Assessing the Correlations Between Pathology and Hippocampal Volume in Neurodegenerative Diseases Using 7T Postmortem MRI

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Introduction

Advantages of postmortem ex vivo MRI

- Acquire high-resolution and high-contrast images
- Bridge in vivo MRI and pathology data

Why hippocampus?

- Crucial for memory
- Earliest area compromised in neurodegenerative diseases

Goals

- Present a 7T postmortem MRI protocol using intact hemispheres in agar with an efficient acquisition time
- Focus on Alzheimer's disease (AD) and Down syndrome (DS)
- Correlate the hippocampal volume to neuropathology burden

Methods

Neuroimaging

- Fixed in 10% formalin or 4% paraformaldehyde for 3 weeks
- Embedded in 1.5% agar/ 30% sucrose in a 3D-printed container
- Scanned with a Tic-Tac-Toe head coil [1-3] at 7T
- Acquired T1w MP2RAGE & T2w SPACE at 0.4 mm resolution
- Registered by rigid registration and segmented using ITK-SNAP
- In vivo T1w MPRAGE at 3T with 0.8-1.2 mm resolution segmented using FreeSurfer

Neuropathology

- Immunohistochemistry for beta-amyloid, phospho-Tau, and modified Bielschowsky stains to generate Thal phase, Braak NFT, and neuritic plaque density for ABC scores
- TDP-43 positive
  - Category – limbic-predominant age-related TDP-43 encephalopathy (LATE) or frontotemporal lobar degeneration (FTLD) with TDP-43 pathology
  - Severity – one method as described previously [4] and the other method on a semiquantitative scale of 0-3
- Hippocampal sclerosis (HS) present
  - Assessed anterior hippocampus and mid-hippocampus at the level of the lateral geniculate body
  - Based on severe neuronal loss and gliosis in CA1/subiculum

Statistics

- Correlations: Pearson's correlation
- Comparisons: Unpaired t-test or one-way ANOVA and Tukey's

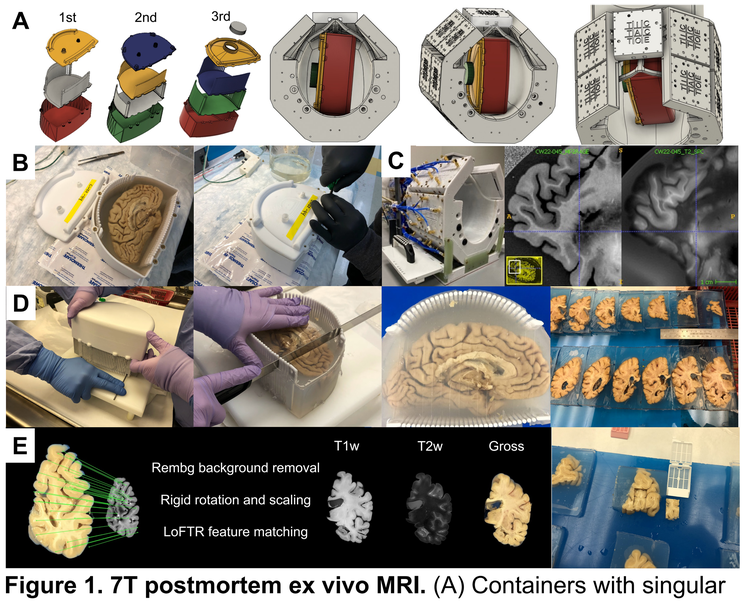

Figure 1. 7T postmortem ex vivo MRI. (A) Containers with singular and dual cutting guides have been designed for optimal contrast. (B) The left hemisphere is embedded in agar inside a container and (C) high-resolution MR images are acquired. (D) The brain is cut coronally along the cutting guides. (E) T1-weighted, T2-weighted, and gross images of coronal slabs are aligned for tissue sampling and subsequent histology.

Results

Table 1. Postmortem brain sample characteristics (n=77).
AD/LBD, Alzheimer's disease/ Lewy body dementia.

	DS	Non-DS	
	n=12	n=65	
		AD/LBD	Other diagnosis
		n=55	n=10
Age	59.4 ± 4.6	79.7 ± 12.0	77.4 ± 13.6
Sex, female	41.7%	49.1%	50.0%
Last MMSE score	n/a	16.5 ± 7.6	19.5 ± 6.3
MMSE-death interval		3.0 ± 2.6	1.4 ± 1.5
Age at disease onset		65.6 ± 10.0	65.0 ± 10.4
Dementia duration		11.1 ± 4.3	8.0 ± 3.1
Postmortem interval	7.5 ± 5.8	8.7 ± 5.5	17.4 ± 14.0
Brain weight	989.4 ± 86.7	1165.0 ± 165.5	1112.7 ± 132.3
TDP-43 positive	8.3% (LATE)	41.8% (LATE)	40% (FTLD)
HS present	8.3%	14.5%	10%

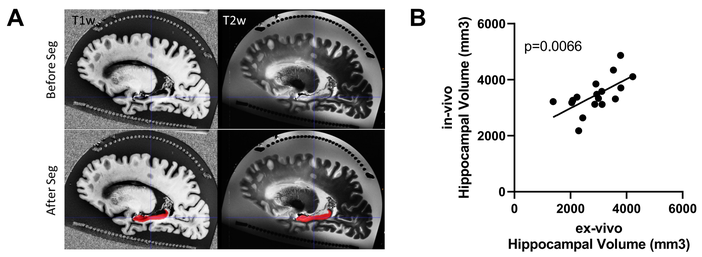

Figure 2. Ex vivo and in vivo comparison. (A) Representative T1w and T2w images before and after manual segmentation (B) The ex-vivo hippocampal volume is significantly correlated with the in-vivo hippocampal volume (n=17, scan interval 3.8 ± 3.5 years).

