

## The Role of High-Field Magnetic Resonance Imaging in Parkinsonian Disorders: Pushing the Boundaries Forward

Stéphane Lehericy, MD, PhD,<sup>1\*</sup> David E. Vaillancourt, PhD,<sup>2</sup> Klaus Seppi, MD,<sup>3</sup> Oury Monchi, PhD,<sup>4</sup> Irena Rektorova, MD, PhD,<sup>5</sup> Angelo Antonini, MD, PhD,<sup>6</sup> Martin J. McKeown, MD,<sup>7</sup> Mario Masellis, MD, PhD,<sup>8</sup> Daniela Berg, MD,<sup>9</sup> James B. Rowe, MD, PhD,<sup>10</sup> Simon J. G. Lewis, MD,<sup>11</sup> Caroline H. Williams-Gray, MRCP, PhD,<sup>12</sup> Alessandro Tessitore, MD, PhD,<sup>13</sup> Hartwig R. Siebner, MD,<sup>14</sup>  
on behalf of the International Parkinson and Movement Disorder Society (IPMDS)-Neuroimaging Study Group

<sup>1</sup>*Institut du Cerveau et de la Moelle épinière – ICM, Centre de NeuroImagerie de Recherche – CENIR, Sorbonne Universités, Groupe Hospitalier Pitié-Salpêtrière, Paris, France*

<sup>2</sup>*Department of Applied Physiology and Kinesiology, Department of Neurology and Centre for Movement Disorders and Neurorestoration, Department of Biomedical Engineering, University of Florida, Gainesville, Florida, USA*

<sup>3</sup>*Department of Neurology, Medical University Innsbruck, Innsbruck, Austria and Neuroimaging Research Core Facility, Medical University Innsbruck, Innsbruck, Austria*

<sup>4</sup>*Department of Clinical Neurosciences, Department of Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada*

<sup>5</sup>*First Department of Neurology, School of Medicine, St. Anne's University Hospital, Brain and Mind Research Program, Central European Institute of Technology, Masaryk University, Brno, Czech Republic*

<sup>6</sup>*Parkinson and Movement Disorders Unit, istituto di ricovero e cura a carattere scientifico (IRCCS) Hospital San Camillo, Venice and Department of Neurosciences (DNS), Padova University, Padova, Italy*

<sup>7</sup>*Pacific Parkinson's Research Center, Department of Medicine (Neurology), University of British Columbia Vancouver, BC, Canada*

<sup>8</sup>*Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada*

<sup>9</sup>*Department of Neurology, Christian-Albrechts-University of Kiel and Hertie-Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany*

<sup>10</sup>*Department of Clinical Neurosciences, Cambridge University, and Medical Research Council Cognition and Brain Sciences Unit, Cambridge, UK*

<sup>11</sup>*Parkinson's Disease Research Clinic, Brain and Mind Centre, University of Sydney, Sydney, Australia*

<sup>12</sup>*John Van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK*

<sup>13</sup>*Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Second University of Naples, Naples, Italy*

<sup>14</sup>*Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Department of Neurology, Copenhagen University Hospital Bispebjerg, Hvidovre, Denmark*

\*Corresponding author: Dr. Stéphane Lehericy, Institut Cerveau Moelle, CENIR, Hôpital Pitié-Salpêtrière, 47 boulevard de l'Hôpital, 75651 Paris Cedex 13, France; stephane.lehericy@upmc.fr

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Historically, magnetic resonance imaging (MRI) has contributed little to the study of Parkinson's disease (PD), but modern MRI approaches have unveiled several complementary markers that are useful for research and clinical applications. Iron- and neuromelanin-sensitive MRI detect qualitative changes in the substantia nigra. Quantitative MRI markers can be derived from diffusion weighted and iron-sensitive imaging or volumetry. Functional brain alterations at rest or during task performance have been captured with functional and arterial spin labeling perfusion MRI. These markers are useful for the diagnosis of PD and atypical parkinsonism, to track disease progression from the premotor stages of these diseases and to better understand the neurobiological basis of clinical deficits. A current

research goal using MRI is to generate time-dependent models of the evolution of PD biomarkers that can help understand neurodegeneration and provide reliable markers for therapeutic trials. This article reviews recent advances in MRI biomarker research at high-field (3T) and ultra high field-imaging (7T) in PD and atypical parkinsonism. © 2017 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

**Key Words:** Parkinson's disease; atypical parkinsonism; MRI; iron; neuromelanin; diffusion MRI; fMRI; resting state fMRI; 7T

Parkinson's disease (PD) and other parkinsonian disorders are growing health problems because populations are constantly aging. The positive and differential diagnosis of these diseases is therefore an important challenge for modern neuroimaging techniques. Early diagnosis would allow early therapeutic or preventive strategies as well as a better understanding of the dynamics of lesion deposition in the central nervous system. Early diagnosis includes the identification of the premotor features that precede overt classical symptoms by many years to decades.<sup>1</sup>

Magnetic resonance imaging (MRI) of the brain now provides complementary techniques that can detect disease-related changes in many brain regions affected by parkinsonian disorders. Current MRI biomarkers in PD fall into several categories. Biomarkers of neurodegeneration include atrophy on structural MRI and probably neuromelanin-sensitive signal changes. The biomarkers of tissue microstructure include diffusion imaging measures. The biomarkers of iron deposition are extracted using  $R2^*$  measurements and quantitative susceptibility mapping (QSM). The biomarkers of brain function have been used to study the neural correlates of motor and nonmotor symptoms in terms of neural circuits and neurochemistry. These markers have been used to categorize PD patients from healthy controls (HCs) to follow disease progression and to differentiate parkinsonian disorders.

