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Using Structural and Diffusion Magnetic Resonance Imaging To Differentiate the Dementias

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Abstract Dementia is one of the major causes of personal, societal and financial dependence in older people and in today's ageing society there is a pressing need for early and accurate markers of cognitive decline. There are several subtypes of dementia but the four most common are Alzheimer's disease, Lewy body dementia, vascular dementia and frontotemporal dementia. These disorders can only be diagnosed at autopsy, and ante-mortem assessments of "probable dementia (e.g. of Alzheimer type)" are traditionally driven by clinical symptoms of cognitive or behavioural deficits. However, owing to the overlapping nature of symptoms and age of onset, a significant proportion of dementia cases remain incorrectly diagnosed. Misdiagnosis can have an extensive impact, both at the level of the individual, who may not be offered the appropriate treatment, and on a wider scale, by influencing the entry of patients into relevant clinical trials. Magnetic resonance imaging (MRI) may help to improve diagnosis by providing non-invasive and detailed disease-specific markers of cognitive decline. MRI-derived measurements of grey and white matter structural integrity are potential surrogate markers of disease progression, and may also provide valuable diagnostic information. This review summarises the latest evidence on the use of structural and diffusion MRI in differentiating between the four major dementia subtypes.

Keywords Structural MRI · Diffusion MRI · Alzheimer's disease · Vascular dementia · Frontotemporal dementia · Lewy body dementia

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Introduction

By 2050, it is estimated that over 135 million people worldwide will live with dementia [1]. "Dementia" is an umbrella term for the loss of function and ability in different cognitive domains beyond that expected in normal ageing [2]. This review focuses on the four major subtypes of dementia, viz. Alzheimer's disease (AD), Lewy body dementia (LBD), vascular dementia (VaD) and frontotemporal dementia (FTD). These disorders can only be diagnosed at autopsy by an examination of their neuropathological features, and a clinical diagnosis of "probable dementia (e.g. of the Alzheimer type)" is usually driven by patient history and performance on cognitive tests. However, few patients present with clear-cut clinical symptoms, and current estimates suggest that only 20–50 % of dementia patients receive a formal diagnosis, potentially leaving a large proportion of affected individuals without access to appropriate treatment and care [3]. Moreover, because of overlapping behavioural deficits, especially in the later stages of the illness, misdiagnosis is common. A recent study of 15,367 patients with VaD reported that 16.6 % were misdiagnosed with AD [4]. Similarly, many patients with LBD have been given an ante-mortem diagnosis of AD [5, 6].

Differentiating between the dementias is critical, as it will guide the course of treatment. For instance, whereas AD and LBD patients may be treated with acetylcholinesterase

inhibitors [7, 8], patients with FTD show differing and in some cases unfavourable responses to these drugs [9]. Notwithstanding the treatment consequences, misdiagnosis may also have severe financial impacts and confound the outcome of therapeutic clinical trials [4].

There is therefore a pressing need to identify markers that can accurately differentiate between the dementias. The development of advanced neuroimaging techniques has enabled us to non-invasively examine subtle changes in brain architecture between the dementias; these imaging methods have therefore been recommended as part of the mandatory diagnostic workup [10]. As strategies for the treatment of dementia are moving towards the identification of therapies aimed at early abnormalities in the predementia stage, the importance of timely and accurate diagnoses is increasing, as is the need for sensitive measures for tracking disease progress. Magnetic resonance imaging (MRI)-derived measurements (together with positron and single photon emission tomography) have become principal surrogate markers of treatment response in clinical trials of neurological disorders [10], and allow for the possibility of reduced sample sizes and consequently more economical trials [11].

This review summarises the latest evidence about neuroimaging markers of dementia, specifically structural and diffusion MRI of AD, LBD, VaD and FTD. We begin with a description of dementia-specific changes in grey matter (GM) macrostructure visualised using structural MRI, follow with a discussion of white matter (WM) microstructural abnormalities measured using diffusion tensor imaging, and conclude by highlighting limitations of cross-study comparisons.

Structural MRI

Structural MRI (in contrast to X-ray computed tomography and emission tomography) does not carry any radiation load, and can hence be applied to large numbers of patients presenting with cognitive impairment. Different imaging sequences are used, depending on the focus of the investigation; e.g. T1-weighted imaging to examine brain parenchyma, T2-weighted imaging to view the ventricles or possible oedema, and fluid-attenuated inversion recovery for abnormal tissue, such as WM lesions (WMLs) and/or WM hyperintensities.

Attempts to diagnose dementia using structural MRI have largely focused on assessing GM atrophy and/or WMLs. WMLs appear as hyperintensities on T2-weighted MRI, and are visually assessed using established scales such as the Fazekas scale [12]. Although the numbers of periventricular and deep WMLs are increased in dementia patients compared with controls, they are usually similar in distribution and severity for the four subtypes [13] and hence are unlikely to aid in differential diagnosis. This section describes the potential for the use of focal and global GM atrophy as disease-specific structural markers.

