Diffusion Imaging, White Matter, and Psychopathology

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Abstract

The functional significance of the brain’s white matter was not fully appreciated until new imaging methods were developed to visualize fiber pathways and connections in the living brain. Rapid advances in diffusion tensor imaging (DTI) have led to substantial insights into human brain development and disease processes and have thrust white matter into the focus of researchers and clinicians alike. The full clinical potential of this relatively new technique remains to be determined, but early indicators suggest that DTI will be a significant new technology in mapping mechanisms of human health and disease. Here we review brain changes that have been studied with DTI over the human lifespan and findings in a variety of neuropsychiatric disorders. We also suggest future areas where DTI is likely to have significant impact.
Voxel: a volume element representing a value measured on a regular grid in 3D space (analogous to a pixel in 2D); the size of the voxel depends on the resolution of the image.

Because diffusion images also contain directional information on fiber orientations, they may also be analyzed using tract tracing techniques. These methods track fiber pathways connecting one brain system to another, revealing the 3D trajectories of fiber pathways, their connection patterns, and the integrity of these connections. What has been termed WM “tractography” is the visualization and characterization of major fiber bundles in vivo. Tractography essentially follows the primary eigenvector of diffusion from one voxel to the next to develop a model of fiber trajectory through the brain (Basser et al. 2000). Except in regions with fiber crossing or mixing, the principal eigenvector of the diffusion process is a reliable indicator of the dominant fiber orientation. Plotting the path of the primary diffusion direction across contiguous voxels may be used to follow the direction of the fiber pathway and its termination or intersection with crossing fibers (Figures 2 and 3).

Tractography provides substantial anatomical insight on an individual level, for example, in neurosurgical planning. But by collecting these scans from large cohorts of patients and healthy subjects in a variety of conditions and over time, brain connectivity may be studied in remarkable detail. Systematic patterns can be identified, including characteristic deficits in brain disorders. These anatomical networks may also be related to patterns of functional connectivity or activation measured using resting-state MRI or task-related functional MRI. Clinically, changes in local diffusion measures are often a sign of alterations in functional, clinical, or behavioral measures, and they offer unique insight into the cellular microstructure of the living brain.

At a conceptual level, diffusion tensor imaging (DTI) tunes into how much randomly diffusing water molecules prefer to go in one direction, as opposed to all directions, and infers from this the properties and directions of the tissues that contain the water molecules. In brain cerebral spinal fluid (CSF), diffusion is unrestricted—water molecules diffuse equally in all directions. By contrast, in the brain’s WM, movement is constrained to
occur along the fiber tracts. Perpendicular to these tracts, water diffusion is hindered by the tight packing of cellular axons and the fatty, myelin sheaths that encapsulate the axon fibers.

It is worth reviewing the basic principles of the MRI signal to understand how MRI may be tuned to detect directional diffusion and then infer fiber properties and their directions. MRI does not involve the injection of radioactive isotopes, which is one of the main reasons it has been widely used. Instead, MRI is based on measuring a quantum-mechanical property of atomic nuclei, known as the spin. The water molecules in brain tissue contain hydrogen atoms. When the brain is placed in a strong magnetic field, the spin states of these nuclei can be driven into an excited state by using radio-frequency pulses of short duration. The slow return, or decay, of this signal to the unexcited state occurs with an exponential time constant (decay constant) that depends on the tissue type. This makes it possible to reconstruct images of gray and white matter that are clearly differentiated. Pathologies can also be identified if they alter the decay of the MRI signal (such as edema, in which tissue water content is elevated, or stroke, in which diffusion is restricted).

In 1956, Torrey showed how the Bloch equations for the decay of the MRI signal would change in the presence of water diffusion, which tends to make the MR signal decay even faster. Stejskal & Tanner (1965) found that by applying an extra magnetic field gradient in a specific direction, the MRI signal would decay at a rate that reflected the rate of water diffusion in that direction. So by applying many different diffusion-sensitive gradients, in many different directions, the local profile of diffusion could be reconstructed. In early experimental studies, the direction of fastest diffusion was confirmed to match that of the underlying WM fibers. Early DTI studies by Le Bihan, Basser, and Moseley in the early 1990s showed that it was feasible to apply a set of six diffusion-sensitized gradients to the brain, in different directions, and compare the rate of MRI signal decay to that seen in a reference scan without any diffusion weighting (a standard MRI scan; Basser et al. 1994, Le Bihan 1995, Moseley et al. 1990, Pierpaoli et al. 1996). These seven diffusion-weighted scans are sufficient to estimate a diffusion tensor, which expresses the shape of the diffusion profile as water molecules diffuse out from each point in the brain. A tensor can be represented by an ellipsoidal shape that is elongated along the axis of fastest diffusion but squashed along directions where diffusion is restricted.

From the estimated diffusion tensor at each voxel, one can derive eigenvalues that reflect the magnitude of diffusion and corresponding eigenvectors that reflect the directions of maximal and minimal diffusion. By taking the mean of the three eigenvalues ($\lambda_1, \lambda_2, \text{and} \lambda_3$) the mean molecular diffusion, or mean diffusivity (MD), value is obtained. As mentioned above, this value reports the presence of barriers to free diffusion in the volume, but it does not provide information about the direction of movement. Based on the ratio of the eigenvalues to one another, one can determine the degree to which diffusion is directionally constrained. This scalar measure—termed fractional anisotropy (FA)—ranges from 0 to 1, where 0 represents no preferred direction (isotropic diffusion), and 1 represents unidirectional movement (anisotropic diffusion) (see Figure 1).

**White Matter Microstructure and Diffusion Tensor Imaging**

Clinical DTI studies primarily rely upon FA and MD as markers of cerebral integrity. More recently, additional DTI-derived parameters have been applied to clinical questions, and with time the parameters themselves have become easier to interpret. For example, some recent studies report individual or group differences in axial and radial diffusivity, measured from the individual eigenvalues. Axial diffusivity is derived from the largest of the three eigenvalues and measures the rate of diffusion in the direction of fastest diffusion, often detecting

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**Resting state MRI:** a method to study functional connectivity in a neural network consisting of distinct brain regions by obtaining whole-brain functional MRI data as a participant rests quietly while awake in the scanner

**DTI:** diffusion tensor imaging

**CSF:** cerebrospinal fluid

**Fractional anisotropy (FA):** a scalar value between 0 and 1 that describes the degree of anisotropy of water diffusion in the brain; high values typically indicate constrained diffusion in one dominant direction, along a tract
Neurotrophic factor: a protein that promotes growth or maintenance of certain neurons of the central or peripheral nervous system; it may support the survival of existing neurons or encourage the growth and differentiation of new neurons and synapses through axonal and dendritic sprouting

CC: corpus callosum
Fasciculus: a bundle of axons (nerve fibers)
AD: Alzheimer’s disease

longitudinal diffusion along axons. A related measure is radial diffusivity. This is derived by taking the average of the second and third eigenvalues, representing the transverse direction of diffusion, which is more constrained by cellular structure and myelination.

Collectively, these values (FA, MD, axial, and radial diffusivity) are interpreted as indicators of WM microstructure. In damaged or atrophied WM, MD values are higher as a result of increased free diffusion. Usually, FA also decreases due to loss of coherence in the preferred direction of movement. Decreased axial diffusion will result from increased barriers to organized diffusion in the primary plane, whereas damage to WM may result in an increase in radial diffusion through the loss of barriers to perpendicular diffusion.

These values are not independent reporters—all are derived from the same three eigenvalues of the tensor. Their values are often correlated; however, many smaller studies report no significant relationship between FA and MD metrics in select patient samples.

Cause and Effect
To some extent, electrical activity in axons regulates the myelination of axons, and conversely, the gross geometry of axons (i.e., diameter or packing density) is expected to influence the ability to rapidly relay electrical signals. These ideas are also supported experimentally (i.e., Demerens et al. 1996). DTI measures of the brain’s WM reflect brain function but are also influenced, over a longer time course, by behavior. WM changes therefore represent an ongoing interaction between the biology of the brain and the environment.

