

# Effects of Repeated Hypoglycemia on Cognitive Function

## A psychometrically validated reanalysis of the Diabetes Control and Complications Trial data

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**OBJECTIVE** — To test the conclusion that there is no association between multiple episodes of severe hypoglycemia and cognitive decrements by reanalyzing the data from the Diabetes Control and Complications Trial (DCCT) with psychometrically validated cognitive factors and to conduct a novel analysis of the association between individual differences in baseline cognitive ability and episodes of severe hypoglycemia documented after baseline.

**RESEARCH DESIGN AND METHODS** — The factor structure of cognitive ability in the neuropsychological data from the DCCT study was derived. Four cognitive factors (spatial ability, processing speed, memory, and verbal ability) were extracted. Changes in patients' cognitive scores for each year of follow-up were obtained, and paired comparisons of these change scores were performed between groups experiencing zero and five or more hypoglycemic episodes. The association between cognitive ability at baseline and number of subsequent episodes of severe hypoglycemia was also examined.

**RESULTS** — Repeated episodes of hypoglycemia were found not to be associated with cognitive decline in any of the validated cognitive factors. No significant association was found between prospectively documented numbers of severe hypoglycemic episodes and baseline cognitive ability level.

**CONCLUSIONS** — Repeated episodes of hypoglycemia were not related to cognitive decrement, and initial mental ability level was not associated with eventual numbers of hypoglycemic episodes in this group of patients.

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**A**cute hypoglycemia is a common side effect in the treatment of type 1 diabetes with insulin. Hypoglycemic episodes inevitably cause a temporary deficit in the supply of glucose to the brain. It is therefore reasonable to consider the possibility that repeated episodes of severe hypoglycemia may be associated with brain damage. The indicator of such damage would be the observation of cognitive decrements in people with diabetes who have had many severe hypoglycemic

episodes compared with matched control subjects who have had few or no such events. Studies of the lasting effects of repeated severe hypoglycemia on cognitive functions have produced mixed results. Some cross-sectional studies (1–4) have reported lower scores on neuropsychological and cognitive measures in patient groups experiencing many severe hypoglycemic episodes compared with control groups of nondiabetic subjects or patients with diabetes who had not expe-

rienced such episodes. Longitudinal studies (5,6), however, have reported no lasting detrimental effects of repeated severe hypoglycemia on cognitive function in cases where recovery from individual episodes is uncomplicated.

In particular, a null result was reported from the Diabetes Control and Complications Trial (DCCT) (6). In this large-scale study, patients undergoing intensive and conventional insulin therapy were followed in a longitudinal design. Patients completed a comprehensive battery of neuropsychological measures at baseline and after intervals of 2, 5, 7, and 9 years. The number of severe hypoglycemic events experienced by each patient was recorded prospectively. Each neuropsychological test was assigned to one of eight cognitive domains (e.g., problem solving, memory). The criterion for assigning a test to a particular domain was based on the face validity of the test. Analysis of the domain scores showed that repeated episodes of hypoglycemia had no effect on performance in any of the cognitive domains. This analysis has been criticized (7,8) for failing to consider the current psychometric understanding of the structuring of human abilities.

There is a consensus (9–11) that human mental abilities are structured in a hierarchical manner. Correlations between ability test scores are generally positive; a substantial part of the variance of each test can be attributed to a general factor. This factor can be regarded as measuring a general capacity or ability to perform a range of ability tests and is referred to as general ability. At the next level of the hierarchy, broad groups of abilities such as verbal, problem solving, and memory emerge, whereas more specific abilities are found at lower levels. The existence of, for example, a verbal ability factor corresponds with the fact that tests of verbal skills are somewhat more strongly correlated with each other than they are with test scores for, for example, mathematical or spatial skills. When analyzing a group of cognitive tests, the consensus among psychometricians is that

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**Abbreviations:** DCCT, Diabetes Control and Complications Trial; IQ, intelligence quotient.

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

the appropriate method is to uncover the underlying ability structure by using the statistical technique of factor analysis. This is a multivariate statistical technique that seeks to reduce the dimensionality of a complex data set by accounting for the correlations between variables by using a small number of underlying dimensions or factors. A more detailed account of the factor analysis method and its application to human ability structure can be found in the text by Kline (11). Using scores on psychometrically valid ability factors provides a more rigorous basis on which to test the effects of hypoglycemic episodes on cognitive functioning than does a method based on the face validity of individual cognitive tests.

