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MRI reveals brain abnormalities in drug-naïve Parkinson's disease

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Abstract

Most brain studies of Parkinson's disease (PD) focus on patients who are already taking anti-parkinsonian medication. This makes it difficult to isolate the effects of disease from those of treatment. We review MRI evidence supporting the hypothesis that early-stage, untreated PD patients have structural and functional abnormalities in the brain, some of which are related to motor symptoms.

Keywords

diffusion tensor imaging (DTI); functional magnetic resonance imaging (fMRI); parkinsonism; grip force; subtype; de novo; movement

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized clinically by bradykinesia, rigidity, rest tremor, and postural instability. It affects approximately 1% of the population over the age of 60 years and is associated with increased morbidity and mortality. Although the pathophysiological mechanisms are not understood completely, the motor symptoms of PD result from degeneration and dysfunction within the basal ganglia-thalamo-cortical circuitry. Histologically, PD is characterized by a significant reduction of dopaminergic cells in the substantia nigra pars compacta (SNc) [9] and the resultant dopamine deficiency in specific nuclei of the basal ganglia. Along with this substantial neuronal loss, the main pathological hallmark of PD is the presence of intracellular α -synuclein-positive inclusions, known as Lewy bodies and Lewy neurites, throughout subcortical and cortical brain regions [3]. In fact, it has been shown that the injection of synthetic α -synuclein pre-formed fibrils in mice induces Lewy body-like pathology, progressive dopaminergic cell loss in the SNc, and motor impairments [14]. Further, the pathology and progression of PD has been shown to differ between motor subtypes. For example, tremor dominant (TD) patients have a slower rate of progression and

better prognosis than akinetic/rigid, or non-tremor dominant (NTD), patients [22]. Postmortem research has shown that, compared to TD patients, NTD patients have reduced dopamine levels in the internal globus pallidus (GPi) [23] and higher mean overall Lewy body scores, particularly in the frontal cortex [26].

Although invaluable to our understanding of PD, postmortem studies are often limited to the end stages of disease and do not provide information about brain function. Neuroimaging techniques allow brain structure and function to be studied at different stages of disease. However, most PD research is performed on patients with relatively advanced symptomatology who are already being treated with anti-parkinsonian medication. Acute and chronic use of the anti-parkinsonian medication levodopa has been shown to affect brain function in PD [4, 8, 11], and its effect on brain structure is currently under debate [16]. As such, it is often unclear whether the results of PD studies are due to the disease, medication, or a combination of both factors.

Over the past several years, our laboratory has focused on studying early-stage, untreated (i.e., *de novo*) PD patients using magnetic resonance imaging (MRI) at 3 Tesla (T) to gain a better understanding of the disease irrespective of pharmacological treatment. MRI is a widely-available, noninvasive imaging tool that can be used to study the brain structure and function *in vivo*. It does not involve exposure to ionizing radiation and thus can be performed safely (and repeatedly) in most individuals, except those with ferromagnetic implants such as pacemakers and certain stents. Several MRI techniques have been used to study PD, including conventional MRI, volume-based MRI, iron-based MRI (R_2^*), diffusion tensor imaging (DTI), functional MRI (fMRI), and resting-state fMRI. To date, DTI and fMRI have provided the most extensive information about the neurological basis of *de novo* PD. Here we present evidence from DTI and fMRI supporting the central hypothesis that *de novo* PD patients have microstructural alterations in the SN and thalamus, and functional abnormalities throughout the basal ganglia circuitry (i.e., basal ganglia, thalamus, motor cortex, and cerebellum). In addition, we consider these MRI-based abnormalities in the context of motor symptom severity and the NTD and TD subtypes. It is important to note that while PD patients typically present with mild motor symptoms initially [i.e., total score on the motor subsection of the Unified Parkinson's disease Rating Scale (UPDRSm) less than about 30], some studies discussed herein may have included patients who first presented with more severe motor symptoms.

DTI REVEALS MICROSTRUCTURAL BRAIN ABNORMALITIES IN DE NOVO PD

Diffusion tensor imaging (DTI) is sensitive to the magnitude and direction of molecular diffusion in biological tissues. Given that water molecules tend to diffuse parallel to highly organized tissues rather than perpendicular to them, DTI can serve as an indirect measure of tissue microstructure. To model water diffusion, a 3-D ellipsoid known as the diffusion tensor is applied to each voxel in the brain. The diffusion tensor consists of three eigenvalues, which correspond to the magnitude of diffusion along different axes. The primary eigenvalue represents diffusion parallel to the axonal tract (longitudinal diffusivity, LD), whereas the average of the secondary and tertiary eigenvalues corresponds to diffusion perpendicular to the axonal tract (radial diffusivity, RD). In general, LD and RD are ascribed to axonal integrity and the degree of myelination, respectively [27].

