Visual information processing during controlled hypoglycaemia in humans

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Summary
A general impairment of cognitive performance occurs during acute insulin-induced hypoglycaemia, but little objective evidence is available for disruption of more specific cognitive processes. The effect of controlled hypoglycaemia on the early stages of visual information processing and contrast sensitivity was examined in a homogeneous group of 20 non-diabetic human subjects. Hypoglycaemia caused a significant disruption in general cognitive performance as assessed by a digit symbol task (P < 0.001) and the trail making B task (P < 0.05). Hypoglycaemia also produced a highly significant deterioration in performance on all of the visual information processing tasks, namely inspection time (IT) (P = 0.01), visual change detection (VCD) (P < 0.005) and visual movement detection (VMD) (P < 0.005). A significant deterioration in contrast sensitivity was observed during hypoglycaemia (P < 0.005). In contrast, no significant effect of hypoglycaemia was demonstrated on standard clinical measures of visual acuity or stereoscopic vision. Thus, although hypoglycaemia caused no detectable deterioration in visual acuity as measured by Snellen-type tests, a marked deterioration occurred in the speed of visual information processing and in contrast sensitivity. As many decisions are made under conditions of limited perceptual time and low visual contrast (e.g. when driving), the disruptive effect of moderate insulin-induced hypoglycaemia on visual perception will have important practical implications in diabetic humans exposed to this metabolic stress. The present results are congruent with other evidence which shows that the early stages of visual information processing are susceptible to deterioration by general cerebral insults.

Keywords: hypoglycaemia; cognition; visual perception; visual contrast sensitivity; visual acuity

Abbreviations: IT = inspection time; LED = light-emitting diodes; VCD = visual change detection; VMD = visual movement detection

Introduction
Cognitive effects of hypoglycaemia
The human brain is almost entirely dependent on glucose as its energy source and, because of this, significant neuroglycopenia will cause an impairment of brain functioning in humans. This has been demonstrated and quantified in studies using a variety of neuropsychological (Holmes et al., 1983, 1984, 1986; Pramming et al., 1986; Heller et al., 1987; Hoffman et al., 1989; Stevens et al., 1989; Blackman et al., 1990; Widom and Simonson 1990; Mitrakou et al., 1991; Cox et al., 1993a; Gonder-Frederick et al., 1994; Mellman et al., 1994) and neurophysiological tests (Pramming et al., 1988; Tamburrano et al., 1988; Blackman et al., 1990; Jones et al., 1990; Talaro et al., 1990; Ziegler et al., 1991). Tasks which primarily involve higher cognitive processes are thought to be more sensitive to neuroglycopenia than motor tasks (Cox et al., 1993a). Moreover, tasks that involve rapid responses and those which are more cognitively complex and attention demanding tend to show substantial impairment during neuroglycopenia, whereas ability on simple motor and cognitive tasks such as finger-tapping, digit span and simple reaction times are relatively well preserved (Deary, 1993).

The pattern of cognitive dysfunction that occurs during neuroglycopenia is of practical and theoretical interest but has remained largely uninvestigated. Most studies of cognitive dysfunction during acute insulin-induced hypoglycaemia have employed measures of general cognitive performance. A problem with this approach lies in our limited knowledge of the brain processes involved in most psychometric tests (Anastasi, 1988). The fundamental information processing
functions affected by hypoglycaemia therefore remain obscure because most standard tests cannot be reduced reliably to a specific set of psychological processes. In addition, it is not clear to what extent a significant disruption in general cognitive performance tests provides a useful index of abilities that are important in everyday cognitive functioning (Anastasi, 1988). Thus, very little detailed information is available on the effects of controlled hypoglycaemia upon specific information processing abilities.

