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Modeling the Effects of Hypoglycemia on a Two-Choice Task in Adult Humans

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Objective: Previous research has demonstrated that hypoglycemia causes reaction times to be slower and more variable. Reaction time tests, however, use multiple cognitive and noncognitive processes. This study is the first to use a validated sequential sampling model (diffusion model) applied to results obtained from a simple 2-choice task in adult humans to assess the effects of hypoglycemia on the basic parameters of decision making. ***Method:*** Fourteen adult volunteers were tested on a numerosity discrimination task with and without reduced blood glucose concentrations. The results were analyzed with a model that dissects the components of processing that underlie decisions: the quality of the information on which a decision is based (drift rate), the critical amount of evidence that must be accumulated before a decision is made (boundary separation), and the time taken by nondecision processes. ***Results:*** Hypoglycemia resulted in a reduction of mean drift rate from 0.290 to 0.211, $t(13) = 4.10$, $p < .05$. No effect of experimental state was observed on the amount of evidence required to make a decision or peripheral and motor processes. ***Conclusion:*** This study locates the precise processing deficit associated with hypoglycemia and provides further understanding of the precise cognitive effect of hypoglycemia. Further research into the amelioration of these effects is required.

Keywords: hypoglycemia, reaction time, central processing, diffusion model

Experiments aimed at understanding brain function can be informative, especially if precise manipulation of brain state can be accomplished so that the resulting change in cognitive competences can be dissected using a mental task that has a model with validated performance parameters. In this study, we induced a precisely controlled state of cerebral neuroglycopenia during hypoglycemia and studied its effects on individual components of decision making.

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Glucose is the obligate fuel of the brain that, despite being only 2% of the body's weight, consumes 20% of its energy resources (Sokaloff, 1989). Therefore, the manipulation of cerebral glucose supply achieves precise control over cerebral metabolism. The need for such manipulation originated from the desire to understand the mental consequences of hypoglycemia, which is a frequent side effect of the treatment of diabetes with insulin, a hormone that has blood glucose-lowering effects. The development of the glucose clamp technique (De Fronzo, Tobin, & Andres, 1979), which involves the simultaneous intravenous infusion of insulin and glucose to "clamp" the blood glucose at a predetermined concentration and the frequent sampling of "arterialized" blood, provided a tool for inducing and maintaining a precise glycemic state. Thus, the brain's fuel can be set at a specific level. Typically, hypoglycemia is induced by lowering the blood glucose level to about 45 mg/dl (2.5 mmol/L); fasting blood glucose concentrations in healthy adults normally range from 70 to 100 mg/dl (3.9 to 5.6 mmol/L). Such a level (45 mg/dl) can be maintained safely and reversibly; in experimental studies in humans, it can be tolerated for up to about 1 hr.

Hypoglycemia and Cognitive Functions

The glucose clamp technique has been used to study the effects of hypoglycemia—typically compared with a counterbalanced normoglycemic (euglycemic) state—on a range of cognitive and motor functions. These range from practical tasks to more information-processing-oriented measures. Hypoglycemia causes deterioration in aspects of driving (Cox, Gonder-Frederick, Kovatchev,

Julian, & Clarke, 2000), which is of interest for reasons of health and safety and has legal import. Such high-level performance says little that is specific about the more precise brain functions that are affected. Hypoglycemia is known to cause deterioration in psychometric and neuropsychological tests assessing the cognitive domains of memory (Sommerfield, Deary, McAulay, & Frier, 2003a, 2003b; Warren, Zammitt, Deary, & Frier, 2007), attention (McAulay, Deary, Ferguson, & Frier, 2001; McAulay, Deary, Sommerfield, & Frier, 2005), reasoning (McAulay et al., 2005), and psychomotor function (Geddes, Deary, & Frier, 2008). At an even lower level, hypoglycemia causes reaction times (RTs) to be slower and more variable (Deary, Hepburn, MacLeod, & Frier, 1993; Strachan et al., 2001), and visual (McCrimmon, Deary, & Frier, 1997) and auditory (McCrimmon, Deary, Huntly, MacLeod, & Frier, 1996) information processing becomes less efficient. The latter studies used tasks from psychophysics and experimental psychology. Even in these studies, an overall test score was used, not precise parameters related to cognitive-processing stages. To date, no studies have examined the effects of hypoglycemia on a task that assesses basic parameters of decision making. Such fundamental information about the effect of fuel deprivation on the brain's basic capabilities would be useful for basic brain science and applied research. In this study, for the first time, we examined the effects of hypoglycemia on a task that has validated information-processing parameters. The task itself is a numerosity discrimination task. Between 31 and 70 asterisks is presented—randomly placed in a 10 by 10 array—on a computer screen. The subject is required to decide whether the number of asterisks is large (greater than 50) or small (less than 50). The results are analyzed using the diffusion model that dissects the components of processing that underlie decisions: the quality of the information on which a decision is based (drift rate), the critical amount of evidence that must be accumulated before a decision is made (boundary separation), and the time taken by nondecision processes such as stimulus encoding, memory access, and response output (nondecision processes). A more detailed account of the model is given below.