The two most widely reported DTI measures, fractional anisotropy (FA) and mean diffusivity (MD), are derived from the three eigenvalues. FA quantifies the degree of anisotropy in a given voxel by comparing diffusion in the longitudinal direction to the two radial directions. FA values range from 0 to 1, with values near 0 reflecting isotropic

diffusion (i.e., equal in all directions) and presumably disrupted microstructure, and values near 1 reflecting anisotropic diffusion (i.e., directionally dependent) and highly organized tissues. One of the limitations of FA is that it is a summary of diffusion in all three directions and therefore nonspecific. It is unclear whether changes in FA correspond to changes in diffusion in the longitudinal and/or radial directions. To gain insight into the underlying pathological processes accompanying FA, some studies also assess LD and RD. Mean diffusivity (MD) quantifies the magnitude of diffusion within a voxel irrespective of direction, and is calculated as the average across all three eigenvalues. High MD values reflect an overall increased rate of diffusion and presumably tissue loss.

In the brain, DTI is typically used to study the connectivity and integrity of white matter tracts, especially changes related to development, aging, injury, and disease. However, there is evidence from a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD, in which dopaminergic neurons in the SN are destroyed, that DTI is also sensitive to changes in grey matter [2]. Specifically, 5 to 7 day post-MPTP-treated animals were shown to have reduced FA and increased MD, RD, and LD in the SN compared to time-matched saline controls. The loss of dopaminergic neurons may reduce physical barriers and disrupt the microstructural integrity of the SN, thereby increasing the magnitude of molecular diffusion (MD) and reducing its directional dependence (FA), respectively. However, the pathology underlying DTI changes in grey matter have not been fully characterized, and the effect of neuronal loss on molecular diffusion remains to be determined.

Several researchers have investigated whether DTI can detect PD-related degeneration in the SN. Table 1 summarizes these DTI studies on the SN and includes all of the reported measures, while the review focuses on the main dependent measure across the studies (i.e., FA). Most of these studies used a region of interest (ROI)-based analysis approach to examine the SN. In general, this method involves manually or semi-automatically defining specific brain regions on an individual basis, and then calculating DTI measures from each region. Given that the motor symptoms of PD become apparent after approximately 50% of the cells in the SNc have been lost, with the most severe loss in the ventrolateral and caudal regions [9], we hypothesized that DTI could detect this degeneration in early-stage, untreated PD patients. Figure 1 shows the mean FA values from two ROI-based studies of the SN, our study on de novo PD patients [34] and a study by Du and colleagues on early-stage (< one year since diagnosis) and later-stage (> 6 years since diagnosis) PD patients already receiving pharmacological treatment [6]. As illustrated, we found that 14 de novo PD patients had significantly reduced FA values in the caudal and middle, but not rostral, regions of the SN compared to 14 age- and sex-matched controls [34]. Moreover, the FA values in the caudal SN differentiated the PD patients from controls with 100% sensitivity and specificity, suggesting that DTI has the potential to serve as a noninvasive early trait biomarker of PD. Consistent with these findings, Du et al [6] recently reported a more substantial reduction in FA values in the caudal than rostral SN of 15 early-stage, but not drug-naïve, patients with PD compared to 28 age- and sex-matched controls. FA in the rostral SN was only reduced significantly in the later-stage patients. Several studies have reported reduced nigral FA values in pharmacologically-treated PD patients compared to controls, but none achieved complete group separation [5, 6, 7, 17, 24, 37, 39]. This relatively lower sensitivity and specificity may be due to disease effects, medication status, and/or methodological differences such as scanner field strength, ROI placement/size, and number of gradient directions.

Although research on de novo and treated PD patients has shown that DTI is sensitive to microstructural abnormalities in the SN, it does not reveal how early in the disease process these changes can be detected and how they may be related to motor symptom severity. Research on healthy aging suggests that SN cell loss less than 50% can be detected by DTI

[35]. Postmortem work has shown that healthy adults lose approximately 33% of the neurons in the SN, primarily in the dorsal region, between the ages of 20 and 90 years [9]. Using DTI, we found reduced FA values in the dorsal, but not ventral, SN of 15 healthy older adults compared to 16 healthy younger adults [35], suggesting that it may be possible for DTI to detect PD before the onset of motor symptoms. Moreover, when taken together with our DTI study on de novo PD [34], these results are consistent with the known patterns of degeneration in healthy aging and PD (i.e., greater cell loss in the dorsal SN in healthy aging and ventral SN in PD) [9].