## High-Field MRI of Parkinsonism and Its Progression

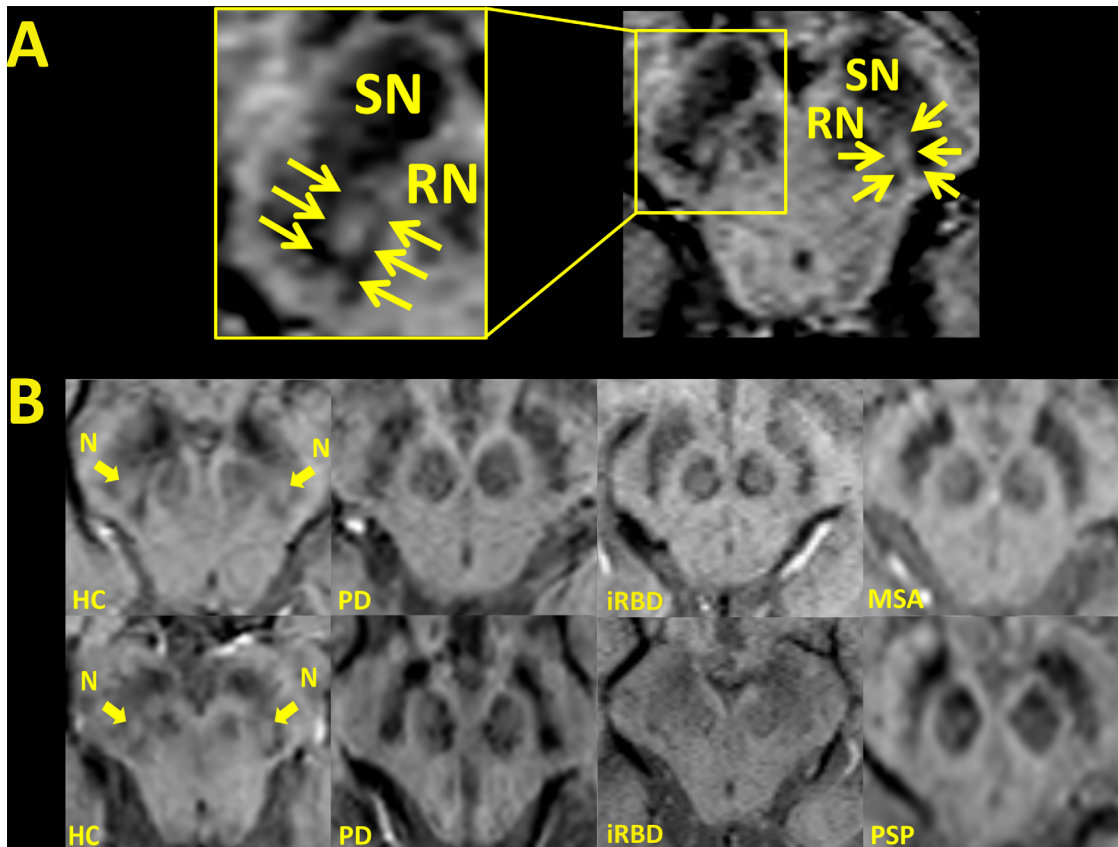
### Diagnosis of PD and Premotor PD Versus Healthy Controls

#### Magnetic Resonance Imaging Techniques

A number of MRI techniques can now detect changes in the substantia nigra (SN) in PD. Iron

content can be quantified using iron-sensitive techniques such as the  $R2^*$  relaxation rate or susceptibility-weighted imaging and QSM, 2 techniques that use information in phase images about variations in the local magnetic field. Nigral changes reflecting increases have been consistently reported in PD at 1.5T and 3T.<sup>2-7</sup> However, PD values overlapped with those of HCs, and a few studies found no changes in PD, limiting its clinical use as disease marker today.<sup>8-10</sup> Increased iron content was also reported in symptomatic and asymptomatic leucine-rich repeat kinase 2 (*LRRK2*) and *Parkin* mutation carriers.<sup>3</sup> Asymptomatic carriers had  $R2^*$  values in the range of PD values, suggesting that iron deposition may occur early during the preclinical phase of the disease.<sup>3</sup> QSM may have higher sensitivity than  $R2^*$  for delineating PD-related changes in the substantia nigra (SN) pars compacta (SNpc) and better correlate with clinical measures, suggesting a higher potential of QSM as a biomarker of iron-related pathology.<sup>11</sup>

Recently, a new MRI finding has been described in the SN in PD using iron-sensitive MRI. Controls consistently displayed a hyperintense, ovoid area within the dorsolateral border of the otherwise hypointense SNpc. Histopathological correlation (Fig. 1A)<sup>12</sup> suggested that this dorsolateral nigral hyperintensity (DNH) or nigral hyperintensity corresponded to nigrosome-1, a calbindin-negative subregion in the SNpc.<sup>13,14</sup> Across studies, the signal loss of DNH had a high sensitivity (79% to 100%) and specificity (84.6% to 100%) to separate PD from HC (Fig. 1B)<sup>13-17</sup> and may be helpful in differentiating PD from uncertain movement disorders such as drug-induced parkinsonism,<sup>17</sup> essential tremor, and dystonic tremor.<sup>14</sup> DNH signal loss was found in at least 2/3 of patients with idiopathic rapid eye movement sleep behavior disorder (iRBD)<sup>18</sup> (Fig. 1B) and in clinically



**FIG. 1.** The dorsolateral nigral hyperintensity. (A) susceptibility-weighted imaging (SWI) image of a healthy control (HC), demonstrating the magnified dorsolateral nigral hyperintensity (DNH) within the right substantia nigra (SN). Yellow arrows mark the DNH in the survey as well as in the magnified illustration. (B) SWI images demonstrating the DNH in two healthy controls, its absence in two patients each with PD and idiopathic rapid eye movement sleep behavior disorder (iRBD) as well as its absence in one patient each with multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). RN, red nucleus.

asymptomatic *LRKK2* carriers,<sup>19</sup> suggesting that this sign may assist in the identification of prodromal degenerative parkinsonism.

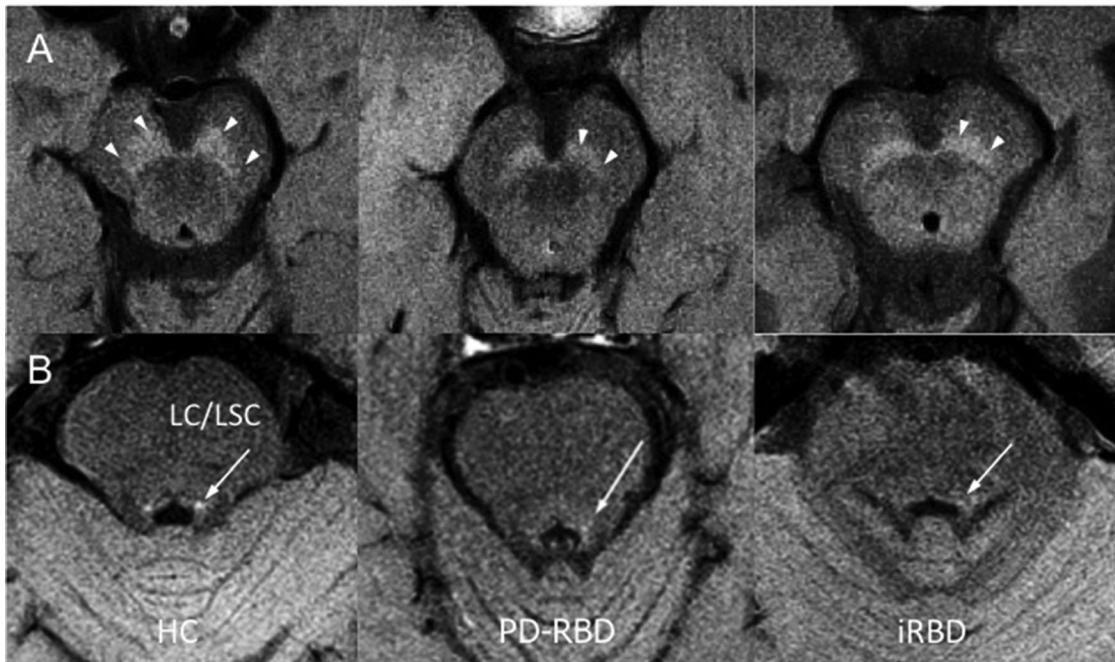
High-resolution spin echo T1-weighted images are sensitive to the paramagnetic properties of neuromelanin, a pigment that is contained in the SNpc and show the SNpc as an area of high signal intensity (Fig. 2).<sup>20</sup> The reduced size and signal intensity of the SN was reported in PD patients using neuromelanin-sensitive imaging with high diagnostic accuracy.<sup>20</sup> This technique may help distinguish PD from essential tremor.<sup>21</sup> Biomarker changes in PD were shown to predominate in the SNpc delineated using neuromelanin-sensitive imaging when compared with T2 imaging.<sup>22</sup>

