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Review

Structural brain imaging in diabetes: A methodological perspective

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Abstract

Brain imaging provides information on brain anatomy and function and progression of cerebral abnormalities can be monitored. This may provide insight into the aetiology of diabetes related cerebral disorders. This paper focuses on the methods for the assessment of white matter hyperintensities and brain atrophy on structural brain images, mostly magnetic resonance imaging, in diabetes. These methods range from visual rating scales to advanced semi-automated and automated image processing techniques such as volumetry and voxel-based morphometry. The findings of previous imaging studies in diabetes are discussed from a methodological perspective and recommendations for future research are given.

Keywords: Diabetes; Brain; Image analysis; Segmentation; Voxel-based morphometry; White matter hyperintensity; Cerebral atrophy; Magnetic resonance imaging; MRI

Contents

1. Introduction . . . 208
2. White matter hyperintensities . . . 209
 2.1. Assessment of white matter hyperintensities . . . 209
 2.2. White matter hyperintensities in type 1 diabetes . . . 211
 2.3. White matter hyperintensities in type 2 diabetes . . . 211
 2.4. Open questions — leads for further studies . . . 212
3. Cerebral atrophy . . . 212
 3.1. Assessment of cerebral atrophy . . . 212
 3.2. Brain volume in type 1 diabetes . . . 214
 3.3. Brain atrophy in type 2 diabetes . . . 214
 3.4. Open questions — leads for further studies . . . 215
4. Concluding remarks . . . 215
Acknowledgements . . . 215
References . . . 216

1. Introduction

Diabetes mellitus is a common metabolic disease characterized by hyperglycaemia due to insufficient availability of, or insensitivity to, insulin. Diabetes is associated with slowly progressive end-organ damage in the eyes, kidneys, blood

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vessels, and peripheral nerves, as well as in the brain. It is now well recognized that both type 1 and type 2 diabetes are associated with impaired cognitive functioning. In type 1 diabetes mellitus this is reflected in a mild to moderate slowing of mental speed and a diminished mental flexibility (Brands et al., 2005). In type 2 diabetes cognitive changes mainly affect learning and memory, mental flexibility, and mental speed (Cukierman et al., 2005; Strachan et al., 1997). In older individuals with diabetes the risk of dementia is increased (Biessels et al., 2006; Cukierman et al., 2005). The pathogenesis of these cognitive impairments is not completely understood. Both diffuse cerebral pathology related to glucose toxicity and abnormalities in insulin metabolism and focal and diffuse vascular lesions have been implicated (Biessels et al., 2006).

Brain imaging provides a way to study the relation between cognitive impairments and brain anatomy and function. It may thus provide insight into the aetiology of diabetes induced cerebral disorders. Brain imaging techniques can also be used to monitor the progression of cerebral complications and may be of value in providing surrogate outcome measures in treatment studies. Over the past years, the number of brain imaging studies in patients with diabetes has been increasing steadily. A recent systematic review on this topic concluded that there is convincing evidence for an association between diabetes and cerebral atrophy and lacunar infarcts, but that it is still uncertain whether or not diabetes is associated with so-called white matter hyperintensities (van Harten et al., 2006). It was suggested that this latter uncertainty was at least partly due to the methods that have been used to assess white matter hyperintensity severity. These methods may not have been sufficiently sensitive to detect subtle alterations. Questions also remain with regard to the risk factors for abnormalities on brain imaging in diabetes and to the relation between imaging abnormalities and cognition (van Harten et al., 2006).

Developments in brain imaging and, in particular, image analysis are providing powerful tools for filling the gaps in our knowledge on the effects of diabetes on the brain. Where early studies relied on relatively crude ordinal visual scales to assess abnormalities on brain images, more sophisticated volumetric analysis techniques are now becoming commonplace. The present paper provides an overview on techniques that can be used to measure and quantify cerebral abnormalities on structural brain images, and on the application of these techniques in patients with diabetes. We will focus on assessment of white matter hyperintensities and of brain volume and atrophy. Previous reviews have addressed brain imaging studies on the relation between diabetes and infarcts (van Harten et al., 2006) and microbleeds (Cordonnier et al., 2007). We will address advantages and disadvantages of different assessment methods. In addition, the findings of currently available studies of patients with diabetes will be discussed from a methodological perspective and leads for future studies will be offered.

2. White matter hyperintensities

White matter hyperintensities are observed frequently in aging individuals (de Leeuw et al., 2001). White matter hyperintensities progress over time (Enzinger et al., 2007). White matter hyperintensity presence and severity are associated with impaired cognition and with accelerated cognitive decline (Charlton et al., 2006; de Groot et al., 2002; van den Heuvel et al., 2006b; Longstreth et al., 2005). The development of white matter hyperintensities has been linked to vascular risk factors and vascular disease, but the exact underlying pathophysiology of white matter hyperintensities is still unclear (van Dijk et al., 2004; van den Heuvel et al., 2004; Kuller et al., 2004).