Postmortem studies of PD have shown that disease-related changes occur beyond the SNc, including in the thalamus and cortex [3]. DTI at 3 T has revealed reduced FA values in the whole thalamus of PD patients receiving anti-parkinsonian medication compared to controls [17, 39]. Given that the thalamus is composed of many distinct nuclei, which *ex vivo* research has shown are differentially affected in PD [25], it is possible that the DTI findings on the whole thalamus were driven by the disruption of only a few select nuclei. It is also unclear whether thalamic changes are present in the early stages of disease. As such, we used DTI to investigate the integrity of the fibers projecting from specific thalamic nuclei in 20 de novo PD patients and 20 age- and sex-matched controls [18]. FA values were calculated in the fibers projecting from ROI seeds in the anterior nucleus, ventral anterior nucleus, ventral lateral nucleus, ventral posterior lateral/ventral posterior medial nuclei, dorsomedial nucleus, and pulvinar. The results showed that indeed only select thalamic nuclei were affected in de novo PD. In particular, FA values were reduced significantly in fibers projecting from the anterior nucleus, dorsomedial nucleus, and ventral anterior nucleus, and reduced marginally in fibers projecting from the ventral lateral nucleus, of the PD group compared to the control group. Another study that examined the ventral lateral nucleus also failed to observe a significant difference in FA values between 12 treated PD patients and 8 age-matched controls [37].

In summary, the evidence presented supports the hypothesis that de novo PD patients have degraded microstructural integrity in subregions of the SN and thalamus compared to healthy controls. An important next step will be to compare these groups using a voxel-based analysis. This approach allows for the detection of local microstructural differences across the entire brain in an operator-independent manner, and may reveal changes in other subcortical and cortical areas of de novo PD.

Relationship between FA values and the Motor Symptoms of de novo PD

Alterations in FA values in PD are presumed to reflect disease pathology and may therefore be related to clinical motor symptoms. In our study of the SN in de novo PD, however, we found that FA values in the three studied subregions did not correlate significantly with motor symptom severity, as measured by the UPDRSm [34]. While one study on treated PD patients also reported the same result for FA values in the rostral and caudal subregions [6], two others observed significant negative correlations between FA values in the whole SN and measures of motor symptom severity [5, 39]. One possible explanation for these discrepant findings is the range of motor symptom severity scores, which tended to be greater in the studies that reported significant correlations. Longitudinal studies will be better able to address the issue of disease progression, as well as the relationship between DTI measures and clinical motor severity. In the thalamus of de novo PD patients, we found a significant negative correlation between UPDRSm scores and FA values in the anterior nucleus [18]. The relationship between motor symptom severity and microstructural integrity of the anterior nucleus, which is involved in emotion and memory, requires further investigation.

Few studies have investigated microstructural brain differences between subtypes of PD. Using DTI at 1.5 T, Tessa et al [31] performed a whole-brain analysis of FA histograms in 11 NTD, 13 TD, and 3 mixed-type patients with de novo PD, as well as 16 age- and sex-matched controls. There was a significant increase in the 25th percentile of the FA histogram in the PD groups compared to controls, with a more marked increase in the NTD group. However, FA values did not correlate significantly with motor symptom severity and could not differentiate the PD patients from controls. The authors suggested that these results reflect a subtle loss of grey matter in de novo PD, and that structural brain differences between NTD and TD patients may be present from the early stages of disease. In a recent DTI study at 4 T, it was reported that the pattern of reduced FA values across the brain varied between treated NTD and TD patients, and that putaminal degradation may be more closely related to the TD subtype [39]. The clinical usefulness of histogram and spatial correlation measures is unclear, and it remains to be determined whether they are predictive of clinical outcomes in NTD and TD patients.

BOLD FMRI IN HEALTHY ADULTS AND DE NOVO PD DURING MOTOR TASKS

Given that PD is a movement disorder, it is not only important to characterize disease-related structural changes in the brain, but also functional changes in response to motor tasks. One common method for studying brain function is blood oxygenation level-dependent (BOLD) contrast fMRI, which relies on the magnetic properties of blood to measure the changes in local hemodynamics related to neuronal activity, namely input and intracortical processing [13]. In other words, BOLD fMRI is sensitive to the metabolic demands of active neurons and can serve as an indirect measure of brain function. It is important to note that BOLD fMRI is a relative, not absolute, measure of brain activity. To investigate what brain areas are functionally involved in a particular task, the BOLD signal is compared between the task and a rest or control condition. As such, the choice of control condition in fMRI experiments is important because it affects the findings.