The Diffusion Model

The diffusion model apportions parameter values to data from the relevant cognitive task and uses the parameter values representing the components of processing to interpret, for example, the effects of aging or sleep deprivation on performance (Busemeyer & Townsend, 1993; Palmer, Huk, & Shadlen, 2005; Ratcliff, 1978, 1981, 1988, 2006; Ratcliff, Cherian, & Segraves, 2003; Ratcliff & Rouder, 2000; Ratcliff & Smith, 2004; Ratcliff, Van Zandt, & McKoon, 1999; Smith, Ratcliff, & Wolfgang, 2004). The model (see top panel of Figure 1) assumes that evidence from the stimulus is noisy and it is accumulated from a starting point (z) toward one or the other of the boundaries (a or 0). The mean rate of accumulation of evidence is called drift rate (v), and the assumption here is that the perceived numerosity is mapped into drift rate. Within-trial variability (noise) causes processes with the same drift rate to terminate at different times (producing RT distributions) and sometimes to terminate at the wrong boundary (producing

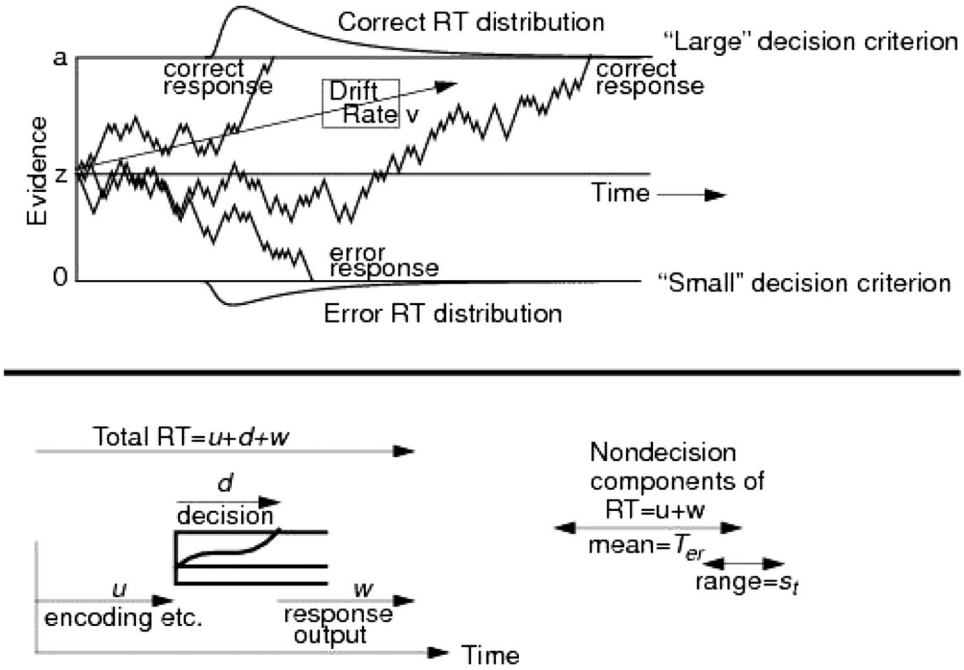

Figure 1. An illustration of the diffusion model. The top panel illustrates the diffusion model with starting point z, boundary separation a, and drift rate v. Three sample paths are shown illustrating variability within the decision process, and correct and error response time (RT) distributions are illustrated. The bottom panel illustrates the components of processing besides the decision process d with the duration of the encoding process u and the duration of processes after the decision process w. These two components are added to give the duration of nondecision component T_{er} and it was assumed to have range s_t.

errors). The values of the components of processing vary from trial to trial. Drift rate is assumed to be normally distributed across trials with *SD* η. Starting point is assumed to be uniformly distributed across trials with range s_z (which is equivalent to variability in decision criteria if the variability is not too large). Contaminant responses are modeled by assuming that on some proportion of trials (p_o), there is a random delay added to the decision RT, due to a moment's distraction, lack of attention, and other factors. The distribution is assumed to be uniform, but recovery of diffusion model parameters is robust to the actual form of the distribution (Ratcliff & McKoon, 2008; see Figure 1).

The bottom panel of Figure 1 shows encoding and response execution processes-processes that occur before and after the decision process, respectively. The nondecision processes are combined, with a mean RT for the combination that is labeled T_{er}. Also, the nondecision component is uniformly distributed with range s_t. The uniform distribution does not affect the overall shape of the RT distributions because it is combined (convolved) with the much wider decision process distribution (Ratcliff & Tuerlinckx, 2002).