**Hypoglycaemia and vision**

Acute controlled hypoglycaemia does have an effect upon the eye with documented changes in intra-ocular pressure (Frier et al., 1987) and anterior chamber dimensions (Hepburn et al., 1993) but it is not known whether these physical changes translate into clinically relevant abnormalities of vision. Blurring of vision and diplopia are recognized features of acute hypoglycaemia (Hepburn, 1993). When symptom profiles reported during acute insulin-induced hypoglycaemia are analysed, blurring of vision clusters together with the neuroglycopenic symptoms of hypoglycaemia (Hepburn et al., 1991). Corrected visual acuity does not appear to deteriorate during insulin-induced hypoglycaemia (Harrad et al., 1985), nor is there evidence of a significant change in colour vision (Hardy et al., 1995). These results are inconclusive and afford data of limited practical relevance because real-world visual perception involves making decisions about transitory and low contrast stimuli. An important example of such a task is driving, and the deleterious effects of hypoglycaemia on driving ability have been found using a driving simulator (Cox et al., 1993b).

Inspection time (Vickers et al., 1972), and VCD and VMD (Philips, 1974), are psychophysical measures of the efficiency of the early stages of visual information processing for high-contrast stimuli. There is now a considerable body of research in which the early stages of visual information processing, involving the extraction of visual information from sensory stores and its passage to decision-making processes, has been examined. Deficits in such 'iconic' processing have been found in pre-senile Alzheimer's disease (Deary et al., 1991), multiple sclerosis (Kužala et al., 1994), alcoholism (Wilson et al., 1988), head injury (Mattson et al., 1994), following recovery from general anaesthetic (Chittleborough et al., 1992) and in major behavioural disorders such as schizophrenia and mania (Green et al., 1994). Mental processing speed can also be affected by various pharmacological agents such as scopolamine (Brandeis et al., 1992), anti-epileptics (Gillham et al., 1988), noradrenergics (Halliday et al., 1994), dopaminergics (Halliday et al., 1987) and anaesthetic agents (Chittleborough et al., 1992). Inspection time is known to deteriorate with age (Nettelbeck, 1987), and ability on the inspection time task correlates with psychometric intelligence (Nettelbeck, 1987), and perhaps more specifically with fluid-type intelligence tasks (Deary et al., 1991). This suggests that mental processing speed is an important aspect of general mental ability, and also that it is sensitive to mild cognitive impairment.

Contrast sensitivity provides a more subtle measure of speed-independent visual function (Di Leo et al., 1992) than standard acuity tasks, and is more relevant to everyday human visual perception. Contrast sensitivity provides a measure of the amount of contrast required to detect a visual target. Subclinical visual dysfunction is more likely to be detected by degrading the stimulus (visual target) intensity when more demanding visual assessment is used (Di Leo et al., 1992).

The aim of the present study was, therefore, to examine two important aspects of visual perception during controlled hypoglycaemia, namely speed of iconic processing and contrast sensitivity. Standard tests of general cognitive performance gave a measure of the degree of general cognitive disruption during hypoglycaemia. Simultaneous standard measurements of visual acuity were recorded.

**Methods**

**Subjects**

Twenty (18 male, two female) healthy, non-diabetic human subjects were studied. All subjects had a visual acuity (measured by a Snellen chart) of 6/6 or better. The mean age of the subjects was 26 years (range 23–30) and they had a mean body mass index of 23 kg m⁻² (range 19–26). All of the subjects had above average intellectual ability as assessed by the National Adult Reading Test and the Alice Heim 4 Test (standard tests of general intellectual ability). None of the subjects had any previous medical history or a family history of diabetes, and none were taking any regular medication. Subjects were recruited by advertisement and were not paid for their participation in this study. Each subject was informed that they would be required to attend the department on three separate occasions. On two of these occasions they would undergo the experimental procedure during which they would either be kept at euglycaemia or rendered hypoglycaemic. Subjects were made aware that they would undergo both study conditions but would not be informed as to which condition was being performed on each study day. The study was approved by the local medical ethics advisory committee, and written consent was obtained from all subjects.

**Experimental procedure**

The subjects were studied on three separate occasions, each at least 2 weeks apart. The initial visit was to familiarize the subjects with the tests that would be used during the experimental condition. During familiarization subjects completed all of the psychometric tests, the order and duration of which were the same as that of the experimental condition. Familiarization was used to help minimize any practice
Fig. 1 This shows the study design. Each subject completed both Studies 1 and 2, which were arranged in a counterbalanced manner. I = insulin; G = glucose; SQ = hypoglycaemia symptom questionnaire, CF = tests of general cognitive function, VA = measures of visual acuity, IP = information processing tasks.

effects that might occur. The results from this session for each individual subject were discarded.

