Curr Neurol Neurosci Rep (2013) 13:400
DOI 10.1007/s11910-013-0400-1

NEUROIMAGING (DJ BROOKS, SECTION EDITOR)

The Evolving Role of Diffusion Magnetic Resonance Imaging in Movement Disorders

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Published online: 18 September 2013

Abstract Significant advances have allowed diffusion magnetic resonance imaging (MRI) to evolve into a powerful tool in the field of movement disorders that can be used to study disease states and connectivity between brain regions. Diffusion MRI is a promising potential biomarker for Parkinson's disease and other forms of parkinsonism, and may allow the distinction of different forms of parkinsonism. Techniques such as tractography have contributed to our current thinking regarding the pathophysiology of dystonia and possible mechanisms of penetrance. Diffusion MRI measures could potentially assist in monitoring disease progression in Huntington's disease, and in uncovering the nature of the processes and structures involved the development of essential tremor. The ability to represent structural connectivity in vivo also makes diffusion MRI an ideal adjunctive tool for the surgical treatment of movement disorders. We review recent studies using diffusion MRI in movement disorders research and present the current state of the science as well as future directions.

Keywords Diffusion magnetic resonance imaging · Diffusion tensor imaging · Movement disorders · Parkinson's disease · Parkinsonism · Dystonia · Huntington's disease · Essential tremor

This article is part of the Topical Collection on *Neuroimaging*

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Introduction

Although the clinical use of magnetic resonance imaging (MRI) has revolutionized the diagnosis and management of neurological diseases, its utility in neurodegenerative diseases was initially limited to the exclusion of other diagnoses [1]. During the past three decades, significant advances have been made in the field of MRI that have increased its value in the study of neurodegenerative diseases, and these advances have occurred in a time period that has largely paralleled the maturation of the field of movement disorders as a neurologic subspecialty [2]. During this time period, diffusion MRI has emerged as a powerful tool in the field of movement disorders, both in research settings and in clinical settings for evaluating white matter (WM), gray matter (GM), and connectivity.

Diffusion MRI makes use of the random translational motion of molecules that occurs secondary to thermal energy and is influenced by a variety of microstructural factors, including organelles, neurofibrils, and membranes. Diffusion can be relatively directional (anisotropic) or can occur relatively equally in all directions (isotropic). The degree and direction of diffusion can be used to produce accurate contrast images, and a tensor can be calculated to estimate diffusivity in three-dimensional space [3]. From this tensor one can calculate the mean-squared displacement of molecules (mean diffusivity, MD) and the degree to which diffusion is directional (fractional anisotropy, FA, which ranges between 0 and 1). Additional scalars such as axial diffusivity and radial diffusivity can be used to estimate the magnitude of diffusion parallel and perpendicular to the principal axis of diffusion, respectively. As underlying fiber orientation can be inferred from the orientation of the longest axis of the tensor, fiber orientation in neighboring pixels can be repeatedly reconstructed to produce streamlines to reconstruct WM pathways in a process called tractography, making diffusion MRI especially useful in the analysis of WM tracts in the brain. Figure 1 shows some of the major analytic

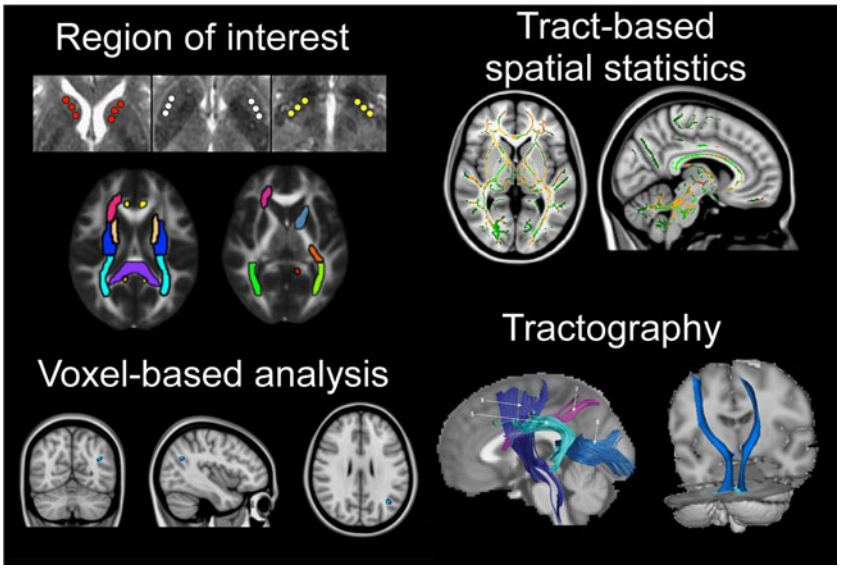

Fig. 1 Visual representations of the major diffusion magnetic resonance imaging analysis methods that are currently in use. *Clockwise from top left*: manual selection of regions of interest; automated tract-based spatial statistics aligns a combined fractional anisotropy map on a fractional anisotropy skeleton; tractography involves tract reconstruction based on the orientation and magnitude of diffusion, after which probabilities of connectivity can be analyzed; automated voxel-based analysis registers diffusion maps into a standard space. (Reproduced with permission from Prodoehl J et al. [4••], Zheng et al. [5], Saini et al. [6], Argyelan et al. [7], Wang et al. [8], and Zhang et al. [9])

approaches that have been used, and includes region of interest (ROI) analysis, voxel-based analysis, tract-based spatial statistics (TBSS), and tractography.

The interpretation of diffusion MRI measures, including the specific abnormalities that these proxy measures represent and the conclusions that can be drawn from abnormal values in disease, can be controversial [10]. Results can be highly dependent on the appropriateness of the methods of acquisition and data processing [11]. With these caveats in mind, changes in diffusion MRI scalars can reveal important information about the microstructural properties of underlying tissues. FA is higher in areas of highly coherent fiber structure and is affected by myelination. Reduced axial diffusivity has been correlated with axonal injury, whereas increased radial diffusivity has been suggested to represent incomplete or damaged myelination [11]. Reduced probabilities of tractography are believed to represent compromised WM fiber integrity or a reduction in fiber myelination or number [12].

