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Cognitive and psychomotor function in hypoglycemia: response error patterns and retest reliability

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Abstract

Hypoglycemia has been shown to impair cognitive and psychomotor function, but it has been unclear which measures are most reliable and sensitive for detecting these effects. In a single-blind repeated measures design, healthy young adults ($N = 17$, 8 male, mean age 27 years) performed three PC-based cognitive and psychomotor function tests: a paced auditory serial addition task (PASAT), an adaptive five-choice reaction time test (CRTT), and a manual tracking test on two occasions 4 weeks apart. In each session, a hyperinsulinemic clamp method was used during a normoglycemic (plasma glucose: 4.7 mmol/l) baseline testing period, followed in one session by a normoglycemic target testing period, and in the other session by a hypoglycemic (2.7 mmol/l) target testing period. All cognitive and psychomotor function measures showed high test–retest reliability (r ranging from .69 to .95) and sensitivity to hypoglycemia ($P < .01$). A new finding is that on the PASAT, hypoglycemia appears to differentially increase the rate of omission errors more than it increases false responses. Data on PASAT reaction time (RT) are also presented.

Keywords: Hypoglycemia; Blood glucose; Neuropsychological testing; Paced auditory serial addition task; Verbal reaction time; Choice reaction time test; Tracking test; Attention

1. Introduction

Hypoglycemia has been shown to impair cognitive and psychomotor functions (Amiel, 1998). However, it remains unclear which cognitive and psychomotor function tests best reflect such impairment (Deary, 1999). In the one published functional imaging study of hypoglycemia during cognitive and psychomotor testing (Rosenthal et al., 2001), hypoglycemia-induced decrements in test performance were generally associated with decreased blood oxygen level-dependent activation in motor areas of the brain (consistent with clinical observations of diabetic patients experiencing particularly impaired fine motor function during acute hypoglycemia). For the present study, we chose tests with clear motor function impact that are also computer controlled, and thus applicable in event-related brain activation studies.

Information has also been lacking on the test–retest reliability of the measures. The present report provides such data for three cognitive and psychomotor function tests: a paced auditory serial addition task (PASAT), an adaptive five-choice reaction time test (CRTT) and a manual tracking test.

All these tests share the benefits of being brief (typically 3 min) and automatable with a PC. None of them is claimed to measure a distinct presumed mental process. Rather, they reflect various combinations of sustained attention, concentration, information processing speed and reaction time (RT), spatial performance, eye–hand coordination, working memory, and strategic thinking. Thus, they may be considered tests of global cognitive function, which differ in the extent to which motor control contributes to overall test performance (motoric function is a minor aspect of PASAT performance but a more important component of the CRTT and manual tracking test).

Although some investigators have sought to examine noninvasively the assumed effect of acute nutrition on mental status (Brody and Wolitzky, 1983), the use of a hypoglycemic clamp delivers specific, stable blood glucose

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levels for prolonged periods (DeFronzo et al., 1979; Heine, 1993). The major objectives of hypoglycemic clamp studies are improved understanding of basic issues of glucose metabolism (level) and its impact on mental function in health and disease.

The present report addresses two issues: (1) determining the test–retest stability of the three cognitive and psychomotor function tests, and (2) providing more detailed results on cognitive and psychomotor function test response patterns reflecting impairment during hypoglycemia than have been provided in other such studies (for the first time, PASAT RT, and the relative influence of hypoglycemia on PASAT omissions vs. false responses is measured).

2. Methods

2.1. Subjects

Seventeen healthy volunteer university students (9 female; mean age 27 years, range 21–37 years) participated. All had normal findings on physical examination, routine blood chemistry and hematology, and standard electrocardiography. Exclusion criteria were current tobacco smoking or sedative use, or any history or other evidence suggestive of illicit drug use. Subjects were asked to refrain from food, alcohol, and caffeinated beverages for 12 h before the experimental sessions. Subjects read and signed an institutional review board approved informed consent form prior to participating in the study. The study was approved by the ethics committee of the University of Basel Medical School.

