Brain Changes Underlying Cognitive Dysfunction in Diabetes: What Can We Learn From MRI?

Diabetes is associated with cognitive dysfunction and an increased risk of dementia. This article addresses findings with brain MRI that may underlie cognitive dysfunction in diabetes. Studies in adults with type 1 diabetes show regional reductions in brain volume. In those with a diabetes onset in childhood, these volume reductions are likely to reflect the sum of changes that occur during brain development and changes that occur later in life due to exposure to diabetes-related factors. Type 2 diabetes is associated with global brain atrophy and an increased burden of small-vessel disease. These brain changes occur in the context of aging and often also in relation to an adverse vascular risk factor profile. Advanced imaging techniques detect microstructural lesions in the cerebral gray and white matter of patients with diabetes that affect structural and functional connectivity. Challenges are to further unravel the etiology of these cerebral complications by integrating findings from different imaging modalities and detailed clinical phenotyping and by linking structural MRI abnormalities to histology. A better understanding of the underlying mechanisms is necessary to establish interventions that will improve long-term cognitive outcomes for patients with type 1 and type 2 diabetes.

Interest in the effect of diabetes on the brain is growing. It is now clear that type 1 diabetes is associated with modest decrements in cognitive functioning, which are most marked in patients with an early childhood diabetes onset (1). These decrements in adults with type 1 diabetes are most evident in the domains of general intelligence, psychomotor speed, and mental flexibility (2). On these domains, the magnitude of the decrements is ~0.3 to 0.7 SD units relative to people without diabetes (2). This implies that, on average, the performance of people with diabetes on these domains is at the 30th to the 40th percentile of control values. The progression of cognitive decrements in adults with type 1 diabetes, relative to people without diabetes, is generally slow, except in subgroups of patients with marked microvascular complications, who may show more marked decline (1).

Modest decrements in cognitive functioning, evident on the domains of verbal and visual memory, information processing speed, and executive functioning, have also been noted in people with type 2 diabetes across all age groups (3). Similar to type 1 diabetes, effect sizes are small to moderate (0.3 to 0.4 SD units) (4) and follow a slow progression over time, only modestly exceeding the rate of normal aging-related cognitive decline (3). In older people, however, particularly older than the age of 65, type 2 diabetes is also associated with more severe forms of cognitive impairment. Data from large epidemiological surveys link diabetes to an increased dementia risk. A meta-analysis estimated that people with type 2 diabetes have a relative risk of vascular dementia of 2.5 (95% CI 2.1–3.0) and that of Alzheimer disease is 1.5 (95% CI 1.2–1.8) relative to individuals without diabetes (5). To prevent the progression of subtle cognitive decrements in dementia in patients with diabetes, we need to develop an understanding of the causative mechanisms at the earliest stages of cognitive decline.
This article addresses brain changes that may underlie cognitive dysfunction in adults with diabetes, focusing on MRI. We will address the effect of diabetes on brain volumes, markers of small-vessel disease (SVD), and on structural and functional connectivity. We will also consider methodological aspects that may help to interpret the existing data and support the design of future studies.

BRAIN VOLUMES

Brain volumes can be assessed with various methods, ranging from visual rating scales to automated segmentation methods. Visual rating scales are tolerant to differences in image quality and scan protocol, but their downside is that they are operator dependent and provide only a qualitative and rather insensitive measure of atrophy (6). Automated segmentation methods, including voxel-based morphometry (VBM), probabilistic tissue classification, and surface-based parcellation techniques, offer an operator independent and quantitative assessment of brain volumes (6). Furthermore, VBM and surface-based parcellation techniques allow for investigation of local differences in brain anatomy by comparing volume measures across brains at every voxel. Because quantitative techniques are more sensitive to detect subtle differences in gray or white matter tissue, they are preferred methods to measure brain volume in patients with diabetes (7).

