

DIFFUSION TENSOR IMAGING OF THE BRAIN IN TYPE 1 DIABETES

Jo Ann V. Antenor-Dorsey,^a Joshua S. Shimony,^b *Tamara Hershey^{a-c}

Psychiatry,^a Radiology,^b and Neurology^c Departments, Washington University School of Medicine, St. Louis, Missouri, USA

*Correspondence to tammy@wustl.edu

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ABSTRACT

Individuals with Type 1 diabetes mellitus (T1DM) are required to carefully manage their insulin dosing, dietary intake, and activity levels in order to maintain optimal blood sugar levels. Over time, exposure to hyperglycaemia is known to cause significant damage to the peripheral nervous system, but its impact on the central nervous system has been less well studied. Researchers have begun to explore the cumulative impact of commonly experienced blood glucose fluctuations on brain structure and function in patient populations. To date, these studies have typically used magnetic resonance imaging to measure regional grey and white matter volumes across the brain. However, newer methods, such as diffusion tensor imaging (DTI) can measure the microstructural properties of white matter, which can be more sensitive to neurological effects than standard volumetric measures. Studies are beginning to use DTI to understand the impact of T1DM on white matter structure in the human brain. This work, its implications, future directions, and important caveats, are the focus of this review.

Keywords: Type 1 diabetes mellitus, diffusion tensor imaging, white matter, hyperglycaemia.

INTRODUCTION

Individuals with Type 1 diabetes mellitus (T1DM) are required to carefully manage their insulin dosing, dietary intake, and activity levels in order to maintain optimal blood sugar levels. Despite these goals, on average, patients are hyperglycaemic (plasma glucose >180 mg/dL) up to 50% of the day and hypoglycaemic (plasma glucose \leq 70 mg/dL) for an hour or more each day.¹ Over time, exposure to hyperglycaemia is known to cause significant damage to the peripheral nervous system in the form of neuropathy, neuropathic pain, and retinopathy.² The impact of hyperglycaemia on the central nervous system (CNS) has not been studied so well, despite the fact that the brain uses more glucose by weight than any other organ in the body.³ Profoundly low or high blood glucose levels clearly affect brain function and structure in the short-term and, in some documented cases, the long-term.^{2,4} These findings have motivated researchers to explore the cumulative impact of the less

profound and more commonly experienced blood glucose fluctuations on brain structure and function in patient populations. To date, these studies have typically used magnetic resonance imaging to measure regional grey and white matter volumes across the brain, and these limited but intriguing results have been reviewed in detail recently.⁵⁻⁷

However, animal (and some human) studies have shown that glycaemic extremes can impact the brain in more subtle ways than can be detected with gross regional volume measurements. For example, pathological examination of animal models of diabetes exhibit demyelination,⁸ axonal atrophy and degeneration, and failure to re-innervate.⁹ Similarly, diabetic patients also exhibit demyelination and decreased axonal diameter in peripheral nerves.¹⁰ If such changes occur in the human brain, *in vivo* neuroimaging using diffusion tensor imaging (DTI) could be used to detect their imaging correlates. DTI is a newer imaging methodology that measures the microstructural properties of white matter.

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BACKGROUND ON DTI

DTI relies on the properties of water molecule diffusion to characterise brain microstructure.¹¹ It is easiest to interpret DTI parameters in well-defined white matter tracts but these measures can also be acquired in grey matter. Traditional DTI parameters include fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). FA reflects the degree of directionality of water molecule diffusion. Well-defined white matter tracts have strong directionality, as water molecules tend to move parallel to the fibres that compose the tracts. Histological studies in animal models have shown that increases in fibre diameter and density, myelination, and intravoxel fibre-tract coherence are reflected as higher FA.¹² AD is a measure of the degree of water diffusivity along the primary axis of diffusion. Increased fibre coherence and structure of axonal membranes, as well as decreased axonal branching, can result in higher AD.¹³ Axonal damage can lead to a decrease in AD. RD is the mean of the diffusivities perpendicular to the predominant direction of water diffusion, and is thought to represent myelin and membrane integrity. Increased level of myelination leads to decreased RD while decreased myelin sheath and/or membrane integrity leads to higher RD.¹⁴ MD is the average of diffusion in all three directions. General loss of neuronal tissue can lead to an increase in MD.