Nature and Nurture
The growing body of work combining genetic information with DTI is beginning to investigate the relative contributions of nature and nurture to brain circuitry and fiber integrity. In healthy subjects, FA is moderately correlated with cognitive measures, such as full-scale intelligence quotient (IQ) and its subscales (Chiang et al. 2009). Additionally, twin studies assessing correlations between identical and fraternal twins and fiber integrity as assessed by FA have shown that FA is highly heritable. According to bivariate genetic models, IQ is influenced by some of the same genes that influence fiber integrity (Chiang et al. 2009). These studies—linking genes, WM integrity, and cognition—have renewed interest in determining specific genetic variations that account for the relatively high heritability of fiber integrity.

Even single-nucleotide polymorphisms in one gene can impact the development of major WM pathways (Thomason et al. 2010). In one study of 435 twins, a very common variant in the gene for brain-derived neurotrophic factor (BDNF)—found in 20% of all normal individuals—was associated with lower WM integrity in the splenium of the corpus callosum (CC), inferior fronto-occipital fasciculus, left optic radiation, and corona radiata (Chiang et al. 2010a). Furthermore, BDNF variation influenced the association between IQ and fiber integrity, suggesting that the BDNF gene may affect intellectual performance by modulating WM development. In a related study, Braskie et al. (2010) found that fiber integrity was lower in carriers of a very common risk gene for Alzheimer’s disease, CLU (also known as clusterin, or apolipoprotein J). In 325 healthy young adults, each CLU C risk allele was associated with identifiable deficits in brain fiber integrity in a selective anatomical pattern. CLU is a lipoprotein involved in lipid transport and remyelination, is carried by ~88% of people of European ancestry, and was recently discovered to increase the lifetime risk for Alzheimer’s disease (AD) by 16%. These brain differences may explain the greater vulnerability to AD in those who carry the CLU risk variant (Braskie et al. 2010).

Conversely, the effect of experience on the brain is clearly demonstrated in several DTI studies. In one DTI study of people blind from an early age, Lee et al. (2007b) found severe deficits in fiber integrity in the brain’s visual...
system, likely due to prolonged sensory deprivation, as well as compensatory increases in other brain systems. Musicians also show lasting changes in brain WM resulting from years of intensive practice since early childhood (Bengtsson et al. 2005). Perhaps surprisingly, DTI studies have shown WM changes resulting from behavioral training in humans over intervals as brief as six weeks (Scholz et al. 2009). Studies such as these suggest that the structure of WM is not rigid but rather is very much shaped by our human experiences.

Clearly, the fiber architecture of the brain is to some extent inherited from our ancestors, but what we are capable of doing with it—and how it matures, adapts, and declines—depends upon our environment and experiences.

**WHITE MATTER CHANGES IN NORMAL DEVELOPMENT AND AGING**

**White Matter Development**

DTI data is now available for typically developing samples of hundreds of subjects and for age ranges spanning up to 70 years, giving a solid outline to the patterns of WM microstructural change associated with maturation and aging (Hasan et al. 2007). Beyond the rapid changes in infancy, brain WM FA increases in a somewhat linear fashion into the third decade of life. At that point the trajectory of FA plateaus and then gradually declines with age. The trajectory of brain WM development may be fitted using standard linear and quadratic functions. This yields a standard parabola with a peak value of FA around age 33 (Hasan et al. 2007). In other words, we observe a steady arched increase in brain WM FA through the third decade of life, then a peak, and arched onset of decline in the middle of the third decade. These WM changes mirror the overall trajectory of many cognitive and behavioral processes across the lifespan. As a result, the functional significance of brain FA is a topic of great interest in contemporary neuroscience.

Increasing brain FA in WM in youth may indicate more tightly regulated fiber orientation and more robust myelination in major WM tracts as maturation proceeds. This change in youth coincides with a progressive reduction in FA in brain gray matter, which is thought to reflect axonal and neuronal pruning.

Finer-grained analysis reveals some regional variation and ordering in the rates and trajectories of fiber tract maturation. Lebel and colleagues studied more than 200 participants, ages 5 to 30, with DTI, and examined the order of maturation of specific tracts. Fronto-temporal connections (e.g., the uncinate fasciculus and cingulum) were the most protracted in their developmental time-course (Lebel et al. 2008). Additional work linked the development of cognitive functions to the rate and onset of myelination in tracts that mediate them. Nagy and colleagues observed that maturation of frontal and left temporoparietal fiber tracts coincides with the development of working memory capacity and reading ability, respectively (Nagy et al. 2004). Altogether, there is no overwhelming consensus on the order of tract maturation or whether there are sex differences in these age-related changes; however, WM maturation may follow a dynamic pattern from the rostral-lateral-ventral pole toward a dorsal-medial-caudal pole (reviewed in Gogtay et al. 2004). Females may develop faster than males, owing in part to the earlier onset of puberty in girls than in boys (Asato et al. 2010).

Recent research has also measured the relative contributions of genetic and environmental factors in the development of brain WM. In a DTI study of gene x environment interactions, Chiang et al. (2010b) examined 705 twins ages 12 to 29, and showed a waning trajectory of genetic effects on brain circuitry throughout 17 years of development. Gene effects were greater in adolescence versus adulthood; genetics had a greater contribution to fiber integrity in higher-IQ subjects versus lower-IQ subjects (Chiang et al. 2010b). This appears to confirm the Turkheimer hypothesis that genetic effects dominate when adverse environmental factors are reduced. Supporting this, WM integrity was
more strongly genetically controlled in those with higher socioeconomic status (Turkheimer et al. 2003). This provides strong evidence that genetic control of brain integrity is context dependent. The knowledge that gene effects dominate in early life and in certain subpopulations should be useful in the search for specific genes that affect fiber integrity or confer risk for disease.

**Aging**

Albeit through different mechanisms, myelin breakdown seems to recapitulate the developmental processes of myelination in reverse. Areas that demonstrate protracted development (such as the temporal lobes) are among the first to degenerate with age. This model of aging was termed “retrogenesis” by Reisberg (see Reisberg et al. 1999) and is increasingly borne out by data from new imaging modalities such as DTI.

George Bartzokis’s model of mental illness suggests that the vulnerability to Alzheimer’s disease (AD) and other forms of cognitive impairment is increased by myelin loss that follows a specific anatomical pattern. In his influential work on the topic, he explains that the effects of myelin breakdown are progressive, as oligodendrocyte cell loss leads to a reduced machinery available to combat toxins in the brain, and these higher levels of brain-compromising toxins (i.e., free radicals, cholesterol, and elevated iron content) contribute to further cellular compromise (Bartzokis 2004). This model highlights myelin’s vital role in impulse transmission. This has ramifications for higher cognitive function and synchronicity of functional connectivity across large-scale brain networks (Bartzokis et al. 2008).

In aging, myelination deteriorates in a sequence that is largely the reverse of that seen during normal WM development. The vulnerability of WM to age-related decline depends on the physical composition of WM, which differs in early- versus late-life myelinating brain regions. Later myelinating regions are among the first to show cellular compromise—these have smaller diameter axons and lower oligodendrocyte-to-axon ratios. Such regions include the medial temporal lobe and neocortical. By contrast, early developing motor and sensory cortical areas tend to be more resilient to disease. These areas have large-diameter axons and higher oligodendrocyte cell composition. The order of these processes is relevant to the pattern of cognitive decline seen in old age. In AD, the trajectory of brain atrophy follows a characteristic sequence in which amyloid plaques and neurofibrillary tangles build up in the brain (Braak & Braak 1991, Braskie et al. 2008). Even so, in time-lapse maps of this process, the sequence of changes recapitulates, in reverse, the order in which cortical regions emerge during development (Gogtay et al. 2004, Thompson et al. 2003). This supports the hypothesis that the early maturing primary systems of the brain—which are among the most heavily myelinated—are most resilient to amyloid pathology and environmental stressors. Late-maturing regions tend to be more vulnerable.

