Harnessing advances in structural MRI to enhance research on Parkinson's disease

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Parkinson's disease (PD) is a devastating neurodegenerative disorder that affects nearly 2% of individuals over age 65, totaling five million people worldwide. The disease progresses relentlessly, ultimately leaving many patients wheelchair bound and dependent on caregivers. In the next two decades, the incidence of PD is projected to double, making research on the causes and treatments of PD timelier and more relevant to global public health than ever before. At the same time, conventional structural magnetic resonance imaging (MRI) techniques have not proven to be effective tools for diagnosing PD and have been of little utility even in experimental studies of PD. This editorial will briefly review recent advances in applying new MRI methods to the study of PD and will suggest new directions that are likely to yield better MRI-based research and diagnostics tools.

Brain structures affected by PD

PD is typically characterized by its cardinal motor symptoms: resting tremor, muscular rigidity, bradykinesia, postural instability, and gait abnormality [1]. In terms of clinical presentation, however, heterogeneity of symptoms is the rule in PD. For example, studies show the presence of distinct subgroups related to severity of motor symptoms, rate of disease progression, and cognitive and emotional fluctuations. These non-motor sequelae of the disease can be markedly debilitating [2].

The cardinal motor symptoms of PD are largely explained by degeneration of the dopaminergic substantia nigra, pars compacta (SNpc) [1]. In contrast, cognitive, emotional, and psychiatric aspects of PD likely result from disruptions in multiple neurotransmitter systems, including nondopaminergic nuclei such as the cholinergic basal forebrain and noradrenergic locus coeruleus. Research on the differential neuroanatomical underpinnings of motor and nonmotor aspects of the disease, however, has been hindered by a lack of sensitive MRI methods for visualizing the affected subcortical structures. The availability of new MRI biomarkers for classifying patients into subgroups with distinct patterns of brain abnormalities will enable clinicians to predict which patients are likely to develop particular symptoms and to shape therapies to meet each patient's needs.

Current limitations of MRI in PD

A major impediment to research on the neural basis of functional heterogeneity in PD is a paucity of safe, fast, and effective brain imaging methods for visualizing the affected

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structures. This ineffectiveness is due predominantly to the limited contrast of most current MRI methods [3, 4], which are unable to detect PD abnormalities. Because conventional structural MRI techniques cannot visualize the brain changes that are at the core of this disease, progress in developing MRI-based biomarkers for diagnosing and tracking disease progression has been slow.

A few methods for imaging the SNpc have met with some success, such as evaluation of T2 relaxation times [5], T2*- and diffusion-weighted imaging [6], inversion-recovery sequences [7], and proton density-weighted imaging [8]. Other studies have resolved the basal forebrain on T2-weighted images, demonstrating reduced thickness of this structure in mildly demented PD patients, compared to controls [9]. A limitation of these previous structural neuroimaging studies, however, is that the MRI sequences were typically optimized to resolve one particular structure, and, therefore, were not well suited for visualizing other brain areas. We recently reported new multispectral MRI methods that begin to reverse this serious shortcoming [10], paving the way to the development of new MRI-based biomarkers that are capable of detecting subcortical brain abnormalities in early stages of the disease.

Traditionally, the MPRAGE scan has been the gold standard for performing morphometric analyses, such as volumetrics [11] and surface-based analyses [12], because the resulting T1-weighting provides relatively good contrast between gray matter, white matter, and cerebrospinal fluid. The MPRAGE scan is less useful, however, for distinguishing subcortical structures, because T1-weighting doesn't provide sufficient contrast between small, neighboring gray matter nuclei. Additional morphometric information can be obtained through different sequences, such as T2-SPACE [13] and multiecho FLASH (ME-FLASH) [14]. Combining these different scans is complicated by variability in their relative distortions resulting from different bandwidths among these sequences. The T2-SPACE and ME-FLASH employ a high bandwidth, while maintaining good signal-to-noise; however, the conventional MPRAGE requires a lower bandwidth in order to achieve comparable signal-to-noise. Differing bandwidths lead to massive variations in the B0 distortions, resulting in images that are not able to be coregistered.

Application of multispectral MRI to PD

To overcome these obstacles, our colleagues developed a multiecho MPRAGE sequence that is bandwidth-matched to the T2-SPACE and ME-FLASH [15]. We have shown that high-bandwidth T1-weighted multiecho-MPRAGE (ME-MPRAGE) data are superior to conventional T1-weighted images for anatomical analyses of cortical structures [15, 16]. Further, multiecho sequences are less prone to distortion and have a higher contrast-to-noise ratio for subcortical structures [15]. Thus, these scans provide a valuable new approach to visualizing the subcortical structures that have been implicated in PD.

