

# CHAPTER 8

## **A detailed profile of cognitive dysfunction**

### **and its relation to psychological distress in patients with type 2 diabetes mellitus**

A.M.A. Brands, E. van den Berg, S.M. Manschot, G.J. Biessels, L.J. Kappelle,

E.H.F. de Haan & Roy P.C. Kessels,

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### Introduction

Type 2 diabetes mellitus is a highly prevalent metabolic disorder, especially in older people, and is characterised by high blood glucose levels due to resistance to insulin accompanied by an inadequate compensation in the secretion of insulin (American Diabetes Association, 2002). Type 2 diabetes is a disease of slow onset. Initially, compensatory increases in insulin secretion (hyperinsulinemia) maintain normal glucose concentrations by counteracting the reduced sensitivity of tissues to insulin. The aim of treatment is to maintain normal glucose levels in order to prevent several complications, such as nephropathy, retinopathy and neuropathy. In patients with type 2 diabetes this treatment initially consists of dietary restrictions and exercise. Oral hypoglycemic drugs or insulin injections are prescribed in later stages.

In the past decades, it has become increasingly evident that diabetes also affects the central nervous system in several ways, a complication referred to as diabetic encephalopathy (Gispén and Biessels, 2000). Numerous studies have been conducted to evaluate the neuropsychological functioning of individuals diagnosed with type 2 diabetes. These studies differ with respect to demographic characteristics of the research participants, e.g. age or gender distribution, or diabetic characteristics (diabetes duration, treatment regime and comorbidity or complications) (Awad et al., 2004; Stewart and Liolitsa, 1999). Studies also varied in neuropsychological domains covered and in methodological designs (cross-sectional, or longitudinal; clinic- or population-based). Although these differences make cross-study comparisons difficult, several attempts have been made to integrate findings and draw commonalities (Awad et al., 2004; Stewart and Liolitsa, 1999). The most common finding is that diabetes is associated with mild to moderate impairments of cognitive functioning with lowered performance on tests of speed of information processing, episodic memory and, although less consistently, on tests of mental flexibility (Awad et al.,

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2004; Stewart and Liolitsa, 1999). Effect sizes are small to moderate between 0.4 to 0.8 (Cohen, 1988). Cognitive domains that are less likely to show significant differences between type 2 diabetic patients and controls include visuospatial processing, auditory or visual attention, long-term semantic knowledge and language abilities (Awad et al., 2004). The pattern and severity of the cognitive changes varies between studies (Awad et al., 2004; Stewart and Liolitsa, 1999), and the variability in findings could (partially) be accounted for by differences in methodology. Inconsistencies across studies may also be related to the neuropsychological sensitivity of the test measures used. Also, in several studies a selection was made with respect to the cognitive domains that were assessed and a rationale for that selection was not always provided (Awad et al., 2004). This has thus led to the difficulty in asserting any potential dysfunction. The question arises whether inconsistent findings are due to the fact that type 2 diabetes causes a global rather non-specific decline in all cognitive domains, or that the observed cognitive changes follow a certain pattern in which limitations in one area, such as speed of information processing, explain the performance decline in other cognitive domains. This emphasises the need for an extensive neuropsychological study to examine the major cognitive domains in detail.

Studies which examined relations between different disease variables and cognitive functioning showed that patients with worse glycemic control were more likely to show cognitive deficits (Strachan et al., 1997). A number of other factors, such as depression, cardiovascular and cerebrovascular disease, are also thought to increase cognitive deficits (Awad et al., 2004). Moreover, although most studies did not use age as an independent predictor, the largest effect of type 2 diabetes on cognitive function was observed in studies in which patients were older (Ryan and Geckle, 2000). As they age, people with type 2 diabetes develop other related pathologies such as hypertension, atherosclerosis, macro- and microvascular disease that pro-

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duce further cognitive deficits, which become most apparent in later life.

Only few studies have specifically addressed brain MRI abnormalities in patients with type 2 diabetes. These studies indicate that modest cortical and subcortical atrophy and symptomatic or asymptomatic infarcts are more common in type 2 diabetic patients than in controls (Araki et al., 1994; Vermeer et al., 2003). We have recently shown that cognitive impairments in type 2 diabetes are associated with MRI abnormalities, more specifically with white-matter lesions, infarcts and atrophy (Manschot et al., 2006).

