*For debates***Cognitive function testing in studies of acute hypoglycaemia: rights and wrongs?****S. A. Amiel**

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The most devastating effect of hypoglycaemia is the effect upon cognitive function. It is the loss of personal control and normal conscious behaviour, as much as the risk of frank coma, that is feared by the patient with drug treated diabetes mellitus and, as we begin to untangle the mechanisms of hypoglycaemia and counterregulation, it is perhaps not surprising that so much discussion and controversy is generated about the most appropriate ways to measure cognitive function in this context. What is surprising is the view, apparently held by many clinical research workers in the field of hypoglycaemia research, is that there is a right (and a wrong) way to test cognition in this arena, and that there should be a consensus on just what tests should be used. There are, or should be, as many cognitive function tests (CFT) as there are cognitive functions and the critical question is not how to test cognitive function in studies in acute hypoglycaemia but what is the best test (or group of tests) to answer a specific question in a specific research design.

What is the test designed to do?

Consider the questions currently demanding answers in the field of insulin-induced hypoglycaemia, particularly as it causes a problem for patients with insulin-treated diabetes. What brain functions are susceptible to hypoglycaemia? Are all brain functions equally susceptible? Does recurrent acute hypoglycaemia acclimatise the whole brain to function better at lower glucose levels in future? Does the glucose level for clinically significant cognitive function vary

according to the age of the patient? His (or her) previous glycaemic experience? The presence of complications? Does recurrent hypoglycaemia cause permanent impairment of brain function? Or is there a central neuropathy, with impaired cognitive function as a result of chronic hyperglycaemia (and therefore preventable by means of intensified insulin therapy with its apparently intrinsic increased risk of recurrent hypoglycaemia)? Are the defects of counterregulation seen in patients with IDDM due to alterations in brain functions? What plasma glucose level is safe for a car driver? An operator of heavy machinery? A steeplejack? A student sitting a critical examination? How soon after hypoglycaemia can any such person resume his/her activity? This investigator believes that these (and other) questions require different studies to achieve answers and the suggestion that any single set of cognitive function tests can be used to answer them all is not tenable.

The tools we have to measure cognitive function were not designed to answer some of the questions we now ask. Most were designed to measure performance in potential disease states or suspected developmental delay in paediatric practice; to test particular areas of brain after structural damage or look for areas of damaged brain; to assess conscious level during some insult or recovery of function thereafter (e.g. anaesthesia) or to establish progression of cerebral development; or cerebral diseases such as dementia. In these circumstances, one session of testing, or sessions repeated at intervals of hours, days, weeks or months is usual. In the study of brain function in acute hypoglycaemia however, we want to apply the same tests repeatedly over hours in order to measure changes in cognitive performance as blood glucose levels fall. Rather than taking a couple of hours to obtain a picture of "cognitive function", we want to make multiple assessments of "cognitive function" within that time frame. It follows that we cannot ex-

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Abbreviations: CFT, Cognitive function tests.

pect to assess all aspects of cognitive performance in this setting. Controversy has arisen over what tests then to use. Some have used single tests, which can clearly only assess one function, as a marker. Others have used batteries of tests, designed to provide a more comprehensive estimate of cognition – but how much more effective three – or even six – tests can be in assessing the complexities of brain function is arguable. The tests that will look for clinically significant cognitive effects of acute hypoglycaemia are unlikely to be the same as the tests that attempt to unravel the central nervous system pathways most affected by changes in glucose supply, which will be different again from the tests appropriate to investigate the potential for recurrent acute hypoglycaemia to cause lasting cognitive damage.

The problems

Whatever test(s) are chosen, some rules and confounders are universal. There is high inter-individual variation [1, 2], although intra-individual variation is less [2]. Performance of most tests of cognitive function will improve with familiarity – a practice effect – and may deteriorate with boredom or irritation [2]. The former means that effects of hypoglycaemia may be underestimated if subjects are not fully practiced – this usually means they should have become familiar with the test paradigms before the day of study and several test runs may be needed on the day, prior to the start of the study, to ensure a stable baseline. Anxiety may be a confounder – if a test requires fine motor co-ordination, for example, the peripheral autonomic responses to hypoglycaemia may interfere with performance, independent of cortical malfunction. This has not been well explored, although infusion of catecholamines alone does not appear to deteriorate performance in at least some of the tests used in studies of acute hypoglycaemia [3]. However, some tests, for example the digit span test of short-term memory, are known to be adversely affected by anxiety [4] and where changes in glucose threshold for impaired performance of a CFT march with changes in glucose threshold for autonomic reactions, there will always be the possibility that the latter has affected the former directly and conclusions about the onset of cortical malfunction may be less secure.