**CLINICAL RESEARCH**

**Neuropsychiatric Disorders**

**AD/mild cognitive impairment and the dementias.** Dementia is a serious and often progressive loss of cognitive ability beyond what is expected from normal aging. Mild cognitive impairment (MCI, or incipient dementia) resides at the less-affected end of the phenotypic spectrum, whereas AD represents the more insidious behavioral phenotype. Physical markers in the brain have long been sought as correlates of dementias for their etiological value. They are also useful for diagnosis and prognosis (Frisoni et al. 2010, Kohannim et al. 2010).

Known brain correlates include widespread cortical changes, neuronal and synaptic loss, pathological WM changes, and the accumulation of amyloid plaques and neurofibrillary tangles. Pathological WM changes associated with AD include increased myelin density,
depletions of myelin basic protein, loss of oligodendrocytes, and microglial activation.

Dementias are characterized by sharp decline in declarative memory processes, and therefore alterations in medial temporal lobe structures have been a primary focus in MRI investigations of MCI and AD. WM pathology contributes to this decline. The most consistent effects in DTI studies of AD and MCI are found in three key regions: (a) subregions of the medial temporal lobe: hippocampus, entorhinal cortex, and parahippocampal WM; (b) temporal lobes proper; and (c) the posterior cingulum (reviewed by Stebbins & Murphy 2009).

What has emerged from DTI studies of AD and MCI is a picture of disconnection in critical memory-processing brain regions. Network connectivity is also impaired between the entorhinal cortex/hippocampus and the rest of the brain. The entorhinal cortex receives input from multiple cortical regions and transmits to the hippocampus via the perforant pathway. Parahippocampal WM fibers provide these connections between the entorhinal cortex and hippocampus. They also connect these areas to the rest of the brain through the posterior cingulum.

Loss of WM integrity is more severe in AD than in MCI, in line with the intermediate or less-severe effects of MCI along the continuum of the dementias. That is, AD patients demonstrate significant decreases in FA and increases in MD compared to healthy age-matched control participants, and MCI patients fall somewhere in the middle. Loss of WM integrity is therefore considered to be a pathological change related to the development of AD.

**Schizophrenia.** Schizophrenia is a mental disorder characterized by abnormalities in the perception or expression of reality. It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking with significant social or occupational dysfunction. A major hypothesis of schizophrenia is that the disorder manifests from disruptions in neural circuitry (Friston & Frith 1995).

The disconnection hypothesis of schizophrenia has gained support from DTI studies. Across studies, groups of individuals with schizophrenia show a characteristic and somewhat consistent reduction in deep WM FA in the frontal and temporal lobes. This localization is consistent with the patterns of cortical gray matter atrophy in first-episode schizophrenia (Thompson et al. 2009) and in children with a rare, early-onset form of the disorder (Thompson et al. 2001, Vidal et al. 2006).

WM tracts with the most marked differences between schizophrenic patients and healthy comparison subjects are the cingulate (an area involved in error detection and attention, and a key link between limbic and higher cortical functions), the CC (critical for interhemispheric transfer), and WM of the frontal lobes. Less commonly implicated are the superior longitudinal fasciculus (SLF), infero-frontal occipital fasciculus (IFOF), uncinate fasciculus, frontal longitudinal fasciculus, and arcuate fasciculus. These tracts provide for intra- and interlobar transfer of neural signals, and in all reports it is the schizophrenia group that has lower FA. Several studies also report lower FA in the cerebral peduncles in individuals with schizophrenia. The cerebral peduncles include the corticospinal/corticopontine tracts that transmit sensorimotor information. Lower FA in these circuits supports trait disruption in cortico-cerebellar-thalamo-cortical circuitry that has been suggested as underlying the schizophrenic disorder. DTI findings are not always replicated or consistent for specific major WM pathways, but the overall picture is one of reduced WM integrity in schizophrenia (reviewed by White et al. 2008). This indirectly supports the hypothesis of disrupted neural connectivity as participating in the etiology and pathophysiology of schizophrenia.

Studies that consider heritability within the prodromal research framework (cf. Cannon et al. 2003) have begun to address whether WM changes are likely to participate in pathophysiology of schizophrenic disorder as opposed to representing consequences or epiphenomena of...
the disease. This framework relies on repeated observations of brain structure and/or function in adolescent/young adult patients with subthreshold symptoms of psychosis. The goal of prodromal research is to identify changes that predict transition to full-blown disease. With detailed evaluations prior to, or at early stages of, disease onset, researchers can study whether specific neurobiological changes precipitate disease. Furthermore, by distinguishing neurobiological alterations linked to genetic risk (i.e., that also appear within patients’ first-degree relatives) from those that occur proximally to the initial onset of psychosis but that are not associated with genetic risk, one can be more specific about the neurodevelopmental influences likely involved in the etiology and pathophysiology of disease. A recent DTI prodromal research study in youth at high risk for psychosis showed that lower brain FA is present prior to disease onset. WM development also predicted deterioration in social functioning at 15-month follow-up (Karlsgodt et al. 2009). These results suggest that early WM integrity may predict functional outcomes. Future prodromal studies (across a variety of clinical disorders) are likely to identify neurobiological processes involved in the etiology and pathophysiology of disease.

In addition to the known neurobiological changes preceding onset of disease, several studies have examined the functional significance of altered FA in schizophrenia (reviewed by White et al. 2008). Lower FA correlates with poorer performance in orienting to attention, with increased saccadic latency and with poorer performance in tasks measuring emotion comprehension. In addition to studies that relate performance measures to brain FA in major WM pathways, recent studies have targeted the neural correlates of clinical symptoms. CC and IFOF FA have been linked to the severity of hallucinations, and lower FA in fronto-temporo-limbic circuits has been associated with increased impulsivity in patients. Linking clinical and behavioral phenotypes to DTI measures is likely to resolve some of the observed heterogeneity in observed differences between groups, as these measures may more tightly travel with neural correlates than with disease boundaries.

**Mood disorders.** Unipolar depression, or major depressive disorder (MDD), is a disabling condition characterized by low mood accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities. Known brain correlates include dysfunction in frontal-subcortical circuits that underlie cognitive, motivational, and appetitive behaviors. Specifically, disruptions in orbital frontal, anterior cingulate, lateral prefrontal, and limbic function have been related to MDD. MRI studies of hyperintensities, biochemical composition (spectroscopy), and magnetization transfer as well as postmortem studies have indicated altered brain WM in MDD. Additionally, genetic analysis of postmortem tissue has shown decreased expression of oligodendroglia-related genes in depressed and bipolar subjects (Sokolov 2007, Tkachev et al. 2003). DTI studies reliably show lower FA in MDD subjects in superior frontal and temporal WM (Sexton et al. 2009). Decreased anisotropy may indicate a disconnection syndrome within neural circuits encapsulating frontal cortical and basal ganglia and thalamus regions. Network dysfunction in these circuits would be expected to modify executive function and motivated behavior, two hallmarks of the altered function observed in MDD.

Bipolar disorder (BP) is typified by alternating periods of mania and depression and in some cases psychotic symptoms. Episodes of depression include low mood, loss of interest in activities, fatigue, poor sleep and appetite, hopelessness, poor concentration, and suicidal ideation. Episodes of mania include elevated or irritable mood, flight of ideas, pressure of speech, inflated self-esteem, and increased engagement in destructive activities such as excessive spending, risk taking, or sexual promiscuity. In contrast to the more consistent results obtained in DTI studies of MDD, the results of BP DTI studies are more variable and more difficult to interpret. Abnormal inter- and intrahemispheric connectivity may represent a
marker for BP, but the directionality of the findings is inconsistent. Lower FA has been observed in individuals with BP in prefrontal and frontal regions, and in projection, associative and commissural fibers. Less consistent findings have been reported for subcortical and nonfrontal WM connectivity (Heng et al. 2010). Perhaps the most predominant finding is that MD is higher and FA is lower in the CC in patients with BP compared to a control group (reviewed by Bellani et al. 2009). One study examined treatment effects in BP. After treatment with mood stabilizers, BP patients showed normalization of FA in the right anterior thalamic radiation and left optic radiation (Versace et al. 2008). An important area for future DTI research will be to directly compare BP and MDD groups to examine systematic WM differences between subjects with these different disorders.