Type 2 diabetes is also associated with changes in psychological well-being. For example, the prevalence of depressive symptoms is elevated in patients with type 2 diabetes (Anderson et al., 2001), and depressive symptoms might be related to cognitive dysfunction (Elderkin-Thompson et al., 2003; Lockwood et al., 2002). Although it is well known that the burden of a chronic illness in general may result in elevated levels of psychological distress, biomedical factors may also play a role, since it has been reported that depressive symptoms are related to white-matter abnormalities (Jorm et al., 2005) and severity of diabetic complications (Leedom et al., 1991). The association between white-matter abnormalities and depressive symptoms in older people has been labeled “vascular depression” (Alexopoulos et al., 1997). Others refer to the co-occurrence of cognitive impairments, depressed mood and vascular dysfunction as “vascular dementia” (Baldwin et al., 2006) or “pseudodementia”, i.e. geriatric depression with reversible cognitive deficits (Alexopoulos et al., 1997). The question how psychological well-being is related to MRI abnormalities in type 2 diabetes has not been examined yet.

The aim of this study is twofold. The first aim is to give a detailed description of the deficits on cognitive tasks and the neuropsychological interpretation thereof. The second aim is to examine the subjective level of psychological well-being and

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to examine its relation to both the cognitive deficits and to the white-matter abnormalities observed in these patients. This study is the first study to combine neuropsychological data, MRI data and questionnaires on psychological well-being, using a relatively large sample of patients and control participants. It is this combination that, in our opinion, adds new insights to the current literature. The study was part of a larger project on determinants of impaired cognition in diabetes in older adults. Detailed data on brain MRI findings and biomedical determinants of impaired cognition are reported separately (e.g. Manschot et al., 2006).

### **Methods**

#### *Research Participants*

The Utrecht Diabetic Encephalopathy Study (UDES) is a cross-sectional, population-based study on determinants of impaired cognition in diabetes in older adults. Between September 2002 and November 2004 122 patients with type 2 diabetes (age 56-80 yrs), 40 patients with type 1 diabetes (52-77 yrs), and 61 controls (53-78 yrs) were included. Type 2 diabetic patients were recruited through their general practitioner. Controls were recruited among the spouses or acquaintances of the patients. For inclusion in the current substudy, participants had to be 55 to 80 years of age, functionally independent, and Dutch speaking. Type 2 diabetic patients had to have a minimal diabetes duration of 1 year. Patients with diabetes-related comorbid conditions, such as hypertension or macrovascular events (e.g. non-invalidating stroke or myocardial infarction) or mood disorders could be included, since this co-morbidity is an integral part of the diabetic condition. Controls with these conditions could also be included. All other neurological (e.g. Parkinson Disease, Multiple Sclerosis) or psychiatric disorders (e.g. schizophrenia, bipolar disorder),

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as well as a history of alcohol or substance abuse were considered exclusion criteria for all participants. An additional exclusion criterion for the controls was a fasting blood glucose  $\geq 7.0$ .

**Table 1.** demographic and biomedical characteristics of patient and control group

	DM2 patients (N=119)	Controls (N=55)
Age	65.9 (5.7)	65.2 (5.2)
Sex (males)	62 (52%)	24 (44%)
Educational level (median, IQR)	4 (3-5)	4 (3-5)
Estimated premorbid IQ	98.8 (15.4)	101.8 (13.3)
Diabetes duration (years)	8.7 (6.1)	-
Non-invalidating stroke	7 (6%)	2 (4%)
Hypertension	95 (80%)	20 (36%)*
Any microvascular disease	56%	17%**
Any macrovascular event	32%	6%**
History of severe hypoglycemia	6%	-
Mild head trauma	12%	10%
HbA1c (%)	6.9 (1.2)	5.5 (0.3)***
Current alcohol consumption (median, IQR)	1 (0-2)	2 (1-3)*

Data are presented as mean (SD) or n (%) unless specified. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

The study was approved by the medical ethics committee of the University Medical Center Utrecht and written informed consents were obtained. Participants attended the hospital on two consecutive days and participated in MRI examination of the brain, and neuropsychological and neurological examinations. Medical his-

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tory and medication use was recorded. Fasting blood samples were collected, blood pressure was recorded and urine was collected overnight.

Education level was recorded using 7 categories and transferred to years of education. Premorbid intellectual level was estimated with the Dutch version of the National Adult Reading Test (Schmand et al., 1992). Scores can be translated into estimated IQ scores based on normative data, since performance on this test is considered to reflect “best ever” global cognitive performance and is relatively resistant to the effects of organic brain disease (Lezak et al., 2004).

In order to match both groups on age, the age range was restricted for this neuropsychological study from 56 to 78, resulting in the inclusion of 119 type 2 diabetic patients and 55 control participants. All but one type 2 diabetic patient and all control participants were Caucasian. The groups were well balanced for age, sex, level of education, and estimated IQ (Table 1).