Diffusion weighted imaging is sensitive to microstructural tissue changes that alter the regional diffusion of water molecules. Using diffusion tensor imaging, reduced fractional anisotropy (FA) in the SN was reported, although with a large variability of results across studies.<sup>23</sup> More advanced diffusion modeling approaches including free-water measurements<sup>24</sup> or neurite orientation dispersion and density imaging<sup>25</sup> may provide more reliable results to distinguish PD patients from HCs. Free water (ie, the

fractional volume of unconstrained diffusion) and free-water corrected FA (ie, a measure of the tissue compartment of the voxel) can be extracted from diffusion data using a bitensor model (Fig. 3). Free water in the SN is elevated in PD when compared with HCs, suggesting that this measurement is robust.<sup>24</sup> Measuring diffusion changes in the ventrolateral SN is also important to find consistent effects,<sup>22,26</sup> and this region corresponds with pathology in PD.<sup>27</sup> Last, structural connectivity of the SN with the basal ganglia and thalamus is reduced in PD patients as shown using diffusion-based fiber tracking.<sup>28,29</sup>

Resting-state fMRI (rs-fMRI) using blood oxygen level-dependent contrast (BOLD) has allowed the exploration of brain connectivity between functionally linked cortical regions constituting resting-state networks (RSNs).<sup>30</sup> The rs-fMRI in PD showed that dopamine depletion leads to a remapping of cerebral connectivity characterized by decreased coupling in the cortico-striatal sensorimotor network and between the striatum and the brain stem.<sup>28,31-36</sup> Increased coupling, interpreted as compensatory, was observed in PD in the associative networks<sup>28,37</sup> and intraregionally

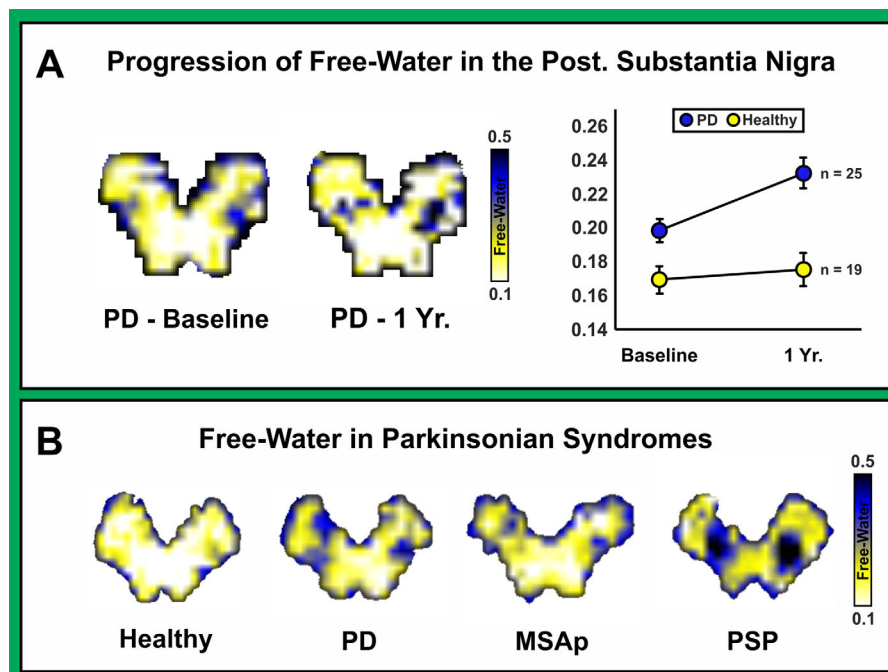




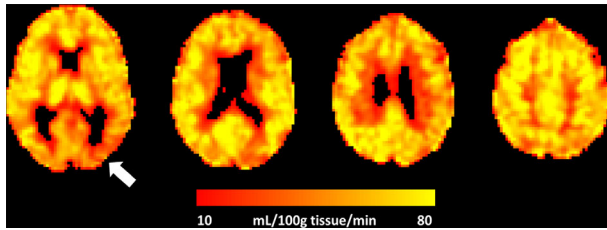
**FIG. 2.** Neuromelanin imaging. (A) Axial neuromelanin-sensitive T1-w images of the SN and (B) the locus coeruleus/subcoeruleus area (LC/LSC) in a healthy control (HC), a patient with PD with rapid eye movement sleep behavior disorder (PD-RBD), and a patient with idiopathic rapid eye movement sleep behavior disorder (iRBD). The normal SN (arrowheads) and the locus area (arrows) are visible as areas of high signal intensity. There is a decrease in size and signal intensity of the substantia nigra (SN) and locus area in participants with RBD.

within the primary motor cortex (M1) and the cerebellum.<sup>31</sup> Connectivity changes were modulated by levodopa.<sup>33,38</sup> Functional alterations in M1 may be

related to prolonged dopaminergic treatment rather than PD per se because alterations were not detected in drug-naïve patients.<sup>33</sup> Changes in functional



**FIG. 3.** Diffusion imaging and free water. Free-water values from individual participants and group-level values are shown for PD, multiple system atrophy parkinsonian variant (MSAp), and progressive supranuclear palsy (PSP). (A) Progression of free water in an individual patient with PD. Free water is shown in a color scale from yellow = low free water and blue = high free water. It is clear that free water is elevated in the posterior region of the substantia nigra at baseline and becomes further elevated at 1 year of progression (1 Yr.).<sup>24,212</sup> (B) Free-water maps from individual control, PD, MSAp, and PSP participants are shown. Free-water accumulation becomes worse in the PSP participant when compared with the PD and MSAp participants.<sup>76</sup>



