Cognitive function and information processing in Type 2 diabetes

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Abstract

**Aims** To determine whether uncomplicated Type 2 diabetes is associated with impairment of cognitive function and information processing ability.

**Methods** Thirty-eight participants with uncomplicated Type 2 diabetes and 38 non-diabetic controls were studied. The two groups were comparable for age and premorbid intellectual ability, and did not have other medical disorders likely to affect cognitive function. An extensive battery of tests was administered which assessed different levels and domains of cognitive functions including verbal and visual memory, executive function, general mental ability and efficiency of information processing.

**Results** No significant differences were found between the diabetic and control groups on any measure of cognitive function or information processing. The performance on these tests was not associated with recent glycaemic control (assessed by HbA1c). Duration of diabetes, however, correlated significantly with poorer performance on several measures of verbal memory.

**Conclusions** The results of the present study suggest that some aspect of Type 2 diabetes (as indexed by the estimated duration of the disorder) does relate significantly to cognitive function within the group with diabetes. However, other diabetes-related factors, such as macrovascular disease, hypertension and depression, may contribute more to previously observed cognitive decrements in Type 2 diabetes.


**Keywords** Type 2 diabetes, cognitive function, information processing, glycaemic control, memory

Introduction

The question of cognitive impairment in people with Type 2 (non-insulin-dependent) diabetes has been the subject of much speculation in recent years. Chronic hyperglycaemia is known to have serious adverse effects on many tissues and organs, such as the eyes and kidneys, through vascular damage. Potential long-term effects on the brain have not been proven in humans.

Cognitive function has been examined in people with Type 2 diabetes in a small number of studies with variable results [1–3]. The most consistent finding was that verbal memory appears to be impaired in groups with Type 2 diabetes when compared with non-diabetic controls. Defined as memory tested by stimuli that are spoken or presented in another verbal format, verbal memory was significantly impaired in nine out of 15 studies in which it was tested [1]. Other cognitive domains, including visuospatial memory, attention and concentration, and frontal lobe/executive function, have tended to be less consistently affected. Although some studies have not demonstrated any cognitive impairment in people with...
Type 2 diabetes, no studies have found cognitive performance to be better in people with Type 2 diabetes compared with non-diabetic controls. In addition, impairment in verbal memory was found to be associated with history and duration of Type 2 diabetes in a recent study of the Framingham cohort [4].

Additionally, some studies have used electrophysiological techniques to assess cognitive function, also with variable results. In two studies measuring event-related potentials (ERP) whilst administering an auditory odd-ball paradigm [5,6], latencies of the P300 wave were reported to be slowed in the group with Type 2 diabetes compared with non-diabetic controls, but in a third study no such difference was demonstrated [7]. An additional study administering both an auditory and visual odd-ball paradigm observed only a trend towards impairment in the diabetes cohort [8].

Many of the previously reported studies on Type 2 diabetes and cognitive function have methodological problems [1]. This includes inadequate matching of participants with Type 2 diabetes with controls, particularly with regard to baseline, or premorbid, mental ability, a prerequisite in retrospective case control studies of this type to allow valid comparisons of current mental ability and cognitive function. Factors such as educational achievement and/or occupational status have been used inappropriately as control variables, when this may reflect lack of opportunity rather than lack of ability.

The present study aimed to assess cognitive function and information processing in people with Type 2 diabetes who had had the disorder diagnosed for at least 2 years and were free from other medical conditions. Two types of analysis were conducted. First, they were compared with an appropriately matched control group of non-diabetic participants who were either spouses or siblings of the patients with diabetes to enhance matching for socioeconomic status. Second, we sought factors within the group of people with diabetes that might be correlated with cognitive function.

**Patients and methods**

**Patients**

Thirty-eight participants (16 male and 22 female) with Type 2 diabetes were recruited from the out-patient clinic of the Department of Diabetes, Royal Infirmary of Edinburgh, along with 38 non-diabetic control participants (15 male and 23 female) who were mostly relatives of the participants with diabetes. All participants were recruited after reviewing the case notes of patients with Type 2 diabetes prior to their attendance for a routine review appointment at the out-patient clinic. Potential participants were required to have had Type 2 diabetes for at least 2 years (from time of formal diagnosis) and be aged between 40 and 75 years. With reference to case notes and a structured questionnaire, strict criteria and a conservative level of screening were applied to exclude people with other medical factors that might affect cognitive function. These included any mention of a history of psychiatric disorder, drug or alcohol abuse, neurological conditions such as transient ischaemic attack, cerebrovascular disease or epilepsy, previous serious head injury, any sensory or motor disorder that would preclude psychological testing (including blindness), hypertension necessitating drug treatment, or any other systemic illness likely to result in cognitive impairment. Patients who were taking medication known to have psychoactive effects such as benzodiazepines, β-adrenergic receptor antagonists, steroids, major tranquillisers and antidepressants were also excluded. Participants were required to have a minimum visual acuity of 6/9 (20/30) on the Snellen chart in one eye.