In the two subsequent visits to the laboratory, subjects underwent a glucose clamp procedure as follows. Following a light breakfast at 07.00, subjects were asked to attend the department at midday, and a Teflon cannula was inserted into an antecubital vein in the non-dominant arm under local anaesthetic (lignocaine 1%). This was used to infuse human soluble insulin (Humulin S, Eli Lilly, Indianapolis, Ind., USA) and a variable infusion of 10% dextrose. A second cannula was inserted in a retrograde direction into a vein on the back of the hand. The cannulae were flushed regularly with heparinized 0.9% saline. The hand was placed in a heated Plexiglas box (60°C) to arterialize venous blood. A modified hyperinsulinaemic glucose clamp technique (De Fronzo et al., 1979) was used to maintain the blood glucose at predetermined levels. Insulin was infused at a constant rate of 60 mU m$^{-2}$ min$^{-1}$ using an IMED Gemini PCI pump; the rate of glucose infusion was adjusted according to the blood glucose concentration measured at the bed-side (Yellow Springs Instrument 2300 Stat, Yellow Springs, Ohio, USA). Glucose was infused using an IVAC Site Saver pump. Arterialized venous blood samples were initially obtained at 3 min intervals, then at 5 min intervals once a stable blood glucose concentration had been achieved.

Each subject underwent two laboratory sessions (Fig. 1). On each occasion the arterialized whole blood glucose concentration was initially stabilized at 4.5 mmol l$^{-1}$ (baseline phase) for 1 h. In one study session hypoglycaemia (2.5 mmol l$^{-1}$) was then induced and maintained for 1 h and in the other the blood glucose concentration was maintained throughout at 4.5 mmol l$^{-1}$ (euglycaemia). An interval of 20 min was interposed between baseline and the hypoglycaemic or euglycaemic phases to allow achievement of the new glycaemic level. Subjects were not informed of their blood glucose level at any time during the laboratory sessions.

During each phase of the study (each baseline, euglycaemia and hypoglycaemia) the subjects underwent tests of (i) visual information processing, (ii) general cognitive function and (iii) visual acuity and contrast sensitivity, and a hypoglycaemia symptom questionnaire was administered (Fig. 1). During each study phase the blood glucose was stabilized for 10 min at the target glycaemic level before the assessment of information processing. The subjects underwent the experimental conditions in a counterbalanced fashion (i.e. half the subjects underwent hypoglycaemia first followed by the euglycaemic control condition, and half the reverse).

Symptom questionnaire
A symptom questionnaire was completed by the subject at each phase [baseline(s), euglycaemia and hypoglycaemia] of the study. Hypoglycaemia symptoms were classified as autonomic (palpitations, sweating, shaking and hunger), neuroglycopenic (confusion, drowsiness, odd behaviour, speech difficulty and inco-ordination) or non-specific (nausea and headache) (Edinburgh Hypoglycaemia Scale; Deary et al., 1993a). Each symptom was graded on a scale of 1–7 (1 = not present; 7 = very intense). The total for each sub-group of hypoglycaemic symptoms was calculated.

Psychometric tests of general cognitive function
Two tests of general cognitive performance, known to be affected by moderate hypoglycaemia (Hoffman et al., 1989; Stevens et al., 1989; Kerr et al., 1991; Deary 1993), were included in the test battery. Both the digit symbol task and the trail making test B have a closer relationship to 'fluid' than to 'crystallized' (vocabulary-oriented) cognitive ability. These tests were included to provide an indication of general brain functioning in our study group during controlled hypoglycaemia.
Digit symbol task. This is a performance sub-test of the Wechsler Adult Intelligence Scale Revised (Wechsler and Stone, 1981). Nine digits are represented by nine different symbols, and subjects are required to write down the appropriate symbol for each in a given array of numbers over a fixed time period.

Trail making test B. This is a divided attention task from the Halsted-Reitan Neuropsychological Battery (Reitan and Davison, 1974). The subject has to connect correctly an alternating series of numbers (1–13) and letters (A–L) in their respective orders as quickly as possible.