BOLD fMRI Activation in Healthy Adults during Motor Tasks

In order to shed light on the normal functioning of the basal ganglia-thalamo-cortical circuitry, we conducted a series of fMRI studies on healthy adults while they performed precision grip force tasks. Figure 2 shows the (A) MRI-compatible force-sensitive transducer developed by our laboratory, (B) visual displays that provided cues and feedback to the subjects, and (C) force output from a representative healthy control subject and a patient with de novo PD during the 4-s and 2-s visually-guided force tasks. There are two main reasons for using precision grip force tasks to examine brain function. First, they have ecological validity. One of the most important functions of the hand is to grip objects, especially in the presence of visual input. Further, these tasks do not involve gross body movement, thereby minimizing head motion, which can compromise MRI data. Overall, our fMRI research on healthy individuals has shown that, while all basal ganglia nuclei, the thalamus, several cortical areas, and the cerebellum respond to precision grip force, each area responds preferentially to different aspects of the tasks.

Gripping an object involves several parameters related to force production (i.e., output), including amplitude and rate of change. To examine BOLD activation in relation to force amplitude, we scanned 12 healthy individuals as they produced 4-s pulses against the force-sensitive transducer (Figure 2A) with their dominant right hand [30]. Visual cues and feedback were provided via two vertically displaced bars on a screen, a white cursor bar below a red/green target bar (Figure 2B). The subjects were instructed to generate force pulses when the target bar was green and relax when it was red. The white cursor bar moved

upward in proportion to the amount of force applied to the transducer. The goal was to overlay the white cursor bar on the green target bar. The force level required to reach the green target bar ranged between tasks from 5 to 80% of the subject's maximum voluntary contraction (MVC). The results showed that BOLD activation increased in the primary motor/somatosensory cortex (M1/S1), GPi, subthalamic nucleus (STN), and ventral thalamus, but not the external globus pallidus (GPe), caudate, and anterior and posterior putamen as force amplitude and rate of change of force increased. In a follow-up study that focused exclusively on the cerebellum, BOLD activation was shown to be related to force amplitude in lobule V and vermis VI, rate of change of force in lobule VIIb, and both force amplitude and rate of change of force in distinct sub-regions of lobule VI and crus I/II [28]. Specifically, the BOLD signal was positively correlated with force amplitude and negatively correlated with the rate of change of force.

The basal ganglia-thalamo-cortical circuitry has also been implicated in planning aspects of movement, such as selecting the level of force to apply to an object from a range of possibilities. We investigated the role of these brain areas in force amplitude selection and production by measuring BOLD activation in 10 healthy individuals as they performed two memory-guided precision grip force tasks [36]. In both tasks, subjects viewed a computer screen and produced 2-s force pulses with their dominant right hand when the target bar turned from red to green. In the "same" task subjects were instructed to produce the same level of force on each trial (15% MVC), whereas in the "different" task subjects were instructed to vary their force level from trial-to-trial (average 15% MVC). No visual feedback was provided. The "same" task, which only involves force production, activated the GPi, STN, posterior putamen, M1, and SMA. When compared to the "same" task, the "different" task activated the caudate, dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC), suggesting that these areas are involved in selecting the level of force. The pre-SMA, anterior putamen, and GPe were activated in both tasks, but more so in response to the "different" task, suggesting that these areas may play a role in transforming the selected force amplitudes into a series of produced pulses.

In summary, fMRI on precision grip force in healthy individuals has shown that the anteriorly located basal ganglia nuclei (i.e., anterior putamen, caudate, GPe), DLPFC, ACC, and pre-SMA are more involved in force selection, whereas the posteriorly located basal ganglia nuclei (i.e., GPi, posterior putamen, STN), M1, and SMA are more involved in aspects of force production [36]. In the cerebellum, activation related to force amplitude was located superior and medial, whereas activation related to force rate was inferior and lateral [28]. At present, it is not known whether areas within the cerebellum are preferentially involved in force production and selection.

BOLD fMRI Hypoactivation in de novo PD during Motor Tasks

Based on the results from healthy individuals, we hypothesized that de novo PD patients would show widespread dysfunction in the basal ganglia circuitry during precision grip force tasks. Using fMRI, we compared BOLD activation between 14 de novo PD patients and 14 age-, sex-, and handedness-matched controls producing 2-s and 4-s visually-guided force pulses of the same amplitude [29]. Patients used their most-affected hand and controls used the same hand as their PD match. Figure 2C shows the force output from a healthy control subject and de novo PD patient performing each of the tasks. During the 4-s task the PD patients were hypoactive only in the putamen, GPe, and thalamus, whereas in the 2-s task they were hypoactive in all basal ganglia nuclei, the thalamus, M1, and SMA. As shown in Figure 3, the reduced BOLD activation in these areas during the 2-s task was replicated in a larger sample of 20 de novo PD patients and 20 controls [20]. Further, there was a significant interaction between group and time in these areas during the 2-s task, but not the 4-s task [29]. Figure 4 shows the BOLD signal from the anterior putamen, posterior

