High resolution MRI at 21.1 T of the hippocampus and temporal lobe white matter in the differential classification of Alzheimer's Disease and Diffuse Lewy Body Disorder

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Introduction: The two most common forms of cognitive disorders that induce dementia are Alzheimer's disease (AD) and diffuse Lewy Body disorder (DLBD). Although these conditions differ histopathologically such that AD is associated with amyloid (Aβ) plaques and neurofibrillary tangles while DLBD is an α-synucleinopathy, clinical similarities make it difficult to distinguish between them. In pathological animal and human tissue [1-3], Aβ plaques appear to coincide with iron-induced hypointensities observed in T_2- and T_2*-weighted MR images. Similarly, the presence of Lewy bodies, or rather α-synuclein, also has been linked to increases in iron content; however, the underlying pathomechanism for both these findings are yet to be understood [4]. In this work, fixed postmortem sections of human hippocampi diagnosed with AD and DLBD were evaluated using MRI at 21.1 T. Specifically, the samples were analyzed using high resolution 3D datasets, diffusion-weighted imaging and relaxation maps of T_2 and T_2* compared to histology.

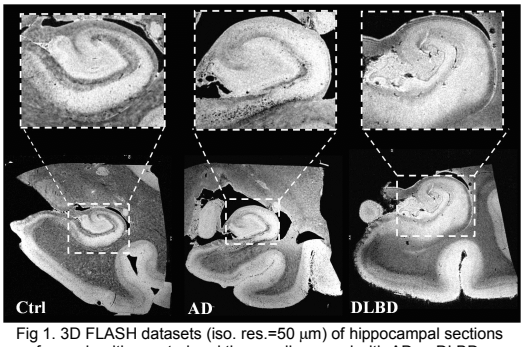
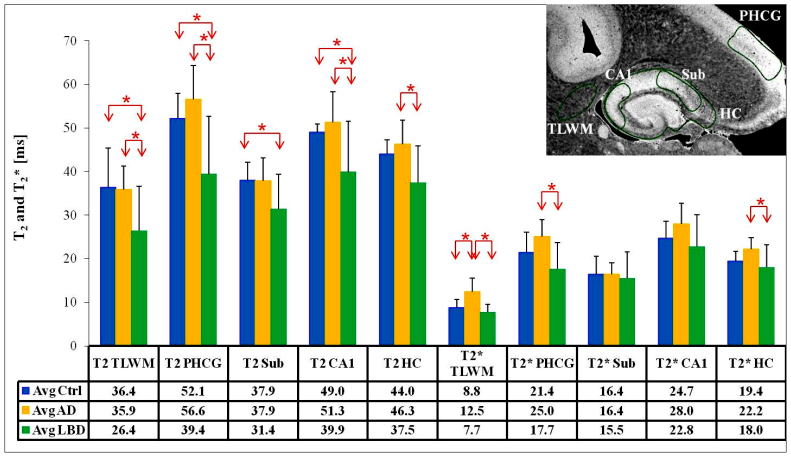


Fig 1. 3D FLASH datasets (iso. res.=50 μm) of hippocampal sections from a healthy control and tissues diagnosed with AD or DLBD.

Methods: Fixed postmortem specimens harvested from sex- and age matched patients displaying AD (n=13) and DLBD (n=7) were compared to healthy subjects (n=6). The fixed samples were washed in phosphate buffered saline and placed in Fluorinert (FC-43, 3M Corp.) to reduce susceptibility artifacts [5]. MR data were acquired using a 21.1-T, ultra-widebore (105-mm) vertical magnet equipped with a Bruker Avance III console and specially built, 1 T/m/A triple axis gradient system (RRI Inc., Billerica MA) [6,7]. Utilizing a 33-mm birdcage coil, 3D Fast Low Angle Shot (FLASH) images were acquired at an isotropic resolution of 50 μm over 4.3 hours at 14 ˚C. T_2*-weighted multiple gradient recalled echo (GRE) and T_2-weighted spin-echo (SE) sequences were acquired over a range of echo times to generate relaxation maps. Multi-slice diffusion-weighted spin echo (DWSE) sequences with four diffusion weightings (b values = 0-1500 s/mm^2) also were acquired. For quantitative analysis of T_2, T_2* and signal intensity (SI), separate manually drawn regions of interest (ROIs) were traced over the temporal lobe white matter (TLWM), Parahippocampal gyrus (PHCG), Subiculum (Sub), CA1 and the entire hippocampus (HC). Histology included stains for iron (Prussian Blue, PB) and ferritin-L. Neural density and vacuolation were quantified with hematoxylin & eosin (H&E).