Alzheimer's Disease

AD is the most common form of dementia, and accounts for nearly 50–75 % of all dementia cases [1]. It is characterised by progressive deterioration in memory, language, perceptual skills, attention, orientation and problem solving. Amyloid plaques and neurofibrilliary tangles originating in the medial temporal lobe (MTL) regions are crucial to the pathological diagnosis of AD [14].

Focal Atrophy

The most robust finding in AD is regional atrophy of the MTL, particularly in the hippocampus and entorhinal cortex. This is found in 80–90 % of AD patients, in comparison with 5–10 % of healthy age-matched controls [15]. In the clinic, atrophy is typically assessed using visual inspection against a semiquantitative scale. Such rating scales have demonstrated 80–85 % sensitivity and specificity at differentiating AD patients from those with no cognitive impairment [16], and have shown high accuracy against post-mortem diagnosis [17]. Volumetric hippocampal measurements are also accurate in differentiating AD patients from cognitively healthy elderly individuals [18]. Automated region of interest methods that detect patterns of hippocampal subfield atrophy have been reported to increase the accuracy of distinguishing between AD and mild cognitive impairment (MCI), which is a prodromal stage of AD [19, 20].

Notably, the degree of MTL atrophy correlates with neuropathological disease progression as well as with clinical cognitive deficits [21, 22] and performance on memory tests, such as the Mini-Mental State Examination (MMSE) [15]. However, despite being highly *sensitive* for AD, MTL atrophy alone is insufficient for an accurate diagnosis, largely owing to the decline in *specificity* with age [23]. Further, perhaps the biggest obstacle to its diagnostic applicability is that MTL atrophy is also common in other subtypes of dementia [13]. Nonetheless, it may be a useful prognostic marker since hippocampal atrophy is thought to start some years before symptoms first appear and the clinical diagnosis is made [24, 25••]. In mild-stage AD compared with controls, there is already a 15–30 % reduction in hippocampal volume [26]. The rate of atrophy, measured by serial scans, appears to be particularly informative [27]. Yearly atrophy rates of 15 % have been reported in AD patients compared with just 1.5 % in healthy controls [28]. Some studies indicate that MTL atrophy can predict conversion from MCI to AD with 80 % accuracy [29], whereas others have reported 73 % sensitivity and 81 % specificity for progression from MCI to AD [30].

Global Atrophy

Progressive global atrophy is a characteristic finding in AD. The medial and posterior regions of the brain, particularly the limbic and posterior cingulate areas, are frequently atrophied, usually in a symmetric pattern [31, 32]. The lateral and third ventricles, as well as the anterior and lateral fissures, are significantly larger in AD patients than in controls [31].

Global atrophy can be assessed using visual inspection or automated methods, although scales for these lack the diagnostic validity of those used in assessing MTL atrophy [10]. Automated methods have most frequently used voxel-based morphometry (VBM), where the GM volume of a subject is assessed over the whole brain and compared with the GM volume from a library of normal subjects. This is limited by the quality of image registration and the amount of spatial smoothing.

Attempts have been made to standardise atrophy measures. One such, the STAND (for "*st*ructural *a*bnormality i*nd*ex"), an AD-specific structural abnormality index based on tissue densities, correlates with measures of cognitive performance, such as the Clinical Dementia Rating score and the MMSE score [32, 33]. Deformation-based morphometry may also be used to track GM and WM changes in MCI and AD [34], and has been reported to correlate with cognition and pathological biomarkers [35]. Cortical thickness is another proxy measure of atrophy. Lerch et al. [36, 37] found reduced cortical thickness in temporal, orbitofrontal and parietal regions in AD patients, and subsequently used an automated method to distinguish AD patients from controls. This "cortical signature" for AD [38] correlates with the MMSE score and progression of disease [37] and may also help to distinguish AD from FTD [39].

In terms of prognosis, rates of global atrophy appear to be useful. In AD patients the rates are up to four times greater than in controls [40, 41], and are correlated with cognition [42–44]. Structural markers are more sensitive to conversion of MCI to moderate dementia than markers of amyloid deposition [44, 45], and a recent meta-analysis of VBM studies identified one significant cluster of GM volume reduction within the left hippocampal and parahippocampal gyrus in amnestic MCI to dementia converters [46].

Lewy Body Dementia

Lewy body dementia (LBD) is named after the neuronal inclusions, α-synuclein-positive Lewy bodies, found predominantly in the brainstem, limbic cortex and neocortex of affected patients [47]. In addition to cognitive impairments, LBD is clinically characterised by a triad of fluctuating consciousness, parkinsonism and visual hallucinations [48]. However, not all people with LBD exhibit these features, and patients may sometimes present with clinical symptoms similar to those of AD, making differential diagnosis difficult [49–52]

Focal Atrophy

Atrophy of the midbrain, hypothalamus and substantia innominata, with a relative preservation of the temporal and parietal lobes, is suggestive of LBD, and this may aid in the differentiation of LBD from AD [53]. Somewhat surprisingly, given the prevalence of visual hallucinations in LBD, and the hypometabolism and hypoperfusion observed in positron emission tomography and single photon emission computed tomography studies [54, 55], gross occipital lobe atrophy has not been robustly demonstrated [56, 57], although there are reports of isolated left occipital gyrus atrophy [58]. Atrophy of the hippocampus, amygdala and caudate nucleus is found in LBD, but seems to be less pronounced than in AD [17, 59, 60].