In signal detection theory, all variability would be attributed to the numerosity estimate (the estimate of whether the number of asterisks was larger or smaller than 50), with variability normally distributed across trials. In the diffusion model, this corresponds to variability in drift rate across trials. However, in the diffusion model, the different sources of variability, within-trial, starting point, and the nondecision component are separately identified when the model is fit to data. If predicted data are generated from the model and the model is fit back to the predicted data, the parameter values are recovered accurately so that, for example, high variability in drift across trials is not misidentified as high variability in starting point (Ratcliff & Tuerlinckx, 2002).

For this numerosity discrimination experiment, we assume that drift rates are equal and opposite for small responses to small stimuli and large responses to large stimuli. For example, the drift rate for 31–35 asterisks has the same numerical value as the drift rate for 66–70 asterisks. However, subjects can have a bias in the zero point of drift, so we use a drift criterion to be added to each drift rate (Ratcliff & McKoon, 2008). The addition of a positive drift criterion, for example, makes a drift rate for the condition with 31–35 asterisks larger numerically than the drift rate for the condition with 66–70 asterisks. For further details of the model, see Ratcliff and McKoon (2008) and Ratcliff and Tuerlinckx (2002).

Method

Participants

Fourteen nondiabetic adult humans (five men and nine women) were recruited from members of staff at the Royal Infirmary of Edinburgh. None had any relevant previous medical history of family history of diabetes, and none were taking regular medication (other than the oral contraceptive pill). Five of the nine female participants were taking the oral contraceptive pill. All subjects had a corrected visual acuity of 6/6 or greater in both eyes, as measured with the Snellen chart. The median (interquartile range) age was 28 (27–35) years and the mean body mass index (*SD*) was 22.8 (2.61) kg/m^2. All of the subjects had above average intellectual ability as assessed by the National Adult Reading Test (Nelson & Willison, 1991). The mean (*SD*) National Adult Reading Test correct score for 14 subjects was 41.5 (4.2). The local Medical Research Ethics Committee approved the study, and all subjects gave their written informed consent.

Study Design

Each subject participated in two laboratory sessions, each separated by at least 2 weeks. The studies were conducted in the Clinical Research Facility of the Royal Infirmary of Edinburgh. During the experimental visits, subjects underwent a modified hyperinsulinemic glucose clamp. The subjects completed both experimental conditions in a counterbalanced fashion, that is, half of the subjects underwent the euglycemia condition first, followed by the hypoglycemia condition; the other half underwent the experimental conditions in reverse order. The subjects were not informed which condition was being studied at each visit.

Procedure

Each session commenced at 0800 following a 10-hr overnight fast. A Teflon cannula was inserted into the antecubital vein under local anesthetic (2% lignocaine). This cannula was used to infuse human soluble insulin (Actrapid, Novo Nordisk Pharmaceuticals, Crawley, U.K.) and 20% dextrose. A second cannula was inserted in a retrograde direction into a vein on the dorsum of the hand, which was placed in a heated blanket to arterialize the venous blood. Arterialized blood samples were obtained throughout the study for measurement of whole blood glucose at the bedside using a glucose oxidase method (Yellow Springs Instrument 2300 Stat, Yellow Springs, OH). A modified hyperinsulinemic glucose clamp technique (as described above) was used to maintain blood glucose at predetermined levels. After a brief priming regimen, insulin was infused at a steady rate (based on whole body surface area) of 60 mU/m^2 per minute using an IVAC Signature Gold pump (Alaris Medical Systems, San Diego, CA); 20% dextrose was infused, also using a IVAC Signature Gold pump, at a variable rate depending on the blood glucose value. Arterialized blood glucose was measured initially every 3 min, until a stable level had been achieved, and then at 5-min intervals. At each laboratory session, arterialized blood glucose was initially stabilized at 4.5 mmol/L (81 mg/dl) for a period of 30 min. Following this, the blood glucose concentration was either maintained at 4.5 mmol/L (euglycemia) or lowered to 2.5 mmol/L (45 mg/dl; i.e., hypoglycemia), and the neuropsychological tests were administered. The subjects were not informed about their blood glucose concentration during any phase of the study. A period of 20 min was allowed to elapse between the baseline and the attainment of euglycemia or hypoglycemia to allow the blood glucose concentration to stabilize. The target glucose concentration was maintained for a further 10 min before the tests were administered and was maintained for a further 60 min while the tests were administered. At the end of the hypoglycemia session, the blood glucose was restored to 4.5 mmol/L. Subjects were provided with a meal after completion of each condition.

