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# Impaired cognitive processing speed in type 1 diabetic patients who had severe/recurrent hypoglycaemia

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ABSTRACT

*Aims:* To detect whether adults with type 1 diabetes mellitus (T1DM) have lower cognitive performance than healthy individuals and to detect risk factors for low cognitive performance.
*Methods:* Twenty-six adults with T1DM and twenty-six healthy subjects matched for age, gender and educational level were compared for cognitive performance by a chronometric computerized test measuring visuo-spatial working memory (N-Back) and by two validated neuropsychological tests (Mini Mental State Examination, Animal Naming Test). Clinical data about diabetes duration, average daily insulin dosage, glycated haemoglobin, retinopathy, urine albumin-creatinine ratio, previous hypoglycaemic coma and awareness of hypoglycaemia were obtained from medical records. Basal pre-test glycemia and blood pressure were measured for each patient.
*Results:* No differences were found between patients ($n = 26$) and healthy controls ($n = 26$) in neuropsychological tests. Within diabetic patients, those with impaired awareness of hypoglycaemia ($n = 7$) or history of coma in the recent 1–3 years ($n = 5$) had psychomotor slowing at the N-Back test (592 ± 35 vs. 452 ± 21 ms and 619 ± 40 vs. 462 ± 19 ms, respectively; both $p < 0.01$). The variables related to diabetic severity did not show a relationship with reaction times of the N-Back test.
*Conclusion:* Psychomotor speed slowing is detectable in patients with T1DM who have a history of previous hypoglycaemic episodes or coma.



## 1. Introduction

T1DM is characterized by acute and chronic complications. The main long-term complication is diabetic angiopathy, which is classified as microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (atherosclerosis). Neurological sequelae can be neuropathic (distal symmetric polyneuropathy, autonomic neuropathy, mononeuropathy) or cognitive (depression, cognitive decline). Evidence about type 1 diabetes-associated cognitive decline (DACD) is conflicting, both on magnitude of impairment and on which cognitive domains are involved. The most common deficits consist in the slowing of cognitive processing speed (CPS) and the worsening of mental flexibility.[1,2] The specific nature of the deterioration of memory, sustained attention, executive functions, general intelligence and visuoconstruction is uncertain, and the pathogenesis of DACD is still unknown.

The main variables affecting the risk appear to be the age of onset of diabetes, the development of microvascular complications and the level of glycaemic control (hypoglycaemia or hyperglycaemia). Early onset of diabetes (4–7 years of age) is linked to greater neurocognitive dysfunctions and structural alterations than late onset. This event is probably due both to the duration of diabetes and to its effects on neurodevelopment.[3,4] In adults with T1DM, the occurrence of microvascular complications is related to increased and early cognitive decline.[5,6] Moreover, in some neuroimaging studies, type 1 diabetic patients with retinopathy have shown an augmented focal cortical atrophy and a reduced white matter volume.[7,8] Longitudinal studies have demonstrated that patients with elevated glycated haemoglobin (>8%) present worse cognitive efficiency and velocity than subjects with good glycaemic control.[9,10] These deficits seem to be reversed by improved metabolic control. The intensive use of insulin to prevent hyperglycaemia and its complications has incremented the incidence of hypoglycaemic crises. Patients treated with an intensive therapeutic regimen, especially

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those with glycated haemoglobin near the non-diabetic range, have a 3 times greater risk of severe hypoglycaemia than subjects with a less intensive insulin therapy. Subjects affected by T1DM have on average 2 episodes of mild hypoglycaemia a week; about one third of them present a severe episode annually.[11]

The severe detrimental effects of acute hypoglycaemia on cognitive performance, especially on memory and executive functions, are widely known. However, the role of hypoglycaemia and its complications on long-term cognitive decline are still uncertain. Some studies support the hypothesis that the brain may adapt to hypoglycaemic insult.[5,12,13] Other studies, in contrast, argue that hypoglycaemia can sensitize neurons, increasing the negative effects of glycopenia.[14] Recurrent episodes of hypoglycaemia cause both a down-regulation of counter-regulatory response (hypoglycaemia-associated autonomic failure–HAAS) and a reduction of autonomic hypoglycaemic symptoms (resulting in unawareness of hypoglycaemia), which are associated with a sixfold increase in the risk of severe hypoglycaemia and a prolonged encephalic exposure to glycopenic insult.[15,16] Perros et al.[17] underlined that alteration of EEG, induced by hypoglycaemia can become permanent after severe or recurrent crises. Increased brain susceptibility to hypoglycaemia seems to occur especially from birth to 20 years of age.[4,18] However, at a later age also, the brain may become unable to cope with hypoglycaemia.

Thus, since *i)* the occurrence of cognitive alterations in T1DM and the role that hypoglycaemia may have in their pathophysiology is debated and *ii)* there are few data about the cognitive sequelae of individuals with or without hypoglycaemia awareness, we designed a study to detect whether adults with T1DM have lower cognitive performance than healthy individuals, as well as to investigate the risk factors for low cognitive performance in type 1 diabetic subjects.