### *Neuropsychological Assessment*

All participants participated in a comprehensive neuropsychological test battery that consisted of eleven tests with 20 test indices. The tests covered the major cognitive domains and were sensitive enough to detect small to moderate differences in cognitive ability. The tests were administered in a fixed order by two trained neuropsychologists (EvdB and AMAB) and took about 90 minutes to complete. The test results were summarised in five cognitive domains in order to reduce the amount of neuropsychological variables for statistical analysis and for clinical clarity. The division was made a priori, according to standard neuropsychological practice and cognitive theory, as described in detail in Lezak’s “Neuropsychological Assessment (Lezak, Howieson, and Loring, 2004).

The domain “Abstract Reasoning” was assessed by Raven Advanced Progressive

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Matrices (12-item short form) (Raven et al., 1993). The number of correct responses was recorded.

The domain “Memory” was divided into four sub-domains (e.g. Working Memory, Immediate Memory and Learning Rate, Forgetting Rate, and Incidental Memory). “Working Memory” was assessed by the forward and backward Digit Span of the Wechsler Adult Intelligence Scale – 3rd edition (DS-WAIS-III) (Wechsler, 1997) and the Corsi Block Tapping-Task (Berch et al., 1998; Kessels et al., 2000). The product scores of the maximum number of digits (actual span score) times the number of correctly recalled sequences were recorded (Kessels et al., 2000). “Immediate Memory and Learning Rate” was assessed verbally and non-verbally with the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) (Van der Elst et al., 2005) and the Location Learning Test (LLT) (Bucks et al., 2000; Kessels et al., 2005). For the RAVLT the mean of the total number of words remembered in five learning trials was recorded and a learning index was calculated as an estimate of the learning curve. For the LLT, both the total number of displacements over five trials and a learning index was calculated. “Forgetting Rate”, as a measure of decay over time, was also calculated in the RAVLT and the LLT in which the scores in the delayed recall condition were corrected for the score obtained in the fifth learning trial. “Incidental Memory” was measured with the delayed recall trial of the Rey-Osterrieth Complex Figure Test (CFT) (Rey, 1941). This score was also corrected for the score obtained in the copy condition.

The domain “Information Processing Speed” was assessed with the Trail Making Test part A (TMT-A) (Corrigan and Hinkeldey, 1987), the Stroop Color-Word Test parts I and II (Stroop, 1935) and the WAIS-III subtest Symbol Digit Substitution (SS-WAIS III). For the TMT-A the time to complete the task was recorded in seconds. For the Stroop Color-Word Test parts I and II the mean of the total time (in

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seconds) to complete part I and II was calculated and the total correct number of copied symbols within two minutes was recorded for the SS-WAIS-III.

The domain “Attention and Executive Functioning” consisted of four sub-domains (e.g. Response Inhibition, Divided Attention, Concept Shifting, and Verbal Fluency). “Response Inhibition” was assessed by the Stroop Color-Word Test Part III (Stroop, 1935). The time to complete this task was recorded in seconds and was corrected for the time to complete the Stroop Color-Word Test part I and part II. “Divided Attention” was assessed with the Trail Making Test part B (Corrigan and Hinkeldey, 1987), controlling for baseline performance on TMT-A. “Concept Shifting” was assessed by the Brixton Spatial Anticipation Test (Burgess and Shallice, 1997) where the number of errors were recorded. “Verbal Fluency” was assessed both with a category naming task (Animal Naming, 2 min) and two lexical fluency tasks (‘N’ and ‘A’, 1 min each) (Deelman et al., 1981). The total number of correct responses was recorded.

Finally, the domain “Visuoconstruction” was assessed by the copy trial of the Rey-Osterrieth Complex Figure Test (Rey, 1941).

### *Psychological Assessment*

Mood was assessed with the Dutch version of the Beck Depression Inventory – 2nd Edition (BDI-II (Beck et al., 1996)). Both the total score on this self-rated depressive symptoms inventory and the percentage of people scoring above the cut-off criterion of 13 (Lustman et al., 1997) were recorded. To consider possible somatic overlap, which is necessary when depressed mood is assessed in a medical population, we also recorded the scores on the Somatic, Cognitive and Affective subscales (Beck et al., 2002).

The Dutch version of the Symptom Checklist – Revised (SCL-90-R) was com-

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pleted by all participants as a measure of overall cognitive, psychological and physical complaints (Derogatis et al., 1976). This version of the SCL-90-R consists of 90 items that are subdivided into nine different subscales: Anxiety, Agoraphobia, Depression, Somatization, Cognitive Performance Difficulty, Interpersonal Sensitivity and Paranoid Ideation, Anger-Hostility, and Sleep Disturbances. The Global Severity Index (GSI), calculated as the average score of all 90 items, represents the overall level of distress (Kessels et al., 1998).

