

Acute Hypoglycemia in Humans Causes Attentional Dysfunction While Nonverbal Intelligence Is Preserved

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OBJECTIVE — Experimentally induced hypoglycemia in humans causes progressive but reversible cognitive dysfunction, but it is not known to what extent neuropsychological tests index abilities of cognitive functioning that are important in everyday life. This study examines the effects of acute insulin-induced hypoglycemia on attention and intelligence in nondiabetic humans.

RESEARCH DESIGN AND METHODS — A hyperinsulinemic glucose clamp was used to achieve controlled euglycemia (4.50 [0.22] mmol/l) and hypoglycemia (blood glucose 2.59 [0.19] mmol/l) in 20 healthy volunteers. Subjects were studied on two occasions in a counter-balanced order. During each study condition, subjects completed parallel tests of cognitive function. Cognitive function was assessed by the Test of Everyday Attention and Raven's Progressive Matrices.

RESULTS — Hypoglycemia induced a significant deterioration in tests sensitive to both visual and auditory selective attention. During hypoglycemia, attentional flexibility deteriorated and speed of information processing was delayed. Sustained attention was preserved and intelligence scores did not deteriorate during hypoglycemia.

CONCLUSIONS — During hypoglycemia, a significant deterioration occurs in attentional abilities, whereas fluid intelligence is preserved. On the basis of these results, it can be surmised that many complex attention tasks relevant to everyday life are impaired during moderate hypoglycemia.

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Hypoglycemia rapidly provokes deterioration in cognitive function through the effects of acute neuroglycopenia on the human brain (1). Experimentally induced hypoglycemia in humans causes progressive but reversible cognitive dysfunction when arterialised blood glucose concentrations decreased to <3.4 mmol/l (2,3). In general, psychological tests that involve attention, concentration, psychomotor skill, and the ability to ignore distracting information tend to deteriorate at blood glucose concentrations <3.0 mmol/l (4–9). Al-

though it is recognized that cognitive function is impaired during hypoglycemia, it is not clear which basic brain processes are affected by neuroglycopenia, nor is it fully known to what extent such neuropsychological tests (which typically engage several putative mental processes) index abilities of cognitive functioning that are important in everyday life. Because cognitive abilities are important for work and leisure activities, this information is of considerable practical as well as theoretical importance.

Attention is a complex mental ability

involving multiple subcomponent processes (10,11), and because attention is a fundamental cognitive process that is integral to many neuropsychological tests, it is difficult to study attentional dysfunction in isolation. Classical neuropsychological tests purporting to assess attention have deteriorated during controlled hypoglycemia in nondiabetic subjects (8) and in adults with type 1 diabetes (6, 12,13). However, little detailed information is available on the effects of controlled hypoglycemia on the brain's specific information-processing abilities, and further research is needed to demonstrate that impairments in laboratory cognitive tasks have a bearing on mental performance in real life. Furthermore, we need a study using a validated batch of attention tests during hypoglycemia.

As a major construct within the psychometric study of intelligence, general fluid intelligence reflects adaptive (problem-solving) ability and is largely nonverbal in nature. Raven's Progressive Matrices (RPM) (14) are an acknowledged key test of this ability (15). General intelligence is a key finding and theoretical construct in the psychometric structure of human abilities (16) and is an important influence on many everyday activities (17). Although some studies of acute hypoglycemia have shown a deterioration in aspects of intelligence in both patients with diabetes (7,18) and nondiabetic subjects (19,20), previous studies in humans have not included subtests that were designed specifically to measure aspects of nonverbal intelligence.

The aim of the present study was to examine the effects of acute controlled, insulin-induced hypoglycemia on (1) general nonverbal intelligence and (2) various aspects of attention.

RESEARCH DESIGN AND METHODS

Subjects

A total of 20 healthy volunteers (11 women, 9 men) were studied. The mean

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Abbreviations: RPM, Raven's Progressive Matrices; TEA, Test of Everyday Attention.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(SD) age was 28.7 (5.3) years, and the mean (SD) BMI was 23.7 (1.9) kg/m². The mean (SD) National Adult Reading Test number correct score was 28.9 (5.8). None of the participants had a history of chronic disease, personal or family history of diabetes, prior head injury, or psychiatric disorder. None of the participants had an intercurrent illness, and none were taking medications (other than the combined oral contraceptive pill). The protocol was approved by the Healthy Volunteer Studies Subcommittee of the Lothian Medicine Ethical Advisory Committee. All subjects gave written informed consent for the study.