putamen, and GPe for the 2-s and 4-s tasks. The BOLD hypoactivation in the PD group was more marked near the end of the 2-s task than near the beginning. Thus, a motor task that required increased alternations between muscle contraction and relaxation resulted in more widespread activation deficits in the basal ganglia of de novo PD patients, and this abnormal activation became more pronounced with prolonged task performance. Consistent with these findings, an earlier study at 1.5 T that focused exclusively on the cortex revealed reduced BOLD activation in contralateral M1 and SMA of 8 de novo NTD patients compared to 10 age-matched controls during an auditory-paced finger opposition task [4]. There was also a significant correlation between motor task performance and the BOLD signal in contralateral M1 for all patients and SMA for most patients. Activation in these areas increased and motor task performance improved following the administration of levodopa.

The hypoactivation in motor cortex is hypothesized to be the result of “functional deafferentation” [32], or reduced excitatory signaling from the thalamus to the cortex in the basal ganglia-thalamo-cortical circuitry [1]. Two fMRI studies at 1.5 T have reported hypoactivation in contralateral M1/S1, as well as bilateral cerebellum, when de novo PD patients performed simple or complex self-paced motor tasks without visual feedback using their most-affected dominant right hand [32, 33]. In addition, the PD patients were hyperactive during the simple continuous tapping task in the contralateral temporal-parietal cortex, parietal superior and inferior gyri, temporal superior gyrus, and ipsilateral M1/S1 [32]. As suggested by the authors, this mixed pattern of hypo- and hyperactivation may reflect the coexistence of functional deafferentation and compensatory mechanisms [32].

The reduced BOLD activation in M1 of de novo PD patients is contradictory to fMRI studies of treated PD patients with more advanced symptomology, in which increased BOLD activation was observed during simple motor tasks. Further, BOLD hypoactivation, particularly in the basal ganglia, is not as widespread in these patients. In a study of PD patients already receiving dopamine replacement therapy, we showed that only the putamen, SMA, and pre-SMA were hypoactive and that M1 and the cerebellum were hyperactive compared to age- and sex-matched controls during both automatic and cognitively-controlled motor timing tasks using the right thumb [38]. The BOLD signals from the cerebellum and putamen were correlated negatively with each other, suggesting that the cerebellum may be compensating for the dysfunctional basal ganglia. On the other hand, the BOLD signal in M1 was correlated positively with rigidity subscores from the UPDRSm, suggesting that M1 hyperactivation may reflect the motor symptoms of PD. Overall, fMRI on de novo and treated PD patients suggests that functional deafferentation may explain the widespread hypoactivation in the early stages, whereas compensation and disease symptomology may explain cerebellar and M1 hyperactivation, respectively, in the later stages.

BOLD fMRI and the Motor Symptoms of de novo PD

To examine the relationship between brain function and motor symptom severity in de novo PD, we performed a correlation analysis between the BOLD signal in the basal ganglia, thalamus, and several cortical areas during the 2-s visually-guided “same” pulse task and UPDRSm scores [20]. For total UPDRSm scores, there were significant negative correlations observed in bilateral caudate, putamen, STN, thalamus, contralateral GPe, and contralateral SN. The relationship between the BOLD signal and the UPDRSm subscores of tremor, bradykinesia, axial function, and rigidity were also examined. The bradykinesia subscore most consistently predicted the BOLD signal in all basal ganglia nuclei (except ipsilateral GPi and bilateral SN) and the thalamus, whereas the tremor subscore was most closely related to the BOLD signal in contralateral GPi. During a complex motor task using the hand, another study at 1.5 T reported that activation in several areas, including M1/S1 and SMA, and contralateral supramarginal, parietal inferior, parietal superior and frontal

superior gyri, and ipsilateral parietal and angular gyri increased with motor symptom severity in de novo PD patients [33]. Collectively, these results suggest that fMRI has the potential to serve as a noninvasive state biomarker of PD. Of course, studies that relate the BOLD signal in specific brain areas to motor symptom severity over time are needed to evaluate this possibility.

To the best of our knowledge, only two fMRI studies have investigated whether there are functional brain differences between subtypes of PD. We used fMRI to study 10 TD and 10 NTD patients who were drug-naïve and 20 age-matched controls during the 2-s visually-guided “same” pulse task [19]. As shown in Figure 5, NTD patients had reduced activation compared to TD patients in several areas, including bilateral DLPFC, contralateral pre-SMA, ipsilateral IPL, ipsilateral thalamus, contralateral caudate, and contralateral GPi and GPe. Further, NTD patients had reduced BOLD activation in GPi, GPe, and ipsilateral DLPFC compared to TD patients and controls, whereas TD patients had increased activation in contralateral DLPFC compared to NTD patients and controls. The finding of GPi dysfunction in NTD patients is consistent with previous fMRI and postmortem work [20, 23], suggesting a role of this area in parkinsonian tremor. NTD patients have also been shown to have higher mean overall Lewy body scores than TD patients, particularly in frontal areas [26], which may help explain the reduced BOLD activation in ipsilateral DLPFC. These fMRI results suggest that differences in BOLD activation in the basal ganglia-thalamo-cortical circuitry between de novo PD patients and controls are driven primarily by patients with the NTD subtype. Further, the widespread activation deficits observed in the NTD patients, but not the TD patients, may be able to help differentiate the subtypes.

