# Effects of Sleep Deprivation on Hypoglycemia-Induced Cognitive Impairment and Recovery in Adults With Type 1 Diabetes

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## OBJECTIVE

**To ascertain whether hypoglycemia in association with sleep deprivation causes greater cognitive dysfunction than hypoglycemia alone and protracts cognitive recovery after normoglycemia is restored.**

## RESEARCH DESIGN AND METHODS

**Fourteen adults with type 1 diabetes underwent a hyperinsulinemic, hypoglycemic clamp on two separate occasions. Before one glucose clamp, the participants stayed awake overnight to induce sleep deprivation. Participants were randomized and counterbalanced to the experimental condition. Cognitive function tests were performed before and during hypoglycemia and for 90 min after restoration of normoglycemia.**

## RESULTS

**Cognitive impairment during hypoglycemia did not differ significantly between the sleep-deprived and non–sleep-deprived conditions. However, in the sleep-deprived state, digit symbol substitution scores and choice reaction times were significantly poorer during recovery ($P < 0.001$) and hypoglycemia symptom scores were significantly higher ($P < 0.001$), even when symptoms that may have been caused by sleep deprivation, such as tiredness, were removed.**

## CONCLUSIONS

**Hypoglycemia per se produced a significant decrement in cognitive function; coexisting sleep deprivation did not have an additive effect. However, after restoration of normoglycemia, preceding sleep deprivation was associated with persistence of hypoglycemic symptoms and greater and more prolonged cognitive dysfunction during the recovery period.**


The neuroglycopenia resulting from acute hypoglycemia rapidly affects cognitive function; complex tasks such as working memory and choice reaction time are most impaired, and mood, motivation, and psychomotor function are also affected (1). Recovery of several cognitive domains may be delayed for up to 70 min after normoglycemia has been restored (2).

Sleep deprivation, both total and partial, has detrimental effects on neurocognitive performance but is characterized by wide inter- and intraindividual variability, so it can be difficult to interpret (3,4). Sleep plays an important role in the encoding, consolidation, and processing of memory (5,6). Sleep deprivation, both before and

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after learning tasks, results in deficits in performance (6). Attention, vigilance, and alertness are all affected; individuals perform well initially but their performance deteriorates with duration of the task (4). Mood and emotion are also affected with an increase in negative mood states after sleep deprivation (3,7).

The combined effect of sleep deprivation and hypoglycemia (blood glucose 2.5 mmol/L; 45 mg/dL) has been examined previously during normal sleep, partial sleep deprivation, and total sleep deprivation in male adults without diabetes (8). Reaction times and auditory evoked potentials were assessed at baseline and during hypoglycemia, but not after restoration of normoglycemia. Total sleep deprivation caused a significant deterioration in both measures at the normoglycemic baseline, but no significant deterioration was observed after partial sleep deprivation. Hypoglycemia caused significant deterioration from baseline after normal sleep and after partial sleep deprivation, but no additional effect was observed after full sleep deprivation, suggesting that the detrimental neurocognitive impacts of sleep deprivation and hypoglycemia were not additive. Alternatively, a ceiling effect may be present that limits the magnitude of cognitive deterioration that can be demonstrated with these neurocognitive tests, although the investigators asserted that the relatively short reaction times would prevail against this interpretation.

Sleep deprivation and hypoglycemia may share a final common pathway to influence the depletion of cerebral glucose (9). Adults with type 1 diabetes may experience these conditions concomitantly in everyday life, particularly if they are involved in shift work, and little is known about the effect of this dual insult on cognitive function. It is plausible that exposure to both conditions simultaneously could have an additive or even synergistic effect on cognitive impairment and/or protract the delay in recovery after normoglycemia has been restored. In the current study, these hypotheses were tested in adults with type 1 diabetes, using a range of cognitive tests that are sensitive to both hypoglycemia and sleep deprivation.

## RESEARCH DESIGN AND METHODS

Participants were recruited from hospital diabetes outpatient clinics in the Lothian region of Scotland. Written, informed consent was given by all participants, and ethical approval for the study was obtained from the local medical research and ethics committee. Those studied were adults aged between 18 and 40 years with type 1 diabetes for >1 year, normal awareness of hypoglycemia, BMI 20–30 kg/m$^2$, and $HbA_{1c}$ 6.5–10% (48–86 mmol/mol). Exclusion criteria included significant coexistent systemic disease or malignancy, a past history of a severe reaction to hypoglycemia (such as seizure or neurological deficit), cerebral injury, epilepsy, and chronic alcoholism or psychiatric disorder. People who were not fluent in written or spoken communication in English were excluded (as the cognitive tests used are validated only in English) and were excluded if they were pregnant (pregnancy testing was performed on all potential female participants).