The other generic issue in CFT in studies of acute hypoglycaemia relates to the complexity of the tasks undertaken and the potential areas of brain involved. As a general rule, more complex tasks are more susceptible to hypoglycaemia. In children, attention tasks, digit vigilance, choice reaction time and simple reaction time (in that order) are most susceptible, tests of mental flexibility are more robust and motor skills very resistant to deterioration

in acute hypoglycaemia [5]. In adults, choice reaction time is more sensitive than simple reaction time and choice reaction time and Stroop tests are among the most sensitive of all [6]. Trail and attention tasks are associated with activation of frontal cortex and interconnected brain regions, speed involves subcortical white matter and the different regions may well be different in their response to glucose deprivation.

The critical issue is the point of the investigation. One of the concerns expressed by patients is that recurrent hypoglycaemia may cause chronic or permanent impairment of cognitive performance, perhaps particularly affecting some aspects of memory. Studies of responses to acute hypoglycaemia have been criticised if they do not include some test of memory, but such tests may not be relevant to performance of complex tasks during an acute hypoglycaemic episode, especially if performance is affected by anxiety. Recent data, again in children, suggest that imperfect recall of events during hypoglycaemia may be impaired but recall of pre-existing information may be much less susceptible to impairment during hypoglycaemia [5]. The choice of the test again therefore should be made on the basis of the question being raised.

One test or many?

The question then is which tests are most appropriate to assess the effect of acute hypoglycaemia on cognition: is one test better than many and is one test or set of tests “right” while others are “wrong”? In other words, can we (or should we) obtain a consensus on the best way to test cognition in this type of research? There are strong advocates at each end of the spectrum – supporting either one (or very limited) tests as a sensitive marker for cognitive impairment or a whole battery to try and assess a fuller range of cognitive functions.

There are advantages to single tests as markers of cognitive function (provided the marker test assesses a function that is likely to be important in a clinical setting) and to batteries of tests to assess more aspects of cortical function. Performance on CFTs shows high inter- and some intra-individual variability of batteries of tests even at euglycaemia, although much may be achieved by practice [1]. A battery of tests may be more likely to show deficits because more functions are being tested – provided individual test scores are reported. Summing scores into a single number runs the risk of diluting results of tests that are sensitive to hypoglycaemia with tests that are either resistant to acute hypoglycaemia or irrelevant to acute performance. In the study by Mitrakou and colleagues [6], a battery of 11 tests was applied repeatedly during stepped reduction of blood glucose

concentrations in diabetic adults, and compared against data obtained in euglycaemic control studies. Thresholds were not quoted but inspection of the published raw scores suggests that choice reaction time (threshold probably 3.7 mmol/l) followed by simple reaction time and Stroop tests (threshold probably 3.1 mmol/l) are much more sensitive to hypoglycaemia than Trail A tests and Forward digit span (no change at 2.4 mmol/l), although conversion of all the raw scores to a single Z score only shows an effect of hypoglycaemia at 2.4 mmol/l.

A problem with a test battery is that it takes much longer to administer than single or small numbers of tests. No one has decided a minimum number of tests that constitute a satisfactory test battery – early studies used 12 or more, which takes approximately 45 min to administer [4]. This has two potential problems in studies of acute hypoglycaemia – cognitive performance may change over time at any given glucose level, making identification of thresholds for change more difficult and studies become very long, which may introduce tiredness (with its effects on performance) as a confounding variable. There are data to suggest that adrenergic and symptomatic responses at any given degree of hypoglycaemia take time to manifest [7] (i.e. are not evident immediately upon achieving a particular glucose level) and may remit with time spent at that glucose level [8] – preliminary data suggest that at least some of the most hypoglycaemia-sensitive CFT do show deterioration immediately, which is sustained over time [7, 9], but more work needs to be done in this area.

Examining the mechanisms of hypoglycaemia unawareness

The current debate over the “best” way to test “cognitive function” in studies of acute hypoglycaemia has arisen because of controversy particularly in the area of hypoglycaemia unawareness, where results of different tests have produced different results.