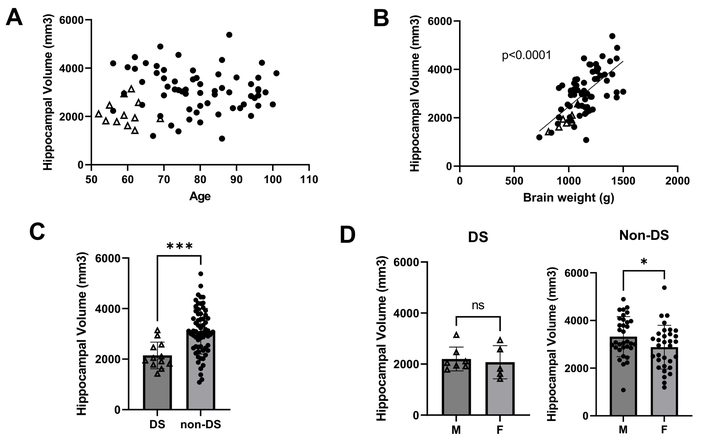

Figure 3. Cohort overview. (A) DS cases (hollow triangles) are younger than Non-DS. (B) The hippocampal volume is highly correlated with the whole brain weight. (C) DS has a lower hippocampal volume. (D) While there is no sex difference in DS cases, males have a significantly higher hippocampal volume than females in Non-DS.

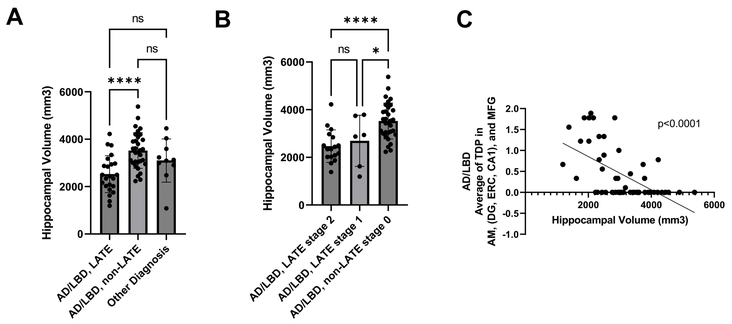

Figure 4. TDP-43 pathology and LATE stages. (A) In Non-DS cases, a significant difference in hippocampal volume is detected between LATE and non-LATE cases. (B) Stage 2 and Stage 1 are significantly different from Stage 0. (C) The hippocampal volume is negatively correlated with TDP pathology severity in the amygdala, hippocampus, and middle frontal gyrus.

Results

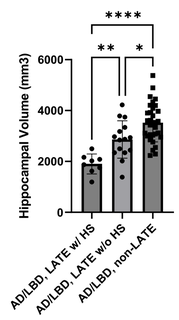

Figure 5. Hippocampal sclerosis. In AD/LBD group, eight LATE cases were given a diagnosis of hippocampal sclerosis, but none of the non-LATE cases were. The hippocampal volume is lower in hippocampal sclerosis when compared to those without.

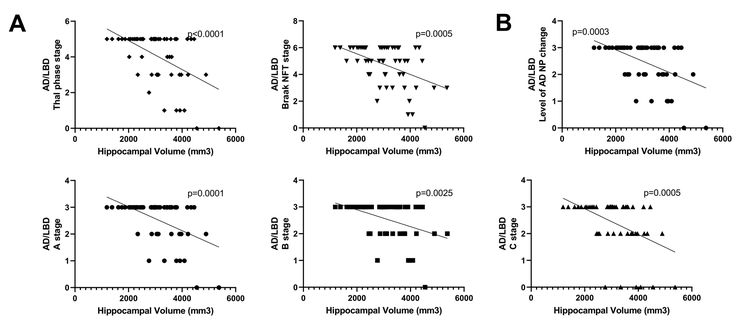

Figure 6. ABC scores. (A) In AD/LBD group, the hippocampal volume is correlated with the Thal phase, Braak stage, and ABC scores. (B) A negative correlation is also found between hippocampal volume and overall level of AD NP change.

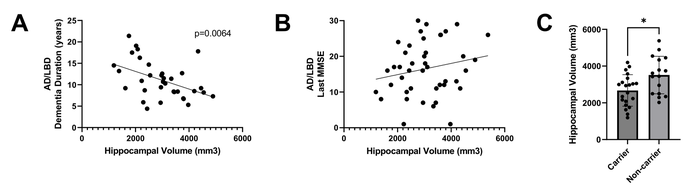

Figure 7. Clinical information. (A) In AD/LBD group, the hippocampal volume is significantly correlated with the dementia duration (B) No significant correlation is observed in the last MMSE. (C) The hippocampal volume of APOE carriers is smaller than that of non-carriers.

Summary

We present a novel postmortem imaging protocol, utilizing ultra-high field MRI and a feasible acquisition time of three hours per brain, and demonstrate accurate measurement of hippocampal volumes and correlation with postmortem measures of neuropathology burden.

Next steps:

- Obtain the amygdala volume
- Train a deep learning model for automated segmentation
- Register in vivo and ex vivo MRI

References

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[2] Krishnamurthy, et al. 2019 PLOS ONE 14(1): e0209663
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[4] Nelson, et al. 2019 Brain 142(6):1503-1527

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