2.2. Hypoglycemic clamp and procedure

On the day of medical screening (prior to the first experimental session day), all subjects were familiarized with the cognitive and psychomotor function test procedures.

The two experimental sessions, separated by a 4-week interval, were conducted in the psychophysiological laboratory of the Basel University Hospital, following standard hypoglycemic clamp protocols (DeFronzo et al., 1979; Heine, 1993). On both study days, subjects entered the facility at 8:00 a.m. after a 12-h fast.

The hypoglycemic clamp procedure began with insertion of an intravenous catheter into a dorsal vein of the left hand (in the retrograde direction). The hand was then placed in a box heated to 52 °C so as to open shunt vessels in the hand, and thereby yield a venous sample quite reflective of arterial blood glucose levels. Another intravenous catheter was inserted into a cubital vein of the same arm for glucose and insulin infusion. The subjects received a loading dose of regular human insulin (HI) (Actrapid, Novo Nordisk; 0.01 U/kg body weight), followed by continuous insulin infusion (1 mU/kg/min). Glucose infusion (20% glucose solution) was started at 2.5 mg/kg/min and was adjusted on the basis of plasma glucose determinations conducted every 5 to 10 min throughout the experimental session. Arterialized blood samples (1.5 ml) were collected and centrifuged, and then plasma glucose concentrations were determined with glucose oxidase and a hydrogen peroxide sensor (glucose analyzer 2300 STAT Plus, YSI, Yellow Springs, OH).

At both sessions, the first (baseline) period of the study involved targeting plasma glucose at normoglycemic fasting levels (4.7 mmol/l). During the second (target) period of the session, the insulin infusion was increased to 2 mU/kg/min and the glucose infusion rate was adjusted in one of the sessions (randomly counterbalanced across subjects) to maintain a normoglycemic level or lowered to a hypoglycemic plasma glucose level of 2.7 mmol/l. Plasma glucose was allowed to fall rapidly by reducing the glucose infusion rate. Patients were not informed about the blood glucose target level (single-blinded design). The plasma glucose levels actually achieved with the clamp procedures were at or very close to targeted levels: 4.7 ± 0.1 mmol/l during normoglycemic baseline (N1) and 4.8 ± 0.1 mmol/l during the normoglycemic target period (N2) of the normoglycemic clamp study day; and 4.8 ± 0.1 mmol/l during normoglycemic baseline (H1) and 2.7 ± 0.1 mmol/l during the hypoglycemic target period (H2) on the hypoglycemic clamp study day (see Fig. 1).

Before the baseline period testing began, subjects practiced all three tests (prebaseline; data discarded). The baseline period lasted a total of approximately 120 min, and the target period lasted approximately 90 min. As depicted in Fig. 1, baseline performance data were assessed 100 min after the initiation of the session. Baseline (normoglycemic) data for the session which subsequently had the normoglycemic clamp target condition are labeled N1; and

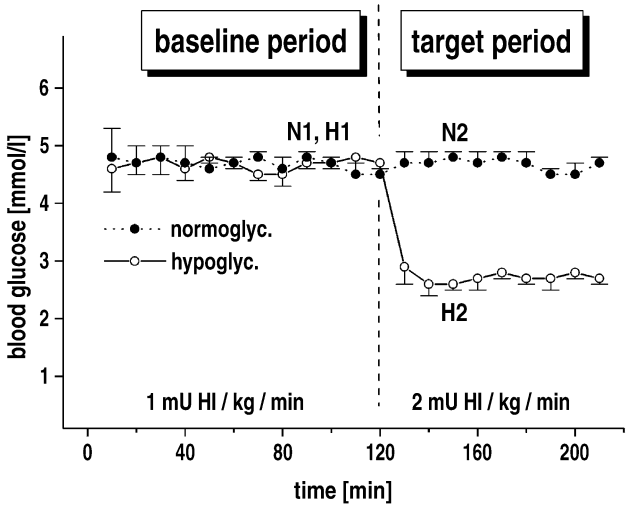

Fig. 1. Timing of testing and hyperinsulinemic clamp glucose effects. In a crossover repeated measures design, hyperinsulinemic clamp studies using HI were performed on two occasions, 4 weeks apart. On one occasion, a normoglycemic (plasma glucose: 4.7 mmol/l) baseline was followed by a hypoglycemic (2.7 mmol/l) target period. On the other occasion (control condition), the normoglycemic baseline was followed by a normoglycemic target period.

