Ultra-High Field MR Microscopy of the Postmortem Human Brainstem

Yosef Berlow[1], Mara Bahri[1], Laura McMahon[1], John Nutt[2], Susan Goelz[3], Ted Yednock[3], Wagner Zago[3], Randall Woltjer[4], C.Dirk Keene[5], and William Rooney[1]

[1]Advanced Imaging Research Center, Oregon Health & Science University, Portland, Oregon, United States, [2]Department of Neurology, Oregon Health & Science University, Portland, Oregon, United States, [3]Prothena, CA, United States, [4]Department of Pathology, Oregon Health & Science University, Portland, Oregon, United States, [5]Department of Pathology, University of Washington, Seattle, Washington, United States

Introduction: Parkinson's disease (PD) is a neurodegenerative, movement disorder characterized by degeneration of dopaminergic cells within the substantia nigra pars compacta and accumulation of alpha-synuclein inclusions within neurons, known as Lewy bodies. The loss of dopaminergic cells within the midbrain displays regional specificity, with greatest loss occurring in the calbindin-poor regions within the pars compacta known as the nigrosomes.[1] Nigrosome 1 has been characterized as having the greatest degree of cell loss in PD and has also been found to contain relatively low iron content compared to the surrounding regions of the substantia nigra.[1,2] This feature provides an endogenous contrast mechanism that allows for the visualization and quantification of this region and its change in PD using MRI.[2] The goal of this study was to collect high quality MRI on postmortem brainstems from patients with and without PD to investigate nigrosomal differences and other potential MR biomarkers of PD pathology.

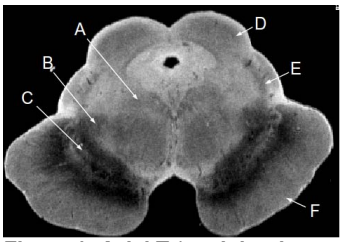

Figure 1: Axial T_2*-weighted image illustrating anatomical details in the midbrain. A. Central tegmental tract; B. Medial lemniscus; C. Substantia nigra; D. Superior colliculus; E. Lateral leminiscus: F. Crus cerebri

Methods: Eleven midbrain specimens were obtained at autopsy from the Departments of Pathology at Oregon Health & Science University (OHSU) and the University of Washington (UW) in accordance with policies and procedures established at each institution. The specimens included three cases from male patients with clinical PD, one case from a male subject with pre-clinical Lewy Body Disease (LBD) (mean age 77±5 years) and seven control cases that were free of neurological disease (2 women, mean age 76±14 years). All MRI data were acquired using an 11.75 T MRI instrument (Bruker). Brainstems were placed in a 120mL syringe, back filled with Fluorinert and positioned in a 500 MHz Alderman-Grant transceiver RF coil. Imaging sequences included high resolution, 3D multi-gradient echo (MGE) series (FOV: 7.68cm x (3.84 cm)^2; matrix 768x(384)^2; TR:30ms; TEs: 4.76, 8.84, 12.91 and 16.99 ms; averages: 2; and FA: 30). Quantitative T_2* maps were generated by fitting a monoexponential decay curve at each voxel of MGE dataset. Anatomical images used for region of interest (ROI) analysis were created by averaging magnitude images from the four echo times and down sampling this averaged image by factor of two. A mask of the substantia nigra was manually identified bilaterally in the midbrain using the areas of hypointensity to define the borders. Voxels within this mask were sorted into three classes using an automated algorithm [3] and the most hyperintense class was edited to include voxels in the ten slices caudal to the red nucleus and identified as nigrosome. Average T_2* values within these regions of interest were calculated.

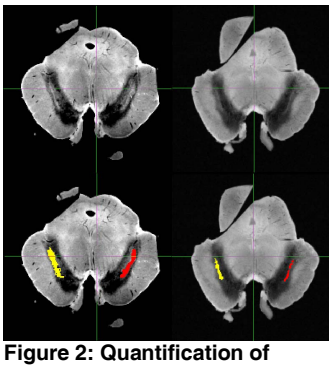

Figure 2: Quantification of nigrosome regions. Axial T_2* weighted MRI of control (left column) and PD (right column) brainstem just caudal to red nucleus (yellow =anatomical left, red = anatomical right).