Global Atrophy

Whole-brain atrophy rates of 1.4 % have been reported in LBD patients, which is three times that seen in the general population, but still less than in AD [41]. A similar pattern is found for ventricular expansion rates, with 4.8 % in LBD patients and 8.3 % in AD patients [53].

Vascular Dementia

Another common cause of cognitive impairment in the elderly is VaD, which requires the coexistence of cognitive impairment and cerebrovascular disease [61, 62]. In contrast to AD, memory disturbance is less prominent initially, and the clinical picture often involves gait disturbance, urinary symptoms, pseudobulbar palsy (difficulty swallowing and slurred speech) and psychomotor retardation. VaD patients typically present with impairment in semantic memory, executive/attentional function and perceptual skills. These impairments are largely due to cerebrovascular lesions, the location and extent of which determine the severity of cognitive dysfunction [63]. VaD may be caused by large-vessel or small-vessel disease, with the latter being the most common underlying cause [64, 65]. Small-vessel disease involves extensive lesions of the WM (more than 25 %), and appears on MRI scans as infarcts, cerebral atrophy, WMLs, or microbleeds. Neuroimaging evidence of relevant cerebrovascular disease including multiple large-vessel infarcts, or a single strategically placed infarct, as well as multiple basal ganglia and WM lacunes, or extensive periventricular WMLs is required by commonly used diagnostic criteria [66].

Focal Atrophy

Atrophy in VaD follows infarction, and hence may either be generalised or target the cortex or ventricles, depending on the location of infarcts. Hippocampal atrophy has been described in VaD, with up to 59.8 % of VaD patients showing significant MTL atrophy [67], which may be unilateral or bilateral [68]. However, it is difficult to distinguish between VaD and LBD or AD on the basis of MTL or caudate atrophy alone [69, 70].

Global Atrophy

Global atrophy is common in VaD, and may convey prognostic rather than diagnostic information. No significant difference has been found between VaD and LBD on whole-brain volumetric analysis [59]. However, the annual rate of global atrophy in VaD patients has been reported to be higher than that in LBD patients and controls, but lower than that in AD patients [41].

Infarcts and Microbleeds

Infarcts may be visualised using structural MRI in cortical, lacunar or strategic brain areas such as the thalamus [66]. Lacunar infarcts are commonly "silent" and can be found in cognitively normal subjects; hence, they are of limited diagnostic use for VaD, but rather serve as a marker of increased risk of future dementia. Increasingly reported in the literature are microbleeds, which are thought to represent haemosiderin deposits in the brain. They are found more commonly in VaD than in other subtypes (65 % compared with 18–20 % in AD, [71]), but their exact clinical significance remains unclear as they can also be "silent" in normal controls [72].

Frontotemporal Dementia

Whereas AD, LBD and VaD typically manifest themselves after 65 years, FTD is more common in younger patients, and usually presents between 40 and 65 years. FTD is a behaviourally and pathologically heterogeneous range of disorders with a relatively focal involvement of the frontal and temporal lobes. Three main syndrome variants are recognised: behavioural variant FTD (bvFTD), which presents with predominant personality changes; semantic dementia (SD), which presents as an impairment of semantic memory; and progressive non-fluent aphasia (PNFA), which presents with predominant speech production difficulties [73].

Focal Atrophy

Hippocampal atrophy is seen in FTD, but to a lesser degree than in AD [74]. The different clinical phenotypes are associated with characteristic patterns of brain atrophy: bvFTD is associated with bilateral frontal atrophy [75], SD with predominantly left anterior temporal lobe atrophy [76, 77], and PFNA with left perisylvian atrophy [78].

Global Atrophy

Perhaps unsurprisingly, the pattern of atrophy in FTD, particularly bvFTD, is more focused on frontal and temporal lobes than in AD [24]. The atrophy tends to be more asymmetric than in AD [79]. Whole-brain atrophy rates are greater than in controls but do not distinguish FTD from other subtypes of dementia.

There is a substantial overlap in the presence of these biomarkers between FTD subtypes, particularly with regard to hippocampal atrophy and WMLs; hence, one should remain cautious about differentiating dementia subtypes on the basis of structural MRI findings alone.

In summary, together with clinical assessments, structural MRI can improve diagnostic accuracy, exclude other abnormalities such as space-occupying lesions, and additionally act as a prognostic marker of AD progression. Although there are abnormalities that are characteristic of the dementia subtypes, e.g. MTL atrophy in AD, subcortical atrophy in LBD, infarcts and microbleeds in VaD and frontal atrophy in FTD, there is substantial overlap in the presence of macrostructural changes between the dementias, particularly with regard to WMLs. Hence, although conventional structural MRI alone is insufficient to precisely differentiate between the dementias, it can perhaps be used in combination with other imaging markers that may increase the accuracy of diagnosis.