### *Biomedical characteristics and MRI ratings*

In a standardised interview, participants were asked about diabetes duration, history of hypertension, hypoglycemic events, head trauma, stroke or cardiovascular disease, medication use, smoking and alcohol consumption habits. Furthermore, all participants measured their blood pressure at home at nine different time points during the day (Omron MX3; Omron, Mannheim, Germany).

Of every participant glycosylated haemoglobin (HbA<sub>1c</sub>) was determined, which reflects the average blood glucose level in the preceding 6-8 weeks. Hypertension was defined as an average systolic blood pressure  $\geq 160$  mm Hg and/or diastolic blood pressure  $\geq 95$  mm Hg and/or self reported use of blood pressure lowering drugs. Microvascular and macrovascular complications were also assessed. Neuropathy was defined as a score  $\geq 6$  on the Toronto Clinical Neuropathy Scoring System (Bril et al., 2002). Retinopathy was assessed with fundus photographs, which were rated according to the Wisconsin Epidemiologic Study of Diabetic Retinopathy scale (Klein et al., 1986). Albuminuria was defined as microalbuminuria (albumin 30-250mg/l) or macroalbuminuria (albumin  $\geq 250$ mg/l or positive protein dipsticktest) in the overnight urine sample. "Any microvascular disease" was defined as retinopathy, or micro- or macroalbuminuria, or neuropathy. "Any macrovascular event" was defined as

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a history of myocardial infarction, stroke, or surgery or endovascular treatment for coronary, carotid or peripheral (legs, abdominal aorta) artery disease.

A history of severe hypoglycemia was defined as an episode that required external assistance for recovery. Mild head trauma was defined trauma with a brief loss of consciousness without apparent persistent neurological deficits. Alcohol consumption was recorded using 6 categories which can be transferred to number of units alcohol consumption per week: 0, 1-3, 4-10, 11-20, 21-30, >30, respectively.

White-matter lesions, atrophy and silent infarcts were rated on hard copies of the MRI, or on digital images on a personal computer (Manschot et al., 2006). In 9 patients with type 2 diabetes and 5 controls no MRI could be obtained, due to MRI contraindications, such as claustrophobia or a pacemaker. White-matter lesions were distinguished into periventricular and deep (subcortical) regions and rated according to the Scheltens rating scales (Scheltens et al., 1993). Periventricular white-matter lesions (PWML) were rated on a severity scale (0-2) at the frontal and occipital horns and the body of the lateral ventricle, at the left and at the right side, with the total PWML score being the sum of these six scores (range 0-12). For the rating of deep white-matter lesions (DWML) the brain was divided into six regions: frontal, parietal, occipital, temporal, basal ganglia and infra-tentorial. Per region the size and number of the WML were rated, on a scale ranging from 0 to 6, with the total DWML score being the sum of these six scores (range 0-36). Furthermore, brain infarcts were scored, by location (cortical and subcortical), size (lacunar or large) and number. Cortical atrophy was evaluated by the frontal interhemispheric fissure ratio (FFR) and the Sylvian fissure ratio (SFR): the maximal width of the interhemispheric fissure or the average of the maximal Sylvian fissure widths, divided by the trans-pineal coronal inner table diameter respectively (Gomori et al., 1984). Subcortical atrophy was evaluated by the bicaudate ratio (BCR) and by the bifrontal

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ratio (BFR) measured on the same cut as the BCR (Gomori et al., 1984). BCR and BFR are defined as the minimal distance between the caudate indentations of the frontal horn or the distance between the tips of the frontal horns divided by the distance between the inner tables of the skull along the same line, respectively. In order to relate cerebral atrophy to levels of psychological well-being, the raw data were converted into a cortical atrophy z-score and subcortical atrophy z-score, based on the pooled mean of the whole group. A more detailed description of the biomedical and MRI-rating procedures has been published previously (Manschot et al., 2006).

### *Analyses*

For the population characteristics between-group differences were analysed with analyses of variance, Mann-Whitney U for non-parametric data and chi-square test for proportions. In order to directly compare the five different cognitive domains the raw-scores were standardised into z-scores. These z-scores were calculated on the mean and pooled SD of the whole group. The domain and sub-domain scores were derived by calculating the mean of the z-scores comprising the domain. To investigate whether patients differed from controls, the domain scores were analysed using *t*-tests. Only in the case of a significant difference in the performances in a specific cognitive domain the subdomains were statistically compared for the two groups as well. Rather than looking at the statistical significance of between-group differences, effect sizes (ES) (Cohen's *d*) (Cohen, 1988) were calculated with the MetaWin software package, that is, the standardised difference between the type 2 diabetes group and the control group based on the standard deviation of the whole group, in order to determine the magnitude of cognitive deficits on individual tests. Negative ES reflect worse performance of the type 2 diabetes group.

