involving ORs may require an increase in memory load compared with sentences involving SRs, with increased vulnerability to the effects of hypoglycemia.

Second, two types of "reduced relative" sentences were contrasted (e.g., 2a and 2b, respectively):

2a. Plausible misanalysis: The lawyer sent/by the governor/arrived late.
2b. Implausible misanalysis: The package sent/by the governor/arrived late.

The correct interpretation of these sentences is that the lawyer or package has been sent. However, in sentence 2a, it is temporarily possible that the lawyer did the sending, and readers appear to misanalyze such sentences and experience difficulty. Less difficulty occurs in 2b, because packages cannot plausibly send anything (31).

Participants were presented with 48 sentence pairs (12 each of types 1a, 1b, 2a, and 2b) in randomized order and interspersed with 72 fillers using the psychological experimentation software package E-Prime (Psychology Software Tools Inc., Pittsburgh, PA). Each sentence was presented in three fragments

Table 2—Example of scoring on reading span test

Example	Answers	Total word score
The tools in the bag were sharp APPLE	Apple, table	2
The plans for the house were detailed TABLE		
The boys in the classroom were naughty GLASS	Glass, dog	2
The fruit in the basket was fresh DOG		
The cars in the showroom were expensive BALL	Ball, window	2
The trees in the field were tall WINDOW		

The total word score for this reading span is 6 (2 + 2 + 2). Marks for this reading span = 1 (all three sets of two unrelated words recalled correctly). Similar exercises to those above were given for three sets of three, four, five, and six sentences, respectively.

on a computer screen (defined by "/" in examples 1 and 2), with participants pressing the number 4 on a computer keyboard to advance to the next sentence fragment. After the whole sentence had been presented, participants saw a question with a yes/no answer, designed to assess comprehension. The participant was asked to answer the question by pressing either 3 for "yes" or 5 for "no" on the computer keyboard. The number of mistakes in sentence comprehension was recorded for each sentence type. For each correct answer, the time taken to complete the reading of each sentence fragment and answer each question was recorded for each experimental condition. Participants were asked to read as fast as they could while ensuring adequate comprehension. They were allowed to pause for a rest at any time between questions. Examples are shown in Table 3.

Sixteen variables for correct answers were considered for each experimental condition (for each of the four sentence subtypes, the time to read each of the three sentence fragments and the time to answer the yes/no question that followed each sentence was recorded). These were expressed as median (range) given vulnerability to outlier values. For the group data, median response times were normally distributed, as assessed by the Kolmogorov-Smirnov test; hence, all data were then analyzed by ANOVA.

Subject-Verb Agreement

This test, adapted from Hartsuiker and Barkhuysen (32), examined whether hypoglycemia affects the accuracy of subject-verb number agreement. Agreement in number between the subject and verb is obligatory in sentences in English and many other languages. It is part of the stage of syntactic planning in production (19). The study of the processes involved in subject-verb agreement has been particularly important in attempts to understand how people produce sentences.

Much evidence exists in published research on language production that subject-verb agreement is controlled by grammatical number information (i.e., the grammatical number of the subject noun phrase) but that it is also influenced by conceptual information (whether the subject noun phrase refers to an individual thing or a multitude of things). For instance, Eberhard (33) showed that speakers of English were more likely to (incorrectly) produce a plural verb when completing a singular subject referring to multiple tokens (e.g., the face on the coins, as in example 4b below) than after a subject referring to only a single token (e.g., the bedroom for the guests, as in example 3b below).

Previous studies have demonstrated that a reduction in working memory capacity affects the ability to construct verb agreement. A study in Dutch healthy elderly participants showed a conceptual number effect similar to the study by Eberhard (33), whereas aphasic subjects were affected only by grammatical mismatch (34). It is possible therefore that a severe capacity shortage alters the interplay between conceptual and grammatical information. A dual-task study, in which healthy young participants held an extrinsic three-word load in memory while completing sentences, showed an increase in the number of agreement errors under load versus no-load conditions (as in Fayol et al. [35]) but no modulation of the conceptual number effect (32). If hypoglycemia induces a relatively mild reduction in working memory, one would predict that a similar pattern would be observed.