All patients in Lothian with type 1 diabetes were assessed (~1,500), and those meeting the age criteria were contacted by post and then by person when attending routine clinic appointments. Of a total of 129 patients who communicated an interest in participating (either verbally, by post, or e-mail), 24 did not meet the inclusion criteria and 90 decided not to participate. Of the remaining 15 subjects, all completed the study protocol apart from 1 subject who could not be made hypoglycemic using the standard glucose clamp technique.

### Experimental Procedure

Participants underwent hypoglycemic clamps on two separate occasions, performed at least 2 weeks apart. Two experimental conditions were randomized and counterbalanced: one after induction of short-term total sleep deprivation by staying awake all night and one after a full night of sleep. Some participants were at work during the night preceding the glucose clamp, whereas those at home were asked to send a short text message to the investigator every 30 min to demonstrate that they were awake. The study was deferred if more than one text message was omitted during the night or if they experienced symptomatic or biochemical hypoglycemia during the 24 h preceding the study.

Participants attended at 0800 h and a modified hyperinsulinemic clamp (10) was used to maintain blood glucose at predetermined levels of 5.0 mmol/L (90 mg/dL) during euglycemia (run-in and recovery) and 2.5 mmol/L (45 mg/dL) during hypoglycemia. Blood samples were taken every 5 min and analyzed at the bedside using a glucose oxidase method (Yellow Springs Instrument 2300 Stat, Yellow Springs, OH). During the run-in period, the participants were asked to practice the cognitive test battery (digit symbol substitution test, choice reaction time, and hypoglycemia symptom scale) to familiarize themselves with the tests and to eliminate a potential learning effect. The cognitive battery took ~5 min to complete and was repeated multiple times during the study (Fig. 1). After completion of baseline cognitive tests, blood glucose was lowered gradually to 2.5 mmol/L (45 mg/dL) over ~20 min and was maintained at this level for 1 h, during which further cognitive tests were

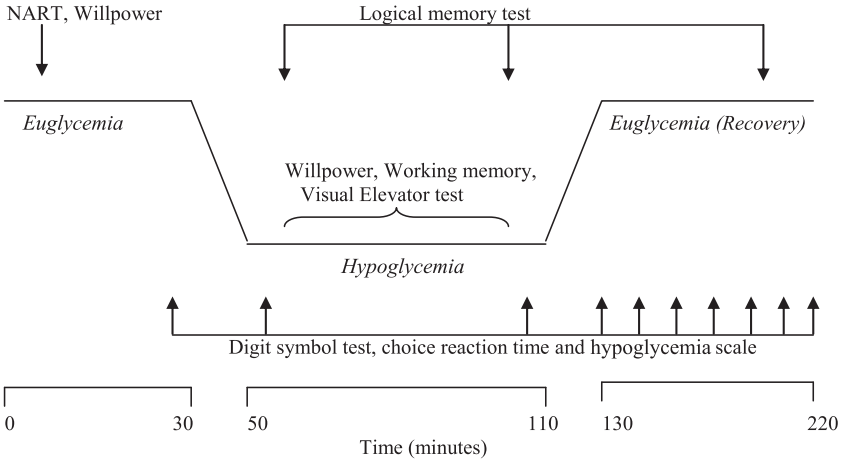


**Figure 1**—Outline of study design showing timing of cognitive tests in relation to blood glucose concentration.

performed (Fig. 1). Once normoglycemia had been restored, the battery of cognitive tests was repeated at intervals for 90 min. Testing in the recovery period was carried out at 10, 20, 30, 40, 55, 70, and 85 min after blood glucose had risen to >4.0 mmol/L (72 mg/dL), using the same time schedule as in a previous study by our group in which recovery of cognitive function after hypoglycemia was examined (2). Intravenous infusion was then discontinued and the participants received a meal.