Diffusion MRI can be used to study differences in tissue properties at specific locations in the brain between individuals or groups, to look for relationships between diffusion MRI properties and other variables (such as task performance), and to investigate connectivity between GM and WM or alternatively to attempt to reconstruct specific WM pathways [10]. Recently, diffusion MRI studies have made major contributions in a variety of subdisciplines within the field of movement disorders, with wide-ranging implications for pathophysiology, differential diagnosis, surgical treatment, and the search for possible biomarkers of disease.

In this review, we discuss the evolving role of diffusion MRI in the study of movement disorders, and we emphasize the most important publications in the field within the past year. As our scope is focused across all movement disorders, this work is not intended to be exhaustive (the reader is directed to disease-specific reviews of diffusion MRI for such purposes). We do, however, hope to present the state of the science regarding the role of diffusion MRI in movement disorders research, and we will discuss diffusion MRI in the context and framework of prior research within each field.

Diffusion MRI in Parkinsonism

The study of Parkinson's disease (PD) and parkinsonism has evolved into a multifaceted field that has many different avenues of approach, and many of these areas of interest are actively making use of diffusion MRI technology to answer research questions. Table 1 reviews the manner in which diffusion MRI has been used in the past year to study parkinsonism. In addition, we recommend a recent systematic review and meta-analysis [33••] that includes many studies that predate the studies described.

One of the most important and exciting aspects of PD research has been the quest for a biomarker of disease that can facilitate diagnosis, allow objective monitoring of disease progression, and evaluate the efficacy of potential therapeutic and neuroprotective therapies [34]. Diffusion MRI is among those modalities being investigated in this regard. Many

Table 1 Summary of recent studies in parkinsonism using diffusion magnetic resonance imaging (*dMRI*) (2012–2013)

Authors	Hypothesis/study intent/diseases of interest	dMRI methods[a]	No. of subjects	Regions studied with dMRI	Select dMRI findings
dMRI in PD					
Zhan et al. [13]	dMRI as a biomarker in PD; correlations with severity and subtype	ROI, TBSS	12 PD, 20 NC	Whole brain WM; ROI of cortical WM, IC, EC, SN, PUT, AN	TBSS: decreased FA in PD in precentral/postcentral gyri, posterior striatum, frontal WM and projections to the SMA, IC, EC, PUT, TH, and SN. ROI: confirmed most VBA differences in FA, no differences in MD after correction; SN FA negatively correlated with increased UPDRS score; spatial correlations between subregions demonstrated
Prakash et al. [14]	Investigated asymmetry of SN FA in early PD	ROI	11 PD, 12 NC	Caudal, middle, and rostral SN	No difference in FA and MD between PD and NC; asymmetric FA and MD in the rostral SN in both PD and NC; UPDRS score positively correlated with FA in the left rostral SN
Planetta et al. [15]	Analysis of specific thalamic tracts in early PD	ROI	20 PD, 20 NC	6 subregions in the TH	Decreased FA in WM tracts from the AN, VA, and DM; UPDRS score negatively correlated with FA in the AN
dMRI in genetic PD					
Agosta et al. [16]	Compared dMRI measures in PD and *GBA* mutation carriers with PD	TBSS, ROI (VBM)	14 PD, 15 *GBA*, 16 HC	Whole brain WM, ROI	No differences in voxelwise dMRI between *GBA*-PD and PD; post hoc ROI showed decreased FA in CC, olfactory tracts, cingulum, ECs, and left anterior IC; FA in the CC, EC, and olfactory tracts correlated with verbal fluency in patients
dMRI in PD—combining neuroimaging methods					
Du et al. 2012 [17]	Combined dMRI/R2* study of the SN	ROI	40 PD, 28 NC	6 rostral and caudal SN subregions (3 rostral and 3 caudal)	Decreased FA in PD caudal SN (early) greater than in rostral SN (late); increased RD in caudal SN in PD; increased R2* in rostral and caudal SN in PD; no correlations between FA and UPDRS score or disease duration; caudal R2* correlated with UPDRS score, disease duration, and LEDD
Sharman et al. [18]	Combined dMRI/resting state fMRI	ROI, tractography	36 PD, 45 NC	3 cortical and 5 subcortical; tractography from these connections	Decreased probability of connectivity in PD in SMC-PUT, SMC-TH, GP-TH, and SN-TH; decreased functional connectivity in GP-PUT, GP-TH, SMC-TH, and SN-GP; increased functional connectivity in associative-PUT, limbic-TH, and PUT-TH. No correlation with UPDRS score, disease duration, or H&Y. dMRI and fMRI decreased connectivity overlapped in PD in TH to SMC, GP, and SN
dMRI in PD—nonmotor and specific symptoms					
Carlesimo et al. [19]	Multimodal (dMRI/VBM) examining cognitive performance and MRI	ROI and VBA (VBM)	25 PD, 25 HC	Hippocampus MD	Increased MD in PD in the hippocampus; increased hippocampal MD associated with reduced memory performance in PD patients

Table 1 (continued)