In general, all the individuals with diabetes were free of diabetic complications. However, one participant had sensorimotor neuropathy, two had peripheral neuropathy and two others had background retinopathy. In addition, episodes of hypoglycaemia were very uncommon in the diabetes group (Table 1).

Information regarding age at diagnosis of diabetes, estimated duration of illness and recent glycaemic control (HbA1c, measured by gel electrophoresis) was obtained from individual case notes. For the present study glycaemic control was calculated as the average HbA1c measured at (up to) three visits to the out-patient clinic prior to testing. HbA1c was measured using high performance liquid chromatography (A. Menarini Diagnostics, Firenze, Italy) based on an ion-exchange reverse-phase partition method. The non-diabetic range for HbA1c measured in our laboratory was 5.0–6.5%.

The non-diabetic control participants were also required to meet the same exclusion criteria. Before inclusion a random blood glucose was measured in each control participant to exclude anyone with unsuspected asymptomatic hyperglycaemia.

**Procedure**

Each participant with diabetes performed a blood glucose measurement before and after cognitive assessment to identify any possibility that hypoglycaemia was affecting cognitive performance. All participants completed a demographic questionnaire giving information concerning age, previous education (in years, calculated from the age of 5 to age of leaving full-time education) and general health, as well as alcohol consumption and smoking habit. The participants with diabetes were questioned about preceding episodes of hypoglycaemia. The Hospital Anxiety and Depression Scale (HADS [9]), and a self-report memory questionnaire [10] concerning perceptions of the state of their own memory and other cognitive functions were also completed.

**Assessment battery**

The assessment battery, which took approximately 3 h to complete (with rest pauses), placed special emphasis on verbal memory because of previous observations in people with Type 2 diabetes [1]. The assessments administered are commonly used in neuropsychological research and details of the tests are described elsewhere [11,12].
Cognitive function assessments

The National Adult Reading Test (NART) [13]. This test is based on vocabulary and gives an estimate of the mental ability level of normal subjects, and an estimate of the premorbid mental ability level of individuals who are suffering from cognitive deterioration. It is superior to demographic variables in estimating premorbid mental ability as word reading ability is preserved even in generalized cognitive decline [14–16]. The test involves the participant attempting to pronounce 50 irregular English words. The score is recorded as the number of errors committed.

Raven’s Progressive Matrices (RPM) [17,18]. This assesses abstract reasoning and is considered to be a good measure of ‘fluid’ intelligence and general mental ability. Participants are required to solve a series of multiple-choice problems which become progressively more difficult, the easier items serving as a learning experience for the later more difficult items. Each item contains a pattern problem with one part removed and six to eight answer options, only one of which contains the correct pattern. Participants are given 20 min to complete as many problems as possible from the 60 items presented.

The Wechsler Memory Scale Revised (WMS-R) [19]. The verbal paired associates, visual paired associates and logical memory subtests are used to assess short- and long-term memory function in both verbal and visual modalities. Delayed recall is assessed in all three subtests after 30 min.

The Rey Auditory Verbal Learning Test (AVLT) [20]. This assesses short- and long-term verbal learning and memory function. It consists of five aural presentations with recall of a 15-word list, one presentation of a second (distracter) list, and a sixth recall. Delayed recall is assessed after 30 min.

The Borkowski Verbal Fluency Test [21]. This is a test of executive/frontal lobe functioning and requires the participant to think of as many different words (in 60 s) that begin with each of the letters J, S, M and U.

Information processing assessments

Choice Reaction Time (CRT) [22]. This is a widely used index of information processing efficiency. The CRT has two indices: decision time (DT) which indexes the cognitive aspects of the task, and movement time (MT) which indexes the motor aspects. Decision times, their standard deviations and the slope of the choice vs. decision time regression line tend to be related to higher cognitive functions.

Inspection Time (IT) [23,24] and Visual Change Detection (VCD) [24] are indices of the efficiency of the early stages of visual information processing and are described in detail elsewhere [25].