Because of the high quality of the DCCT data in terms of range of tests conducted, number of patients, and extent of follow-up, it is important that a reanalysis of the data using a psychometrically valid methodology be performed. In the absence of such a reanalysis, the finding of no hypoglycemia-associated cognitive decline is questionable because the cognitive tests were not analyzed with an optimal method. In addition, these data allow a novel analysis of the reverse hypothesis (i.e., a test of the association between ability levels at baseline and the eventual number of episodes of severe hypoglycemia). A plausible

mechanism for such an association would be that less-able patients may be less skilled at detecting the signs of incipient hypoglycemia in time to instigate preventive measures and may hence be more likely to experience severe hypoglycemic episodes.

**RESEARCH DESIGN AND METHODS**

— Details of the patient characteristics, mental tests, and study procedures have been described previously by the DCCT Research Group (6). The DCCT initially recruited 1,441 patients aged 13–39 years who had type 1 diabetes for 1–15 years. Neuropsychological test batteries were administered at baseline and at years 2, 5, 7, and 9 of the study. Patient numbers at each time point were 1,441 (baseline), 1,411 (year 2), 1,423 (year 5), 626 (year 7), and 266 (year 9). The DCCT data were made available to the authors of this study. The neuropsychological test data were inspected to determine if any pairs of tests were redundant or contained strongly related information (e.g., time taken to perform a test and number of errors made in the same test). In addition, certain measures were rekeyed so that higher scores on all measures represented higher ability. A list of scores retained appears in Table 1.

To derive the factor structure of cognitive ability in this sample, the baseline data for the selected ability tests were subjected

to a principal components analysis followed by rotation to simple structure (11,12). Although, technically, the rotated principal components should not be described as factors, this usage is widespread and convenient. Inspection of the scree diagram suggested a four-factor solution that explained 47.5% of the variance; this result is acceptable in terms of accounting for sufficient variance for the factor analysis solution to be meaningful. Four oblique factors were extracted and identified by their main loadings as corresponding to spatial ability, processing speed, memory, and verbal ability. (Factor loadings correspond to the correlation of each variable with the factor, so the nature of the underlying factor can be elucidated by examining the high-loading variables.) One test, finger tapping, did not load strongly on any factor and was analyzed separately.

Each patient's scores on the four factors were obtained at baseline and at follow-up years 2, 5, 7, and 9 of the DCCT by first computing a set of standardized Z scores for each test; this was done separately for data from each time point. The rationale for this procedure is that it provides a more meaningful set of factor scores than those obtained by totaling unscaled test scores. This is because combining unscaled scores causes the sum to be dominated by tests with higher mean scores. Factor scores

**Table 1—Factor structure obtained from baseline neuropsychological test scores**

Test	Factor loadings				
	General ability	Spatial ability	Processing speed	Memory	Verbal
Verbal Fluency	<b>0.46</b>	−0.04	0.36	<b>0.63</b>	−0.04
Similarities	<b>0.45</b>	0.17	−0.14	<b>0.61</b>	0.04
Picture Arrangement	<b>0.46</b>	0.37	−0.19	<b>0.43</b>	0.01
Block Design	<b>0.68</b>	<b>0.67</b>	−0.01	0.17	0.12
Tactual Performance (memory)	<b>0.48</b>	<b>0.42</b>	−0.08	−0.09	0.35
Symbol-Digit Learning	<b>0.52</b>	0.02	−0.08	−0.10	<b>0.74</b>
Short-Term Memory	<b>0.55</b>	−0.14	0.08	0.35	<b>0.57</b>
Embedded Figures	<b>0.40</b>	<b>0.57</b>	0.16	0.05	−0.18
Object Assembly	<b>0.59</b>	<b>0.69</b>	−0.03	0.09	0.04
Digit Vigilance (time)	<b>0.23</b>	−0.03	<b>0.76</b>	0.04	−0.13
Digit Span	<b>0.44</b>	−0.18	0.13	<b>0.60</b>	0.07
Digit Symbol Substitution (number correct)	<b>0.51</b>	0.00	<b>0.76</b>	0.05	0.22
Trail Making	<b>0.54</b>	0.13	<b>0.43</b>	0.23	0.18
Category Test	<b>0.58</b>	0.28	−0.09	0.31	0.32
Total Tactual Performance	<b>0.53</b>	<b>0.64</b>	0.09	−0.06	0.06
Pegboard (sum of dominant and nondominant hands)	<b>0.42</b>	0.33	<b>0.50</b>	−0.14	0.05
Visual Reproduction (sum of delayed and immediate)	<b>0.51</b>	0.30	0.05	−0.21	<b>0.53</b>
Memory (sum of logical and long-term memory scores on the same material)	<b>0.53</b>	−0.09	0.00	0.24	<b>0.64</b>