2.1. Assessment of white matter hyperintensities

Various techniques have been developed to assess white matter hyperintensity load, ranging from qualitative dichotomization to quantitative volumetric measures. Visual rating scales have been used frequently. Advantages of these scales are ease of application, scanner independence, and tolerance to variation in image quality and format, which is of particular value in multi-center studies.

For cross-sectional studies the inter- and intra-rater reliability have been shown to be moderate to good (Kapeller et al., 2003; Scheltens et al., 1998). However, rater reliability is dependent on lesion load (Wardlaw et al., 2004). Moreover, in longitudinal studies inter-rater agreement on lesion progression is poor (Kapeller et al., 2003; Prins et al., 2004), as is the correlation with white matter hyperintensity volume (Prins et al., 2004). Scales that distinguish between a limited number of grades of white matter hyperintensity severity have limited resolution and sensitivity in distinguishing small differences in white matter hyperintensity load. Moreover, some scales suffer from ceiling effects (van Straaten et al., 2006; Wardlaw et al., 2004). Although correlation between scales is high (Pantoni et al., 2002), inconsistencies in association of white matter hyperintensities with clinical signs or underlying risk factors can result from the use of different rating scales (Mäntylä et al., 1997). Visual rating scales have been shown to correlate well with clinical data such as gait disturbance and cognition (Gouw et al., 2006; van Straaten et al., 2006).

Determination of white matter hyperintensity volume offers a quantitative measure of white matter hyperintensity severity, but requires high-quality images and advanced image processing techniques or time-consuming manual interaction. White matter hyperintensity volumetry has been performed with different degrees of automation. Implementation of (semi-) automated techniques is time-consuming because both technical issues as well as tailoring of the algorithm to the specifics of the images and patient population need to be addressed. However, once operational, large amounts of data can be processed efficiently.

Manual outlining of lesions is very labour intensive, but can be applied for measuring lesion progression in large cohorts e.g. (Schmidt et al., 2003). Semi-automated techniques decrease the time required for lesion segmentation and improve reproducibility compared to manual segmentation. Various approaches have been used. Payne et al. (2002; used in Taylor et al., 2003a, 2005) use manually selected seed points (see Box 1) to initialize

Box 1

Image analysis terminology

Classification — the process of assigning each voxel to a single tissue class based on knowledge derived from learning data

Clustering — the process of grouping voxels based on (intensity) similarity

Histogram — graph showing the frequency of every intensity in the image

Probabilistic classification — the process of assigning each voxel to multiple tissue classes with a different probability for each class based on knowledge derived from learning data

Registration — the process of estimating an optimal spatial transformation between two images

Seed point — manually selected point that serves as initialization of an algorithm, for example region growing

Segmentation — the process of dividing an image into meaningful parts or segments

Template image — reference or atlas image of the spatial distribution of a tissue class

Threshold — an intensity value above which voxels are included and below which they are excluded

a classification algorithm that segments brain images based on the different intensities of a tissue on proton density and T2 weighted magnetic resonance (MR) images. Jeerakathil et al. (2004) determine a white matter hyperintensity threshold based on the analysis of image intensity histograms. Slice-by-slice thresholding was used by van Straaten et al. (2006) to segment white matter hyperintensities from MR fluid attenuated inversion recovery (FLAIR) images.

Fully automated methods allow operator independent and reproducible white matter hyperintensity segmentation. Wen and Sachdev (2004a) have automatically segmented white matter hyperintensities based on voxel intensity on MR FLAIR images combined with a template of white matter distribution. Admiraal-Behloul et al. (2005) have combined clustering of image intensities from MR FLAIR, T2 weighted and proton density images with a subsequent rule-based segmentation to segment white matter hyperintensities. Anbeek et al. (2004, 2005) have developed a method for probabilistic classification of MR FLAIR and inversion recovery images based on the *k*-nearest neighbour classification algorithm. Using both intensity and spatial information each voxel is assigned a probability for every tissue class. The algorithm produces probability images for white matter hyperintensities as well as for white matter, gray matter, cerebrospinal fluid (CSF) and lateral ventricles (Fig. 1).