Study design

The subjects were studied on two occasions, separated by at least 1 week, in a counterbalanced order, i.e., half of the subjects underwent the euglycemia session first followed by the hypoglycemia study, and the remaining subjects were studied in the reverse order. A modified hyperinsulinemic glucose clamp technique (21) was used to set the blood glucose at a predetermined level. In one condition, hypoglycemia was induced (blood glucose 2.6 mmol/l), and in the other condition, euglycemia, the blood glucose concentration was maintained at 4.5 mmol/l. During the two study conditions (euglycemia and hypoglycemia), the subjects were asked to perform tests of cognitive function and to complete a questionnaire about the symptoms of hypoglycemia. Subjects were blinded to the order of the studies and to their prevailing blood glucose concentration at all times throughout the procedure.

Procedure

After overnight fasting, the subjects attended the research laboratory at 0800. Intradermal lignocaine (1%) was used for local anesthesia, and two cannulas were placed in the nondominant arm, one inserted retrogradely into a distal hand vein. This hand was used for sampling and was placed in a warm blanket to "arterialize" venous blood. A second intravenous cannula was placed in the antecubital fossa for infusion of 20% dextrose and human soluble insulin (Humulin S; Eli Lilly, Indianapolis, IN). After a brief priming regimen, insulin was infused in supraphysiological concentrations at a constant rate of 60 mU · m⁻² · min⁻¹ into a peripheral vein using an IMED Gemini

PCI pump (Gemini, Irvine, CA). A variable infusion of 20% dextrose was administered simultaneously and adjusted according to the blood glucose concentration measured at the bedside (2300 Stat; Yellow Springs Instruments, Yellow Springs, OH). Samples of arterialized venous blood were collected for glucose estimation initially at 3-min intervals and then at 5-min intervals after a stable blood glucose concentration had been attained.

In each study condition, the arterialized blood glucose concentration was stabilized at 4.5 mmol/l (baseline) for a period of 30 min, after which it was either maintained at 4.5 mmol/l (euglycemia) or lowered to 2.6 mmol/l (hypoglycemia). An arterialized blood glucose concentration of 2.6 mmol/l was chosen for the degree of hypoglycemia to be tested, because several previous studies have demonstrated significant impairment of cognitive functions at this level (3). A period of 20–30 min elapsed between the baseline plateau and the attainment of hypoglycemia to allow the blood glucose concentration to stabilize. The target blood glucose concentration was maintained for an additional 10 min before the tests were administered. Blood glucose was maintained at the study level for 90 min, during which time the cognitive function tests were administered.

Cognitive function tests

The Test of Everyday Attention (TEA) (22) and RPM (14) were used to measure attention and intelligence, respectively. The order of the tests was identical during each study condition.

TEA

The TEA was developed to improve existing methods of assessing attentional problems. It gives a broad-based measure of the most important clinical and theoretical aspects of attention and is the only test of attention based on everyday materials. An age-, sex-, and IQ-stratified sample of 154 normal participants was given these tests, along with a number of existing tests of attention (23). The factor structure revealed by these data matched the contemporary evidence for a set of functionally independent attentional circuits in the brain and included factors for sustained attention, attentional switching, selective attention, and auditory-verbal working memory. The TEA was developed and standardized on the basis of these

subtests, has high test-retest reliability, and correlates significantly with existing measures of attention (23). The discriminative validity of the TEA subtests has been shown in patients with closed head injury (24).

The TEA is divided into eight subtests and has parallel forms. In the present study, the subjects were asked to pretend that they were on vacation in Philadelphia, PA, and were told that they would be asked to perform various tasks, such as looking for symbols on maps and consulting telephone directories.

1. Map Search (visual selective attention) This is a test of selective attention. The subjects had to search for a particular symbol, such as a sign that represented a garage, on a color map of the Philadelphia area. The score is the number of symbols circled out of a possible maximum of 80 in 2 min. After the first minute had elapsed, the subjects were given a pen with a different color ink to continue circling the map signs, to enable the number of targets located in the first minute to be identified and compared with the final total number of symbols circled.

