Parkinsonism and Related Disorders 33 (2016) 12–26

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Review article

# Diffusion alterations associated with Parkinson's disease symptomatology: A review of the literature

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ARTICLE INFO

*Article history:*
Received 21 April 2016
Received in revised form
28 July 2016
Accepted 26 September 2016

*Keywords:*
Parkinson's disease
White matter tracts
Diffusion tensor imaging
Heterogeneity

ABSTRACT

Parkinson's disease (PD) is a heterogeneous neurological disorder with a variety of motor and non-motor symptoms. The underlying mechanisms of these symptoms are not fully understood. An increased interest in structural connectivity analyses using diffusion tensor imaging (DTI) in PD has led to an expansion of our understanding of the impact of abnormalities in diffusivity on phenotype. This review outlines the contribution of these abnormalities to symptoms of PD including bradykinesia, tremor and non-tremor phenotypes, freezing of gait, cognitive impairment, mood, sleep disturbances, visual hallucinations and olfactory dysfunction. Studies have shown that impairments in cognitive functioning are related to diffusion abnormalities in frontal and parietal regions, as well as in the corpus callosum and major fibres connecting midbrain and subcortical structures with the neocortex. However, the impact of diffusion alterations on motor, mood and other symptoms of PD are less well understood. The findings presented here highlight the challenges faced and the potential areas of future research avenues where DTI may be beneficial. Larger cohort studies and standardized imaging protocols are required to investigate current promising preliminary findings.



## 1. Introduction

Parkinson's disease (PD) is classified as a movement disorder with its cardinal motor symptoms of bradykinesia, muscle rigidity and resting tremor predominantly arising from nigrostriatal dopaminergic denervation. However, it has become evident that PD is a multisystem disorder extending beyond the loss of dopamine [1]. Indeed, PD can be better characterized as a heterogeneous disorder with a wide variety of both motor and non-motor symptoms, including cognitive impairments, sleep-wake disturbances, mood disorders, autonomic dysfunction and visual hallucinations [2]. The complexity of this disorder is emphasised by its clinical diversity with symptoms differing greatly across patients [3]. This degree of heterogeneity has hampered the understanding of the neural underpinnings of each symptom, leaving many symptoms poorly managed or even unable to be treated. In an attempt to mitigate these issues, magnetic resonance imaging (MRI) techniques have been used to investigate tissue alteration and abnormalities that may be present in order to provide a more thorough understanding of the neural basis underlying symptomology in PD [4,5].

One such structural imaging technique, diffusion tensor imaging (DTI) is a non-invasive imaging approach that analyses the diffusivity in brain tissues. It is sensitive to the flow of water molecules, and as water predominantly diffuses along axons, DTI can be used to infer white matter tracts throughout the brain [6,7]. The organization of axons and their properties (i.e. axonal ordering, diameter, density, myelination, microstructural complexity and white

*Abbreviations:* PD, Parkinson's disease; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; TBSS, tract-based spatial statistics; ROI, region of interest; SN, substantia nigra; SLF, superior longitudinal fasciculus; IF-OF, inferior fronto-occipital fasciculus; PPN, pedunculopontine nucleus; PIGD, postural instability and gait disorder; FOG, freezing of gait; MCI, mild cognitive impairment; VH, visual hallucinations; RBD, REM sleep behaviour disorder.

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http://dx.doi.org/10.1016/j.parkreldis.2016.09.026
1353-8020/

matter integrity changes) are the main contributors that influence the flow of water molecules along neural pathways. Water molecules move much faster along parallel white matter fibres compared to perpendicular fibres. Fractional anisotropy (FA) is a measure that reflects the degree of diffusivity in the different directions and can inform our understanding of the microstructural organization of the tensors; an organized multidimensional array of numerical values, expressing a relationship between vectors [8]. A decrease in FA values may arise from demyelination, axonal loss or changes in the size of axons. Mean diffusivity (MD) represents the overall movement of water molecules within the brain. Structurally intact white matter has high FA and low MD, whereas structurally compromised white matter has low FA and high MD. Additionally, DTI provides an estimate of diffusivity along (axial diffusivity; AxD) and perpendicular (radial diffusivity; RxD) to the main fibre direction. RxD increases in response to demyelination [9], whereas a decrease in AxD is indicative of axonal damage [10]. Grey matter abnormalities can also be detected with DTI analyses. Anisotropy in grey matter is much lower as the cellular membranes are not positioned along a preferential direction [11]. As such, MD, rather than FA, is an appropriate metric for cortical and subcortical grey matter, and can inform about the possible breakdown of barriers to diffusion, resulting in higher MD values. DTI can detect microscopic tissue abnormalities and might be able to detect these changes earlier than conventional structural MRI sequences. DTI data can be analysed using: i) tract based spatial statistics (TBSS) [12] (white matter) and voxel-based analyses (VBA; white and grey matter), which entail a whole-brain unbiased hypothesis-free approach, and/or ii) a probabilistic tractography approach which estimates the most likely fibre orientation at each voxel tracing a single tract (in contrast with streamline or deterministic tractography). Probabilistic tractography is a valuable and informative technique for testing *a priori* hypotheses.

