ABSTRACT: Psychiatric disorders are common throughout the world and are a leading cause of disability. There is a growing appreciation of the importance of connectivity to brain function. Disruption of this connectivity can result in brain dysfunction manifested in impaired cognitive functioning and the development of clinical symptoms. White matter forms the basis of anatomical connectivity. Diffusion tensor imaging (DTI) is a useful tool for examining and quantifying white matter microstructure. Clinical research studies in alcoholism, HIV-1 infection, geriatric depression and schizophrenia using DTI have revealed abnormalities in white matter microstructure. The use of complementary imaging methods may be helpful in further characterizing these abnormalities. Other psychiatric disorders may also have white matter involvement amenable to study with DTI. Advances in acquisition and analysis methods will be necessary to further advance work in this field. The study of animal models and postmortem tissue may be helpful in elucidating the neurobiological underpinnings of abnormalities observed with DTI. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: neuropsychiatric disorders; diffusion tensor imaging; magnetic resonance imaging; schizophrenia; alcoholism

INTRODUCTION

Psychiatric disorders are common throughout the world with five of the 10 leading causes of disability being attributable to psychiatric conditions—major depression, alcohol use, bipolar disorder, schizophrenia and obsessive compulsive disorder (OCD). In the USA, about 1 in 5 adults suffers from a diagnosable psychiatric disorder in a given year. Much attention has been focused on developing a better scientific understanding of these brain disorders, improving treatment and possibly even prevention.

Our understanding of brain organization, structure and function has been advancing rapidly. The classic view of higher cognitive function, based on lesion studies, has been one in which a single region of the brain is responsible for a specialized function. An alternative view is that higher cognitive function is a property of the interactions between functionally specialized, anatomically separate brain regions. This alternative view is more consistent with the brain’s architecture, which is characterized by extensive and reciprocal anatomical connections between different brain regions. Such a network of spatially distributed regions requires coordinated communication which commonly occurs through axons that are carried in the white matter of the brain. As reviewed below, magnetic resonance studies have revealed evidence of altered white matter organization in several neuropsychiatric disorders.

A dramatic example of the neuropsychiatric consequences of impaired cortical communication can be found in metachromatic leukodystrophy, a disorder of sulfitide metabolism, which leads to demyelination of the central and peripheral nervous system. In the central nervous system, subfrontal white matter is affected, resulting in disruption of corticocortical and corticosubcortical connections. If disruption of the cortical connections occurs between 12 and 30 years of age, patients can develop psychotic symptoms including complex auditory hallucinations and bizarre delusions.

Magnetic resonance imaging techniques have been invaluable for neuroscientists, providing insight into the structure, biochemistry and function of the living human brain. Diffusion tensor imaging (DTI) in particular
provides a window into white matter microstructure and organization not available with other imaging methods. DTI provides a quantitative method to assess the integrity of anatomical connectivity in white matter. In this paper we review how DTI has been applied to four brain disorders with neuropsychiatric consequences: alcoholism, HIV infection, geriatric depression and schizophrenia. These disorders demonstrate the broad range of putative white matter pathophysiological processes detectable by DTI, including neurotoxic, infectious, vascular and neurodevelopmental. We then discuss current issues and future directions for the study of neuropsychiatric disorders.

ALCOHOLISM

Alcohol use is a major source of disability in the world. In 1992, it was estimated that 7.4% of people in the USA met diagnostic criteria for alcohol abuse or dependence.\(^6\) The estimated economic cost of alcohol abuse was estimated to be $148 billion for 1992.\(^7\) Besides its behavioral and economic effects, alcohol has direct neurotoxic effects on the brain. Interacting with the neurotoxic effects is the poor nutrition that accompanies chronic alcoholism, leading to vitamin deficiencies that can have neural consequences including peripheral neuropathies, anterior lobe cerebellar degeneration and mamillary body destruction. Even after detoxification, patients with chronic alcoholism are observed to have cognitive deficits and symptoms of anxiety and depression. Postmortem studies of chronic alcoholism have found tissue loss with greater involvement of white matter.\(^8,9\) Postmortem studies have also uncovered evidence of white matter degradation including demyelination and axonal deletion. In a study of brains from alcoholics, a DNA microarray analysis found a reduction in genes coding for myelin components.\(^10\) While conventional in vivo MRI techniques have been able to demonstrate white matter volume reductions in cortical white matter and the corpus callosum, they lack the sensitivity to examine white matter microstructural changes.