**Anxiety disorders.** Anxiety disorders include generalized anxiety disorder, panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder; all of these have been examined to various extents using DTI. These are debilitating chronic conditions, present from an early age or beginning suddenly after a triggering event. They are chronic but prone to flare up at times of high stress.

Patients with OCD experience egodystonic intrusive thoughts that they attempt to reduce by engaging in repetitive and/or compulsive behavior. Often compulsion is inexplicable, based on an urge to complete a ritual behavior triggered by apparent nervousness. The cingulum has long been implicated in the pathogenesis of OCD, but FA results in this fasciculus are mixed. Different studies report increased or decreased FA in the cingulum, and no consensus has been reached. Increased FA has been observed in the internal capsule and CC, along with decreased FA in parietal lobes, supramarginal gyri, and left lingual gyrus in the occipital lobe. Furthermore, in a treatment study, drug-naïve OCD patients showed significantly higher FA in the CC, the internal capsule, and WM in the area superolateral to the right caudate, and this increase in FA was mostly no longer observed after patients were treated with 12 weeks of citalopram (Yoo et al. 2007).

**Developmental Disorders**

**Autism.** Autism is a developmental disorder characterized by impaired social interaction, communication difficulties, and by restricted and/or repetitive behavior. It is thought that information processing is altered in the autistic brain and that the connections between neural regions are differently organized. As a result, there is emerging interest in applying DTI to study autism.

DTI work in autism reliably shows that reduced FA and increased diffusivity is associated with disease and linked to cognitive performance (Alexander et al. 2001). Interestingly, these results show some regional specificity, with lower FA in the fusiform gyrus and superior temporal sulcus (STS), regions implicated in processing socially relevant material, and also in the vmPFC, ACC, temporoparietal junction, and amygdala, regions implicated in theory-of-mind processing (Barnea-Goraly et al. 2004). Moreover, this direction of findings has been replicated in both voxel-based and tractography approaches.

What makes the DTI results in this disorder most perplexing is not the idea that autistic individuals show WM disturbances but rather that the direction of results is unexpected. That is, one of the most replicated findings in autism neuroanatomy to date is the tendency toward unusually large brains, particularly in early development, and in brain WM volume especially (Herbert 2005). Ten years ago, myelin staining of postmortem brains found little difference between autistic and typically developing children. At that time, positron emission tomography investigations also showed increased serotonin synthesis in autistic children (Chugani et al. 1999). As a neurotrophic factor, serotonin would be expected to promote axonal outgrowth during development (Lauder 1990). Thus, it was uncertain how sheer volume would relate to coherence in fiber tracts and to...
the functional connectivity between spatially disparate neural regions.

The growing application of DTI, together with expanded modeling of functional connectivity across neural circuits, is advancing neural models of autism. Lower FA and higher diffusivity measures may reflect decreased myelination, decreased axonal density, or abnormal axonal organization. This may reconcile the contrasting findings above.

**Attention deficit hyperactivity disorder.** Attention deficit hyperactivity disorder (ADHD) involves prolonged development of impulse control. It often manifests in childhood and is often (but not always) either outgrown or diminished by compensatory mechanisms with maturation and cumulative experience. ADHD predominantly involves frontal brain regions that allow problem solving, planning ahead, understanding others’ actions, and impulse control.

The early picture that has emerged from imaging WM in the developing ADHD brain is somewhat different from the disruptions in presumed connectivity observed in other psychiatric conditions. ADHD adolescents have been characterized as having uniquely high FA in frontal WM. This is a rare example of a case where higher FA is indicative of pathology. In the recent study by Davenport et al. (2010), the primary group differences were situated in the anterior corona radiata, an area composed of frontostriatal connections that branch outward (Davenport et al. 2010). Here, higher brain FA may represent either less branching (i.e., more net coherence in singular direction) or compensatory mechanisms.

FA values are not uniformly higher in ADHD. On the contrary, in children, lower FA values have been described in several WM regions, including right premotor and striatal regions, bilateral cerebral peduncles, cerebellum, and left parieto-occipital, as well as in corticospinal and SLF regions of interest. Reduced WM FA in the right cingulum and SLF has also been measured in adults who had ADHD as children, indicating that these neural WM alterations may be relatively stable traits of the disorder. The application of DTI methods to ADHD has, therefore, slightly shifted the focus of this disorder from one residing purely in the brain’s frontal lobes to the networks that relay information to and from the frontal cortex, which span widespread brain regions.

A recent study looked for areas of convergence and divergence between brain FA in samples of adolescents with either ADHD or schizophrenia and a control sample. A region in the left posterior fornix showed lower FA for both ADHD and schizophrenia groups (Davenport et al. 2010). Because both psychiatric conditions are associated with similar cognitive and behavioral deficits, such as impairments in working memory, sustained attention, and response inhibition, observed commonality between them in lower posterior fornix FA may later be proven to be a critical hub in the neural disruption that underlies related aspects of these conditions.

**Dyslexia.** Difficulty in learning to read, or dyslexia, affects 5% to 17% of English-speaking children. This deficit in language fluency may relate to low-level perceptual deficits. Quite certainly educational opportunity, stress, socioeconomic status (SES), and many other sociocultural factors influence the ability of children to acquire language proficiency. Thus, it is the interaction of neurophysiology, possibly down to primary perceptual mastery (i.e., rapid discrimination of basic speech sounds such as phonemes that necessitate differentiation at rates faster than 40 msec), and environment that seems to predict the reader’s fluency with language.

Neuroscientists have applied DTI methodology, believing that it may provide more objective diagnoses of reading disability and illuminate the mechanisms of reading acquisition more generally. Neuroimaging and postmortem studies indicate that disruption in left temporo-parietal cortex pathways is associated with poor reading. Using DTI, Deutsch et al. (2005) demonstrated that brain FA in left temporo-parietal WM was positively
correlated with cognitive measures of reading, spelling, and rapid naming performance across a sample of children with and without dyslexia (Deutsch et al. 2005). This was the first in vivo work to relate disruptions in WM to reading ability. This work suggests that higher FA in the temporo-parietal junction (reflecting greater coherence in axonal trajectories) is advantageous in the disorder, as well as in typically developing children.

**Neurogenetic Developmental Disorders**

**Fragile X syndrome.** Fragile X syndrome is associated with the expansion of a single trinucleotide gene sequence (CGG) on the X chromosome and results in a failure to express the FMR1 protein, which is required for normal neural development. The result is disruption in the development of dendrites and synapses. DTI shows sparse and aberrant WM connectivity in the developing brains of female children with the mutation. The most consistent differences have been found in WM in the fronto-striatum and parietal sensory-motor tracts, where relative to controls, females with fragile X exhibit lower FA values. These differences are consistent with the known profile of anatomical brain abnormalities in fragile X syndrome, including alterations in striatal circuitry (Gothelf et al. 2008, Lee et al. 2007a).

**Williams syndrome.** Williams syndrome (WS) is caused by a deletion of about 26 genes from the long arm of chromosome 7. Cognitive hallmarks of WS include severe visuospatial deficits and relative strengths in face and object processing. DTI applied to this neurodevelopmental disorder has revealed alterations in WM that are regionally specific, in line with earlier studies showing consistent patterns of volumetric excesses and deficits, abnormal cortical complexity, WM atrophy, and alterations in CC shape (Chiang et al. 2007, Luders et al. 2007, Thompson et al. 2005).