Automated segmentation techniques, however, also have some limitations. The accuracy of the automated tissue segmentation depends on the image contrast and therefore on the quality of the MRI scans. Brain images acquired from different scanners or with different scan parameters will thus lead to variation in volume estimates. A second limitation is that VBM comparison methods require spatial normalization and registration of the brain to a standard template. The degree of spatial normalization or smoothing can greatly affect the results. If one averages over larger regions, the effect of misregistration is reduced, but too much smoothing may mask local volume loss. Finally, when analyzing across multiple voxels, statistical corrections should be applied to limit the chance of finding false-positive effects (i.e., type I error). Researchers usually tend to choose multiple correction methods that have high power to detect differences, such as the false discovery rate method, at the costs of increasing the risk for type I errors. These processing steps should be considered when interpreting the below-mentioned findings in patients with diabetes and may also explain some of the discrepancies between studies.

Type 1 Diabetes

Cross-sectional case-control studies in adults (20–60 years) with type 1 diabetes have used automated segmentation methods to demonstrate modest reductions in brain volume compared with control subjects (8–11). One study reported an overall 7% reduction in gray matter volume (8), but most studies do not report overall differences in brain volumes and only show regional differences in gray matter volume or density within the frontal (8–11), posterior (9,12), and temporal cortex (9) and in subcortical gray matter (10). The exact location of the alterations in brain volume varies greatly across studies, which highlights the difficulty of detecting small regional differences with techniques that are sensitive to interindividual differences in head size and shape.

Two of the above-mentioned studies directly related alterations in brain volume to cognitive functioning. Results showed an association between decreased brain volume and slowing of information processing speed, reduced attention, and lower IQ subtest scores (12,13). Furthermore, smaller brain volumes in patients were related with poor metabolic control, reflected by chronic hyperglycemia (9,12) and hypoglycemic events (9,10). However, not all studies observed these associations, even with large sample sizes (n > 100) (8).

Importantly, type 1 diabetes commonly has its onset in childhood or adolescence, when the brain is still developing. Brain volume reductions in adults may thus reflect changes that already occurred during brain development. Studies in children with type 1 diabetes indeed show that alterations in brain volume are already detectable in childhood (14). This may be due to the interaction of diabetes with processes such as neuronal pruning and neuronal growth, resulting in regions of decreased as well as increased brain volume (14). That smaller brain volumes are observed in adults with early onset of diabetes relative to those with a later onset supports the view that childhood brain changes leave their fingerprint up until adulthood (12,13). Longitudinal imaging studies are needed to disentangle the effects of abnormal brain development from atrophy as a result of exposure to diabetes-related factors later in life.

Type 2 Diabetes

Type 2 diabetes has consistently been associated with global brain atrophy in cross-sectional studies (Fig. 1) (15). The reduction in mean total brain volume is 0.2–0.6 SD units, comparable with 3–5 years of normal aging (16–18). Longitudinal case-control and population-based studies have demonstrated brain volume loss in patients with diabetes that is similar to or up to three times the atrophy rate of normal aging (16–19). The loss of brain tissue is most clearly reflected by accelerated expansion of the ventricles (16,17,19). These findings may indicate that type 2 diabetes–associated atrophy is most pronounced in regions surrounding the ventricles, such as subcortical gray matter or white matter regions. Another possible explanation is that the ventricles are less sensitive to segmentation errors due to the relatively high signal contrast and smooth border between brain tissue and cerebrospinal fluid. This can also explain why global brain volume loss is often detected in these regions.
Given the association between diabetes and Alzheimer disease, much attention has been directed to the hippocampus. Studies that used manual and automated segmentation methods to assess hippocampal volume in type 2 diabetes found that hippocampal volumes of patients are indeed smaller than those of age-matched control participants (20). However, a pooled analysis of three cohort studies showed that the degree of hippocampal volume loss in type 2 diabetes is comparable to the degree of total brain volume loss (Wisse et al., unpublished observations), indicating that the hippocampus is not more severely affected than the rest of the brain. Furthermore, studies have found little evidence that brain atrophy specifically contributes to memory deficits in diabetes. Most cross-sectional studies report an association between brain volume and executive functioning or processing speed (21). One longitudinal study found an association between baseline brain atrophy and decline in immediate memory but not in delayed memory (18). Two studies directly examined whether brain volume mediated the relationship between type 2 diabetes and cognitive dysfunction and reported contrasting results: gray matter volume significantly mediated the relationship with executive functioning and memory in one study (22), but in another study, between-group differences in cognition were largely independent of MRI markers of brain atrophy (19). Small brain volumes in diabetes have been associated with greater insulin resistance and longer diabetes duration (23,24), suggesting that long-term exposure to diabetes-related risk factors is especially harmful to the brain.