Cognitive Function Tests

Signal detection. For each trial, between 30 and 70 asterisks were generated from a signal distribution. The asterisks were

placed in random positions in a 10 × 10 array of blank characters on a computer screen (Sony Vaio TR2A Notebook). The subjects were asked to decide whether the number of displayed asterisks was "large" or "small" by pressing the *z* key on the computer keyboard for the "large" group and the *?* key on the keyboard for the "small" group. Accuracy feedback was given on all trials. There were 30 blocks of 40 trials per session. For the data analyses, the numbers of asterisks were grouped into eight experimental conditions so that the mean RTs and accuracy values were about the same for the stimuli within a group. RTs less than 250 and greater than 3,000 ms were excluded, as were the first trial in a block and the first block.

Digit Symbol Substitution Test. The Digit Symbol Substitution Test consists of eight rows containing, in total, 200 small blank squares, each with a randomly assigned number from 1 to 9. Above these rows is a printed key that pairs each number with a different symbol. The subject is asked to fill in as many of the blank squares as possible with the appropriate symbol that matches the number above the box in a time limit of 120 s. The score is the number of squares that are completed successfully within the time limit. This test is performed routinely during hypoglycemia clamp experiments as a validity check on the cognitive effects of hypoglycemia.

Symptoms of Hypoglycemia

The Edinburgh Hypoglycemia Scale (Deary et al., 1993), a validated, subjective self-rating questionnaire, was used to document the symptoms of hypoglycemia, which were classified as autonomic (hunger, palpitations, sweating, tremor), neuroglycopenic (confusion, drowsiness, difficulty concentrating, weakness), and malaise (nausea, headache). Each symptom was graded on a Likert scale ranging from 1 (*not present*) to 7 (*very intense*).

Statistical Analysis

The diffusion model was fit to the data by minimizing a chi-square value with a general SIMPLEX minimization routine that adjusts the parameters of the model until it finds the parameter estimates that give the minimum chi-square value (Ratcliff & Tuerlinckx, 2002). The data entered into the minimization routine for each experimental condition were the 0.1, 0.3, 0.5, 0.7, 0.9 quantile RTs for correct and error responses and the corresponding accuracy values. The quantile response times and the diffusion model were used to generate the predicted cumulative probability of a response by that quantile RT. Subtracting the cumulative probabilities for each successive quantile from the next higher quantile gives the proportion of responses between adjacent quantiles. For the chi-square computation, these are the expected values to be compared to the observed proportions of responses between the quantiles (i.e., the proportions between 0, 0.1, 0.3, 0.5, 0.7, 0.9, and 1.0, which are 0.1, 0.2, 0.2, 0.2, 0.2, and 0.1) multiplied by the number of observations. Summing over (Observed–Expected)^2/Expected for all conditions gives a single chi-square value to be minimized. When there were too few observations (e.g., less than 5) for the extreme low error conditions for some of the subjects to form quantiles, a single chi-square value based on the response proportion alone was added to the overall chi-square value.

Results

All results are reported as mean (*SD*) unless otherwise stated. A stable blood glucose plateau was achieved during both study conditions. The mean (*SD*) blood glucose concentration during the euglycemia condition was 4.58 mmol/L (0.18); during the hypoglycemia condition, it was 2.57 mmol/L (0.14).

Symptoms and Digit Symbol Performance

Scores from the hypoglycemia symptom questionnaire were significantly higher during hypoglycemia for autonomic, $p = .004$, $\eta^2 = .515$, neuroglycopenic, $p = .001$, $\eta^2 = .584$, and malaise symptoms, $p < 0.001$, $\eta^2 = .706$, compared with scores obtained during euglycemia. The mean score of the Digit Symbol Substitution test deteriorated from 99.4 (19.4) during euglycemia to 91.7 (21.7) during hypoglycemia, $p = .009$, $\eta^2 = .451$. These findings establish that the hypoglycemic intervention had the anticipated effects as demonstrated in similar hypoglycemic clamp studies.

Diffusion Model

Descriptive statistics. Responses from the first block of each session, short and long outlier RTs in all blocks, and the first response in each block were eliminated from data analyses. RT cutoffs used were a lower cutoff of 250 ms and an upper cutoff of 3,000 ms. Summaries of the basic data are shown in Figure 2. The top panels show the proportion of "large" responses as a function of the eight conditions (eight groups of numbers of asterisks) for the experimental and control conditions. The bottom panels show mean RT for "large" and "small" responses as a function of the number of asterisks for the two conditions. Note that mean RTs for the two extreme error conditions are not plotted because some subjects had zero error responses in those conditions. If a mean was computed with those subjects eliminated, the mean might be biased toward faster and less accurate subject means. As the figures show, the probability of a "large" response varies across the eight conditions from near 1 for stimuli with large numbers of asterisks to near 0 for stimuli with small numbers of asterisks. RT becomes longer for the conditions with intermediate numbers of asterisks.