Event Related Potentials (ERPs) [26]. An auditory ‘odd-ball’ procedure was used to elicit ERPs. Commonly, the odd-ball testing paradigm (the participant is asked to ignore frequently presented stimuli and to note rare—‘oddball’—stimuli) elicits
an electrical response with a positive peak at or after 300 ms following rare stimuli. This is a late cortical neurophysiological event, and is considered to reflect the speed of neuronal events underlying information processing and the efficiency of higher cognitive processes in the brain [27,28]. An EEG machine (Biologic Brain Atlas) was used to collect and analyse the ERPs that were recorded at the vertex (Cz) and referred to the left and right preauricular points, with the nasion earthed. Electrode placement was made using the 10–20 international system and impedance was kept below 10 kΩ and was below 5 kΩ in almost all cases. Measuring an epoch of 1024 ms, two types of tone (1000-Hz target tone and 250-Hz non-target ‘odd-ball’ tone) were delivered biaurally through headphones at 60 dB with a rate of 0.9 per second. Participants were required to count the infrequent target tones which were presented at random with a probability of 0.25. The maximum number of target tones was set at 50. Neural responses to the two types of stimuli were averaged and recorded separately. The oddball paradigm evokes a characteristic trace usually containing the P300 component, the latency of which is thought to reflect speed of processing while the amplitude reflects attentional ability. The P300 component was defined as the largest peak occurring between 240 and 400 ms following stimulus onset, the latency and voltage of which were measured.

Two researchers (R.C., A.D.), who were not blind to participant status due to being involved in recruitment, assessed participants in pairs (diabetic and control). One participant performed the cognitive function tests while the other underwent the information testing processes. The order in which the participants with Type 2 diabetes and controls performed each section of tests was counterbalanced.

Statistical analysis

Independent t-tests were performed on the individual demographic variables to assess differences between the groups. Mann-Whitney U-tests were used for those variables that were not normally distributed. χ² tests were used to assess any categorical differences between groups. To investigate any between-group (diabetes vs. control) differences in terms of cognitive function or information processing, multivariate analyses of covariance (MANCOVA) were performed with the NART (premorbid mental ability) score and age acting as covariates. Pearson’s correlation coefficient (r) was calculated to assess associations between diabetes-related and cognitive function and information processing variables within the group of people with diabetes. In the case of duration of diabetes, which was not normally distributed, the data were transformed using a natural logarithm transformation prior to calculating correlations.

Power calculations were made for the between-groups study (controls vs. people with diabetes) and the within-group (people with diabetes only) study. With α set at 0.05 (two-tailed) the power of the study to detect a between-groups difference of 0.65 SD units (midway between medium and large effect sizes) was 79%. For the correlational study within the group with diabetes the study had 81% power to detect a Pearson’s r of 0.45 with α set at 0.05 (two-tailed), which again reflects a medium to large effect size.

Results

The demographic variables of the diabetes and control groups are shown in Table 1. There were no significant differences between the groups in terms of age, gender and years of education, in addition to lifestyle variables such as the number of units of alcohol and number of cigarettes consumed annually. In addition, the mood variables were similar across the groups.

The two groups did not differ significantly with respect to the NART error score, indicating that both groups had equivalent premorbid intellectual abilities. However, because non-significant differences in a covariate may still produce confounding, the cognitive and information processing test results were analysed using a MANCOVA procedure with NART error score and age as covariates to adjust for the differences in premorbid intellectual ability and age. In particular, age was used as a covariate because it was significantly correlated with a number of the cognitive and information processing variables in the diabetes and control groups (see Table 3).

Table 2 shows the results of the MANCOVA performed on the cognitive and information processing test variables. With regard to all the cognitive tests, with the exception of the Logical Memory subtest of the WMS-R, the control group performed better than the diabetes group. However, this overall difference was not significant (Wilks’ Λ = 0.86, d.f. = 10,60, P = 0.474). Univariate tests confirmed that there were no significant differences between the two groups in terms of any individual cognitive test. With regard to the information processing tests, the control group exhibited better performance on almost all of the tests, though this multivariate difference was not significant (Wilks’ Λ = 0.92, d.f. = 7,45, P = 0.796). The univariate tests confirmed that no single variable was significantly different between the groups. The average ERPs for the two groups are shown in Fig. 1. It is evident that the average P300 wave of the control group was greater in amplitude and slightly shorter in latency than the diabetes group; however, neither was statistically significant. There was no significant difference between the two groups with regard to the motor functioning (movement time of the CRT). When a measure of socio-economic status (number of years of education) was entered as a covariate in the main analysis the results were not affected (data not shown).