2. Elevator Counting (sustained attention) This subtest was presented on audiotape and consisted of a simple counting procedure. Subjects were asked to pretend that they were in an elevator in which the floor indicator was not functioning. They were to ascertain at which floor they had arrived by counting a series of tones presented on the audiotape. Two practice items were provided at the beginning of the tape to familiarize the subjects with the tones. This subtest is based on the procedure devised by Wilkins et al. (25), which has been validated as a measure of right frontal lobe–based sustained attention. The version used in the TEA is a variation of the task addressed by Wilkins et al., as devised by Brooks et al. (26), and loads on the sustained-attention factor of the factor analysis of data obtained from normal subjects.

3. Elevator Counting with Distraction (auditory selective attention) This subtest is similar to Elevator Counting and was also presented on audiotape. It differed in that subjects had to count the same tone that they had heard previously while ignoring a distracting tone of higher frequency. The task commenced with two examples to demonstrate the difference between the two tones and to give the subject practice in counting.

4. Visual Elevator (attentional switching)

In this subtest, the subject was asked to imagine that they were traveling up and down in an elevator, which in this case was represented by a series of pictures of elevator doors. Large arrows showed the direction of counting between pictures. This reversal task is a measure of attentional switching and, hence, cognitive flexibility. It is self-paced, and the “number correct” score loads on the same factor as the number of categories on the Wisconsin Card Sorting Test (27).

5. Elevator Counting With Reversal (auditory selective attention)

This subtest was the same as the visual elevator subtest, except that it was presented at a fixed speed on audiotape. It loads on the auditory-verbal working memory factor.

6. Telephone Search (visual selective attention) In this test, the subjects were to look for key symbols while searching through pages in a telephone directory. This subtest loads on the selective attention factor.

7. Telephone Search While Counting (divided/sustained attention)

In this test, the subject was to search for key symbols in a (different) telephone directory while simultaneously counting a series of strings of tones presented on audiotape. By combining the scores for this subtest and the time-per-target score for the previous telephone search, this test aims to provide a measure of divided attention, a “dual-task decrement.” In the factor analysis of normal data, this task loads on the sustained attention factor.

8. Lottery (sustained attention) In this final subtest of sustained attention, subjects were to listen for their (predetermined) winning lottery numbers. To do this, they were to listen to a 10-min series of numbers presented on audiotape of the form “BC143,” i.e., two letters followed by three numbers. The task was to write down the two letters preceding all lottery numbers ending in certain numbers, e.g., “55.”

RPM

RPM was used to examine general nonverbal intelligence and specifically measure the eductive ability to find and apply rules that make it easier to bring order to complex situations and events (28). The standard and parallel forms of the matrices are made up of five sets of diagrammatic puzzles exhibiting serial change in two dimensions simultaneously. Each

puzzle has a part missing, which the subject is to find among the options provided. The test consists of 60 problems divided into 5 sets, consisting of 12 problems. Subjects were assigned two scores for this test: the number correct at 20 min and the number correct at completion (no time limit). RPM is considered to be the single best test of general fluid intelligence (15) and measure eductive ability, one component of general intelligence identified by Spearman. General ability (*g*) is a broad factor of general intelligence that typically accounts for ~50% of the variance in performance in a variety of intellectual tasks (16). Eductive mental ability involves the development of new insights, going beyond the given to perceive that which is not immediately obvious, and forming (largely nonverbal) constructs that facilitate the handling of complex problems that involve many mutually dependent variables. The tasks in the RPM items are rule-finding and applying these rules simultaneously to the stimuli.

Symptoms of hypoglycemia

A subjective self-rating system (The Edinburgh Hypoglycemia Scale) (29) was used at four time points: baseline, before the TEA, after the TEA, and after RPM. The symptoms of hypoglycemia were classified as autonomic (palpitations, sweating, shaking, and hunger), neuroglycopenic (confusion, drowsiness, inability to concentrate, speech difficulty, and blurred vision), and nonspecific (nausea and headache). Each symptom was graded on a Likert scale of 1 (not present) to 7 (very intense). The total for each subgroup of hypoglycemic symptoms was calculated.