So far, different approaches to volumetric white matter hyperintensity segmentation have not been compared systematically. Admiraal-Behloul et al. (2005) and Anbeek et al. (2004, 2005) have evaluated their methods using the similarity index, a measure of overlap with gold standard segmentations, which demonstrated high performance of both algorithms. Volumetry has been observed to be slightly more sensitive to detect correlations with clinical data than elaborate visual rating scales (van Straaten et al., 2006). Comparison of an elaborate

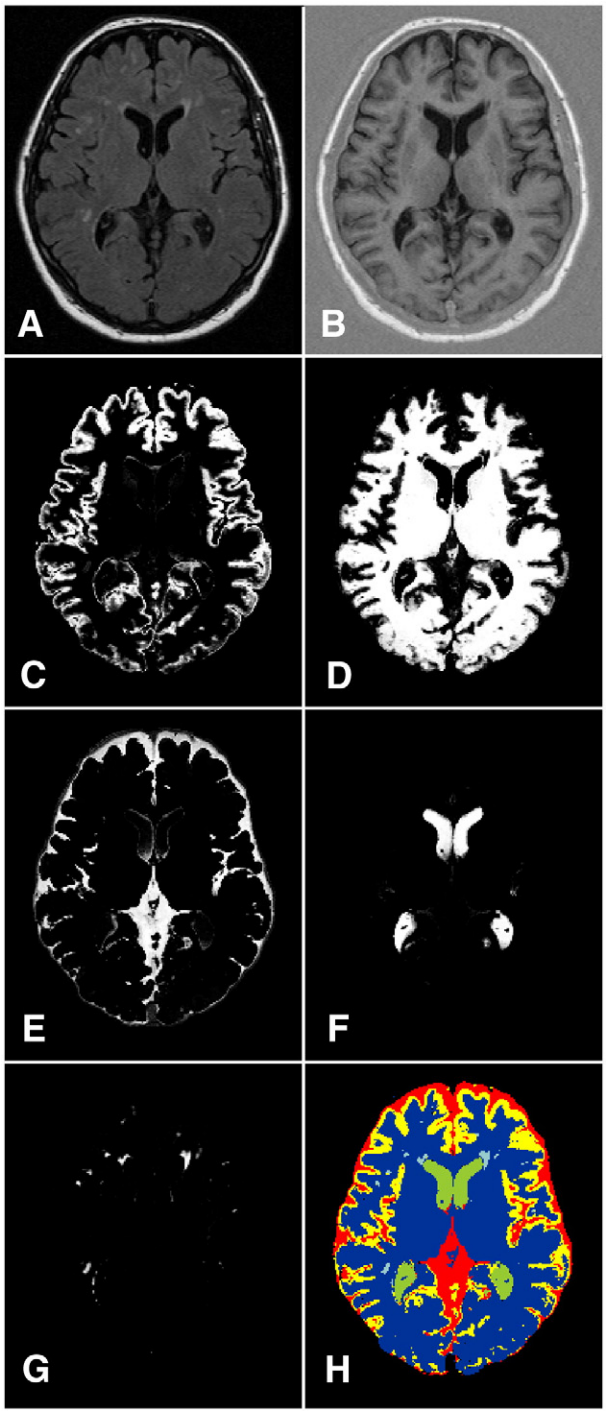

Fig. 1. Example of *k*-nearest neighbour-based probabilistic segmentation of MR FLAIR (a) and inversion recovery (b) images of a 73-year-old man with type 2 diabetes. Probabilistic segmentations of gray matter (c), white matter (d), cerebrospinal fluid not including the lateral ventricles (e), lateral ventricles (f), and white matter hyperintensities (g) are shown. A composite image (h) shows the segmentations after application of the optimal thresholds: gray matter (yellow), white matter (dark blue), cerebrospinal fluid (red), lateral ventricles (green), and white matter hyperintensities (light blue).

visual rating scale (Scheltens et al., 1993) with assessment of white matter hyperintensity volume (Admiraal-Behloul et al., 2005) showed that intra- and inter-rater reliability was higher, association of white matter hyperintensity severity and progression with age was stronger, and longitudinal white matter hyperintensity regression was less for the volumetric method (van den Heuvel et al., 2006a).

Direct comparisons between visual rating scales and volumetry indicate that several rating scales do correlate well with measured lesion volume, particularly those with more detailed white matter hyperintensity grading (Kapeller et al., 2003; van Straaten et al., 2006; Tiehuis et al., 2008). However, the relation of rating scale scores with volume is nonlinear and the ability of rating scales to discriminate between absolute white matter hyperintensity volumes is limited. For application in studies on the relation between white matter hyperintensities and diabetes we propose the following: 1) In small cross-sectional studies on white matter hyperintensities in diabetes, the use of elaborate and relatively sensitive rating scales can be adequate, given their good performance in cross-sectional designs and their ease of application. 2) In larger cross-sectional studies, the efforts needed to get an automated system up-and-running may be equivalent to rating all images manually; therefore, the use of more consistent and sensitive automatic volumetry methods is advisable. 3) For longitudinal studies, rating scales do not provide sufficient sensitivity, thus, assessment of white matter hyperintensity volume is necessary. In addition, white matter hyperintensity segmentations can be used to construct maps to investigate the spatial distribution of white matter hyperintensities (DeCarli et al., 2005; Taylor et al., 2003b; Wen and Sachdev, 2004a,b; Wen et al., 2006). Lesion maps provide detailed information on lesion location that is not captured when using rating scales or volumetry.