The correlations between the diabetes-related variables and cognitive functioning and information processing variables are shown in Table 3. No associations were found between current glycaemic control (HbA₁c) and any cognitive function or information processing variable. However, significant correlations of moderate effect size were observed between various cognitive function variables and the estimated known duration of diabetes. Since age correlated with duration of diabetes and some of these
variables, partial correlations removing the effects of age were calculated (Table 3, shown in parentheses). Significant correlations were found between duration of diabetes (with age partialled out where appropriate) and WMS-R Verbal pairs ($r = -0.42, P = 0.009$) and WMS-R Logical memory, immediate ($r = -0.39, P = 0.01$) and delayed recall ($r = -0.39, P = 0.01$). Scatter plots for these variables are shown in Fig. 2.

Evident from Fig. 2b,c are two, and one outliers, respectively. When these are removed the correlation with duration of diabetes for WMS-R logical memory immediate recall was $-0.57$ ($P < 0.001$) and for delayed recall was $-0.64$ ($P < 0.001$). The effect of age was partialled out where appropriate. Because previous research had demonstrated impairment in verbal memory [1] we wished to investigate this and other domains individually, rather than a general null hypothesis; consequently a correction for multiple analyses, setting $\alpha$ at 0.003 (0.05/19), was not used [29].

**Discussion**

Numerous case-control studies have shown that the cognitive performance of adults with Type 2 diabetes is approximately 0.6–1.0 SD poorer than that of age- and sex-matched non-diabetic adults [1–3]. Not all domains of cognitive function are impaired by Type 2 diabetes to an equal extent. Memory function in elderly patients appears to be particularly affected and this has led to the suggestion that Type 2 diabetes promotes accelerated ageing of the brain [30,31]. More profound degrees of cognitive impairment, dementias, are also associated with diabetes. Longitudinal studies have demonstrated that people with diabetes have a two- to three-fold increased risk of developing both vascular and Alzheimer’s-type dementia [32–34]. However, the aetiology of Type 2 diabetes-related cognitive impairment remains to be elucidated.

The complexity of the syndrome of Type 2 diabetes is well established, but hinders attempts to clarify the cause of diabetes-related cognitive decrements. Factors such as hypertension, hyperlipidaemia, macrovascular disease, and depression are all more common in diabetes and may, in their own right, be associated with cognitive decrements [10,35–37]. The purpose of the present study was to try to remove the effect of these potential ‘confounding’ factors by examining the cognitive performance of a group of patients with uncomplicated Type 2 diabetes.
No significant differences were found in any area of cognitive functioning or information processing between the groups of patients with Type 2 diabetes and non-diabetic controls, suggesting that, in uncomplicated Type 2 diabetes, any decrement in cognitive function is below a medium to large effect size. Although the between-group comparisons were negative, significant correlations were found between the estimated duration of diabetes (after accounting for the effect of age) and various measures of verbal memory (WMS-R Logical memory immediate and delayed recall, and WMS-R Verbal paired associates immediate recall). These results support previous studies that have suggested that increasing duration of diabetes is associated with cognitive decline [4,38,39]. In particular, in the Framingham Study, history and duration of Type 2 diabetes were linked to a decline in verbal memory [4]. A possible explanation for these findings may be that uncomplicated diabetes does affect cognitive function to a limited extent: learning and memory skills seem to be particularly affected. The results here suggest a dose-response relationship: the longer the duration of chronic