Visual acuity, stereoscopic vision and contrast sensitivity tests
Visual acuity was examined using a series of standard clinical tests. An assessment of static contrast sensitivity was also taken to provide evidence for any subtle changes in peripheral vision.

Visual acuity. Distance vision for each eye was assessed using a standard Snellen chart positioned 6 m from the subject. Visual near-point acuity (binocular) and reading acuity (monocular) were assessed using a Royal Air Force Metre (Clement Clarke International Ltd, Essex, UK).

Stereoscopic vision. The ability of subjects to judge the relative distances of objects by means of binocular vision, was assessed using Stereo-test Circles (Stereo-Optical Company Limited, Chicago, Ill., USA).

Contrast sensitivity. Static contrast sensitivity was measured using the Cambridge Low Contrast Gratings (Clement Clarke International Ltd). In each item of this test the subject views two adjacent pages of a booklet positioned at a distance of 6 m, only one page of which contains horizontal lines (a grating). Each ‘line’ in the grating is composed of small black dots on a white background separated from each other by equal distances. Viewed from a distance the subjective impression is of grey lines with white spaces between them. The opposite page of the booklet has the same number of dots evenly dispersed (i.e. not as lines). Here the subjective impression, when viewed from 6 m, is of a blank page. The subject’s task is to identify the page that contains the lines (the grating). The task is very difficult when the lines are composed of few, widely spaced black dots, where the impression is of very faint grey lines on the page. Therefore, by varying the number of dots, and the distance between them, a series of gratings are produced with different levels of contrast. The gratings have 11 levels of difficulty, all with the same spatial frequency of 4 cycles per degree. In this study, the subject was presented with a block of 50 presentations (10 trials of each of the five most difficult gratings; contrast was 0.37, 0.27, 0.19, 0.14 and <0.14%) in random order, and the total number correct was used as the score. The lighting in the room was adjusted so that the luminance of the non-grating plate in the demonstration pair (contrast = 13%) was 100 cd m−2. This was kept constant for all visual assessments.

Visual information processing tests
The test battery so far has involved an assessment of vision and of cognitive function according to standard clinical measures. The next section of our test battery provided a more detailed examination of visual information processing, the tests of which are described below.

Inspection time
The visual inspection time test used in this study was a simple two-choice discrimination task. It is a measure of the speed of the early stages of visual information processing (Vickers et al., 1972). The object of the test is to determine the stimulus duration required by a subject in order to reach a given level of correct responding in a very simple discrimination task. In the IT task used here the subject is required to indicate which of two parallel vertical lines, of markedly different lengths, the longer. During the test the experimenter varies the stimulus duration, with briefer durations being more difficult. Only the correctness of responses at different stimulus durations is examined. Response speed is not recorded and the subject is instructed and encouraged to respond at leisure to achieve maximum accuracy. The IT stimuli and backward masks have been described in detail by Deary et al. (1993b). A mask is designed to prevent the further processing of information from a briefly presented stimulus. The stimulus presentation unit was a box which carried a 16×16 array of circular red light-emitting diodes (LEDs). This display area (61 mm2) was built up from four Siemens PD 1165 display modules, each of which had an 8×8 grid of LEDs of 0.11 inch diameter on 0.15 inch centres. All stimuli were created with these LEDs. The cue which preceded the IT stimulus, was an inverted U-shape; it was 16 mm across and 14 mm high and shared the same cross-bar as the IT stimulus. In the IT stimulus the long line (29 mm) and short line (14 mm) were joined at the top by a crossbar (16 mm). Thus the vertical lines were aligned at the top. The backward mask was formed by lines 40 mm long and 10 mm wide, i.e. the masking lines were wider and longer that the stimulus lines and completely covered them (Fig. 2). The stimulus presentation unit was controlled by a BBC computer which also collated the response data.

