REVIEW PAPER/*ARTYKUŁ POGLĄDOWY*

Diffusion tensor imaging in Alzheimer disease and mild cognitive impairment

Obrazowanie tensora dyfuzji u pacjentów z chorobą Alzheimera i łagodnymi zaburzeniami poznawczymi

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Abstract

A wide range of imaging studies provides growing support for the potential role of diffusion tensor imaging (DTI) in evaluating microstructural white matter integrity in Alzheimer disease (AD) and mild cognitive impairment (MCI). Our review aims to present DTI principles, post-processing and analysis frameworks and to report the results of particular studies.

The distribution of AD-related white matter abnormalities is widely discussed in the light of deteriorated connectivity within certain tracts due to secondary white matter degeneration; primary alterations are also assumed to contribute to the pattern. The question whether it is more effective to assess the whole-brain diffusion or to directly concentrate on specific regions remains an interesting issue. Assessing white matter microstructure alterations, as evaluated by group-level differences of tensor-derived parameters, may be a promising neuroimaging tool for differential diagnosis between AD, MCI and other cognitive disorders, as well as being particularly helpful in the interpretation of underlying pathological processes.

Key words: Alzheimer disease, diffusion tensor imaging, mild cognitive impairment.

Streszczenie

Rosnąca liczba badań naukowych wskazuje na znaczenie obrazowania tensora dyfuzji (DTI) w ocenie mikrostrukturalnej integralności istoty białej w chorobie Alzheimera (ChA) i łagodnych zaburzeniach poznawczych (ŁZP). W niniejszej pracy przeglądowej omówiono zasady obróbki danych oraz analizy DTI i przedstawiono wyniki poszczególnych badań prezentujących różne modele charakterystycznych dla ChA zmian w istocie białej.

Szeroko dyskutowane jest rozmieszczenie uszkodzeń w istocie białej, głównie w odniesieniu do wtórnego zwyrodnienia poszczególnych włókien wskutek zaniku istoty szarej lub pierwotnego zwyrodnienia istoty białej. Interesujący i nierozstrzygnięty pozostaje dylemat, czy bardziej efektywne jest obrazowanie zmian dyfuzji w całym mózgu, czy skupianie się na konkretnych strukturach. Zastosowanie DTI w ocenie mikrostrukturalnych zmian zachodzących w istocie białej mózgu może być obiecującym narzędziem w różnicowaniu pomiędzy ChA, ŁZP i innymi zaburzeniami poznawczymi; jest szczególnie przydatne przy interpretacji leżących u ich podłoża procesów patologicznych.

Słowa kluczowe: choroba Alzheimera, obrazowanie tensora dyfuzji, łagodne zaburzenia poznawcze.

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Introduction

Diffusion-tensor imaging (DTI) is a noninvasive magnetic resonance imaging (MRI) technique developed to better characterize the directionally dependent nature of proton diffusion in cerebral tissue. By taking advantage of the anisotropic nature of water diffusion in tissues [1,2], DTI has become a promising method in the detection of in vivo microstructural white matter alterations [3-5]. In this approach, variability of diffusion in each voxel is described by a mathematical model of diffusion tensor. The diffusion ellipsoid is characterized by three eigenvectors that represent the orientations of the main axes and three eigenvalues that represent the diffusivity along each axis. To calculate the tensor, at least 6 diffusion-weighted images (acquired by non-collinear motion probing gradients) and at least one non-diffusion-weighted image need to be obtained [6].

Basic parameters characterizing the diffusion tensor

In an isotropic environment (such as a glass of water), diffusion follows a Gaussian distribution and exhibits the same behaviour in all directions. When the random motion of water molecules is directionally restricted (e.g. inside a cylinder), it is referred to as anisotropic. The degree of this restriction is often expressed as fractional anisotropy (FA), which ranges from zero (for isotropic diffusion) to unity (for diffusion exclusively along one direction). In healthy (well-organized) white matter tracts water diffuses more freely along the axonal fibres and FA is expected to be high [7], while diffusion perpendicular to the fibres is relatively restricted.