Authors	Hypothesis/study intent/diseases of interest	dMRI methods[a]	No. of subjects	Regions studied with dMRI	Select dMRI findings
Rae et al. [20]	Compared two different methods in the study of cognitive measures	TBSS, VBA	14 PD, 15 HC	Whole brain WM	TBSS: decreased FA and increased MD throughout cerebral WM; decreased FA in the right splenium of CC correlated with UPDRS score; decreased FA and increased MD in anterior CC and prefrontal WM correlated with cognitive scores. VBA: similar WM pattern differences only at a more liberal significance threshold
Deng et al. [21]	dMRI analysis of WM abnormalities and cognitive impairment in PD, PD-MCI, and PD-D	ROI	64 PD, 21 NC	Cortical WM, cingulate bundles, CC, midbrain CST, IC CST, SLF	Decreased FA in left frontal, right temporal, and bilateral anterior cingulate bundles in PD-MCI and PD-D vs NC; decreased FA in the left occipital and left anterior cingulate bundles in cognitively normal PD vs NC; decreased FA in the left anterior cingulate bundle in PD-D vs other groups and in the left occipital WM vs cognitively normal PD; some WM abnormalities correlated with cognitive dysfunction; no differences in FA in the CST in any group vs NC
Surdhar et al. [22]	Examined dMRI measures in PD with or without depression and NC	Tractography (volumetric)	6 PD, 6 PD-dep, 6 NC	CC and bilateral uncinate fasciculus	No dMRI differences between groups (smaller amygdala volumes in PD-dep vs NC)
Zheng et al. [5]	Evaluated retrospectively the relationship between dMRI measures and cognitive performance	ROI, VBA	16 PD	40 ROIs encompassing most of the cortical and subcortical WM	Cognitive performance in distinct domains correlated with dMRI in different areas; dMRI measures correlated with executive function and language mostly in the frontal WM tracts, attention diffusely in WM, and memory in fornix and anterior cingulate cortex; no correlation was found between dMRI measures and visuospatial performance. Post hoc VBA confirmed most correlations
Gallagher et al. [23]	Investigated the relationship between dMRI and cognition (especially executive function)	TBSS	15 PD, 15 NC	Frontal subcortical WM	Decreased FA in PD vs NC in portions of the anterior limb of the IC and anterior CR, body of CC, inferior ILF and inferior fronto-occipital fasciculus, uncinate fasciculus, and deep cerebellar WM. Increased MD in PD patients in portions of most tracts. FA correlated with executive function in PD but not in NC. Both decreased FA and increased MD correlated with increased susceptibility to interference in the Stroop task
Kamagata et al. [24]	Examined the relationship between dMRI measures and cognitive performance	TBSS/tractography	20 PD, 20 PD-D, 20 NC	Whole brain WM/genu of CC	No difference between PD and NC in FA and MD; decreased FA and increased MD in major WM tracts of PD-D vs NC; decreased FA and increased MD in WM adjacent to prefrontal area and genu of CC in PD-D vs PD; FA correlated with MMSE score in combined but not separate PD groups; no correlation between dMRI and disease duration, H&Y, or levodopa dose
Ford et al. [25]	Evaluated dMRI measures in PD with or without RBD by questionnaire	TBSS (VBM)	124 PD	Whole brain WM	No difference in FA or MD when adjusted for multiple comparisons based on the presence of RBD

Table 1 (continued)

Authors	Hypothesis/study intent/diseases of interest	dMRI methods[a]	No. of subjects	Regions studied with dMRI	Select dMRI findings
dMRI in the differential diagnosis of parkinsonian syndromes					
Tsukamoto et al. [26]	MSA-C, MSA-P, PSP, PD, NC (retrospective)	ROI	5 MSA-P, 20 MSA-C, 20 PSP, 17 PD, 18 NC	CN, TH, PUT, GP, midbrain, pons, SCP, MCP, DEN, cerebellar WM	In MSA: increased MD in the pons, MCP, cerebellar WM, and DEN vs the PSP and PD and NC; increased MD in the posterior PUT vs PSP and NC. MD in MSA-P greater than MD in MSA-C in PUT, GP, and CN; MD in MSA-C greater than MD in MSA-P in pons, MCP, an cerebellar WM. In PSP: increased MD in GP and midbrain vs MSA and PD and NC; increased MD in CN and SCP vs MSA and NC. In PD: no difference in any region vs NC
Agosta et al. [27]	PSP-RS, PSP-P, NC (retrospective)	TBSS, ROI (VBM)	21 PSP-RS, 16 PSP-P, 42 NC	Whole brain WM (TBSS), infratentorial and supratentorial WM, TH (ROI)	No corrected difference between PSP-P and PSP-RS
Haller 2012 [28]	PD and AP (retrospective)	TBSS	17 PD, 23 AP	Whole brain WM	Increased FA and decreased RD and MD in multiple brain areas (especially right frontal WM) on TBSS; correctly classified PD and AP up to 97 %
Prodoehl et al. [4••]	PD, MSA-P, PSP, ET, NC	ROI	15 PD, 14 MSA-P, 12 PSP, 14 ET, 17 NC	CN, PUT, GP, SN, RN, SCP, MCP, ICP, DN	AUC and sensitivity/specificity in distinguishing PD vs AP 0.99 (sensitivity 90 %; specificity 100 %), PD vs ET 0.96 (sensitivity 92 %; specificity 87 %), PD vs MSA-P 0.99 (sensitivity 94 %; specificity 100 %); PD vs PSP 0.96 (sensitivity 87 %; specificity 100 %), and PSP vs MSA-P 0.97 (sensitivity 90 %; specificity 100 %)
Nair et al. [29]	Decision tree analysis using conventional/volumetric and dMRI in PD and MSA	ROI (volumetric)	26 PD, 13 MSA	PUT, SN, pons, MCP, CBM	Significant dMRI measures (included in decision tree): rostral SN compacta FA, MCP FA, cerebellar FA, and MCP MD. Decision tree diagnostic accuracy: sensitivity 92 %; specificity 96 %; PPV 0.92; NPV 0.96
dMRI in PSP					
Whitwell et al. [30]	Examined the association between clinical scale and MRI	ROI (linear and volumetric)	22 PSP	SCP	SCP FA correlated with clinical scores; no correlations between rates of change in dMRI measures and clinical scores
Saini et al. [31]	Evaluated dMRI measures in PSP-RS and PSP-P	TBSS (VBM)	13 PSP-RS, 11 PSP-P, 26 NC	Whole brain WM	Decreased FA, increased MD, increased AD, and increased RD in various WM areas in PSP vs NC; decreased FA in bilateral frontal WM and CC in PSP-RS vs PSP-P; decreased AD in right frontal region in PSP-RS vs PSP-P. No correlation between dMRI and UPDRS score
dMRI in MSA					
Lu et al. 2013 [32]	Combined network analysis and dMRI in MSA-C	Tractography	19 MSA-C, 19 NC	Whole brain fiber tracking	Small-world architecture/network strength/ efficiency (more pronounced in cerebellar vs cerebral network) was reduced in WM networks of MSA-C vs controls, with abnormalities correlating with clinical scores