### Cognitive Assessments and Symptom Evaluation

#### *National Adult Reading Test*

The National Adult Reading Test (NART) contains 50 words that, if unfamiliar to the reader, would be mispronounced when read aloud. This test is used to provide an estimate of premorbid intelligence (11).

### Willpower Questionnaire

This six-item, scaled questionnaire gauges an individual's expectations about how well they would engage with mental work and was modified from the questionnaire of Job et al. (12).

### Modified Hypoglycemia Symptom Scale

A modified version of the validated Edinburgh hypoglycemia score (13,14) was used to record symptoms on a 7-point Likert scale throughout both study sessions. In recognition that two of the hypoglycemia symptoms (sleepiness and drowsiness) might be influenced disproportionately by sleep deprivation, these were excluded from the symptom score analysis. The other 15 symptoms included autonomic symptoms (sweating, warmness, pounding heart, hunger, and trembling), neuroglycopenic symptoms (confusion, difficulty speaking, inability to concentrate, blurred vision, anxiety, and tingling of the lips), and nonspecific symptoms (weakness, dizziness, nausea, and headache).

### Cognitive Tests

These tests were chosen as they are sensitive to the effects of hypoglycemia (2,15–17) and to sleep deprivation (18,19).

General cognitive test battery (performed at baseline, during hypoglycemia, and at multiple time points during recovery):

1. Digit symbol substitution test. This is a test of sustained attention, response speed, and visuo-motor coordination and is a subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (20). Rows of blank squares are displayed on a piece of paper. Each blank square is paired with a number from 1 to 9. A printed key pairs each number with a different symbol, and the participant fills the blank squares with the symbols that match the numbers. The score is the number completed within 2 min.
2. Choice reaction time. The subject presses one of four keys as quickly as possible in response to the appearance of a cross on the screen in a position corresponding to one of the keys (21). The subjects completed 40 trials with an interstimulus interval of 1–3 s. The response was recorded if it occurred within 200 to 1,500 ms. The mean response time for correct answers was used in the analysis.

Memory tests (performed during hypoglycemia only; logical memory repeated once during recovery):

1. Logical memory test. In this subtest from the Wechsler Memory Scale (22), a short story is read to the subject, who is then required to recount it. Points are obtained for recollection of specific details and story themes. Recollection was tested both immediately and at two further time points (Fig. 1).
2. Working digit span test–backward (22). In this test of working memory, a series of lists of numbers are presented verbally to the subject. Subjects are asked to recall the numbers in reverse numerical order. For example, for the sequence 2-6-1-5-3, the correct response is 6-5-3-2-1. The test score is the number of lists that are remembered correctly.
3. Letter/number sequencing test. In this working memory test from the Wechsler Memory Scale (22), a series of sequences of numbers and letters that increase in length are presented verbally. The subject is asked to reorder and repeat, giving the numbers in ascending order, followed by the letters in alphabetical order. The score is the number of correctly reordered sequences.

Attention test (performed during hypoglycemia only):

1. Visual elevator. This is an indirect test of cognitive flexibility assessing visual switching (23). Subjects are asked to imagine they are traveling up and down in an elevator, represented by a series of pictures of elevator doors. Arrows indicate the direction of counting between pictures and the subject is timed as they count up and down the floors.

### Statistical Analysis

A repeated-measures ANOVA was used to assess the effect of sleep deprivation on the cognitive tests performed during hypoglycemia. Experimental condition (sleep deprivation or normal sleep) was the within-subject factor, and order of session (sleep-deprived or control study first) was a between-subject factor. Cohen's $d$ and partial $\eta^2$ were calculated to assess effect size (threshold for a large effect size is 0.8 and 0.5, respectively).

In order to address the issue of multiple comparisons resulting in spurious significant findings, the cognitive test battery was then analyzed by linear mixed models, estimated using the lme4 package for R, version 1.1-7 (http://cran.r-project.org/package=lme4). The first set of models tested the effect of sleep deprivation on the two measurements of cognitive function during hypoglycemia, also testing whether sleep deprivation affected either the first or the second cognitive measurement more strongly (i.e., a test for a time × condition interaction). The second set of models was similar but tested the effect of sleep deprivation on cognitive function across the seven measurements during recovery. All models included a random (individual-specific) intercept for each participant. The time × condition interaction in this situation tested whether the trajectory of cognitive ability differed according to the two sleep deprivation conditions. In both sets of models, the effect of sleep deprivation on the hypoglycemia symptom scale was also tested at each of the measurement points. All models adjusted for the baseline (prehypoglycemia) cognitive or symptom score (as applicable) in each condition by including this variable as a predictor.