As fibres lose integrity due to underlying pathological processes that affect axonal density and homogeneity, changes in the diffusion characteristics of water molecules are reflected in DTI metrics. DTI has therefore been applied in the examination of a variety of neurodegenerative disorders, in Alzheimer disease (AD) [8-10], mild cognitive impairment (MCI) [11,12] and age-related white matter changes [13]. In these studies (and many others), microstructural white matter alterations were evaluated by means of FA, along with the mean diffusivity (MD) [5,7]. Moreover, additional scalars may be derived from the diffusion tensor, such as axial and radial diffusivity, which characterize diffusivities parallel and perpendicular to white matter tracts, respectively [13,14] (Fig. 1).

Based on Monte Carlo simulations, it has been reported that at least 30 gradient directions are required for robust MD calculation [16] and minimally 20 gradient directions for FA [6,9,16]. In practice, the number of motion-probing gradients used will depend on the hardware and scan time available. Additionally, a direct comparison of results reported by various authors is difficult as the signal-to-noise ratio (SNR) is very rarely reported and the quality of tensor fit cannot be guessed.

Comparing diffusion parameters

The comparison of DTI results across studies is further complicated by the fact that authors have used various methods of analysis, such as region-of-interest (ROI) or voxel-wise approaches, with further corrections and additional refinements. The choice of methodology pertaining to image analysis seems to be an important factor affecting the results of various DTI studies.

ROI-based analysis

DTI studies on AD and MCI have reported reduced FA in a variety of white matter areas using a region

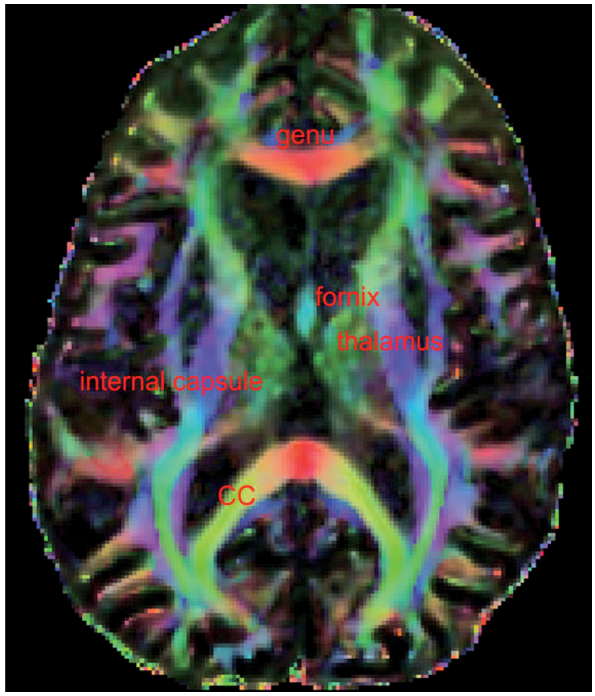

Fig. 1. Viewing diffusion tensor imaging data with FSLView (tool from FRMIB Software Library). The present map is showing the principal direction of diffusion tensor. Red colour corresponds to medio-lateral direction, green to anterior-posterior, and blue- to dorso-ventral orientation. CC – corpus callosum

of interest-based approach, often combined with manual tracing, masking or tractography to guide ROIs [17-24]. ROI-based analysis represents the most common approach in DTI studies, with advantages concerning the statistical analysis of results. Nevertheless, it has numerous limitations that have been described by various authors. It is time consuming [25], not easily reproducible, and not optimal for mapping white matter abnormalities in the whole brain [11,26]. Furthermore, it is dependent on an a priori hypothesis regarding the regional distribution of white matter alterations, due to the fact that it is based on examination of various tracts [11,27,28]. Therefore, ROI-based analyses seem to be useful only when the target tract is already known and anatomically identified [11]. Artefactual results are related to the shape and size of ROIs, as well as the accuracy with which they are placed [8,25, 29,30].

Another limitation is that the data obtained by this method are easily contaminated by unintended fibres [11]. DTI metrics may also be affected by partial voluming [26] in the proximity of grey matter or cerebrospinal fluid (CSF). Although the application of smaller ROIs may reduce partial volume effects, it is accompanied by a concomitant decrease in SNR [25,29]. Nevertheless, despite the constantly growing reliability and accuracy of anatomical information provided by ROI-based analysis, definitions of anatomical borders vary across studies [14].