In conclusion, type 1 and type 2 diabetes are both associated with alterations in brain volume. However, it is important to note that there is as yet no definite proof that (patterns of) atrophy relates to specific etiologies. Pathological processes leading to brain atrophy are heterogeneous and not necessarily indicative of neuronal loss (6). Loss of glial cells and axons, white matter rarefaction and shrinkage, and arteriolosclerosis and venous collagenosis may all produce changes in brain volume. To better understand the pathological process of brain atrophy in diabetes, imaging and histopathological findings should be integrated. Techniques are now being developed that can register blocks of serially stained histological sections to postmortem brain MRI scans and will allow us in the near future to directly relate local brain imaging findings to their pathophysiological substrates.

**SVD**

Cerebral SVD refers to pathological processes that affect the small arteries, arterioles, venules, and capillaries of the brain in the context of aging and vascular risk factors. Brain MRI is a powerful tool to detect SVD, although we note that MRI shows the consequences of SVD in the brain tissue (i.e., parenchymal lesions) rather than abnormalities in the small vessels themselves. An international working group has recently proposed standardized definitions for the core MRI features of SVD, including:

- lacunes, which are round or ovoid, subcortical, fluid-filled cavities 3–15 mm in diameter, compatible with a previous acute small deep-brain infarct or hemorrhage in the territory of a single perforating arteriole;
- white matter hyperintensities (WMH), noted as signal abnormalities of variable size in the white matter that are hyperintense on fluid-attenuated inversion recovery and T2/proton density-weighted images without cavitation (Fig. 2); and
- cerebral microbleeds, characterized as small, mostly 2–5 mm areas of signal void with associated “blooming” on T2* or other MR sequences sensitive to paramagnetic material (Fig. 2) (6).
Indeed, studies that have reported WMH in patients with type 1 diabetes, that there are only a few reports on SVD but did not report negative findings. Nevertheless, on the basis the currently available data, MRI markers of SVD do not appear to be a key determinant of type 1 diabetes–associated cognitive decrements in young adults.

The etiology of the different SVD lesions on MRI is heterogeneous. Lacunes are most often due to occlusive disease of a perforating arteriole but can also be due to an embolus. Postmortem studies have shown that WMH reflect tissue abnormalities that range from slight disentanglement of the white matter structure to varying degrees of myelin and axonal loss (27). The etiology includes ischemia, hypoperfusion, blood-brain barrier leakage, inflammation, degeneration, and amyloid angiopathy (27). Postmortem validation of MRI lesions suggestive of microbleeds shows hemosiderin-laden macrophages consistent with previous vascular leakage of blood cells (6,27). The underlying vascular pathology most commonly involves hypertensive vasculopathy or cerebral amyloid angiopathy (27). The heterogeneity in etiologies of SVD lesions on MRI is important to consider when interpreting findings from studies in patients with diabetes. It implies that underlying mechanisms cannot be reliably inferred from lesion patterns or severity.

Type 1 Diabetes
In light of the increasing number of papers on brain MRI in patients with type 1 diabetes, that there are only a few reports on SVD is surprising. It could well be that several studies assessed SVD but did not report negative findings. Indeed, studies that have reported WMH in patients with type 1 diabetes observed no difference on visual rating scales compared with control subjects (28,29). Moreover, although type 1 diabetes is an established risk factor for lacunar stroke (30), there are limited data on the occurrence of lacunes on brain MRI in people with type 1 diabetes (29). One recent study on microbleeds reported no difference in the overall occurrence of these lesions relative to control subjects in a small cohort of patients with type 1 diabetes but did observe an increased occurrence in the subgroup of patients with proliferative diabetic retinopathy (31).