2.2. White matter hyperintensities in type 1 diabetes

There are a limited number of studies on white matter hyperintensity severity in patients with type 1 diabetes. Early studies on this topic had methodological limitations such as small sample size, lack of appropriate non-diabetic controls, selective sampling of patients, and the use of insensitive rating scales (Dejgaard et al., 1991; Lunetta et al., 1994; Nakamura et al., 1991; Perros et al., 1997). Moreover, these studies mostly involved adults below the age of 40–50 years. The combination of relatively young study populations with small sample sizes puts marked constraints on statistical power. Hence, these studies provide no definite information on the severity of white matter hyperintensities in patients with type 1 diabetes relative to controls.

Brands et al. (2006) have recently reported on white matter hyperintensity severity in older (average age 61) patients with type 1 diabetes, using a detailed ordinal rating scale (Scheltens et al., 1993). Although the patients performed slightly worse on cognitive tests than matched non-diabetic controls, white matter hyperintensity severity was not significantly different between the groups. Within the patient group, white matter hyperintensity severity was not significantly associated with cognitive performance. Interestingly, a direct comparison between these patients with type 1 diabetes and an age, sex, and education matched group of patients with type 2 diabetes revealed a more severe white matter hyperintensity load in the type 2 diabetes group, despite a much shorter known duration of diabetes (34 versus 7 years) (Brands et al., 2007).

In a cross-sectional study of patients with type 1 diabetes, presence of diabetic retinopathy, an indicator of chronic exposure to hyperglycaemia, was associated with small punctate white matter hyperintensity, i.e. enlarged perivascular spaces, and moderate cognitive impairments, whereas recurrent severe hypoglycaemia was not associated with changes in brain structure or cognition (Ferguson et al., 2003). Furthermore, diabetes onset before the age of seven was associated with small punctate white matter hyperintensities in the hippocampus, but not with other white matter hyperintensities (Ferguson et al., 2005).

2.3. White matter hyperintensities in type 2 diabetes

The systematic review by van Harten et al. (2006) included 25 studies that compared the occurrence of white matter hyperintensities in patients with type 2 diabetes with a reference population. A meta-analysis of these studies revealed no consistent association between type 2 diabetes and white matter hyperintensity across different study populations. This inconsistency was attributed, at least in part, to methodological issues like the selection and size of study cohort, study design, and the methods used for white matter hyperintensity measurement. The 25 included studies mostly used relatively crude visual rating scales. Such scales may lack the sensitivity required to detect relatively subtle differences in white matter hyperintensity load between patients with diabetes and controls.

Over the past two years, several studies have appeared that provide further insight into the relation between diabetes and white matter hyperintensities. A large population-based cohort study, that applied a 10-point rating scale (Bryan et al., 1994), observed no significant differences in white matter hyperintensity severity between patients with type 2 diabetes and controls (Korf et al., 2006). On the other hand, two large case–control studies, that both used the detailed Scheltens white matter hyperintensity rating scale (Scheltens et al., 1993), observed significantly more deep white matter hyperintensities in patients with type 2 diabetes than in control subjects (van Harten et al., 2007a; Manschot et al., 2006). In one of these studies white matter hyperintensity severity was also assessed with an automated volumetric method (Jongen et al., 2007), using probabilistic classification (Anbeek et al., 2005). White matter hyperintensity volumes in patients with type 2 diabetes were 56% larger than in controls (Jongen et al., 2007). Another case–control study that used seeds and region growing on MR FLAIR images to perform volumetric measurement of white matter hyperintensities in a somewhat smaller sample of patients with type 2 diabetes did not detect differences in total white matter hyperintensity volume relative to controls, but did observe regional differences in lesion volume between the groups (Novak et al., 2006).

Recent studies have also provided initial leads regarding the possible causes and consequences of white matter hyperintensities in patients with type 2 diabetes. Diabetes duration, glycated haemoglobin (HbA_{1c}) and insulin levels, blood pressure and the presence of infarcts have all been linked to white matter hyperintensity severity (van Harten et al., 2007a; Manschot et al., 2007). In addition, cerebral blood flow velocity was reported to be negatively associated with periventricular white matter hyperintensity volume (Novak et al., 2006). Finally, several studies report associations between white matter hyperintensity severity and cognitive functioning, in particular on measures of processing speed (Akisaki et al., 2006; van Harten et al., 2007b; Manschot et al., 2006).

