

Cognitive performance in type 1 diabetes patients is associated with cerebral white matter volume

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Received: 10 January 2007 / Accepted: 23 April 2007 / Published online: 2 June 2007
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Abstract

Aims/hypothesis Cognitive performance in type 1 diabetes may be compromised as a result of chronic hyperglycaemia. The aim of this study was to investigate the cognitive

functioning of patients with type 1 diabetes (including a subgroup with a microvascular complication) and nondiabetic controls, and to assess the relationship between cognition and cerebral grey and white matter volumes.

Materials and methods Twenty-five patients with type 1 diabetes (of whom ten had proliferative retinopathy) and nine nondiabetic controls (matched in terms of sex, age and education) underwent a neuropsychological examination and magnetic resonance imaging of the brain. Fractional brain tissue volumes (tissue volume relative to total intracranial volume) were obtained from each participant.

Results Compared with nondiabetic controls, patients with diabetes performed worse on tests measuring speed of information processing and visuoconstruction; patients with microvascular disease performed worse on the former cognitive domain ($p=0.03$), whereas patients without complications performed worse on the latter domain ($p=0.01$). Patients with a microvascular complication had a significantly smaller white matter volume than nondiabetic controls ($p=0.04$), and smaller white matter volume was associated with worse performance on the domains of speed of information processing and attention and executive function.

Conclusions/interpretation Patients with diabetes demonstrated several subtle neuropsychological deficits, which were found to be related to white matter volume. Since patients with diabetic retinopathy had a smaller white matter volume, this suggests that cognitive decline is at least partly mediated by microvascular disease. This needs to be addressed in future studies.

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Keywords Cognitive performance · Grey matter volume ·
Microvascular disease · Type 1 diabetes ·
White matter volume

Abbreviations

CES-D	Center for Epidemiological Studies Scale for Depression
DRP	diabetic retinopathy
GMF	grey matter fraction
MRI	magnetic resonance imaging
NDRP	no diabetic retinopathy
TI	inversion time
TICV	total intracranial volume
VBM	voxel-based morphometry
WAIS	Wechsler adult intelligence scale
WMF	white matter fraction
WML	white matter lesion

Introduction

Individuals with type 1 diabetes show mild performance deficits on a range of neuropsychological tests compared with nondiabetic controls, but the mechanisms underlying this cognitive deterioration are poorly understood [1]. Retrospective studies in adult patients with type 1 diabetes have demonstrated an association between a history of recurrent severe hypoglycaemia and a modest degree of cognitive impairment [2–7], but large prospective studies failed to find such an association [8–10].

Two studies have found that of all biomedical variables examined, clinically significant distal symmetrical polyneuropathy and/or elevated glycosylated haemoglobin values were most strongly associated with psychomotor slowing [11, 12]. These findings indicate that diabetes-associated mental slowing may be associated with hyperglycaemia-induced complications (particularly retinopathy), resulting in cerebral microangiopathy. Other evidence for a damaging effect of chronic hyperglycaemia comes from the work of Ferguson et al. [13]. Subjects with background retinopathy performed worse across most cognitive domains examined. Furthermore, background diabetic retinopathy (DRP) was associated with small focal white matter hyperintensities, corresponding to enlarged perivascular spaces, in the basal ganglia.

Prior studies from our research project also indicate the existence of an association between retinopathy and functional and structural changes in the brain [14, 15].

To date, several other studies on structural brain abnormalities in patients with type 1 diabetes [7, 13, 16–20] have reported conflicting results concerning the presence of white matter lesions and cortical atrophy. The majority of these studies have been based on manual or semiautomated region-of-interest guided measurements. It is now well known that whole grey and white matter volume, as compared with lesion burden, is more closely

related to neuropsychological performance and neuropsychiatric symptoms [21–24]. Measures of tissue atrophy including whole brain and central atrophy are especially well correlated with and predictive of cognitive impairment. Moreover, conventional measures of brain atrophy are more strongly associated with neuropsychological dysfunction than measures of lesion burden. White matter atrophy has been shown to be the best predictor of mental processing speed and working memory, whereas grey matter atrophy was associated with verbal memory, euphoria and disinhibition. These results indicate that both grey and white matter atrophy play a salient role with possible different functional or behavioural consequences of the disease. Because abnormal signal intensities from conventional magnetic resonance imaging (MRI) alone may not enable prediction of future clinical benefit, increased attention has been focused on whole brain atrophy, which may indirectly indicate the total disease burden.