Statistical analysis

The results were analyzed independently for each subtest of the TEA and RPM. A general linear model (repeated measures analysis of variance) was used with order of session as a “between subjects” factor with two levels (euglycemia-hypoglycemia or hypoglycemia-euglycemia) and condition as a “within subjects” factor with two levels (euglycemia versus hypoglycemia). A similar model was used to analyze the symptoms of hypoglycemia, with the addition of time as a “within subjects” factor with four levels. A *P* value <0.05 was considered significant. All analyses were performed using SPSS for Windows software (Version 10.0; SPSS, Chicago, IL).

RESULTS— The mean (SD) fasting venous blood glucose level was 4.3 (0.3) mmol/l and did not differ between the two study days. Stable blood glucose plateaus were achieved during both conditions. The mean (SD) blood glucose concentration during the hypoglycemia clamp was 2.6 (0.2) mmol/l, and during euglycemia, the mean (SD) blood glucose concentration was 4.5 (0.2) mmol/l. The initial statistical analysis revealed that no significant order effects had occurred for any of the outcome variables in this study, other than for the “Elevator Counting With Reversal” task.

Symptoms

The autonomic symptom score increased from a mean (SD) of 5.4 (1.8) at baseline to 12.6 (1.2) during hypoglycemia (*P* < 0.0001). The neuroglycopenic symptom score increased from a mean (SD) of 5.1 (1.7) at baseline to 9.1 (2.3) during hypoglycemia (*P* = 0.003). A significant increment was also observed in general malaise symptom scores, which increased from 2.1 (0.5) at baseline to 3.3 (0.3) during hypoglycemia (*P* = 0.01). There were no significant changes in symptom scores during the euglycemia condition. The symptom reports confirmed symptomatic awareness of hypoglycemia at the predetermined low blood glucose concentration and, more pertinently, that symptomatic neuroglycopenia had developed.

Visual selective attention

Acute hypoglycemia caused a significant deterioration in tests sensitive to a visual selective attention deficit (Table 1). The mean (SD) number of map symbols circled during euglycemia in 1 min was 46.1 (10.0) vs. 39.9 (10.2) during hypoglycemia (*P* = 0.009). The mean (SD) number of symbols circled in 2 min was also lower at 68.1 (11.3) during hypoglycemia, compared with 71.8 (6.9) in the euglycemia condition, but the difference did not achieve statistical significance (*P* = 0.1). In the telephone search task, no difference was demonstrated between euglycemia and hypoglycemia in the number of symbols located (Table 1). However, the mean (SD) time taken to complete the task increased from 51.7 s (7.3) during euglycemia to 57.0 s (11.2) during hypoglycemia (*P* = 0.005) (Table 1). The results demonstrate that a visual selective

Table 1—Attentional function during euglycemia and hypoglycemia in healthy volunteers (n = 20)

Attentional system	Subtest	Euglycemia	Hypoglycemia	P value
Visual selective attention	Map search symbols in 1 min	46.1 (10.0)	39.9 (10.2)	0.009
	Map symbols circled in 2 min	71.8 (6.9)	68.1 (11.3)	0.1
	Telephone search time (s)	51.7 (7.3)	57.0 (11.2)	0.005
	Telephone search correct symbols	18.8 (1.3)	18.8 (1.4)	0.8
	Telephone search raw score (symbols/s)	2.7 (0.4)	3.1 (0.7)	0.005
Attentional switching	Visual elevator raw score	9.1 (1.3)	8.8 (1.6)	0.4
	Visual elevator timing score (symbols/s)	3.0 (0.6)	3.6 (0.5)	<0.0001
	Visual elevator time (s)	112.7 (15.0)	137.9 (22.6)	<0.0001
Auditory selective attention	Elevator counting with distraction	9.2 (1.4)	7.8 (2.0)	0.003
	Elevator counting with reversal	7.3 (2.6)	7.1 (2.3)	0.7
Sustained attention	Elevator counting	6.9 (0.3)	6.8 (0.4)	0.1
	Lottery tickets	9.4 (1.0)	9.1 (1.5)	0.2
Divided attention	TSWC time (s)	55.9 (9.5)	60.0 (14.6)	0.1
	TSWC correct symbols	18.3 (1.9)	17.6 (2.2)	0.2
	TSWC time/target score	3.1 (0.8)	3.4 (0.6)	0.02
	Dual task decrement	0.8 (0.9)	0.7 (0.7)	0.2

Data are means (SD). TSWC, Telephone Search While Counting.

attention decrement had developed during hypoglycemia.