Voxel-based analysis

A growing number of studies employ methods of analysis that circumvent the limitations of an a priori defined ROI, enabling a more detailed assessment of microstructural white matter changes. Voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) studies assess white matter differences on a voxel-by-voxel basis [14,31]. Among the advantages of the voxel-based approach is the ability to assess the entire brain [12,30,32], in contrast to the ROI regional bias. This advantage, on the other hand, may be considered a disadvantage in terms of statistical analysis [32]. Voxel-based analysis can circumvent manually introduced errors (in the manual placement of ROIs) and is a fully automated method of analysis [12]. Voxel-based morphometry (VBM) was originally developed for the assessment of grey matter changes [33]; modified VBM analysis can be applied as a voxel-wise investigation of whole brain anisotropy. Numerous previous AD and MCI studies, using voxel-by-voxel analysis, have shown reduced FA in particular brain regions [27,34,35]. However, voxel-based approaches often suffer from low statistical power due to the fact that information from each voxel can be highly noisy [32] and can be problematic in relation to the precise alignment of tract anatomy [30,36].

In order to conduct comparative examination of the entire white matter changes between the subjects, DTI data have to be previously normalized to a template space. The normalisation-based approach is often combined with matching DTI data with atlas-based anatomical information [32].

Whole brain analysis vs. structure specific analysis

Tract-based spatial statistics (TBSS), a part of FMRIM Software Library (FSL) [36], is another automated whole-brain analysis technique, which uses voxel-based analysis on tensor-derived data [37]. Once the TBSS approach was suggested to provide even more consistent results across subjects than traditional voxel-based and manual ROI-based approaches [37], it has become a popular method for assessing white matter integrity in AD and MCI patients [8,28,39,40]. In this approach white matter information is condensed to 'mean FA skeleton' [37]. TBSS was created to alleviate misalignment problems and to reduce data contamination by adjacent structures. Applying sophisticated algorithms for DTI registration that solve problems related to the proper alignment of FA images across multiple subjects, it can facilitate subsequent voxelwise analysis.

Another method, structure-specific statistical mapping of white matter tracts, is involved in segmentation of major white matter tracts, fitting them with deformable geometric medial models and followed with the subsequent projection of white matter information to previously defined white matter tracts [38]. To account for the connectivity differences, tractography-driven structure-specific statistical mapping may be even more effective than that performed on the whole brain [38].

Pathophysiology

Pathological changes in AD include the accumulation of amyloid plaques and neurofibrillary tangles, along with neuronal loss culminating in gross cerebral

atrophy. Consistent with previous pathological and structural MRI studies, these changes originate in the medial temporal region, including the transentorhinal cortex, entorhinal cortex and hippocampus, subsequently spreading over wider temporal and parietal cortices [41]. Degenerative changes may also lead to decreased white matter integrity in the cortical association areas [30].

Overall, DTI studies have shown an inhomogeneous pattern of white matter abnormalities in AD and MCI in regions connected with association cortices [8,9, 14,25]. Zarei *et al.* suggested that the distribution of degenerative changes is determined, at least partially, by the connectivity of regions that are anatomically and functionally linked [42].

There is still discussion regarding the pathophysiology underlying white matter abnormalities in AD and MCI. The main issue is whether deteriorated connectivity within certain white matter tracts is due to primary white matter pathology or secondary, due to perikaryal degeneration [8,25].

Wallerian degeneration

One theory regarding white matter changes in AD and MCI patients is that microstructural white matter changes occur as a result of Wallerian degeneration [43]. According to this theory, white matter abnormalities follow the pattern of grey matter pathology [41] and may involve impairments close to the cortical areas with the greatest pathological burden [44]. DTI metrics, reflecting the diffusion characteristics of water in the tissue, are potentially influenced by increased extracellular fluid following the degeneration of axonal fibres secondary to neuronal cell loss [20,45]. Correspondingly, Cho *et al.* noted that atrophy of the callosal body in AD may occur as a result of Wallerian degeneration due to cortical lesions, along with the loss of interhemispheric fibres [26]. There is further evidence for diminished white matter integrity and decreased FA in the temporal lobe of AD and MCI patients, including parahippocampal white matter.

Consistently, Huang *et al.* suggested that perikaryal degeneration in the cerebral cortex can lead to axonal loss in the adjacent white matter [9]. Overall, several researchers have supported the hypothesis that neurodegeneration is related to microstructural changes in the cerebral white matter of subjects with AD and MCI [4,27,30,46].