Hoeft et al. (2007) measured higher FA in the right SLF, but not the left SLF or the bilateral inferior longitudinal fasciculus, in WS children. The higher FA observed for WS in the right SLF was significantly associated with deficits in visuospatial ability. This result is one of the few examples in the literature that indicates that performance decrements are associated with higher FA (which is usually a sign of more robust WM).

**22q11.2 deletion syndrome.** 22q11.2 deletion syndrome (qIIDS), also known as velocardiofacial syndrome, is caused by the loss of a segment of genetic material in chromosome 22. The features of this syndrome vary widely and may include birth defects such as congenital heart disease, palatal and skeletal abnormalities, learning disabilities, autoimmune disorders, hearing loss, growth hormone deficiencies, and seizures. The mechanism that causes the associated features of the syndrome is unknown but expected to involve migration defects of neural crest-derived tissues.

Studies of regional brain volumes in children with qIIDS show parietal but not frontal lobe differences after adjusting for total brain volume, which is reduced by 8.5% to 11% in children and adolescents with the syndrome, along with a characteristic pattern of cortical gray matter thinning and gyrification (Bearden et al. 2007, 2009). Frontal preservation along with parietal reduction supports a rostro-caudal gradient theory in qIIDS that specifies that the global brain shape of children and adolescents with qIIDS is altered along the antero-posterior axis, in a rostro-caudal gradient.

DTI studies corroborate this theory, confirming that FA differences in interhemispheric tracts were situated around the parieto-parietal connections. Gothelf et al. (2008) provide a useful survey of the brain-imaging studies in qIIDS, including a study that found a correspondence between FA in the inferior parietal lobe and arithmetical performance in children with the syndrome. In addition, our work has shown that the catechol-O-methyltransferase (COMT) gene that is contained within the
missing genetic material of chromosome 22 in qIIDS affects WM pathways, presumably by impacting dopamine availability (Thomason et al. 2010).

Movement Disorders

Huntington’s disease. Huntington’s disease (HD) is a neurodegenerative genetic disorder that affects motor and cognitive function, typically becoming noticeable in middle age. Individuals with preclinical HD carry the genetic mutation for disease but do not manifest clinical symptomatology. HD is associated with progressive degeneration in the basal ganglia, particularly in the caudate nucleus and putamen, which together form the striatum. The basal ganglia play an essential role in movement and behavior control via cognitive executive neural circuits and motor circuits.

Recent neuroimaging studies have helped to explicate how the basal ganglia are altered in HD. In diffusion-weighted imaging studies of HD patients, striatal diffusivity abnormalities correlate with increasing symptom severity and also with mutation repeat number. Across studies, higher MD and lower FA values have been obtained in HD patients compared to controls in superior and middle frontal, sensorimotor, and thalamic WM, as well as in parietal, CC, and external capsules, cerebral peduncles, and brainstem regions. Remarkably, Kloppel et al. (2008) identified voxels in the putamen and globus pallidus of the basal ganglia for which FA was a powerful predictor of whether an individual brain was that of a preclinical mutation carrier or healthy comparison subject (adapted from Kloppel et al. 2008). Comparisons between preclinical and clinical HD groups have shown that WM degeneration is more extensive in clinical HD. This latter finding corroborates the role of basal ganglia degeneration in disease progression and in conversion to the disorder.

Parkinson’s disease. Parkinson’s disease (PD) is a degenerative disorder characterized by motor and speech impairments as well as more subtle, but progressive, disturbances in cognition, affect, and sensory processing. Individuals with PD often experience muscle rigidity, tremor, and a slowing of physical movement, and in extreme cases, a significant loss of physical movement, or so-called akinesia. The neural basis of the disease is primarily attributed to dysfunction in the dopaminergic neurons of the basal ganglia that project to the motor cortex. Many researchers speculate that the neural basis of PD extends beyond cerebral gray matter dysfunction to WM pathways critical for information relay. Recent work using DTI has substantiated this. Several studies demonstrate significant reductions in FA in individuals with PD bilateral frontal regions that include the supplementary motor area, the presupplementary motor area, and the cingulum. More work is needed to understand how WM or diffusion properties in gray matter can help to untangle the neural basis of this disease. Certainly, application of DTI to mapping the progression of the disease is very timely, particularly in following individuals over time to learn how the disease course is altered by treatment and what neural changes are associated with clinical outcome measures.

FUTURE AIMS FOR CLINICAL NEUROIMAGING SCIENCE

DTI methods are expected to have the greatest relevance to clinical practice in five areas.

1. Detection of preclinical disease markers. For many neurobiological diseases, there is now unequivocal evidence that neurophysiological changes occur before clinical diagnosis is likely to be made. For instance, carriers of a risk gene for Alzheimer’s disease, CLU, have a 16% increased lifetime risk for Alzheimer’s disease and, at least as a group, show deficits on DTI scans over 40 years before the disease is typically detected. Early detection of disease onset has twofold value. First, it may lead to timely initiation of appropriate treatment. Second, understanding the neurobiological
precursors of disease can help identify the mechanisms and multiple pathways and risk factors that may lead to psychiatric dysfunction. Thus, there is both applied and intrinsic value to this discovery.

2. Treatment assessment. As noted above, prior DTI studies have tested the effects of periods of medication on integrity of neural WM. Serial DTI scans have been used to follow behavioral interventions as well as cell transplantation treatments. For example, one study assessed patients with Krabbe disease given stem cell transplantation at birth. They had higher FA values at one-year follow-up compared to those transplanted several months after birth, closer to illness onset (McGraw et al. 2005). DTI is also useful for neurosurgical planning and follow-up. Thus, DTI methods are beginning to show broad applicability for treatment evaluation as well as monitoring in neurorehabilitation after traumatic brain injury, for example.

3. Microstructural abnormalities in disease detected by DTI. There have been several reports of cases where DTI can quantify and visualize subtle alterations in brain microstructure that could not be observed by conventional MR imaging. For example, in a study of brain stem WM in patients with holoprosencephaly, cases were identified in which the pyramidal tract did not extend into the spinal cord and the medial lemniscal tracts remained fused (Albayram et al. 2002). Thus, DTI revealed abnormalities not visible on conventional MRI. It also separated patients into groups that could provide additional insight into the clinical variability observed in holoprosencephalies.

4. Accounting for phenotypic variability in disease using DTI/new disease classification [e.g., the Research Domain Criteria (RDoC) project]. An important phenomenon that needs to be addressed is the immense phenotypic variability across patients, even within a disorder. Individuals may differ in terms of symptom development (i.e., which symptoms develop first), symptom prominence (i.e., motor, psychiatric, cognitive, or combination), and rate of symptom progression. This pursuit is further confounded by the preponderance of comorbidity. Nonetheless, basic science fortifies in the presence of challenge. Many researchers and clinicians see neurobiology as an opportunity for novel classification of disease traits. Neuroimaging and genetic research has linked otherwise disparate disorders as having a common basis in the brain or in genetic background. This calls into question the independence of otherwise separate diseases. One current National Institute of Mental Health initiative, the RDoC project, seeks to develop new ways to classify psychopathology based on dimensions of observable behavior and neurobiological measures. This effort will draw upon large sets of neural, behavioral, and genetic data. The work is planned to impact basic science but may also be beneficial for clinical practice: If findings identify features that cut across traditional disease boundaries, this work may illuminate novel ways to improve patient care. DTI is expected to play a significant role in this and related efforts for understanding the neural mechanisms of disease.

5. Using DTI to examine structure–function relationships in disease. DTI provides a means to examine the functional implications of altered WM microstructure. Karlsgodt et al. (2008) found that in schizophrenia, decreased FA in the SLF correlated with working memory performance (Karlsgodt et al. 2008). Because the SLF connects frontal and parietal regions essential for working memory processing, this result provides an example where characteristic variations in the integrity of WM connections may have functional consequences.