Results/Discussion: The high resolution, MGE images provide excellent contrast and detail to identify multiple aspects of brainstem anatomy, as illustrated in **Figure 1**. Nigrosome identification and analysis was completed in seven aged match control cases, three clinical PD cases and one preclinical LBD case. Results from the preclinical LBD case were combined with the PD cases to form the LBD group. Examples of the nigrosome identification are illustrated in **Figure 2**. Nigrosome volumes were nominally lower in the LBD group on both the left [LBD mean (±SD), 6.34(±2.65) mm^3; Controls 9.72±4.42 mm^3) and right (LBD 5.12(±2.28) mm^3; Controls 9.41(±5.57) mm^3] (see **Figure 3**). The LBD cases were found to have greater asymmetry [1.48(±0.29)] compared to controls [1.18(±0.15)] (t(9)=2.35, p=0.043)(**Figure 3**). Interestingly, the pre-clinical LBD case showed the greatest asymmetry, and despite many years of established disease, the PD specimens also retained significant left-right nigrosome asymmetry. ROI analysis was completed in six of the aged matched control cases and three LBD cases (including the preclinical LBD case) as shown in **Figure 3**. T_2* time constants were remarkably similar for most regions analyzed, including regions with abundant iron content, such as the substantia nigra and red nucleus. In contrast, the locus coeruleus analysis displayed nominally increased T_2* values in the LBD group (ns). This increase in T_2* would be consistent with loss of neuromelanin or generalized loss of macromolecules in the locus ceruleus.

Conclusion To improve the utility of in vivo MRI for early PD detection, intensive and extensive MRI properties of the postmortem human brainstem were investigated at high spatial resolution using quantitative relaxaographic approaches. The results of this study indicate that both loss and asymmetry of the nigrosome and increased T_2* of the locus ceruleus are promising candidates for early in vivo detection of PD.

Grant Support: Elan/Prothena, NIH UL1-RR02410-S1, Oregon Opportunity, F30-DA033094, T32-AG023477, T32-GM067549

References: **1.** Damier P, Hirsch EC, Agid Y, Graybiel AM. Brain. 1999; 122 (Pt 8):1437-48. **2.** Blazejewska AI, Schwarz ST, Pitiot A, Stephenson MC, Lowe J, Bajaj N, Bowtell RW, Auer DP, Gowland PA. Neurology. 2013; 81(6):534-40. **3.** 3.Zhang, Y. and Brady, M. and Smith, S. IEEE Trans Med Imag, 2001; 20(1):45-57.

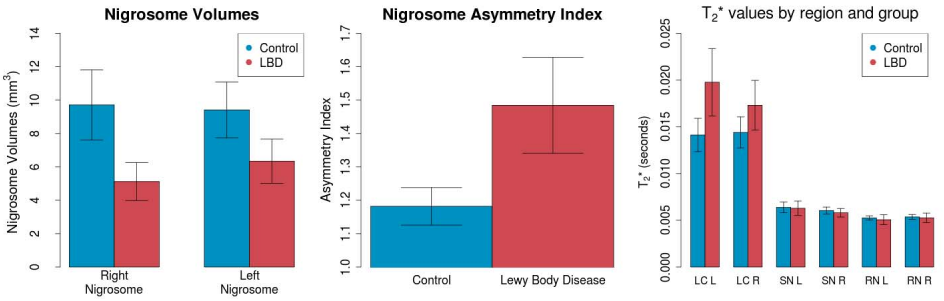

Figure 3. Potential MR biomarkers of Parkinson's Disease pathology. Left: Volumetric analysis of the nigrosome. Middle: Asymmetry index analysis of the nigrosome. Right: Region of interest analysis of T_2 values in the locus coeruleus (LC), substantia nigra pars compacta (SN) and red nucleus (RN).