Auditory selective attention/auditory verbal working memory

With the auditory elevator test with distraction, the achieved score declined from a mean (SD) of 9.2 (1.4) during euglycemia to 7.8 (2.0) during hypoglycemia ($P = 0.003$). By contrast, the score attained on the elevator test with reversal did not deteriorate during hypoglycemia, with a mean (SD) score of 7.3 (2.6) during euglycemia compared to 7.1 (2.3); $P = 0.7$ during hypoglycemia.

Sustained attention

Sustained attention did not deteriorate during hypoglycemia using either the lottery ticket test or the elevator counting test (Table 1).

Attentional switching

In the visual elevator task, no difference was observed in the raw score between the two study conditions. The mean (SD) raw score during euglycemia was 9.1 (1.3) compared with 8.8 (1.6) during hypoglycemia ($P = 0.4$). However, a significantly longer time was required to complete the visual elevator task during hypoglycemia with a mean (SD) time of 137.9 s (22.6), compared to 112.7 s (15.0) during euglycemia ($P < 0.0001$).

Divided attention

In the task that involved the search of a telephone directory while counting, no

significant difference was observed in the number of symbols that were located during either study condition (Table 1). The time taken to complete the task was higher during hypoglycemia, with a mean (SD) of 60.0 s (14.6) compared with 55.9 s (9.5) during euglycemia, but this difference was not significant ($P = 0.1$). The time per target score, which is the ratio of the number of circled symbols divided by the time taken for the task, was higher with a mean (SD) of 3.4 targets/s (0.6) during hypoglycemia compared with 3.1 targets/s (0.8) during euglycemia ($P = 0.02$). The dual task decrement was not significantly different between the two conditions.

Nonverbal intelligence

Using RPM, no significant differences were observed between euglycemia and hypoglycemia in the scores achieved either at 20 min or upon completion of the test. The mean (SD) RPM score at 20 min was 48.4 (5.7) during euglycemia and 47.2 (5.1) in the hypoglycemia condition ($P = 0.1$). Upon completion, the mean (SD) score was 49.5 (5.6) in the euglycemia condition and 48.7 (4.9) during hypoglycemia ($P = 0.3$). No significant differences were found between the two study conditions in the times taken to complete the test.

CONCLUSIONS— The present study demonstrates that controlled hypoglycemia causes attentional dysfunction in nondiabetic humans. A decline in the rate

of information processing was demonstrable in visual and auditory selective attention and in attentional switching. By contrast, nonverbal intelligence was not affected by hypoglycemia.

Although previous investigators have attempted to demonstrate attentional problems during acute hypoglycemia using psychological tests, to our knowledge, the present study is the first to confirm dysfunction of subdivisions of attention during hypoglycemia using a test battery designed specifically to measure attention. The TEA was devised from the evidence on separable attention systems in the brain (10). Using the concept that attention is fractionated into different supramodal systems, it has been proposed that attention consists of at least three separate systems (10), as follows: a selection system is responsible for selecting relevant stimuli/processes and inhibiting irrelevant ones; a vigilance system maintains readiness to respond in the absence of external cues; and an orientation system is responsible for engaging, moving, and disengaging attention in space. The TEA attempts to measure aspects of the selection and vigilance systems and correlates significantly with existing measures of attention. For example, using the statistical technique of factor analysis, the map search and telephone search load on the selective attention factor, along with the Stroop Test and the Trail Making B test (22).

In the present study, a significant deterioration in tests of visual selective

attention was demonstrated during hypoglycemia, with an inability to ignore irrelevant information and to select specific targets from complex visual arrays. Accuracy was preserved at the expense of speed in both the Telephone Search and the Visual Elevator test (which assesses cognitive flexibility). This feature has been observed previously in studies of hypoglycemia (12,18) and may indicate either that the speed of response is slower during hypoglycemia or that individuals adopt a more cautious approach in an attempt to avoid errors. However, it is important to note that in two previous studies by Holmes and colleagues (12,18), verbal fluency and math recall were the variables from which this conclusion was derived. These are, to some extent, measures of "crystallized ability" and demonstrated that although the retrieval of previously acquired information remained accessible during hypoglycemia, the rate of retrieval of this information was much slower. The present study demonstrates that this principle holds true for the acquisition of new information in familiar everyday tasks.