Each subject carried out all the IT test sessions under the same lighting conditions and in the same room to ensure that stimulus contrast remained stable. A 300 ms warning cue was presented at the start of each trial. The IT stimulus was presented 1000 ms after onset of the cue for the appropriate duration (range 1–400 ms). The backward mask was presented...
immediately after IT stimulus offset to prevent further processing of the stimulus. The duration of the mask was adjusted to compensate for the variable stimulus duration so that stimulus plus mask duration remained at 600 ms. After the mask was turned off, the subject was required to respond by indicating which stimulus line was the longer. Responses were made on two buttons linked to the stimulus presentation unit. There was no feedback as to the correctness of the response. In this study a response from the subject initiated the next trial (i.e. no reaction time was taken and the subject was continually reminded that the emphasis was on accuracy rather than speed of response).

The IT test algorithm measured the stimulus presentation time (in milliseconds) required by each subject to achieve 85% accuracy in responding (50% representing chance responding). Stimulus presentation times were determined according to the PEST (efficient estimate on probability function) adaptive staircase algorithm (Taylor and Creelman, 1967). Starting at a presentation time of 200 ms with a minimum of five trials per step, the first step size was 75 ms. The step size was halved with each reversal and the stopping step size was 1 ms. Most subjects required about 90–130 trials to reach their IT. This algorithm has the advantage of using reliability of response as its stopping criterion and provides a reliable index of visual information intake efficiency (Deary et al., 1991).

**Visual change detection.** This test is based on the work of Phillips (1974) on change detection, as described by Wilson et al. (1988). This test, like IT, assesses the speed of early visual processing. However, in this task the subject must identify the locus of a discrete change in a large array of homogeneous stimuli. Therefore, whereas IT measures perceptual speed for detecting a difference in a stimulus occurring at a specific, predictable location, the VCD task requires the subject to attend to a wider stimulus field, so emphasizing parallel processing. However, like IT, it is the timing (i.e. speed) of the stimulus change that is manipulated and in this task, as with IT, the subject is allowed to respond without any pressure of time.

The stimulus display used for this test consisted of an array of 49 small rectangles on a computer monitor screen to which, after a variable interval, a single (target) rectangle was added. The subject's task was to identify this additional rectangle. The time interval between the onset of the 49-rectangle array and the target can be manipulated by the experimenter; tests with shorter intervals are more difficult. The display was generated by randomly lighting 49 of 100 potential rectangles in a regular 10X10 array upon a computer screen. The overall array size was 185x105 mm; the rectangles each measured 5 mm vertically and 3 mm horizontally, and were non-contiguous. The cue which preceded the stimulus by a fixed interval was a circle located in the centre of the screen. The time intervals employed between the onset of the array and the onset of the target were 14, 28, 42, 56, 70 or 86 ms. A response was made by touching the screen on the relevant rectangle, and the subject was given feedback on each trial. In this test the subject initiated the next presentation and, as with IT, was reminded that accuracy of responding was being measured and not reaction time. Each subject was tested on a random block of 60 presentations: 10 trials of each of the six different stimulus durations were presented at random. A total score of accuracy of responding was obtained.

**Visual movement detection.** (Philips, 1974, Wilson et al., 1988). In this task a subject's efficiency of detecting the movement of a single stimulus in a large array is assessed. The VMD resembles the VCD task in all respects except one: the target rectangle, rather than appearing after the rest of the array, appears with the array and after a variable interval moves to the right or left by a distance identical to its width (i.e. 3 mm). As with the test of visual change detection this test display was generated by randomly lighting 50 rectangles in a potential 10X10 array. The array measured 185x105 mm, and each rectangle measured 5 mm vertically and 3 mm horizontally. After a variable interval one (target) rectangle was deleted and re-displayed 3 mm away horizontally, thus creating the subjective sensation of sudden movement. The subject's task was to point to the rectangle which appeared to move. The cue was the same as that used for the visual change detection task. The interval between the onset of the array and the movement of the target rectangle was 14–86 ms as for the VCD task. The subject responded by touching the computer screen over the rectangle thought to be the target. A random block of 60 presentations (10 trials of six different stimulus durations) was also employed in this test, and the total number of correct responses was obtained and used as the score.