We computed mean accuracy and mean correct RT for each subject over the eight conditions and performed paired *t* tests to determine whether accuracy and mean correct RT differed between the experimental and control conditions. For accuracy, there was a significant difference, $t(13) = 6.14$, $p < .05$, and means were 0.815 for the hypoglycemia condition and 0.858 for the control condition. For mean correct RT, the difference was large, 716 ms for the hypoglycemia condition and 674 ms for the control condition, but the difference only tended toward significance, $t(13) = 1.60$, $p = .07$.

Diffusion model fits. The diffusion model was fit to the data from each subject for each session. To display the fits, we computed the average over subjects for the quantile RTs and the response proportions for the data and, for the model, we generated predictions from the parameter values averaged over subjects.

We use quantile probability functions to display the quality of the fit of the model to the data, and these are shown in Figure 3. For each plot, the 0.1, 0.3, 0.5 (median), 0.7, and 0.9 quantiles of

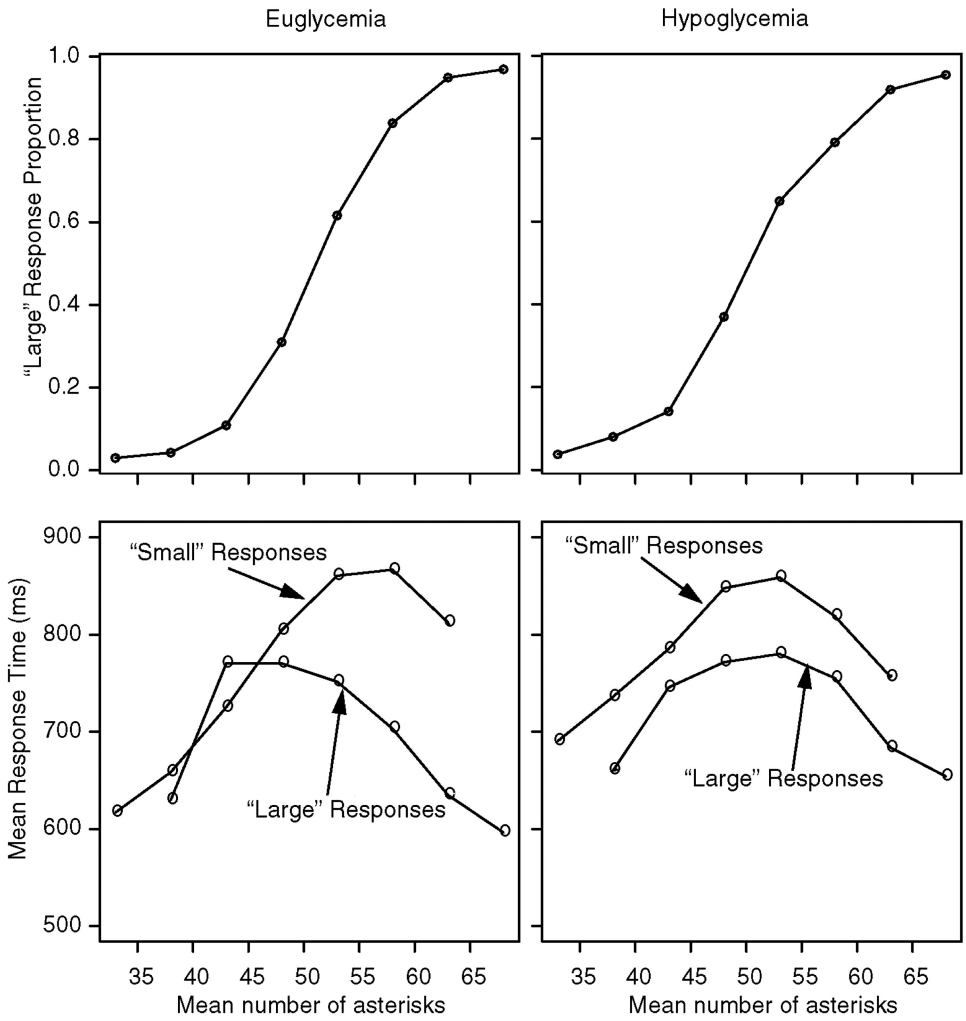

Figure 2. Accuracy and mean response time (RT) as a function of condition.

the RT distribution for each of the eight experimental conditions are plotted as a function of response proportion. The xs are the data points and the os and the lines are the best fitting functions predicted from the best fitting average parameter values from the diffusion model. As noted above, there were too few error responses for a number of the subjects to form error RT quantiles for most of the extreme conditions. Therefore, in the plots, we present a single median RT for the extreme error conditions, which in some cases is based on the responses from most but not all of the subjects.

