Effects of Acute Insulin-Induced Hypoglycemia on Spatial Abilities in Adults With Type 1 Diabetes

ROHANA J. WRIGHT, MRCP[1]
BRIAN M. FRIER, MD[1,2]
IAN J. DEARY, PHD[2,3]

OBJECTIVE — To examine the effects of acute insulin-induced hypoglycemia on spatial cognitive abilities in adult humans with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Sixteen adults with type 1 diabetes underwent two counterbalanced experimental sessions: euglycemia (blood glucose 4.5 mmol/l [81 mg/dl]) and hypoglycemia (2.5 mmol/l [45 mg/dl]). Arterialized blood glucose levels were maintained using a hyperinsulinemic glucose clamp technique. During each session, subjects underwent detailed assessment of spatial abilities from the Kit of Factor-Referenced Cognitive Tests and two tests of general cognitive function.

RESULTS — Spatial ability performance deteriorated significantly during hypoglycemia. Results for the Hidden Patterns, Card Rotations, Paper Folding, and Maze Tracing tests were all impaired significantly ($P \leq 0.001$) during hypoglycemia, as were results for the Cube Comparisons Test ($P = 0.03$). The Map Memory Test was not significantly affected by hypoglycemia.

CONCLUSIONS — Hypoglycemia is a common side effect of insulin therapy in individuals with type 1 diabetes, and spatial abilities are of critical importance in day-to-day functioning. The deterioration in spatial abilities observed during modest experimental hypoglycemia provides novel information on the cerebral hazards of hypoglycemia that has potential relevance to everyday activities.

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Hypoglycemia is a common side effect of insulin treatment of diabetes. Strict glycemic control limits the development and severity of vascular complications of diabetes, but hypoglycemia is a frequent consequence. Strict glycemic control can increase the incidence of severe hypoglycemia by threefold (1). Hypoglycemia has an adverse effect on cognitive functions, as the human brain relies solely on glucose as its source of energy (2). It has a pronounced effect on complex cognitive tasks both in diabetic and nondiabetic individuals, whereas simple mental tasks are relatively unaffected (2). Cognitive function deteriorates when arterialized blood glucose concentrations decline to <3.0 mmol/l (3–6). Simple and choice reaction times, speed of mathematical calculation, verbal fluency, attention, memory, and psychomotor function have all been demonstrated to be affected during hypoglycemia (7–10). The recovery of different aspects of cognitive function may vary from between 40 and 90 min after restoration of blood glucose to normal (2,11).

Whereas hypoglycemia impairs many domains of cognitive function, the effect of hypoglycemia on spatial cognitive abilities has not been investigated in detail, although spatial ability is undoubtedly a component of some of the tests used to assess other aspects of cognition (12). Spatial abilities may be defined as the ability to generate, retain, retrieve, and transform or manipulate structured visual images to orientate and interpret the surrounding environment. In real-life terms, spatial ability is concerned with how human beings deal with issues concerning two- and three-dimensional objects, space, navigation, and pathfinding. Practical daily cognition often involves inferring how shapes and objects will appear and function when they are rotated or otherwise oriented or viewed differently. In everyday interactions with the environment, this process is very important, with particular relevance for complex tasks such as driving and map reading. A large variety of mental tests are available for the assessment of spatial abilities. Largely, these tests can be separated into tests of spatial perception, namely the ability to determine spatial relations despite distracting information; spatial visualization, which is the ability to manipulate complex, multistep spatial information; and mental rotation, which is the ability to rotate two- or three-dimensional figures in one's mind (13). The present study was designed to investigate the effects of acute insulin-induced hypoglycemia on spatial abilities in adults with type 1 diabetes, using a well-characterized battery of spatial tests that incorporate all of these components of spatial cognition.