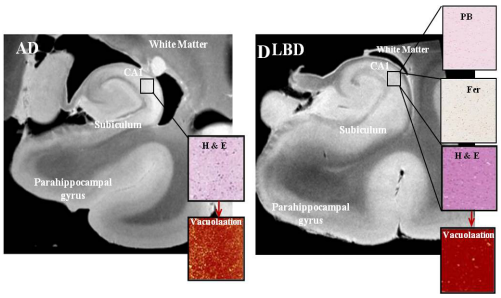
Results & Discussion: High resolution datasets, parametric relaxation maps and regional quantification of T_2 and T_2* provided significant distinctions between healthy and pathological specimens diagnosed with AD or DLBD. With respect to T_2 and T_2*, the largest difference from controls and AD was evaluated for the TLWM while DLBD showed the largest impact on the PHCG. More importantly, the MR related findings of this study, as confirmed by the histological analysis, allowed for the quantitative distinction between AD and DLBD. This data suggests that lower T_2 and T_2* times are correlated with chronic DLBD rather than chronic AD or control sections while increased relaxation values and ADC (not shown) coincide with chronic AD pathology. H&E for vacuolization indicated a larger loss of cells and neuropils in AD compared to both controls and DLBD. While T_2 times correlated with vacuolation in TLWM, PHCG and CA1 and inversely with ferritin in TLWM and CA1, neural cell count did not correlate with either T_2 or T_2*.



	T2 TLWM	T2 PHCG	T2 Sub	T2 CA1	T2 HC	T2* TLWM	T2* PHCG	T2* Sub	T2* CA1	T2* HC
Avg Ctrl	36.4	52.1	37.9	49.0	44.0	8.8	21.4	16.4	24.7	19.4
Avg AD	35.9	56.6	37.9	51.3	46.3	12.5	25.0	16.4	28.0	22.2
Avg LBD	26.4	39.4	31.4	39.9	37.5	7.7	17.7	15.5	22.8	18.0

Fig 2. Quantified T_2 and T_2* times displaying the differences between the various groups and in particular the opposite trend between AD and DLBD versus controls. Brackets indicate statistical significance from a one-way ANOVA and LSD test ($p < 0.05$).

In conclusion, this work suggests that it is possible to differentiate quantitatively between neurologically healthy brain tissue and pathological specimens diagnosed with AD or DLBD. Although evaluated at 21.1 T, these quantifiable MR parameters have potential for translation to lower clinical fields and could provide clinicians with the opportunity to differentiate between the two pathologies. Though histological findings correlate well with relaxation and are in agreement with previous research, the relatively low %PB and high %Fer detected in the AD and DLBD cases may indicate brain iron deficiencies that develop in the chronic stages of these pathologies.



	% PB			% Fer		
ROI	Control	AD	DLBD	Control	AD	DLBD
PHCG	0.05±0.03	0.06±0.04	0.04±0.01	3.9±3.5	4.6±0.4	8.1±5.7
Sub	0.04±0.02	0.10±0.06	0.03±0.02	1.9±0.3	3.9±3.4	8.8±3.5
CA1	0.04±0.02	0.08±0.05	0.03±0.01	1.9±0.6	3.1±1.6	9.1±4.7

Fig 3. ***L:*** T_2-weighted MSME images overlaid with histological outserts of the CA1 showing H&E for vacuolization in AD and PB, Fer and H&E for vacuolation for DLBD and burden of total iron (%PB) and Ferritin (%Fer). ***R:*** Brackets indicate statistical significance in a one-way ANOVA and LSD test ($p<0.05$).

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