CLASSIFICATION—Long-standing type 1 diabetes is associated with deficits on neurocognitive testing that suggest central white matter dysfunction. This study investigated whether diffusion tensor imaging (DTI), a type of magnetic resonance imaging that measures white matter integrity quantitatively, could identify white matter microstructural deficits in patients with long-standing type 1 diabetes and whether these differences would be associated with deficits found by neurocognitive tests.

RESEARCH DESIGN AND METHODS—Twenty-five subjects with type 1 diabetes for at least 15 years and 25 age- and sex-matched control subjects completed DTI on a 3.0 Tesla scanner and a battery of neurocognitive tests. Fractional anisotropy was calculated for the major white matter tracts of the brain.

RESULTS—Diabetic subjects had significantly lower mean fractional anisotropy than control subjects in the posterior corona radiata and the optic radiation ($P < 0.002$). In type 1 diabetic subjects, reduced fractional anisotropy correlated with poorer performance on the copy portion of the Rey-Osterreith Complex Figure Drawing Test and the Grooved Peg Board Test, both of which are believed to assess white matter function. Reduced fractional anisotropy also correlated with duration of diabetes and increased A1C. A history of severe hypoglycemia did not correlate with fractional anisotropy.

CONCLUSIONS—DTI can detect white matter microstructural deficits in subjects with long-standing type 1 diabetes. These deficits correlate with poorer performance on selected neurocognitive tests of white matter function. Diabetes 57:3083–3089, 2008

Type 1 diabetes is a complex metabolic disease that can have devastating effects on multiple organ systems. Although complications involving the kidneys, nerves, and eyes have long been recognized, the effect of diabetes on cognition has not been as clearly understood. Patients with type 1 diabetes have been found to have deficits on standard neurocognitive tests of information processing (1–4), psychomotor efficiency (1,2), motor speed (3,5–7), visuoconstruction (4,8), attention (4), somatosensory examination, motor strength (7), and executive function (9). Based on the type of cognitive deficits observed in patients with diabetes, there has been speculation that abnormalities in white matter may be at least partly responsible for cognitive dysfunction, particularly in patients with type 1 diabetes (2). Supporting this hypothesis, several studies have found gross morphological changes (10) and reduced white matter volume as measured by voxel-based morphometry (4) in patients with type 1 diabetes. However, prior studies have not looked specifically at the microstructural aspects of white matter integrity.

Over the last decade, a new type of magnetic resonance imaging (MRI) called diffusion tensor imaging (DTI) has been developed that is uniquely suited to assess white matter microstructure. DTI measures the magnitude and directionality of water diffusion in tissues, which may permit identification of tissue injury before it has progressed to the point of detection by more conventional imaging techniques. Without barriers, water molecules move uniformly in all directions, a phenomenon referred to as isotropic diffusion. In the presence of barriers, such as cell membranes, fibers, and myelin, the diffusion rate is greater in one direction, which is termed anisotropic diffusion. Fractional anisotropy provides a quantitative measure of the degree of diffusion anisotropy. Fractional anisotropy is high in regularly organized and structured white matter, such as the corpus callosum, and is lower in less organized tissues, such as gray matter (11,12). Previous DTI studies have shown that reduced fractional anisotropy correlates to cognitive dysfunction in a variety of conditions, including schizophrenia (13,14), depression (15), chronic alcohol use (16), Alzheimer’s disease (17,18), and chronic cocaine use (19). In addition, a decrease in brain fractional anisotropy correlated negatively with viral load in patients with known HIV infection (20). This is of particular interest because patients living with HIV have many of the cognitive impairments that patients with type 1 diabetes exhibit, including decreased attention and speed of information processing (11).

To determine whether abnormalities in white matter...
was outside of this glycemic range, appropriate therapy was administered by
blood glucose was between 5.5–13.9 mmol/l (100 –250 mg/dl). If blood glucose
a separate day but within 2 weeks of the neurocognitive testing, subjects
University of Minnesota for neurocognitive testing after breakfast or lunch. On
five healthy volunteers without diabetes and free of the exclusion criteria
shrapnel, claustrophobia, etc.). Education history was also assessed. Twenty-
white matter regions. This analysis was done to test the
assess performance on tasks believed to be supported by
completed a battery of standardized neurocognitive tests to
subject-pair and an unstructured covariance matrix for the
thought to be associated with white matter function were compared simulta-
Neurocognitive test scores were compared between diabetic
Control: The neurocognitive testing battery included the
Wechsler Abbreviated Scale of Intelligence (WASI) and tests of psychomotor
speed and executive function that have been found to be impaired in subjects
Duration of diabetes (years) 30.3
Sex (F/M) 17/8
AIC (%) 7.4 ± 1.0
Blood glucose before MRI (mmol/l [mg/dl]) 9.3 ± 3.6 (168 ± 64)
Blood glucose before neurocognitive testing (mmol/l [mg/dl]) 8.4 ± 2.7 (152 ± 49)

Data are means ± SD. NA, not applicable.