**Statistical analysis**

The results were analysed independently for each measure of visual function, tests of general cognitive function, and information processing tests. A mixed model ANOVA was used with order of session as a ‘between subjects’ factor with two levels (euglycaemia–hypoglycaemia or hypoglycaemia–euglycaemia), and study type as a ‘within subjects’ factor.
Fig. 3. Blood glucose profiles during the two different study conditions: euglycaemia (A) and hypoglycaemia (B). Vertical bars show standard errors.

with two levels (euglycaemia versus hypoglycaemia). Test results at baseline were used as variable covariates in each analysis. Due to a computer fault on a single occasion one of the subjects was unable to complete the assessment of visual change detection and visual movement detection during hypoglycaemia.

Results
The glycaemic plateaus for each experimental condition were achieved precisely with little variation across subjects (Fig. 3). Overall (mean±SD) plasma glucose was 2.60±0.1 mmol l⁻¹ during the hypoglycaemic clamp and 4.98±0.05 mmol l⁻¹ during the euglycaemic clamp. The initial statistical analysis revealed that no significant order effects (asymmetrical transfer effects) had occurred for any of the outcome variables in this study.

Symptoms
There was a significant increase in total autonomic symptom scores \( F(1,18) = 33.31, \ P < 0.001 \) and total neuroglycopenic symptom scores \( F(1,18) = 12.86, \ P < 0.005 \) during the hypoglycaemia condition of the study. Hypoglycaemia-associated non-specific malaise symptom scores showed a tendency to increase though this did not achieve a conventional level of significance \( F(1,18) = 4.25, \)
detect differences in contrast \( F(1,18) = 13.70, P < 0.005 \)
P < 0.005].

Deterioration was observed in the ability of the subjects to
unaffected during moderate hypoglycaemia, a significant
and concurrent deterioration in cognitive performance.

No significant changes were observed in visual acuity, or
visual near-point during hypoglycaemia (Table 1). Visual
acuity, for both eyes tested separately, was not significantly
affected by hypoglycaemia \( F(1,18) = 2.22, P = \text{n.s.}, \)
and \( F(1,18) = 1.08, P = \text{n.s.} \). Visual near point for binocular
vision \( F(1,18) = 0.81, P = \text{n.s.}, \) and reading point, for
both eyes tested separately \( F(1,18) = 0.00, P = \text{n.s.}, \)
and \( F(1,18) = 0.16, P = \text{n.s.} \), showed no significant changes
during hypoglycaemia. Stereoscopic vision was also
unaffected \( F(1,18) = 0.00, P = \text{n.s.} \). Therefore, standard
tests of visual acuity were unaffected during controlled
hypoglycaemia, indicating that no disruption in vision, as
detectable by these tests, had occurred despite a significant
and concurrent deterioration in cognitive performance.

Although visual acuity for highly contrasting symbols was
unaffected during moderate hypoglycaemia, a significant
deterioration was observed in the ability of the subjects to
detect differences in contrast \( F(1,18) = 13.70, P < 0.005 \)
(Fig. 4). This implies that visual dysfunction is demonstrable
when the visual system is stressed by symbols of low visual
contrast (i.e. by degradation of the stimulus).

### Visual acuity and contrast sensitivity

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<th>Baseline</th>
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<tr>
<td></td>
<td>Euglycaemia study</td>
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<tr>
<td>Inspection time</td>
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<tr>
<td>(ms)</td>
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<tr>
<td>(score)</td>
<td></td>
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<td>Contrast sensitivity</td>
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<td>Visual acuity—right</td>
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<td>(cm)</td>
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<td>6/6±2</td>
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<tr>
<td>Near point</td>
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<td>10.97±2.41</td>
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<td>(cm)</td>
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<td>TMT-B (s)</td>
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DST = digit symbol test; TMB-B = trail making test B. Values are means±standard deviation.

### General cognitive function

In the present study scores achieved on the digit symbol task
were significantly lower \( F(1,18) = 69.97, P < 0.001 \),
and times taken to complete the trail making test B were
significantly longer \( F(1,18) = 4.66, P < 0.05 \) during
hypoglycaemia when compared with euglycaemia (Table 1).
This confirms that these standard measures of general
cognitive dysfunction were significantly affected at a blood
glucose of 2.6 mmol l\(^{-1}\).