To the best of our knowledge, the relationship between total brain grey and white matter volume and cognitive performance in type 1 diabetes has not been studied. The aim of this study was: (1) to investigate cognitive functioning in patients with type 1 diabetes and nondiabetic controls; (2) to determine differences in cognitive performance between patients with type 1 diabetes with and without a microvascular complication (i.e. proliferative retinopathy); (3) to determine differences in fractional grey and white matter volumes (tissue volume relative to total intracranial volume [TICV]) between the groups; and (4) to establish whether there is an association between cognitive performance and grey and white matter volume.

Subjects and methods

Participants Twenty-five patients with type 1 diabetes (WHO, 1999 criteria [25]), of whom ten had a severe microvascular complication, i.e. diabetic proliferative retinopathy (DRP) (grade 5 DRP according to the EURODIAB classification [26]), and 15 no diabetic retinopathy (NDRP) (no microvascular complication, maximum three microaneurysms), and nine nondiabetic controls were included. Groups were matched for age, sex and education (participants had to adhere to stringent inclusion criteria to make sure [beforehand] that the three groups were similar as to age, sex and level of education) (Table 1).

More detailed information on these participants has been published previously [14, 15]. All subjects were right handed and were normotensive (<140/90 mmHg). Four DRP patients were known to have nephropathy; two other DRP patients were known to have nephropathy and neuropathy. Exclusion criteria were previous alcohol or drug abuse, history of psychiatric disease/treatment, history

Table 1 Characteristics of participants

Characteristics	NDRP ^a	DRP ^a	Nondiabetic	<i>p</i> value
<i>n</i>	15	10	9	
Age (years)	42.1±4.5 (34–50)	42.3±5.3 (37–53)	40.9±8.5 (31–52)	0.85
Sex (male:female)	7:8	3:7	3:6	0.66
Level of education ^b	5.2±0.9 (3–7)	5.2±1.1 (4–6)	5.7±0.9 (5–7)	0.48
HbA _{1c} (%)	7.8±1.1 (5.3–9.8)	8.0±1.2 (5.4–9.8)	NA	0.69
Duration of diabetes (years)	26.4±8.1 (14–37)	32.4±7.6 (23–48)	NA	0.08

NA Not applicable

Data are means±SD and range. The *p* values are for comparison of the three groups by one-way ANOVA (for continuous variables) or the χ^2 test (for binomial variables).

^a Two pictures of the retina, one with the macula and one with the optic disc in the centre (using a Topcon non-mydratic camera) of each eye were made.

^b Education was assessed by a Dutch scoring system [50] that consists of an eight-point scale, ranging from unfinished primary school (level 1) to university (level 8).

of severe head trauma accompanied by loss of consciousness, stroke, epilepsy, history of severe recurrent hypoglycaemia (defined as more than five episodes that required external assistance for recovery) [27], pregnancy and concomitant diseases that could possibly affect cognitive function. Written consent was obtained from all subjects and the protocol was approved by the local medical ethics review committee. The investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Neuropsychological examination Cognitive functioning of all subjects was determined by means of a neuropsychological test battery which focused primarily on attention and executive functioning and speed of information processing.

Participants experiencing incipient hypoglycaemia, or hypoglycaemia in the preceding 24 h, were excluded before neuropsychological assessment. Evidence of symptomatic hypoglycaemia or evidence of biochemical hypoglycaemia or hyperglycaemia (blood glucose <3.5 or >15 mmol/l [28], respectively) resulted in rescheduling of the neuropsychological session, since this could affect performance. Blood glucose values were checked (and adjusted if necessary) before and during testing using a finger prick.