RESEARCH DESIGN AND METHODS
Twenty-five type 1 diabetic subjects were recruited from the Endocrine Clinics at the University of Minnesota Medical Center–Fairview and through institutional review board–approved fliers distributed around the University of Minnesota campus. To ensure that the subjects resembled those included in previous studies assessing cognitive function in diabetes (3,21), only subjects with a diabetes duration of 15 years or more were eligible for participation. Exclusion criteria included a history of or current evidence of any substance abuse disorder other than tobacco or caffeine dependence; severe psychiatric disorder, including major depressive disorder; seizure disorder (not related to hypoglycemia); transient ischemic attack; stroke; head injury; other diseases of the central nervous system; chemotherapy; and any condition that pre-
cluded the performance of MRI (weight >300 lbs [subjects of this size cannot fit into the magnetic resonance instrument], presence of metal implants or shrapnel, claustrophobia, etc.). Education history was also assessed. Twenty-
five healthy volunteers without diabetes and free of the exclusion criteria were recruited from the University of Minnesota community to match the subjects with respect to age and sex (Table 1).

All subjects reported to the General Clinical Research Center at the University of Minnesota for neurocognitive testing after breakfast or lunch. On a separate day but within 2 weeks of the neurocognitive testing, subjects reported to the Center for Magnetic Resonance Research at the University of Minnesota for DTI, again after either breakfast or lunch. Diabetic subjects were instructed to manage their condition in their usual manner. Upon arrival, diabetic subjects performed fingerstick blood glucose testing to ensure that blood glucose was between 5.5–13.9 mmol/l (100–250 mg/dl). If blood glucose was outside of this glycemc range, appropriate therapy was administered by the investigator to bring them into target within 1 h or the study was rescheduled. AIC was also measured in diabetic subjects using a blood sample obtained on the day of neurocognitive testing.

Neurocognitive testing. The neurocognitive testing battery included the Wechsler Abbreviated Scale of Intelligence (WASI) and tests of psychomotor

The mean fractional anisotropy was computed for the white matter of four brain regions defined by anatomical landmarks that include the genu and splenium of the corpus callosum and the anterior and posterior commissures (Fig. 1A). The Tract-Based Spatial Statistics (TBSS) analysis program bundled with FSL (27) was used to determine average fractional anisotropy values at the center of several tracts of interest. TBSS generated a fractional anisotropy skeleton of the major white matter tracts of the brain for each subject. The fractional anisotropy map from the control subject with a brain size at the median for the controls was used to align the fractional anisotropy maps from the other control subjects and diabetic subjects. Once the fractional anisot-
ometry maps were aligned, a common white matter skeleton was generated and then further segmented into anatomically defined tracts using the primary eigenvector information for the target subject’s DTI data based on atlas information from Mori et al. (28). These tracts were selected on the basis of relative size and ease of differentiation from surrounding tracts. The resulting tracts from this procedure included bilateral forceps minor, cingulum bundle, medial corona radiata, superior longitudinal fasciculus, and optic radiation (Fig. 2A). Additionally, six regions of interest ( genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium, in order of decreasing fractional anisotropy) were defined.

Statistics. Neurocognitive test scores were compared between diabetic subjects and control subjects using t tests as an initial screening. Tests thought to be associated with white matter function were compared simulta-
neously in a general linear mixed model (SAS Proc Mixed) with a random intercept for each subject-pair and an unstructured covariance matrix for the repeated test scores within subjects. The same model was used with the three groups of brain regions to compare fractional anisotropy measurements between diabetic subjects and control subjects. Results are reported as mean ± SE. Spearman correlation is reported as a measure of association. All computations were performed in SAS version 9.1.3 (SAS Institute, Cary, NC). Throughout this statistical analysis, all results were corrected for multiple comparisons.

