High Resolution 1H MRI of Postmortem Human Brain Sections Performed at 21.1 T

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Introduction – MR microscopy (MRM) can provide high resolution 3D digital datasets based solely on endogenous contrast mechanisms that are sensitive to factors such as iron content [1], cellular density and white/gray matter ratios [2]. In addition to visual observation and comparison of tissue microstructure in high resolution MR images (*i.e.* healthy control tissue versus pathological sections), quantitative analysis of T_2 and T_2* relaxation times may provide invaluable information about altered intrinsic factors (such as the accumulation of iron in specific regions) that are implicated in a variety of neurodegenerative diseases. In this study, the first MRM evaluations of human pathological tissue at 21.1 T, the highest magnetic field available for MRI, are presented. This ultra-high field strength provides improved sensitivity and enhanced contrast, particularly for those mechanisms that exploit differences in magnetic susceptibility between tissues and pathologies. Specimens harvested from human patients displaying differing degrees of Alzheimer and Parkinson related pathology were analyzed using high resolution imaging and parametric maps of T_2 and T_2* to assess the impact of these diseases on neuroanatomical structures.

Methods – Prior to imaging, fixed postmortem human samples (per structure; n=16) of *substantia nigra* (SN), *globus pallidus* (GP) and hippocampus (HC) were washed in phosphate buffered saline (1xPBS) and immersed in Fluorinert (FC-43, 3M Corp). All MR data were acquired using a 21.1-T vertical magnet equipped with a Bruker Avance III console and Micro2.5 gradient system. Utilizing a 33-mm birdcage coil, high resolution ^{1}H scans were acquired at 14 C. Three-dimensional Fast Low Angle Shot (FLASH) scans (TE = 4-12 ms; TR = 50 ms) were acquired over 4.3 hours at the isotropic resolution of 50 µm. T_2 relaxation was quantified using multi-slice spin-echo sequences (MSSE) acquired with TR = 2.5 s and TEs ranging between 7.9-94.8 ms. To determine T_2* relaxation, multiple gradient echo (MGE) sequences were acquired with TR = 0.75 s and TEs ranging between 3.5-45.5ms. For all relaxation measurements, spatial resolution was 100x100x550 µm. T_2 and T_2* relaxation were fitted by single exponential regression using manually drawn ROIs placed on certain structures and a pixel-by-pixel analysis for parametric mapping.

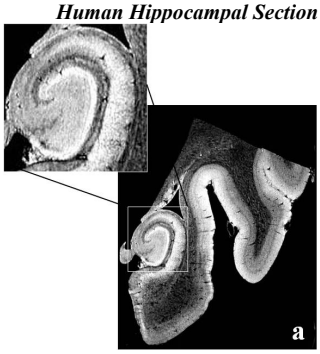

Fig 1. 3D FLASH partitions (TE/TR=12/50 ms, iso. R=50 µm, acquisition time=4.3 hrs) of a (a) healthy hippocampal section at 21.1 T (900 MHz). Inset: magnified views of the hippocampus.

Results & Discussion – Compared to controls, 3D micrographs of neurodegeneration display heterogeneity in MRM contrast that appears related to iron distribution, particularly for specimens expressing higher degrees of Parkinsonism. Meanwhile, Alzheimer's specimens displayed pronounced alterations in tissue microstructure. Pathological sections of SN and GP demonstrate a significantly stronger T_2/T_2* contrast in the structures and surrounding fiber tracts, possibly due to accumulation of iron, than sections obtained from healthy control subjects. Control images of the hippocampus display strong cell layer delineation (Fig 1.), with hippocampal regions (CA 1-3) clearly visible, while dementia-related pathological sections, in particular from sclerotic patients, lack hippocampal definition and display significantly reduced volume as well as cell layer compression.

Based on an ROI analysis, pyramidal tracts of the brainstem demonstrated T_2/T_2* increases for all pathologies compared to controls. The basal ganglia's putamen shows decreased T_2 while the external GP display decreased T_2* for all pathologies. Statistical significance also was found between hippocampal control sections and all other pathologies for T_2 in gray matter and CA1, while T_2* measurements display significance in CA2 and CA3. Parametric maps (examples in Fig 2-4) display additional differences between pathologies that not evident from the ROI analysis. For example, for severe Parkinsonism, parametric maps display significant drops in T_2/T_2* values in regions of the SN and GP where iron is known to accumulate. In these specific areas, relaxation values dropped below the threshold of the parametric mapping; however, this information may prove valuable in categorizing the severity of the Parkinsonism pathology. Histological evaluations are underway to verify the biophysical origins of MRM contrast.

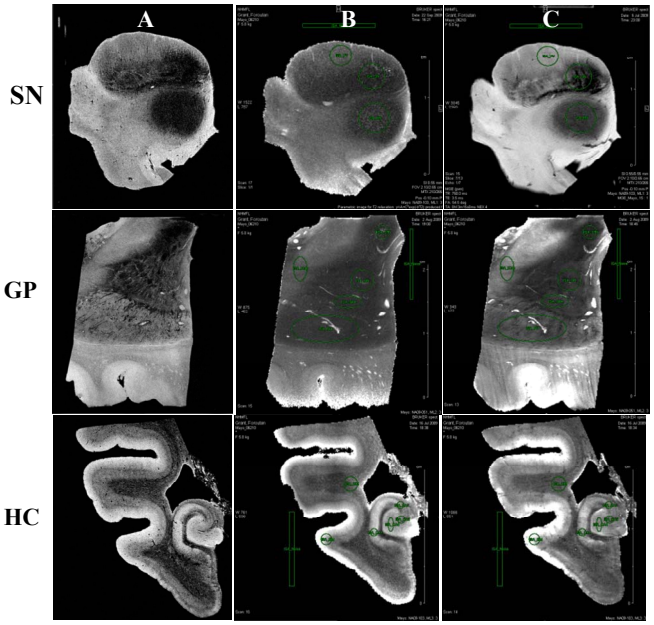

Fig 2. A) High resolution (50-µm isotropic) GRE image, B) T_2 map, C) T_2* map of SN, GP and HC.

Conclusions – In this study, the first MRM evaluations of human pathological tissue at 21.1 T are presented. Because of its specificity and spatial resolution, histological and immunological staining continues to be the standard for pathological evaluation. However, MRM offers additional complementary information that is disease specific and possibly elucidates severity. This ultra-high field strength simultaneously provided increased sensitivity and contrast while maintaining high resolution for the analysis of structural alterations of regions known to be affected in certain neurodegenerative diseases. Quantitative analysis of relaxation proved very sensitive in identifying control versus pathological tissue, while parametric mapping demonstrated the potential for categorizing severity. Interestingly, the neurodegeneration related to the various pathologies thus far studied appears to be more pervasive than expected, extending well beyond the regions normally considered to be affected by either Alzheimer's or Parkinson's disease alone [3,4]. As a pathological tool, MRM has potential to elucidate the extent and severity of such neurodegeneration, and hopefully, may improve the diagnostic capabilities of MRI as higher magnetic fields become available.

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