**FIG. 4.** Pseudocontinuous arterial spin labeling MRI to quantify regional cerebral blood flow in an individual with PD and mild cognitive impairment. Low occipital perfusion is noted (arrow).

connectivity were also detected in asymptomatic LRRK2 G2019S mutation carriers, suggesting that functional changes may occur early during the preclinical phase of the disease, whereas structural changes were not detected in these patients.<sup>39,40</sup> Last, functional connectivity (FC) mapping within the basal ganglia networks differentiated PD patients from both HCs and other neurodegenerative diseases with high accuracy.<sup>38,41</sup>

Arterial spin labeling MRI (ASL-MRI) permits the quantification of cerebral tissue perfusion using magnetically labeled protons in arterial blood water as an endogenous tracer.<sup>42</sup> Studies have shown symmetrical posterior > anterior cortical hypoperfusion in PD involving predominantly the parieto-occipital regions (Fig. 4) and dorsolateral prefrontal cortex.<sup>43-46</sup> The posterior perfusion deficits predominated in PD with versus without dementia.<sup>43</sup> ASL perfusion deficits overlapped with fluorodeoxyglucose PET metabolic deficits in PD.<sup>47</sup>

Proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) allows the quantification of changes in brain metabolites that have reported a number of metabolic changes at various levels of the central nervous system in PD.<sup>48-50</sup> In the SN, results were often contradictory probably because of the small size of the structure.<sup>48</sup> A recent study has shown that MRS detected metabolic changes in the putamen in PD that were reversed by L-dopa therapy, suggesting a possible role of MRS to monitor treatment effects.<sup>48</sup>

### Transcranial B-Mode Sonography (TCS)

An alternative method to measure iron-level content is TCS. Increased echogenicity of the SN has been observed in idiopathic PD using TCS and related to increased tissue iron.<sup>51</sup> TCS is highly sensitive for PD and easily applicable, but the method is not entirely specific as SN hyperechogenicity was also detected in other neurodegenerative diseases such as progressive supranuclear palsy (PSP) and corticobasal degeneration.<sup>52</sup> In HCs ( $\geq 50$  years), SN hyperechogenicity was associated with a more than 20 times increased risk to develop PD within 5 years.<sup>53</sup> Thus, TCS can help patient stratification and the identification of individuals at risk. TCS-MRI fusion imaging has shown that the 2 techniques provide complementary findings.<sup>54</sup> Limitations of TCS include reduced specificity,

because SN hyperechogenicity is found in 10% to 15% of the healthy population, and insufficient bone window in more than 10% of the elderly population.

### Data Fusion

High-field imaging offers the exciting possibility to fuse information from different modalities. When combining nigral relaxometry with other quantitative MR parameters sensitive to complementary tissue characteristics (ie, multimodal neuroimaging), better discrimination compared with the single markers alone could be achieved.<sup>55,56</sup> For instance, cortical thinning, rs-fMRI (fractional amplitude of low frequency fluctuations), and mean FA in a set of brain regions were jointly used to accurately discriminate between PD patients and HCs.<sup>57</sup> Because the importance of combining biomarkers in PD is becoming increasingly recognized,<sup>58</sup> it is expected that imaging data fusion approaches will become more widespread in the future.

### Neural Correlates of Motor and Nonmotor Symptoms in PD

Studies using functional or structural imaging have offered insights into the pathophysiology underlying key symptoms in PD.<sup>59,60</sup> The effect of dopaminergic medication as well as the influence of genetic polymorphisms have also been investigated. These studies detailed below have confirmed the interaction between the basal ganglia and cortex and suggested that the neurobiological processes in PD reflect the interaction of more complex interconnected neural networks rather than being related to discrete “circuit failures.”

### Motor Symptoms

PET and fMRI during the performance of motor tasks have provided variable results across studies. A recent quantitative meta-analysis identified consistent functional abnormalities in PD.<sup>61</sup> The most consistent abnormality was a relative decrease in motor activation in the posterior motor putamen, globally increasing with the degree of motor impairment.<sup>61</sup> Dopaminergic medication consistently caused a relative increase in putaminal activity. Motor activation also differed between PD patients and HCs in a set of frontoparietal areas, including pre-SMA, M1, and the inferior and superior parietal lobules.<sup>61</sup> However, both increases and decreases in activity were reported for these regions, indicating a complex relationship between altered cortical activation during motor tasks and nigrostriatal dopaminergic denervation. Using rs-fMRI, studies have shown that functional correlations between the striatum and the brain stem correlated with the UPDRS III score in PD.<sup>36,62</sup> Functional imaging studies have also suggested that different motor phenotypes may be related to distinctive underlying

pathophysiology. Cognitively unimpaired akinetic-dominant PD patients showed decreased FC in the default mode network (DMN; a task-negative network operating across the hippocampal formations, posterior cingulate, and intraparietal sulcus) when compared with tremor-dominant patients and HCs.<sup>63</sup> An effective connectivity study suggested that tremor might result from a pathological interaction between the basal ganglia and the cerebellothalamic circuit<sup>64</sup> arising in the internal globus pallidus and being propagated to the cerebellothalamo-cortical circuit via the motor cortex.<sup>65</sup>

**Freezing of Gait (FOG).** Although early work examined FOG using an imagined gait paradigm,<sup>66</sup> more recent studies used a virtual reality approach.<sup>67-71</sup> These fMRI studies have identified the abnormal interplay that occurs in PD between the motor, basal ganglia, pedunculopontine, and cognitive control networks that would normally coordinate effective automatic movement. Diffusion-based tractography in FOG patients showed reduced connectivity of the pedunculopontine nucleus with the cerebellum, thalamus, and the frontal cortex.<sup>72</sup>

**Levodopa-Induced Dyskinesia.** Levodopa-induced dyskinesia (LID) represents a major debilitating side effect of long-term dopaminergic treatment in PD. fMRI has been successfully used to study the impact of aberrant striatal response to levodopa on the motor system in PD patients with LID. Using fMRI during the performance of visuomotor tasks, PD patients with LID off medication showed stronger activation of the SMA and reduced activation of the right inferior frontal gyrus than patients without LID.<sup>73</sup> A single fast-acting dose of soluble levodopa triggered an abnormal activation in the pre-SMA and putamen in PD patients with peak-of-dose LID relative to patients without LID,<sup>74</sup> and abnormal effective connectivity between the pre-SMA and M1.<sup>75</sup> This network reorganization in the time period preceding dyskinesias strongly predicted clinical ratings of dyskinesia severity. PD patients with LIDs also expressed alterations in functional coupling between the frontal cortex and putamen in the absence of motor activity.<sup>76,77</sup> These fMRI studies provided evidence for an aberrant dopaminergic modulation of putaminal activity and cortico-putaminal connectivity as a central abnormality in PD patients with LID. This abnormal cortico-putaminal connectivity may be a promising target for therapeutic brain stimulation<sup>78</sup> and may be used to screen for the efficacy of new antidyskinetic treatments.