RESEARCH DESIGN AND METHODS

— Sixteen adults with type 1 diabetes (seven male and nine female) participated in the study. Subjects were recruited from the diabetes clinic at the Royal Infirmary of Edinburgh. Baseline demographic characteristics were a median age of 28 years (interquartile range 25–37.5 years), median duration of diabetes 10 years (4.2–19 years), BMI (means ± SD) 26.4 ± 4.01 kg/m^2, and A1C 7.91 ± 0.92%. A1C was measured by high-performance liquid chromatography (nondiabetic reference range 5.0–6.05%; Bio-Rad Laboratories, Munich, Germany) and was Diabetes Control and Complications Trial–aligned. The subjects had no history of hypertension or macrovascu-

From the [1]Department of Diabetes, Royal Infirmary of Edinburgh, Edinburgh, U.K.; the [2]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, U.K.; and the [3]Department of Psychology, University of Edinburgh, Edinburgh, U.K.
Corresponding author: Ian J. Deary, i.j.deary@ed.ac.uk.
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lar disease was excluded before recruitment. The presence of retinopathy was sought using digital retinal photography, neuropathy was assessed by clinical examination, and nephropathy was identified by the presence of microalbuminuria. Subjects were excluded if they had a history of impaired awareness of hypoglycemia or a history of a previous severe reaction to hypoglycemia. None of the participants had a history of head injury, seizure, blackouts, alcohol or drug abuse, or psychiatric illness. Subjects were not taking any medications other than insulin or the oral contraceptive pill. All subjects gave written informed consent before participating in the study, which had been approved by the local research ethics committee.

Each subject underwent two laboratory sessions, separated by at least 2 weeks. The study was conducted at the Clinical Research Facility at the Royal Infirmary of Edinburgh. A modified hyperinsulinemic glucose clamp (14) was used to maintain blood glucose at a predetermined level: euglycemia at 4.5 mmol/l (81 mg/dl) and hypoglycemia at 2.5 mmol/l (45 mg/dl). Each subject underwent a euglycemia study and a hypoglycemia study in a randomized, counterbalanced fashion. The subjects were blinded to the experimental condition.

Study procedure

The experimental session began at 0830 h. All subjects monitored their blood glucose with care for the preceding 48 h, including bedtime testing, and the study was postponed if they had any blood glucose value <3.5 mmol/l or any symptoms suggestive of hypoglycemia. After an overnight fast the subjects omitted their morning insulin dose. A retrograde intravenous cannula for regular blood glucose sampling was inserted into the nondominant hand and was placed in a heated blanket to arterialize the venous blood (15). A further cannula in the nondominant antecubital fossa was used to infuse soluble insulin (Human Actrapid; Novo Nordisk Pharmaceuticals, Crawley, U.K.) and 20% dextrose. Insulin was infused at a constant rate of 1.5 $mU \cdot kg^{-1} \cdot min^{-1}$ using a Gemini PCI pump (Alaris Medical Systems, San Diego, CA). Dextrose (20%) was infused at a rate that varied according to the arterialized blood glucose concentration, which was measured at 5-min intervals using the glucose oxidase method (2300 Stat; YSI, Yellow Springs, OH).

On each study day, the arterialized blood glucose was initially stabilized at 4.5 mmol/l for a period of 30 min. It was then either maintained at that level throughout the study (euglycemia condition) or it was lowered over 20 min to 2.5 mmol/l and maintained at that level for the duration of the study (hypoglycemia condition). The experimental period lasted for 60 min, after which time the blood glucose concentration was restored to 4.5 mmol/l. Subjects were given a meal after completion of each study.

Cognitive function tests

Tests of spatial ability were drawn from the French and Ekstrom Kit of Factor-Referenced Cognitive Tests (16,17). In addition, the Digit Symbol Substitution Test and Trail Making B Test were administered to confirm the recognized effect of hypoglycemia on cognitive function, as described previously (7–10).

Spatial ability tests

Hidden patterns test. The Hidden Patterns Test requires subjects to identify a figure that is hidden among other lines. The figure is the same throughout, with the same orientation, and subjects have 3 min to correctly identify as many of the patterns in which the figure is concealed as possible.

Card rotations test. The Card Rotations Test requires the subject to look closely at a shape on the left-hand side of a page and then assess whether the eight shapes on the right-hand side are the same shape rotated through a variable number of degrees or whether the shapes are different and have in fact been reversed or are a mirror image of the initial shape. Three minutes are allowed to complete as many items as possible.