It is now widely accepted that hypoglycaemia unawareness is associated, at least where it has been investigated, by defective endogenous glucose counter-regulatory mechanisms. Most work recently has been done in the situation of intensified insulin therapy and after induced antecedent hypoglycaemia. A lowering of the glucose level triggering centrally mediated autonomic responses in these two settings is now well described by many different groups [10–13], using different research protocols, although it should be noted that it was not until very gradual [11] or controlled stepped [10] hypoglycaemia was used as the stimulus that this phenomenon was described. There is however now little dispute that the central glucose sensors adjust their metabolic capacity in some way to function better at lower glucose levels and hence

not trigger autonomic symptomatic counterregulatory responses until lower glucose levels are obtained. One suggestion is that cerebral endothelial glucose transporters are upregulated after antecedent hypoglycaemia, allowing more glucose to enter brain tissue in subsequent hypoglycaemic episodes [14]. The critical question is whether this is a global effect of brain metabolism and function. If the whole brain can make such adjustments to intensified diabetes therapy or antecedent hypoglycaemia, the downregulation of the glucostat is not of concern. In practice, we can simply advise our patients with impaired counterregulation to depend only on symptoms to alert them to hypoglycaemia – if the glucose level is not low enough to trigger counterregulation it will not be low enough to cause significant impairment of “cognitive function”. However, this does not match reports that patients with hypoglycaemia unawareness are more prone to severe hypoglycaemia [15, 16] and the data in the literature are controversial. Using limited batteries of tests of specific cognitive function tests, several groups describe a delayed onset or diminished magnitude of cognitive dysfunction, associated with delayed and diminished counterregulation, as plasma glucose levels are reduced in healthy volunteers and diabetic patients previously exposed to recurrent or subacute hypoglycaemia and in patients with insulin secreting tumours [17–21]. These groups have argued that the whole human brain can adjust its metabolic capacity (in response to prior hypoglycaemic experience) to function better at lower glucose concentrations. In contrast, using the complex psychomotor test, the 4 choice reaction time, as a functional marker of cortical activity, my group have consistently found the glucose threshold for impaired performance to be unaffected by prior glycaemic experience [22–24]. Thus, in our hands, the glucose level at which the cerebral glucose sensor malfunctions (and triggers counterregulatory responses) falls below that for deterioration in this particular CFT, creating the dangerous situation of impaired cognition (at least one aspect thereof) preceding symptom generation as plasma glucose levels fall (Fig. 1, A). We would not suggest our patients are safe to drive just because they are asymptomatic.

We are not unique in finding defective preservation of cognition in hypoglycaemia adapted or unaware individuals. In one early study, performance on a battery of CFTs during acute hypoglycaemia was found to be worse in hypoglycaemia-experienced diabetic subjects compared with hypoglycaemia-naïve non-diabetic control subjects [3]. This study used an uncontrolled rapid hypoglycaemic challenge and could not look at thresholds but Widom and Simonson [25] later reported the effect of hypoglycaemia on a small battery of individual CFTs according to glycaemic control. There were no statistically significant differences between poorly controlled and

Fig. 1. Effect of antecedent or recurrent hypoglycaemia on protective hierarchy of autonomic, symptomatic and cognitive responses to hypoglycaemia during a progressive glucose fall, using different CFTs. Data from my own group (A) show preservation of the glucose level associated with deteriorated performance on a marker of cognitive function, despite reduction in the glucose levels required to trigger autonomic or symptomatic responses from the hypoglycaemia aware (left) to the hypoglycaemia unaware state (right) [22, 23]. This explains the loss of protection from severe hypoglycaemia experienced by diabetic subjects exposed to recurrent hypoglycaemic episodes. Data from Boyle and Fanelli (B and C) [17, 18] suggest at least some shift in glucose thresholds for cognitive dysfunction (two tests or a battery of several) when thresholds for autonomic and symptomatic responses are altered after antecedent hypoglycaemia in non-diabetic volunteers (B left to right) or after hypoglycaemia avoidance (C right to left). Nevertheless, as the shift in thresholds for autonomic and symptomatic responses is so much greater than that for cognitive impairment even in these studies, the protective window between these and cognitive dysfunction is lost

well-controlled diabetes in glycaemic thresholds for dysfunction in digit span (attention and memory and anxiety level); word recall (short-term memory); perceptual speed (visuo-motor skills) or symbol digit modalities. A trend towards a higher glucose level for deterioration in Trail Making A and B (visual-conceptual and visual spatial skills) in poorly controlled diabetic subjects did not achieve significance (2.3 (> 2.2 to 3.2) non-diabetic vs 2.3 (< 2.2 to 3.2)