the baseline (normoglycemic) data for the session which subsequently had the hypoglycemic clamp target condition are labeled H1. Testing during the target period began 20 min after target plasma glucose levels were achieved in the hypoglycemic target condition (H2) or at a comparable time (N2) in the normoglycemic target condition. Within each block of tests, the CRTT was always given first, followed by the manual tracking test and PASAT.

Following each session, the blood glucose level of each subject was stabilized, and the subject was supervised during a high-carbohydrate lunch. They were paid 500 Swiss francs for their participation in the study.

2.3. Paced auditory serial addition task

The PASAT was adapted from prior research (Gronwall, 1977) and the dependent measures were augmented by also automatically measuring verbal RT. The PASAT involves listening to a series of single-digit pseudorandom numbers delivered via stereo headphones from a PC. The task consists of adding each new number to the previous number as quickly and accurately as possible, and reporting the sum aloud. Subjects continue the task until all 61 items of the number series have been presented during the 150-s PASAT testing. Stimuli were presented with an interstimulus interval (ISI) of 2.5 s (chosen because a pilot hypoglycemia clamp study indicated that verbal response onset was unlikely to occur later than 2.5 s after stimulus onset; any later responses were scored as omission errors). On a given testing day, different stimulation sequences of the PASAT of equal test difficulty were administered in the baseline and target phases. The same sets of sequences were also used on both study days.

The PASAT dependent variables were: percentage correct, omission errors, and false responses, and verbal RT for correct responses (RT for false responses did not differ from RT for correct responses, so only the RT for correct responses is presented).

Verbal responses were digitized and recorded for offline analysis (1 kHz, 12-bit resolution). The RT was detected with customized software (the precision of which was ±2 ms for a 1000-Hz signal during customized internal laboratory testing) in conjunction with manual verification of when the numeric response began (as opposed to an interjection or other sound).

Further details of our PASAT and other test protocols (including downloadable files) are available at: http://www.endo-diabasel.ch/hypoglyc-res.htm.

2.4. Choice reaction time test

The CRTT lasted 3 min and required subjects to quickly and accurately press a button of the same color as the one of five (red, blue, white, yellow and green) which flashed. The stimuli were presented in random sequence. Using a computer-based algorithm, the ISI was adjusted by 50 ms according to performance in a continuously moving window of the last seven stimulus–response pairs. The ISI decreased when four or more stimulus–response pairs were correct; otherwise, the interval increased. Thus, test difficulty was adjusted to achieve a subject false response rate of 50%, which makes for a demanding task (Langewitz et al., 1994; Schachinger et al., 2000). The dependent variables were mean RT (for correct responses) as well as ISI (which, as noted, is in a closed looped association with RT) for the last 2 min of the test (Langewitz et al., 1987; Schachinger et al., 1999). RT less than 300 ms was considered artifactual and therefore discarded.

2.5. Manual tracking test

The manual tracking test required subjects to direct a pointer (small cross) as close as possible to a target (white circle) orbiting at variable speed on a screen in distorted ellipses. Using standard PC equipment and peripherals (Logitech trackball), a customized program registered target

Table 1
Cognitive and psychomotor performance during normoglycemia: means, differences, and retest reliabilities