Cube comparisons test. This test involves pairs of cubes, such as the wooden building blocks played with by children, with a letter or shape on each facet of the cube. Subjects have 3 min to analyze as many pairs of cubes as possible and must determine whether the two cubes could be the same cube viewed from different sides or whether they must be different cubes if the letters on the sides did not correspond with each other had the cube been turned over.

Paper folding test. The Paper Folding Test involves showing participants a sequence of folds in a piece of paper, through which a set of holes is then punched. The participants must choose which of a set of punched and unfolded papers corresponds to the one they have just seen.

Map memory test. This is a test of the subject's ability to remember the position of buildings on a street map. Four minutes are permitted to memorize the map and then a further 4 min to place the buildings correctly on a blank version of the map.

Maze tracing test. This is a test of the subject's ability to find a path through a maze quickly. A pencil line must be drawn through the maze without crossing any of the "walls." The maze is broken down into blocks, and the score is the number of blocks that are successfully navigated in 3 min.

Other cognitive function tests

Digit symbol substitution test. This test is from the Wechsler Adult Intelligence Scale-III and assesses the ability of the subject to perform coding as quickly as possible. The subject is given a key of numbers 1–9, which each have a corresponding symbol. They must then fill in as many symbols as possible for a list of numbers in 120 s.

Trail making B test. The Trail Making B Test is a computerized version of the test and similar in principle to the classic test from the Halstead Reitan battery. It is used to assess complex visual processing and also assesses motor function with regard to visual motor tracking. It is performed on a handheld computer. The subject is presented with a grid containing letters and numbers in a random order and must connect the numbers and letters in numerical and alphabetical order, alternating the number with the letter in the fashion "1-A-2-B-3-C . . ." etc.

Hypoglycemia symptom score. The Edinburgh Hypoglycemia Scale was used to assess the symptoms experienced by subjects during each experimental session. It is a validated self-rating questionnaire comprising a list of common symptoms of hypoglycemia that can be classified into autonomic, neuroglycopenic, and nonspecific symptoms. Each symptom is scored on a Likert scale from 1 (not present) to 7 (intensely present) (18).

Statistical analysis

Results were analyzed using SPSS (version 15.0 for Windows; SPSS, Chicago, IL). A general linear model (repeated-measures ANOVA) was used, with order of session (euglycemia-hypoglycemia or hypoglycemia-euglycemia) as a between-subjects factor and condition (euglycemia

Table 1—*Spatial ability test scores*

Spatial test	Euglycemia score	Hypoglycemia score	*P*	Cohen's *d*	η_p^2
Hidden Patterns	94.5 ± 21.8	73.7 ± 21.0	<0.001	0.97	0.627
Card Rotations	51.9 ± 15.5	40.4 ± 18.7	0.001	0.67	0.580
Cube Comparison	11.7 ± 4.1	9.4 ± 5.7	0.03	0.46	0.298
Paper Folding	6.0 ± 1.9	4.7 ± 2.0	0.001	0.67	0.604
Map Memory	8.6 ± 3.1	7.8 ± 2.1	0.3	0.30	0.081
Maze Tracing	11.1 ± 3.0	9.4 ± 2.5	<0.001	0.62	0.621

Data are means ± SD. Significance level was $P < 0.05$; effect sizes were computed as Cohen's *d* and η_p^2.

or hypoglycemia) as a within-subjects factor. $P < 0.05$ was considered to be significant. Effect sizes were calculated using η_p^2 to assess the degree to which hypoglycemia accounts for the variance in results, and Cohen's *d* was used to establish the extent of any effects of hypoglycemia on spatial abilities. Results are expressed as means ± SD unless stated otherwise.

RESULTS

Blood glucose

The target blood glucose levels were achieved for each experimental condition. The blood glucose concentration achieved during the hypoglycemia condition was 2.46 ± 0.22 mmol/l and during the euglycemia condition was 4.53 ± 0.24 mmol/l.