Retrogenesis

The alternative retrogenesis theory assumes that diminished white matter integrity is the result of myelin breakdown (that occurs in reverse order to myelogenesis), suggesting that white matter degeneration is a direct consequence of AD pathology [47,48]. It has been hypothesized [30,49] that regions which become myelinated later in brain development (including neocortical association and allocortical fibres) are characterized by a smaller amount of oligodendrocytes that support a greater amount of axons in comparison to regions that become myelinated earlier (including primary sensorimotor regions). Oligodendrocytes in these regions are particularly taxed in the metabolic sense, because they maintain distributed axonal networks. Therefore, axonal fibres in cortical association areas are more susceptible to pathological processes, such as oxidative stress [30]. According to the retrogenesis model, pathways with small diameter fibres that myelinate later in normal development are the first to be affected by the AD degenerative process [47] and pathways with large diameter fibres that myelinate first in development (such as primary motor fibres) are the last to be affected by AD [23]. Consistently with the retrogenesis model, significantly lower FA values in AD patients were noted in late-myelinating corticocortical association fibre pathways (uncinate fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus), limbic pathways (fornix, stria terminalis, cingulum) and commissural pathways (splenium of the corpus callosum) [14,17,23]. In contrast, no significant differences in FA were seen in the early-myelinating pathways: primary motor and sensory regions, cerebral peduncles, internal capsule, and corona radiata. Overall, the entire sequence is compatible with the progression of cognitive changes in AD (memory, language and executive function deficits [23]), with relative preservation of sensory and motor functions.

Mixed model

Despite numerous contributions to the retrogenesis theory [25,28,35], there is no clear consensus across studies in support of one neuropathological mechanism explaining white matter changes occurring in AD. Many studies have included remarks distinctive for both models [22,34,40,50,51]. Late-myelinating structures (splenium, fornix, stria terminalis and cingulum) connect to medial temporal lobe structures that are affected early

in AD, so it is also possible that the observed white matter changes may reflect Wallerian degeneration secondary to neuronal loss as well [43]. Even though direct results of many studies are compatible with the retrogenesis model, possible contributions from Wallerian degeneration to white matter changes in AD cannot be excluded. For instance, it has been hypothesized that white matter changes are more likely to occur in the inferior longitudinal fasciculus than in the superior longitudinal fasciculus, because the inferior longitudinal fasciculus contains connections between the occipital area and medial temporal lobe affected earlier in the AD neuropathological process [23].

In contrast, the superior longitudinal fasciculus primarily connects the parietal and frontal lobes, which are affected later in the disease process than medial temporal lobe structures [23]. Other studies have additionally displayed white matter changes observed in the frontal association fibres, suggesting that they may occur at a relatively early stage of the disease process [17,25,50]. Whereas this area is generally considered to be altered later in AD, evaluation of early changes found in the frontal white matter may be of benefit in the early diagnosis of AD.

Furthermore, findings concerning the corpus callosum contribute to the retrogenesis theory, since the genu of the corpus callosum, projecting to the prefrontal cortex, is myelinated later than the splenium [47]. However, in light of the fact that most authors have reported FA and MD changes in the splenium, a structure consisting of abundant fibres connecting temporo-parieto-occipital regions, it could be therefore interpreted as providing greater support for Wallerian degeneration than for retrogenesis [14].

Vascular changes

Subcortical vascular damage is another important finding, reflected mainly by white matter hyperintensities, and is common to aging, MCI, AD, as well as cerebrovascular disease. Such white matter damage could also alter white matter integrity through direct injury to subcortical axonal fibres, which has been particularly emphasized in studies focusing on the interhemispheric connections of the corpus callosum [21]. However, it has been shown that regional patterns of white matter hyperintensities and alterations in white matter FA are at least partially distinct for both cerebrovascular disease and neurodegenerative processes [21].

DTI findings

Since cognitive functions depend on the cooperation of various brain networks, reduced FA and increased MD can be observed in widespread brain regions. In the last decade, a great number of AD and MCI studies have focused on the following regions: frontal white matter, temporal white matter, parietal white matter, hippocampus, cingulum (posterior, middle, anterior), corpus callosum (genu, splenium), superior longitudinal fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus. A large number of studies examining white matter integrity, particularly within distributed temporal networks, have shown differences between AD patients, MCI subjects and controls in several subcortical regions [8,10,25,30,39]. Huang *et al.* suggested that reductions in FA may follow a regional pattern, reflecting the greatest white matter abnormalities in the temporal brain regions, followed by changes in the parietal, then frontal white matter, whereas no significant changes are present in the occipital white matter [9]. Nevertheless, in a meta-analysis conducted by Sexton *et al.*, the authors reported decreased FA in AD patients in all regions, except for parietal white matter and the internal capsule [14]. Changes in MCI seem to generally follow the pattern that differentiates AD patients from healthy subjects. Subsequently, according to the same authors, FA values in MCI were lower in all white matter regions, except for parietal and occipital white matter.