well-controlled diabetes vs 2.7 (< 2.2 to 3.2 mmol/l poorly controlled diabetes). This was despite significant lowering of the glucose level triggering counter-regulatory hormone responses in the well-controlled diabetic group (e.g. for adrenaline secretion 3.3 (3.0 to 3.8) vs 2.7 (< 2.2 to 3.3) vs 3.9 (2.6 to 4.4) mmol/l, respectively, $p = 0.005$ well-controlled vs poorly controlled diabetes). Gold and colleagues [26] report that hypoglycaemia unaware patients show greater deterioration on a battery of CFTs during hypoglycaemia than others, and Cryer's group [11] found a small worsening of performance at hypoglycaemia in diabetic subjects tested after one episode of antecedent hypoglycaemia, and, although it could be argued that this was not a sufficiently rigorous protocol of the effects of antecedent hypoglycaemia, the study did detect a significant reduction in adrenaline and pancreatic polypeptide responses. It could be argued that no significant change was found either because of the relatively high inter-individual variability of the glucose thresholds for dysfunction, or because the tests used were relatively insensitive to hypoglycaemia (median glucose level for dysfunction ranging from < 2.2 (i.e. no change noted in study) to 2.8 mmol/l). 4-choice reaction time is more sensitive to hypoglycaemia [6] and we have found it to deteriorate consistently (3.1 ± 0.1 to 2.8 ± 0.1 mmol/l) in poorly controlled hypoglycaemia aware and tightly controlled hypoglycaemia unaware diabetes, in a cross-sectional study [22] and in a longitudinal study in which hypoglycaemia unawareness was reversed

and glucose levels for counterregulatory hormone release were restored from 2.2 ± 0.2 to 3.5 ± 0.1 mmol/l, $p < 0.002$) [23]. Most recently, we have failed to find any effect of poor or improved control in Type 2 (non-insulin-dependent) diabetic patients on thresholds for deterioration of reaction time (3.1 ± 0.1 vs 3.1 ± 0.1 mmol/l), despite shifts in threshold for adrenaline release from 4.4 ± 0.2 to 3.5 ± 0.2 , $p < 0.01$ [24]. Yet during infusion of lactate, the glucose level associated with prolonged reaction time fell from 2.8 ± 0.1 to 2.4 ± 0.1 mmol/l, $p < 0.01$ [28]. One possible explanation for these various findings is that different brain regions respond differently to hypoglycaemia in different situations.

What function tests become differently susceptible to hypoglycaemia in hypoglycaemia unawareness? The latency of the P300 event-related potential has been reported as increasing at 3.0 mmol/l in healthy volunteers, 3.5 mmol/l in people with poorly controlled diabetes but not until a blood glucose of 2.2 mmol/l in intensively treated (and by implication, hypoglycaemia adapted and unaware) diabetic patients [20]. (Latency of the P140, a potential testing sensory processing, is not affected by hypoglycaemia [29]). This lowering of the glucose level was associated with a lowering of the glucose level for adrenaline secretion and symptom generation. This parameter is believed to be a test of information processing but its clinical relevance is uncertain. In one study, prolongation of P300 latency was observed at 4 mmol/l [30] and although this intolerance of hypoglycaemia has not been reproduced in other studies [20, 29], it did lead to the suggestion that this electrophysiological change was a very early response to hypoglycaemia and the hypothesis that changes in cerebral metabolism were necessary to trigger centrally mediated counterregulation. But what is the significance of these changes in brain electrophysiology? In an insulin tolerance test (now not usually used for detecting potentially subtle differences in responses to hypoglycaemia because of its uncontrolled and rapid glucose fall), hypoglycaemia unaware diabetic subjects showed reduced vigilance and evidence of EEG deceleration at remarkably high plasma glucose levels (up to 3.89 mmol/l, and delta waves at 2.4 ± 0.2 vs 2.0 ± 0.1 mmol/l in hypoglycaemia aware subjects) about 20 min before detectable change in cognitive performance [31]. The authors of this study suggested that the early changes in cerebral activity in the hypoglycaemia unaware might be a protective mechanism, aimed at delaying cerebral energy failure, in the hypoglycaemia unaware subjects, and not evidence of delayed onset of important cerebral functions.