Table 1 (continued)

Authors	Hypothesis/study intent/diseases of interest	dMRI methods[a]	No. of subjects	Regions studied with dMRI	Select dMRI findings
dMRI in other parkinsonian syndromes					
Wang et al. [8]	Investigated dMRI measures in VP	Global analysis, VBA, tractography	12 VP, 12 NC	Whole brain WM	Globally decreased FA and increased MD in VP vs NC; decreased FA on VBA in left TH, right frontal subcortical WM, and left anterior IC vs NC; increased MD on VBA in frontal subcortical WM in VP vs NC; FA and MD in the regions mentioned above correlated with PIGD clinical scores in VP patients; FA in fiber tracts in the anterior IC negatively correlated with PIGD clinical scores; MD in fiber tracts in the anterior CC correlated with PIGD clinical scores

AD axial diffusivity, *AL* ansa lenticularis, *AN* anterior nucleus, *AP* atypical parkinsonism, *AUC* area under the curve, *CBT* corticobulbar tract, *CC* corpus callosum, *CMB* cerebellum, *CN* caudate nucleus, *CR* corona radiata, *CST* corticospinal tract, *DM* dorsomedial nucleus, *DEN* cerebellar dentate nucleus, *EC* external capsule, *ET* essential tremor, *FA* fractional anisotropy, *fMRI* functional magnetic resonance imaging, *GP* globus pallidus, *HC* healthy controls, *H&Y* Hohn and Yahr scale score, *IC* internal capsule, *ICP* inferior cerebellar peduncle, *ILF* inferior longitudinal fasciculus, *LEDD* levodopa-equivalent daily dose, *MCP* middle cerebellar peduncle, *MD* mean diffusivity (apparent diffusion coefficient), *MMSE* mini mental state examination, *MSA* multiple system atrophy, *MSA-C* multiple system atrophy—cerebellar subtype, *MSA-P* multiple system atrophy—parkinsonism subtype, *NC* normal controls, *NPV* negative predictive value, *PD* Parkinson's disease, *PD-D* Parkinson's disease with dementia, *PD-dep* Parkinson's disease with depression, *PD-MCI* Parkinson's disease with mild cognitive impairment, *PIGD* modified postural instability gait difficulty subscore of the Unified Parkinson's Disease Rating Scale, *PPV* positive predictive value, *PSP* progressive supranuclear palsy, *PSP-P* progressive supranuclear palsy—parkinsonism subtype, *PSP-RS* progressive supranuclear palsy—Richardson syndrome subtype, *PUT* putamen, *R2** 1/T2* relaxation rate, *RBD* REM sleep behavior disorder, *RD* radial diffusivity, *RN* red nucleus, *ROI* region of interest, *SCP* superior cerebellar peduncle, *SLF* superior longitudinal fasciculus, *SMA* supplementary motor area, *SMC* sensorimotor cortex, *SN* substantial nigra, *TBSS* tract-based spatial statistics, *TH* thalamus, *UPDRS* Unified Parkinson's Disease Rating Scale, *VA* ventral anterior nucleus, *VBA* voxel-based analysis, *VBM* voxel-based morphometry, *VP* vascular parkinsonism, *WM* white matter

[a] *Parentheses* indicate non-dMRI methods

different GM and WM structures have been investigated using diffusion MRI, and abnormalities in a variety of areas have been reported [33••]. However, given what we know about the pathogenesis of PD, it is not surprising that the substantia nigra (SN) has been the most commonly studied area. Although not all studies have found a reduction in FA in the SN [35, 36], a recent meta-analysis [33••] found a significant pooled effect size for reduction of FA in the SN across studies. One study achieved 100 % sensitivity and specificity in distinguishing early medication naive patients from controls in the ventral SN [37]. A recent follow-up study [38] demonstrated that, in normal aging, FA decreased and radial diffusivity increased in the dorsal SN but not in the ventral SN, again consistent with earlier histopathology studies. These studies further the suggestion put forth by animal models that diffusion MRI may act as a proxy for dopaminergic degeneration in the SN [39]. They also highlight the critical importance of where ROIs are defined in obtaining meaningful results [38] as well as the possible potential of diffusion MRI of the SN as a biomarker for PD [40].

Diffusion MRI is also being investigated in combination with other neuroimaging modalities. Diffusion MRI measures have been combined with inverse T2* (R2*) [41], another MRI measure that has been shown to be increased in PD patients and is thought to correlate with iron concentration, to see if the combined measures improve separation between PD and controls [42••]. Mean FA was reduced and R2* was increased in the SN of patients compared with controls, with improved discrimination between groups when the modalities were combined. Further, there was no correlation between the two measures, which the authors of the study suggested could indicate that these measures could reflect independent ongoing pathological processes in the SN. A follow-up study from the same group [17] expanded these earlier findings and showed that the decrease in FA in the SN in PD was significant early in the caudal region of the SN, whereas in the rostral SN the decrease in FA was only significant in late stages of the disease. R2* in the caudal SN also correlated with clinical scores, disease duration, and levodopa dosage.