Fuller details and references for the neuropsychological tests appear in a study by the DCCT Research Group (6). Each factor loading is the value of the correlation of the relevant variable with the factor. Loadings >0.4, shown in bold, correspond to tests used in calculating the factor scores.

were obtained for each patient in each year of the trial by totaling their Z scores for each test with a loading >0.4 on the relevant factor as shown in Table 1. In addition, a general ability factor score for each patient was obtained by totaling their Z scores on all tests except finger tapping. To facilitate the interpretation of the change in factor scores, all scores were transformed to a conventional intelligence quotient (IQ) scale ( $100 \pm 15$  [mean  $\pm$  SD]).

Data for each year of follow-up were analyzed by obtaining a change score from baseline for each patient on the ability factors. In each study year, patients were divided into three groups according to the number of severe hypoglycemic episodes reported to date: zero, one to four, and five or more. The five or more level corresponds with numbers of severe hypoglycemic episodes found to be associated with significant cognitive decrements in cross-sectional studies (2,4). The possibility of

cognitive decrements as a result of repeated severe hypoglycemia was therefore investigated by means of paired comparisons between the two extreme groups. Published information about the DCCT study (6) reported that one patient incurred a head injury during the course of the trial. Although this patient was not identified specifically in the data made available to us, the DCCT Research Group (6) provided sufficient information (age, sex, time of accident, and a clinical rating indicator for significant neuropsychological worsening at year 5 and later) to allow this patient (who had an anomalously high cognitive decline) to be identified and removed from the analysis.

**RESULTS**— Table 2 shows the cognitive score factor changes. Note that the transformation of all scores to a psychometric IQ-type scale means that the scores have an SD of 15. The largest group differ-

ence in the table is thus only  $\sim 0.4$  of an SD; differences of this magnitude and the corresponding group deviations from the population mean are not likely to be clinically significant. The cognitive factor score changes are generally not significantly different for patients experiencing zero and five or more hypoglycemic episodes to date in years 2, 5, 7, and 9. There is one instance of a significantly enhanced score in the five or more hypoglycemic episodes group compared with the zero hypoglycemic episodes group (i.e., an effect direction opposite that expected [processing speed, year 7]). Thus, this analysis provides no evidence for hypoglycemia-induced cognitive decline.

The possibility of a reverse association was investigated (i.e., that there may be an association between baseline IQ and the eventual number of severe hypoglycemic episodes). A negative association may suggest that more-able patients avoid hypo-

**Table 2—Comparisons of cognitive score changes for groups with 0 (group 1) and five or more (group 2) hypoglycemic episodes**