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) has recently emerged as a useful tool for assessing subtle changes in WM microstructure within the brain [80]. DTI is sensitive to the directional diffusion of water within tissues, and depends on the interaction of water molecules with obstacles to diffusion, such as membranes. The movement of water in WM is unrestricted in directions parallel to the axon, but is hindered orthogonally owing to the presence of the myelin sheath, i.e. its diffusion is anisotropic. This anisotropy is characterised by DTI-derived measures, such as fractional anisotropy (FA), whereas mean diffusivity (MD) reflects the magnitude of water diffusion [81]. Both FA and MD are considered sensitive measures of disease-related changes in WM. Axon damage is typically represented by an increase in MD or a decrease in FA. These changes in microstructure can precede atrophy of the brain, so DTI can potentially detect subtle changes that may be missed by volumetric methods. When used in combination with conventional structural MRI, DTI is believed to increase the

accuracy of early and differential diagnosis of the dementias [82].

Alzheimer's Disease

AD has traditionally been thought of as a disorder of the GM starting with the deposition of neurofibrillary tangles and amyloid β plaques in and around neuronal cell bodies. Of late, however, it is the relationship between GM atrophy and WM damage that has gained interest, with reports of associations between WM disruption and MTL atrophy [83], as well as with decline in cognitive function [84] in AD. Although often believed to be secondary to GM damage, WM damage has recently been suggested to occur independently of, and perhaps even before, GM damage [85]. It is therefore likely that DTI can detect WM changes before they are associated with atrophy on structural MRI. It has been suggested that increases in hippocampal diffusivity may be better predictors of conversion from MCI to AD than hippocampal atrophy measured with conventional structural MRI [86–88].

Several DTI studies in AD patients have reported early WM degeneration in the posterior parts of the brain, with progression to the limbic and frontal regions during the later stages of the disease [89–91]. Specifically, relative to healthy controls, AD patients show significant reductions in FA and increases in MD in the fornix, corpus callosum, posterior cingulum, superior longitudinal fasciculus, uncinate fasciculus, parahippocampal gyrus and hippocampus [88, 92–100]. These regions make up the limbic pathways connecting to the MTL, play a role in cognition and memory, and are notably also the first regions to be affected by AD pathological changes, thus strengthening the association between WM and GM degeneration in AD.

Although DTI seems to be a valuable marker of AD-related degeneration relative to cognitively healthy controls, the difficulty arises in distinguishing AD from other dementias. In evaluating the efficacy of DTI as a dementia-specific imaging marker, most studies have considered AD as a prototype of dementia, and used it as a standard of comparison with other dementia types. The following sections examine how LBD, VaD and FTD differentially influence WM relative to AD and healthy controls (Table 1).

Lewy Body Dementia

Perhaps one of the most fitting assessments of the diagnostic applicability of DTI in distinguishing between LBD and AD is to examine whether WM microstructural changes correlate with the differences in clinical symptoms or pathological processes between the two dementias. Up to 44 % of LBD patients and only 3 % of AD patients first present with visual hallucinations [118], making visual impairments potential indicators of LBD [48]. Diffusion imaging studies have found WM correlates of visual deficits in LBD. Several studies have reported reductions in WM integrity in LBD patients compared with healthy controls, specifically in the inferior longitudinal fasciculus (ILF) and precuneal occipital WM tracts, which form part of the ventral and dorsal visual streams, respectively [102, 104•, 119–121]. Notably, increases in diffusivity of the ILF are significantly more pronounced in LBD patients who experience visual hallucinations than in those who do not. LBD patients also show increases in diffusivity within the amygdala relative to controls [119], which is of importance given that dysfunction of the occipitoamygdaloid connections have been implicated in visual hallucinations and LBD-related disease [122]. However, this finding was not replicated [82] and must be interpreted as preliminary.

Using a tractography-based approach, Kiuchi et al. [102] reported that despite similar severity of dementia, it is LBD patients and not AD patients who show marked reductions in FA in the bilateral inferior occipitofrontal fasciculus and ILF relative to healthy controls. The inferior occipitofrontal fasciculus and ILF contain fibres that project from the visual association areas and have been implicated in semantic, emotional and visual memory [123]. Damage to these temporo-occipital projection tracts could underlie, and be a helpful signature of, the visual deficits commonly observed in LBD patients [102].

Nevertheless, it is the similarities between the AD and LBD that seem to limit the diagnostic potential of diffusion imaging. Ninety-nine per cent of AD patients and 57 % of LBD patients initially present with memory impairments [118], and some studies report similar reductions in WM integrity in regions involved in memory processing in both LBD and AD patients. Specifically these similarities have been reported in the precuneus [82], uncinate fasciculus [102], corpus callosum and pericallosal fibres [103, 124] and temporal lobe [101], and probably reflect the overlap in neuropsychological impairment between both dementias.