### Nonmotor Symptoms

**Hyposmia.** Hyposmia is a well-established and early nonmotor symptom of PD<sup>79,80</sup> with a possible role as

a potential biomarker of PD progression and cognitive decline.<sup>81,82</sup> PD patients with hyposmia, compared with those without hyposmia, showed decreased FC in both olfactory- and non-olfactory-related cortical areas and increased FC in the left anterior/posterior cingulate cortex, with a potential compensatory role.<sup>83</sup> Atrophy was also reported in olfactory regions in association with olfactory deficits.<sup>84</sup>

**RBD.** RBD has shown an incomparable potential as a prodromal PD marker, with an estimated period of 10 to 15 years of progressive neuronal loss before the onset of the core motor symptoms.<sup>85</sup> This motivated several studies that have investigated the neural correlates of iRBD in recent years.<sup>86-90</sup> RBD has been related to the damage of the locus coeruleus-subcoeruleus complex, a region that contains neuromelanin-containing catecholaminergic neurons (Fig. 2B).<sup>91</sup> A reduced neuromelanin signal was observed in patients with PD and RBD<sup>91</sup> as well as those with iRBD (Fig. 2B).<sup>92</sup> Two recent studies have shown that the nigrostriatal connectivity pattern is altered in patients with iRBD<sup>93</sup> and that basal ganglia connectivity measures may differentiate both iRBD and PD from HC.<sup>94</sup>

**Depression.** Depression in PD may be considered a disease-related dysfunction at the interface between emotional and cognitive processing.<sup>95</sup> Using different rs-fMRI approaches, an intrinsic dysfunction within the dorsolateral prefrontal cortex has been observed in depressed PD patients.<sup>96,97</sup> This cortical area has a pivotal role in the prefrontal-limbic network and is also involved in cognition and executive functions.<sup>98,99</sup> Using rs-fMRI, the role of abnormal connectivity of the amygdala in dysfunctional mood modulation has been emphasized in depressed PD patients.<sup>100,101</sup> The presence of apathy in PD was associated with a disrupted FC in frontostriatal pathways.<sup>102,103</sup>

**Fatigue.** Fatigue is a common and disabling symptom in PD patients.<sup>104</sup> A recent rs-fMRI study has revealed that fatigue was associated with a divergent FC pattern within the sensorimotor and DMN in drug-naïve PD patients.<sup>105</sup> Fatigue severity correlated with connectivity changes, suggesting that an efficient functional interplay between these cortical areas might be necessary to maintain motor performance without the development of fatigue.

**Visual Hallucinations.** Visual hallucinations are common neuropsychiatric features in more advanced PD. Reduced gray matter was reported in limbic regions in these patients.<sup>106</sup> Although the ability to capture hallucination-related activity using fMRI is restricted,<sup>107</sup> recent work has demonstrated that visual hallucinations seem to arise from an increased engagement



of the DMN with the primary visual system.<sup>108,109</sup> This is paralleled by a disengaged dorsal attention network (representing regions of the frontal eye fields and superior parietal lobule). The disengagement of the dorsal attention network might indicate a deficient protective mechanism that could help prevent the emergence of hallucinations. These findings may provide the basis of future treatments targeting pathological network activity.<sup>110</sup>

**Autonomic Dysfunction and Pain.** Dysautonomic and especially cardiovascular symptoms are frequent and present early in PD.<sup>111</sup> Abnormal heart rate frequency variability assessed during rapid eye movement sleep in PD correlated with changes in diffusion measures in the medulla oblongata, suggesting that damage in this region underlies cardiac autonomic dysfunction.<sup>112</sup> Orthostatic hypotension is also a common and disabling autonomic feature most frequently seen in late-stage PD and is associated with falls and cognitive impairment.<sup>113,114</sup> In PD patients with cognitive impairment, a larger orthostatic drop in blood pressure correlated with lower posterior cerebral ASL-MRI perfusion, which in turn was associated with visuospatial and attentional deficits on neuropsychological testing.<sup>115</sup> MRI also showed that persistent pain in PD was associated with cortical thinning and resting-state functional changes in the frontal, temporal, and insular areas as well as a accumbens–hippocampus disconnection.<sup>116</sup>

### Cognitive Decline

**Volumetry and Cortical Thickness.** Cognitive decline in PD was associated with greater atrophy in many brain regions, including the frontal, parietal, and temporal areas and substantia innominata. Atrophy is greater in PD with dementia than with mild cognitive impairment (PD-MCI) and accelerates with disease progression.<sup>60</sup> Impairment in specific domains correlated to both anterior and posterior cortical thinning in PD-MCI.<sup>117</sup> Two recent longitudinal MRI studies reported a higher rate of cortical thinning in PD-MCI patients in the SMA/preSMA area, superior temporal gyrus, superior parietal region, and basal forebrain when compared with PD with normal cognition and HCs and the magnitude of cortical thinning correlated with cognitive decline.<sup>118,119</sup> These results indicate that early MCI in PD is indicative of a faster neurodegeneration process. The findings also suggest that anatomical MRI could be helpful in distinguishing subtypes of MCI that are associated with cortical pathology and subsequent progression to dementia.<sup>120</sup>

**White Matter Signal Hyperintensities (WMH).** WMH seen on T2, FLuid Attenuated Inversion Recovery (FLAIR), and proton density-weighted MR sequences

most commonly represent cerebral small vessel disease. A large prospective cohort study demonstrated that the presence of more than 2 cardiovascular risk factors was associated with worse UPDRS III motor scores and cognitive impairment and that WMH were associated with worse cognition and postural instability.<sup>121</sup>

**Task-Based fMRI.** A large number of fMRI studies have looked at cognitive deficits in PD using tasks relying on executive processes that solicit frontostriatal pathways.<sup>122</sup> fMRI studies while performing attentional set-shifting tasks indicated reduced frontostriatal activity in PD.<sup>123,124</sup> Prefrontal cortex activity in PD patients depended on whether the striatum was necessary for the task.<sup>124,125</sup> Reduced prefrontal–caudate activation was reported in PD-MCI patients off medication during the performance of a set-shifting task<sup>126</sup> or in drug-naïve PD-MCI patients during the performance of a working-memory task.<sup>127</sup> Other task-based fMRI and PET results support the idea that the integrity of medial temporal function is important for preserving cognitive function in PD and may compensate for deficient striatal and prefrontal activation.<sup>126,128,129</sup> The respective effects of dopamine replacement therapy on the ventral and dorsal striatum in PD was also studied using fMRI. In PD patients, dopamine replacement impaired encoding and facilitation across trials relying on the ventral striatum, whereas it enhanced interference related to assimilating conflicting influences on selection across trials relying on the dorsal striatum.<sup>130</sup> These studies support the concept that impairments specific to the ventral striatum in PD patients can be explained by the ventral tegmental area dopamine “overdose” hypothesis.<sup>131,132</sup> In summary, fMRI studies of cognitive deficits in PD have argued for frontostriatal and also temporal lobe deficits at least in some patients, suggesting the involvement of both the nigrostriatal and the mesocortical dopaminergic pathways.