	Baseline 1st clamp	Baseline 2nd clamp	Δ	*P*	Test–retest *r* (4 weeks)	*P*
PASAT						
Accuracy [%]	85.8 ± 11.1	91.4 ± 9.2	5.6 ± 8.1	.01	.73	.001
Verbal RT [ms]	1093 ± 248	1076 ± 218	− 17 ± 158	.66	.89	.0001
Omission [%]	8.7 ± 9.0	4.3 ± 6.3	− 4.4 ± 7.1	.02	.69	.002
False [%]	5.5 ± 4.6	4.3 ± 5.0	− 1.2 ± 5.5	.39	.71	.001
5-CRTT						
ISI [ms]	720 ± 71	703 ± 76	− 17 ± 37	.08	.85	.0001
RT [ms]	647 ± 76	628 ± 80	− 19 ± 42	.08	.88	.0001
Tracking test						
Distance [ln Δ_{pixels}]	2.89 ± 0.23	2.80 ± 0.24	− 0.09 ± 0.12	.005	.95	.0001

Descriptive statistics consist of mean ± S.D. (Δ = difference between 1st and 2nd studies). The test–retest reliability coefficients for the 4-week interval are shown with their respective significance levels.

Table 2
Cognitive and psychomotor performance: effects of hypoglycemia and test repetition

	N1	N2	ΔN	*P*	H1	H2	*F**(1,16)	*P**
PASAT								
Accuracy [%]	86.7 ± 10.9	88.4 ± 8.5	1.7 ± 7.5	.37	90.5 ± 9.8	73.2 ± 18.9	27.26	.0001
Verbal RT [ms]	1104 ± 247	1066 ± 239	− 37 ± 115	.20	1065 ± 217	1234 ± 251	11.92	.003
Omission [%]	7.9 ± 8.7	7.4 ± 6.7	− 0.6 ± 6.3	.71	5.1 ± 7.1	19.1 ± 18.3	19.69	.0004
False [%]	5.4 ± 5.3	4.7 ± 4.1	− 0.7 ± 3.7	.46	4.4 ± 4.3	7.7 ± 6.9	4.08	.06
5-CRTT								
ISI [ms]	721 ± 76	715 ± 83	− 6.5 ± 44	.55	702 ± 71	800 ± 122	36.56	.0001
RT [ms]	647 ± 81	633 ± 83	− 14 ± 41	.17	628 ± 75	705 ± 109	53.51	.0001
Tracking test								
Distance [ln Δ_{pixels}]	2.86 ± 0.25	2.83 ± 0.22	− 0.03 ± 0.08	.20	2.84 ± 0.22	3.00 ± 0.25	18.41	.0006

Descriptive statistics consist of mean ± S.D. During normoglycemia, there was no significant short-term improvement of performance attributable to test repetition (*P* from paired *t* tests). Performance data of PASAT, CRTT, and manual tracking test indicate significant impairment of all response measure during hypoglycemia (H2) (results from 2 × 2 ANOVA for repeated measurements; *F**, *P** = statistics and significance of Treatment × Time interaction term).

and pointer position and saved the data to a file for offline analysis. In accordance with standard pursuit rotor tests, the program recorded the distance between target and pointer (Hagan et al., 1980). The dependent variable was the mean distance between pointer and target but a natural logarithm transformation (ln Δ_{pixel}) was used for analyses because of the nonnormal distribution of test results. The duration of the test was 3 min, of which only the last 2 min were analyzed. Response measures from all tests were calculated offline by a research assistant blind to the corresponding plasma glucose levels.

2.6. Statistical analysis

Hypoglycemic effects are reflected in the interaction term (Intervention × Time) of the 2 × 2 repeated measures ANOVA. Paired *t* tests were used to examine possible effects of test repetition within the normoglycemic study day. Long term (4 weeks) test–retest stability was based on the normoglycemic baseline data (N1, H1) of both study days (evaluated with Pearson correlation coefficients and paired *t* tests). However, as subjects differed in the sequence of experimental days, data are organized in Tables 1 and 2 as 1st and 2nd clamp study baseline.

Mean ± S.D. and exact, nonadjusted two-tailed *P* values are reported in text and Tables 1 and 2. All statistical calculations were performed with SAS software (release 8.0, WinNT, SAS Institute, Cary, NC, USA).