In this test, the participant saw an adjective such as "large" on the computer screen. The adjective was then replaced by a sentence fragment, such as "the bedroom for the guests." Participants were instructed to repeat the sentence, placing the adjective at the end and inserting a suitable verb (using only

Table 3—Examples of the different types of questions that were administered in the self-paced reading test

Sentence type	Fragment 1*	Fragment 2*	Fragment 3*	Question§	Answer
1a. SR	The hiker that	passed the fisherman	got lost and had to be rescued	Did someone have to rescue the hiker?	Yes
1a. SR	The tenant that	despised the landlord	phoned the newspaper to complain	Did the tenant write to the newspaper?	No
1b. OR	The babysitter that	the child chased	tripped over the toy dump truck	Did someone trip over a toy truck?	Yes
1b. OR	The flight attendant that	the pilot complimented	feared flying before this job	Had the flight attendant never been frightened of flying?	No
2a. Plausible misanalysis	The speaker proposed	by the group	turned out to be disastrous	Was the speaker a failure?	Yes
2a. Plausible misanalysis	The man paid	by the parents	saved their son's life	Did the son die?	No
2b. Implausible misanalysis	The portrait sketched	by the artist	was very beautiful	Was the picture extremely attractive?	Yes
2b. Implausible misanalysis	The evidence examined	by the lawyer	turned out to be unreliable	Were people able to trust the lawyer?	No
Filler	The athlete practiced hard	but he was not chosen to join	the national team	Did the athlete practice hard?	Yes
Filler	John worked hard	for the last year and a half	to get a long holiday in Spain	Did John want a holiday in America?	No

*The participant had to press 4 on the computer keyboard to advance to the next sentence fragment on the next screen. §The participant had to press either 3 for yes or 5 for no on the computer keyboard in response to the question.

the verbs "is/are" or "was/were"). In this example, the correct answer would be "the bedroom for the guests is/was large." The participants were presented with 40 critical items embedded in a list with fillers, in four conditions, with examples listed below. In the mismatch conditions, the fragment either referred to a single entity (single token, e.g., examples 3a and 3b below) or multiple entities (multiple token, e.g., examples 4a and 4b below). Versions of the same items in the match conditions served as control stimuli. Note that only in the multiple token mismatch condition (example 4b) there is a mismatch between the noun's grammatical number (singular) and notional number (plural).

Examples:

3a. Single token match (single subject noun, single modifier noun), e.g., "the bedroom for the guest."
3b. Single token mismatch (single subject noun, plural modifier noun), e.g., "the bedroom for the guests."
4a. Multiple token match (single subject noun, single modifier noun), e.g., "the face on the coin."
4b. Multiple token mismatch (single subject noun, plural modifier noun), e.g., "the face on the coins."

The answers were recorded using a portable tape recorder. Responses were grouped into categories depending on whether the response was correct or whether there was an error of number agreement or a miscellaneous response (e.g., an error in production of the sentence fragment, a missing completion, or an ambiguous response).

Statistical Analysis

The results were analyzed independently for each cognitive test outcome. A general linear model (repeated-measures ANOVA) was used. Experimental order (euglycemia-hypoglycemia or hypoglycemia-euglycemia) was a between-subject factor, and glycemic condition (euglycemia or hypoglycemia) was a within-subject factor. A *P* value <0.05 was considered significant. Effect sizes are given as Cohen *d* (calculated using the mean and SD) and η squared (η^2) (where η^2 is the proportion of the variance in the test scores accounted for by study condition [euglycemia vs. hypoglycemia]). All analyses were performed using SPSS statistical software (version 12.0 for Windows; SPSS, Chicago, IL). The power of the study was high to detect the principal outcome of interest, the effect of hypoglycemia on language functioning overall; with $\alpha = 0.05$ (two tailed) and $n = 40$ (repeated measures), there was 80% power to detect an effect size (Cohen *d*) of 0.45. The power was lower to detect whether the effects were significantly different in people with and without diabetes; with $\alpha = 0.05$ (two tailed) and $n = 20$ in each of the two groups, there was 80% power to detect an effect size (Cohen *d*) of 0.91.