However, results were more variable (with lower statistical significance) in the MCI group of patients. In order to precisely evaluate the disease progression, several cross-sectional and longitudinal AD and MCI studies examined correlations between DTI parameters and cognitive scores measured by neuropsychological tests. Most notably, reduced scores in the Mini-Mental State Examination (MMSE) were significantly associated with reduced FA [4,10,46] or increased MD [4,27,46] in the evaluated white matter regions. No significant differences in DTI parameters were observed when comparing degenerative white matter alterations between hemispheres in AD and MCI patients [14].

Changes in DTI metrics, measured in AD and MCI subjects, may be observed in both the anterior and posterior cerebral white matter [10,25,34,50]. Some studies have reported white matter changes in AD patients predominantly in anterior regions (e.g. genu of corpus callosum) [17,25,46,50], whereas others have reported that white matter changes occur predominantly

in posterior regions, such as the posterior cingulum and the posterior corpus callosum [11,20,22,27,30,34,51]. However, because of the inconsistencies across these and numerous other studies, the issue of posterior or anterior predominance in AD still remains open for further DTI studies. Further information could possibly provide more insight into the pathophysiological nature of AD and MCI, as spatial distribution of white matter changes may reflect a particular kind of pathogenesis.

Corpus callosum (genu vs. splenium)

The corpus callosum, as the major white matter network, consists of corticocortical interhemispheric fibres. Corticocortical disconnections, occurring due to atrophy of this highly myelinated structure, correspond to cognitive impairment [21,26]. Numerous DTI studies have examined global or regional corpus callosum changes in AD and MCI patients [10,12,20,21,23, 25, 27,46,50,51]. Most of these studies concentrated directly on investigating FA and MD alterations in the genu and the splenium of the corpus callosum, but not in the middle corpus callosum (middle and posterior body). However, there are studies that measured AD-related FA values in all corpus callosum regions [21]. Lee *et al.* hypothesized that both degenerative and cerebrovascular processes in AD additively affect the anterior corpus callosum (genu), whereas the main impact of the white matter degenerative process is prominent essentially in the posterior corpus callosum (splenium). These results are also compatible with those of Kavcic *et al.* It has been proposed that the selective vulnerability of posterior cerebral white matter distinguishes AD patients from healthy subjects, while anterior and middle white matter integrity may be relevant to cognitive decline in both healthy and AD subjects, supposedly due to the additional vascular impact [20,21]. In a meta-analysis by Sexton *et al.*, it was shown that changes in FA and MD are characteristic for both the splenium and the genu of AD patients, with the changes in the splenium appearing more significant [14]. These findings support the theory that deteriorated integrity of the splenium is closely associated with secondary degenerative changes of axonal fibres, corresponding to the Wallerian degeneration model [14,21].

Nevertheless, there are numerous inconsistencies across publications; a wide range of DTI studies on the splenium have reported FA/MD changes not only in patients with established AD [4,25,46,50] but also in patients with MCI [22,26]. Zhang *et al.* found significantly reduced FA in the splenium of the corpus callosum in AD, but not in MCI [51]. Wang *et al.* observed decreased FA in the genu of the corpus callosum in MCI patients [24]. Chen and Lin *et al.* and Chen and Chen *et al.* reported that the genu is involved in both AD and MCI groups, whereas more prominent white matter impairment in the splenium of the corpus callosum appears to be related specifically to AD progression [25,44]. Therefore, assessing changes in the genu of the corpus callosum may be helpful in distinguishing MCI patients from healthy controls. A further assumption could be made that reduced FA and elevated MD in the genu and splenium of the corpus callosum may possibly constitute useful AD markers. However, our knowledge about regional corpus callosum changes in AD and MCI remains insufficient [21]. Moreover, there are numerous discrepancies concerning the conversion rate from MCI to AD. Subsequently, longitudinal studies are necessary to indicate whether FA and MD measured in corpus callosum regions are reliable neuroimaging biomarkers in terms of AD progression and MCI conversion to AD.