By examining all of the parameters of water molecule diffusion in a white matter tract, certain interpretations can be made about the underlying nature of the tissue based on animal model histology findings. For example, in animal models of multiple sclerosis,¹⁵ lower FA, higher RD, and lower AD has been correlated to acute axonal degeneration when compared to controls, while similar FA, higher RD, and lower AD, compared to controls, has been correlated with demyelination of white matter tracts.¹⁵ However, higher FA is not always beneficial, as it has been associated with decreased dendritic branching, when seen in the context of lower RD and AD.¹⁶ DTI findings are also difficult to interpret in regions with a large amount of crossing fibres, due to partial volume effects. Thus, one must be cautious in interpreting DTI parameters in isolation.

Our understanding of how altered DTI parameters relate to grey matter microstructure is much less advanced. This is due to the difficulty in measuring DTI values in the thin cortical grey matter which is volume-averaged with the nearby cerebral spinal fluid of the subarachnoid space. Importantly, definitive conclusions about the meaning of DTI measures can only be made through direct histological examination of biological tissue.

APPLICATION OF DTI TO T1DM

The application of DTI to human T1DM populations has a relatively short history and, to date, is represented by only five unique samples with published papers split between adult and child cohorts. The first study appeared in 2008 and reported that middle-aged adults with T1DM had decreased FA in specific regions (posterior corona radiata and optic radiation) compared to controls.¹⁷ Diffusivity (MD, RD, or AD) was not examined. Within the T1DM group, regional FA was negatively correlated with age, duration of diabetes, and recent hyperglycaemia, but not with a history of severe hypoglycaemia.¹⁸ Lifetime history of hyperglycaemia was not assessed. A secondary analysis of the same subjects and scans found reduced cortical thickness in the regions with high connectivity to the optic radiations and posterior corona radiate tracts.¹⁹ In a much larger cohort of adults with T1DM,¹⁹ patients had lower FA and AD in multiple white matter tracts, including inferior fronto-occipital and corticospinal tracts and higher RD, primarily in the corpus callosum, compared to controls. Patients with microangiopathy had lower FA and higher RD compared to those without microangiopathy. Severe hypoglycaemia was not related to any DTI parameters, and lifetime or recent hyperglycaemia was not examined.

Although studies in adults with long-standing T1DM are an important contribution to the field, it can be difficult to determine in such complicated patients which facet of T1DM (i.e. hyperglycaemia, hypoglycaemia, diabetic ketoacidosis [DK], age of onset, duration) is most closely associated with alterations in white matter microstructure. By studying children and adolescents with T1DM, with a more limited diabetes history and few comorbid conditions (e.g. hypertension), these factors can often be more clearly investigated. However, it is important to take into account that DTI measures change during normal brain development. In general, FA in white matter tracts increases from

birth to adulthood and is quite heterogeneous in the adult brain, having the highest values in the corpus callosum and the lowest values in subcortical white matter.^{20,21} MD tends to decrease from birth to adulthood in white matter, primarily driven by decreasing RD,^{21,22} and becomes increasingly homogenous across the brain over time. This pattern of normal development proceeds in a posterior-to-anterior and central-to-peripheral direction of maturation.²³ Most changes in DTI values occur within the first 4 years of life,²¹ but surprisingly, more brain regions exhibit increases in FA and decreases in MD during the teenage years than during the 8-12-year-old time period,

suggesting two epochs of rapid white matter development.²¹ Furthermore, developmental changes in diffusion properties within grey matter structures, especially in the basal ganglia, show maturational decreases in the diffusion of water along the three different axes, resulting in decreased MD, AD, and RD.

Several DTI studies (Table 1) have examined T1DM within this diverse and rapidly changing context. Our group examined T1DM youth (mean age 16 years old), and found that they had lower AD in multiple white matter tracts, similar to the van Duinkerken study¹⁸ in adults.

Table 1: DTI studies in T1DM, listed by age of the study samples [table is organised by the age of the study population].

