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Illuminating Basal Ganglia and Beyond in Parkinson’s Disease

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Across the globe, we have been witnessing considerable growth in the number of people diagnosed with Parkinson’s disease. Estimates from the Global Burden of Disease Study indicate that from 1990 to 2015 the number of PD diagnoses doubled, with more than 6 million people who currently carry the diagnosis.3,4 As the population ages, Dorsey and Bloem5 suggest that anywhere between 12 and 14.2 million people will be diagnosed in 2040. As the number of diagnoses increases and the cost of health care continues to rise, cost-effective biomarkers will be needed to improve diagnosis, prognosis, and the monitoring of drug trials. Magnetic resonance imaging (MRI) is a technology with a substantial upside as it is noninvasive, and many markers have been developed recently to study brain pathology in many areas of the central nervous system.

In this issue of Movement Disorders, 4 articles have used magnetic resonance imaging to uncover new insights into the structural deficits in Parkinson’s disease in a key region of importance, namely, the substantia nigra (SN). Three types of biomarkers were investigated that can investigate iron load, neuromelanin content, and microstructural changes using diffusion imaging in the SN. The findings from these articles use different designs and cut across pathological validation and longitudinal progression of MRI iron-sensitive markers in the SN, the relationship between neuromelanin changes in the SN and brain stem atrophy in PSP, and diffusion changes in a novel at-risk cohort.3-6

Lewis and colleagues5 provide a unique study to compare susceptibility measurements from a T2*-weighted multigradient-echo sequence and pathology from tissue in the same individuals. The authors compared R2* and quantitative susceptibility mapping (QSM) of the SN directly with pathology, including SN cell counts, α-synuclein, tau, and iron quantification. An added strength of the R2* and QSM measures are that they are reliable and reproducible markers from the SN and other regions.7 Lewis and colleagues5 found increased R2* for those subjects positive for α-synuclein staining, whereas QSM was not different for the presence of α-synuclein, and neither MRI measure related to the presence of tau in the SN. Perls’ staining reflects iron deposition, and the QSM measure was significantly correlated with the presence of iron, but the R2* measure did not quite reach significance. Previous pathological studies have shown Perls’ staining overlapped with areas of low T2* in the SN,8 and T2 and T2* mapping can distinguish between the neuromelanin-iron complex and ferric iron.9 This study is important because it demonstrates for the first time that an MRI marker in the substantia nigra relates directly to the presence of α-synuclein pathology in the same individuals, and it suggests that R2* and QSM relate to pathology differently. In the study by Du and colleagues,3 these same imaging parameters, R2* and QSM, were compared longitudinally from baseline to 18-month follow-up, in both control subjects and PD. The investigation of both controls and PD is a critical aspect of the study design, as it helps to rule out the effects of age on the biomarker under question, and without this comparison it is difficult to indicate that the change observed longitudinally is specific to PD. Du and colleagues3 studied 3 PD subgroups based on disease duration: PD early (<1 year), PD middle (<5 years), and PD late (>5 years). Interestingly, both R2* and QSM were higher in the SN for PD versus controls at baseline, but only the R2* measure changed longitudinally. In particular, the R2* measure showed a faster increase than the control group in the PD late group, although the PD early and PD middle groups did not show a significant increase compared with the control group. In other work, free-water measures from diffusion-weighted MRI within the posterior substantia nigra have been found to
increase longitudinally within 1, 2, and 4 years of being diagnosed with PD. It may be useful to consider the combination of these SN markers in future studies to compare the progression of PD in different stages of the disease.

It is established that PSP patients have considerable atrophy of the midbrain and the SN is affected in PSP to a greater extent than PD. It is less clear how midbrain atrophy and markers from the SN are related and how these markers relate to motor deficits in PSP. The study by Taniguchi and colleagues examined this unique question using neuromelanin-sensitive MRI, and a T1-weighted MRI sequence for examining midbrain atrophy. The study also included a control group and a group of patients with PD. It was found that neuromelanin-sensitive measures and midbrain volume were reduced in the PSP group compared with the PD group and control groups, whereas the neuromelanin-sensitive SN measures related to motor deficits in PD and the midbrain volume related to motor deficits in PSP. Interestingly, there was not a significant correlation between neuromelanin-sensitive measures from the SN and midbrain volume for both disease groups. This set of findings is interesting because it suggests a distinction between a marker from the SN and midbrain atrophy. It is possible that the lack of correlation relates to the degeneration in PSP that is occurring beyond the substantia nigra. One also wonders if these 2 markers were not correlated because the measures were taken at the same time, and if there was a temporal offset between the markers, then the relation may be revealed for the PSP group. Given the high presence of tau in the midbrain region and the relation between midbrain volume and PSP motor deficits, earlier interventions and more sensitive early markers are needed to prevent this midbrain atrophy.

In a unique study examining a group of people that are at risk for PD, Heldman and colleagues show new insights into neuroimaging abnormalities that are associated with PD risk markers. The authors combined both diffusion tensor imaging and transcranial sonography (TCS) to study a group of older adults that do not have a PD diagnosis. They used TCS of the SN to determine which individuals have the SN hyperchogenicity sign and those who do not. Then they compared these 2 groups using diffusion tensor imaging and found several differences. The people with positive hyperchogenicity in the SN showed elevated mean diffusivity in the posterior thalamus, inferior longitudinal fasciculus, fornix, and corticospinal tract. Further, there was a negative relation between the mean diffusivity for the posterior thalamus and the corticospinal tract with smell function. The authors did not observe any differences between groups for neuropsychological measures or PD motor deficits. Further, voxel-based morphometry and cortical thickness did not differ between groups, further emphasizing that diffusion imaging is more sensitive to early structural changes than T1-weighted imaging. Given that the authors identified regions of the brain that can be associated with limbic and cognitive functions raises the possibility that some of the nonmotor circuitry may be abnormal in those with the SN hyperchogenicity sign. Other studies may also consider measuring R2*, QSM, and neuromelanin in these types of cohorts and compare with the TCS results. The findings by Heldman and colleagues combined with several other studies examining imaging and PD risk markers provide a unique opportunity to discover new cohorts for both discovery of pathophysiological mechanism that predate clinical diagnosis and, possibly, for therapeutic intervention in the future.

The search for MRI biomarkers in parkinsonism is an active and promising area of research that will improve the diagnosis, prognosis, and monitoring of parkinsonian syndromes. Much remains to be done to validate these markers against pathological data, to assess their interest in disease monitoring and in the context of therapeutic trials, to identify subjects at risk, and to better understand the development of the pathological process before the clinical onset of the disease. These 4 articles have contributed to this growing field of research.

References