Thirteen neuropsychological tasks were administered in a fixed order, which took about 2 h to complete. Each task was allocated to one of five cognitive domains to reduce the amount of neuropsychological variables and for clinical clarity. This division was made a priori, according to standard neuropsychological practice and cognitive theory, as described in detail in Lezak et al. [29]. The domain ‘memory’ consisted of Digit span forward and backward [30], the 15 Words test [31], the Rey Complex Figures test, delayed recall condition [32] and the Wechsler adult intelligence scale (WAIS) Symbol Substitution, incidental learning test [30]. The domain ‘speed of

information processing’ included the Trail Making Test Part A [33], the Stroop Colour Word Test (Part I and II) [34, 35] (28, 29) and the WAIS Symbol Substitution, coding [30].

The domain ‘attention and executive function’ was assessed by the Stroop Colour Word Test (Part III) [34, 35], the Trail Making Test Part B [33], the D2 test [36], GIT sorting [37], the Wisconsin Card Sorting Test [38] and Wechsler intelligence scale for children Mazes [39]. The domain ‘fluency’ included the Category Word Fluency task [40] and the domain ‘visuoconstruction’ was assessed by the Rey Complex Figures test, copy trial [32] and WAIS Block Design [30].

As depression is known to have an impact on cognitive performance [41], and may be associated with white matter disease [42] we included assessment of depressive symptoms with the Dutch version of the Center for Epidemiological Studies Scale for Depression (CES-D) (range 0–60) [43, 44]. Scores >16 indicate likely depression.

MRI acquisition Imaging was performed on a 1.5 T Siemens Sonata (Siemens, Erlangen, Germany) scanner using a standard circularly polarised head coil, with foam padding to restrict head motion. A localiser scan was first performed for positioning of the image planes, followed by an automated shim procedure to improve magnetic field homogeneity. Scans were obtained as whole brain inversion time (T1)-weighted magnetisation prepared rapid acquisition gradient echo volumes and were acquired in the coronal plane (T1=950 ms, repetition time=2,700 ms; echo time=5.15 ms; flip angle=8°; 160 slices, voxel size: 1×1×1.5 mm).

MRI data analysis Global brain volumes, calculated from the T1-weighted images, were analysed using statistical parametric mapping (SPM) software (SPM2; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; available from <http://www.fil.ion.ucl.ac.uk/spm/>, last

accessed in May 2007) with the voxel-based morphometry (VBM) tool Jena script (available from <http://dbm.neuro.uni-jena.de/vbm.html>, last accessed in May 2007) in MATLAB version 6 (The Mathworks, Natick, MA, USA). SPM yielded whole brain volumetric data, in ml, for three different tissue types: cerebral spinal fluid, grey matter and white matter. TICV was defined as the sum of the three tissue types. White matter fraction (WMF) was defined as white matter volume divided by TICV and grey matter fraction (GMF) was defined as grey matter volume divided by TICV.

Statistical analysis Statistical analysis was performed using SPSS version 11.0 (SPSS, Chicago, IL, USA). Demographic data of patients and nondiabetic controls were analysed using a one-way ANOVA (for continuous variables) and by a χ^2 test (for binomial variables).

For each cognitive test, raw scores were converted into standardised z scores ($M=0$; $SD=1$), using the mean and SD values from the nondiabetic comparison group. Domain z scores were calculated as the mean z value of the cognitive tests assigned to that specific domain. Multivariate ANOVA, adjusting for age and level of education and Bonferroni post hoc comparison, was used to compare cognitive performance within each domain between the groups and to study differences in volumetric measures between the groups. Pearson correlation coefficients were used to assess the presence of associations between demographic, clinical, volumetric and neuropsychological measurements. For the between-group comparisons, $p<0.05$ was considered statistically significant.

Results

Cognitive performance There was a significant difference (after adjusting for age and education) on cognitive performance between the groups on the domain of speed of

information processing ($p=0.024$) and the domain of visuoconstruction ($p=0.035$). Contrasts revealed that, on the domain of speed of information processing, DRP patients performed worse compared with the control group ($p=0.025$; effect size 0.5). No significant differences were observed between the DRP and the NDRP group and between the NDRP group and the nondiabetic controls on this domain. On the domain of visuoconstruction, it appeared that NDRP patients performed worse as compared with the nondiabetic reference group ($p=0.031$; effect size 0.4).