## RESULTS

### Participants

A total of 14 participants (5 female) completed the study, with a median

(range) age of 27.5 years (20–38). The median (range) duration of diabetes was 10 years (3–26), and mean $HbA_{1c}$ was 8.0 ± 0.9% (64 ± 9 mmol/mol). Seven had background retinopathy, two had microalbuminuria (raised albumin creatinine ratio of ≥3.5 mg/mmol [female] or ≥2.5 mg/mmol [male]), and none had peripheral neuropathy. Mean BMI was 25.9 ± 3.0 kg/m$^2$. Participants were of higher than average intelligence, as measured by a mean NART (11) score of 31.5 ± 6.5 correct answers, equivalent to an IQ of 112.

### Blood Glucose

Blood glucose (mean ± SD) during the baseline period was 5.4 ± 0.6 mmol/L (97 ± 11 mg/dL) in the control condition and 5.2 ± 0.5 mmol/L (94 ± 9 mg/dL) in the sleep-deprived condition. During hypoglycemia, mean blood glucose was 2.5 ± 0.2 mmol/L (45 ± 4 mg/dL) for both study conditions. Mean blood glucose level at recovery was 5.2 ± 0.6 mmol/L (94 ± 11 mg/dL) for both study conditions.

### Tests Performed During Baseline and Hypoglycemia

Although there was a trend toward poorer performance during the sleep-deprived condition on the baseline cognitive tests (i.e., before hypoglycemia), the difference between the control and sleep-deprived scores did not reach statistical significance for any test (Table 1). Scores on the willpower questionnaires were unaffected by the sleep condition. As expected, the general cognitive test battery scores deteriorated during hypoglycemia compared with baseline ($P < 0.01$).

During hypoglycemia, the performance on cognitive tests, including memory, willpower, and attention testing did not differ significantly between the two sleep conditions (Table 1). The linear mixed models showed that the results of the cognitive test battery did not differ significantly between the two conditions (Table 2). No significant interactions were observed between time and condition; the variables did not change more rapidly between the two measurements taken during hypoglycemia in one condition more than the other (*P* values for the time-condition interaction = 0.41, 0.53, and 0.22 for the hypoglycemia symptom scale, choice reaction time, and digit symbol substitution test, respectively).

The effect of the order in which studies were performed had an impact only on the modified hypoglycemia symptom scale. Symptom scores were higher at the start of the period of hypoglycemia during the first study visit, independent of sleep condition.

### Recovery Tests

The hypoglycemia symptom score results are shown in Fig. 2. Even after controlling for baseline, the modified symptom scores were significantly higher in the sleep-deprived condition during recovery (Table 2). However, no interaction occurred between time and condition ($P = 0.22$), indicating that the trajectory of the symptom scores did not differ between the sleep-deprived and the control conditions. When the symptoms were subdivided into autonomic, neuroglycopenic, and nonspecific groups, the results remained significantly different for both the autonomic and neuroglycopenic symptoms, but not for the nonspecific symptoms.

Figure 2 shows that performance was consistently better on the choice reaction and digit symbol tests in the control condition during recovery; sleep deprivation slowed performance on both tasks, and this remained significant after adjustment for baseline score. Performance on the digit symbol but not the choice reaction tests decreased significantly across each