Another recent fMRI study at 3 T examined 8 NTD and 9 TD patients who were treated and 14 age-matched controls while they performed a sequential finger tapping task with their dominant right, but not necessarily most-affected, hand [12]. The percentage of activated voxels in ROIs within the striatal-thalamo-cortical circuit (STC) and cerebellar hemisphere/vermis-thalamo-cortical (CHTC/CVTC) circuits was compared between the groups. The STC circuit was comprised of the lentiform nucleus (i.e., putamen and globus pallidus), thalamus, SMA, and M1. Both CTC circuits included the thalamus, lateral premotor cortex, and S1. In addition, the cerebellar hemisphere was in the CHTC circuit and the cerebellar vermis/dentate was in the CVTC circuit. Overall, PD patients had increased activation in all of the circuits, which is consistent with previous research on pharmacologically-treated patients showing hyperactivation in M1 and the cerebellum [38]. Compared to controls, the NTD patients were hyperactive in the contralateral CTC circuits and TD patients were hyperactive in the contralateral STC and CTC circuits. When the PD subtypes were compared directly to each other, the NTD patients had increased activation in the ipsilateral STC and CTC circuits. There were no significant between-group differences for any individual ROIs within the circuits. This work showed that the STC and CTC circuits are differentially affected in the NTD and TD subtypes of PD, which may account for the heterogeneous clinical presentation of the disease.

SUMMARY AND FUTURE DIRECTIONS

MRI is a noninvasive and objective means to study the brain *in vivo*. Given that chronic pharmacological treatment may influence imaging results, it is important to study drug-naïve and treated patients to gain a clear understanding of the neurological basis of PD. Figure 6 summarizes DTI and fMRI work on de novo PD patients in a simplified schematic diagram of the basal ganglia circuitry. As illustrated, the results support the hypothesis that early-stage, untreated PD patients have altered microstructural integrity in the SN and thalamus,

and abnormal functional activation in the basal ganglia, thalamus, motor cortex, and cerebellum.

DTI research using an ROI-based analysis approach has shown that the microstructural integrity of the middle and caudal SN and specific nuclei of the thalamus are disrupted in de novo PD [18, 34]. Although these results are consistent with postmortem research showing degeneration of the SN and thalamus in PD [9, 25] they do not shed light on the neurological extent of the disease. A histogram analysis of whole-brain grey and white matter FA maps suggests that there is a global reduction in grey matter in de novo PD [31]. However, voxel-based analyses of DTI data are needed to provide a more comprehensive picture of the microstructural changes in these patients.

fMRI has revealed reduced BOLD activation in all of the basal ganglia nuclei, the thalamus, several cortical areas [20, 29], and the cerebellum [32, 33], in de novo PD patients during motor tasks compared to rest. In addition, the BOLD signal is related to bradykinesia in most basal ganglia nuclei and tremor in GPi. Moderate PD patients who are already receiving pharmacological treatment have reduced activation in the putamen, SMA, and pre-SMA, but increased activation in M1 and the cerebellum [38]. This pattern of hypoactivation in the early stages and a combination of hypo- and hyperactivation in the later stages may reflect the reduced outflow from the thalamus during the earliest stages of disease and compensatory neural reorganization as the disease progresses. Longitudinal studies of PD are necessary to assess how disease progression and anti-parkinsonian medication affect the structure and function of the brain.

As highlighted by the dashed boxes in Figure 6, fMRI has also shown that de novo TD and NTD patients have differential BOLD activation in the globus pallidus and DLPFC [19]. These results suggest that fMRI may be useful in studying how targeted therapeutic interventions affect PD subtypes. An important next step will be to determine whether BOLD activation differs between other subtypes of PD, and if so, whether it is related to current or future behavioral impairments.