The Perugia group were the first to describe restoration, at least in part, of defective counterregulation in diabetic subjects with hypoglycaemia unawareness [32]. In this study, they used a battery of "standard" tests – Trail making B, verbal fluency, the Stroop

Table 1. Glucose thresholds for deterioration of performance in cognitive function tests during acute hypoglycaemia

Test	Blood glucose level (mmol/l)
Four-choice reaction time [22–24]	2.8–3.1
Stroop tests [17, authors unpublished data]	2.9–3.1
Immediate recall [17]	2.5
Late recall [17]	2.5
Finger tapping [7, authors unpublished data]	< 2.2 to 2.4
Z score [6, 17]	2.3

interference test, digit vigilance, Trail making A, verbal memory, forward and backward digit span. Applying this battery takes approximately 20 min. As a result of careful manipulation of glycaemic control, the glucose levels associated with adrenaline release and symptomatic awareness were raised over 3 months from 2.8 ± 0.1 to 3.5 ± 0.1 mmol/l and from 2.3 ± 0.1 to 3.1 ± 0.1 mmol/l respectively, all highly significant changes (Fig. 1, C). The glucose levels for deterioration in a summed Z score are not given, although we are told that this was lower than in healthy volunteers in the initial study (2.4 ± 0.1 vs 2.8 ± 0.1 mmol/l, $p < 0.05$) and not significantly different from the non-diabetic subjects after restoration of hypoglycaemia awareness. There were however no differences between the diabetic subjects' summed Z scores at 3.0 mmol/l before or after restoration of awareness and none of the groups showed significant change in summed Z score from euglycaemic performance until plasma glucose was 2.3 mmol/l.

Are these data reconcilable within a single hypothesis or is it true that one system of testing is right and another wrong? It is true that a single cognitive function test cannot claim to assess global "cognitive function". However, selective use of a single test, known to be sensitive to hypoglycaemia and capable of rapid reproducible application as a marker of cognition, is valid. The 4-choice reaction time fulfills the criteria needed for such a marker, changing at relatively high glucose levels (Table 1) and reflecting a function that is important in the way patients behave during acute hypoglycaemia. Its use in other circumstances of temporary brain insult is well-described [33, 34]. Few would argue that delayed or inaccurate choice reaction time is unlikely to interfere with complex activities of daily life, such as driving and indeed similar defects of slowed and less accurate responses during hypoglycaemia have been observed in driving simulators [35]. While tests of memory and other functions thought to deteriorate in hypoglycaemia may be important, such functions may not be particularly relevant to the safety of an individual patient during a hypoglycaemic attack. The use of multiple tests does allow assessment of more aspects of cognitive performance but it is only when test results are examined individually that many of the data match

the findings of the single marker studies. Some do not – Boyle for example finds preservation of performance on finger tapping and Stroop testing in hypoglycaemia unaware subjects with defective counterregulation [17, 18] and Jones et al. [20] describe delayed onset of increased latency of P300s in similar subjects. These apparent discrepancies are however real differences. Even within studies, different tests show different degrees of adaptation to antecedent hypoglycaemia – in Boyle's studies for example word recall showed no preservation in hypoglycaemia adaptation. There are two possible explanations for such an apparent discrepancy. It is possible that finger tapping, Stroop tests and P300s are affected by anxiety levels – deterioration may depend upon activation of the autonomic responses, as discussed above. An alternative explanation is that the different tests involve different brain areas and connections – some of which are in brain regions that can adapt to antecedent hypoglycaemia, while others cannot. Regional variations in brain glucose metabolism have been clearly documented [36]. But it is the very diversity of protocols used to assess aspects of cognition in acute hypoglycaemia that has allowed us to begin to unravel the mechanisms of cognitive dysfunction in hypoglycaemia. There is no reason to suppose that any of these data are wrong – merely that each is measuring a unique function, any of which may respond differently to recurrent hypoglycaemia.

Conclusions

Can we reach any clinically useful conclusions from the data currently available? In clinical practice, what matters is how much warning patients with diabetes have as blood glucose begins to fall, before there is a change in a cerebral function that makes a difference to their ability to perform effectively. Attempts have been made to try and reconcile perceived discrepancies. For example, in studies where the measure of cognitive function does seem to adapt to preceding glycaemic experience, the change in glucose level associated with malfunction is significantly less than the change in glucose level associated with symptomatic adrenergic responses (Fig. 1) [16–18]. If the two responses, cognitive impairment and subjective awareness are brought closer together as blood glucose falls, a degree of protection against the former is lost (Fig. 1). It is this loss of protection that has clinical relevance and this has been adequately shown with relatively simple protocols and small numbers of CFTs. There is no consensus as to how many CFTs make a minimum appropriate assessment of cognition in studies of acute hypoglycaemia, but we would argue that deterioration in any important cognitive function prior to subjective awareness of hypoglycaemia puts the patient's life at risk and

4-choice reaction time demonstrates this unequivocally. Meanwhile, more extensive tests tell us other things about brain function in acute hypoglycaemia and the compilation of many such tests and studies should lead us closer to an understanding of this most worrying acute complication of insulin therapy. There are many paths to the end goal and probably none of them is better than any other. They are simply different.

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