In the first application of DTI to alcoholism, Pfefferbaum et al.\(^11\) used DTI to study the genu and splenium of the corpus callosum and the centrum semiovale of 15 detoxified alcoholic men in comparison with 19 nonalcoholic control subjects. In addition, exploratory analyses examined functional correlates of indices of white matter microstructure with the prediction that lower anisotropy and fiber coherence in the alcoholic patients would be related to poorer performance on neurocognitive tests requiring attention and working memory. These tests are commonly disturbed in individuals with alcoholism and may be sensitive to disruption of connectivity within prefrontal and parietal regions as well as between these two regions.

In this study, fractional anisotropy\(^12\) (FA) was computed on a voxel-by-voxel basis from the DTI data set. In addition, a coherence image was constructed using the average of the angle between the eigenvectors of the largest eigenvalues of a given voxel and its eight neighbors, providing a measure of the degree to which the vectors point in the same direction and are therefore coherent. The value ranged between 0 and 1.0, with 1.0 being perfect coherence. From a brief neurocognitive battery, an attention composite score was obtained from the attention sub score of the Dementia Rating Scale and a working memory composite was constructed from the Backward Digit and Block Spans and Trail Making Part B.

The alcoholic group had lower FA than the control group in the genu and centrum semiovale. The coherence was also lower in the alcoholics, but only in the splenium. Working memory correlated positively with splenium FA \((r = 0.59, p = 0.01)\) but not genu coherence, whereas attention correlated positively with genu coherence \((r = 0.50, p = 0.03)\) but not splenium FA. These results provide in vivo evidence for disruption of white matter microstructure in alcoholism and suggest that interruption of white matter fiber coherence contributes to disturbances in attention and working memory in chronic alcoholism.

HIV-1 INFECTION

HIV-1 remains a worldwide health problem, especially in poorer countries where upwards of 10% of the population may be infected. The availability of highly active antiretroviral treatment in developed countries has dramatically altered the course of the disease for those able to afford treatment. However drug toxicity and the development of drug resistance limit the long term effectiveness of these treatments. HIV-1 enters the central nervous system during the early stages of infection and preferentially affects the subcortical white matter. Diffuse white matter pallor is the most frequent neuropathological feature of HIV-1 infection and has been found to be particularly prominent in the advanced stages of the disease.\(^13\) Immunohistochemical and in situ hybridization studies of HIV encephalitis have found that HIV-1 infected macrophages and multinucleated giant cells preferentially invade the white matter of cerebral hemispheres, corpus callosum and internal capsule.\(^14\) Even in asymptomatic HIV-1 positive patients, white matter involvement is detectable in the form of vasculitis and gliosis.\(^15\)

Psychiatric symptoms such as anxiety and depression are common in HIV-1-infected individuals. Impairments in attention, learning and speed of information processing are also common and can range in severity from a mild cognitive motor disorder to dementia in later disease stages. There is great interest in developing neuroimaging techniques that are sensitive to early HIV-1
involvement in the brain. Such techniques may be useful in early detection of cognitive impairment and the monitoring of response to treatment.

Two studies have used DTI to study white matter in patients with HIV-1 infection. Filippi et al. used DTI to study 10 patients with HIV-1 and five controls. The patients had a range of viral loads from undetectable to greater than 400,000. ROIs included the genu and splenium of the corpus callosum and bilaterally in frontal subcortical white matter, parietal-occipital subcortical white matter and centrum semiovale. Mean diffusivity (Trace/3) and an anisotropy index were computed from the DTI data. All MRI scans were normal except for mild atrophy. The patients were divided into those with lowest, intermediate and highest viral load levels. Patients with undetectable viral loads had normal diffusion anisotropy and mean diffusivity. Those patients with the intermediate and highest viral loads had significantly decreased diffusion anisotropy in the genu and splenium. Only in patients with the highest viral loads was the mean diffusivity found to be significantly increased in the genu and splenium.

In the second study, Pomara et al. studied six HIV-1 patients and nine controls with DTI. The patients were non-demented, ambulatory and had no evidence of white matter pathology on conventional MRI scans. Mean diffusivity and fractional anisotropy were calculated from the DTI data. Regions of interest (ROIs) were placed in the genu, splenium, and bilaterally in internal capsule, frontal white matter, parietal white matter and temporal lobe white matter. No significant differences were found in mean diffusivity in any ROI. Compared with the controls, fractional anisotropy was found to be significantly decreased in the frontal white matter and increased in the internal capsule. These two studies point to the sensitivity of DTI to detect subtle white matter abnormalities in normal appearing white matter. Further studies of white matter in HIV infection are needed to replicate findings of relationships between white matter microstructure and viral load as well as to examine the relationship of white matter microstructure with cognitive status and treatment.