Diffusion tensor MRI can detect alterations in white matter in the early stages of PD and has therefore proven useful as a biomarker in our understanding of PD [13]. Lewy neurites, a pathological hallmark of PD, might affect axons and dendrites in the brain and can be present from the early stages of PD [14]. Lewy neurites might not only appear before Lewy bodies but they could extend subsequently to develop Lewy bodies [15]. White matter damage could add to the PD pathophysiology by disrupting neuromodulator projection systems [16]. Indeed, white matter atrophy has been shown to have a greater influence on remote metabolism than grey matter alterations in Alzheimer's disease [17]. Additionally, altered patterns of functional connectivity correlate with axonal injury [18,19].

DTI analysis of white matter changes has been shown to successfully distinguish PD patients from healthy controls [13] and from Parkinsonian syndromes [20]. Several studies using an *a priori* region of interest (ROI) approach have confirmed the widespread nature of PD by reporting alterations in diffusivity in subcortical structures as well as an association between reduced FA in the substantia nigra (SN) pars compacta and increasing motor severity [13,21,22].

Although these interesting results provide insight into PD pathology, it is important to investigate the clinical diversity of this disorder in order to determine better treatment options and predictions of progression. Therefore, the aim of this review is to provide an overview of studies that have investigated the association between alterations in diffusivity and PD motor symptoms, such as tremor, bradykinesia and freezing of gait (FOG) as well as non-motor symptoms, including cognitive impairment, mood disturbances, visual hallucinations (VH), REM sleep behaviour disorder (RBD) and autonomic dysfunction. With the accumulated knowledge regarding the neural underpinnings of such symptoms, a more complete understanding of the underlying heterogeneity in PD will potentially result in improved symptom management and highlight the challenges faced and the potential areas of future research avenues where DTI may be beneficial.

## 2. Search strategy

A literature search was carried out between September and December 2015 using the search engines PubMed and Scopus. We used the criteria of English language and human studies with no time scale restrictions. The following key words were used in the literature searches: Parkinson's disease (MeSH); diffusion tensor imaging (MeSH), white matter; fractional anisotropy, mean diffusivity, tractography. In total, 243 articles were found and 91 articles were selected based on titles and abstracts. Articles were excluded when they were unrelated to the topic (e.g. focusing on Parkinsonism). These were further examined, and articles were excluded if they used DTI to investigate anatomical differences between PD and healthy controls (without relation to a specific PD symptom (28)), anatomical studies of the progression of PD (6), to inform deep brain surgery (16), or the influence of medication (1). Seven articles were added after scanning the reference lists of the selected articles. A total of 47 articles met the criteria and were included in this review (see Fig 1). An overview of these results is provided in Table 1.

## 3. Results

### 3.1. Motor correlates

Motor dysfunctions are typically the initial signs of PD that lead to diagnosis and the administration of medication. The severity and progression of these motor symptoms can be assessed by rating scales including the Unified Parkinson's Disease Rating Scale (UPDRS) [23], the Hoehn and Yahr clinical motor scale (H&Y) [24] and scale Schwab and England (SE) scale [25]. Lenfeldt and colleagues investigated the progression of alterations in diffusivity with motor deterioration [26]. They reported that worsening scores on the H&Y and SE scale correlated with an increase in MD in the putamen, globus pallidus and thalamus, while this correlation was not observed for the UPDRS [26]. However, these are measures of generalised motor functioning and more specific symptoms have

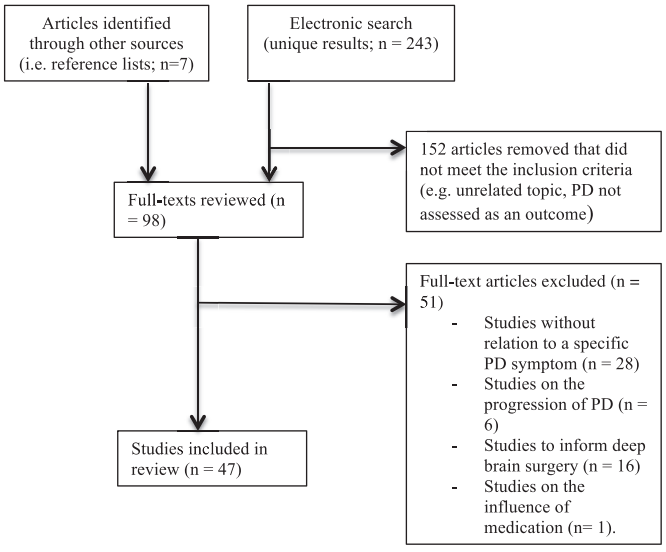


**Fig. 1.** Flowchart of search strategy.