Going forward, there is a good deal of...
work to be done to move from identifying what differences exist between patients and matched controls to what differences have the greatest impact on disease progress and are therefore the more important clinical targets.

CURRENT CHALLENGES TO CLINICAL DIFFUSION TENSOR IMAGING

The advances in basic science and clinical approaches to disease processes outlined in this review support the unmistakable benefits provided by this imaging modality. However, several practical decisions must be made when designing a DTI study and interpreting its results.

Best Practices Are Constantly Being Refined

Minimum number of diffusion gradients. With rapid developments in imaging hardware, DTI has moved from a standard protocol with a six-direction DTI acquisition to allow datasets to be collected with over 100 directions in under 15 minutes of scanning time. The acquisition of higher numbers of directions in the diffusion data is analogous to sampling more surface points on a 3-dimensional hollow figure. With only six points on a surface, one is able to fit that surface with a smooth balloon, stretched at the places where diffusion values are highest (principal eigenvalues) so that the balloon becomes elongated and oval. However, modeling the diffusion process in full detail may be limited when the model is constrained to have a balloon-like elliptical shape or when the number of angular samples (directions) is too low to reliably assess diffusion anisotropy. Low angular sampling rates could not resolve, for example, the behavior of two crossing fibers that would best be represented by a cross. The result instead would be a pancake-like balloon. The opportunity to better resolve the shape of water movement within the voxel will undoubtedly lead to more accurate reconstruction of the major fiber pathways of the brain, one of the ultimate goals of DTI technology.

Optimizing diffusion-imaging sequences for examining fiber integrity in the brain is a key issue in neuroscience and radiology. There is a consensus (for simpler studies of fiber integrity) that close to 30 directions along with three or so nondiffusion-weighted acquisitions is an acceptable standard. Zhan et al. (2010b) studied how increasing the number of diffusion-sensitized gradients improved the signal-to-noise ratio for common DTI-derived measures, such as FA and MD, to help people decide on the best trade-off between scan duration and accuracy in DTI. The signal-to-noise ratio was near-maximal with 66 and 58 gradients for FA and MD, and with 55 gradients for a related measure of anisotropy called the geodesic anisotropy (Zhan et al. 2010b). Zhan et al. found that there is an optimal ratio of nondiffusion-weighted images to diffusion-weighted images—around 1:11 for FA and 1:26 for MD. For this reason, it is often worth the time for diffusion imaging studies to collect more than one reference image; this affects the uncertainty of the MD measure more than the FA measure.

Now that it is feasible to measure diffusion in hundreds of directions, the diffusion tensor method has been criticized because it overlooks clinically and scientifically important information by fitting a simple ellipsoid (football shape) to the diffusion data. Part of the reason the detail saturates quickly is that the tensor model of diffusion is just an ellipsoid with six free parameters. Once these are fitted adequately, collecting more diffusion directions provides little added benefit. To avoid limitations of the single tensor model, higher-order models of diffusion have been proposed that more accurately measure FA where fibers cross. One such model, the tensor distribution function (Leow et al. 2009), fits multiple tensors at each voxel and weights the estimate of FA depending on relative contribution of each of the detected fibers. This method can correctly measure FA, which is underestimated in brain regions where fibers mix or cross. We performed several empirical studies showing that this modified
FA measure is much more accurate in fiber crossing regions where conventional FA is inaccurate or misleading (Zhan et al. 2009a, b). These improvements boost the power of any study, making studies more efficient and requiring less time and resources.

**Trade-offs of Speed versus Accuracy.** When it comes to asking a patient to lie still inside a scanner, prolonged data collection has a significant cost. Lengthy scans lead to more lost data due to patient motion, attrition, and discomfort. For a multisite DTI study of Alzheimer’s disease, we studied a range of DTI scanning protocols that took no more than seven minutes (Jahanshad et al. 2010), given the need to collect other scans assessing anatomy, blood flow, and resting state connectivity within a total scan time of 30 minutes. Although it may seem that using the highest spatial resolution would be best, we found that using larger voxel sizes (2.7 mm) allowed enough time to estimate diffusion in more directions. This greatly reduced the error in tracking fiber directions and pathways in the brain, reduced the noise in maps of FA, and improved the reproducibility of the anisotropy measures over time. Although it may seem that using the highest spatial resolution would be best, we found that using larger voxel sizes (2.7 mm) allowed enough time to estimate diffusion in more directions. This greatly reduced the error in tracking fiber directions and pathways in the brain, reduced the noise in maps of FA, and improved the reproducibility of the anisotropy measures over time. Although it may seem that using the highest spatial resolution would be best, we found that using larger voxel sizes (2.7 mm) allowed enough time to estimate diffusion in more directions. This greatly reduced the error in tracking fiber directions and pathways in the brain, reduced the noise in maps of FA, and improved the reproducibility of the anisotropy measures over time. Although it may seem that using the highest spatial resolution would be best, we found that using larger voxel sizes (2.7 mm) allowed enough time to estimate diffusion in more directions. This greatly reduced the error in tracking fiber directions and pathways in the brain, reduced the noise in maps of FA, and improved the reproducibility of the anisotropy measures over time. Although it may seem that using the highest spatial resolution would be best, we found that using larger voxel sizes (2.7 mm) allowed enough time to estimate diffusion in more directions. This greatly reduced the error in tracking fiber directions and pathways in the brain, reduced the noise in maps of FA, and improved the reproducibility of the anisotropy measures over time.

**Tractography.** Standard DTI tractography relies on procedures that trace the path of greatest diffusion across voxels (direction of the eigenvector with the largest eigenvalue of the diffusion tensor) (Basser et al. 2000). Contemporary approaches to tractography often derive trajectories that are both anatomically plausible and conform to well-characterized major bundles. However, tractography methods utilize various algorithms for construction of fiber tracts and, like any neuroimaging technique, the derived results can be influenced by methodological details. We review some of the mathematical assumptions of current DTI analysis algorithms in Lenglet et al. (2009), including situations where they can fail.

In summary, the best practices for DTI analysis are still being established. As data collection becomes more efficient, analyses are also changing from regional summaries to more advanced voxel-based, tract-based, or connectivity matrix comparisons. More advanced measures of local diffusion are also being used. In addition, many features identified using tractography have not been thoroughly validated in structured comparisons with the underlying anatomy. Together, these areas leave a wide area for further improvements in DTI imaging methodology.

**Mixed Inferences from the Measurements**

**Does higher FA necessarily mean better neuronal function?** Currently, there is common misconception in interpreting the most widely reported dependent variable of DTI, FA. Higher FA relative to other groups is generally interpreted as consistent with healthier WM. In many circumstances, higher FA does reflect fibers that are more numerous, more dense, more myelinated, or more coherent in orientation. Thus, for the most part, higher FA is considered to be beneficial. Furthermore, in normal adults, full-scale IQ is moderately correlated with FA. Even so, standard FA measures may be unreliable where fibers mix—the definition of FA relies on there being a single underlying dominant fiber direction. So in areas of crossing fasciculi, reports of higher FA must be treated with caution.

There may also be specific disease processes or developmental stages where higher FA—at the wrong place or at the wrong time—is not beneficial to behavioral or other outcomes. Patients may concurrently have abnormally high and low FA in different brain regions (e.g., FA is not always better; see Hoeft et al. 2007). Thus, the meaning of higher FA is specific to the region and the sample studied. For some patient groups, areas of increased FA could represent
compensatory mechanisms. As another example, in a developmental study, higher FA too early may represent less cognitive flexibility. This may be detrimental to neural network organization during active learning. To illustrate this idea, we observed somewhat surprising results in a DTI study of the impact of the COMT gene on brain PFC development. Despite the cognitive advantage reported for met-allele carriers, we observed relatively lower FA in those children (Thomason et al. 2010). These examples provide a basis for our assertion that higher FA does not necessarily indicate an advantage.