3. Results

3.1. Paced auditory serial addition task

The PASAT dependent variables ‘‘accuracy’’ and ‘‘verbal RT’’ showed moderate to high long-term test–retest stability (see Table 1). As shown in Table 2, hypoglycemia increased RT, and decreased PASAT accuracy by increasing omissions and (at a marginal significance level) false responses. Under both normoglycemic and hypoglycemic conditions, errors are predominantly omissions. However, during normoglycemia, omission errors are about 1.5 times more likely than false responses, but during hypoglycemia, this ratio increases to about 2.5 (see Tables 1 and 2). PASAT performance improved from the first to the second study day (see Table 1) for all PASAT response measures except RT. This apparent learning effect was evident across days, but not within the normoglycemic day (see Table 2).

3.2. Choice reaction time task

Hypoglycemia significantly impaired CRTT RT and the related measure of ISI (see Table 2). Both CRTT dependent measures showed high long-term test–retest reliability (see Table 1). There was a nonsignificant trend toward improved test performance across days (see Table 1), but not within the normoglycemia test day (see Table 2).

3.3. Manual tracking test

The tracking test response measure ‘‘distance’’ was significantly impaired by hypoglycemia (see Table 2). It showed very high long-term test–retest reliability (see Table 1). There was significant improvement of test performance across study days (see Table 1), but not within the normoglycemia day (see Table 2).

3.4. Intercorrelations between tests

The correlations between hypoglycemia-induced changes of the various dependent measures ranged from nonexistent to moderate. The significant ones were: PASAT accuracy with CRTT RT: $r = -.48$, $P = .05$; CRTT RT with tracking test: $r = .54$, $P = .025$; PASAT omission rate with CRTT RT: $r = .56$, $P = .02$; and PASAT RT with CRTT RT: $r = -.57$, $P = .02$.

4. Discussion

In this study of healthy young adults, the hypoglycemic clamp method produced clear impairment as demonstrated by three PC-based cognitive and psychomotor function tests (PASAT, CRTT, and manual tracking test). The test–retest reliabilities during normoglycemic hyperinsulinemic clamp conditions ranged from r=.69 to r=.95 for a moderately long (4 weeks) interval.

Normoglycemic performance improved across testing sessions significantly for two of the three tests (and marginally for the third), but did not improve within the normoglycemic testing session. This raises the possibility that some time is required for consolidation of the improved test performance. It also implies a need for normoglycemic control conditions in such studies, because of a potential interaction between practice effects and blood glucose changes.

None of the three tests was clearly superior to the others. Cohen's (1988) effect size δ was 1.07 for the tracking test, 1.31 for PASAT accuracy, and 1.83 for the CRTT RT; all of these are "large" effect sizes. The manual tracking test (with its relatively large motoric load) had the highest reliability, but the CRTT displayed more impressive effect size (suggesting greater sensitivity), and the PASAT was intermediate on both of those key dimensions (and readily adaptable to different levels of performance). The functional imaging study which included tests with a major motor component (including a CRTT) implied that—besides task specific visual cortex activity—motor areas of the brain are most affected by hypoglycemia (Rosenthal et al., 2001). We found that the functional impairment of PASAT (the test with the smallest motor component but a greater cognitive component) performance during hypoglycemia was similar to that of the tests that demand more motor involvement.

The PASAT (Gronwall, 1977) has been utilized previously in hypoglycemia research. It is considered to measure sustained and divided attention, concentration, working memory, and speed of information processing (Diehr et al., 1998). Although a recent study indicated that another divided attention test (a Telephone-Search-While-Counting test) was not particularly sensitive to hypoglycemia (McAulay et al., 2001), our data show that the PASAT is quite sensitive to hypoglycemia. Previous research has also shown that the PASAT is highly sensitive to mild cognitive deficits (Rao et al., 1991).