Although the commonest cause of parkinsonism is PD, the syndromes of multiple system atrophy, progressive supranuclear palsy (PSP), and corticobasal degeneration, as well as a variety of other disorders, can also result in parkinsonism, and the clinical differentiation between these diseases can sometimes be difficult [43]. In addition to detecting PD, the ability of diffusion MRI to differentiate PD from atypical parkinsonism and the atypical parkinsonism disorders from each other is also being investigated. A recent study [4••] used a multitarget approach based on prior diffusion MRI studies and areas of the brain that are known to be affected by specific diseases in a population of patients with PD, multiple system atrophy, parkinsonism subtype (MSA-P), PSP, and essential tremor (ET) and healthy controls. Receiver operating characteristic analyses demonstrated an area under the curve of 0.99 (sensitivity 90 %, specificity 100 %) in distinguishing PD from atypical parkinsonism. Areas under the curves of 0.99, 0.96, and 0.97 were achieved for distinguishing PD versus MSA-P, PD versus PSP, and MSA-P versus PSP, respectively, with unique diffusion MRI measures and subcortical ROIs for each group. The study also found excellent separation between PD and ET. Given the recent finding of increased FA in the somatosensory cortex in PD [13], future analyses that include a cortical ROI may further improve classification.

In summary, diffusion MRI in the SN and in other areas of the brain is a promising potential biomarker for PD and other forms of parkinsonism. It may also provide a powerful method to distinguish PD from atypical parkinsonism and the atypical parkinsonism disorders from each other, and can possibly answer questions, such as the temporal order of structural abnormalities that occur in parkinsonism, that cannot be answered by neuropathology studies. Diffusion-related measures have been correlated with motor dysfunction and cognitive performance in domains such as executive function, language, and attention [5]. Diffusion MRI can be useful to evaluate genetic forms of disease, to study specific symptoms, and to complement other imaging and nonimaging modalities to better understand the underlying pathophysiology and network-level dysfunction.

Diffusion MRI in Other Movement Disorders

As in parkinsonism, diffusion MRI has been used to investigate the structural and network underpinnings of other movement disorders. Table 2 describes the articles published in the last year involving diffusion MRI in the study of dystonia, Huntington's disease (HD), and ET. Additionally, the use of diffusion MRI techniques in movement disorders surgery is also described.

Dystonia

Although dystonia was traditionally considered a disease of the basal ganglia, the pathophysiology of dystonia is now thought to involve multiple levels of the neuraxis, with a loss of motor inhibition as well as disordered sensory processing, neuroplasticity, and somatotopic organization [43]. Neuroimaging studies have been crucial in the development of a broader network model of dystonia pathophysiology that includes the multiple brain regions that are likely involved in its development. Structural abnormalities giving rise to secondary dystonia have been demonstrated throughout the brain, and the results of nuclear imaging studies, functional

Table 2 Summary of recent studies in movement disorders other than parkinsonism using dMRI (2012–2013)

Authors	Hypothesis/study intent	dMRI methods[a]	No of subjects	Regions studied with dMRI	Select dMRI findings
dMRI in Dys					
Horovitz et al. [44]	Combined VBM/dMRI study of blepharospasm	TBSS (VBM)	14 Dys, 14 NC	Whole brain, CBT	No significant difference in dMRI between groups
Van der Meer et al. [45]	dMRI study of M-D	ROI (WM VBM)	16 M-D, 18 NC	Cortical, BG, brainstem, CBM	Increased FA in the right subthalamic brainstem and thalamocortical WM of M-D vs NC; decreased MD in the WM underlying the SMC and near the subthalamic areas and right thalamus in M-D vs. NC
Blood et al. [12]	Investigated dMRI measures in *DYT1* -negative cervical dystonia patients	Tractography	12 Dys, 12 NC	Bilateral pallidum and AL for tractography	Decreased FA in the WM near the left SCP and increased FA near and in the left SN; reduced probability of connectivity in Dys vs NC in the left AL projections to the ipsilateral brainstem; increased probability of connectivity in Dys vs NC in connections between the pallidum and brainstem
Cheng et al. [46]	Evaluated dMRI measures in *DYT6* dystonia and subcellular distribution of THAP1	ROI	6 Dys, 6 NC	SMC, SLF, cingulate cortex, CC, CST, IC, SCP, MCP, cerebellar WM	Decreased FA in the SMC area in Dys vs NC; increased MD in the right SLF and right supracapsular CST
dMRI in HD					
Delmaire et al. [47]	Evaluated relationship between dMRI measures and clinical measures in early HD patients from the TRACK-HD study	VBA	27 HD, 24 NC	SVC: BG, IC, EC, centrum ovale, cingulate bundle, SLF, and CC	Detailed list of motor and cognitive tasks correlated with abnormal dMRI (increased MD and decreased FA) measures in multiple distinct areas of GM and WM in the brain
Di Paola et al. [48]	dMRI of CC in preclinical and early HD	TBSS	17 PC-HD, 17 HD, 17 NC	WM of CC	Decreased FA and increased AD in the isthmus of CC in PC-HD vs NC; decreased FA, increased AD, and increased RD in HD vs NC; decreased FA, increased AD, and increased RD in CC of HD vs PC-HD
Van Camp et al. [49]	Combined histopathology and dMRI study of a quinolinic acid rat model of HD	VBA, ROI	9 Quin, 6 sham, 5 NC	IC, EC, 3 subregions of CN/PUT	dMRI discriminated Quin rats with or without cortical lesions; dMRI was more sensitive than histology in detecting microstructural changes in the caudate, putamen, and IC/EC in cortically lesioned rats
Dumas et al. [50]	Investigated dMRI in HD and PC-HD as part of the TRACK-HD study	ROI, tractography	16 HD, 27 PC-HD, 28 NC	CN, TH, CC, and WM pathways	Increased MD in the CC and WM fibers of the SMC in PC-HD vs NC; no differences in FA between PC-MD and NC; increased MD in CC, CN, and WM tracts of CC, TH, SMC, and prefrontal regions in HD vs NC; decreased FA in the CC and WM tracts of the CC and motor and prefrontal cortices; MD in multiple regions correlated with motor/cognitive tasks, as well as the probability of onset and burden of disease

Table 2 (continued)