**Table 1—Results of tests performed at baseline, during hypoglycemia, and at the first recovery test**

| | | | Control | | Sleep deprived | | Difference between conditions | | Experimental order effect | |
|---|---|---|---|---|---|---|---|---|---|---|
| Condition | | Test | Mean | SD | Mean | SD | *P* | Cohen's *d* | *P* | $\eta^2_p$ |
| Baseline (normoglycemia) | Baseline battery | Willpower | 25.3 | 4.4 | 23.7 | 5.5 | 0.39 | 0.32 | 0.09 | 0.226 |
| | | Mod hypo symptom scale | 24.8 | 8.4 | 28.8 | 11.3 | 0.31 | −0.40 | 0.79 | 0.007 |
| | | Digit symbol substitution | 87.7 | 18.3 | 81.8 | 17.4 | 0.16 | 0.33 | 0.14 | 0.186 |
| | | Choice reaction time | 449.0 | 59.0 | 459.0 | 61.0 | 0.74 | −0.17 | 0.07 | 0.286 |
| Hypoglycemia | Hypo 1 battery | Mod hypo symptom score | 36.6 | 14.0 | 38.3 | 16.0 | 0.98 | −0.11 | **0.01** | 0.559 |
| | | Digit symbol substitution | 68.7 | 14.2 | 67.5 | 13.4 | 0.80 | 0.09 | 0.80 | 0.006 |
| | | Choice reaction time | 503.0 | 88.0 | 518.0 | 100.0 | 0.80 | −0.16 | 0.11 | 0.232 |
| | | Logical memory (immediate) | 14.0 | 4.7 | 11.6 | 4.6 | 0.18 | 0.52 | 0.09 | 0.226 |
| | | Visual elevator (timing) | 7.5 | 4.6 | 6.4 | 3.8 | 0.62 | 0.26 | 0.14 | 0.173 |
| | | Working digit span backward | 7.7 | 2.6 | 7.9 | 2.6 | 0.59 | −0.08 | 0.13 | 0.185 |
| | | Letter number sequencing | 9.4 | 2.9 | 9.6 | 2.7 | 0.81 | −0.07 | 0.97 | 0.000 |
| | | Logical memory (delayed 1) | 12.0 | 4.2 | 9.7 | 4.2 | 0.16 | 0.55 | 0.16 | 0.155 |
| | Hypo 2 battery | Mod hypo symptom scale | 43.2 | 13.3 | 45.9 | 17.0 | 0.81 | −0.18 | 0.09 | 0.242 |
| | | Digit symbol substitution | 73.3 | 12.2 | 66.9 | 16.6 | 0.22 | 0.44 | 0.45 | 0.054 |
| | | Choice reaction time | 515.0 | 109.0 | 513.0 | 100.0 | 0.59 | 0.02 | 0.65 | 0.022 |
| | | Willpower | 26.6 | 5.4 | 27.1 | 4.9 | 0.39 | −0.10 | 0.06 | 0.262 |
| Recovery (normoglycemia) | Rec 1 battery | Mod hypo symptom scale | 25.1 | 5.8 | 29.1 | 13.2 | 0.19 | 0.39 | 0.47 | 0.053 |
| | | Digit symbol substitution | 86.1 | 16.6 | 78.4 | 16.8 | 0.14 | 0.46 | 0.07 | 0.263 |
| | | Choice reaction time | 451.0 | 56.0 | 475.0 | 73.0 | 0.16 | −0.37 | 0.86 | 0.003 |
| | | Logical memory (delayed 2) | 12.1 | 4.0 | 8.9 | 4.2 | 0.07 | 0.78 | 0.09 | 0.220 |

Differences between conditions were calculated using a general linear model comparing sleep deprived with non–sleep deprived, with experimental order as a between-subject factor. Hypo battery, general cognitive tests performed at start (1) and end (2) of hypoglycemia; Rec 1, first recovery time point (10 min); mod hypo symptom score, modified hypoglycemia symptom score (see text). Significantly different data appear in boldface.

**Table 2—Results from linear mixed models of the cognitive test battery during hypoglycemia and during recovery**

| | Hypoglycemia symptom scale | | | Choice reaction time | | | Digit symbol substitution | | |
|---|---|---|---|---|---|---|---|---|---|
| Effect | β | SE | *P* | β | SE | *P* | β | SE | *P* |
| Measurements made during hypoglycemia | | | | | | | | | |
| Condition | 0.04 | 0.14 | 0.77 | −0.03 | 0.14 | 0.83 | −0.05 | 0.16 | 0.72 |
| Time | 0.19 | 0.07 | 0.01 | 0.02 | 0.07 | 0.78 | 0.07 | 0.07 | 0.34 |
| Baseline | 0.46 | 0.10 | <0.001 | 0.62 | 0.12 | <0.001 | 0.63 | 0.15 | <0.001 |
| Measurements made during posthypoglycemia recovery | | | | | | | | | |
| Condition | 0.87 | 0.07 | <0.001 | 0.34 | 0.08 | <0.001 | −0.23 | 0.06 | <0.001 |
| Time | −0.22 | 0.03 | <0.001 | 0.02 | 0.04 | 0.61 | 0.11 | 0.03 | <0.001 |
| Baseline | 0.22 | 0.05 | <0.001 | 0.09 | 0.10 | 0.34 | 0.52 | 0.08 | <0.001 |