**Resting-State fMRI.** Resting-state fMRI studies have provided evidence of FC changes both within and between individual RSNs, including particularly the DMN, frontoparietal, salience, and associate visual networks, which seem to be crucial for cognitive performance success in PD. DMN connectivity or its coupling with other networks was disrupted in PD with normal cognition<sup>133–136</sup> although not in all studies,<sup>137</sup> as well as in PD-MCI<sup>135</sup> and PD with mild dementia.<sup>138</sup> In contrast, the occurrence of cognitive deficits in PD was associated with abnormal FC within the frontoparietal network or between this network and other RSNs even after controlling for dopaminergic medication in PD with MCI<sup>135,139</sup> and dementia.<sup>138,140</sup> The changes in FC differed in patients with executive and visuospatial/memory deficits. Executive performance was associated with FC in frontoparietal

areas<sup>139,141,142</sup> and with the nigrostriatal dopaminergic function assessed using DAT.<sup>141</sup> The normally existing anticorrelation between the attentional frontoparietal networks and the DMN was decreased in PD-MCI.<sup>133,139</sup> Decreased memory and visuospatial and executive functions were related to abnormal interactions between the dorsal attentional and the DMN.<sup>62</sup> In PD-MCI, impaired visuo-spatial functions were related to abnormal FC in the parietal and temporal regions.<sup>139</sup> FC changes in more posterior regions may be associated with the evolution to dementia as shown in a 3-year longitudinal study.<sup>142</sup> Altogether, these results are consistent with the concept of 2 distinct cognitive syndromes in PD, which include dopaminergically mediated frontostriatal executive impairments and a “posterior cortical syndrome” more frequently associated with the later development of dementia.<sup>143,144</sup> Longitudinal studies will have to demonstrate whether these changes may predict cognitive impairment and dementia in early PD.

**fMRI in the Study of the Genetic Basis of Cognitive Heterogeneity in PD.** Cognitive heterogeneity in PD may be mediated through the common genetic variation of several genes, including catechol-o-methyltransferase (*COMT*), microtubule-associated protein tau (*MAPT*), and *APOE*.<sup>145</sup> The *COMT* gene (val<sup>158</sup>met) polymorphism, which alters the activity of this dopamine-regulating enzyme,<sup>146</sup> has been shown to influence performance on prefrontally based tasks in PD.<sup>144,147,148</sup> Early PD patients homozygous for the *COMT* methionine allele when compared with the valine allele showed impaired behavioral performance on executive tasks and a reduced BOLD signal in the frontoparietal networks (Fig. 5).<sup>149,150</sup> This is likely to reflect reduced dopamine turnover and higher presynaptic dopamine levels in the frontal cortical regions (with lower *COMT* enzyme activity), as demonstrated using [18F]-dopa PET.<sup>151</sup> Moreover, in HCs, val homozygotes had impaired set-formation ability and lower dorsolateral prefrontal cortex activation than met homozygotes, whereas in patients, the opposite relationship was observed.<sup>152</sup> These data suggest a regionally specific effect of *COMT* on cortical dopamine that modulates executive performance in a disease-specific way. This may be explained by the well-established hypothesis of an inverted U-shaped relationship between frontal dopamine levels and executive cognitive function, with both higher and lower dopamine levels having a detrimental effect on performance depending on the individual’s underlying dopaminergic status.<sup>145</sup>

A common inversion polymorphism in the *MAPT* gene region with 2 distinct haplotypes, H1 and H2,<sup>153</sup> is associated with PD risk.<sup>154</sup> The H1 haplotype may also increase the risk of developing dementia in PD,<sup>155,156</sup> although this association was not found in

all studies.<sup>157,158</sup> In early PD patients without cognitive impairment, the H1/H1 genotype was associated with subtle impairment of memory recall ability, and fMRI revealed reduced activation of the medial temporal lobe during memory encoding.<sup>159</sup> Hence this genetic variant may be a general modifier of memory function in PD even prior to clinical onset of disease. Another fMRI study showed that the *COMT*, *MAPT*, and *APOE* genotypes had dissociable effects on executive, visuospatial, and memory performance, which were associated with regionally specific changes in cortical BOLD activation in the frontostriatal (*COMT*), parietal (*MAPT*), and temporoparietal regions (*APOE-ε4*).<sup>160</sup>

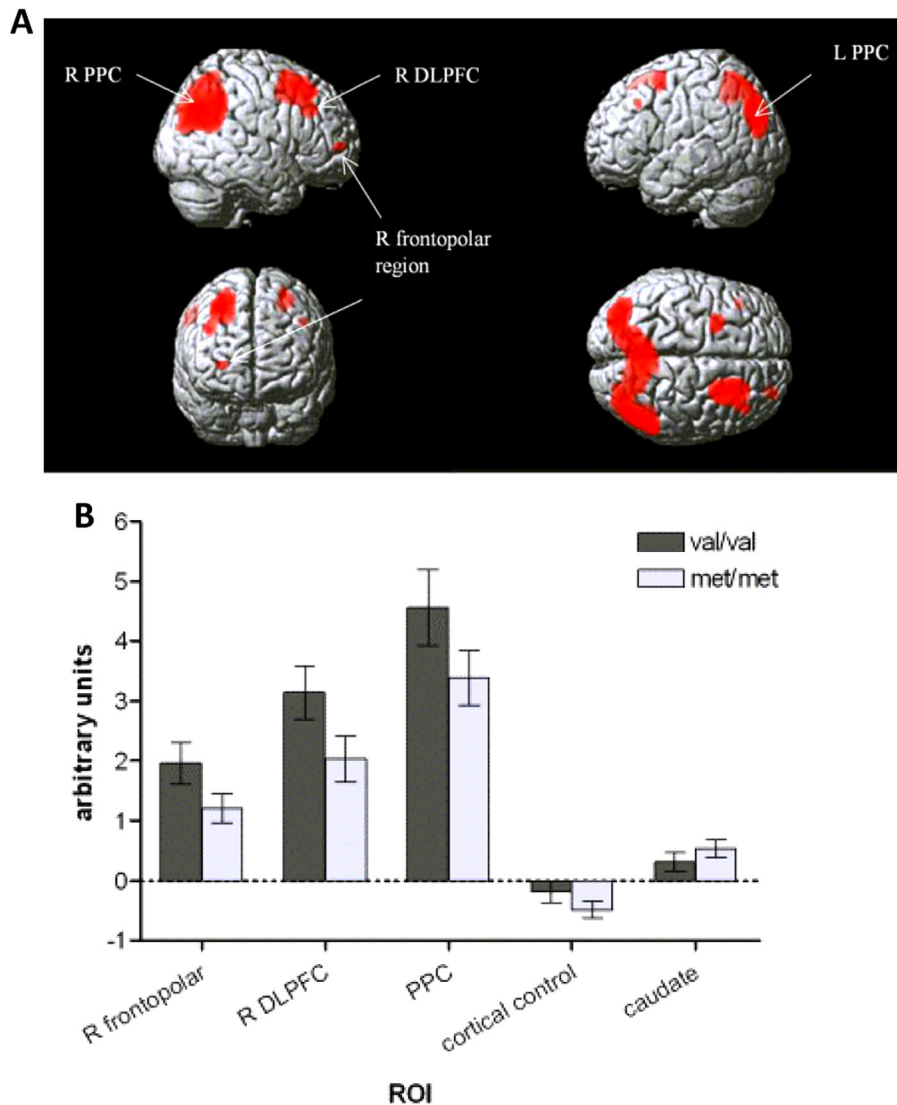
In summary, genetic fMRI studies support the concept of distinct cognitive syndromes in early PD, including a frontally based dysexecutive syndrome reflecting dysfunction in dopaminergic networks and influenced by the *COMT* genotype and a more posterior cortically based cognitive syndrome dependent on age and tau genotype.<sup>145</sup>