Multispectral MRI refers to a set of sequences designed to overcome a major hurdle in brain morphometry studies. Specifically, accurate alignment of multiple scans with different contrasts requires that the images have similar distortions. For multispectral MRI, we acquire four bandwidth-matched sequences in a single visit: ME-MPRAGE, ME-FLASH with proton density weighting, T2-SPACE, and T2-SPACE Fluid-Attenuated Inversion Recovery (FLAIR). We then use linear discriminant analysis to create a weighted average of the multiple scans to obtain weighting coefficients with optimized contrast-to-noise ratio for each structure of interest. The final product is a weighted average of the multispectral images with optimal contrast for a particular structure, which is then labeled manually.

Because this new multispectral MRI method provides excellent contrast for the SNpc and basal forebrain, we applied these methods to data from PD patients and controls to show that

these structures display different trajectories of volume loss early in the disease [10], confirming a prominent hypothesis regarding the pattern of disease progression in PD. While these multispectral methods represent a significant advance in the utility of MRI for studying PD, obstacles remain. Namely, semi-automated segmentation and parcellation packages do not currently work with multispectral data, thus requiring the laborious task of manually labeling each structure of interest. In addition, while multispectral MRI provides improved contrast for subcortical structures, delineation of small nuclei remains limited by the resolution of the multispectral sequences (1mm isotropic) and the field strength (3T) at which the scans are collected.

Advancing brain mapping with *ex vivo* MRI

Recent progress in using an *ex vivo* model has led to greater accuracy in MRI-based brain mapping [17, 18]. The term *ex vivo* refers to scanning autopsied tissue. *Ex vivo* imaging provides validation to histological stained sections and long scan sessions without motion, resulting in exceptional contrast and high signal-to-noise. Moreover, no delay between the MRI and histology exists so that it authenticates the MRI. This critical validation represents the cornerstone of *ex vivo* brain mapping. Of course, *ex vivo* imaging has the limitation that registration (between the lower resolution scan of a whole hemisphere and the high resolution scan of a smaller tissue block that contains the region of interest) can be challenging, especially in cases with poor contrast or deformations. Nonetheless, the advantages outweigh the disadvantages and *ex vivo* imaging produces precise maps based on additional histological information and not just topographical sulcal patterns.

Currently, the segmentation of SNpc and basal forebrain, as well as numerous other small subcortical nuclei, lack specific labels in most automated parcellation packages. In recent work, we demonstrated cortical architecture with *ex vivo* methods that map cortical areas in the medial temporal lobe and even outlined subareas 35a and 35b in perirhinal cortex [19, 20]. A future goal is to use similar *ex vivo* neuroanatomical modeling to augment multispectral MRI. In particular, higher resolution *ex vivo* methods, which are capable of achieving a resolution of $100\mu m^3$ when images are acquired at 7T, may resolve the SNpc from the functionally and anatomically distinct substantia nigra pars reticulata, leading to better probabilistic mapping of dopaminergic and other small nuclei. Thus*, ex vivo* methods hold promise for enhancing our ability to visualize very small structures, such as the noradrenergic locus coeruleus and the serotonergic raphe nuclei, degeneration of which may underlie sleep disturbances and depressive symptoms associated with PD [2].

Conclusion

Combining multispectral and *ex vivo* MRI methods to map precisely the structures of the basal ganglia will constitute a much needed advance in research on PD. The combination of multispectral imaging with better morphometric MRI evaluation will enable categorization of patients based on patterns of brain changes and will establish biomarkers for patient subgroups. Such improvements will ultimately enhance patient care by paving the way for fine-tuning diagnosis and tracking of the disease, as evidenced by parallel progress in other neurodegenerative diseases [21-23]. Better categorization, earlier diagnosis, and the ability to track the disease longitudinally will improve treatments and patient well-being. These advanced methods will enable scientists and physicians to derive a detailed profile of brain changes in each patient and thereby tailor therapies on an individual basis.

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References

1. Shulman JM, De Jager PL, Feany MB. Parkinson's disease: genetics and pathogenesis. Annual review of pathology. 2011; 6:193–222.