One way to improve the diagnostic utility of DTI in classifying individual cases of AD and LBD is to combine diffusion measures and neuropsychological tests. Although O'Donovan et al. [82] found no WM microstructural differences between AD and LBD within the amygdala or precuneus, they were able to separate the two dementias when they found a statistically significant positive relationship between amygdala diffusivity and Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) scores (which measure the severity of parkinsonism) in LBD patients but not AD patients, and between precuneal FA and MMSE scores (which measure cognitive impairment) in AD patients but not LBD patients. The association between amygdala diffusivity and UPDRS-III scores in LBD patients has also been reported elsewhere [119, 121] and is suggestive of a link between the high Lewy body burden in the amygdala, and substantia nigra, which could underlie symptoms of motor parkinsonism in

Table 1 Summary of diffusion tensor imaging findings in Lewy body dementia (*LBD*), vascular dementia (*VaD*) and frontotemporal dementia (*FTD*) relative to Alzheimer's disease (*AD*)

Study	Scan	Analysis	Tracts	Subjects	Findings
LBD					
Firbank et al. [101]	1.5 T, 24 directions	FSL/SPM2	Whole brain and ROI: putamen and caudate, genu and splenium of CC, anterior and posterior pericallosal area, internal capsule, thalamus and parietal/frontal/occipital/temporal WM	15 AD, 16 LBD, 15 HC	LBD vs HC: significantly lower FA in the precuneus AD vs HC: significantly higher diffusivity in the left temporal lobe
O'Donovan et al. [82]	3 T, 16 directions	FSL	ROI: bilateral thalamus, precuneus, pons, midbrain and amygdala	36 AD, 35 LBD, 35 HC	LBD and AD vs HC: significantly lower FA/higher MD in the precuneus. No significant difference in FA/MD in any other ROIs LBD vs AD: no significant difference in FA/MD in ROIs. Positive correlation between amygdala MD and UPDRS-III score in LBD but not AD
Kiuchi et al. [102]	1.5 T, 6 directions	dTV II	Tractography: UF, IOFF and ILF	26 AD, 26 LBD, 26 HC	LBD and AD vs HC: significantly lower FA in UF LBD vs HC: significantly lower FA in bilateral IOFF and left ILF LBD vs AD: no significant difference but LBD had lower FA values than AD, especially in visual WM
Bozzali et al. [103]	1.5 T, 8 directions		ROI: same as Firbank et al. [101]	15 LBD, 10 HC	LBD vs HC: significantly lower FA/higher MD in the frontal, parietal, occipital WM, CC and pericallosal areas, and caudate nucleus
Kantarci et al. [119]	3 T, 3 directions		ROI: amygdala, hippocampus, parahippocampal gyrus, posterior cingulate gyrus and precuneus	30 LBD, 30 AD, 60 HC	LBD vs HC: significantly higher MD in the amygdala and lower FA in the ILF. ILF diffusivity was associated with the presence of visual hallucinations and amygdala diffusivity was associated with UPDRS-III scores in LBD AD vs HC: significantly higher MD in the medial temporal, temporal and parietal lobe association cortices and lower FA in fornix, CB and ILF
Ota et al. [104•]	1 T, 12 directions	DtiStudio	ROI: ILF, visual pathway and splenium CC	14 LBD, 13 HC	LBD vs HC: significantly lower FA in ILF
FTD					
Mahoney et al. [105••]	3 T, 64 directions	Camino/TBSS	Whole brain and ROI: UF, CB, CC, SLF, ILF, ATR and CST	27 bvFTD, 25 AD, 20 HC	bvFTD vs HC and AD: significantly lower FA/higher diffusivity in UF, cingulum, and CC, and less prominently in SLF, ILF, ATR, and fornix
Matsuo et al. [106]	1.5 T, 15 directions	PRIDE	Tractography and ROI: genu, splenium, AF, UF, ILF and pyramidal tracts	20 FTD, 17 HC	FTD vs HC: significantly lower FA in genu, splenium, AF, UF, and ILF. No significant difference in pyramidal tracts
Lu et al. [107]	1.5 T, 12 directions	–	ROI: genu, splenium and frontal WM	8 bvFTD, 12 early-onset AD, 12 HC	bvFTD vs AD and HC: significantly lower FA/higher MD in frontal WM and genu AD vs bvFTD and HC: trend to higher MD in splenium WM
Zhang et al. [108]	4 T, 6 directions	dTV II/Volume-one /SPM8	Whole brain voxelwise	20 AD, 20 bvFTD, 21 HC	AD vs HC: significantly lower FA in parietal, temporal, and some frontal lobe regions, particularly posterior CC, left posterior CB, and periventricular deep WM bvFTD vs HC: significantly lower FA in frontal, temporal, and anterior CC, and anterior CB bvFTD vs AD: significantly lower FA in frontal deep WM, anterior CC, and anterior CB. No regions where AD had worse WM than bvFTD
Zhang et al. [109]	4 T, 6 directions	SPM8/dTV/Volume-one	Whole brain and ROI: CC, CB, parahippocampal cingulum, UF, AF and fornix	13 bvFTD, 6 SD, 6 PFNA, 19 HC	bvFTD vs HC: significantly lower FA in bilateral frontal/temporal WM. Significantly higher diffusivity in anterior CC, fornix, UF and anterior CB. Across dementia: dementia-specific regions of WM atrophy