GERIATRIC DEPRESSION

Major depression is the leading cause of disability worldwide. It is estimated that 5% of American adults are affected each year. While depression can develop at any age, the increasing age of the population in developed countries such as the USA has made late life depression an increasing important health issue. While the causes of late-life depression are not well understood, imaging studies using MRI have reported increased white matter hyperintensities (WMH) in this population. Subcortical vascular changes may be an important contributor. Attention has been focussed on the location of the lesions in the hope that they may provide information in determining the neuroanatomic substrates of depression. A statistical parametric mapping of white matter lesions in late-onset depression found increased lesion density in medial orbital prefrontal white matter. Functional imaging studies have found abnormalities in the prefrontal cortex, anterior cingulate, amygdala and striatum. Dysfunction of one or more of the cortical-basal ganglia-thalamic neuronal loops has been implicated. Neuropathological evidence of altered neuronal and glial cell morphology and density in the frontal cortex has been reported.

In treatment studies of late-life depression, aspects of executive dysfunction appear to be important predictors of treatment response and relapse. Neuropsychological studies of late-life depression have reported disturbances in attention, speed of processing, and executive function, processes which require integrity of frontostriatal structures. The anatomical connections between the prefrontal cortex and the striatum pass through the frontal white matter, providing an opportunity to assess the integrity of the connectivity using DTI.

In an imaging study of late-life depression, Alexopoulos et al. used DTI to examine the white matter contributing to frontostriatal connections, hypothesizing that the integrity of the frontal white matter would be associated with treatment response. Thirteen elderly subjects with major depression received open-label but controlled treatment with the antidepressant citalopram. DTI scans were collected on the patients. ROIs were placed in frontal white matter at −5, 0, 5, 10 and 15 mm from the anterior–posterior commissural (AC–PC) plane. Remission was defined as not having symptoms of depression for a consecutive two-week period. Using these criteria, eight subjects achieved remission and five remained depressed. Survival analysis with proportional risk factors was used to examine the relationship of fractional anisotropy of the five frontal regions to the occurrence of remission. Since fractional anisotropy changes with age, age was used as a covariate in the analyses. Fractional anisotropy of frontal white matter at 10 and 15 mm above the anterior–posterior commissural (AC–PC) plane was associated with remission of depressive symptoms (15 mm: right—chi square 4.36, p < 0.037, left—chi square 3.67, p < 0.05; 10 mm: right—chi square 3.2, p < 0.07, left—chi square 4.4, p < 0.04). There was no significant relationship between remission and the FA of frontal regions inferior to +10 mm from the AC–PC plane, suggesting that the relationship was specific to the 10 and 15 mm levels. The frontal white matter ROIs at 10 and 15 mm from the AC–PC plane are lateral to the anterior cingulate and contain fibers of the cortico-striatal pathways. These preliminary results suggest that depressed patients with lower frontal FA (reduced white matter integrity) do not respond to antidepressant treatment as well as patients with higher frontal FA (better white matter integrity).
SCHIZOPHRENIA

Schizophrenia is a brain disease characterized by loss of reality testing, the hearing of auditory hallucinations, decreased motivation, impaired cognition and poor personal interactions. Approximately 1% of the population has schizophrenia, making it a relatively common disorder. Tragically, symptoms often begin in early adulthood, striking these young people just as they are about to become independent members of society. While medications are helpful in controlling some of the more florid symptoms such as the auditory hallucinations, they have not been very effective in treating the more insidious symptoms of decreased motivation and impaired cognition, which reduces the capacity of the affected individual to live and work independently. Many of these patients require some degree of continuous support and supervision with the burden falling to family and the public social systems.