Furthermore, to investigate if patients with and without insulin treatment differed

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on cognitive tasks and on levels of psychological distress, the patient group was divided in two groups (oral glucose lowering drugs or dietary treatment versus insulin treatment). Between-group differences were calculated with analysis of covariance, correcting for age, estimated IQ, sex, diabetes duration and HbA<sub>1c</sub> levels.

To examine if patients with and without signs of depression differed on cognitive measures, the patient group was divided into a non-depressed group (BDI-II <13) and a group with mild depressed mood (BDI-II ≥ 13) (Lustman et al., 1997). Between-group differences were determined with analysis of covariance, correcting for age, IQ, sex, diabetes duration and HbA<sub>1c</sub> levels.

A Pearson's correlation analysis was performed to identify the specific variables of SCL-90-R and BDI-II that were associated with cognitive performance on the various domains. Furthermore, a correlation analysis was performed to identify if diabetes duration, HbA<sub>1c</sub> levels, the occurrence of "any microvascular disease" or "any macrovascular event", hypertension or white-matter abnormalities were associated with measures of psychological well-being. More detailed data on these complications in relation to cognition and brain MRI have been reported separately (Manschot et al., 2006).

### Results

Table 1 shows the characteristics of the participants. No significant differences were found between the diabetes and the non-diabetes groups on age, sex distribution, education or estimated premorbid IQ. Type 2 diabetic patients had diabetes for nine years on average.

The diabetic characteristics (e.g. HbA<sub>1c</sub>, total cholesterol, triglycerides, blood pressure and body mass index) of the patients with type 2 diabetes are similar to

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those reported in large population based surveys of type 2 diabetic patients in the Netherlands (Goudswaard et al., 2004). Mean HbA<sub>1c</sub> was 6.9% in our type 2 diabetes population, which indicates a moderately good controlled diabetes. The two groups differed significantly on deep white-matter abnormalities (DM2: median= 7; Inter Quartile Range (IQR) =3.5-10.5; CON: median= 5; IQR=2-8.5;  $p<0.05$ ), cortical (z-score DM2: mean= 0.19; SD= 0.93; CON: mean= -0.43; SD= 0.71;  $p<0.001$ ) and subcortical atrophy (DM2: mean= 0.11; SD= 0.92; CON: mean= -0.25; SD= 0.85 ;  $p<0.05$ ) but not on periventricular white-matter abnormalities or on silent infarcts. For more detailed imaging results see (Manschot et al., 2006).

Table 2 shows the standardised performance (z-values) for the cognitive domains. Significantly worse performance was found on Attention and Executive functioning ( $t(172)=2.24$ ;  $p=0.027$ ), Information Processing Speed ( $t(172)=3.29$ ;  $p=0.001$ ) and Memory ( $t(172)=2.56$ ;  $p=0.011$ ). No statistical significant differences were found on Abstract Reasoning ( $t(169)=1.13$ ;  $p=0.26$ ) and Visuoconstruction ( $t(163)=1.23$ ;  $p=0.22$ ). With respect to the subdomains of significantly different cognitive domains Verbal Fluency ( $t(167)=2.14$ ;  $p=0.035$ ) and Concept Shifting ( $t(169)=2.54$ ;  $p=0.012$ ) were impaired within the domain Attention and Executive functioning.

No significant differences were found on any of the subdomains of Memory (all  $t$ -values  $<1.85$ ). ANCOVA on the levels of cognitive performance with SCL-90-R Depression scores as covariate did not affect the statistically significant between group differences.

Table 3 shows the effect sizes for the individual tests, showing that these are in the small to moderate range (ES between 0.2-0.6).

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**Table 2.** Standardised z-scores (and SD) on the five cognitive domains and sub-domains

Cognitive domains	DM 2 patients	Controls
1. Abstract reasoning	-0.06 ± 1.06	0.13 ± 0.87
2. Memory	-0.06 ± 0.50	0.14 ± 0.42 *
Working memory	-0.06 ± 0.80	0.13 ± 0.71
Immediate memory & learning	-0.03 ± 0.64	0.07 ± 0.61
Forgetting Rate	-0.06 ± 0.76	0.16 ± 0.66
Incidental memory	-0.09 ± 1.04	0.18 ± 0.90
3. Information processing speed	-0.14 ± 0.94	0.25 ± 0.61 **
4. Attention & Executive function	-0.06 ± 0.62	0.14 ± 0.55 *
Response inhibition	-0.02 ± 1.02	0.04 ± 0.97
Divided attention	-0.04 ± 1.12	0.08 ± 0.66
Concept shifting	-0.13 ± 1.01	0.28 ± 0.93 *
Verbal fluency	-0.09 ± 0.92	0.20 ± 0.75 *
5. Visuoconstruction	-0.07 ± 1.06	0.14 ± 0.85

Domain scores are presented as z-scores ± SD. Negative z-values indicate worse performance.