Table 1 (continued)

Study	Scan	Analysis	Tracts	Subjects	Findings
Whitwell et al. [110]	3 T, 21 directions	SPM5	Whole brain and ROI: left and right frontal, temporal, parietal, and occipital lobes and basal ganglia. Anterior CB, UF, SLF, right anterior ILF and right CST	16 bvFTD, 7 PNFA, 4 SD, 19 HC	bvFTD vs HC: significantly lower FA/higher DR in bilateral UF, AC, anterior SLF, left posterior SLF, and anterior ILF. Significantly lower FA in CSF. Significantly higher DR in genu CC and posterior ILF Across dementia: dementia-specific regions of WM atrophy
Santillo et al. [111]	3 T, 48 directions	TrackVis version 0.5.0	Tractography: CB and CC	14 bvFTD, 22 HC	bvFTD vs HC: significantly lower FA/higher MD in anterior CB, but not posterior CB
Borroni et al. [112]	1.5 T, 6 directions	BrainVisa 1.6	Whole brain	23 HC, 28 bvFTD, 8 tvFTD	bvFTD vs HC: significantly lower FA in right SLF tvFTD vs HC: significantly lower FA in ILF, IFOF, left callosal radiations, and left SLF
Zhang et al. [113]	4 T, 6 directions	dTV/Volume-one	Whole brain and tractography: CC, UF, CB and CST	18 bvFTD, 18 AD, 19 HC	bvFTD vs HC: significantly lower FA/higher DR in anterior CC, anterior and descending CB, and UF AD vs HC: significantly lower FA in posterior and descending CB, left anterior CB, and left UF bvFTD vs AD: significantly lower FA in anterior CC, and significantly higher DR and DA in bilateral UF. No regions where AD had worse WM than bvFTD
VaD					
Sugihara et al. [114]			ROI: genu/splenium of CC, and the anterior and posterior cerebral WM	20 AD, 20 VaD, 10 HC	AD vs HC: significantly lower FA in posterior WM VaD vs HC: trend to lower FA in anterior WM than in posterior WM (p=0.07)
Thong et al. [115]	3 T, 61 directions	HARDI	Whole brain voxelwise and HARDI deterministic tractography	20 AD, 25 HC, 30 MSVCI	AD vs HC: significantly higher MD in ILF, posterior CR, and SLF. Significantly lower FA in superior CR. MSVCI vs HC: significantly lower FA/higher MD in SLF, ILF, IC, CSF, body of CC, IFOF, thalamus, and UF MSVCI vs AD: no significant difference in FA/MD. But major fibre tracts in AD: posterior WM bundles. Major fibre tracts in MSVCI: anterior WM bundles
Zarei et al. [116]	1.5 T, 60 directions	FSL/TBSS	Tractography within CC	13 VaD, 16 AD, 22 HC	VaD vs AD: significantly lower FA in forceps minor/transcallosal prefrontal tracts
Chen et al. [117]	1.5 T, 25 directions	GE Workstation	ROI: temporal lobe, genu, splenium of CC and anterior and posterior subcortical and periventricular WM	30 AD, 18 SIVD, 10 MCI, 7 FTD, 20 HC	SIVD vs AD: significantly lower FA/higher MD in bilateral posterior periventricular WM FTD vs AD significantly higher MD in bilateral temporal WM

AC anterior cingulate, *AF* arcuate fasciculi, *ATR* anterior temporal lobe, *bvFTD* behavioural variant frontotemporal dementia, *CB* cingulum bundle, *CC* corpus callosum, *CR* corona radiata, *CST* corticospinal tract, *DA* axial diffusivity, *DR* radial diffusivity, *FA* fractional anisotropy, *HC* healthy controls, *IC* internal capsule, *IFOF* inferior fronto-occipital fasciculus, *ILF* inferior longitudinal fasciculus, *MCI* mild cognitive impairment, *MD* mean diffusivity, *MSVCI* moderate to severe vascular cognitive impairment, *PFNA* progressive non-fluent aphasia, *ROI* region of interest, *SD* semantic dementia, *SIVD* subcortical ischaemic vascular dementia, *SLF* superior longitudinal fasciculus, *tvFTD* temporal variant frontotemporal dementia, *UF* uncinate fasciculus, *UPDRS-III* Unified Parkinson's Disease Rating Scale Part III, *WM* white matter

LBD [119]. Further reports of a correlation between letter fluency (which measures executive function) and FA/MD in the precuneus, precentral gyrus and corpus callosum in LBD patients but not AD patients indicate that a combination of cognitive tests and DTI may be more clinically relevant than either of the two measures alone [121].