Question of Cause or Effect

It is not clear whether aberrant measures of WM microstructure in clinical samples precede or accompany the onset of illness. Studies of disorders emerging in longitudinal samples are needed to model the ordering of disease-related processes. Combined behavioral, multimodal neuroimaging, and diagnostic tests will be particularly useful for determining the temporal sequence in which biomarkers of disease emerge. It is possible that even before the emergence of disorder can be detected clinically, that neural markers will distinguish at-risk individuals from healthy individuals in nonaffected samples; in Alzheimer’s disease, for example, carriers of the clusterin gene—which boosts the lifetime risk for disease by around 16%—already have reduced fiber anisotropy in brain regions that deteriorate in overt AD.

THE FUTURE OF DIFFUSION TENSOR IMAGING

Developments

Going forward, several areas of innovation will significantly impact what we can learn from diffusion imaging. Methods for data acquisition and utilization are undergoing significant improvement.

Acquisition. High angular resolution diffusion imaging (HARDI) has emerged as an alternative to conventional DTI. HARDI is a diffusion-weighted MRI technique that relays additional information about composite nerve fiber structure as shown in Figures 4, 5, and 6. By sampling diffusion in more directions than the seven that are required to fit a diffusion tensor, fibers that mix or cross can be disentangled. For example, diffusion in the shape of an “X” occurs where the CC and other tracts mix (see Figure 4). Tractography methods that use the full HARDI signal can correctly follow fibers in these regions (see Figures 5 and 6).

A second advance in diffusion imaging is so-called hybrid diffusion imaging (HYDI; Wu et al. 2008) or diffusion spectrum imaging (DSI; Wedeen et al. 2005). These methods exploit the fact that diffusion is more complicated than is described by the single tensor model used in DTI. In any diffusion-imaging study, one parameter setting that must be chosen—the $b$-value—affects the level of diffusion weighting and the types of diffusion that are seen; typical $b$-values are 1,000 to 3,000 s/mm$^2$. If this value is set very high, it is possible to emphasize different components of the diffusion that may be sensitive to interesting and useful physiological properties. Fitting of more advanced models to the diffusion process suggests that it has at least two components. “Fast” diffusion is better detected when $b$-values are low, but “slow” diffusion (Assaf & Cohen 2000) becomes visible when $b$-values are high (4,000 or higher). Higher $b$-values are achieved by increasing the strength of the diffusion-sensitized magnetic field gradients of the scanner. The slower diffusion process is quite useful in acute stroke for predicting the final extent of a cerebral infarction and may provide superior detection of nerve fiber loss in the WM that is caused by vascular disease.

HYDI combines the high angular sampling of HARDI and the ability to pick up both fast and slow diffusion by collecting data at multiple $b$-values (Zhan et al. 2010b). By varying the diffusion weighting ($b$-value) and increasing the angular resolution (to over 100 directions), fiber integrity and directions can be more accurately recovered (see Figure 6);
we have also shown how to reconstruct the full 3D diffusion process by integrating data from multiple $b$-values. In our studies (Zhan et al. 2010b), higher $b$-values gave improved orientation estimations but poorer eigenvalue estimates (which are important for studying fiber integrity). The opposite strengths and weaknesses were found at lower $b$-values. Combining these strengths, HYDI, especially with a “staggered” angular sampling, outperformed all of the HARDI scanning protocols, even when overall scanning time was held constant. Finally, $q$-space imaging, or diffusion spectrum imaging, also allows full sampling of the diffusion process by collecting an entire set of diffusion images by slowly stepping through a 3D grid of different $b$-values and diffusion directions. It is called $q$-space imaging because the parameter $q$ is a vector that defines the $b$-value and the diffusion directions. Different schemes for sampling $q$-space can be compared in terms of their efficiency and accuracy. So far, the main application of these techniques has been to perform more precise tractography.

Despite the advantage of offering more information than DTI, HARDI, HYDI, and DSI raise new challenges, such as complex modeling of the data and nonintuitive and computationally demanding visualization. These may be barriers to researchers and clinicians hoping to rapidly implement these methods in practice. However, these beyond-DTI methods are among many new achievements in the optimization of diffusion-weighted imaging. As with all worthy new advances, the challenges therein will be addressed as needed to advance the science. An acid test of these methods will be whether they can discover biomarker or diagnostic information that is more useful than that from standard DTI measures. If so, they will likely begin to replace DTI for routine clinical and scientific use.

**Genetics of DTI.** One area likely to see sustained innovation is the study of genetic factors that influence brain connectivity and integrity, as observed with DTI. Although there are, as yet, many more genetic studies of brain morphometry than of DTI, initial twin studies show that FA is highly heritable in both adults and children and that common genes underlie both full-scale IQ and FA (Chiang et al. 2009). In addition, maps of the connectivity—or connection strength—between different regions of the brain are also known from twin studies to be highly heritable (Patel et al. 2010), suggesting that specific genes influencing anatomical connectivity are likely to be discovered as soon as enough data has been accumulated to detect and confirm their effects. As noted previously, a handful of commonly carried genes have already been confirmed to influence FA, including variants in growth factors (BDNF), genes that may alter neurotransmitter levels (COMT), and susceptibility genes for disease (CLU) that are quite well understood from molecular and physiological studies. It is likely that no one genetic variant is highly influential

**Utilization.** Computational approaches to neural network models are expected to advance significantly in coming years with the additive advantage of cross-modal brain imaging. DTI will play a special role in the development of these models, carrying information that will inform estimations of which areas are connected, how much information can be transferred, and data transfer rates. Already there is a significant movement afloat to combine DTI with other imaging methods, such as electroencephalography, magnetoencephalography and resting-state functional MRI, to learn more about structure/function relationships fundamental to human brain organization. It is a major goal of many research laboratories to meaningfully combine DTI with other data collected from the same individuals to understand the anatomical basis of function and brain connectivity. For example, some groups have begun to create a connectivity matrix for the brain based on diffusion tensors to see how it relates to the connectivity matrix based on functional MRI data (e.g., resting-state MRI). These methods are just beginning to be combined to create and test elaborate models of brain functional connectivity.
in determining fiber integrity in normal adults. Even so, many genes affect FA in a partial overlapping pattern. Detailed genetic models may be tested in the near future to see how networks of genes interact to contribute, in combination, to cognition and disease risk.

More robust measurement with increased power. An important aspect of DTI use in patients that remains to be comprehensively addressed is that of phenotypic variability. Reasons for variability across diseases include ordering of symptom development, rates of progression, and disease comorbidity. These differences are exaggerated by additional factors such as modifier genes and lifestyle and environmental factors. Yet to be worked out is the specificity of observed differences to disease. The most promising approaches seem to be replication and large-scale studies. As effect sizes are likely to be small, replication is key. International consortia such as the ENIGMA project (Enhancing Neuro Imaging Genetics through Meta-Analysis; http://enigma.loni.ucla.edu) are seeking to form working groups interested in performing meta-analyses. These currently involve multiple laboratories collecting genome-wide association data from populations imaged with DTI and other forms of MRI. The largest neuroimaging studies to date have assessed approximately 1,000 subjects, but many groups have collected imaging genomic data from samples of several hundreds of subjects. In this way, aggregated samples of 10,000 or so subjects may be sufficient to locate and confirm quantitative trait loci for many aspects of fiber integrity and connectivity. In these efforts, issues such as data harmonization, data sharing, and high-performance computing are central, together with the coordinated analysis and checking of data at many sites simultaneously. Also being developed are innovative methods for joint analysis of genetic and imaging data, such as voxel-by-voxel genetic association testing at each location in the brain (Stein et al. 2010). This method has recently been extended to DTI to discover novel candidate genes likely to influence fiber integrity (Hibar et al. 2010).

Several major initiatives are now seeking to disentangle the relative contributions of disease, genes, and other modifiers of brain structure and function by scanning large cohorts of subjects with multimodality imaging as well as using clinical, cognitive, and genome-wide genetic assessment (e.g., Alzheimer’s Disease Neuroimaging Initiative; http://www.loni.ucla.edu/ADNI).