### Parkinsonian Disorders Other Than PD

Multiple system atrophy (MSA), corticobasal degeneration, and PSP are distinct from PD in clinical features, neurobiology, and prognosis. MRI allows differentiating between these disorders from each other and from PD as well as examining their distinctive pathophysiology. On structural images, PSP patients show signs of midbrain and superior cerebellar peduncle atrophy, whereas MSA patients present atrophy and signal changes in the putamen and middle cerebellar peduncle<sup>161-165</sup> (see reviews in refs. 166,167). Reliable automated differentiation of parkinsonian syndromes may be obtained by combining brain volumetry and support vector machine classification.<sup>168</sup> A loss of neuromelanin signal may discriminate moderately between PD and atypical parkinsonism.<sup>169,170</sup> A loss of DNH does not seem to discriminate between PD and other parkinsonian syndromes.<sup>13,14,16</sup> Patients with PSP and MSA can show discrete putaminal changes using iron-sensitive MRI sequences such that these changes can assist in the differential diagnosis of PD from atypical parkinsonism.<sup>171-176</sup>

A meta-analysis suggested that diffusion MRI in regions such as the cerebellum and putamen may help distinguish MSA and PSP from PD.<sup>177</sup> Increased free-water values were found in the anterior and posterior SN of all diseases (Fig. 1B).<sup>178</sup> In addition, elevated free-water values were found in the putamen, caudate, and cerebellum for MSA and in the basal ganglia, thalamus, cerebellum, and corpus callosum for PSP.<sup>178</sup> When combining free-water and free-water-corrected FA, high predictive accuracy was observed regarding the differential diagnosis among these diseases.<sup>178</sup>





**FIG. 5.** fMRI blood oxygen level-dependent activation during performance of the Tower of London planning task in a group of patients with early PD stratified by catechol-o-methyltransferase val158met genotype. **(A)** Blood oxygen level-dependent activation during planning versus a control task in the whole cohort rendered onto a canonical brain image ( $P < .05$ , false discovery rate correction for whole brain volume). **(B)** Activity in val ( $n = 16$ ) versus met ( $n = 15$ ) homozygotes in the regions of interest indicated in (A), showing significant underactivation of the frontoparietal network activated by the planning task in met versus val homozygotes, which was accompanied by an impairment in behavioral performance (not shown), reproduced from ref. <sup>150</sup>. DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; L, left; met, methionine; PPC, posterior parietal cortex; R, right; ROI, region of interest; val, valine.

Motor control studies of patients with PD, MSA, and PSP using fMRI show an abnormal activation of task-related structures.<sup>179</sup> An abnormal fMRI activation was found in the basal ganglia, cerebellum, and cerebrum as well as extensive and widespread volume loss throughout the brain in MSA when compared with PD.<sup>180</sup> Reduced functional activity was found in the contralateral caudate, primary motor and premotor cortex, and ipsilateral putamen in PSP when compared with PD.<sup>181</sup> Highly connected cortical regions suffered a disproportionate loss of FC in PSP, which correlated with the regional expression of the gene *MAPT*.<sup>182</sup> Specific changes in the connectivity of the dorsal midbrain and striatum also occurred in PSP,

including corticostriatal connections that correlated with disease severity.<sup>181,183</sup> These results suggest that the magnitude and topology of functional brain networks is changed by PD, PSP, and MSA.

### Sensitivity of MRI Markers to Disease Progression

Longitudinal studies using iron-sensitive sequences at 1.5T and 3T have revealed conflicting results. Although some of the studies reported increased nigral  $R2^*$  over time,<sup>5,184</sup> no longitudinal changes have been reported by others.<sup>185,186</sup> It seems that late-stage PD might have lower nigral  $R2^*$  values than early-stage PD. A possible explanation of this finding may be that

consecutive gliosis with neuronal degeneration in late-stage PD might lengthen T2 relaxation times within the tissue and thus counteract the increase of relaxation rates.<sup>2</sup> This could also explain that some authors found no difference in iron content between PD patients and HCs,<sup>8-10</sup> whereas most studies did.<sup>2-7</sup> Although relaxometry might track disease progression early in the disease process,<sup>5</sup> available evidence suggests that relaxometry may not be a sufficient staging biomarker by itself.<sup>187</sup> QSM could be a better option, providing a more direct measure of tissue magnetic properties.<sup>11</sup> This remains to be demonstrated as QSM measurements had more variability estimated by standard deviation as compared to R2\*.<sup>188</sup>

Functional and structural MRI can also track the progression of PD and parkinsonism and provide further distinguishable differences between them. Task-based fMRI has shown progressive functional deterioration in the putamen and M1 in PD patients, but not in HCs.<sup>77</sup> In the same study, functional deterioration in MSA was exclusively extrastriatal (M1, SMA, and superior cerebellum), whereas PSP had additional reduction in functional activity in the putamen. PD progression can also be tracked by the loss of cortical gyration. A loss of gyration was accelerated in early-stage PD (1-5 years), whereas later stages (5+ years) were associated with significantly reduced overall gyration as well as prominent bilateral reduction in the frontal and parietal areas.<sup>189</sup> In addition, free-water values in the posterior SN were shown to increase with the progression of PD (Fig. 3).<sup>24</sup>

These findings suggest that distinct markers and rates of disease progression may help distinguish PD, MSA, and PSP. Functional activity levels revealed by fMRI and free-water and FA values derived from diffusion MRI and perhaps iron-sensitive imaging are promising MRI-based markers of the diseases and their progression that may assist clinical assessment and provide more accurate methods of diagnoses.