Authors	Hypothesis/study intent	dMRI methods[a]	No of subjects	Regions studied with dMRI	Select dMRI findings
Georgiou-Karistianis et al. [51]	Quadratic discriminant analysis study using combined dMRI and volumetric data in PC-HD and HD	ROI	33 HD, 35 PC-HD, 36 NC	CN, PUT, pallidum, nucleus accumbens, TH	Group differences in FA in CN, PUT, and right pallidum and accumbens, and MD in CN, PUT, pallidum, and accumbens; the highest level of discriminative accuracy (78 %) was attained when clinical motor scores were added to dMRI and volumetric measures, with MD being the most accurate measure
Matsui et al. [52]	Examined dMRI measures in subregions of the prefrontal cortex in relation to measures of disease burden in PC-HD	ROI	53 PC-HD, 34 NC	Prefrontal cortex	Differences were found for RD and MD, but not FA or AD, in inferior and lateral subregions of the prefrontal cortex between groups. Within presymptomatic patients, abnormalities largely followed disease burden as defined by the age–CAG length calculation
Marrakchi-Kacem et al. [53]	Investigated corticostriatal connectivity using dMRI	TBSS, HARDI, Q-BI	15 HD, 15 NC	Corticostriatal connections	Reduced inferred connectivity from CN to parietal and frontal lobes, and from the PUT to the associative temporal, dorsal, and ventral frontal, parietal, and SMC cortices; the percentage difference between groups in connectivity between areas of the striatum and cortex was reported; relative preservation of limbic connections; reduced inferred connectivity in primary sensory vs motor connections
dMRI in ET					
Saini et al. [6]	Studied dMRI measures of WM in ET patients	TBSS, ROI	22 ET, 17 NC	ROI :CC, SCP, MCP, ICP, CST, anterior limb of IC	TBSS: increased MD in the right hemispheric WM and increased AD throughout the bilateral cortical WM, IC, EC, TH, brainstem, and CBM; no differences in FA between ET patients and NC. ROI analysis: decreased FA in the left SCP and right CST and increased MD in the right anterior limb of the IC and left CST; increased AD in the bilateral SCP and right ICP, CST, and anterior limb of IC. No correlations were found between tremor severity or disease duration and dMRI measures
Buijink et al. [54]	Studied dMRI measures in FCMTE compared with ET and NC	Tractography, ROI	7 FCMTE, 8 ET, 5 NC	CBM	Mean FA was decreased in FCMTE vs ET patients and NC, but FA was not different between ET patients and NC

See Table 1 for explanations of abbreviations other than those explained below.

BG basal ganglia, *Dys* dystonia, *FCMTE* familial cortical myoclonic tremor with epilepsy, GM gray matter, *HARDI* high-angular resolution diffusion-weighted imaging, *HD* Huntington's disease, *M-D* myoclonus–dystonia, *PC-HD* preclinical Huntington's disease, *Q-BI* Q-ball imaging, *Quin* rats infused with quinolinic acid, *SVC* small volume correction, *THAP1* THAP-domain-containing protein 1

[a] *Parentheses* indicate non-dMRI methods

MRI findings of brain activation patterns, and voxel-based morphometry studies of regional GM volumes have differed depending on the type of dystonia studied (for extensive reviews including diffusion MRI studies, see Neychev et al. [55•] and Zoons et al. [56•]).

Diffusion MRI has been useful in evaluating WM connectivity and integrity in hereditary and idiopathic forms of dystonia. In young-onset hereditary dystonia, the evolving notion of the disease as a neurodevelopmental disorder involving pathways of the basal ganglia, cortex, and cerebellum has been heavily influenced by diffusion MRI studies [57]. The earliest diffusion MRI study in *DYT1* carriers (manifesting and nonmanifesting carriers) found decreases in FA in the WM underlying the sensorimotor cortex compared with age-matched controls [58]. Subsequent studies [59] in *DYT1* and *DYT6* patients confirmed this finding and expanded the reduced FA findings to the dorsal pontine brainstem. One of the most promising studies described to date [7] used probabilistic tractography to show reduced probability of connectivity in the proximal cerebellothalamic pathway near the dentate nucleus in mutation carriers, with penetrance regulated by an additional connectivity abnormality in the subrolandic WM of the thalamocortical projections. The authors of the study hypothesized that reduced penetrance in asymptomatic gene carriers may be due to a protective effect of the thalamocortical pathway disruption in altering the effect of the more caudal abnormality. This report has been further strengthened by abnormalities found in thalamocortical and cerebellocortical pathways in torsin A *DYT1* knock-in mice [60•]. In addition to genetic dystonia, abnormalities in diffusion MRI measures in focal dystonias such as torticollis [61–64], writer's cramp [65], and spasmodic dysphonia [66] have also been described in the WM connections of the pathways of the basal ganglia, cortex, and cerebellum, suggesting an important role of these areas in gene-negative primary dystonias.

In addition to the interest in the role of cerebellothalamocortical connections in hereditary dystonia described above [7], recent interest has also focused on collateralized pallidal connections to the thalamus and brainstem and hemispheric differences in diffusion MRI findings in gene-negative primary focal dystonias [12, 67, 68]. In a 2006 study, Blood et al. [68] compared patients with primary focal dystonia and healthy controls and demonstrated increased hemispheric asymmetry in FA in the WM fibers between the pallidum/putamen and the thalamus. Further, this asymmetry was no longer different from that in controls after botulinum toxin injections. Blood [67] hypothesized that these differences might represent abnormal functioning of a distributed (and possibly lateralized) postural control system that could result in dystonia. Recently, Blood et al. [12] used diffusion MRI measures (FA and MD) and probabilistic tractography to further investigate pallidal connections to the brainstem in 12 *DYT1*-negative patients with cervical dystonia and 12 healthy matched controls. Focusing on the bilateral pallidum and ansa lenticularis as their seed ROI, they found reduced FA in the WM near the left superior cerebellar peduncle and increased FA near the left SN. A reduced probability of connectivity was shown in the left ansa lenticularis projections to the ipsilateral brainstem in dystonia patients compared with controls, with the greatest difference demonstrated in the area between the ansa lenticularis and the region of the red nucleus and SN. In the right hemisphere, increased probability of connectivity was found in the connections between the pallidum and the brainstem.

