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MR Spectroscopy: A longitudinal biomarker for substantia nigra pathology in Parkinson disease?

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Much has been learned in the last two decades about the pathophysiology of Parkinson's disease (PD), leading to the availability of a highly effective symptomatic treatment, which is still lacking for most other neurodegenerative diseases. However the clinical care of PD still bears many challenges: Differential diagnosis of idiopathic and atypical parkinsonian disorders is challenging, especially at early stages. Levodopa, the standard of care for idiopathic PD, is efficacious for a limited time, and disease modifying therapies have been elusive.¹ Differential diagnosis and development of mechanism-based treatments for PD will be facilitated by neuroimaging biomarkers that can noninvasively assess aspects of the underlying pathology.

PET and SPECT imaging provide great insight on the striatal dopaminergic dysfunction in PD², but are not widely available and require injections of radioactive tracers making repeat scanning problematic. Despite highly successful applications of radionuclide imaging in Parkinsonian disorders, it is clear that the need for robust neuroimaging biomarkers of other aspects of PD pathology remains. In particular, robust, validated imaging biomarkers of the nigral pathology, the hallmark of PD, are lacking. This need has spurred great interest in MR-based biomarkers for PD. Because conventional MR images of patients with idiopathic PD are typically normal³, recent years marked the development and application of many novel MRI methods to evaluate the SN in PD.⁴ Amongst these, ¹H magnetic resonance spectroscopy (MRS) received considerable interest as it enables non-invasive detection of cellular and metabolic alterations in the central nervous system⁵ and therefore is ideally suited to assess pathological changes in the absence of gross morphological alterations.

Many attempts to investigate the SN by MRS suffered from substantial partial volume effects because the studies utilized relatively large volumes-of-interest (VOI) around the SN.^{6–9} In addition to the small size and location of the SN in the midbrain, broad intrinsic linewidths due to high iron content make MRS of the SN challenging. In this issue of *Movement Disorders*, Seraji-Bozorgzad et al¹⁰ report a longitudinal MRS investigation of the SN by magnetic resonance spectroscopic imaging (MRSI) at higher resolution than most prior reports (point spread function corrected VOI 2mL). They scanned 23 medication naïve patients with PD twice, at baseline and 3 months later and report: 1) lower total N-

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acetylaspartate-to-total creatine ratios (tNAA/tCr) than a small healthy control group (N=6) at baseline; 2) a 4% decrease in tNAA/tCr in patients, but not controls, over 3 months and 3) side-to-side asymmetry in tNAA/tCr in the PD, but not in the control group, consistent with the known pathological asymmetry in early PD. tNAA has been validated as a marker of neuronal viability and tCr may reflect energy status or glial activation.^{5, 11} Therefore a decrease in tNAA/tCr ratio may represent neuronal dysfunction or deficits in energy metabolism / gliosis or both. The paper is an important addition to MRS literature in PD that has mostly been cross-sectional. The authors took advantage of the sensitivity and resolution advantages of 3 tesla (3T) and utilized a clinically feasible protocol that only took 30 minutes. However MRS findings in PD have been widely variable¹², with some papers reporting lower tNAA/tCr in patients vs. controls, while many, including studies of the SN at high field, reporting no significant differences between patients and controls.^{13, 14} The medication status of patients may be important in this respect as patients enrolled in most prior studies have been on PD medications and MRS alterations may only be present in the drug naïve cohort.^{15, 16} Another reason for the discrepancy with prior reports on the SN may be the choice of the echo time. Namely, a difference in tNAA/tCr may have been caused by differential T₂ effects of the disease on tNAA vs. tCr at the long echo time utilized—especially considering that altered T₂ values have been reported in the SN in PD, probably due to iron accumulation.¹⁷ It is unlikely that a better alignment of the VOI with the SN enabled the detection of neurochemical alterations in the Seraji-Bozorgzad study since a recent 7T single-voxel MRS study that did not detect a difference in tNAA or tCr in PD vs. controls¹⁴, utilized an even smaller VOI with minimal partial volume effects. Finally, the inability to consistently demonstrate neurochemical alterations in early-moderate PD by different groups may be a testament to the heterogeneity in disease cohorts, as suggested recently.¹⁸

In any case, the Seraji-Bozorgzad study¹⁰ has accomplished substantial improvement in the reproducibility of metabolite ratio measurements in the SN (Fig. 1c) relative to other recent reports of MRSI of the SN¹⁹, which is essential for robust clinical applications. Therefore the study provides motivation to further investigate the potential of MRS/I as a longitudinal biomarker for early PD in larger cohorts and over longer durations of disease progression. Regarding the asymmetry observed in tNAA/tCr in PD¹⁰, it will be critical to delineate if the tNAA/tCr was lower in VOIs encompassing the SN contralateral to the clinically more severely affected side of patients.