\*:  $p < 0.05$ ; \*\*:  $p < 0.01$

**Table 3.** Raw test scores (mean  $\pm$  SD), Effect Sizes (ES; Cohen's  $d$ ) and 95% confidence interval.

Cognitive domains and tests	DM2 patients	Controls	ES	95% CI
Raven Advanced Progressive Matrices (short form)	6.3 (2.8)	6.8 (2.3)	-0.18	-0.50; 0.14
WAIS-III Digit Span forward	45.2 (19.1)	46.8 (20.0)	-0.08	-0.29; 0.44
WAIS-III Digit Span backward	23.1 (15.4)	29.4 (20.6)	-0.37*	-0.54; -0.20
Corsi Block-Tapping Test forward	37.6 (13.4)	38.4 (9.9)	-0.07	-0.24; 0.10
Corsi Block-Tapping Test backward	37.2 (14.1)	39.3 (13.6)	-0.15	-0.47; 0.17
RAVLT total trials 1-5	39.0 (9.8)	42.3 (10.9)	-0.33*	-0.66; -0.01
RAVLT delayed trial	7.7 (2.9)	8.5 (2.8)	-0.29	-0.67; 0.09
RAVLT recognition	28.2 (2.0)	28.9 (1.4)	-0.39*	-0.72; -0.06
LLT total trials 1-5 #	27.4 (20.1)	23.7 (19.1)	-0.19	-0.51; 0.13
LLT learning index	0.6 (0.3)	0.7 (0.3)	-0.30	-0.68; 0.08
LLT delayed trial #	0.6 (0.3)	0.7 (0.3)	-0.20	-0.52; 0.12
Rey Complex Figure Test copy trial	32.3 (4.1)	33.1 (3.3)	-0.20	-0.53; 0.11
Rey Complex Figure Test delayed trial	17.2 (6.4)	19.2 (5.1)	-0.34*	-0.67; -0.01
Stroop Color Word Test I #	50.93 (11.55)	46.83 (7.90)	-0.39*	-0.72; -0.06
Stroop Color Word Test II #	65.60 (14.10)	61.42 (12.89)	-0.30	-0.68; 0.08
Stroop Color Word Test III #	122.3 (40.8)	113.3 (42.4)	-0.23	-0.40; 0.06
TMT Part A #	49.8 (20.3)	40.4 (10.4)	-0.52*	-0.85; -0.19
TMT Part B #	116.9 (46.2)	94.5 (28.3)	-0.54**	-0.87; -0.21
WAIS-III Symbol Digit Substitution	53.4 (15.6)	57.3 (13.1)	-0.24	-0.56; 0.08
Letter fluency ("N" + "A")	10.3 (4.4)	12.5 (4.4)	-0.40*	-0.73; -0.07
Verbal fluency (Animal naming)	32.8 (9.3)	34.4 (7.0)	-0.19	-0.52; 0.12
Brixton Spatial Anticipation Test #	21.2 (7.2)	18.3 (6.6)	-0.42*	-0.75; -0.09

RIVT: Rey Auditory Verbal Learning Test; LLT: Location Learning Test; TMT: Trail Making Test; WAIS-III: Wechsler Adult Intelligence Scale – Third Revision \* $p < 0.05$ ; \*\* $p < 0.01$ ; # higher test scores reflect worse performance; for effect sizes negative values reflect impaired performance in the DM2 group across all tests.

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**Table 4.** Levels of psychological well-being and depressive symptoms. Data are presented as mean (and SD) unless specified.

Psychological questionnaires	DM2 patients Controls		p-value
	(N=119)	(N=55)	
SCL-90-R			
Anxiety	13.5 (4.1)	12.0 (2.3)	0.004
Agoraphobia	8.5 (2.9)	7.8 (1.6)	0.038
Depression	23.4 (7.3)	20.2 (4.0)	0.001
Somatisation	20.4 (7.5)	18.0 (4.6)	0.012
Cognitive-Performance Difficulty	14.3 (5.3)	12.9 (3.2)	0.030
Interpersonal Sensitivity and Paranoid Ideation	23.1 (6.5)	22.4 (4.3)	0.481
Anger-Hostility	7.1 (1.5)	6.5 (0.9)	0.001
Sleep Disturbance	6.5 (3.2)	5.4 (2.6)	0.029
Other	11.2 (2.4)	10.7 (1.7)	0.160
Global Severity Score	128.6 (32.0)	115.9 (17.5)	0.001
BDI-II			
Raw total score	7.1 (5.3)	4.6 (3.8)	0.001
Cognitive scale	1.0 (1.8)	0.6 (1.0)	0.116
Affective scale	0.8 (1.2)	0.5 (0.9)	0.152
Somatic scale	5.3 (3.8)	3.6 (2.8)	0.005
Cut-off 13, n (%)	10 (8%)	1 (2%)	0.091