CONCLUSIONS

Evidence reviewed here clearly shows the value gained by measuring brain WM in a variety of neurological diseases and psychiatric disorders. We reviewed DTI work that showed a relationship between clinical symptoms and brain WM integrity, and even changes in WM after brief periods of pharmaceutical intervention. These findings support the theory that disturbances in neural connectivity may be at the foundation of several neurobiological disorders. However, this work is complicated; because of the staggering complexity of neural circuitry, disturbances in neural connectivity are associated with broad and heterogeneous disease phenotypes. Making major breakthroughs in treatments of neurobiological illnesses will depend on separating general from specific characteristics to form a more detailed understanding of the mechanisms of disease. We expect that DTI will be at the heart of this endeavor, especially for identifying targeted therapies and in monitoring the efficacy of treatments.

Looking to the future, we suggested new ways to approach data and how best to use the technology and resources of today. Research platforms for understanding the causes of illness must be multifaceted and integrative. We brought up new areas of development in imaging science, including imaging genomics (see expanded discussion in Hibar et al. 2010) and multimodal imaging for the development of models and maps of the human connectome. For instance, we understand today, better than ever, that thousands of genes are involved in
regulating the development and function of neural systems across the life span. Even so, because of biological heterogeneity in the population, a search that begins with a diagnosis and looks for a genetic cause is an enormous endeavor. Major gains in understanding the causes of illness will come from analyses of brain endophenotypes as a bridge between genetics and clinical phenotypes. Furthermore, we highlighted improvements in standards for imaging sciences that will have ramifications in the clinical domain. Specifically, we highlighted imaging data sharing (e.g., the ENIGMA project) as an important new method for testing statistically powerful, neurobiologically based models of systems that underlie disease. Without a doubt, DTI will be an essential contributor to these critical objectives.

### SUMMARY POINTS

1. Diffusion tensor imaging (DTI) measures water diffusion in the living brain and is sensitive to the integrity, orientation, and connectivity of the underlying nerve fibers.
2. DTI may be used to study the neurobiological basis of several clinical disorders.
3. Some disorders, such as Alzheimer’s disease, involve characteristic disruptions in neural connectivity. DTI studies can also relate underlying disruptions in neural circuitry to cognitive and emotional deficits that characterize certain neurological disorders.
4. DTI has revealed the trajectory of WM development and decline across the human lifespan. Tracts that are slowest to mature also deteriorate the earliest with advancing age, supporting a “last in–first out” model of brain maturation (also known as retrogenesis).
5. For some disorders, WM alterations are detectable on DTI prior to the onset of illness; some common genetic variants in healthy subjects and susceptibility genes for disease also affect DTI-derived brain measures.
6. Lower fractional anisotropy and higher mean diffusivity often indicate impaired fiber integrity, but not always; depending on the cellular basis for the changes, abnormally high or low values may indicate dysfunction or may even confer an advantage.
7. DTI is now used in clinical research to determine preclinical signs of disease, to discover genetic and environmental factors that affect disease progression, and to evaluate treatment efficacy in longitudinal studies.

### DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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### LITERATURE CITED


This empirical finding, in Williams syndrome, illustrates that higher fractional anisotropy is not necessarily advantageous, even though it often implies greater fiber coherence and organization.

Large cross-sectional DTI study that assessed 202 subjects ages 5–30 and charted age-related change in white matter tracts. Provides important reference data on normative brain maturation; rates and trajectories of development are shown to vary for different tracts.


Figure 1
Diffusion tensor imaging (DTI) visualization. Panel A shows axial, sagittal, and coronal T1-weighted anatomical images. Panel B shows mean diffusivity (MD). Color-coded FA maps in panel C depict directionality in fiber systems, where red represents right-to-left orientation, green represents posterior-to-anterior orientation, and blue represents inferior-to-superior orientation. The color-coding method of panel C for depicting directionality of fibers, often called RGB maps (Pajevic & Pierpaoli 1999), is presently the most widely used scheme for depicting fiber orientation on 2-dimensional images. Panel D shows MD, and panel E shows thresholded maps of fractional anisotropy overlaid on the T1 for the same subject. The X, Y, and Z coordinates for the image sections are 3, 0, 24, respectively.

Figure 2
Diffusion tensor imaging (DTI) fiber tractography. Whole brain fiber tracts may be reconstructed by placing “seed regions” in a uniform distribution covering the brain and then performing tractography across them to identify axonal pathways. Here we color similarly oriented fibers with similar colors for easier visualization. It is useful to bear in mind that these reconstructions carry no information about which of these are afferent versus efferent projections and also that the spatial resolution of these tracts is much larger than the size of individual axons.
Figure 3
Atlas-based tract parcellation. Strategies for automatic atlas-based tract parcellation are being developed. These methods rely on basic assignment of each fiber to a particular tract based on specific parameters placed in the search algorithm. For instance, the algorithm may allow fibers to fall into a region of interest (ROI) so long as the probability of membership based on spatial conformation exceeds 30% and with the criterion that no fiber can belong to more than one group. Here, this process is demonstrated for four tracts with prefrontal terminations. Whole-brain tractography is performed for the image on the left, where all fibers have been colored purple (sagittal and axial representations). In the center of the image, tract template images are shown for the infero-frontal occipital fasciculus (IFOF; teal), genu of the corpus callosum (GCC; yellow), anterior thalamic radiation (ATR; orange), and uncinate fasciculus (UNC; magenta) on axial projections. To the right of these are the resulting tracts that can be saved as ROIs for computing diffusion tensor imaging measures along entire tract trajectories.
High angular resolution diffusion imaging (HARDI) data reveals more information on water diffusion and fiber connectivity than conventional DTI because it applies many, usually 30–100, diffusion-encoded gradients to resolve diffusion profiles at higher angular resolution. This advantage, however, becomes a barrier to data mining on HARDI: for a single subject, the HARDI dataset is four-dimensional, with one three-dimensional volume of data collected for each gradient direction. This makes intersubject registration and other group analyses of HARDI data difficult, but some methods have been developed, based on information theory and fluid mechanics, to align the full diffusion process as accurately as possible, from one subject to another, using a fluid warping process (Chiang et al. 2008). This also allows multisubject statistical analysis of HARDI signals.
Figure 5
High angular resolution diffusion imaging (HARDI) tractography. We recently developed a method to automatically trace fiber pathways in the living brain using the full information in the HARDI signal (Aganj et al. 2009, 2011). In HARDI data, the full angular complexity of water diffusion is imaged and reconstructed using orientation density functions (ODFs; top left). Note that these shapes are more complex than a diffusion tensor. On the basis of a set of curves fitted through seed points, the ones that optimize a measure of fit through the ODF field are selected (top row). In phantom data from the Montreal Neurological Institute (courtesy of Jennifer Campbell), two excised rat spinal cords are imaged (bottom left), and the algorithm correctly identifies the tracts, even though they cross. In real human brain HARDI, the major tracts of the brain are automatically identified (bottom row, two panels on right). The method is applicable to population studies. (Adapted from Aganj et al. 2011.)
Figure 6
Hybrid diffusion imaging (HYDI) fiber tract renderings (courtesy of Dr. David Shattuck; see Shattuck et al. 2008) obtained after advanced processing of data acquired at 7T field MRI (described in Zhan et al. 2010). Left, middle, and right columns show sequential zooming into axial, coronal, and sagittal views, respectively. The color code for each fiber was assigned on the basis of vector sum of the direction vectors, weighted by length. Primary directions are coded as RGB, and fibers with more complex paths (e.g., U-shaped) are a mixture of their primary direction colors. The structural detail that may be computed from this data is demonstrated well in areas where tracts merge but do not mix [i.e., genu of the corpus callosum and anterior thalamic radiation (GCC/ATR), bottom left; CC/corticospinal, bottom middle; cingulum/u-shaped fibers, bottom right].
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