Vascular Dementia

Differentiating VaD from AD using structural imaging is often difficult, given that WM hyperintensity is a common feature of both disorders. The two share similar cardiovascular and cerebrovascular risk factors and cognitive impairments, and the established neuropsychological criteria for diagnosis are not specific [125]. It has been hypothesised that VaD may in some cases be a "disconnection syndrome", and the ensuing cognitive impairments may be a consequence of disrupted cortical–subcortical connections due to WM tract damage [126, 127]. In this case, DTI may be a more sensitive marker than structural MRI of the pathological changes in VaD.

Relative to cognitively healthy controls, patients with subcortical ischaemic VaD (SIVD; a subtype of VaD with small lacunes in the subcortical WM) have DTI abnormalities in anterior and posterior periventricular areas, bilateral anterior subcortical areas, frontal and parietal WM and the genu of the corpus callosum, and the superior longitudinal fasciculus and ILF [116, 117, 128, 129]. The anterior subcortical changes seem to be specific to VaD, potentially reflecting the executive dysfunction characteristic of this disorder [114, 130], whereas changes in the temporal lobe and hippocampus are more pronounced in AD, explaining prominent impairment in episodic memory [129].

There are few studies that have directly compared VaD with AD. Chen et al. [117] found that SIVD patients had significantly higher MD and lower FA in the posterior periventricular areas compared with AD patients. Whole-brain tract-based spatial statistics has shown that the forceps minor, corona radiata and fronto-occipital tracts are more compromised in VaD than in AD, perhaps owing to SIVD-related periventricular lacunar infarcts and ischaemia-induced disease in these regions [116, 129]. Tractography analysis within the corpus callosum has revealed significantly reduced FA in anterior prefrontal and sensorimotor transcallosal tracts in VaD patients (but not in AD patients) compared with healthy controls, probably attributable to multiple ischaemic events in VaD [116]. Damage to the anterior corpus callosum lends additional support to the "disconnection syndrome" hypothesis, and could possibly explain how WM lesions in the frontal lobe combined with loss of interhemispheric prefrontal connections may lead to cognitive decline, particularly in the domains of executive function and information processing [116].

One study has reported no significant differences in mean FA or MD between AD patients and individuals categorised as having "moderate to severe vascular cognitive impairment" (MSVCI) [115]. However, the authors stressed that the fibre bundles that were compromised in the AD and MSCVI groups (compared with healthy controls) were clearly different, with minimal overlap between the dementias. The AD group showed abnormalities in the posterior fibre bundles, whereas the members of MSVCI group were affected in the anterior brain regions, including the internal capsule, corona radiata, uncinate fasciculus, and anterior thalamic radiations [115]. However, these anterior regions are affected in later stages of AD as well, and it is important to consider the severity of dementia before making any direct comparisons between them.

Frontotemporal Dementia

FTD most commonly affects younger patients [131]. When comparing FTD with AD, one must take into consideration age and the severity of dementia. It is occasionally difficult to differentiate FTD from AD because of overlapping symptoms [132, 133]; at autopsy, nearly 20 % of bvFTD cases show AD-related abnormalities [134]. However, there is increasing evidence to support the sensitivity and specificity of DTI in classifying individual patients with FTD and AD. In fact, distinct patterns of WM abnormalities have been reported in the major subtypes of FTD—i.e. bvFTD, SD and PNFA [109, 110]—and these changes are regionally consistent with tau deposition in WM [135].

Relative to healthy controls, bvFTD patients show widespread reductions in FA in the frontal and temporal WM. These changes have been reported and consistently replicated in association fibres, including the uncinate fasciculus, the genu of the corpus callosum [105••, 106, 112, 113, 117], bilateral anterior cingulum, posterior periventricular areas [108, 117] and, to a lesser extent, in the superior longitudinal fasciculus and ILF [106, 112]. Damage to these essential tracts is believed to result in the memory and personality disturbances characteristic of bvFTD.

Compared with AD patients, bvFTD patients have lower FA values in the genu of the corpus callosum [105••, 107, 113]. Damage to the splenium of the corpus callosum seems to be specific to AD, with callosal abnormalities in FTD patients being predominantly localised to the genu [106, 107, 113, 117], suggesting a characteristic distribution of WM degradation for the two dementias. The genu, which connects the prefrontal cortices of the two hemispheres, is a late-myelinating region, in contrast to the splenium, which is myelinated in early childhood. Late-myelinating regions have fewer oligodendrocytes supporting the high metabolic demands of neurons, making these neurons more susceptible to the pathological changes and behavioural deficits of bvFTD

[136]. Patients with bvFTD also show higher diffusivity, and lower FA in the uncinate fibres and cingulum bundle compared with AD patients [105••, 108, 113], and there are no regions where AD patients have lower FA than bvFTD patients, suggesting a greater vulnerability of WM in bvFTD than in AD [108, 113].