Cingulum (posterior vs. anterior cingulum)

The idea that DTI measures of abnormalities in the posterior white matter may be used as indices of disease progression is further supported by the fact that the posterior cingulum, contrary to the anterior cingulum, is considered to be an important part of the Papez circuit [27]. A bundle of white matter fibres, projecting from the posterior cingulum to the entorhinal cortex, has been shown to be involved in the cognitive network closely related to memory function. It has been hypothesized that the integrity of fibres connecting the medial temporal lobe with the posterior cingulum is diminished even at an early stage of AD [39,51]. Furthermore, consistently with pathological and neuroimaging studies, numerous studies have shown decreased FA in the posterior cingulum [11,12,40,51], along with increased MD [27]. Therefore, diffusion tensor-driven parameters were suggested to be sensitive neuroimaging biomarkers of early AD, including preclinical stages of AD. Kiuchi *et al.* found that FA values in the bilateral posterior cingulum bundles in MCI subjects were significantly decreased when compared to con-

trols; however, no significant differences were demonstrated between MCI and AD subjects [11]. These findings may lead to the assumption that alterations in the posterior cingulum precede the onset of dementia, indicating DTI changes in this region as a possible marker of the earliest stages of AD. However, as mentioned in the previous section, in order to develop reliable markers predicting the conversion of MCI to AD, longitudinal studies are needed. The MCI group would be subsequently considered as a diagnostic category of patients that also potentially includes a number of subjects presenting a preclinical stage of AD [30]. Nevertheless, Cho *et al.* found significant changes in the posterior cingulum in the AD group, but not the MCI group [26]. There are various other studies which have reported contradictory results, finding lower FA in the anterior portion of the cingulum, along with disease progression [10]. A possible explanation is the partial effect of white matter hyperintensities in the anterior region, related to the prevalence of vascular factors, which may influence the outcomes [21].

Uncinate fasciculus, superior and inferior longitudinal fasciculus

Some studies that focused on assessing differences in FA and MD across AD, MCI and healthy subjects have reported additional white matter abnormalities in the superior longitudinal fasciculus, inferior longitudinal fasciculus and uncinate fasciculus [8,11,19,23,26-28, 30,44]. The superior longitudinal fasciculus, connecting frontal and parietal regions, and the inferior longitudinal fasciculus, connecting temporal and occipital lobes, appear to play an important role in memory, attention and executive functions. It has been suggested that the integrity of the superior longitudinal fasciculus and inferior longitudinal fasciculus may be diminished in pathological processes such as AD [19,26,44]. Cho *et al.* found significant changes in the superior longitudinal fasciculus and inferior longitudinal fasciculus in AD and MCI groups compared to healthy volunteers, whereas no significant changes were observed in other temporal, parietal, and frontal white matter [26]. This finding may possibly indicate another biomarker for disease progression. However, when comparing the inferior longitudinal fasciculus (that interconnects between areas affected early in AD) with the superior longitudinal fasciculus (that connects regions affected in advanced AD stages), significant FA alterations are more expected in the inferior longitudinal fasciculus [23].

Diminished integrity of the uncinate fasciculus connecting the prefrontal region with the medial temporal lobe has also been reported in AD [8,11,23,28,30] and MCI patients [11]. Damoiseaux *et al.* raised the issue of the symmetry of white matter degeneration, reporting changes in the bilateral uncinate fasciculus when thresholding mean FA more liberally in TBSS analysis, although significantly decreased FA was reliably reported only in the left uncinate fasciculus. For this reason, when discussing possible lateralization of white matter alterations measured by tensor-derived parameters, it is important to take into consideration limitations of the applied methods of analysis [8].

Fornix and thalamus

In AD patients, decreased FA and elevated MD were observed in the fornix, which is an important outflow tract of the hippocampus [10,19]. Mielke *et al.* found significant differences in fibre integrity for the AD group, but not for the MCI group [10]. Some further DTI studies have demonstrated the presence of hippocampal connections directly to the anterior thalamus via the fornix, and to the pulvinar via the temporopulvinar tract [18,42]. These connections seem to play an essential role in impaired episodic memory in AD patients [52]. The greatest reduction in intra-thalamic FA was noted in the dorsal anterior region of the thalamus [8,42] along with white matter abnormalities found in the proximity of the hippocampal formation. These results signify AD-related decreased fibre integrity of the normally abundant connections between the medial temporal lobe and the thalamus. These outcomes are consistent with previous DTI studies on disrupted connectivity in the pathways leading to the hippocampus [8,10,18,22,34,51].