2. Lim SY, Fox SH, Lang AE. Overview of the extranigral aspects of Parkinson disease. Arch Neurol. 2009; 66(2):167–172. [PubMed: 19204152]

3. Godau J, Hussl A, Lolekha P, Stoessl a J, Seppi K. Neuroimaging: current role in detecting pre-motor Parkinson's disease. Mov Disord. 2012; 27(5):634–643. [PubMed: 22508281]

4. Marek K, Jennings D. Can we image premotor Parkinson disease? Neurology. 2009; 72(7 Suppl):S21–26. [PubMed: 19221310]

5. Kosta P, Argyropoulou MI, Markoula S, Konitsiotis S. MRI evaluation of the basal ganglia size and iron content in patients with Parkinson's disease. J Neurol. 2006; 253(1):26–32. [PubMed: 15981079]

6. Peran P, Cherubini A, Assogna F, et al. Magnetic resonance imaging markers of Parkinson's disease nigrostriatal signature. Brain. 2010; 133(11):3423–3433. [PubMed: 20736190]

7. Hutchinson M, Raff U, Lebedev S. MRI correlates of pathology in parkinsonism: segmented inversion recovery ratio imaging (SIRRIM). Neuroimage. 2003; 20(3):1899–1902. [PubMed: 14642500]

8. Oikawa H, Sasaki M, Tamakawa Y, Ehara S, Tohyama K. The substantia nigra in Parkinson disease: proton density-weighted spin-echo and fast short inversion time inversion-recovery MR findings. Ajnr. 2002; 23(10):1747–1756. [PubMed: 12427635]

9. Oikawa H, Sasaki M, Ehara S, Abe T. Substantia innominata: MR findings in Parkinson's disease. Neuroradiology. 2004; 46(10):817–821. [PubMed: 15316699]

10. Ziegler DA, Wonderlick JS, Ashourian P, et al. Substantia Nigra Volume Loss Before Basal Forebrain Degeneration in Early Parkinson Disease. JAMA Neurol. 2013; 70:241–247. [PubMed: 23183921]

11. Herbert MR, Ziegler DA. Volumetric neuroimaging and low-dose early-life exposures: loose coupling of pathogenesis-brain-behavior links. Neurotoxicology. 2005; 26(4):565–572. [PubMed: 16112322]

12. Ziegler DA, Piguet O, Salat DH, Prince K, Connally E, Corkin S. Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness. Neurobiol Aging. 2010; 31(11):1912–1926. [PubMed: 19091444]

13. Lichy MP, Wietek BM, Mugler JP 3rd, et al. Magnetic resonance imaging of the body trunk using a single-slab, 3-dimensional, T2-weighted turbo-spin-echo sequence with high sampling efficiency (SPACE) for high spatial resolution imaging: initial clinical experiences. Invest Radiol. 2005; 40(12):754–760. [PubMed: 16304477]

14. Fischl B, Salat DH, Van Der Kouwe AJ, et al. Sequence-independent segmentation of magnetic resonance images. Neuroimage. 2004; 23(Suppl 1):S69–84. [PubMed: 15501102]

15. Van Der Kouwe AJ, Benner T, Salat DH, Fischl B. Brain morphometry with multiecho MPRAGE. Neuroimage. 2008; 40(2):559–569. [PubMed: 18242102]

16. Wonderlick JS, Ziegler DA, Hosseini-Varnamkhasti P, et al. Reliability of MRI-derived cortical and subcortical morphometric measures: effects of pulse sequence, voxel geometry, and parallel imaging. Neuroimage. 2009; 44(4):1324–1333. [PubMed: 19038349]

17. Augustinack JC, Van Der Kouwe a J, Blackwell ML, et al. Detection of entorhinal layer II using 7Tesla [corrected] magnetic resonance imaging. Ann Neurol. 2005; 57(4):489–494. [PubMed: 15786476]

18. Eickhoff S, Walters NB, Schleicher A, et al. High-resolution MRI reflects myeloarchitecture and cytoarchitecture of human cerebral cortex. Human brain mapping. 2005; 24(3):206–215. [PubMed: 15543596]

19. Augustinack JC, Huber KE, Stevens a A, et al. Predicting the location of human perirhinal cortex, Brodmann's area 35, from MRI. Neuroimage. 2013; 64:32–42. [PubMed: 22960087]

20. Fischl B, Stevens AA, Rajendran N, et al. Predicting the location of entorhinal cortex from MRI. Neuroimage. 2009; 47(1):8–17. [PubMed: 19376238]

21. Bakkour A, Morris JC, Dickerson BC. The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. Neurology. 2009; 72(12):1048–1055. [PubMed: 19109536]

22. Dickerson BC, Bakkour A, Salat DH, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex. 2009; 19(3):497–510. [PubMed: 18632739]

23. Kantarci K, Ferman TJ, Boeve BF, et al. Focal atrophy on MRI and neuropathologic classification of dementia with Lewy bodies. Neurology. 2012; 79(6):553–560. [PubMed: 22843258]