Figure 3 shows that RT becomes longer for the conditions with intermediate numbers of asterisks, with most of the slowing coming from skewing of the RT distributions (especially from the 0.9 quantile RTs). The advantage of quantile probability functions over other ways of displaying the data is that they contain information about all the data from the experiment: the probabilities of correct and error responses and the shapes of the RT distributions for both correct and error responses.

The number of degrees of freedom are calculated as follows: for a total of k experimental conditions and a model with m parameters, the degrees of freedom, df, are $k\,(12 - 1) - m$, where 12 comes from the number of bins between and outside the RT quantiles for correct and error responses for a single condition (minus 1 because the total probability mass must be 1, which reduces the number of degrees of freedom by 1). There were eight conditions in the experiment, so $df = 76$ (88 – 12, with 12 parameters), and the critical value of chi square was 102.0. The chi-square values in Table 1 show that the average over subjects was not significant for the control condition and was a little larger than significant for the hypoglycemia condition (11 of 14 chi-square values were less than 115). The quality of these fits is quite good; often the average chi-square value is 1.5 to 2 times the critical value (Ratcliff, Thapar, Gomez, & McKoon, 2004).

The parameter values are shown in Table 1. The parameter values were estimated for each individual subject and were also estimated by fitting the average data, that is, the response proportions and RT quantiles averaged over subjects. These two ways of producing parameter estimates do not differ from each other. The only significant difference among model parameters as a function of the experimental manipulation is a reduction of mean drift rate

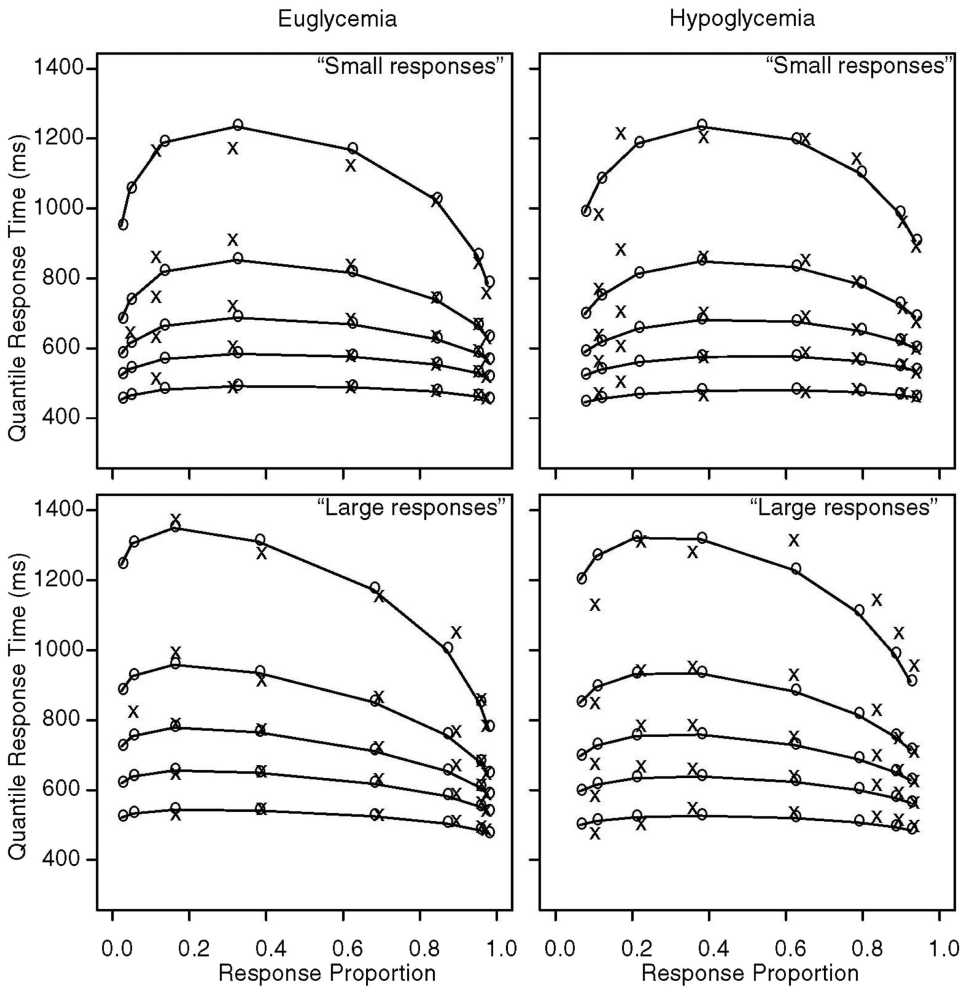

Figure 3. Quantile probability functions for "large" and "small" responses for the two sessions (euglycemia or hypoglycemia). The quantile response times (RTs) in order from the bottom to the top are the 0.1, 0.3, 0.5, 0.7, and 0.9 quantiles in each vertical line of xs. The xs are the data and the os are the predicted quantile RTs from the diffusion model, joined with lines. The vertical columns of xs for each of the eight conditions (dot groups for 31–35, 36–40, 41–45, 46–50, 51–55, 56–60, 61–65, and 66–70 asterisks) are the five quantile RTs and the horizontal position is the response proportion corresponding to that condition. Note that extreme error quantiles could not be computed because there were too few errors (<5) for some subjects for some of the conditions and so these cannot be shown.