Symptom scores

Significant increments occurred in total autonomic ($P < 0.001$), total neuroglycopenic ($P < 0.001$), and malaise symptom scores (<0.001) during hypoglycemia.

General cognitive function

In the present study, scores achieved for the Digit Symbol Substitution Test were significantly lower during the hypoglycemia study period (72.4 ± 20.2) compared with those during euglycemia (84.6 ± 20.7) ($P < 0.001$), confirming that a standard measure of speed of information processing was significantly impaired at blood glucose concentrations of 2.5 mmol/l. Performance on the Trail Making B Test was statistically not impaired by hypoglycemia, with a score of 50.4 ± 20.9 s during hypoglycemia and a score of 38.9 ± 11.5 s during euglycemia ($P = 0.07$).

Spatial ability

Hypoglycemia resulted in a significantly lower score on all of the spatial ability tests except the Map Memory Test (Table 1). Cohen's *d* results have shown that the impact of hypoglycemia on these spatial abilities was medium to large. Moreover, the η_p^2 values indicate that the hypoglycemia condition accounted for a large proportion of the variance in the results (Table 1). No significant effects were observed of order of exposure to glycemic condition or test battery.

CONCLUSIONS

— Acute, insulin-induced hypoglycemia causes significant decrements in most spatial cognitive abilities examined here in a group of adults with uncomplicated type 1 diabetes. This impairment of function was accompanied by a deterioration in speed of mental processing as demonstrated by the decrement in score for the Digit Symbol Substitution Test. The effect sizes obtained indicate the development of medium to large decrements in spatial abilities during hypoglycemia in adults with type 1 diabetes.

The present study examined a group of subjects with type 1 diabetes and did not include a control group of nondiabetic subjects. Although this is a limitation of the present study, in reality it is the everyday effect of hypoglycemia on this group of individuals that is of clinical importance.

Other studies assessing the effects of hypoglycemia on aspects of cognitive function have used tests that require a spatial ability component (12), but to our knowledge no previous study has used a test battery specifically examining spatial abilities, although it has clear importance in the safe conduct of tasks such as driving, which rely heavily upon the interpretation of the surrounding environment.

The Map Memory Test was not affected significantly by the glycemic condition. This test assesses both spatial ability and visual memory. This finding is consistent with previous studies that examined memory function using visual memory tests from the Wechsler Adult Intelligence Scale, which also showed that visual memory is preserved during acute hypoglycemia (19). It is also notable that the Map Memory Test, unlike the other tests used here, does not have multiple items, and so its scores may be more idiosyncratic.

Spatial ability relies on cerebral pathways that predominantly involve the right cerebral hemisphere, particularly the parietal lobe. The frontal cortex, thalamus, and, to some extent, the cerebellum are also involved in the coordination of spatial cognition (20,21). Neuroimaging studies during hypoglycemia have shown attenuation of functional response, e.g., blood oxygenation level–dependent activation, in the premotor and supplementary motor cortex, consistent with recognized areas of importance in spatial functioning (22). In addition, it has been shown previously that general fluid intelligence is impaired during hypoglycemia, and it is fluid intelligence rather than crystallized intelligence that is responsible for spatial cognition (10).

In summary, the present study has shown that acute hypoglycemia has an adverse effect on spatial abilities. These novel data are important for two reasons. First, with regard to our understanding of the domains of cognitive function that experience decrements during hypoglycemia, spatial abilities were a lacuna that has now been partly filled. Second, spatial abilities are relevant to the everyday activities of individuals with type 1 diabetes, and there are now data to show that part of the inability to manage complex tasks during hypoglycemia is the inability to efficiently carry out spatial cognitive operations.