The NDRP group as well as the DRP group reported significantly more depressive symptoms (NDRP: 12.4 ± 8.9 and DRP: 13.0 ± 10.8) than nondiabetic controls (3.2 ± 3.8) (both: $p=0.02$). Six patients (three DRP and three NDRP patients) and no nondiabetic controls scored above the criterion score of 16 for the depression scale (Table 2). Rerunning the analysis with adjustment for the depression score did not change the aforementioned results.

Brain measurements There was a significant difference in WMF between the groups ($p=0.035$). Contrasts revealed that DRP patients displayed significantly decreased WMF compared with the nondiabetic controls ($p=0.035$; effect size 0.4). No differences in WMF were observed between the NDRP group and the nondiabetic control group and the NDRP and the DRP group. Furthermore, no significant differences between the three groups in GMF were observed (Table 3). The results did not change when we adjusted for sex.

The relationship between demographics, clinical variables, volumetric measurements and neuropsychological performance was tested using Pearson correlation coefficients (Table 4). White matter volume was positively correlated with performance on the domain of speed of information processing and attention and executive functioning. No correlation was found between grey matter volume and neuropsychological performance.

Table 2 Cognitive performance

Domain	NDRP	DRP	Nondiabetic
<i>n</i>	15	10	9
Memory	-0.22 ± 0.17	-0.37 ± 0.21	0 ± 0.24
Speed of information processing	-1.12 ± 0.22	-1.41 ± 0.26	-0.26 ± 0.30^a
Attention and executive functioning	-0.32 ± 0.10	-0.06 ± 0.13	-0.05 ± 0.14
Fluency	-0.25 ± 0.20	-0.44 ± 0.25	0.06 ± 0.28
Visuoconstruction	-0.96 ± 0.19	-0.61 ± 0.23	-0.05 ± 0.26^b

Domain scores are z scores \pm SE evaluated at covariates in the model: age and education and adjusted for multiple comparisons (Bonferroni)

^a $p<0.05$ for DRP vs nondiabetic

^b $p<0.05$ for NDRP vs nondiabetic

Table 3 GMF and WMF measurements

Measurements	NDRP	DRP	Nondiabetic	<i>p</i> value
<i>n</i>	15	10	9	
GMF	0.444±0.005	0.430±0.006	0.434±0.006	0.18
WMF	0.273±0.004	0.266±0.005	0.286±0.005	0.04

Data are means±SE evaluated with age as a covariate in the model and adjusted for multiple comparisons (Bonferroni). The *p* values are for comparison of the three groups by one-way ANOVA

Discussion

The results of this study suggest that cognitive performance in relatively young diabetic patients is worse with regard to tests measuring speed of information processing and visuo-construction as compared with sex-, age- and education-matched nondiabetic controls. Notably, patients with a microvascular complication showed a decreased white matter volume compared with nondiabetic controls. Reduced white matter volume was associated with worse performance in the domain of speed of information processing and attention and executive functioning.

Our findings are in line with the literature suggesting that deficits in speed of information processing and cognitive slowing are the fundamental features of clinical disorders characterised by abnormalities in cerebral white matter [45]. For example Sanfilippo et al. [21] found in patients with multiple sclerosis that white matter atrophy

was the best predictor of mental processing speed and working memory. Dow et al. [46] also suggested a relationship between reduced white matter volume and impaired processing speed performance in patients with temporal lobe epilepsy.

Evidence is increasing that psychomotor slowing is a core cognitive deficit associated with diabetes [47], and studies have demonstrated that the presence of microvascular complications like retinopathy is predictive of mental slowing in adults with type 1 diabetes [12, 13]. Furthermore, retinal microvascular abnormalities have been shown to relate to white matter lesions (WMLs) in a population of patients with type 1 diabetes [13] and healthy middle-aged men and women [48]. In this study, we focused on whole grey and white matter volume, as compared with lesion burden, because evidence suggests these are more closely related to neuropsychological performance [21–24]. We found a relationship between white matter atrophy and

Table 4 Pearson correlation coefficients for the relationship between volumetric measurements and clinical and neuropsychological variables for all participants