Higher scores reflect more complaints on SCL-90-R or BDI-II

On the BDI-II and the SCL-90-R, the subscale scores and the global severity index were compared between the two groups. Patients with type 2 diabetes had signifi-

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cantly higher scores on the GSI of the SCL-90-R and on the Agoraphobia, Somatization, Cognitive-Performance Difficulty, Anger-Hostility, and Sleep Disturbance subscales than controls (Table 4). The two groups also differed significantly on the total scores on the BDI-II ( $p=0.001$ ). However, no significant difference between the two groups was observed with respect to the percentage of participants that could be classified as suffering from “mildly depressed mood” using the cut-off criterion of 13 on the BDI-II (chi-square=2.8,  $p=0.091$  (Table 4)). Furthermore, examination of the subscales of the BDI-II revealed that the two groups differed only on the Somatic subscale, but not on the Cognitive and Affective subscales (Table 4).

ANCOVA on the levels of cognitive performance in type 2 diabetic patients with BDI-II total scores above and type 2 diabetic patients below the cut-off criterion of 13, with age, IQ, sex, diabetes duration and HbA<sub>1c</sub> levels as covariates, did not show significant differences. Also, both BDI-II total scores and subscale scores, and SCL-90-R scores were not correlated with cognitive domain scores in the type 2 diabetes group or the control group. Furthermore, these measures of psychological distress were neither significantly correlated with biomedical characteristics (e.g. diabetes duration, HbA<sub>1c</sub>, hypertension, the occurrence of “any microvascular disease” or “any macrovascular event”) nor with any of the MRI findings of the type 2 diabetic patients or the controls (range  $r$ : -0.19 to 0.22; all  $p$ -values >0.05).

Finally, no statistically significant differences were observed between patients with and without insulin treatment on cognitive tasks or on levels of psychological distress with analysis of covariance, after correction for age, IQ, sex, diabetes duration and HbA<sub>1c</sub> levels (all  $t$ -values <1.82; all  $p$ -values >0.05).

## COGNITIVE PROFILE IN TYPE 2 DIABETES

### Discussion

In the present study, we demonstrated that patients with type 2 diabetes showed modest cognitive impairments as well as higher levels of subjective psychological distress compared to control participants. The domains that were most affected were Attention and Executive Functioning (specifically the subdomains Verbal fluency and Concept Shifting), Information Processing Speed and Memory, whereas other domains and subdomains showed no statistically significant performance differences between type 2 diabetic patients and controls. Calculations of effect sizes showed that the magnitude of the differences in performance was modest on all test-scores (effect sizes  $< 0.6$ ). Cognitive functioning in type 2 diabetic patients has been the subject of several studies (for a review Awad et al., 2004; Stewart and Liolitsa, 1999,) generally reporting performance deficits in verbal memory, information processing speed and less consistently, in executive functioning and non-verbal memory. Our results are in line with these findings. Possibly, previously described inconsistencies in affected neuropsychological domains may result partly from a rather non-specific pattern of an overall modest performance deficit. A detailed analysis of test performances in the present study indeed shows that the cognitive impairments found in type 2 diabetes do not appear to be a problem of competence on a specific cognitive domain, but rather of overall performance level. To characterise the nature of this diminished performance level it is important to investigate the specific characteristics of the tests involved. For instance, it has been hypothesised that type 2 diabetic patients perform worse when the cognitive task at hand requires speed of response and where the individual has to respond within a fixed time limit (Robertson-Tchabo et al., 1986). Also, performance on tasks lacking intrinsic structure will require more cognitive processing and thus should present more problems for type 2 diabetic pa-

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tients. Indeed, type 2 diabetic patients were slower than controls on timed tasks such as the Stroop Color Word Test and the TMT, reflecting a slowed rate of information-processing speed (Ponsford and Kinsella, 1992), but the effect size on SS-WAIS-III, which can be considered a more structured measure of information-processing speed, was much smaller. In general, verbal fluency is seen as an excellent (timed) measure how well participants organise their thinking (Estes, 1974). A marked contrast was found in this study between performance on letter and category fluency tasks in the type 2 diabetes group. Indeed, letter fluency is a less structured task than category fluency, since the category fluency draws heavily on the structure of the semantic network (Troyer, Moscovitch et al., 1997). Furthermore, the memory impairment that is reported in this study, as well as in several other studies, could be interpreted as secondary to the problem with unstructured and effortful tasks. This might explain why no performance deficits were observed on the non-verbal Location Learning Task since on this task one can benefit from both a verbal as well as a spatial encoding strategy.