### Visual information processing

Acute insulin-induced hypoglycaemia caused a significant,
and marked deterioration in visual information processing
ability (Table 1). Visual inspection time for the study group
increased (i.e. the presentation times required to discriminate
between the two arms of the stimulus were longer) during
moderate hypoglycaemia \( F(1,18) = 8.35, P < 0.05 \) (Fig. 4).
Hypoglycaemia resulted in an impaired ability to detect visual
change \( F(1,17) = 13.34, P < 0.005 \) (Fig. 4), and an
impaired ability to detect visual movement \( F(1,17) = 14.19, \)
\( P < 0.005 \) (Fig. 4). These results indicate that moderate
hypoglycaemia significantly disturbs the early stages of visual
information processing both for focused stimuli and for
stimuli presented in a wider visual field.

The group's mean (±SE) total score achieved during
euglycaemia and hypoglycaemia for each stimulus duration
on the VCD and VMD tasks (Fig. 5A and B), and for each
level of difficulty on the contrast sensitivity task (Fig. 5C),
demonstrate a shift to the right in the response curve during
hypoglycaemia; the slope of the curve was not affected.
This finding indicates that hypoglycaemia raises detection
thresholds in each of the visual information processing
tasks (Wilkins et al., 1988). A change in subjects' criterion (their
willingness to report a weak sensation) or neural 'noise'
would be expected to alter the slope of the curve.

### Discussion

The present study has demonstrated that controlled
hypoglycaemia provokes significant changes in visual
Fig. 4 Information processing and contrast sensitivity during both study conditions. The continuous line represents the euglycaemia study day and the dashed line represents the hypoglycaemia study day. Values are shown as mean±standard error.

Fig. 5 Scores achieved at each different level of difficulty on the visual change detection (A), visual movement detection (B) and contrast sensitivity (C) tasks during euglycaemia and hypoglycaemia. Mean±standard error values are shown.
information processing in a homogeneous group of non-diabetic human subjects. The disruption in visual information processing was accompanied by general cognitive dysfunction. Despite these effects, no changes in standard measures of visual acuity were found during moderate hypoglycaemia. However, visual dysfunction was detected when subjects were required to discriminate between images of low visual contrast.

The response curves for the VCD, VMD and contrast sensitivity tasks shown in Fig. 5, provide additional information on the effect of hypoglycaemia on each of these visual information processing tasks. In any forced-choice task it is essential to separate the willingness of an observer to report weak sensations (his criterion) from his ability to detect them (his sensitivity). Characteristically changes in sensitivity affect the horizontal position of a response curve and changes in criterion the steepness of the response curve. This aspect of the contrast sensitivity task has been examined in some detail by Wilkins et al. (1988). Rather than ‘criterion’ change, any flattening of the steepness of the psychometric curves in this study could be interpreted as increased noisiness in decision making. Hypoglycaemia has been shown in this study to disrupt cognitive function. It is therefore important to show that hypoglycaemia per se has not lead to a change in the subjects’ criterion as this would influence our interpretation of the effects of hypoglycaemia on visual information processing. Examination of the graphs of mean score at each level of difficulty on the VCD, VMD and contrast sensitivity tasks at euglycaemia and hypoglycaemia shows clearly that it is the position of the response curve on the horizontal (difficulty) axis which has changed as a result of hypoglycaemia and not its steepness. This means that hypoglycaemia has caused a true change in the subjects sensitivity during each of these visual information processing tasks.

The interpretation of the information processing tasks used in the present study has been derived from experimental psychology and psychophysics. This allows a more detailed parsing of the cognitive dysfunction in hypoglycaemia than would be possible with standard neuropsychological tests. The IT, VCD and VMD tasks are thought to measure the efficiency with which information in iconic (sensory) memory is transferred to discrimination processes in working memory (Deary et al., 1991; Philips, 1974). If the early information processing tasks described do reflect the time taken to make a single observation from the sensory input, then it also seems likely that this measure will function as a basic factor limiting perceptual and cognitive performance in general (Vickers et al., 1986). Consistent with this hypothesis are the correlations between mental processing speed and general mental ability, and the sensitivity of mental processing speed to general cognitive stresses. The present study has clearly demonstrated abnormalities in this important early stage of visual information processing in a homogeneous group of human subjects when the brain is stressed by controlled hypoglycaemia. Hypoglycaemia is also a general cerebral stress and therefore it is possible that the abnormalities in early visual information processing may reflect a more general disruption in information processing. The disruption in this fundamental aspect of cognition may have profound effects on the functioning in everyday life of any human subject who is exposed to hypoglycaemia (e.g. the insulin-dependent diabetic patient).