## Ultra-High Field (UHF) Imaging

### Advantages of UHF MRI

Increased static magnetic field results in an increased signal-to-noise ratio, which can be used to reduce measurement time and improve spatial resolution, and improved tissue contrasts because of increased sensitivity to susceptibility. Advantages of 7T imaging include clear separation between the subthalamic nucleus and the SN,<sup>190-195</sup> and visualization of the medullary lamina separating the 2 segments of the globus pallidus and the putamen<sup>192</sup> and thalamic nuclei using either QSM<sup>192</sup> or optimized T1-weighted acquisition.<sup>196</sup> In the SN, the DNH was initially depicted using T2\*w images at 7T,<sup>12,197,198</sup> and sequences were subsequently optimized at 3T.<sup>15</sup> Using

7T, the lateral boundaries of the SN showed an abnormal shape in PD patients.<sup>197,199</sup> Evidence also suggested abnormalities in asymptomatic *LRRK2* carriers.<sup>20</sup> In theory, UHF MRI has the ability to distinguish the loss of function and connectivity of small but critical nuclei such as the subthalamic, the nucleus pedunculopontine nucleus, oculomotor nuclei, or striatal subdivisions.<sup>200,201</sup> Susceptibility-weighted imaging at 7T has allowed the visualization of cortical laminar structure in the cortex and the cerebellum,<sup>202,203</sup> an ability that was used to detect atrophy and signal hypointensity in the deep layers of the primary motor cortex of patients with amyotrophic lateral sclerosis.<sup>204</sup> Using diffusion-based tractography, the improved reconstruction of basal ganglia and brain stem anatomical connections may be achieved in humans in vivo<sup>205</sup> and ex vivo.<sup>206</sup> The imaging of nuclei of biological interest such as <sup>23</sup>Na (using specific hardware and coils) or glutamate (using chemical exchange saturation transfer) becomes feasible, but the interest of these techniques is not known in PD. UHF strongly benefits MRS, providing increased chemical specificity, better separation of metabolites such as glutamate and glutamine, and better detection of metabolites with smaller concentrations (eg, gamma-Aminobutyric acid (GABA)). In mild-to-moderate PD, neurochemical profiles were successfully recorded in the SN at 7T, although this study did not show any significant difference with HCs.<sup>48</sup> The extent to which the functional changes observed in parkinsonism relate to abnormal neurotransmitters and plasticity is also amenable to investigation by UHF MR spectroscopy. For BOLD fMRI, higher field strength provides increased contrast, resolution, and specificity.<sup>207</sup> BOLD fMRI at 7T was able to distinguish activation originating from the subthalamic nucleus and SN.<sup>208</sup> It is expected that 7T fMRI will provide improved sensitivity and spatial resolution for imaging basal ganglia and brain stem structures in PD.

It is not yet known whether 7T imaging will allow better separation of PD from atypical parkinsonism, and its role in distinguishing these diseases remains to be determined.

### Limitations of UHF MRI

Brain imaging at UHF also comes with specific difficulties and challenges that include B<sub>1</sub> inhomogeneity, increased geometric distortions and artifacts, restrictions because of increased power deposition and specific absorption rate, and less available coils. Most of these challenges have been addressed by technical improvements including appropriate multi transmit and receive coil designs generating a B<sub>1</sub> pattern with improved homogeneity, radiofrequency shimming, pulse sequence optimization, and postprocessing techniques. There are more contraindications because of

the presence of implanted metallic devices that are not compatible with UHF systems or have not yet been tested. The 7T systems are expensive and not certified as clinical devices. UHF MR systems still require highly skilled dedicated personnel to be operated efficiently. As a result, UHF MR technology is not yet widely available, but efforts to develop clinical UHF MR systems might change this situation in the coming years.

## Future Directions of MRI

During the past 3 decades, MRI has become a well-established method that can be used for the diagnostic work-up of parkinsonism in clinical routine, providing specific information that point toward the diagnosis of a neurodegenerative condition.<sup>166,209</sup> The role of MRI has progressed from excluding symptomatic parkinsonism because of other pathologies to distinguishing PD from atypical parkinsonism based on specific changes in the basal ganglia and infratentorial structures.<sup>210</sup> A combination of markers may assist in the differential diagnosis of parkinsonism in clinical practice including surface or volume measurements in the brain stem as well as diffusion and iron measurements in the brain stem and basal ganglia. For instance, changes in the putamen and cerebellum on diffusion imaging are not present in typical early-stage PD but represent an atypical parkinsonism.<sup>177</sup> The development of classifiers may also help clinicians to differentiate between these conditions.

Only during the past decade have newer multimodal MRI techniques been applied in patients with PD and atypical parkinsonism and have shown promising results in detecting abnormalities in the SN, nigrostriatal pathway, and outside the nigrostriatal system as summarized in this review. At present, 2 qualitative MRI biomarkers of the SN (DNH and neuromelanin signal changes) seem well enough established to be used in clinical practice in PD. Other quantitative markers are promising, including diffusion imaging using advanced techniques such as free water and iron imaging either using R2\* or QSM. However, these techniques are not yet available on conventional scanners, and clinicians lack normative databases.

Quantitative measurements will be useful in tracking the progression of patients in clinical trials and possibly help to personalize patient care. However, quantitative MRI-based PD biomarkers are still insufficiently validated to be incorporated into therapeutic trials. Probably the best candidate biomarkers for clinical trials include iron, neuromelanin, and other quantitative imaging methods such as diffusion imaging and relaxometry. The validity of these biomarkers of neurodegeneration in PD is insufficiently supported by histological correlation studies. Important questions

are only beginning to be addressed, such as the following: Do markers change with disease progression? Are they correlated with clinical status? Are they sensitive enough to detect changes in a longitudinal study? What is the temporal evolution of biomarkers? Can MR biomarkers predict responses to treatment?<sup>74,75,211</sup> Efforts should also be made to harmonize data collection and processing, paving the way for large multicenter cohort studies that use similar inclusion criteria and data analysis. Standardized pulse sequences for quantitative MRI-based markers should yield more consistent results across sites. Last, UHF imaging appears promising in PD but has been insufficiently studied. ■

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