RESULTS

The mean arterialized blood glucose concentration during the euglycemia condition was 4.51 mmol/L (SD 0.25) and during hypoglycemia was 2.52 mmol/L (SD 0.23) (Supplementary Fig. 1).

Table 4 summarizes the results of the general cognitive (DST and TMB) and language tests (reading span, self-paced reading, and subject-verb agreement). The DST score is the number of symbols decoded in 2 min, so a higher score indicates a better performance. The TMB result is the time in seconds taken to complete the trail so a lower score indicates a better performance. In the reading span test, results are given for the mean number of unrelated words recalled at the end of a set of sentences (span of 2 means that the participant recalled two unrelated words correctly at the end of two sentences). The total number of correct words recalled during the whole test is also given. For both these results, a higher score indicates a better performance. In the self-paced reading test, the results include the number of errors made, the time taken to read each sentence fragment, and the time taken to answer the question at the end of reading the sentence, with a higher number denoting worse performance on all these parameters. In the subject-verb agreement test, where participants had to insert either a plural or a singular verb when completing a sentence, the scores are divided into correct responses, errors of agreement, and miscellaneous responses (e.g., an error in production of the sentence fragment). A higher number of correct answers denoted a better performance.

No significant differences were observed between people with and without diabetes for any cognitive or reading tests, with the exception of the reading time for fragment 1 in the self-paced reading test, discussed below. There were no significant order effects (euglycemia-hypoglycemia order vs. hypoglycemia-euglycemia) for any cognitive or reading test. The only significant condition (euglycemia vs. hypoglycemia) by diagnosis (nondiabetes vs. diabetes) interaction was for reading time of fragment 2 of the self-paced reading test (Table 4 and see below).

DST and TMB

The time taken to complete the TMB test increased significantly from mean 43.9 s (SD 12.0) during euglycemia to 54.2 s (SD 18.7) during hypoglycemia ($P < 0.001$; $\eta^2 = 0.39$; Cohen $d = 0.65$) (Table 4). The mean score of the DST declined from 72.9 (SD 14.8) during euglycemia to 64.2 (SD 12.6) during hypoglycemia ($P < 0.001$; $\eta^2 = 0.46$; Cohen $d = 0.63$).

Language Tests

Reading Span

Acute hypoglycemia caused a significant deterioration in reading span ($P < 0.001$; $\eta^2 = 0.37$; Cohen $d = 0.65$) and a fall in total correct responses ($P = 0.005$; $\eta^2 = 0.19$; Cohen $d = 0.41$) (Table 4).

Self-Paced Reading

Hypoglycemia did not significantly affect the number of errors in sentence comprehension or the time taken to correctly answer questions in the self-paced reading test (Table 4). The reading time for sentence fragment 1, but not fragments 2 or 3 (as indicated by response times), increased significantly during hypoglycemia ($P = 0.039$; $\eta^2 = 0.11$; Cohen $d = 0.25$). In the reading time of fragment 2, a significant condition by diagnosis interaction was observed, in which hypoglycemia affected the healthy volunteer group more than the adults with type 1 diabetes ($P = 0.03$; $\eta^2 = 0.12$; Cohen $d = 0.25$).

Subject-Verb Agreement

Hypoglycemia caused a deterioration of subject-verb agreement (correct responses: $P = 0.011$; $\eta^2 = 0.159$; Cohen $d = 0.31$) (Table 4). Additionally, more miscellaneous errors were made during hypoglycemia ($P = 0.011$; $\eta^2 = 0.157$; Cohen $d = 0.44$).