Given that the uncinate fasciculus, corpus callosum and cingulum are damaged in bvFTD patients relative to controls, and are also more severely damaged in bvFTD than in AD, these WM tracts may serve as a relatively specific index of bvFTD pathological changes. In fact, the mean FA in the left uncinate fasciculus has been reported to show the greatest sensitivity (77 %) and the left cingulum and corpus callosum have been reported to show the highest specificity (80 %) in distinguishing bvFTD from AD [105••]. These major tracts have been implicated in risk-taking behaviours [137], inhibition [138], obsessive–compulsive symptoms and executive dysfunction [137, 139], and are therefore reasonable markers of cognitive deficits in bvFTD. Moreover, comparisons between the DTI metrics have revealed that whole-brain mean FA has high sensitivity (78 %) and specificity (68 %) for differentiating between bvFTD and AD, whereas whole-brain MD has high sensitivity (82 %) and specificity (80 %) for distinguishing bvFTD patients from healthy controls [105••, 109, 111].

The degree of WM microstructural abnormality measured by DTI correlates with the clinical severity of bvFTD (assessed by the Clinical Dementia Rating and MMSE), which allows the use of regional DTI metrics in monitoring disease progression [106, 117]. Symptoms of "emotional blunting", i.e. a loss of emotion, sympathy or empathy, are more prevalent in bvFTD patients than in AD patients, and there is a significant association between ratings of emotional blunting (Scale for Emotional Blunting) and lower FA and higher diffusivity within the genu in bvFTD patients [107]. These correlations are not robust within AD patients and may therefore be specific markers of bvFTD [107]. There is also an inverse correlation between FA in the superior longitudinal fasciculus and ratings of inflexibility, personal neglect, impulsivity and disorganised activity in bvFTD patients, further cementing the close association between WM networks and behavioural manifestations of bvFTD [112].

Conclusion

Changes in WM microstructure may precede gross changes in GM volume, and could therefore aid in the differential diagnosis of the dementias. For instance, structural MRI studies have found no GM atrophy in the occipital lobes of LBD patients [56], whereas DTI studies have revealed WM microstructural abnormalities in key visual tracts in LBD patients, particularly in those experiencing visual hallucinations [119]. Further, WM damage is more prominent than GM atrophy in FTD [108], and on the whole, DTI parameters are more accurate and discriminative than structural MRI in the differential diagnosis of FTD [109, 111]. Indeed, the best parameter of cortical atrophy (measured by VBM) is 82 % accurate in differentiating FTD patients from controls, compared with 92 % for FA and 97 % for MD [111]. However, new methods for combining multimodal imaging data may yield additional sensitivity. Using a support vector machine that selects optimal voxels from structural MRI and DTI, Avants et al. [140] accurately defined AD-relevant and FTD-relevant regions of atrophy that correlated well with MMSE and verbal fluency performances, respectively.

It seems, therefore, that a combination of structural MRI and DTI, together with neuropsychological assessments, may provide the most unique diagnostic information. However, studies investigating their clinical applicability are currently limited by methodological constraints. First, most of the DTI studies discussed in this review had small sample sizes, and no post-mortem confirmations of clinical diagnoses. Since misdiagnosis is fairly common, it must be accounted for in order to accurately evaluate the sensitivity and specificity in distinguishing between the dementias. There are also a substantial number of patients with multiple disorders, to the extent that pathologists cannot agree on a primary diagnosis, e.g. "comorbid AD and VaD" [141]. Second, disease severity must be considered when comparing the dementias. AD initially presents with GM and WM changes in the posterior parts of the brain, which spread to frontal regions as the disease progresses. Therefore, comparing other dementias with late-stage AD is going to paint a picture very different from comparing them with early-stage AD. Third, cross-study comparisons of DTI markers are limited by the differences in analysis techniques, viz. a priori region of interest, histogram or whole-brain voxelwise approaches, each of which have their advantages and disadvantages [117]. Moreover, between-study variations in acquisition sequences, viz. number of directions of diffusion gradients and the use of anisotropic versus isotropic voxels, may cause a bias in the calculation of FA and therefore skew DTI results. Finally, there is an evident dearth of longitudinal studies, which are crucial in monitoring the relationship between neuroimaging markers of dementia and disease progression.

Overall, MRI holds great potential for supporting diagnosis, by developing dementia-specific signatures of changes in GM and WM that may occur before the onset of cognitive decline. It can also be used in the development of viable treatment options and to relate the spread of structural changes to disease progression. Furthermore, there has been a surge of interest in using functional MRI to identify early changes in brain activity that may be predictive of an individual's risk of developing dementia [142, 143]. In this context, a

combination of structural and diffusion MRI with functional imaging may be the most robust method of characterising the specific patterns of early changes associated with the different subtypes of dementia [144].

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Compliance with Ethics Guidelines

Conflict of Interest Sana Suri, Anya Topiwala, Clare E. Mackay, and Nicola Filippini declare that they have no conflict of interest.

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