Unaffected regions

In evaluation of DTI metrics, unaffected white matter regions seem to play an important role. These regions may be used as an internal reference in differentiating between altered and healthy regions. For this purpose, studies have indicated the following bundles of fibres: corticospinal tract [11] and occipital white matter [9]. Other DTI reports have not reported any significant difference between AD and control subjects in early myelinating areas, such as the cerebral peduncles and the posterior limb of the internal capsule [23,40,50,51],

providing support for the retrogenesis pathogenetic models.

Age-related studies

The pattern of degenerative processes occurring in brain white matter has been widely examined in both AD and MCI, and also in aging subjects [8,24,53-57]. The majority of these age-related studies in the healthy population have reported decreased FA predominantly in the frontal white matter and the anterior corpus callosum. In particular studies, diminished white matter integrity was found within parietal regions [8,53,58], whereas according to other reports, parietal and temporal white matter is spared in healthy elderly subjects [55,56]. Head *et al.* hypothesized that age-associated abnormalities are exhibited more anteriorly in comparison with changes characteristic for AD. Overall, a different pattern of diffusivity changes in normal aging and AD patients is compatible with the statement that AD is not a simple acceleration of aging [8].

Discussion

A wide range of imaging studies provides growing support for the potential role of diffusion tensor imaging (DTI) in evaluating AD-related neurodegenerative processes in the brain. Whereas brain atrophy, which is the most characteristic imaging hallmark of AD, can be evaluated on different structural levels (including global brain volume reduction, localised grey matter atrophy and subcortical atrophy), evaluating diffusion data can bring valuable information of microstructural white matter integrity.

In practice, a DTI sequence can be easily included in the standard MRI protocol, along with the conventional structural (T1-weighted) sequence. In the last two decades, a wide range of optimised, robust algorithms for DTI analysis has been developed, focusing particularly on solving problems in terms of spatial alignment and computation of diffusion data, enabling subsequent voxel-based or ROI-wise analysis. However, a direct comparison between different approaches is complicated due to the bias in diffusion data introduced by different acquisition and post-processing steps. The question whether it is more effective to assess the whole brain diffusion or to directly concentrate on specific structures and regions remains a substantial issue that is still open to debate. Nevertheless, it is worth noting that several methods of analysis can be possibly applied within one study, so voxel-based analysis results can be compared with those of region-of-interest or tract-specific analysis.

The pattern and extent of white matter changes in AD and MCI are still under debate, regarding the underlying pathophysiology. The distribution of white matter abnormalities is widely discussed mainly in the light of deteriorated connectivity within certain tracts due to secondary degeneration occurring as a result of grey matter atrophy; however, the contribution of primary white matter degeneration to the general pattern cannot be excluded.

White matter microstructure changes, as evaluated by group level differences of tensor-derived parameters (FA, MD, axial and perpendicular diffusivity), can represent a promising neuroimaging biomarker in the diagnosis of AD. Whereas cross-sectional DTI studies have brought more insight into our understanding of the pathogenesis of AD when compared with healthy controls, further longitudinal studies are needed to assess the role of DTI in monitoring of disease progression and the conversion of MCI to AD.

Furthermore, due to the relatively complex clinical evaluation of neurodegenerative disorders, a noninvasive DTI approach may be a promising tool for differential diagnosis between various dementias, and microstructural white matter integrity assessment can shed more light on interpretation of different underlying pathological processes.

Summary

The aim of our review was to show the potential role of DTI as a powerful tool in evaluating microstructural white matter integrity in Alzheimer's disease. The DTI processing and variability analysis framework has been briefly described and the results of particular DTI studies presented, showing different patterns of AD-related white matter alterations. Assessing white matter microstructure alterations, as evaluated by group level differences of tensor-derived parameters, may be a promising neuroimaging tool for differential diagnosis between AD, MCI and other cognitive disorders, as well as being particularly helpful in the interpretation of underlying pathological processes.

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Disclosure

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