Higher scores on the choice reaction time measure indicate slower (poorer) performance. All values come from models with no condition × time interaction. Condition × time interactions were nonsignificant ($P > 0.05$) for all three tests. Condition is a dummy variable: 0 = control condition and 1 = hypoglycemia condition. β, standardized β value.

of the tests, but no significant interactions between time and condition were observed; the test scores in the sleep-deprived condition did not decline any more steeply than the control scores (*P* values for the time-condition interaction: 0.38 and 0.90 for choice reaction and digit symbol, respectively).

## CONCLUSIONS

In the current study of young adults with type 1 diabetes, the impairment of cognitive function that was associated with hypoglycemia was not exacerbated by sleep deprivation. This is consistent with the report of a previous small study in seven adults without diabetes in which these forms of stress were examined in combination (8). One possible explanation is that hypoglycemia per se exerts a ceiling effect on the degree of cognitive dysfunction as is possible to demonstrate with conventional tests. It is also possible that the mechanism causing cognitive dysfunction during sleep deprivation differs from that during hypoglycemia, so that no additive effect is evident. Both this and the previous study were small and had limited power to detect an effect, which may also have influenced these observations.

However, throughout the recovery period in the current study, a significant deterioration in cognitive function was evident during the sleep-deprived state, even after adjustment for baseline values and using a mixed model that was not susceptible to error through multiple comparisons. This contrasts with the results of a previous study by our group, in which choice reaction time in adults with type 1 diabetes remained prolonged for 70 min after restoration of normoglycemia but had recovered fully by 85 min (2). It is possible that this could have resulted from exacerbation of the sleep deprivation toward the end of the study, by which time the sleep deficit had been protracted by approximately a further 6 h. The absence of a significant time interaction between the two conditions would argue against such an explanation; if greater sleep deprivation was the main causative factor promoting the poor scores during recovery from hypoglycemia, it would be expected that these scores would have worsened over time in the sleep-deprived study to a greater degree than in the control study, which was not observed. The recovery period also differed during the sleep-deprived study in that the hypoglycemia symptom scores were higher. This difference was not observed at baseline, so it cannot be attributed to the symptom questionnaire being sensitive to sleep deprivation per se. As the autonomic symptom scores remained elevated after restoration of normoglycemia, this suggests that the autonomic response to hypoglycemia was enhanced and/or prolonged when the participants were in a sleep-deprived state. This is in contrast to the attenuated epinephrine secretion that occurred in response to hypoglycemia during sleep in a study of eight adults with type 1 diabetes (24). Interestingly, epinephrine concentrations were higher when hypoglycemia occurred overnight when these subjects were awake (1,299 ± 213 vs. 1,616 ± 327 pmol/L) than if hypoglycemia was induced during the daytime. In that study (24), no statistical analysis comparing these results was reported, but it suggests that the epinephrine response to hypoglycemia may be amplified during sleep deprivation. Plasma catecholamine concentrations were not estimated in the current study as a measure of the intensity of the sympatho-adrenal response. Although catecholamines do not generate the autonomic symptoms per se, they can heighten the magnitude of the symptom response (25,26).

The higher neuroglycopenic symptom scores during the recovery period were unexpected. The physiological cause is unclear, but the brain does store a small but significant quantity of glycogen (27), which presumably is used in response to acute neuroglycopenia. Sleep deprivation leads to depletion of cerebral glycogen (28,29), and an important restorative function of sleep may be to replenish stores of this substrate (9,29,30). This effect on neuroglycopenic symptoms may have been exacerbated by depletion of neuronal glycogen reserves associated with sleep deprivation. This would be consistent with prolonged impairment of cognitive function.