**Table 1**
Demographic characteristics, neuropsychological and behavioural performance of the study participants.

| | | Patients with DM1 | Control subjects | p |
|---|---|---|---|---|
| N | | 26 | 26 | – |
| Age (years) | | 45.8 ± 12.6 | 45.9 ± 12.8 | 0.97 |
| Gender (M/F) | | 17/9 | 17/9 | – |
| Education (years) | | 13.4 ± 3.8 | 13.9 ± 3.7 | 0.63 |
| Humeral arterial Pressure (mm Hg) | Diastolic | 75 ± 5 | – | – |
| | Systolic | 129 ± 9 | – | – |
| | Mean | 93 ± 5 | – | – |
| Glycaemia (mg/dl) | | 130 ± 34 | – | – |
| DM1 duration (years) | | 18 ± 10 | – | – |
| Insulin (U/die) | | 49 ± 21 | – | – |
| HbA1c (%) | | 7.3 ± 0.6 | – | – |
| HbA1c (mmol/mol) | | 56 ± 6 | | |
| Retinopathy | Absent | 46% | – | – |
| | Simple | 39% | – | – |
| | Proliferative | 15% | – | – |
| Urine albumin/creatinine (mg/mMol) | | 6 ± 3.5 | – | – |
| Previous hypoglycaemic coma | | 19% | – | – |
| Unawareness of hypoglycaemia | | 27% | – | – |
| CriQ | Education* | 115 ± 21 | 101 ± 13 | 0.03 |
| | Work | 109 ± 15 | 111 ± 16 | 0.66 |
| | Free-time activity | 118 ± 23 | 110 ± 16 | 0.2 |
| | Total | 119 ± 24 | 108 ± 17 | 0.13 |
| MMSE | | 29.4 ± 0.9 | 29.5 ± 0.9 | 0.97 |
| ANT | | 24 ± 6 | 23 ± 5 | 0.6 |
| N-Back condition (ms) | 0-Back | 425 ± 93 | 385 ± 58 | 0.07 |
| | 1-Back | 450 ± 109 | 409 ± 94 | 0.16 |
| | 2-Back | 593 ± 131 | 557 ± 148 | 0.37 |
| | Mean | 490 ± 31 | 451 ± 31 | 0.08 |

Data are mean ± SD; *, statistical significance; Significance level was $p < 0.05$.

## 2. Subjects, materials and methods

### 2.1. Subjects and data

This study involved 26 participants with T1DM and 26 healthy control subjects matched for age, gender and educational level. The demographic characteristics of the two groups are shown in Table 1. Diabetic patients were recruited from the Diabetes Clinic at the University Hospital of Padua where they were seen regularly each month. All participants attended two sessions: in the first, they provided information about their medical history, and then they submitted to preliminary neuropsychological tests (Mini Mental State Examination, Back Depression Inventory-II, Cognitive Reserve Index Questionnaire, Animal Naming Test) to verify the presence of exclusion criteria. Exclusion criteria were: serious systemic disease (heart failure, chronic kidney disease, cirrhosis, severe lungs and airways diseases, addiction), cerebrovascular disease, coronary artery disease, severe neuropathy, major psychiatric disorders and use of tranquillizer, antidepressant or anti-psychotic drugs. Based on tests administered during preliminary evaluation, participants were also excluded if they had cognitive decline (Mini Mental State Examination <26 and Animal Naming Test ≤14) or depression (Back Depression Inventory >13). Clinical data about diabetes duration (years from onset of the disease), average daily insulin dosage (U/die), glycated haemoglobin (HbA1c – %), presence of retinopathy (absent, proliferative, non-proliferative), urine albumin-creatinine ratio (mg/mMol), previous hypoglycaemic coma and awareness of hypoglycaemia were recorded for each patient. In the second session, participants performed the computerized N-Back test. Pre-test glycemia (mg/dl) and pre-test blood pressure (mm Hg) were measured for each diabetic patient by glucometer and sphygmomanometer, respectively. The protocol was reviewed and approved by the Institutional Review Board of University of Padova. The purpose and the nature of the study were explained to all subjects, and informed written consent was obtained before their participation.

### 2.2. Neuropsychological evaluation

- Mini Mental State Examination (MMSE): it assesses cognitive decline. The MMSE explores: spatial and temporal orientation, learning, calculation, comprehension (written and oral), writing and constructional apraxia.[19]
- Beck Depression Inventory – II (BDI-II): a self-administered questionnaire that identifies depressive symptoms and investigates the depression level.[20]
- Cognitive Reserve Index Questionnaire (Cri-q): a test that evaluates cognitive reserve by educational level (school years and extra-scholastic courses), work and free-time activities.[21]
- Animal Naming Test (ANT): a verbal fluency test in which participants have to name as many animals as possible in 1 min. The total sum of animals correctly reported (excluding errors of intrusion or perseveration) represents the final score.[22]

### 2.3. Cognitive test protocol

- N-Back Test: a computerized chronometric test providing insight into both CPS in a go/no-go condition and working memory (WM). The task was an adapted version of the visuospatial N-Back test from Cui et al.[23] and Haberecht et al.[24] The stimuli were administered using a personal computer (17-in. display; resolution: 1024 × 768 pixels) by E-Prime software (Psychology Software Tools, Pittsburgh, PA). The blank screen was divided into 9 equal parts by a black grid during the test. The stimulus was the letter O (66 × 156 pixels), which appeared in one of the grid's sections for 1500 ms. After this period, there was a fixed inter-stimulus interval of 500 ms in which only the grid was displayed. The position of the letter changed in each trial. The test was block design, and it was composed of three conditions with increasing working memory load. During the control condition (0-Back), participants had to press the response button if the letter O appeared in the central

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