Table 4—Test results during euglycemia and hypoglycemia in healthy volunteers and adults with type 1 diabetes

Test	Euglycemia			Hypoglycemia			Within-subject contrasts (EU/HYPO)			Between-subject effects (control/DM)		Interaction condition (EU/HYPO) by group (control/DM)	
	DM	Control	All	DM	Control	All	η^2	Cohen *d*	*P*	η^2	*P*	η^2	*P*
DST	68.3 (15.0)	77.5 (12.7)	72.9 (14.8)	61.3 (10.3)	67.2 (13.7)	64.2 (12.6)	0.457	0.62	**<0.001**	0.065	0.087	0.03	0.287
TMB	60.2 (13.0)	61.5 (6.5)	43.9 (12.0)	69.1 (19.4)	68.5 (8.9)	54.2 (18.7)	0.394	0.65	**<0.001**	0.078	0.081	0.001	0.85
Reading span													
Span	2.7 (0.6)	3.1 (1.0)	2.9 (0.9)	2.4 (0.6)	2.5 (0.8)	2.4 (0.7)	0.369	0.645	**<0.001**	0.031	0.275	0.050	0.165
Total correct answers in span	42.4 (6.7)	43.5 (10.0)	42.9 (8.6)	38.5 (7.7)	41 (5.6)	39.7 (6.9)	0.192	0.41	**0.005**	0.018	0.415	0.011	0.515
Self-paced reading													
Errors	5.0 (2.9)	3.6 (2.6)	4.3 (2.9)	5.4 (3.5)	5.0 (3.3)	5.2 (3.4)	0.051	0.27	0.160	0.031	0.279	0.019	0.395
Response times													
Fragment 1 (ms)	903 (338)	841 (294)	872 (323)	887 (340)	952 (426)	920 (392)	0.107	0.25	**0.039**	0.001	0.851	0.018	0.405
Fragment 2 (ms)	1,055 (317)	948 (314)	1,001 (324)	978 (306)	1,075 (394)	1,026 (360)	0.008	0.07	0.578	0.000	0.960	0.118	**0.030**
Fragment 3 (ms)	1,639 (536)	1,409 (404)	1,524 (495)	1,537 (431)	1,465 (429)	1,501 (437)	0.003	0.05	0.758	0.036	0.244	0.030	0.286
Time to correct answer (ms)	2,391 (576)	2,120 (415)	2,255 (526)	2,412 (674)	2,337 (484)	2,374 (596)	0.062	0.21	0.122	0.030	0.287	0.043	0.199
Subject-verb agreement													
Total correct	32.2 (6.4)	35.1 (4.4)	33.6 (5.7)	30.4 (6.7)	33.2 (4.7)	31.8 (6.1)	0.159	0.31	**0.011**	0.067	0.108	0.000	0.943
Agreement errors	3.0 (3.6)	2.2 (2.8)	2.6 (3.3)	3.0 (4.0)	3.5 (3.1)	3.3 (3.7)	0.039	0.20	0.225	0.000	0.897	0.033	0.261
Miscellaneous errors	1.2 (2.0)	1.4 (2.8)	1.3 (2.5)	3.1 (3.2)	1.8 (1.8)	2.4 (2.7)	0.157	0.44	**0.011**	0.019	0.391	0.073	0.091

Data are shown as mean (SD) unless otherwise indicated. Effect sizes are given as η^2 and Cohen *d*. DM, diabetes; EU, euglycemia; HYPO, hypoglycemia. Boldface indicates statistically significant results.

CONCLUSIONS

The current study, which has examined the effect of hypoglycemia on aspects of language processing, has demonstrated a significant deterioration in the accuracy of subject-verb agreement and also in reading span, a measure of working memory. This latter finding is compatible with the results of a previous study by our group (14) that used a different cognitive test battery but had an identical study design. In the current study, performance in the TMB and DST was significantly impaired during hypoglycemia, consistent with previous observations (5–7,10–12, 24) and confirming that adequate hypoglycemia had been achieved to impair cognitive function.

Reading Span

Reading span is a measure of working memory that is increasingly recognized as having a pivotal role in cognition. Working memory refers to a cognitive system involving planning, coordination, and control of high-level cognitive processes (26). Declination in reading span and recall of total correct responses was observed during hypoglycemia, reflecting the complex nature of working memory.