Investigators using the PASAT usually focus nearly exclusively on the percentage of correct responses. In the present study, additional variables were addressed for the first time. The result of this more detailed analysis was the revelation that hypoglycemia-induced decrements in correct PASAT responses are primarily due to omission of responses, which is a qualitatively different phenomenon than a simultaneous proportionate rise in both omissions and false responses. This pattern of results suggests that relative to a normoglycemic state, when the subject's brain is receiving inadequate supplies of glucose, the subject displays some combination of being so inattentive that some stimuli are not noticed, being momentarily too overwhelmed to respond, and responding with an RT beyond the reasonable maximum period allowed.

PASAT verbal RT showed sensitivity to hypoglycemia as well. To the best of our knowledge, this report is the first providing data on PASAT verbal RT during hypoglycemia. Verbal RT has a benefit of being less likely to be confounded by ceiling effects. Hypoglycemia-induced PASAT changes in accuracy and (for accurate responses) verbal RT were uncorrelated, suggesting that these indices tap different cognitive processes. Therefore, verbal RT appears to offer additional information. Unlike the other tests, the PASAT has verbal and mathematical components, and performance is highly associated with measures of intelligence and correlates thereof, such as years of education (Wingenfeld et al., 1999). In the present study, educational level was quite homogenous, thereby limiting that potential influence. However, such differences have to be taken into account when comparing the present results to those that might be conducted with other samples.

Recent data indicate that forms of the CRTT are very sensitive to hypoglycemia-induced cognitive impairment (Evans et al., 2000; Maran et al., 2000). The CRTT taps sustained attention and executive motor function, and although its usefulness has been shown in this study and others (Amiel, 1998), so far no attempt has been made to standardize the CRTT. Different laboratories use different stimuli, response modalities, and number of choices, stimulation, and response trials. In prior applications of the CRTT to hypoglycemia research, predetermined ISIs were used. The potential disadvantage of a rigid intertrial interval is that test difficulty will vary considerably across subjects. Low test difficulty may induce boredom (Prinzel and Freeman, 1997), which can impact test performance in unforeseen ways, and thus be a source of increased variability within and between subjects (Sawin and Scerbo, 1995). Similarly, too difficult a test can be discouraging or even produce anxiety. Factors such as boredom, anxiety, and task engagement have indeed been found to confound the performance of diabetic subjects (Gonder-Frederick et al., 1994). Adaptive versions of CRTT, such as the PC-based control algorithm used in the present study, might limit the impact of such confounding. The inverse association between PASAT RT and CRTT RT was unexpected, and warrants further attention in future research, rather than speculation at this juncture.

Diabetic patients frequently experience a deterioration of fine motor skills during endogenous hypoglycemia. In the laboratory setting, simple motor tests appear to be less sensitive than cognitive tests to neuroglycopenia (Cox et al., 1993). It is thought that the blood glucose threshold for impairment of motor function is as low as 2.0–2.4 mmol/l (Amiel, 1998). Because higher thresholds for fine motor impairment have been reported in healthy subjects (Rosen-

thal et al., 2001), fine psychomotor skill tests might require reevaluation. The manual tracking test requires fine motor function, which has been found to decline during hypoglycemia (Hoffman et al., 1989). Besides motor function, this psychomotor function test requires attention and coordination. Hypoglycemia-induced changes in tracking performance were correlated only with CRTT RT, suggesting that manual tracking performance only overlaps with basic RT and eye–hand coordination aspects of other cognitive and psychomotor function tests. Recent data have indicated that hypoglycemia is unlikely to cause fine motor impairment by metabolic effects at the peripheral nervous system (Strachan et al., 2001), indicating that the hypoglycemic effect on tracking performance is likely to be central.

The present study indicates high test–retest reliability of the PASAT, CRTT and manual tracking test. Furthermore, these tests (particularly the CRTT and PASAT), including the new variables derived from them, proved to be highly sensitive to moderate hypoglycemia. Our data might also be useful for other laboratories seeking to identify the most reliable and sensitive cognitive and psychomotor function tests for hypoglycemia research in both health and disease.

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