### TABLE 1

| Characteristics of subjects | Subjects with type 1 diabetes | Control subjects |
|-----------------------------|-----------------------------|-----------------|
| **n**                       | 25                          | 25              |
| **Age** (years)             | 45.1 ± 10.5                 | 45.6 ± 10.8     |
| **Sex (F/M)**               | 17/8                        | 17/8            |
| **Education (years)**       | 16.7 ± 1.9                  | 16.1 ± 2.3      |
| **Duration of diabetes (years)** | 30.3 ± 10.8      | NA              |
| **AIC (%)**                 | 7.4 ± 1.0                   | NA              |

Blood glucose before MRI (mmol/l [mg/dl])

| Blood glucose before MRI (mmol/l [mg/dl]) | 9.3 ± 3.6 (168 ± 64) | NA |
| Blood glucose before neurocognitive testing (mmol/l [mg/dl]) | 8.4 ± 2.7 (152 ± 49) | NA |

**DIFFUSION TENSOR IMAGING AND TYPE 1 DIABETES**

The mean fractional anisotropy was computed for the white matter of four brain regions defined by anatomical landmarks that include the genu and splenium of the corpus callosum and the anterior and posterior commissures (Fig. 1A). The Tract-Based Spatial Statistics (TBSS) analysis program bundled with FSL (27) was used to determine average fractional anisotropy values at the center of several tracts of interest. TBSS generated a fractional anisotropy skeleton of the major white matter tracts of the brain for each subject. The fractional anisotropy map from the control subject with a brain size at the median for the controls was used to align the fractional anisotropy maps from the other control subjects and diabetic subjects. Once the fractional anisot-
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**FIG. 1.** Fractional anisotropy in major brain regions. A: Superior frontal region, inferior frontal region, occipital region, and region superior to corpus callosum (going clockwise starting at top left). There is ~15% overlap between the frontal regions and the region superior to the corpus callosum. B: Fractional anisotropy in major brain regions; there was no significant difference in any of the major regions. 

**RESULTS**

**Demographic data.** Clinical and demographic characteristics of the 25 type 1 diabetic subjects and the 25 age- and sex-matched healthy controls are summarized in Table 1. The diabetic subjects and controls were similar in all of the demographic measures collected. Three diabetic subjects reported a history of retinopathy, two reported a history of gastroparesis, and three reported histories of both retinopathy and neuropathy. All but one subject who reported retinopathy had intervention (laser therapy or vitrectomy). No diabetic subjects reported a history of nephropathy. Fifteen of the 25 diabetic subjects reported a history of severe hypoglycemia, defined as having seizures, loss of consciousness, or needing another person’s help to treat the symptoms of low blood glucose.

**Neurocognitive testing data.** No tests included in our battery distinguished type 1 diabetic subjects from control subjects. However, diabetic subjects appeared to have a tendency to perform more poorly on the Rey-O, a test believed to be a measure of white matter function that requires a high degree of visuospatial orientation and planning. This test is scored based on the number of correctly copied elements, and the diabetic subjects had a mean score of 31 ± 0.6, and the controls scored 33 ± 0.6 (P = 0.063).

**DTI data.** In the four large regions of analysis (inferior frontal, superior frontal, superior to the corpus callosum, and occipital regions with ~15% overlap between the frontal regions and the region superior to the corpus callosum), fractional anisotropy was lower but not significantly in type 1 diabetic subjects (Fig. 1). In more specific major white matter tracts, diabetic subjects had significantly lower fractional anisotropy than control subjects in both the posterior corona radiata (0.443 ± 0.004 vs. 0.471 ± 0.004, P < 0.0001) and the optic radiation (0.361 ± 0.004 vs. 0.380 ± 0.004, P = 0.0017) (Fig. 2). Type 1 diabetic subjects also tended to have lower fractional anisotropy than control subjects in the splenium (0.806 ± 0.006 vs. 0.820 ± 0.006, P = 0.0947) and the posterior body of the corpus callosum (0.805 ± 0.007 vs. 0.821 ± 0.007, P = 0.1397).

**Correlation of DTI and neurocognitive testing data.** In diabetic subjects, there was a significant correlation between performance on the copying portion of the Rey-O and fractional anisotropy in the posterior corona radiata, with poorer scores associated with reduced fractional anisotropy (Table 2). These subjects also demonstrated a significant association between longer time required to complete the Grooved Pegboard Test, using both the nondominant hand and dominant hand, and reduced fractional anisotropy in the optic radiation, posterior corona radiata, and splenium of the corpus callosum (Table 2). Control subjects demonstrated a similar correlation between performance on the Grooved Pegboard Test and fractional anisotropy in the optic radiation (dominant hand only) and, unlike diabetic subjects, the fractional anisotropy in the posterior body of the corpus callosum (both hands) (Table 2). For all subjects, correlation between Rey-O and fractional anisotropy in the posterior corona radiata is shown in Fig. 3. To assess the effects of microvascular complications, the group with diabetes was divided into those with (n = 8) and without (n = 17) such complications; both subgroups had significantly lower fractional anisotropy in the posterior corona radiata than controls, and those with microvascular complications also had significantly lower Rey-O scores (Table 3).