2.4. Open questions — leads for further studies

As detailed above the relation between type 1 diabetes and white matter hyperintensity is still uncertain. Studies into cerebral complications of type 1 diabetes are mostly performed in young adult patients. If one intends to investigate white matter hyperintensities in young adults with diabetes, the following considerations should be taken into account: in the general population, white matter hyperintensities are relatively uncommon in this age group and in individuals in whom white matter hyperintensities are present, the volume is small. Based on the currently available data, there is no reason to assume that type 1 diabetes will have a major impact on white matter hyperintensity severity. Consequently, studies that aim to collect reliable data on white matter hyperintensity severity or development in younger patients with type 1 diabetes should have large sample sizes, use sensitive measures of white matter hyperintensity severity and preferably have a longitudinal design. In fact, given the current state of affairs it is questionable if research into structural correlates of impaired cognition in young adults with type 1 diabetes should be directed at white matter hyperintensities at all. Outside the field of diabetes, the relation between white matter hyperintensities and cognition has been scrutinized. Even in older adults with a marked white matter hyperintensity load the relation with cognitive functioning is modest, particularly in cross-sectional studies (Au et al., 2006; de Groot et al., 2000, 2002; Garde et al., 2000). For example, in a large population-based cohort of older individuals, a cross-sectional assessment of the relation between white matter hyperintensity load and cognition showed only modest associations, with a difference in cognitive *z*-score of 0.2 in individuals with the lowest, relative to the highest quintile in white matter hyperintensity load (de Groot et al., 2000). Hence, the tiny lesion volumes that are to be expected in young adults with type 1 diabetes are not likely to be a key determinant of altered cognition.

With regard to type 2 diabetes, a number of studies have now reported an association with increased white matter hyperintensity load both by using visual rating scales as well as by volumetric measures. However, the increase in white matter hyperintensity severity relative to controls is modest, with a two-fold increase in lobar, but not periventricular white matter hyperintensity severity on visual rating scales (Manschot et al., 2006; van Harten et al., 2007a) and 56% higher lesion volume on volumetric measures (Jongen et al., 2007). Although this higher white matter hyperintensity load may account for part of the differences in cognition between patients with type 2 diabetes and controls (Manschot et al., 2006; van Harten et al., 2007a), it has to be acknowledged that on average white matter hyperintensity severity in the patients is within the normal range. In fact, at group level the difference between individuals with type 2 diabetes and those without is relatively small, compared to the large variation in white matter hyperintensity severity that can be observed in otherwise healthy elderly subjects. This stresses the need for adequate study sample sizes, in the order of at least 100 subjects per group, and sensitive white matter hyperintensity rating methods in future studies. Longitudinal studies of lesion progression should be the next step to examine the associations between type 2 diabetes and white matter hyperintensity severity. Combining automated assessment of white matter hyperintensity volume with lesion maps will provide information on both global and local white matter hyperintensity progression and will help to identify determinants of white matter hyperintensity progression.

3. Cerebral atrophy

Cerebral atrophy or the diffuse loss of brain tissue is strongly associated with age and vascular risk factors (Du et al., 2006; Kuller et al., 2005). Cerebral atrophy is associated with cognitive impairment and accelerated cognitive decline (Kramer et al., 2007; Whitwell et al., 2007). On brain imaging, atrophy shows as widening of sulci and/or lateral ventricles.

3.1. Assessment of cerebral atrophy

Atrophy can be measured globally as well as locally. Various methods for atrophy assessment have been developed, ranging from visual rating scales to automated volumetric measurements. Several rating scales for atrophy measurement are in use. The simplest is a dichotomous scale recording atrophy presence or absence. Manolio et al. (1994) developed two ten-level grading scales to assess ventricular and sulcal widening by comparing patient images with reference images displaying various degrees of widening. Scheltens et al. (1997) developed a scale that uses the sum of four-level atrophy ratings over several brain regions. Some scales are also specifically directed at atrophy in certain brain areas, in particular the medial temporal lobe. Scheltens et al. (1992, 1995) have developed a five-point rating scale for the assessment of medial temporal lobe atrophy. Use of this scale for medial temporal lobe atrophy assessment has been compared with volumetry on the ability to correctly classify Alzheimer's disease patients and controls and the rating scale was found to perform as good as volumetry (Bresciani et al., 2005; Wahlund et al., 2000). Brain atrophy can also be assessed by manual linear measures. These measures are usually calculated as the width of the lateral ventricles or central sulcus measured at a predefined position divided by the brain diameter. Examples are the so-called bicaudate ratio for subcortical atrophy and the sylvian fissure or frontal fissure ratio for cortical atrophy (Gomori et al., 1984).