It is important to note that all but one (29) of the available MRI studies on SVD in type 1 diabetes predominantly involved patients younger than 50 years of age. Because SVD on MRI is quite uncommon in young adults, definite insights into the relationship between type 1 diabetes and SVD will require studies with sufficient statistical power, preferentially also involving older participants. Nevertheless, on the basis the currently available data, MRI markers of SVD do not appear to be a key determinant of type 1 diabetes–associated cognitive decrements in young adults.

Figure 2—Markers of SVD on MRI. The image on the left shows a T2-weighted fast field echo image with a microbleed (large open △) and blood vessels that can mimic microbleeds (small open △). The image on the right shows a fluid-attenuated inversion recovery image with periventricular (small closed △) and deep (large closed △) WMH.
of diabetes with memory, processing speed, and executive functioning (33).

In summary, type 2 diabetes is associated with an increased burden of SVD, and MRI markers of SVD are associated with cognitive dysfunction in people with type 2 diabetes. The relation between SVD and cognitive dysfunction is, however, not specific to diabetes, and the extent to which SVD mediates the link between diabetes and cognitive dysfunction remains to be determined.

STRUCTURAL AND FUNCTIONAL CONNECTIVITY

Structural Connectivity

Diffusion tensor imaging (DTI) is an MRI technique that can quantify alterations in the white matter tissue at a microscopic scale by characterizing the diffusion of water molecules within the brain (35). Damage to tissue structure caused by, for example, demyelination or axonal atrophy will lead to alterations in the diffusion of water molecules reflected by a change in mean diffusivity (MD) and fractional anisotropy (FA). As such, DTI can detect microstructural white matter abnormalities that are not visible on conventional MRI scans. A limitation of DTI is that tissue properties unrelated to pathology, but due to, for example, the organization of axonal fibers, will also affect diffusion parameters.

The directionality of the diffusion obtained by DTI allows the creation of maps of white matter tract anatomy and study of the connectivity between brain regions (Fig. 3). More recently, complex network theory has been used to assess the organization of whole-brain white matter connections (36). Network analysis is a promising technique to study the structural basis of cognitive functions that rely on the interaction between widely distributed brain regions, such as executive functioning and information processing speed, cognitive functions that are preferentially affected in diabetes.

**Type 1 Diabetes**

Two studies examined microstructural white matter alterations with DTI in middle-aged adults with type 1 diabetes (37,38). Results showed decreased FA in posterior brain regions compared with control subjects (37). More widespread reductions in FA throughout the brain were found in patients with diabetes and microangiopathy (38). In these studies, lower FA in patients was associated with longer diabetes duration (37) and decreased information processing speed and executive functioning (37,38).

**Type 2 Diabetes**

An increasing number of studies have examined DTI parameters in type 2 diabetes. Most studies observed a global decrease in FA or increase in MD that could not be explained by differences in vascular lesion load or total brain volume (32,39–41). Disruption of white matter connections in the temporal lobe was specifically associated with decreased memory performance (39,41), whereas increased MD in frontal and temporal and posterior fiber tracts was related to reduced information processing speed (39). These findings are in line with current theories about the localization of higher cognitive functions. Interestingly, diffusion alterations have also been observed in patients with diabetes who performed cognitively similar to control subjects (39,40) and in individuals with the metabolic syndrome (42), suggesting that diabetes-associated white matter abnormalities occur early in the disease process.

So far, only one study has used network analysis to examine differences in whole-brain connectivity patterns. Results showed decreased measures of local and global connectivity in patients compared with age-matched control subjects. Network alterations were related to slower information processing in patients, independent of age, sex, education, WMH, and lacunar infarcts (36).