Some hypotheses about the origins of schizophrenia implicate a neurodevelopmental event as early as the second trimester related to cortical connectivity. During adolescence, an extensive cortical rewiring occurs with pruning of synaptic connections. During late adolescence, frank symptoms emerge through a set of unclear events, perhaps due to an interaction between psycho-social stressors and a overpruned cortical network unable to handle the processing load.\textsuperscript{31,32}

Brain imaging findings in schizophrenia tend to be relatively small and subtle. Structural studies have reported abnormalities of frontal lobe, temporal lobe, parietal lobe hippocampus and amygdala.\textsuperscript{33,34} As multiple brain regions appear to be involved, various circuit models have been proposed.\textsuperscript{35} Analyses of the correlations of volumes of cortical regions have found abnormal correlations in schizophrenia, suggesting a problem with interconnection of the brain regions.\textsuperscript{36} Beaumont and Dimond reported impaired interhemispheric transfer in patients with schizophrenia.\textsuperscript{37}

Neuropathological studies have found increased neuronal density and abnormalities in the pyramidal neurons of Layer III of prefrontal cortex.\textsuperscript{38,39} These neurons play a key role in cortical–cortical connectivity, suggesting that cortical connectivity may be altered in schizophrenia. A magnetic resonance spectroscopy assessment of the putative neuronal marker, N-acetyl aspartate (NAA), found reduced levels of NAA in white matter in schizophrenia, possible evidence of reduced neuroaxonal content in white matter.\textsuperscript{40}

Lending further support to white matter involvement in schizophrenia is a recent genome wide expression analysis using DNA microarray technology to examine postmortem tissue from the dorsal lateral prefrontal cortex.\textsuperscript{41} Compared with controls, patients with chronic schizophrenia were found to have altered gene expression including a set of myelination-related genes, suggesting a disruption in oligodendrocyte function in schizophrenia. To date, five studies have used DTI to examine white matter in schizophrenia. Buchsbaum et al.\textsuperscript{42} reported the first use of DTI in a study of five patients with chronic schizophrenia and six controls. All subjects were imaged using a line scan diffusion imaging method for the collection of DTI data. Subjects also received positron emission tomography scans with 18-fluorodeoxyglucose (PET-FDG). Statistical probability mapping of the DTI data found significantly lower diffusion anisotropy in prefrontal white matter. The PET-FDG data found reduced correlation coefficients between metabolic rates in the frontal cortex and the striatum in the patients. This was interpreted as convergent evidence for diminished frontal–striatal connectivity in schizophrenia. In another study of schizophrenia, Lim et al.\textsuperscript{43} used an echo-planar diffusion imaging method to collect DTI data from 10 patients and 10 controls. Tissue segmentation maps were used to select white matter for analysis. FA in the white matter of patients was found to be lower in the patients than controls, despite the absence of a white matter volume deficit. In contrast to the white matter pattern, the FA of the gray matter was not different between the two groups despite a cortical gray matter volume deficit in the patients. Lower white matter FA was widespread, being found in both frontal and occipital regions. Foong et al. performed DTI in 20 patients and 25 controls.\textsuperscript{44} The genu and splenium of the corpus callosum were examined. The mean diffusivity was found to be significantly increased and FA was significantly reduced in the splenium but not in the genu in the patients compared with the controls. Agartz et al. examined 20 patients and 24 healthy subjects with DTI.\textsuperscript{45} FA was reduced in the splenium and adjacent occipital white matter. Steel et al. studied 10 patients and 10 controls with magnetic resonance spectroscopy (MRS) and DTI, examining frontal and occipital white matter regions.\textsuperscript{46} While non-significant reductions in frontal white matter NAA were found in patients, no differences were found in white matter anisotropy. Lower gradient strength of the scanner hardware may have contributed to the lack of a finding. Taken together, these studies illustrate the ability of DTI to provide new information about schizophrenia and to corroborate the neurobiological findings derived from other methods.

FUTURE DIRECTIONS

Other neuropsychiatric disorders may have neurobiological abnormalities involving impaired connectivity, which could be studied using DTI. In many cases, the presence of white matter abnormalities (e.g. hyperintensities) provides the first suggestion of white matter involvement. For example, in bipolar disorder, an increased incidence of subcortical hyperintensities on MRI has been observed.\textsuperscript{47} Recent quantitative neuropathological studies in bipolar disorder have also found reduced pyramidal cell density in layers III and V, layers
found by Breiter and colleagues. Findings of white matter in a separate sample of patients that was reported extended previous findings of decreased posterior average relative coarse spatial resolution available. The current A major technical limitation of DTI has been the /C67/C104/C97/C108/C108/C101/C110/C103/C101/C115 connectivity amenable to study with DTI. Evidence of impaired corticocortical and subcortical matter abnormalities in OCD may thus represent in OCD. Rosenberg et al. found that compared to normal controls, adult patients with OCD had significantly less total white matter. This report extended previous findings of decreased posterior white matter in a separate sample of patients that was found by Breiter and colleagues. Findings of white matter abnormalities in OCD may thus represent evidence of impaired corticocortical and subcortical connectivity amenable to study with DTI.