In all, type 2 diabetes seems to exert a relatively mild decrement in neuropsychological functioning across several domains. This pattern of diminished cognitive efficiency resembles a pattern of cognitive decline described in normal ageing (Tisserand and Jolles, 2003). Also, meta-analyses addressing age-cognition relations in healthy populations indicate that the largest age-related decline is generally found on measures of information-processing speed (Verhaeghen and Salthouse, 1997) and age-related cognitive decline in memory test scores has been described as well (Cohen, 1996; Rabbitt, 1998). Furthermore, it has been suggested that type 2 diabetes has an effect on cognition that is equal to the effect of two to three years of age (Verhaeghen and Salthouse, 1997). It could thus be hypothesised that type 2 diabetes leads to an accelerated brain ageing.

Previous studies in general populations of older people that looked at the relation

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between brain MRI abnormalities and cognitive function show results that are comparable with our results as reported in a previous paper from this project (Manschot et al., 2006). Especially WML and additionally atrophy are associated with diminished speed of information processing, decline of general intellectual capacity and diminished executive functioning (Garde et al., 2006; Gunning-Dixon and Raz, 2000; Jokinen et al., 2005; Ylikoski et al., 1993).

Type 2 diabetic patients report more subjective cognitive problems and show higher levels of psychological distress than controls. In our study we screened for depression with a self-administered inventory. In agreement with a recent meta-analysis (Anderson et al., 2001) we found patients to have higher scores on the BDI-II, but results on the subscales indicate that this mainly reflects a higher incidence of somatic complaints in the type 2 diabetes group. Only one control and eleven type 2 diabetic patients scored above the cut-off criterion of 13, an indicator of mild-depressed mood (Lustman et al., 1997). Thus, the percentage of type 2 diabetic patients reporting serious depressive symptoms or high levels of psychological distress is relatively low, compared to what is reported in general in the literature (Anderson et al., 2001). Similarly, the scores on the GSI of the SCL-90-R were significantly higher in the type 2 diabetes group than in controls, but the actual level of the GSI can only be characterised as “above average” in the type 2 diabetes group and “average” in the control group according to normative data collected in a normal Dutch population (Arrindell and Ettema, 2003). Therefore, the level of psychological distress appears only moderately elevated in the type 2 diabetes group and cannot be compared to the generally observed levels of distress in groups of psychiatric patients where the average GSI score ranges from 193-214 (Arrindell and Ettema, 2003). The means of both the BDI-II and SCL-90-R indicate only subclinical levels of depressed mood and this further questions the meaningfulness of the significant difference in BDI-II and SCL-90-R scores between the two groups. Furthermore, inspection of the

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scores on the subscales of the BDI-II resulted in a significant between-group difference on the Somatic subscale only, indicating substantial somatic overlap, but not differences in mood itself.

In this study levels of psychological distress in type 2 diabetes were not related to levels of cognitive performance or MRI findings. However, MRI studies of patients with major depression have found a higher prevalence of WMLs, particularly in participants with late-depression onset (Videbech, 1997). It has been suggested that late-onset depression could be regarded as “vascular depression”, a late-onset subtype of depression that involves increased cardiovascular risk factors and hyperintensities of deep white-matter or subcortical grey matter (Alexopoulos et al., 1997). The concept of “vascular depression” can thus not be applied in the present group of type 2 diabetic patients as a whole. Furthermore, whereas other studies reported a significant relation between diabetic complications (i.g. neuropathy) and the degree of depressive symptoms (Leedom et al., 1991), our study did not find a correlation between biomedical characteristics of type 2 diabetic patients and the degree of depressive symptoms and levels of psychological distress. Our findings are in agreement with other studies reporting cognitive decrements in type 2 diabetic patients independent of depressive symptoms (Gregg et al., 2000; Lowe et al., 1994).

It can thus be concluded that type 2 diabetes is associated with modest impairments of cognition on “speed of information processing”, “memory” and “attention and executive functioning”. Type 2 diabetic patients have a diminished ability to efficiently process unstructured information which results in a slower performance on neuropsychological tasks and difficulties in memory tasks. Although type 2 diabetic patients reported higher levels of psychological distress, this did not contribute to the cognitive performance, nor could levels of psychological distress be related with MRI findings or biomedical characteristics of the type 2 diabetic patients.