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References

1. Obeso JA, Rodriguez-Oroz MC, Goetz CG, et al. Missing pieces in the Parkinson's disease puzzle. *Nat Med.* 2010; 16(6):653–661. [PubMed: 20495568]
2. Stoessl AJ, Lehericy S, Strafella AP. Imaging insights into basal ganglia function, Parkinson's disease, and dystonia. *Lancet.* 2014; 384(9942):532–544. [PubMed: 24954673]

3. Brooks DJ. Morphological and functional imaging studies on the diagnosis and progression of Parkinson's disease. *Journal of neurology*. 2000; 247(Suppl 2):II11–18. [PubMed: 10991656]
4. Lehericy S, Sharman MA, Dos Santos CL, Paquin R, Gallea C. Magnetic resonance imaging of the substantia nigra in Parkinson's disease. *Mov Disord*. 2012; 27(7):822–830. [PubMed: 22649063]
5. Öz G, Alger JR, Barker PB, et al. The MRS Consensus Group. Clinical proton MR spectroscopy in central nervous system disorders. *Radiology*. 2014; 270(3):658–679. [PubMed: 24568703]
6. Choe BY, Park JW, Lee KS, et al. Neuronal laterality in Parkinson's disease with unilateral symptom by in vivo ¹H magnetic resonance spectroscopy. *Invest Radiol*. 1998; 33(8):450–455. [PubMed: 9704284]
7. O'Neill J, Schuff N, Marks WJ Jr, Feiwell R, Aminoff MJ, Weiner MW. Quantitative ¹H magnetic resonance spectroscopy and MRI of Parkinson's disease. *Mov Disord*. 2002; 17(5):917–927. [PubMed: 12360540]
8. Baik HM, Choe BY, Son BC, et al. Proton MR spectroscopic changes in Parkinson's diseases after thalamotomy. *Eur J Radiol*. 2003; 47(3):179–187. [PubMed: 12927660]
9. Nie K, Zhang Y, Huang B, et al. Marked N-acetylaspartate and choline metabolite changes in Parkinson's disease patients with mild cognitive impairment. *Parkinsonism & related disorders*. 2013; 19(3):329–334. [PubMed: 23238068]
10. Seraji-Bozorgzad N, Bao F, George E, et al. Longitudinal High-field MR Spectroscopic Study of the Substantia Nigra in Parkinson's Disease. *Mov Disord*.
11. Mountford CE, Stanwell P, Lin A, Ramadan S, Ross B. Neurospectroscopy: the past, present and future. *Chem Rev*. 2010; 110(5):3060–3086. [PubMed: 20387805]
12. Martin WR. Magnetic resonance imaging and spectroscopy in Parkinson's disease. *Adv Neurol*. 2001; 86:197–203. [PubMed: 11553978]
13. Öz G, Terpstra M, Tkáč I, et al. Proton MRS of the unilateral substantia nigra in the human brain at 4 tesla: Detection of high GABA concentrations. *Magn Reson Med*. 2006; 55(2):296–301. [PubMed: 16408282]
14. Emir UE, Tuite PJ, Öz G. Elevated pontine and putamenal GABA levels in mild-moderate Parkinson disease detected by 7 tesla proton MRS. *PloS one*. 2012; 7(1):e30918. [PubMed: 22295119]
15. Holshouser BA, Komu M, Moller HE, et al. Localized proton NMR spectroscopy in the striatum of patients with idiopathic Parkinson's disease: a multicenter pilot study. *Magn Reson Med*. 1995; 33(5):589–594. [PubMed: 7596261]
16. Ellis CM, Lemmens G, Williams SC, et al. Changes in putamen N-acetylaspartate and choline ratios in untreated and levodopa-treated Parkinson's disease: a proton magnetic resonance spectroscopy study. *Neurology*. 1997; 49(2):438–444. [PubMed: 9270574]
17. Antonini A, Leenders KL, Meier D, Oertel WH, Boesiger P, Anliker M. T2 relaxation time in patients with Parkinson's disease. *Neurology*. 1993; 43(4):697–700. [PubMed: 8469325]
18. Weiduschat N, Mao X, Beal MF, Nirenberg MJ, Shungu DC, Henchcliffe C. Usefulness of proton and phosphorus MR spectroscopic imaging for early diagnosis of Parkinson's disease. *J Neuroimaging*. 2015; 25(1):105–110. [PubMed: 24325203]
19. Gröger A, Chadzynski G, Godau J, Berg D, Klose U. Three-dimensional magnetic resonance spectroscopic imaging in the substantia nigra of healthy controls and patients with Parkinson's disease. *Eur Radiol*. 2011; 21(9):1962–1969. [PubMed: 21484351]