Challenges

A major technical limitation of DTI has been the relatively coarse spatial resolution available. The current average in vivo voxel volume for DTI of 15 mm³ is approximately an order of magnitude larger compared to structural MRI acquisitions. Achieving higher spatial resolution will be important for anatomical and fiber tracking work. To date most DTI acquisition protocols use EPI due, in part, to EPI’s relative immunity to motion (i.e. each line in k-space has a constant phase relation), but improved resolution in DTI will require compression of both the acquisition and echo evolution time, which places increased demands on gradient performance. Decreasing the acquisition window should also reduce susceptibility to artifacts often seen in inferior frontal brain regions. Since gradients are beginning to reach their maximum performance characteristics with regards to human tolerance, other methods will have to be developed to improve resolution. These may include, for example, hardware approaches for the reduction of readout time using parallel imaging techniques such as SENSE. This, along with the implementation of these techniques at higher magnetic field strengths, should advance our abilities to attain higher spatial resolution. Nevertheless, all new methods will need to balance the issues of signal-to-noise, acquisition time and geometric distortion.

Analysis methodology

Various approaches have been employed to analyze DTI data. These include manually placed ROIs, tissue selection using tissue segmentation and voxel based approaches. There is interest in trying to use directional information from DTI to identify analysis regions, such as white matter tracts, from which to measure the fractional anisotropy. This poses a dilemma since the dependent measure is being used to select the tissue region being measured. Voxel based analysis approaches such as statistical parametric mapping can be very useful. These generally require the data sets to be spatially warped to a standard brain, based on a $T_1$-weighted or $T_2$-weighted averaged brain set. Significant normal spatial variation exists in white matter fiber patterns; this information may not be captured in standard anatomical imaging. New spatial warping methods, which can take into account fiber orientation, may be a useful avenue to explore.

Applications of complementary techniques

The availability of complementary information about the same sample can be very useful in characterizing tissue. MR has the advantage of being able to provide such complementary information using the same instrument during the same scan session. Magnetization transfer imaging (MTI) uses off resonance radio frequency irradiation to transfer energy between bound and mobile pools of water, creating unique contrast sensitive, in part, to protein concentration, exchange kinetics and relaxation rates of the bound water. This method has been used to great advantage in the characterization of white matter in multiple sclerosis, a disease with known white matter involvement. MTI has also been applied to the study of schizophrenia where abnormalities have been detected in temporal lobe white matter. Since myelin contributes to diffusion anisotropy in tissue, methods capable of independently assessing myelin status could provide complementary information to DTI. $T_2$ relaxography, the assessment of $T_2$ relaxation distributions utilizing long echo trains (e.g. 32 echos) and non-linear fitting methods, has been proposed as a method for quantifying water myelin and may provide a measure of myelin content in tissue. The combining of techniques such as MTI and $T_2$ relaxography with DTI could provide complementary information to better characterize tissue abnormalities.

Elucidation of potential neurobiological mechanisms for DTI alterations

While DTI studies have detected abnormalities in neuropsychiatric disorders, the underlying neurobiological structural alterations resulting in the measured changes in microstructure have not yet been elucidated. For example, the reduced white matter FA observed in both schizophrenia and alcoholism may be the result of different pathophysiological mechanisms affecting dif-
ferent cellular components. Several strategies may be useful for gaining a greater understanding of potential mechanisms. Animal models of altered structure such as those provided by mutant mice deficient in myelin, transgenic mice with altered expression of neurofilament and other tissue components, or models of toxin exposure may be useful to examine how DTI is altered in these models. The study of postmortem tissue may provide another avenue of investigation. In brain collections with both fixed and frozen tissue, DTI could be applied to the fixed tissue and biochemical methods could be applied to the frozen tissues.

SUMMARY

Neurobiological studies of neuropsychiatric disorders have found abnormalities suggesting that communication may be altered between different brain regions. DTI provides a powerful tool for the in vivo assessment of the anatomical substrate for brain connectivity and has been found to be sensitive to a wide range of putative pathologies. Improvements in resolution and analysis methods, and the application of complementary methods, should further enhance the information that can be derived from DTI. Finally, further work to better understand the neurobiological underpinnings of altered DTI is also needed.

REFERENCES

32. Keshavan MS, Hogarty GE. Brain maturational processes and