No significant difference in performance at baseline was observed between the sleep-deprived and the non–sleep-deprived conditions, suggesting that the battery of cognitive tests was either not sensitive to the sleep-deprived condition or that the degree of sleep deprivation was insufficient. However, the tests were selected because they are known to assess domains of cognitive function that are affected by sleep deprivation. Cognitive impairment in sleep-deprived people is characterized by high intraindividual variation (4), which is problematic when using a repeated-measures design that assumes that intraindividual variation is minimal, although the multilevel model should have accounted for this. In addition, there is wide interindividual variation in response to sleep deprivation (31), which may have reduced the power of the study to identify significant outcomes, particularly as the number of participants was small. This low level of power is also a concern for the between-condition differences shown in Table 1; only large effect sizes could have produced significant differences in these values. However, the repeated testing increases our power to detect effects in the longitudinal analysis.

The study design can be criticized for the simple method used to induce sleep deprivation resulting in two distinct populations (night shift workers and

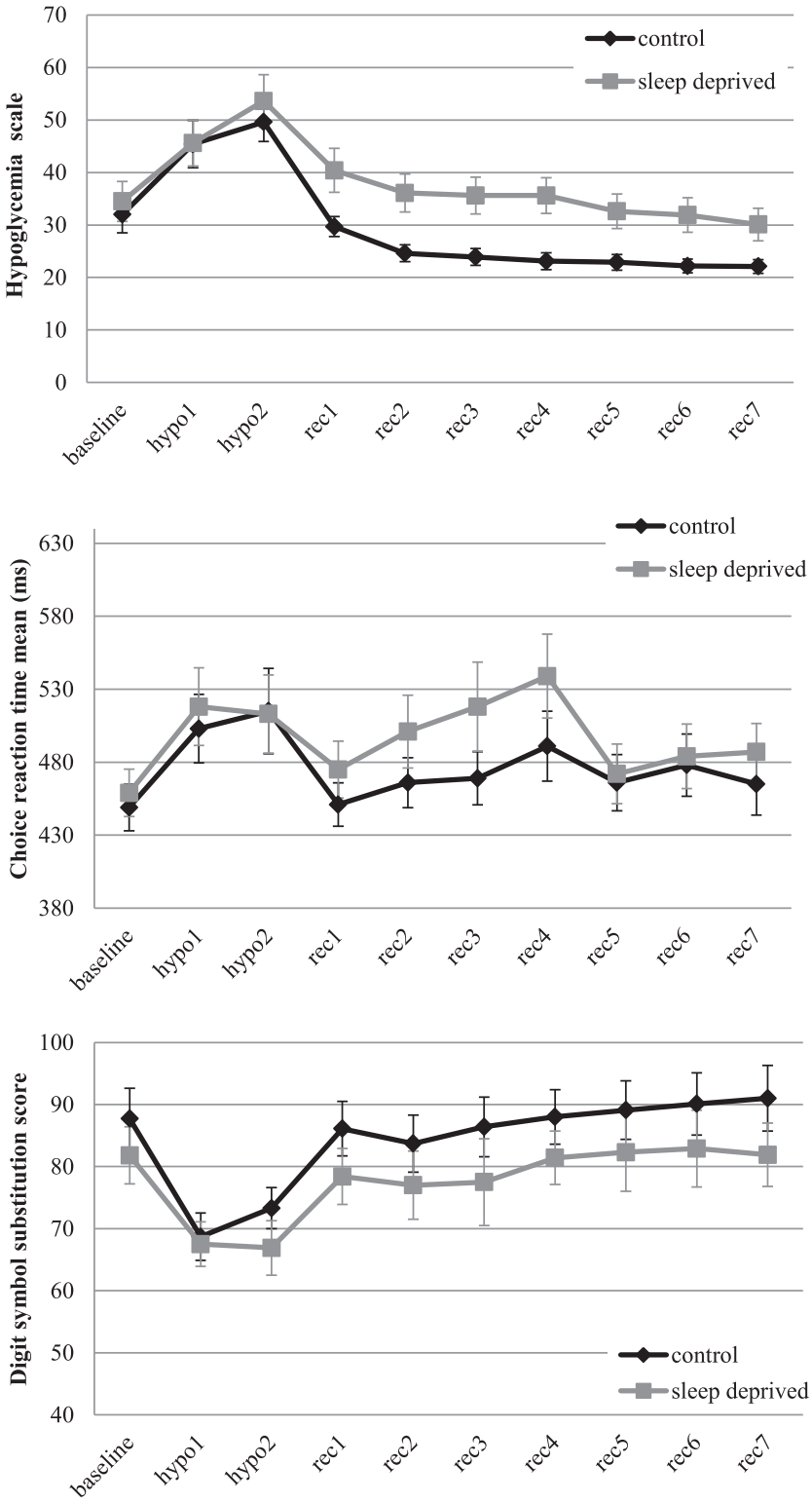


**Figure 2**—Results from hypoglycemia scale (top), choice reaction time (middle), and digit symbol score (bottom). Error bars represent standard error. Overall effect of condition during recovery $P < 0.01$ for all tests. hypo, general cognitive tests performed at start (1) and end (2) of hypoglycemia; rec, recovery time point.