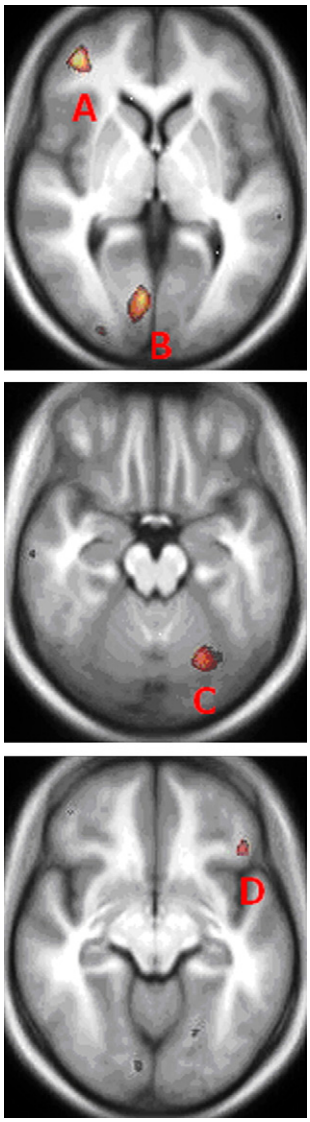

Fig. 2. Voxel-based morphometry in type 1 diabetes shows a reduction in gray matter density in patients with diabetic retinopathy. Changes in gray matter density are shown on a mean normalized structural image in axial planes. Thirteen patients with type 1 diabetes with proliferative retinopathy have been compared with 18 patients without retinopathy. The images show areas of significantly reduced gray matter density ($p<0.05$ corrected for multiple comparisons) in the right frontal gyrus (A), right occipital lobe (B), left cerebellum (C) and left middle frontal gyrus (D) in the patients with diabetic retinopathy. Left in the image is right in the brain. Images courtesy of Dr. A.M. Wessels, VU University Medical Center, Amsterdam, The Netherlands, reproduced from Wessels et al. (2006) with permission from the publisher.

Rating scales and linear measures of brain atrophy are tolerant to differences in image quality and scan protocol. This can be advantageous for large studies that rely on data from different sites or scanners. However, rating scales are observer dependent and provide only a qualitative assessment of atrophy. Linear measures do provide a quantitative measure of atrophy, but measurements are only obtained on a limited number of locations, are performed manually, and are therefore also operator dependent. Therefore, these methods may not be sensitive and reliable enough to detect localised or subtle tissue losses in, for example, patients with diabetes.

Voxel-based morphometry is essentially a qualitative method for the estimation of differences in gray or white matter density between groups of subjects (Ashburner and Friston, 2000). The method consists of spatial normalization of brain images to a template image followed by a segmentation step and finally, statistical analyses per voxel using a general linear model. This allows assessment of differences in small regions for which the size depends on the applied smoothing kernel. The validity and applicability of voxel-based morphometry has been subject of debate (Ashburner and Friston, 2001; Bookstein, 2001; Davatzikos, 2004). Effects of registration and registration errors and of systematic shape differences between groups on the validity of voxel-based morphometric analyses as well as effects of local anatomical variability on the sensitivity to detect differences have been discussed. The original method has been adapted and improved by, for example, the use of study-specific group templates and tissue probability maps to allow more accurate spatial normalization and tissue segmentation (Good et al., 2001; Senjem et al., 2005). Fig. 2 shows results from the study on differences in gray matter density in patients with type 1 diabetes with and without diabetic retinopathy by Wessels et al. (2006) as an example of voxel-based morphology applied to brain imaging in diabetes.

Volumetry provides quantitative information on brain tissue volume. Initially, volumetry solely relied on manual outlining of structures of interest by an expert. Although manual outlining is time-consuming and subject to inter- and intra-rater variability, it is usually considered to be the golden standard for image segmentation procedures. In diabetes research, it has been used to measure hippocampal atrophy in several studies. Automated volume measurements have the advantage of reproducibility and short user-interaction time. Several approaches have been used in the study of diabetes. Atlas-based segmentation is the registration of a pre-labelled atlas image to a patient image such that the atlas label can be projected onto the patient image. Atlas-based segmentation of the hippocampus has been shown to give reasonable results compared to manual outlining in Alzheimer's disease and mild cognitive impairment (Carmichael et al., 2005). Adaptive segmentation is an automated method for whole brain segmentation (Wells et al., 1996). This method iteratively estimates parameters of a model of the intensity distributions of gray matter, white matter, and cerebrospinal fluid. Probabilistic classification has been used for segmentation of the brain into gray matter, white matter, cerebrospinal fluid, lateral ventricle, and white matter hyperintensities (Anbeek et al., 2005). The algorithm uses *k*-nearest neighbour classification to assign tissue class probabilities to each voxel. Evaluation of this method showed excellent agreement with expert manual segmentations (Anbeek et al., 2005). Segmentation of brain images of a patient with type 2 diabetes using this method is shown in Fig. 1.

Other popular brain image segmentation approaches are combining a priori probability maps, which encode knowledge of the spatial distribution of tissues, with models of intensity distribution (Ashburner and Friston, 1997, 2005) and combining intensity distribution models with a hidden Markov random field to incorporate neighbourhood information (Zhang et al., 2001).