from 0.290 to 0.211, $t(13) = 4.10$, $p < .05$. All other model parameters are not significantly different by t tests (as can also be seen from the differences and standard deviations across subjects in Table 1).

Discussion

Hypoglycemia has been demonstrated previously to have a slowing effect on RTs. RT tests, however, use multiple cognitive and noncognitive processes. Until now, we have not be able to ascertain whether the effect of hypoglycemia on RT was a consequence of its effects on all, some, or only one of these cognitive or noncognitive abilities. The present study is the first to use a validated sequential sampling model (diffusion model), which has been applied successfully to other domains, to dissect these effects further. The results of the present study show a powerful dissociation in terms of the diffusion model analysis. The model shows clearly that hypoglycemia reduces drift rates by 0.08 of 0.29 (with an even larger effect on the most accuracy conditions; the mean of v_1 and v_2 is reduced from 0.39 to 0.27). This indicates that hypoglycemia affects central processing and not the quantity of evidence required to make a decision (boundary separation, a) or peripheral and motor processes (nondecision component, T_{er}). This numerosity task was chosen because it is a reasonable control task in that there are no perceptual limitations (such as brief presentation time), no memory limitations as there might be in a memory task, and no limitations dependent on language knowledge. Drift rate in this task represents the estimate of numerosity of the stimulus derived from the array of asterisks. The variability in this estimate comes from the random arrangement of asterisks in the array. As far as we are aware, this is the first study to dissect

Table 1
Parameter Values

Condition	Statistic	a	T_{er}(s)	η	s_z	v_1	v_2	v_3	v_4	p_o	s_t(s)	v_c	z	χ^2
Euglycemia	Fit to mean data	0.141	0.429	.154	0.051	0.423	0.348	0.217	0.078	0.000	0.173	0.039	0.061	
	Average across subjects	0.146	0.431	.156	0.065	0.460	0.379	0.234	0.085	0.001	0.170	0.039	0.064	80
	SD across subjects	0.046	0.060	.070	0.037	0.122	0.095	0.056	0.027	0.002	0.028	0.036	0.019	20
Hypoglycemia	Fit to mean data	0.137	0.430	.119	0.064	0.296	0.236	0.151	0.058	0.019	0.192	0.021	0.060	
	Average across subjects	0.148	0.413	.137	0.073	0.334	0.270	0.174	0.068	0.004	0.176	0.025	0.065	117
	SD across subjects	0.040	0.045	.065	0.032	0.098	0.074	0.061	0.025	0.007	0.026	0.040	0.016	64

Note. The parameters of the model are a = boundary separation; z = the starting point; T_{er} = duration of nondecision components of processing; h = standard deviation in drift across trials; s_z = range of the distribution of starting point (z) across trials; v_1–v_4 = drift rates for the groupings shown in Figure 1; p_o = proportion of contaminants; v_c = drift criterion (a value added to drift rates for "small" responses and subtracted from drift rates for "large" responses); s_t = range of the distribution of nondecision times across trials. χ^2 is the goodness of fit index.

the effects of hypoglycemia in this way. The data now afford the opportunity to compare and contrast, precisely, the cerebral effects of hypoglycemia and other factors.

Acute hypoglycemia is a common side effect in people with insulin-treated diabetes, associated with the nonphysiological doses of insulin that are used in insulin regimens, which often lead to a mismatch between blood glucose and plasma insulin concentrations. The frequency of hypoglycemia has been examined most extensively in people with Type 1 diabetes, in whom mild (self-treated) hypoglycemia occurs on average around twice weekly (Pedersen-Bjergaard, Pramming, & Thorsteinsson, 2003; Pramming, Thorsteinsson, Bendtson, & Binder, 1991). These episodes of acute hypoglycemia lead to an impairment of mental performance and thus have important implications for work performance and the ability to carry out everyday tasks such as driving. However, tasks such as driving require the integration of numerous cognitive functions, including psychomotor, information processing, attention, and others. Hence, the precise neurobiological and cognitive basis of the decrement observed during testing has remained poorly understood. As outlined in the introduction, previous research has more crudely indicated that visual and auditory processing showed decrements during hypoglycemia and that peripheral nerve conduction was not affected (McCrimmon et al., 1996, 1997; Strachan et al., 2001). However, the dissection of specific decision-making parameters that were studied here was not possible.