	Age	Education	Diabetes duration (DM only)	HbA _{1c} (DM only)	CES-D	Memory	Speed of information processing	Attention and executive functioning	Fluency	Visuo-construction	White matter	Grey matter
Age	1											
Education	-0.44**	1										
Diabetes duration (DM only)	0.60**	-0.41*	1									
HbA _{1c} (DM only)	-0.03	0.11	-0.09	1								
CES-D	-0.04	-0.26	0.05	0.27	1							
Memory	-0.33	0.42*	-0.17	0.23	-0.10	1						
Speed of information processing	-0.27	0.53**	-0.18	0.41*	-0.32	0.50**	1					
Attention and executive functioning	-0.24	0.39*	-0.18	-0.16	-0.19	0.33	0.59**	1				
Fluency	0.26	0.08	0.32	0.05	-0.07	0.19	0.17	-0.10	1			
Visuoconstruction	-0.45**	0.45**	-0.32	-0.07	-0.14	0.47**	0.49**	0.40*	-0.20	1		
White matter	-0.19	0.29	-0.23	0.16	-0.19	0.18	0.57**	0.51**	-0.02	0.20	1	
Grey matter	-0.21	0.23	-0.25	-0.03	-0.07	-0.01	0.28	0.32	-0.07	0.12	0.81**	1

DM Diabetes mellitus

**p*<0.05

***p*<0.01

performance in the domain of speed of information processing and attention and executive function. These results are consistent with the notion that temporary storage and manipulation of new information may require rapid communication between different brain regions via white matter tracts, which may become compromised with progression of the disease. This finding indirectly suggests that disruption of centrally located cortical subcortical white matter connections may be responsible for slower processing speed.

In an earlier study, we did demonstrate modest focal cortical grey matter atrophy in patients with a microvascular complication using VBM [15]. VBM is a fully automated whole brain technique that detects regionally specific differences in brain tissue composition on a voxel-by-voxel basis. At its simplest, it involves a voxel-wise comparison of the local concentration of grey matter between groups of subjects [49]. In fact, regional differences in grey matter density are estimated, whereas in the present study we assessed differences in whole brain volume, i.e. a different approach. Apparently, in this particular sample, focally significant differences in grey matter when analysing grey matter differences voxel-wise, are not reflected in whole brain grey matter volume differences, probably because of more noise in the latter technique.

Whether type 1 diabetes is indeed characterised by changes in cerebral white matter or whether diabetes can be characterised by global brain atrophy (affecting both grey and white matter) needs to be clarified in future longitudinal studies.

Limitations of this study are its small sample size (our results should therefore be interpreted with caution) and its cross-sectional design, which does not yield information on the temporal relationship between deficits in white matter volume and cognitive performance. Moreover, we cannot discern whether the smaller white matter volumes are due to loss of normal-appearing white matter or to decreased maturation of white matter. Because we did not use an MRI technique to determine WMLs, the relationship between white matter volume loss, WMLs and cognitive performance could not be explored in the current study. Furthermore, the use of whole brain grey and white matter volumes also precluded any definitive discussion regarding the localisation of brain cognition relationships.

A strength of our study is the inclusion of a nondiabetic control group, matched (on group level) for sex, age and education (although a 1:1 matching would have even been better). This allowed us to investigate the effect of diabetes per se on cognitive performance and on brain measurements. It also enabled us to assess the effect of microvascular disease (i.e. proliferative retinopathy) on these measurements, and link cognitive performance with brain measurements. Our results did not support (or refute) the hypothesis that reduced cognitive performance is associated

with the presence of microvascular disease. The differences found are likely to be associated with diabetes per se, independently of disease status. However, the subtle deficits found were specifically related to white matter volume. Since persons with DRP had a smaller white matter volume; this suggests that cognitive decline is at least partly mediated by microvascular disease. This hypothesis needs to be addressed in future studies. Future longitudinal studies should also utilise newer MRI techniques, such as diffusion tensor imaging, to quantify changes in the integrity of the cerebral white matter and to enhance our understanding of the potential mechanisms underlying structural brain damage and its effect on cognitive performance in patients with type 1 diabetes.

Acknowledgements This project was supported by Dutch Diabetes Research Foundation Grant 2001.11.012.

Duality of interest We declare that we have no dualities of interest.