It is not clear what pathological condition underlies the alterations in white matter diffusion parameters in diabetes. Possible mechanisms include inflammation, microvascular lesions, enlarged perivascular spaces, and blood-brain barrier disruption (43). In summary, DTI has low specificity but high sensitivity to white matter pathology. In patients with diabetes, diffusion measures show relatively strong and robust correlations with cognition. For these reasons, DTI measures have high potential as an MRI outcome marker to track disease progression in clinical trials.

**Functional Connectivity**

Functional brain imaging allows researchers to bridge the gap between variations in brain structure and cognitive performance by assessing measures related to neuronal activity. Imaging modalities that are used to measure...
brain function include functional MRI (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). Most studies in diabetes have used fMRI, a technique that estimates regional increases in the blood-oxygen-level-dependent (BOLD) contrast in response to neuronal activity. By examining the correlation in BOLD activity between brain areas, studies have identified large-scale functional networks that are spontaneously active during rest. These resting-state networks strongly overlap with task-related networks and are compromised in various cognitive disorders, including mild cognitive impairment and Alzheimer disease (44). The interest in resting-state fMRI in the field of dementia is rapidly growing, and studies continue to demonstrate the relevance of these techniques for detecting functional brain changes in Alzheimer disease as well as in vascular cognitive impairment.

It should be noted, however, that the link between the BOLD response and neural activity (i.e., neurovascular coupling) may be altered in patients with cerebrovascular disease. An attenuated BOLD response in patients with diabetes may thus be caused by impaired vascular reactivity and does not directly imply impaired neuronal activity. For this reason, the assessment of fMRI in patients with cerebrovascular disease is often combined with the assessment of cerebral vasoreactivity by using a breath-holding test or CO₂ inhalation test. Alternatively, neuronal activity can be measured more directly with EEG or MEG. The studies below have not combined these techniques, which should be considered when interpreting their results.

**Type 1 Diabetes**
Only a few studies have used fMRI to examine resting-state functional connectivity in patients with type 1 diabetes. One study found reduced functional connectivity in the ventral attention network in patients compared with control subjects, but only in patients with microangiopathy (45). Patients with diabetes without microangiopathy were not significantly different from control subjects. Evidence for altered functional connectivity in type 1 diabetes also comes from neurophysiological studies using EEG and MEG (46,47). EEG and MEG measures do not rely on neurovascular coupling; thus, these reports support the hypothesis that neuronal communication in diabetes is altered. However, the results of these two studies vary considerably with respect to affected brain regions and frequency bands.

**Type 2 Diabetes**
In patients with type 2 diabetes, reduced functional connectivity has been observed between regions of the so-called default mode network, including the medial frontal gyrus, precuneus, and medial temporal gyrus (48). The default mode network regions are among the most highly connected regions in the brain, suggesting an important role in global cognitive processing. Indeed, impaired default mode network connectivity was related to reduced memory, executive functioning, and processing speed in older individuals free from Alzheimer pathology (44). Abnormalities in resting-state brain activity have been observed in patients with type 2 diabetes, with decreased low frequency fluctuations in the postcentral gyrus and occipital cortex (49). Decreased brain activity in these areas was observed in the absence of structural brain changes and was related to worse memory performance and executive functioning.

Together, these findings clearly indicate that diabetes is associated with alterations in structural as well as functional brain connectivity. The next step is to integrate findings from different imaging modalities to determine 1) whether the reduced correlations in BOLD response are indeed due to altered neuronal activity or also reflect altered vascular reactivity, 2) whether alterations in functional connectivity are a direct consequence of disruption of white matter tracts, and 3) which processes underlie disruption of these tracts. To achieve this, standardization of processing methods across studies are needed as well as more adequate sample sizes to prevent type I and type II errors.