	Year 2	Year 5	Year 7	Year 9
<b>General ability</b>				
Group 1	$-0.04 \pm 0.23$ (1,121)	$-0.10 \pm 0.28$ (943)	$0.91 \pm 0.56$ (371)	$1.00 \pm 0.90$ (139)
Group 2	$-3.32 \pm 3.64$ (8)	$1.06 \pm 1.51$ (30)	$4.50 \pm 2.41$ (30)	$1.11 \pm 2.16$ (18)
P	0.24	0.46	0.08	0.97
Total sample size	1,301	1,256	561	249
<b>Spatial ability</b>				
Group 1	$0.12 \pm 0.30$ (1,148)	$-0.04 \pm 0.33$ (980)	$0.32 \pm 0.59$ (391)	$1.34 \pm 1.01$ (146)
Group 2	$-3.47 \pm 3.55$ (8)	$0.06 \pm 1.89$ (31)	$1.76 \pm 2.01$ (32)	$-0.74 \pm 2.25$ (19)
P	0.33	0.96	0.50	0.48
Total sample size	1,333	1,302	591	250
<b>Processing speed</b>				
Group 1	$0.02 \pm 0.30$ (1,202)	$0.18 \pm 0.34$ (1,010)	$-0.40 \pm 0.65$ (397)	$-0.27 \pm 1.08$ (152)
Group 2	$0.03 \pm 2.56$ (8)	$1.72 \pm 2.05$ (32)	$4.41 \pm 1.98$ (34)	$2.65 \pm 3.17$ (21)
P	1.00	0.43	0.04	0.35
Total sample size	1,395	1,342	601	258
<b>Verbal</b>				
Group 1	$0.06 \pm 0.31$ (1,156)	$-0.12 \pm 0.35$ (983)	$1.15 \pm 0.62$ (380)	$1.28 \pm 0.93$ (148)
Group 2	$-3.32 \pm 3.35$ (8)	$-0.04 \pm 1.81$ (32)	$4.49 \pm 2.42$ (34)	$-0.37 \pm 1.96$ (20)
P	0.37	0.97	0.13	0.53
Total sample size	1,343	1,309	581	254
<b>Memory</b>				
Group 1	$-0.02 \pm 0.32$ (1,198)	$0.18 \pm 0.38$ (1,005)	$2.97 \pm 0.64$ (398)	$1.88 \pm 1.11$ (153)
Group 2	$-3.46 \pm 3.90$ (8)	$0.75 \pm 1.70$ (31)	$3.77 \pm 2.11$ (34)	$3.33 \pm 2.15$ (20)
P	0.38	0.79	0.72	0.65
Total sample size	1,390	1,339	604	260
<b>Finger tapping</b>				
Group 1	$-0.29 \pm 0.35$ (1,200)	$-0.11 \pm 0.41$ (1,015)	$-0.16 \pm 0.67$ (399)	$1.54 \pm 1.08$ (154)
Group 2	$2.09 \pm 2.36$ (8)	$2.75 \pm 2.17$ (32)	$4.23 \pm 2.89$ (35)	$7.20 \pm 3.13$ (21)
P	0.58	0.22	0.07	0.07
Total sample size	1,393	1,349	606	262

Data are means  $\pm$  SEM (n). Total sample size includes patients experiencing 1–4 hypoglycemic episodes. Negative changes represent decrements from baseline, and positive scores are increments. All score changes are based on an IQ-type scale (SD = 15).

glycemia by managing their treatment more successfully. The rank-order correlation coefficient between number of hypoglycemic episodes and baseline general ability at year 7 was calculated. The baseline IQ scores were  $100 \pm 15$  by definition; the IQ range was 41–142. The distribution of number of severe hypoglycemic episodes experienced by year 7 was strongly skewed (mean 0.9, median 0.0, SD 1.95, range 0–19). Year 7 was chosen because it corresponds with the latest year of follow-up at which a reasonably large number of patients was still in the study. The value of the rank-order correlation coefficient was  $-0.027$  ( $n = 583$ ,  $P = 0.51$  [NS]). Thus, the data do not support any association between initial ability level and the later occurrence of severe hypoglycemia.

**CONCLUSIONS** — This reanalysis of the DCCT data demonstrates that repeated episodes of hypoglycemia are not linked to cognitive decrements in this group of patients. The use of psychometrically valid methods to determine cognitive function changes invalidates a criticism of the original analysis (7,8); the broader question of hypoglycemia and cognitive decline remains unresolved. This problem arises partly from contradictory findings in previous studies. The design of the DCCT also suggests that it was not optimal for investigating cognitive changes (7,8). The patients were young, had a short duration of disease, had a high mean intellectual ability, were followed up for a relatively short period of time, and did not generally experience high numbers of hypoglycemic episodes. By contrast, it seems reasonable to assume that hypoglycemia-related cognitive decline, if it occurs, is a long-term cumulative process that may require several decades to develop. Moreover, the DCCT study included adolescents, some of whom changed from adolescent to adult versions of the tests as the trial progressed. These features could induce additional variance in cognitive ability changes. One potential source of additional variance is developmental; adolescent IQ scores may change over time in a different manner from those of adults. In addition, subjects given the same ability tests repeatedly demonstrate a practice effect. Thus, in a study of 85 adult patients with type 1 diabetes, mean Wechsler Adult Intelligence Scale performance IQ increased by 3.5 points between two test sessions separated by 18 months (13). It is possible that such effects may differ

between adolescents and adults. Finally, the change between adolescent and adult ability tests for some patients in the DCCT could have introduced additional variance because these patients would presumably lose some or all of the benefit of practice.