Although a full discussion is beyond the scope of this review, it is important to mention other MRI-based techniques, namely iron-based MRI (R_2^*) and resting-state fMRI, that show promise in understanding de novo PD. R_2^* is a structural technique that is sensitive to iron concentration, which is higher in the SN of PD patients than controls. In pharmacologically-treated patients with PD, R_2^* values in the SN are elevated [6, 7, 17], and in the rostral and caudal portions of the SN they are positively correlated with motor symptom severity [7]. Resting-state fMRI measures the level of spontaneous temporal BOLD co-activation of different brain regions while at rest. As such, this technique provides insight into the function of the brain irrespective of task or task performance. Several resting-state fMRI studies have been conducted on PD. However, only one has focused on de novo patients, showing that functional connectivity in the SMA was reduced significantly compared to controls, and that administration of levodopa increased functional connectivity to normal levels in these patients [8].

In conclusion, MRI-based work shows that the microstructural integrity of the SN and thalamus, and functional activation in the basal ganglia, thalamus, motor cortex, and cerebellum are abnormal in de novo PD compared to controls. It is not surprising then that recent research suggests combining multiple structural MR measures (including FA, MD, and R_2^*) from multiple brain targets helps to improve the differentiation between PD patients already receiving anti-parkinsonian medication and controls [7, 15, 17]. Future research should investigate whether a multi-modal approach can identify brain differences between de novo PD (including subtypes) and controls, and if so, whether they provide

increased sensitivity and specificity for differentiating the groups. By including techniques such as DTI and fMRI, this approach would also help elucidate the relationship between structural and functional brain abnormalities in de novo PD.

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Figure 1.

Mean fractional anisotropy (FA) values in the substantia nigra (SN) across two diffusion tensor imaging (DTI) studies at 3 T that compared patients with Parkinson's disease (PD) to healthy controls [6, 34]. In Vaillancourt et al [34], FA values were calculated from the rostral, middle, and caudal segments of the SN in healthy controls and de novo PD patients. In de novo PD, there was a significant reduction in FA values only in the middle and caudal segments of the SN. Du et al [6] calculated FA values from the rostral and caudal portions of the SN in several groups. Here we present their data from healthy controls, patients with early-stage PD (mostly mild symptoms), and patients with later-stage PD (mostly moderate symptoms). Both of these patient groups had already started treatment with anti-parkinsonian medication. In the caudal segment, FA values were reduced significantly in both PD groups compared to controls, whereas in the rostral segment, FA values were only reduced significantly in the later-stage patients. Taken together, these studies suggest the caudal SN undergoes earlier and more significant microstructural changes than the rostral SN. Asterisks indicate significant group differences ($p < 0.05$). [Adapted from (6).

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Figure 2.

Experimental paradigm used in a series of fMRI studies on precision grip force control, and representative force data from a healthy individual and a patient with de novo Parkinson's disease (PD). A. Fiber optic transducer and interrogator used to collect grip force data. B. Visual displays presented during the tasks. The target bar cued subjects when to produce force (green) and when to rest (red). In visually-guided tasks, the white cursor bar provided feedback by moving upward in proportion to the level of force applied to the transducer. In memory-guided tasks, the same displays were shown to cue subjects when to press and release, but the white cursor bar did not move in response to applied force. C. Actual force

traces from one block of the 4-s and 2-s visually-guided force tasks for one control subject (top panel) and one de novo PD patient (bottom panel).

Figure 3.

Brain regions that showed reduced BOLD fMRI activation in de novo PD patients compared to controls during the production of 2-s visually-guided force pulses of the same amplitude. The center panel shows the basal ganglia and cortical regions of interest from which mean percent BOLD signal change (PSC) was calculated. The surrounding plots show the PSC data from the basal ganglia, medial thalamus, and cortical areas in the control subjects (black bars) and de novo PD patients (red bars). Error bars represent standard error of the mean. The z value refers to the superior-inferior point in Talairach space, with positive z values superior to the anterior commissure and negative z values inferior to the anterior commissure. Abbreviations: GPe, external globus pallidus; GPi, internal globus pallidus; SN, substantia nigra; M1, primary motor cortex; SMA, supplementary motor area; STN, subthalamic nucleus. (Reprinted from (20). Copyright © 2010 John Wiley and Sons. Used with permission.)

Figure 4.

Mean percent BOLD signal change plotted over time for de novo PD patients (empty circles) and healthy controls (filled circles). Data shown are from the anterior putamen (top panel), posterior putamen (middle panel), and external globus pallidus (GPe; bottom panel). The 4-s task is shown on the left and the 2-s task on the right. There was a significant effect of group and time for both tasks, but the interaction was only significant for the 2-s task. The difference in the BOLD signal between the groups was greater near the end of the 2-s task (grey areas) than near the beginning. Error bars represent standard error of the mean. Note that 1 TR (repetition time) = 2.5 s.

Figure 5.