**IMPLICATIONS AND FUTURE PERSPECTIVES**
Type 1 and type 2 diabetes are both linked to abnormalities on brain MRI that are likely to underlie diabetes-associated cognitive decrements. Brain MRI abnormalities that are associated with type 1 diabetes occur rather diffusely throughout the brain and are reflected in subtle regional reductions in brain volume and changes in connectivity (Fig. 4). Focal vascular lesions are not a key MRI feature of type 1 diabetes in young adults. Uncertainty still exists regarding the etiology of brain MRI abnormalities in type 1 diabetes and their significance for long-term cognitive decline. In this respect, an important limitation of most of the available studies is their cross-sectional design. Part of the MRI abnormalities in adults with type 1 diabetes may originate from the effects of diabetes on brain development in childhood. To identify potentially modifiable risk factors for progressive brain volume loss (i.e., atrophy) in adulthood, longitudinal studies are clearly needed. Such studies should use quantitative volumetric techniques. Inclusion of a non-diabetic reference group, to be able to identify diabetes-attributable changes on top of those of normal aging, is strongly recommended.

Brain MRI abnormalities that are associated with type 2 diabetes include global cortical and subcortical atrophy, with some variation in severity across brain regions, and an increased burden of SVD, in particular lacunar infarcts (Fig. 5). SVD is likely to contribute to abnormalities in functional and structural connectivity, which is another MRI feature of type 2 diabetes that is clearly linked to cognitive dysfunction. Brain abnormalities and associated cognitive dysfunction in type 2 diabetes occur in the context of brain aging. The challenge is to disentangle the effects of diabetes—and diabetes-associated vascular risk factors—from those of “normal aging.” The different brain
MRI features of type 2 diabetes are unlikely to share the same etiology. On the basis of current insights, chronic exposure to hyperglycemia, insulin resistance, and vascular risk factors—most importantly hypertension—are potentially modifiable risk factors, but other factors, including inflammation, oxidative stress, hypoperfusion, and Alzheimer-type degenerative processes, may also play a role (3).

An open question is how diabetes-related brain abnormalities can be prevented. In this context it is important to mention the Action to Control Cardiovascular Risk in Diabetes-Memory In Diabetes (ACCORD-MIND) study, which showed that after 40 months, the rate of brain atrophy on MRI was reduced in patients with type 2 diabetes receiving intensive glycemic control compared with those receiving standard therapy (51). It seems that what is good for the heart is not necessarily good for the brain.

Owing to the subtle nature of diabetes-associated MRI abnormalities, they are currently only detectable at the group level. In other words, there is no typical MRI signature of type 1 or type 2 diabetes that can be identified in an individual patient. As such, there is no place for brain MRI in the periodic evaluation of patients with diabetes in current clinical practice. However, as shown in this review, brain MRI has clearly established its value as a research tool to further unravel the trajectories of brain changes, identify the primary underlying etiologies, and develop treatment. To fully benefit from the potential that brain MRI has to offer in this context, rigorous methodology is required in study design and also in image acquisition and analysis. Multimodal imaging approaches are recommended, where different structural and functional imaging techniques are combined, where possible also complimented by histological studies, to verify the true nature and etiology of imaging abnormalities. Apart from this, rigorous clinical phenotyping of patients is essential, with careful documentation of long-term functional outcomes and detailed and precise documentation of diabetes-related variables and other risk factors.

Regarding trajectories of brain changes and cognitive outcomes, it would be a major advance if we could pinpoint those imaging abnormalities that are predictive of long-term poor cognitive outcome in individual patients, because this would help to select patients who are likely to benefit most from novel therapies. Hopefully, brain imaging can also help to identify etiological processes at an individual level in the near future that may guide the selection of the appropriate therapy. An example of this in the field of Alzheimer disease is
amyloid positron emission tomography imaging, which helps to identify people at high risk of cognitive decline due to Alzheimer-type pathologies at an early stage of the disease when intervention may be most effective.

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Appendix

Literature Search Strategy and Selection

We searched PubMed from 2000 to February 2014 with the terms (and synonyms) “diabetes,” “brain,” “white matter,” “cortex,” “hippocampus,” “MRI,” “magnetic resonance,” “atrophy,” “diffusion tensor imaging,” “fMRI,” “small vessel disease,” “lacunar infarct,” and “microbleed.” We also extracted relevant papers from our records. We only considered studies on human subjects—particularly involving adults—published in English.

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