**Correlation of DTI with characteristics of diabetic subjects.** Age, duration of diabetes, and A1C were negatively correlated with reduced fractional anisotropy of the optic radiation and posterior corona radiata, whereas duration of diabetes was also negatively correlated with reduced fractional anisotropy of the splenium of the corpus callosum (Table 4). No significant correlations were identified between severe hypoglycemia or microvascular complications and reduced fractional anisotropy in any of the major white matter tracts.
DISCUSSION
In this investigation, we found that white matter integrity, as measured by fractional anisotropy using DTI, was lower in several white matter tracts, including the posterior corona radiata and optic radiation, in patients with long-standing type 1 diabetes compared with age- and sex-matched controls. We also observed there to be a significant correlation between reduced fractional anisotropy in white matter tracts and reduced performance on neurocognitive tests thought to assess white matter function, including the Rey-O copy and the Grooved Pegboard Test. Together, these results demonstrate for the first time that microstructural abnormalities can be identified in the brains of subjects with long-standing type 1 diabetes that may underlie the cognitive dysfunction identified in this population. This work may open the door for the development of a novel biomarker for cognitive dysfunction that can be used to better understand the cerebral complications of diabetes. If such a biomarker can be developed, future study could focus on identifying interventions that can prevent the appearance or slow the progression of white matter microstructural changes in patients with diabetes.

Over the last 10 years, investigators have used a variety of imaging techniques, including MRI, single photon emission computed tomography (30,31), and positron emission tomography (32), to determine whether structural abnormalities could be identified in the brains of subjects with type 1 diabetes. Such abnormalities were found in several white matter tracts, including the posterior corona radiata and optic radiation. These findings suggest that microstructural changes in these tracts may be early markers of cognitive dysfunction in patients with type 1 diabetes.

**TABLE 2**

|                         | Optic radiation | Posterior corona radiata | Splenium corpus callosum | Posterior body of corpus callosum |
|-------------------------|-----------------|--------------------------|--------------------------|-------------------------------|
|                         | Type 1 diabetes | Control                  | Type 1 diabetes          | Control                       | Type 1 diabetes | Control |
| Rey-O copy              | 0.10            | -0.10                    | 0.46*                    | 0.06                          | -0.07            | 0.02    |
| Grooved Peg Board, nondominant | -0.66*         | -0.42*                   | -0.72*                   | -0.56*                        | -0.32            | -0.60*  |
| Grooved Peg Board, dominant | -0.40*         | -0.39                    | -0.70*                   | -0.48*                        | -0.24            | -0.53*  |

*Significantly different from zero (P < 0.05).
type 1 diabetes. Although Biessels et al. (10) observed high signal lesions in cerebral white matter (or leukoaraiosis) in these patients, most studies have not confirmed this finding (1,33,34). Others have found increased cerebral spinal fluid and cerebral global atrophy (35,36), stable hippocampal and amygdala volumes (36), and decreased cerebral gray matter density (37,38) in type 1 diabetic subjects. Some of these structural abnormalities have corresponded to age of diabetes onset (35), A1C levels, hypoglycemia (37), and the presence of retinopathy (38). Recently, Wessels et al. (4) applied MRI voxel-based morphometry to measure white matter volumes in patients with type 1 diabetes and found subjects with proliferative retinopathy to have significantly smaller white matter volumes than diabetic subjects who were free of proliferative retinopathy and control subjects without diabetes. In the Wessels et al. study, reduced white matter volume correlated with worse performances on tests for attention, speed of information processing, and executive function. Whether reduced white matter volumes correlates with a reduction in fractional anisotropy is uncertain, but in our study, we did not find a relationship between the presence of retinopathy and either reduced fractional anisotropy or mild cognitive impairment. Future investigation should focus on this point because an association with retinopathy suggests that a common mechanism may be responsible for the development of both retinopathy and changes in white matter structure.