In summary, diffusion MRI (and especially tractography) has made major contributions to our current thinking regarding the pathophysiology of dystonia, and has helped to expand our focus beyond the basal ganglia to include related connections to and between the brainstem, cerebellum, and cortex. These studies have proposed models to explain reduced penetrance, directed attention to possible hemispheric differences in the disease, and fueled hypotheses incorporating dysfunction of postural control in models of dystonia. Examination of the similarities and differences between diffusion MRI abnormalities in the various forms of dystonia may shed light on a shared pathophysiology as well as how dystonia can be focal in presentation [56•]. Diffusion MRI studies in patients treated with botulinum toxin might elucidate the manner in which the toxin exerts a central effect though motor afferent feedback, and may suggest new treatment modalities. Expanding diffusion MRI analyses to include dystonia-plus syndromes and secondary dystonias may further elucidate characteristics that are shared between and that differentiate the various dystonia subtypes.

Huntington's Disease

HD is a neurodegenerative disorder that produces progressive degeneration and volume loss of the striatum and other GM and WM structures in a process that begins well before the onset of clinical symptoms. The symptoms of HD are progressive and include motor dysfunction, cognitive decline, and neuropsychiatric disturbances [43].

As would be expected from neuropathology data, conventional and volumetric brain imaging have shown reductions in the volumes of the striatum and putamen in symptomatic and presymptomatic HD, as well as cortical GM loss and whole brain atrophy in some studies [69]. These findings of volume loss in the striatum have been confirmed in large multicenter studies such as PREDICT-HD [70] and TRACK-HD [71], and caudate volume abnormalities have been correlated with cognitive function, repeat length, and age of manifestation of clinical symptoms [51]. However, not all T1-weighted structural imaging studies have yielded consistent results [72].

A number of studies have investigated diffusion characteristics in symptomatic and preclinical HD [73–82], demonstrating microstructural changes in multiple areas of the brain (for a

comprehensive review, see Esmaeilzadeh et al. [83•]). Some caution has, however, been raised that the changes in FA reported in some of these studies might be due to misregistration of images due to neurodegenerative changes [72], and diffusion MRI findings have also not been consistent across all studies [50]. Among the studies that have looked at diffusion MRI measures longitudinally, some studies [84] have found worsening abnormalities in diffusion MRI measures over time, whereas some have not [85]. Many of the diffusion MRI scalar abnormalities have been shown to correlate with clinical features [84–86]. Unified Huntington's Disease Rating Scale score has been shown to correlate with MD in the corpus callosum in an area demonstrated by tractography to connect to premotor and supplementary motor areas, and radial diffusivity in areas of the corpus callosum projecting to the prefrontal cortices has also been demonstrated to correlate with cognition [82]. In tractography studies of presymptomatic HD patients, a reduction of streamlines directed to the caudate was demonstrated, with the degree of impairment of voluntary saccades correlating with fewer fiber tracking streamlines between the caudate and the frontal cortex [87].

The studies using diffusion MRI techniques to study HD published within the past year have spanned human and animal models of the disease, and have included established as well as new diffusion MRI techniques in a variety of different areas of the brain. The first diffusion MRI study [49] of quinolinic acid induced excitotoxicity, a commonly used lesioning model of HD in rats [88], found that diffusion MRI discriminated between rats that developed cortical lesions from those that did not secondary to lesioning. In addition, diffusion MRI measures were more sensitive than histology in detecting microstructural changes in the caudate, putamen, and internal and external capsules, complementing data from the same group [89], who presented the first diffusion MRI data in a transgenic mouse model of HD.

One study [51] combined motor and cognitive measures with diffusion MRI and volumetric analysis in patients with and without symptoms and healthy controls and found the highest level of discriminative accuracy (78 %) was attained when motor and cognitive scores were added to neuroimaging measures. This level of accuracy was slightly higher than that (76 %) found using machine learning approaches and voxel-based volumetric analysis [90]. Another study [47] found that motor and cognitive tasks were correlated with abnormal diffusion MRI measures in multiple areas of GM and WM, suggesting that dysfunction in extrastriatal areas of the brain is related to clinical manifestations in a region-specific manner. Dumas et al. [50] found more widespread diffusion MRI abnormalities in early-manifesting HD compared with premanifesting HD, with correlations between diffusion MRI and clinical measures. A study [52] that examined diffusion MRI measures in the subregions of the prefrontal cortex in presymptomatic HD patients and controls found that diffusion MRI abnormalities largely followed "disease burden" as defined by the age–CAG length calculation, and a recent tractography study [53] examined symptomatic HD patients and healthy controls and developed detailed maps and percentages of reduced inferred connectivity from the striatum to the cortex.

In summary, diffusion MRI has the potential to contribute to the study of HD on a number of different fronts. Although genetic testing generally negates the need for a biomarker for diagnosis, a quantitative method of monitoring disease progression would be useful should more effective treatment options become available [69, 91]. It could potentially allow objective investigation into the relationship between specific clinical findings and microstructural changes and function as a means of predicting the time to symptom onset and monitoring disease progression [51]. Combining diffusion MRI measures with other neuroimaging measures, as well as clinical data, might be better than diffusion MRI alone. As the sequence of pathogenic events that occur in HD remain poorly understood [92], specific measures of diffusion MRI may be useful as in vivo representations of these processes, and are being investigated as such [84]. In addition, diffusion MRI studies in animal models of disease may also be useful in developing novel connectivity-based markers of HD-related pathological processes [92].