References

1. Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP (2005) The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care* 28:726–735
2. Wredling R, Levander S, Adamson U, Lins PE (1990) Permanent neuropsychological impairment after recurrent episodes of severe hypoglycaemia in man. *Diabetologia* 33:152–157
3. Langan SJ, Deary IJ, Hepburn DA, Frier BM (1991) Cumulative cognitive impairment following recurrent severe hypoglycaemia in adult patients with insulin-treated diabetes mellitus. *Diabetologia* 34:337–344
4. Deary IJ, Crawford JR, Hepburn DA, Langan SJ, Blackmore LM, Frier BM (1993) Severe hypoglycemia and intelligence in adult patients with insulin-treated diabetes. *Diabetes* 42:341–344
5. Lincoln NB, Faleiro RM, Kelly C, Kirk BA, Jeffcoate WJ (1996) Effect of long-term glycemic control on cognitive function. *Diabetes Care* 19:656–658
6. Hershey T, Craft S, Bhargava N, White NH (1997) Memory and insulin dependent diabetes mellitus (IDDM): effects of childhood onset and severe hypoglycemia. *J Int Neuropsychol Soc* 3:509–520
7. Perros P, Deary IJ, Sellar RJ, Best JJ, Frier BM (1997) Brain abnormalities demonstrated by magnetic resonance imaging in adult IDDM patients with and without a history of recurrent severe hypoglycemia. *Diabetes Care* 20:1013–1018
8. Group TDCaCTR (1996) Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med* 124:379–388
9. Reichard P, Berglund B, Britz A, Cars I, Nilsson BY, Rosenqvist U (1991) Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm Diabetes Intervention Study (SDIS) after 5 years. *J Intern Med* 230:101–108
10. Austin EJ, Deary IJ (1999) Effects of repeated hypoglycemia on cognitive function: a psychometrically validated reanalysis of the Diabetes Control and Complications Trial data. *Diabetes Care* 22:1273–1277
11. Ryan CM, Williams TM, Orchard TJ, Finegold DN (1992) Psychomotor slowing is associated with distal symmetrical