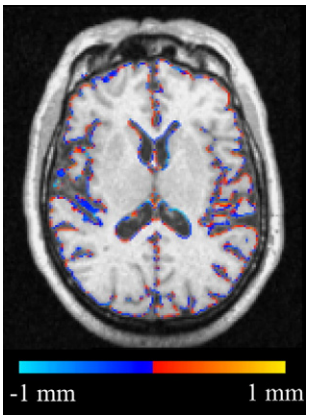

Fig. 3. Example of an edge-displacement map of a 66-year-old patient with type 2 diabetes with mild cognitive impairment overlaid on the baseline axial MR image. Time between baseline and follow-up MR scans was 1 year and 5 months. Estimated rate of atrophy was −1.4%/year. Dark-blue to light blue represents mild to severe local contraction, which implies atrophy. Red to yellow indicates mild to severe local expansion of brain tissue. Note that for display purposes, edge motion was truncated at 1 mm in this figure. Image courtesy of Dr. J.D. Sluimer, VU University Medical Center, Amsterdam, The Netherlands.

Longitudinal changes in brain volume can be measured by estimating the displacement of the brain boundary between baseline and follow-up scans. This approach has, for example, been adapted in the structural image evaluation using normalization of atrophy (SIENA) method (Smith et al., 2001, 2002). Images from two time-points are co-registered using the skull surface to control scaling. Fig. 3 shows an example of atrophy assessment using SIENA in a patient with type 2 diabetes. A similar method is the brain boundary shift integral (Freeborough and Fox, 1997). Other approaches to assess volume change over time have fluidly warped baseline to follow-up scans to determine volume changes from the deformation field, such as tensor-based morphometry (Ashburner and Friston, 2003) and Jacobian integration (Boyes et al., 2006). Validation studies showed good discrimination between control and Alzheimer's disease patients by SIENA as well as boundary shift integral methods, with SIENA performing slightly better (Gunter et al., 2003; Smith et al., 2007). Longitudinal assessment of atrophy in multiple sclerosis patients using SIENA was more precise and sensitive than volumetry based on thresholding and manual editing (Anderson et al., 2007) and Jacobian integration has been shown to perform better in atrophy assessment in Alzheimer's disease patients than the boundary shift integral (Boyes et al., 2006).

When determining which automated technique to use for assessment of brain atrophy it is important to consider that the nature of voxel-based morphometry and volumetry is different. Voxel-based morphometry is a qualitative measure that provides relative differences in tissue density across the whole brain without the need for prior definition of regions of interest. Brain volumetry provides quantitative measures of volume, but accurate segmentation of small regions of interest, such as the hippocampus, is difficult to achieve automatically and manual segmentation is time-consuming. When both methods are applied in the same subjects, different results are sometimes obtained. For example, assessment of age related decreases in frontal cortical volume with voxel-based morphometry and manual outlining resulted in different regional associations (Tisserand et al., 2002), suggesting that voxel-based morphometry may be used to identify additional regions of interest for volumetric assessment. In another study, voxel-based morphometry more accurately discriminated between Alzheimer's disease patients and controls than manual outlining of the hippocampus, but the discrimination was improved by combining voxel-based morphometry and volumetry (Testa et al., 2004). Thus, application of both voxel-based morphometric and volumetric analyses may have added value.

Longitudinal assessment of atrophy by determining brain boundary displacement or by using deformation fields seems more accurate than volumetry and is particularly suited to assess regional atrophy rates in individual subjects. Group analysis can be obtained by registering individual subjects to a reference image and mapping individual atrophy rates to the reference image. These data provide insight in local differences in atrophy rates and, in addition, may be used to guide regional volumetric assessment of atrophy.

3.2. Brain volume in type 1 diabetes

Studies on brain volume in type 1 diabetes have used both manual linear measures and volumetric techniques. Using linear measures in a small number of patients with type 1 diabetes, Lunetta et al. (1994) found ventricular enlargement relative to controls. Brands et al. (2006) found similar cortical and subcortical atrophy in patients with type 1 diabetes and controls, but patients with diabetes performed worse on cognitive tests. Manual outlining of the hippocampus showed similar volumes in patients with type 1 diabetes and control subjects, but estimates of the cerebral volume were significantly smaller in the patients with type 1 diabetes (Lobnig et al., 2006). Voxel-based morphometric analyses indicated lower gray matter densities in several brain regions in patients with type 1 diabetes compared to controls (Musen et al., 2006). Furthermore, in patients with type 1 diabetes with diabetic retinopathy reduced gray matter density in several brain regions was found when compared to patients without retinopathy or to controls (Wessels et al., 2006 (see also Fig. 2)). Patients with type 1 diabetes without retinopathy did not differ from controls (Wessels et al., 2006).

In patients with type 1 diabetes an early age of diabetes onset ($\leq$7 years) has been associated with a larger ventricular volume (Ferguson et al., 2005). Furthermore, chronic hyperglycaemia and acute severe hypoglycaemia as well as presence of retinopathy have been associated with reduced gray matter densities (Musen et al., 2006; Wessels et al., 2006).

3.3. Brain atrophy in type 2 diabetes

The systematic review by van Harten et al. (2006) included nine studies that compared measures of brain atrophy in patients with type 2 diabetes to a reference population (van Harten et al., 2006). The majority of these studies used relatively crude

ordinal rating scales. Nevertheless, all but one showed an association between type 2 diabetes and cerebral atrophy, but atrophy measurements were too heterogeneous for meta-analysis.