Essential Tremor

Compared with other movement disorders, relatively few studies investigating ET with diffusion MRI have been published. The first report that used diffusion-weighted imaging to study patients with ET used an ROI approach and found no differences in MD values between ET patients and normal controls in the cerebellum, basal ganglia, and frontal WM [93]. Subsequent studies using diffusion MRI found reduced FA in areas of the cerebellum, pons, and the WM of the midbrain and cerebral cortex in a voxel-wise analysis [94] and reduced FA in the dentate nucleus and the superior cerebellar peduncle (along with increased MD), with no overlap in FA values between patients and controls in the dentate nucleus [95]. A 2011 study found an increase in MD in the red nucleus but no differences in FA among the basal ganglia, thalamus, red nucleus, and SN of ET patients compared with controls [96]. Another group the same year [97] showed increased MD in the bilateral inferior cerebellar peduncle, adjacent to the left parieto-occipital sulcus, and in bilateral frontal and parietal WM, with decreased FA in the right inferior cerebellar peduncle and a correlation between tremor scores and MD values in some WM regions in patients with ET.

Two articles have reported use of diffusion MRI techniques in the study of ET within the past year [6, 54]. The first of these [6] used TBSS and ROI analysis of specific WM tracts

in 22 patients with definite or probable ET and 17 normal matched controls. TBSS showed increased asymmetric MD changes and increased axial diffusivity throughout the bilateral cortical WM, potentially suggesting axonal damage. No correlations were found between diffusion MRI measures and tremor severity or disease duration. The most recent work [54] to analyze diffusion MRI measures in ET did so as part of a study to evaluate cerebellar WM in familial cortical myoclonic tremor with epilepsy, showing that mean FA was significantly decreased in patients with familial cortical myoclonic tremor with epilepsy compared with the other groups, but FA was not different between ET patients and controls.

In summary, the body of diffusion MRI literature in ET is not as developed as in other movement disorders, which may be due to both a smaller study number and the nature of the disease. The syndrome of ET itself is likely more heterogeneous [98], and the abnormalities present in ET might be subtler and more difficult to identify. Despite these challenges, a number of useful observations have been made to guide future research. Studies that focus on the cerebellum might be best approached with ROI analysis, as involvement of these regions is guided by strong hypotheses and data from the greater literature and thus they may produce more robust results than voxelwise comparisons [97]. Laterality of tremor and handedness may also be important factors, and should be carefully considered in future studies [6], and certainly larger sample sizes are needed. Although some the findings of some reports have been interpreted as supporting the notion of ET as a neurodegenerative disease [94], it is important to consider that microstructural WM abnormalities suggested by diffusion MRI do not differentiate between changes due to a neurodegenerative process and those that might occur secondary to ongoing abnormal oscillatory activity in a tremorogenic network. Further correlation with neuropathology data might shed light on the underlying microstructural changes that the diffusion MRI abnormalities represent in the ET brain.

Diffusion MRI in Movement Disorders Surgery

The ability to represent structural connectivity in vivo makes diffusion MRI an ideal adjunctive tool for deep brain stimulation (DBS) surgery for movement disorders, and diffusion MRI will likely be increasingly used in the planning of DBS surgical procedures in the future [11]. As DBS technology advances, the ability to target specific subregions of GM in a given individual for stimulation will be important in optimizing clinical benefit and minimizing side effects [99, 100]. Diffusion MRI is already being used to investigate interindividual variability in DBS targeting [101] in patient-specific partitioning of thalamic areas on the basis of the probability of connectivity with motor cortices [102], a concept that has been validated [103] and for which refinement of methods is continuously being sought [104]. Further, as WM tracts may sometimes be more ideal targets for neurostimulation than GM structures, diffusion MRI may allow direct targeting of WM pathways [105]. Tractography studies guided by effective DBS placement can be used as a starting point to elucidate network connectivity such as in tremor [106•].

Conclusions

Diffusion MRI has evolved into an invaluable tool in the study of movement disorders, and is used in studies of disease states, connectivity between brain regions, and brain development [3]. In a variety of disorders, diffusion MRI is showing promise as a biomarker of disease, which is encouraging since MRI is noninvasive, is widely available, and generates reproducible data that can be analyzed offline if required [107]. However, in the absence of standardized techniques, variability in methods of acquisition, image processing, and analysis can affect the reproducibility of findings. The sensitivity and specificity of potential diffusion MRI biomarkers may vary throughout the course of the disease [74], and the future role of diffusion MRI as a biomarker could be as part of a battery of tests. Future studies will help to determine the degree to which diffusion MRI measures can serve as a proxy for disease presence and progression in movement disorders.

Acknowledgments Christopher W. Hess has received fellowship funding from the Parkinson's Disease Foundation. Michael S. Okun has received research grants from the National Institutes of Health, the National Parkinson Foundation, the Michael J. Fox Foundation, the Parkinson Alliance, the Smallwood Foundation, the Bachmann-Strauss Dystonia & Parkinson Foundation, the Tourette Syndrome Association, the Dystonia Medical Research Foundation, and the University of Florida Foundation. David E. Vaillancourt has received grant support from the National Institutes of Health, the Michael J. Fox Foundation, the Bachmann-Strauss Dystonia & Parkinson Foundation, and Tyler's Hope for a Dystonia Cure.

Compliance with Ethics Guidelines

Conflict of Interest Christopher W. Hess, Edward Ofori, and Umer Akbar declare that they have no conflict of interest.

Michael S. Okun serves as a consultant for the National Parkinson Foundation. He has received royalties for publications with Demos, Manson, Amazon, and Cambridge University Press (movement disorders books). He has participated in continuing medical education activities on movement disorders sponsored by the University of South Florida's continuing medical education office, PeerView, and Vanderbilt University. The institution and not Michael Okun receives grants from Medtronic and ANS/St. Jude, and Michael Okun has no financial interest in these grants. He has participated as a site principal investigator and/or co-investigator for several National Institutes of Health, foundation, and industry sponsored trials over the years, but has not received honoraria.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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