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References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive insulin treatment of diabetes on the

development and progression of long term complications. N Engl J Med 1993; 329:977–986
2. Deary IJ. Symptoms of hypoglycaemia and effects on mental performance and emotions. In *Hypoglycaemia in Clinical Diabetes.* 2nd ed. Frier BM, Fisher M, Eds. Chichester, U.K., John Wiley & Sons, 2007, p. 25–48
3. Hoffman RG, Speelman DJ, Hinnen DA, Conley KL, Guthrie RA, Knapp RK. Changes in cortical functioning with acute hypoglycemia and hyperglycemia in type 1 diabetes. Diabetes Care 1989;12: 193–197
4. Mitrakou A, Ryan C, Veneman T, Mokan M, Jenssen T, Kiss I, Durrant J, Cryer P, Gerich J. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. Am J Physiol 1991;260:E67–E74
5. Widom B, Simonson DJ. Glycemic control and neuropsychologic function during hypoglycemia in patients with insulin-dependent diabetes. Ann Intern Med 1990;112:904–912
6. Wirsen A, Tallroth G, Lindgren M, Agardh C. Neuropsychological performance differs between type 1 diabetic and normal men during insulin-induced hypoglycaemia. Diabet Med 1992;9:156–165
7. McAulay V, Ferguson SC, Deary IJ, Frier BM. Acute hypoglycemia in humans causes attentional dysfunction while nonverbal intelligence is preserved. Diabetes Care 2001;24:1745–1750
8. Sommerfield AJ, Deary IJ, McAulay V, Frier BM. Moderate hypoglycemia impairs multiple memory functions in healthy adults. Neuropsychology 2003; 17:125–132
9. Sommerfield AJ, Deary IJ, McAulay V, Frier BM. Short-term, delayed, and working memory are impaired during hypoglycemia in individuals with type 1 diabetes. Diabetes Care 2003;26:390–396
10. Warren RE, Allen KA, Sommerfield AJ, Deary IJ, Frier BM. Acute hypoglycemia impairs non-verbal intelligence. Diabetes Care 2004;27:1447–1448
11. Zammitt NN, Warren RE, Deary IJ, Frier BM. Delayed recovery of cognitive function following hypoglycemia in adults with type 1 diabetes: effect of impaired awareness of hypoglycemia. Diabetes 2008;57:732–736
12. Geddes J, Deary IJ, Frier BM. Effects of acute insulin-induced hypoglycaemia on psychomotor function: people with type 1 diabetes are less affected than non-diabetic adults. Diabetologia 2008;51: 1814–1821
13. Linn MC, Petersen AC. Emergence and characterisation of gender differences in spatial abilities: a meta-analysis. Child Dev 1985;56:1479–1498
14. De Fronzo R, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;273:E214–E223
15. Abumrad NN, Rabin D, Diamond MP, Lacy WW. Use of a heated superficial hand vein as an alternative site for the measurement of amino acid concentrations and for the study of glucose and alanine kinetics in man. Metabolism 1981; 30:936–940
16. Ekstrom RB, French JW, Harman HH, Dermen D. *Kit of Factor-Referenced Cognitive Tests.* Princeton, NJ: Educational Testing Service, 1976
17. Ekstrom RB, French JW, Harman HH. Cognitive factors: their identification and replication. Multivariate Behav Res Monogr 1979;79:3–84.
18. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type 1 diabetes with impaired awareness of hypoglycemia. Diabetes Care 1994;17:697–703
19. Warren RE, Zammitt NN, Deary IJ, Frier BM. The effects of acute hypoglycaemia on memory acquisition and recall and prospective memory in type 1 diabetes. Diabetologia 2007;50:178–185
20. Harris IM, Egan GF, Sonkkila C, Tochon-Danguy HJ, Paxinos G, Watson JDG. Selective right parietal lobe activation during mental rotation. Brain 2000;123: 65–73
21. Vogel JJ, Bowers CA, Vogel DS. Cerebral lateralization of spatial abilities: a meta-analysis. Brain Cogn 2003;52:197-204
22. Rosenthal JM, Amiel SA, Yaguez L, Bullmore E, Hopkins D, Evans M, Pernet A, Reid H, Giampetro V, Andrew CM, Suckling J, Simmons A, Williams SCR. The effect of acute hypoglycemia on brain function and activation: a functional magnetic resonance imaging study. Diabetes 2001;50:1618–1626