| Table 3  Correlations between the cognitive function and information processing variables and diabetes-related variables |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | HbA1c           | Duration of diabetes* | Age (diabetes group) | Age (control group) |
| Age (diabetes group)           | -0.04           | -0.36†            | -0.05            | -0.10           |
| Age of onset of diabetes       | -0.15           | -0.14             |                  |                 |
| Cognitive function             |                |                  |                 |                 |
| NART (errors)                  | -0.02           | 0.15             | -0.05           | -0.10           |
| RPM                            | 0.01            | -0.39† (-0.30)   | -0.37†           | -0.49‡          |
| Wechsler Memory Scale          |                |                  |                 |                 |
| Verbal pairs (imm.)            | -0.11           | -0.42†           | -0.15           | -0.35†          |
| Verbal pairs (del.)            | 0.02            | -0.10            | -0.37†           | -0.17           |
| Visual pairs (imm.)            | 0.01            | -0.29            | -0.34†           | -0.42‡          |
| Visual pairs (del.)            | 0.04            | 0.01             | -0.22            | -0.30           |
| Logical memory (imm.)          | -0.18           | -0.39†           | -0.25            | -0.16           |
| Logical memory (del.)          | -0.03           | -0.47† (-0.40†)  | -0.32†           | -0.26           |
| Rey AVLT                       |                |                  |                 |                 |
| Total (trials 1–5)             | 0.08            | -0.40† (-0.31)   | -0.42†           | -0.31           |
| Delayed recall                 | 0.09            | -0.23            | -0.30            | -0.13           |
| Verbal fluency                 | -0.06           | -0.21            | 0.02             | 0.09            |
| Information processing         |                |                  |                 |                 |
| Choice reaction time (CRT)     |                |                  |                 |                 |
| Decision time                  | 0.00            | 0.32             | 0.20             | 0.35            |
| Slope                          | 0.15            | 0.19             | 0.15             | 0.00            |
| Average SD                     | 0.16            | 0.27             | 0.29             | 0.46‡           |
| Inspection time                | -0.20           | -0.13            | 0.26             | 0.33†           |
| Visual change detection        | -0.11           | 0.32             | 0.54‡            | 0.46‡           |
| Event related potentials       |                |                  |                 |                 |
| P300 latency                   | -0.24           | -0.26            | 0.26             | 0.28            |
| P300 amplitude                 | 0.22            | -0.23            | 0.23             | -0.37†          |
| Motor functioning              |                |                  |                 |                 |
| CRT movement time              | 0.16            | 0.08             | 0.06             | 0.05            |

NART, National Adult Reading Test; RPM, Raven’s Progressive Matrices; AVLT, Auditory Verbal Learning Test; imm., immediate recall; del., delayed recall. Figures in parentheses represent partial correlations with the effect of age removed.

*Correlation calculated from the natural logarithm of the duration of diabetes.
†P < 0.05; ‡P < 0.01.
hyperglycaemia, the greater the likelihood that mnestic processes will be disrupted to some extent.

The results of the two analyses (between- and within-group) of this study may at first appear contradictory; however, this is not the case. The patients with Type 2 diabetes performed less well on cognitive tests than controls, but not significantly so. However, within the diabetes group it is possible to imagine a range of ‘impact’ on cognitive function, such that some people had very little cognitive impairment (i.e. they were more like controls) and some had considerably greater cognitive impairment. Though the ‘average impact’ in the diabetes group was too small to result in a significant between-groups comparison, within the group with diabetes it is possible to imagine a range of ‘impact’ on cognitive function, such that some people had very little cognitive impairment (i.e. they were more like controls) and some had considerably greater cognitive impairment. Though the ‘average impact’ in the diabetes group was too small to result in a significant between-groups comparison, within the group with diabetes it is possible to imagine a range of ‘impact’ on cognitive function, such that some people had very little cognitive impairment (i.e. they were more like controls) and some had considerably greater cognitive impairment. This result encourages similar, but larger-scale, between-group studies of Type 2 diabetes and cognition.

Given that much larger effects of Type 2 diabetes on cognitive function were observed in other studies (which included subjects with more complicated diabetes), the results from the between-groups analysis suggest that abnormalities intrinsic to diabetes, such as chronic hyperglycaemia, may not be responsible for a substantial decline in cognitive performance. However, it should be noted that the diabetic subjects who participated in the present study were younger and of higher premorbid intelligence than in most previous investigations. The importance of age, in particular, has been highlighted by a recent study of middle-aged adults with Type 2 diabetes [40], in which the diabetic subjects showed no deficits in learning and memory performance (in contrast to previous case-control studies in older adults with Type 2 diabetes), but did demonstrate impaired psychomotor skills.

In addition to the stringent recruitment criteria, the present study also utilized an extensive cognitive test battery. The components of a cognitive test battery were chosen to ensure that a wide range of abilities were examined and that the tests used were likely to be sensitive to small changes in cognitive functioning. In addition, the present study used the National Adult Reading Test, a valid and reliable measure of premorbid mental ability [14–16], which has been used in only one previous study [41]

In conclusion, the results of the present study suggest that some aspect of Type 2 diabetes (as indexed by the estimated duration of the disorder) does relate significantly to cognitive function within the group with diabetes. However, other diabetes-related factors, such as macrovascular disease, hypertension and depression, may contribute more to previously observed cognitive decrements in Type 2 diabetes.

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