First Author	Year	Study Groups	n	Mean Age	DTI Findings
Barnea-Goraly ²⁶	2013	T1DM Controls	127 67	7.1 7.0	T1DM had lower AD; no differences seen in FA and RD. Earlier age of onset correlated with increased RD. Longer duration of disease correlated with decreased AD and RD and increased FA. Hyperglycaemia negatively correlated with FA and positively correlated with RD.
Aye ²⁵	2012	T1DM Controls	26 16	7.8 7.2	T1DM had lower AD in multiple regions. No differences were seen in FA and RD. Hyperglycaemia correlated with RD in widespread regions.
Antenor-Dorsey ²⁴	2013	T1DM Controls	73 30	16.8 15.9	T1DM had lower FA and higher RD in the superior parietal lobule, lower RD in thalamus, and lower AD in the cerebellum compared to controls. Severe hyperglycaemic episodes were associated with lower FA and higher RD in the superior parietal lobule and higher RD in the hippocampus. Severe hypoglycaemia was associated with higher FA in the superior parietal lobule.
van Duinkerken ¹⁸	2012	T1DM Controls	100 49	~41.3 36.7	T1DM had lower FA and AD in widespread regions and higher RD in corpus callosum primarily. Lower FA and higher RD were associated with the presence of microangiopathy.
Kodl ¹⁷ and Franc ¹⁹	2008 and 2011	T1DM Controls	25 25	45.1 45.6	T1DM had lower FA in posterior corona radiata and optic radiation, which correlated with age, duration of disease, and greater hyperglycaemia as well as reduced cortical thickness in regions with high connectivity to affected white matter tracts.

DTI: diffusion tensor imaging; T1DM: Type 1 diabetes mellitus; FA: fractional anisotropy; AD: axial diffusivity; RD: radial diffusivity.

In addition, a history of severe hyperglycaemic events was associated with lower FA and higher RD in the superior parietal lobule. Interestingly, a history of severe hypoglycaemic events was associated with higher FA in the superior parietal lobule.²⁴ A small study on much younger subjects (mean age 7 years old) also found that the T1DM group had lower AD in primarily temporal and parietal cortical regions compared to controls.²⁵ No differences were found between groups in FA or RD measures. Greater hyperglycaemia exposure in the past was correlated with higher RD in several white matter tracts, although RD was not different overall between groups. A larger multicentre study on similarly young T1DM patients replicated the findings for AD.²⁶ In addition, an earlier age of disease onset was correlated with increased RD in multiple areas throughout the brain, while longer disease duration correlated with decreased AD, decreased RD, and increased FA. Greater hyperglycaemia (as measured by haemoglobin A1c test measures since diagnosis, and recent continuous glucose monitoring), but not hypoglycaemia (as measured by a history of severe episodes, and recent continuous glucose monitoring), correlated with all three DTI parameters.

DTI abnormalities in T1DM have been inconsistently related to cognitive performance variables within T1DM. However, the specificity of these findings to T1DM, and to particular white matter tracts and cognitive variables, is still unclear. These relationships may also differ depending on the age of the sample as DTI parameters and cognitive function normally undergo dramatic changes across development and ageing. Of the five DTI papers reviewed here, only four performed correlations between cognitive function and DTI parameters, and cognitive batteries and correlational methods differed substantially across these papers. Nevertheless, these studies each found unique associations within their T1DM group between DTI parameters and cognitive variables, such that lower cognitive performance was related to presumed, more abnormal DTI values (e.g. lower FA, higher RD). For example, in a small sample of younger children with T1DM, lower FA in numerous regions was related to lower performance on a speed of processing task and a short-term memory task.²⁵ Higher RD was related to lower IQ and auditory attention. In a larger and similarly aged sample, lower FA was associated with lower IQ, particularly within the right superior temporal gyrus and

bilateral parietal regions. This pattern was not seen in the control group in this study, but has been seen in normal development in other studies.²⁷ In adults with T1DM, lower FA in the posterior corona radiata was associated with lower visuo-motor performance and lower FA in the optic radiation; posterior corona radiata and splenium of the corpus callosum was associated with slower fine motor performance. However, control subjects also demonstrated correlations between FA and performance on these tasks in overlapping - but not identical - regions.¹⁷ Finally, within a different sample of adults with T1DM, but not controls, higher FA of the left corticospinal tract was related to better general cognitive ability and attention. Higher RD in left inferior fronto-occipital and corticospinal tracts were related to lower attention and executive performance.¹⁹ These findings are clearly diverse and hard to compare across studies. Prospective studies using clearly defined cognitive variables are needed to confirm or expand these relationships.