In addition, this study has low statistical power, even though the DCCT results represent the largest longitudinal data set available for exploring the effects of repeated hypoglycemia. As seen in Table 2, only a small number of patients experienced five or more hypoglycemic events during the course of the study. Increasing the power by lowering the threshold for what is considered to be a “large number” of hypoglycemic episodes is not an option in the analysis given that the research hypothesis is associated with the cumulative effects of many such events. Indeed, it can be argued that it would be desirable to set this threshold higher. An ideal but impractical study would follow-up extremely large numbers of patients over a longer period of time to build up large samples of those experiencing 5, 6, or more hypoglycemic episodes. Cross-sectional studies relying on patients’ self-reports of the number of hypoglycemic episodes experienced during the course of their illness provide a more realistic means of obtaining larger sample sizes but are subject to the criticism of relying on self-report rather than on objective data.

It can also be argued that the comparisons of the zero and five or more hypoglycemic episodes groups in a longitudinal study such as the DCCT are not equivalent at different time points in the study. This problem arises because, at year 2, all patients in the second group had experienced five or more hypoglycemic episodes; in later years, these patients were joined by those who had taken longer to accumulate five or more hypoglycemic episodes. It might be argued that these patients fall into two distinct groups, as do those patients who remain in the zero hypoglycemic episodes group throughout the study and those who later experience  $\geq 1$  hypoglycemic episode and hence are excluded from this group. Under the simplest possible theory of the putative hypoglycemia–cognitive decline association, these problems are not however relevant because cognitive decline has been hypothesized to be linked solely to cumulative number of hypoglycemic episodes without regard for their distribution in time. Given the lack of agreement in the literature regarding the applicability of this simple theory, it seems

reasonable to neglect the possibility of more complex individual patterns (e.g., variation in risk of decline as a function of rate of accumulation of hypoglycemic events), detection of which would again require a combination of very large sample sizes and very long-term follow-up for reasonable statistical power to be obtained.

In addition to the problem of low statistical power discussed above, another obstacle impeding research in this area is that counting the number of hypoglycemic episodes experienced by a patient is a poor surrogate for a measure of any brain insult that may have occurred. Mere counting of episodes, even with consistently applied definitions of severity, does not address in detail the effect of a particular episode on an individual. It seems likely that individual effects would depend on, for example, the degree of hypoglycemia and the length of the episode as well as on person-specific factors. A biological marker to assess the extent and location of any hypoglycemia-induced brain damage directly is currently lacking; progress in this direction will be required for a full understanding of the effects of repeated hypoglycemic episodes. These points are discussed in more detail by Deary (8).

Table 2 shows a preponderance of non-significant effects on cognitive scores in the opposite direction to that hypothesized (i.e., increased cognitive scores in the five or more hypoglycemic episodes group). The reason for this finding is not clear; it should be noted that, in addition to the specific features of the DCCT study mentioned above, the analysis of longitudinal data inevitably poses special difficulties associated with “nonrandom dropout.” Nonrandom dropout occurs when volunteers leaving a longitudinal study differ in important characteristics from those who remain in it. A common example is that people who become ill are more likely to be unable to attend follow-up sessions, but other factors such as age and socioeconomic status can also contribute to non-random dropout. In the context of the DCCT and similar studies, such factors may cause patients to leave the study differentially as a function of ability level, number of hypoglycemic episodes, or both.

Finally, the tenable reverse hypothesis (that initial mental ability level is associated with eventual numbers of hypoglycemic episodes) was not supported. Although it appears plausible that more intelligent patients may manage their insulin treatment

more effectively and hence experience fewer episodes of hypoglycemia, the DCCT data provide no evidence of such an effect.

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