- polyneuropathy in adults with diabetes mellitus. *Diabetes* 41:107–113
12. Ryan CM, Geckle MO, Orchard TJ (2003) Cognitive efficiency declines over time in adults with type 1 diabetes: effects of micro- and macrovascular complications. *Diabetologia* 46:940–948
 13. Ferguson SC, Blane A, Perros P et al (2003) Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. *Diabetes* 52:149–156
 14. Wessels AM, Rombouts SA, Simsek S et al (2006) Microvascular disease in type 1 diabetes alters brain activation: a functional magnetic resonance imaging study. *Diabetes* 55:334–340
 15. Wessels AM, Simsek S, Remijnse PL et al (2006) Voxel-based morphometry demonstrates reduced grey matter density on brain MRI in patients with diabetic retinopathy. *Diabetologia* 49:2474–2480
 16. Dejgaard A, Gade A, Larsson H, Balle V, Parving A, Parving HH (1991) Evidence for diabetic encephalopathy. *Diabet Med* 8:162–167
 17. Yousem DM, Tasman WS, Grossman RI (1991) Proliferative retinopathy: absence of white matter lesions at MR imaging. *Radiology* 179:229–230
 18. Araki Y, Nomura M, Tanaka H et al (1994) MRI of the brain in diabetes mellitus. *Neuroradiology* 36:101–103
 19. Lunetta M, Damanti AR, Fabbri G, Lombardo M, Di Mauro M, Mughini L (1994) Evidence by magnetic resonance imaging of cerebral alterations of atrophy type in young insulin-dependent diabetic patients. *J Endocrinol Investig* 17:241–245
 20. Musen G, Lyoo IK, Sparks CR et al (2006) Effects of type 1 diabetes on gray matter density as measured by voxel-based morphometry. *Diabetes* 55:326–333
 21. Sanfilippo MP, Benedict RH, Weinstock-Guttman B, Bakshi R (2006) Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology* 66:685–692
 22. Zivadinov R, Sepcic J, Nasuelli D et al (2001) A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing–remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* 70:773–780
 23. Benedict RH, Weinstock-Guttman B, Fishman I, Sharma J, Tjoa CW, Bakshi R (2004) Prediction of neuropsychological impairment in multiple sclerosis: comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Arch Neurol* 61:226–230
 24. Benedict RH, Carone DA, Bakshi R (2004) Correlating brain atrophy with cognitive dysfunction, mood disturbances, and personality disorder in multiple sclerosis. *J Neuroimaging* 14:36S–45S
 25. World Health Organization (1999) Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation. Part 1. Diagnosis and classification of diabetes mellitus. WHO, Geneva
 26. Aldington SJ, Kohner EM, Meuer S, Klein R, Sjolje AK (1995) Methodology for retinal photography and assessment of diabetic retinopathy: the EURODIAB IDDM complications study. *Diabetologia* 38:437–444
 27. The Diabetes Control and Complications Trial Research Group (1997) Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286
 28. Cox DJ, Kovatchev BP, Gonder-Frederick LA et al (2005) Relationships between hyperglycemia and cognitive performance among adults with type 1 and type 2 diabetes. *Diabetes Care* 28:71–77
 29. Lezak MD, Howieson DB, Loring DW (2004) *Neuropsychological assessment*. Oxford University Press, New York
 30. Wechsler D (1981) *Manual of the Wechsler Adult Intelligence Scale-Revised*. The Psychological Corporation Limited, New York
 31. Saan RJ, Deelman BG (1986) New version of 15 words test (15WTA and 15WTB). In: Bauma AMJ, Lindeboom J (eds) *Neuro-psychological diagnostics handbook*. Swets & Zeitlinger, Amsterdam, pp 13–28
 32. Myers JE MK (1995) *Rey complex figure test*. Psychological Assessment Resources, Odessa
 33. Reitan RM (1958) Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills* 8:271–276
 34. Golden CJ (1978) Stroop colour word test. In: Golden CJ (ed) *A manual for clinical and experimental uses*. Stoelting, Chicago
 35. Jensen AR, Rohwer WD (1966) The stroop color-word test: a review. *Acta Psychologica* 25:36–93
 36. Brickenkamp R (1962) *The d2 test of Attention*. 1st edition. Gottingen: Hogrefe (publication in German)
 37. Luteijn F, van der Ploeg FAE (1983) *Groninger intelligence test: manual*. Swets & Zeitlinger, Lisse (publication in Dutch)
 38. Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G (1993) *Wisconsin card sorting test manual: revised and expanded (WCST)*. Psychological Assessment Resources (PAR), Odessa
 39. Wechsler D (1971) *Manual of the Wechsler intelligence scale for children*. The Psychological Corporation, New York
 40. Thurstone LL, Thurstone TG (1962) *Primary mental abilities*. University of Chicago Press, Chicago
 41. Austin MP, Mitchell P, Goodwin GM (2001) Cognitive deficits in depression: possible implications for functional neuropathology. *Br J Psychiatry* 178:200–206
 42. Tiemeier H (2003) Biological risk factors for late life depression. *Eur J Epidemiol* 18:745–750
 43. Bouma J, Ranchor AV, Sanderman R, van Sonderen E (1995) *Assessing symptoms of depression using the CES-D. A manual*. NCG, Rijksuniversiteit Groningen, Groningen (publication in Dutch)
 44. Radloff L (1977) The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1:185–401
 45. Filley C (2001) *The behavioral neurology of white matter*. Oxford University Press, New York
 46. Dow C, Seidenberg M, Hermann B (2004) Relationship between information processing speed in temporal lobe epilepsy and white matter volume. *Epilepsy Behav* 5:919–925
 47. Ryan CM (2005) Diabetes, aging, and cognitive decline. *Neurobiol Aging* 26(Suppl 1):21–25
 48. Wong TY, Klein R, Sharrett AR et al (2002) Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA* 288:67–74
 49. Ashburner J, Friston KJ (2000) Voxel-based morphometry—the methods. *Neuroimage* 11:805–821
 50. De Bie SE (1987) *Standaardvragen 1987: Standard questions 1987: Proposal for standardisation of questions regarding background variables and interviews*. Leiden University Press, Leiden (publication in Dutch)