Across this fairly limited range of studies, there are few patterns that appear to be emerging. AD is consistently decreased in both adults and children with T1DM, but FA may be more consistently decreased in adults with T1DM and more consistently related to cognitive outcome. This discrepancy may be due to the longer disease duration and/or greater degree of exposure to hyperglycaemia in T1DM adults, underscoring the necessity of conducting separate neuroimaging studies during development. In support of this idea - within both adult and child T1DM samples - hyperglycaemia exposure was consistently associated with lower FA and higher RD. Perhaps with more prolonged exposure over time, group differences in FA and RD would ultimately be detected in these younger samples. Animal studies suggest that decreases in AD reflect axonal degeneration if accompanied by decreases in FA, or demyelination if no difference in FA is observed.¹² Both findings have been reported in T1DM patients. Thus, similar to the T1DM rodent models, T1DM-related DTI changes may be manifestations of demyelination, axonal degeneration, or both, depending on the region examined and the degree of exposure to hyperglycaemia.

There are several issues that may interfere with our ability to detect consistent findings across these studies. The characteristics of the patient samples in these papers differ in many ways, including degree of diabetic complications, the degree

and manner in which their exposure to glycaemic extremes was characterised, the cognitive batteries used, and the type of imaging analyses that were performed (voxel-wise versus region of interest). In addition, all of the studies discussed in this section are cross-sectional, making it difficult to address causality of any relationships between glycaemic control and DTI parameters. Prospective longitudinal studies would best address these issues, but are currently lacking in the literature, although several are underway.

As previously mentioned, white matter structural changes can only be confirmed by direct histological examination of biological tissue. Thus, animal model work is critical for a deeper understanding of results from human DTI studies. For example, DTI analyses of animal models of T1DM found reduced FA, decreased AD, and slightly increased RD in the striatum, and reduced FA with unchanged AD and slightly increased RD in the cortex.²⁸ These regions were then examined histologically in the same animals. Striatal fibre bundles had signs of demyelination (rarefaction of the myelin sheath, myelin loss) and axonal degeneration, and cortical regions had axonal degeneration and/or neuronal loss. Due to the limited number of animals examined histologically in this study, no correlations were performed between diffusion indices and degree of histopathological alteration. However, these results suggest that diabetes-related DTI changes in the brain can reflect demyelination and axonal degeneration.

Multiple mechanisms have been suggested to mediate white matter nerve damage due to hyperglycaemia. Hyperglycaemia causes intracellular activation of the polyol pathway (sorbitol metabolism) resulting in the accumulation of advanced glycation end products (AGE).²⁹ AGE accumulation can also cause non-enzymatic glycation of myelin,³⁰ making myelin more susceptible to macrophages, which, in turn, release proteases that further contribute to demyelination.^{31,32} On the other hand, intracellular AGE interacts with matrix proteins,³³ leading to structural and functional nerve and neuroglia defects. Increased levels of intracellular AGE also cause glycation of cytoskeletal proteins, such as tubulin, neurofilament, and actin,^{30,34,35} resulting

in axonal atrophy. Finally, hyperglycaemia has been shown to cause alterations in mitochondrial dynamics and function,³⁶ leading to accumulation of reactive oxygen species, oxidative stress,³⁷ and impaired axonal transport in CNS axons, which can result in axonal degeneration.³⁸ These mechanisms could be the basis for DTI alterations related to hyperglycaemia, although clearly, more direct investigation is necessary in animal and human tissue to explore these issues.

CONCLUSIONS

Several studies have detected white matter structural differences in T1DM compared to controls, and many of these effects appear to be linked to hyperglycaemia. However, the data on which these conclusions are based are quite limited to date, both in terms of sample size and patient characterisation. The next logical step is to determine how different types of events in the course of diabetes management, such as chronic hyperglycaemia and DK, affect white matter structure during development. The best way to address these complex questions is to conduct prospective longitudinal studies on both paediatric and adult populations, starting with newly-diagnosed diabetics. These types of studies would help tease out normal brain development from diabetes-related changes and provide the basis for more causal interpretations.

One of the main reasons for the interest in examining white matter structural integrity in diabetes is due to subtle, but consistently observed, cognitive deficits in diabetic subjects.³⁹⁻⁴⁵ Given that alterations in white matter structure have been associated with some cognitive function in the existing T1DM studies, this issue requires more investigation to confirm or refute these preliminary findings. It remains to be seen if glycaemic exposure induces these white matter changes in T1DM and whether these changes can predict cognitive outcome. Future longitudinal studies, in both animal models and human populations, across both development and adulthood, will be necessary to support such a causal model. Ultimately, it is hoped that this information will be helpful in guiding treatment choices and preventing future negative cognitive outcomes in individuals with T1DM.

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