Brain regions that showed reduced BOLD fMRI activation in de novo tremor dominant (TD) compared to non-tremor dominant (NTD) patients during the production of 2-s visually-guided force pulses of the same amplitude. A. In the cortex, the TD group had reduced activation in the inferior parietal lobule (IPL), bilateral dorsolateral prefrontal cortex (DLPFC), and pre-supplementary motor area (pre-SMA). The color bar represents the between-group difference in beta coefficients. B. The top panel shows the color-coded Basal Ganglia Human Area Template [21], which was used to identify activation differences in the basal ganglia. The bottom panel shows reduced activation in the contralateral caudate (green circle), external globus pallidus (GPe; red circle), internal globus pallidus (GPi; orange circle), and ipsilateral thalamus of the TD group. The positive z values refer to points that are superior to the anterior commissure and negative z values refer to points inferior to the anterior commissure. Abbreviation: STN, subthalamic nucleus. (Reprinted from (19). Copyright © 2013 American Medical Association. Used with permission.)

Figure 6.

Schematic diagram of the basal ganglia circuitry that shows the areas revealed by magnetic resonance imaging (MRI) to be structurally and functionally abnormal in de novo Parkinson's disease (PD). All functional MRI (fMRI) results refer to BOLD activation during motor tasks and all diffusion tensor imaging (DTI) results refer to fractional anisotropy (FA) values. The black arrows indicate anatomical connections between brain areas and the white arrows indicate whether de novo PD patients had lower or higher fMRI activation/FA values compared to controls. Boxes with dashed lines denote areas that may be differentially affected in the tremor dominant (TD) and non-tremor dominant (NTD) subtypes of PD (see text for details). Abbreviations: ACC, anterior cingulate cortex; AN, anterior nucleus; DLPFC, dorsolateral prefrontal cortex; DM, dorsomedial nucleus; GPe, external globus pallidus; GPi, internal globus pallidus; M1, primary motor cortex; SMA, supplementary motor area; SNc = substantia nigra pars compacta; STN = subthalamic nucleus; VA = ventral anterior nucleus.

Table 1
Diffusion tensor imaging studies of the SN in Parkinson's disease patients and healthy individuals

Study	Subjects	Scanner strength, T	No. gradient directions	Analysis method	DTI measures	Significant group differences
Yoshikawa et al 2004 [37]	12 treated PD (7 early, 5 advanced) 8 age matched controls	1.5	6	Oval ROI in SN; unilateral	FA	FA↓ in early and advanced PD
Chan et al 2007 [5]	73 treated PD 78 age/sex matched controls	1.5	12	Oval ROI in SN; bilateral	FA, MD	FA↓ in PD
Vaillancourt et al 2009 [34]	14 de novo PD 14 age/sex matched controls	3.0	27	Circular ROI in rostral, middle, caudal SN; bilateral	FA, MD, RD, LD	FA↓ RD↑ in middle and caudal SN of PD LD↓ across SN of PD
Menke et al 2009 [15]	10 treated PD 10 age/sex matched controls	3.0	60	Whole SN ROI; bilateral	FA	None
Péran et al 2010 [17]	30 treated PD 22 age/sex matched controls	3.0	30	Whole SN ROI; bilateral; Also VBA	FA, MD	FA↓ MD↑ in PD
Roller et al 2011 [24]	14 treated PD 14 age/sex matched controls	1.5	31	Whole SN ROI; bilateral	FA, MD, RD, LD	FA↓ RD↑ in PD
Du et al 2011 [7]	16 treated PD 16 age/sex matched controls	3.0	42	Whole SN ROI; bilateral	FA, MD, RD, LD	FA↓ in PD
Focke et al 2011 [10]	12 treated PD 13 age matched controls	3.0	24	Whole SN ROI; bilateral	FA, MD	None
Zhan et al 2012 [39]	12 treated male PD, 20 age/sex matched controls	4.0	6	Whole SN ROI, bilateral; Also VBA	FA, MD	FA↓ in PD
Du et al 2012 [6]	40 treated PD (15 early, 14 middle, 11 later stage) 28 age/sex matched controls	3.0	42	Whole caudal and rostral SN ROIs; bilateral	FA, MD, RD, LD	FA↓ in caudal SN of total, early, middle, and later stage PD RD↑ in caudal SN of total and later stage PD FA↓ in rostral SN of total and later stage PD
Vaillancourt et al 2012 [35]	16 younger adults 15 older adults	3.0	27	Two circular ROIs in dorsal and ventral SN; bilateral	FA, MD, RD, LD	FA↓ LD↓ RD↑ in dorsal SN of older adults

Abbreviations: DTI = diffusion tensor imaging; FA = fractional anisotropy; LD = longitudinal diffusivity; MD = mean diffusivity; PD = Parkinson's disease; RD = radial diffusivity; ROI = region of interest; SN = substantia nigra; T = Tesla; VBA = voxel-based analysis