In the Elevator Counting With Reversal test, a significant order effect was apparent. This order effect was most likely a type 1 statistical error and requires replication in future studies. Sustained attention using the lottery and elevator counting tasks did not decline during hypoglycemia. These two subtests involve the ability to sustain attention to repetitive stimuli in the absence of external stimuli. This is in concordance with a previous study in which sustained attention to detail did not deteriorate with hypoglycemia (18) but is at variance with a different study in which sustained attention to detail over a period of time was reported to be profoundly affected by hypoglycemia (30). In the present study, significant ceiling effects were observed with these tasks, and most subjects achieved the highest score possible during both study conditions. However, the task of conducting a telephone directory search while counting also involves a sustained attention element, in that a counting task (similar to the elevator counting) must be performed simultaneously with a visual search task. It is noticeable that the time per target score of this test increased significantly during hypoglycemia. This test is a measure of the ability to handle complex tasks that are a common requirement

of everyday life, for example, writing a note from a telephone message while simultaneously speaking to the person giving the message. It is possible that these tests would have become impaired if the tasks had been of longer duration. The degree of impairment may also have been greater in other tests if the duration of testing had been prolonged. Following our study of attention during hypoglycemia, future studies should examine tests that are more demanding and of longer duration. Finally, it should be noted that the degree of attentional impairment found in this study might underestimate the real-life scenario of hypoglycemia in which the blood glucose level may decrease more rapidly from a higher starting point.

In the present study, nonverbal intelligence did not decline significantly with hypoglycemia. Various reasons may be proposed to explain this. The standard RPM was designed originally to cover the widest possible range of mental ability and to be applicable to persons of all age groups. Because it was designed for children as well as adults, the first and second sets in the test and the introductory problems in the third and fourth sets provide little more than training in the method of working. Therefore, the test may have been too elementary for most adult subjects. However, the RPM test was designed to provide a reliable estimate of a person's capacity to think clearly when allowed to work steadily at their own speed from the beginning to the end of a task without interruption. Although it is sufficiently short not to be unduly exhausting or unwieldy, there are an adequate number of difficult problems to discriminate between adults. However, in the present study, even when subjects were allowed to complete the test in their own time, no significant differences were observed in the scores achieved or the times taken to complete the task during both study conditions.

The hierarchical model of intelligence provides a parsimonious way to consider mental ability factors and may also help explain our results. At the top of the hierarchy is general ability (*g*), a broad general factor that accounts for performance in a great variety of intellectual tasks (16,31). Tests that correlate highly with this factor are "complex" tests requiring abstract problem-solving analysis and rule inferring, such as RPM. Reading comprehen-

sion does not deteriorate during hypoglycemia (18). This suggests that higher level or associative cognitive skills may be less detectable during hypoglycemia, in contrast to brain functioning that involves less complex informational analysis.

The RPM test was administered toward the end of the hypoglycemia session, and it could be surmised that, by this time, the brain may have adapted to function more effectively despite neuroglycopenia. This suggestion is unlikely because the subjects had evidence of overt neuroglycopenia before and also immediately after the RPM test, as demonstrated by their hypoglycemia symptom scores. A previous study of nondiabetic subjects has demonstrated that hypoglycemia of a similar depth and duration (60 min) was not associated with any evidence of cerebral adaptation, in either cognitive function or symptom scores (32).

The present study has demonstrated that a deterioration in attention occurs during acute insulin-induced hypoglycemia in nondiabetic humans, whereas nonverbal intelligence is preserved. Therefore, it can be surmised that many complex attention tasks that are relevant to everyday life are likely to be impaired during moderate hypoglycemia. In the context of hypoglycemia developing during everyday activities, examples of practical problems may include difficulty in filling out forms, interpreting timetables, or locating items on supermarket shelves. The finding that accuracy was preserved at the expense of speed in tests of visual selective attention and attentional switching is also of practical importance. The tests of visual selective attention are pertinent to many of the activities that people encounter on a daily basis. It is likely that people with insulin-treated diabetes, who are often exposed to hypoglycemia, will be subject to a similar deterioration in attention, which could have important practical implications in their everyday lives.

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