those who stayed awake at home) and for the lack of characterization of participants before and during the study. No assessment was made at recruitment for sleep disorder, sleepiness, or chronotype. It is possible that some of the participants may have switched to a nocturnal chronotype, which could have affected their ability to cope with the tests. The degree of sleep deprivation induced was not assessed by polysomnography or with a simple scoring system such as the Epworth score (32) or the Karolinska sleepiness scale (33). The degree of sleep deprivation may therefore have differed between individuals depending on the number of preceding night shifts worked, their usual sleep patterns, and any degree of sleep deprivation before participation in the study. However, this flexibility in approach was necessary to encourage recruitment for what was a demanding research design and protocol; the relative simplicity of the method that was applied was considered to be representative of real-life conditions. By completion of the current study, the participants had been deprived of sleep for around 24 h, which is of similar duration to that used in most studies of sleep deprivation (19).

Ideally the study design should also have included normoglycemia control arms, with and without sleep deprivation, but the existing protocol was demanding and time consuming and to require participants to attend for a further two glucose clamps would have made recruitment extremely difficult. Of the local clinic population of adults with type 1 diabetes (~1,500), only 15 agreed to participate. The participants could not be blinded to the sleep condition, but a significant sleep order effect was observed only for the symptom score when hypoglycemia commenced. (Participants gave higher symptom scores when they first became hypoglycemic on their first study visit, regardless of sleep state.) No significant order effect was seen at any other time, or for any of the cognitive tests.

The repetitive nature of the protocol meant that participants were asked to perform the same general cognitive tests 10 times during each study session. This may have increased their skill at performing the task, and their performance would therefore be expected to improve during the study and potentially from one study to the next. This effect was moderated by having participants practice the tests during the run-in period to familiarize them with the tests. The counterbalanced design ensured that the learning effect would affect both arms of the study equally. The lack of improvement beyond baseline, and indeed a deterioration in choice reaction times, would suggest that a significant learning effect did not occur or that the effect of fatigue, sleep deprivation, or hypoglycemia

was greater than any learning effect that had occurred.

Alternatively, fatigue and inattention due to the repetitive and lengthy nature of the protocol may in particular have had an impact on the sleep deprivation studies. Evidence for this can been seen in the results of the choice reaction time (Fig. 2), which suddenly improves at 55 min after a period of deterioration, similar to that observed in a previous study (2). In both of these studies, this recovery time point coincided with repetition of the logical memory test, so changing the routine of the cognitive test battery. This may have unmasked an element of underlying boredom in the participants, whose interest and concentration were revived when a different test was introduced. The effect was more pronounced in the sleep-deprived condition. It is known that sleep deprivation leads to a classic "fatigue effect" where initial performance is good but deteriorates with increasing duration of the task (4). This could explain why the baseline tests were not affected but performance then deteriorated as the session progressed, particularly with the repetitive cognitive test battery.

The current study in adults with type 1 diabetes has shown that although the cognitive impairment induced by hypoglycemia is not exacerbated by sleep deprivation, the posthypoglycemia recovery takes longer with persistence of both cognitive dysfunction and hypoglycemia symptoms. As these combined forms of stress may be encountered at some time in everyday life by people with insulin-treated diabetes, the delayed posthypoglycemia recovery could have important consequences in situations such as driving. People with diabetes should be advised that exposure to hypoglycemia while suffering from sleep deprivation could prolong the impairment of cognitive function considerably, despite prompt restoration of normoglycemia.

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**Author Contributions.** B.E.I. recruited the study participants, performed data collection and statistical analysis, and prepared the manuscript. N.N.Z., I.J.D., I.M., and B.M.F. conceptualized the study, designed the protocol, and advised on data analysis. S.J.R. performed the statistical analysis. All authors helped to write the manuscript. B.E.I. 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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