Previous studies that were designed to assess neurocognitive dysfunction in patients with type 1 diabetes identified abnormalities with information processing (1–4), psychomotor efficiency (1,2), motor speed (3,5–7), visuoconstruction (4,8), attention (4), somatosensory examination, motor strength (7), and executive function (9). Generally, these cognitive domains, which require the integration of several different tasks, are thought to be associated with the integrity of the white matter tracts that connect gray matter regions. In selecting our neurocognitive battery, we focused on measures like the PASAT, the DVT, the Grooved Pegboard Test, and the Trails A and B, which have previously identified differences in “psychomotor efficiency” between subjects with and without diabetes (2). We also selected measures that assessed other white matter function domains (e.g., processing speed, attention, and visual-spatial processing), such as the JLO, the Trails A and B, the PASAT, the Rey-O, the Grooved Pegboard Test, the CPT-II, and the DVT. Importantly, our battery also included the WASI, a test that screens for intellectual ability, as a control because most studies in type 1 diabetic subjects show no deficits in general intelligence (1–3). Our results demonstrated that no differences could be identified between type 1 diabetic

| TABLE 3 |
| --- |
| Comparison of fractional anisotropy in diabetic subjects with microvascular complications, diabetic subjects without microvascular complications, and control subjects |

|                         | Diabetic subjects with microvascular complications | Diabetic subjects with no microvascular complications | Control subjects | F test | P value |
|-------------------------|--------------------------------------------------|-----------------------------------------------------|------------------|--------|---------|
| Posterior corona radiata| 0.4350 ± 0.0097<sup>a</sup>                       | 0.4470 ± 0.0059<sup>a</sup>                         | 0.4710 ± 0.0042<sup>b</sup> |        | 0.0003  |
| Rey-O                   | 30 ± 1.3<sup>a</sup>                             | 32 ± 0.8<sup>ab</sup>                               | 33 ± 0.6<sup>b</sup>      |        | 0.0696  |

Data are means ± SE. Comparisons are within rows: means that do not share letters are significantly different (P < 0.05).
subjects and control subjects on the WASI or the majority of the other tests performed. Most likely, this is secondary to our relatively small sample size, and with a larger number, perhaps we would have found significance in such tests as the Rey-O Copy and the Grooved Peg Board Test. Nevertheless, there were significant associations between these neurocognitive tests and reduced fractional anisotropy in patients with type 1 diabetes.

In this investigation, we used DTI to evaluate white matter microstructure. Although this form of imaging is known to measure the magnitude and directionality of water diffusion in tissues, what specific biochemical or morphological abnormality underlies the change in diffusion remains unknown. Like diabetes (39), many of the diseases that have similar changes in fractional anisotropy are associated with increases in oxidative stress, including chronic alcoholism (40), depression (41), Alzheimer’s disease (42), chronic cocaine use (43), schizophrenia (44), and HIV infection (45). Based on this, it is tempting to think that oxidative stress could affect the integrity of myelinated fibers in vivo.

There were several limitations to this study. Historical information about the diabetic subjects was limited to self-report and a single AIC value. We did not confirm the presence or absence of retinopathy in our subjects, and if we had, we may have found an association between white matter structure/function and retinopathy as did Wessels et al. (4,38). We did identify a significant relationship between AIC and fractional anisotropy, but an examination of the relationship between a measure of long-term glycaemia and changes in white matter microstructure would provide greater understanding of the role of chronic hyperglycaemia in the development of reduced fractional anisotropy. Similarly, if a detailed history of hypoglycaemia events and an assessment of hypoglycaemia unawareness had been obtained, we may have been able to identify a link between hypoglycaemia and structural changes as Musen et al. (37) did using MRI. Reduced fractional anisotropy was correlated with duration of diabetes; however, it was also correlated with increasing age. Future studies hopefully will be needed to confirm whether the duration of diabetes correlates with fractional anisotropy independent of age.

In summary, we found that DTI reveals white matter microstructure deficits (reduced fractional anisotropy) in patients with longstanding type 1 diabetes compared with controls. In addition, white matter microstructure deficits seen in type 1 diabetic subjects correlate with impaired performance on neurocognitive tests that are thought to be associated with white matter function. Based on these findings, prospective, longitudinal studies are needed to both better understand the natural evolution of cognitive dysfunction in type 1 diabetes and to establish DTI as an ideal methodology to follow cognitive dysfunction in diabetes. If further studies confirm our findings correlating diabetes, white matter microstructural changes, and neurocognitive dysfunction, future work will determine what factors will modify the progression of this diabetic complication (i.e., reducing AIC levels, novel pharmacological interventions, etc.).

ACKNOWLEDGMENTS
This work has received Grant M01-RR-00400 from the NCRR, a component of the NIH; NIH Grant R01-MH-060662; and funding from the Pennock Family Diabetes Research Fund.

We thank Danielle Seim for her contribution to the project.

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