Measures of working memory span have been shown to predict performance reliably in a wide range of complex activities, for example during reading comprehension (26,36), reasoning (37,38), and complex learning (39). It was postulated that a decline in reading span would correlate closely with a decline in comprehension during self-paced reading and subject-verb agreement.

Self-Paced Reading

Different mental functions have been shown to vary in their sensitivity to neuroglycopenia. However, higher-level skills are more vulnerable to hypoglycemia than simple cognitive tasks (1). In addition, during hypoglycemia, speed is usually killed in order to preserve accuracy (1). It was therefore surprising that neither the speed nor accuracy of this relatively complex task was found to deteriorate during hypoglycemia. The lack of an effect on accuracy is conceivably due to a ceiling effect. Previous reassessment of the effect of hypoglycemia on the cognitive domain of nonverbal intelligence identified a ceiling effect when a test was used that was unsuited to the ability level of study participants (6). The test used in the current study was original and therefore not validated against specific population groups.

An alternative possibility that can explain the lack of effects on both speed and accuracy is that parsing (syntactic analysis) and interpretation are such highly practiced skills that they are less vulnerable to hypoglycemia than less practiced cognitive tasks, such as those involved in the reading span test. The self-paced reading task did of course reveal an isolated effect of hypoglycemia on fragment 1, which might indicate that our manipulation resulted in some slight reading difficulty early in the sentence. However, individual tasks within the experiment were constructed to be of a similar level of difficulty so that the OR and reduced relative sentences were matched across conditions for length, frequency, and syllable count. The OR/SR sentences were also matched for concreteness and imagery.

Subject-Verb Agreement

It has been suggested that this aspect of syntactic planning is affected by verbal working memory limitations (the resource-constrained hypothesis) (35), but others have argued that syntactic planning proceeds largely automatically (18). Some studies on agreement errors found effects of an extrinsic memory load on the number of agreement errors (32,35). Evidence also exists for a large change in agreement processes in aphasia (34). Other studies, however, have found little to indicate that agreement production correlates with memory span (40).

The resource-constrained hypothesis received mixed support: fewer correct responses and more miscellaneous responses occurred during hypoglycemia, but no significant increase in the number of agreement errors was observed. These results strongly suggest that hypoglycemia induces difficulties in seemingly easy linguistic tasks such as correctly reading aloud a simple sentence fragment and its completion.

Compared with other clamp studies exploring the effects of hypoglycemia on cognitive function, this was a large study that recruited both participants with and participants without diabetes. The fact that similar results were obtained in both groups suggests that these effects on language relate to acute hypoglycemia rather than to a chronic alternation of glycemic status in diabetes. The NART scores suggested that participants were of above average intelligence, which may limit applicability of these results to the general public. Furthermore, this study has only explored some dimensions of language and further studies could be designed to assess other aspects. However, the implication of these findings is that clinicians should inform people with diabetes that hypoglycemia affects practical aspects of language that relate to everyday use.

To our knowledge, this is the first study to use specific tests to target detailed aspects of language processing during acute hypoglycemia. Hypoglycemia had a significantly deleterious effect on reading span and on subject-verb agreements and possibly on the time to read sentence fragments.

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Author Contributions. K.V.A. collected data and wrote the manuscript. M.J.P. advised on the language tests and reviewed and edited the manuscript. N.N.Z. wrote the manuscript and contributed to discussion. R.J.H. designed the subject-verb agreement test and reviewed and edited the manuscript. M.J.T. advised on the language tests, designed the self-paced reading test, and reviewed and edited the manuscript. B.M.F. conceived the idea for the study, supervised the research, and reviewed and edited the manuscript. I.J.D. conceived the idea for the study, supervised the research and the statistical analyses, and reviewed and edited the manuscript. All authors provided an important scientific contribution to the study and assisted with the drafting or revising of the manuscript. K.V.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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