In the present study the information processing tasks have assessed the ability of each subject to discriminate between stimuli within either a narrow (IT) or a broad (VCD and VMD) attentional field. Both types of test were significantly disrupted by moderate hypoglycaemia. The IT task is a simple two-choice discrimination task with stimuli presented at differing speeds in a fixed location with no distractors, whereas the VCD and VMD tasks incorporate a changing or moving stimulus, respectively, within a broad field of 49 similar images, whilst also changing the stimulus presentation speed. It could be argued therefore, that it is information processing speed per se that is disrupted during moderate hypoglycaemia irrespective of the specificity of the attentional demands, or the complexity, of the task.

The present study has also demonstrated a significant deterioration in contrast sensitivity during moderate hypoglycaemia, but no changes in standard measures of visual acuity. These results indicate that low-contrast test targets (where the image is degraded) reveal visual irregularities that are not shown by high-contrast test targets. Abnormalities in contrast sensitivity have also been documented in Parkinson’s disease (Regan and Maxner, 1987) and multiple sclerosis (Regan et al., 1980). The disruption in contrast sensitivity in these conditions was orientation selective and, as orientation sensitive neurons are only found in the visual cortex, the authors suggested that these abnormalities might be due to a functional abnormality in the striate cortex as opposed to the retina. In the present study there was a general increase in the total score achieved on the contrast sensitivity task on the euglycaemic study day (Fig. 4). This practice effect also suggests the involvement of higher cognitive processing in the contrast sensitivity task. Whilst there are methodological differences preventing direct comparison of the present study with those of Regan and Maxner (1987), it is possible that the contrast sensitivity task may not distinguish between abnormalities at the retina or of higher cognitive processing.

Our results indicate that visual discrimination for standard clinical acuity tests is unaffected by hypoglycaemia despite a concurrent disruption in cognitive performance tasks. This is consistent with a previous study (Harrad et al., 1985). Harrad et al. (1985) did demonstrate abnormalities of colour discrimination (a more sensitive index of macular vision) during hypoglycaemia in a small number of insulin-dependent diabetic and non-diabetic subjects. However, the hypoglycaemia was induced by intravenous bolus injection of insulin and was uncontrolled and often quite profound. Furthermore, the group of insulin-dependent diabetic subjects all had diabetic retinopathy of various degrees. By
contrast, Hardy et al. (1995) examined 10 retinopathic insulin-dependent subjects during controlled hypoglycaemia (2.5 mmol l⁻¹) and found no significant changes in colour discrimination. Hypoglycaemia is a general metabolic stress and it is probable that physiological changes within the retina will influence changes in higher visual pathways and vice versa. In the light of these studies, it is therefore important that any assessment of information processing is conducted using high-contrast stimuli to minimize any subtle changes in visual function at the retinal level.

The results of the present study have important practical and theoretical implications. These results imply that if an examination of visual information processing employs images of high contrast that are produced in a perceptually unspeeded manner then abnormalities of visual processing will not be found during moderate hypoglycaemia. However, if the stimulus is degraded by lowering contrast and/or by shortening its duration then abnormalities of visual processing will be revealed. The important practical implications relate primarily to the insulin-treated diabetic patient for whom real life decisions are often made on the basis of information provided under conditions of low contrast and short perceptual duration. Abnormalities in driving performance during moderate hypoglycaemia have been demonstrated (Cox et al., 1993b) and our findings would suggest that these may stem partially from a more basic disruption in information processing. The present findings may also have implications for the employment of insulin-dependent diabetic subjects in other occupations which rely heavily on decision-making based on visual information (e.g. air-traffic control, commercial pilots or drivers) who may be exposed to intermittent hypoglycaemia of varying severity.

Acknowledgements
The authors wish to thank Carol Wade for her help during the studies. R.J.M. was supported by a Lilly Industries Research Grant.

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Received February 23, 1995. Revised March 12, 1996. Accepted April 1, 1996