Since then, a number of papers have reported results that provide further insight in the association between atrophy and diabetes. No significant associations of atrophy with type 2 diabetes have been observed in a case–control study using rating scales (van Harten et al., 2007b) or in a large population-based study using linear measures (Korf et al., 2006). However, using rating scales in a population-based cohort, Knopman et al. (2005) found a significant association of diabetes with greater ventricular size and Korf et al. (2007) found higher scores of medial temporal lobe atrophy in patients with type 2 diabetes from a large study of elderly individuals selected for the presence of white matter hyperintensities. In a large case–control study linear measures of atrophy showed more cortical and subcortical atrophy in patients with type 2 diabetes than controls (Manschot et al., 2006). In this study, application of a method for probabilistic classification (Anbeek et al., 2005) showed larger lateral ventricle and smaller gray matter volumes in patients with type 2 diabetes than in controls (Jongen et al., 2007). In a small case–control study, manual outlining of several regions of interest showed smaller hippocampal volumes in patients with type 2 diabetes (Gold et al., 2007). In a population-based study SIENA was used to assess longitudinal changes in brain atrophy and significantly higher rates of atrophy were found in subjects with higher HbA_{1c} levels (Enzinger et al., 2005). Furthermore, atlas-based segmentation showed larger longitudinal changes in ventricle-to-brain volume ratio in diabetes subjects in a cohort of patients with vascular disease (Carmichael et al., 2007).

In a case–control study, atrophy, assessed with a rating scale, was not associated with cognitive performance in patients with type 2 diabetes (van Harten et al., 2007b). Other studies, however, did report an association between linear measurements of subcortical atrophy and impaired speed of cognitive processing and memory (Akisaki et al., 2006) and attention and executive function and information processing speed (Manschot et al., 2006). Using adaptive segmentation, cortical and subcortical atrophy was found to be associated with diminished regional cerebral perfusion in patients with type 2 diabetes (Last et al., 2007).

3.4. Open questions — leads for further studies

The available studies clearly indicate that both type 1 and type 2 diabetes are associated with modest reductions in brain volume relative to reference populations.

With regard to type 1 diabetes, it should be noted that it is yet unclear if these reductions in volume should formally be regarded as atrophy. The available studies are cross-sectional and the majority involve young-adult individuals. Because the onset of diabetes was in childhood or adolescence in the majority of the patients involved, differences in brain volume relative to controls may also reflect alterations in brain development. This points to the need for adequate longitudinal studies. Such studies can help to distinguish between alterations in development and actual volume loss. Prospective studies are also better suited to detect risk factors for differences in brain volume between patients with type 1 diabetes, and as such may help to identify patients at increased risk of cerebral complications of diabetes and its treatment.

With regard to type 2 diabetes the main open questions that remain, also relate to the course of development and the risk factors of brain atrophy. Type 2 diabetes develops in the context of a cluster of metabolic and vascular risk factors, also known as the insulin resistance syndrome, or the metabolic syndrome (Reaven, 1988). Metabolic and vascular risk factors associated with type 2 diabetes, such as hyperinsulinemia, hypertension, and dyslipidemia, may precede the actual onset of diabetes by many years. Several of these factors have been linked to accelerated cognitive decline and dementia and to cerebral atrophy (Biessels and Kappelle, 2005; Longstreth et al., 2000). Hence, brain volume loss may already develop in pre-diabetic stages. Detailed longitudinal studies may not only indicate at what stages of (pre-)diabetes volume loss becomes evident and pinpoint risk factors for accelerated atrophy, but may also show which regions of the brain are affected in the early stages of the disease. The latter may be particularly relevant in research on underlying mechanisms and on the relation between structural changes and cognitive functioning.

4. Concluding remarks

This paper has provided an overview on the relation between diabetes and white matter hyperintensities, brain volume, and atrophy. The available data have been summarized from a methodological perspective and leads for future studies have been provided. For a full understanding of the impact of diabetes on the brain, data on white matter hyperintensity severity and atrophy need to be integrated with data on cognitive functioning and relevant disease variables. Other brain imaging techniques may provide additional valuable insights. Diffusion tensor imaging is a promising technique for the investigation of microscopic abnormalities in brain structure, for example changes in white matter integrity, in diabetes. The use of diffusion tensor imaging in the study of dementias has recently been reviewed by Bozzali and Cherubini (2007). Techniques that provide information on cerebral blood flow and vasculature, such as single photon emission computed tomography, perfusion CT or MR imaging, and MR angiography may give insight into the pathophysiology of diabetes. Information on brain metabolism can be obtained using MR spectroscopy, positron emission tomography, or single photon emission computed tomography imaging and functional MR imaging can be used to study brain activation in patients with diabetes.

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