The results of the present study were obtained in healthy nondiabetic volunteers. Whether similar results would be found in those with Type 1 or Type 2 diabetes remains unknown and speculative at present. Whether diabetes per se influences cognitive performance during hypoglycemia has been addressed by measuring cognitive function before, during, and after acute insulin-induced hypoglycemia (arterialized blood glucose 32–36 mg/dl [1.8–2.0 mmol/L]) in 10 men with Type 1 diabetes and in 12 nondiabetic men, matched for age and baseline performance on a variety of cognitive tests (Wirsen, Tollroth, Lindgren, & Agardh, 1992). At euglycemia, no between-groups differences in cognitive performance were apparent; during hypoglycemia, cognitive performance deteriorated significantly in both groups. However, during hypoglycemia, a greater degree of cognitive impairment occurred in those with Type 1 diabetes, suggesting that diabetes confers greater susceptibility to neuroglycopenia. This could represent a "diabetic encephalopathy," developing as a consequence either of repeated exposure to severe hypoglycemia or from the effects of chronic hyperglycemia (Dejgaard et al., 1991; Wirsen et al., 1992). However, cognitive function at baseline did not differ between the two groups, and the diabetic subjects had higher blood glucose concentrations before the induction of hypoglycemia, necessitating a greater reduction in blood glucose to achieve equivalent hypoglycemia. This may have influenced the magnitude of cognitive impairment. In two other studies, no differences between diabetic and nondiabetic subjects were noted in cognitive performance during acute hypoglycemia (Herold, Polonsky, Cohen, Levy, & Douglas, 1985; Widom & Simonson, 1990), and in a further study of diabetic and nondiabetic subjects (Ferguson et al., 2003), differences in cognitive performance between the groups were observed at baseline, thus precluding interpretation of the effects of diabetes on responses during hypoglycemia. Studies from our center in Edinburgh that have examined specific cognitive domains have also revealed similar effects of hypoglycemia in those with and without Type 1 diabetes in visual information processing (Ewing, Deary, McCrimmon, Strachan, & Frier, 1998; McCrimmon et al., 1996), auditory information processing (McCrimmon et al., 1997; Strachan, Ewing, Frier, McCrimmon, & Deary, 2003), attention (McAulay et al., 2001, 2005), and various aspects of memory function (Sommerfield et al., 2003a, 2003b).

Hypoglycemia was previously, speculatively, felt to lead to a temporary aging effect on mental functions; however, the results in the dissociation of model parameters in the present study contrasts with the effects of aging on processing in this task. Ratcliff (2008) and Ratcliff, Thapar and McKoon (2001, 2006) observed that the increase in RT observed in older adults compared with college students was the result of the older participants setting wider boundaries (boundary separation) and taking longer on the nondecision component. No effect was observed on drift rate. Thus, older adults make decisions more slowly and avoid errors. Similar results to the present study were observed by Ratcliff and Van Dongen (2009), who demonstrated that sleep deprivation affected drift rate to about the same degree as hypoglycemia, but also had a small effect on boundary separation. Thus, hypoglycemia and sleep deprivation appear to affect the ability to effectively extract information from stimuli. This, therefore, raises the possibility of a similar effect on neurobiological foundations.

Sleep deprivation is hypothesized to specifically affect cognitive processing in the prefrontal cortex, thereby affecting higher order cognitive functions (Harrison, Horne, & Rothwell, 2000). Hypoglycemia also appears to affect the frontal cortex, with increased blood flow to this region observed during hypoglycemia (MacLeod et al., 1994).

Strengths of the present study include the use of a powerful intervention in a within-subjects design. The task itself has a number of advantages for the beginning of an investigation. First, it has no perceptual or memory demands; the array is presented until the subject responds. In this sense, it provides a useful baseline for other more cognitive or perceptual tasks. Second, by varying the number of asterisks, performance varies from near ceiling (100% accurate) to near floor (50% accurate). Third, the task has been successfully modeled in a number of domains such as in studies examining the effects of development, aging, sleep deprivation, and IQ on performance. It is a limitation of the present study, however, that only young, above-average IQ participants were studied.

In summary, the present study is the first to locate the precise processing deficit that is associated with hypoglycemia. This new information can lead in at least two directions, which are basic and applied. First, further work should bring together knowledge of the precise neurobiological effects of hypoglycemia to link it with what we have now found to be the precise cognitive-processing effects. This can help reveal the neurobiology of thought processes at a mechanistic level that is rarely achieved. Second, understanding the cognitive-processing parameters affected by hypoglycemia and other central nervous system insults can lead to rational strategies for the amelioration of these effects.

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