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

Jaehoon Noh (1), Jr-Jiun Jean Liou (2), Jinghang Li (2), Jacob Berardinelli (2), Nadim Farhat (2), Howard Aizenstein (2)(3), Tamer Ibrahim (2)(3)(4), Julia Kofler (1)

(1) Department of Pathology, (2) Department of Bioengineering, (3) Department of Psychiatry, (4) Department of Radiology, University of Pittsburgh, Pittsburgh PA, 15213

Introduction

Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) is a common proteinopathy found in the brains of elderly individuals. On postmortem neuropathological evaluation, a 3-tiered staging system is utilized to assess disease severity, with each stage corresponding to different regions of the brain that are affected by phospho-TDP-43 proteinopathy.

Recently, we have demonstrated an association between the presence of LATE pathology and smaller hippocampal volume, but the amygdala, one of the first regions of the brain to get affected, has not yet been analyzed. The goal of this study is to study the correlation of amygdala volume to LATE stages in postmortem brains.

Methods

- Postmortem brains from Alzheimer's Disease Research Center
- Fixed in 10% formalin for 3 weeks
- Embedded in a 3D printed container using 1.5% agar and 30% sucrose solution.
- Imaged using a 7T MRI scanner using T1-weighted MP2RAGE and T2-weighted SPACE sequences at a resolution of 0.4 mm
- Registered using rigid registration
- Amygdala volumes obtained using ITK-SNAP
- Immunohistochemistry for pTDP43
- LATE pathology staging:
  - Stage 1: amygdala only
  - Stage 2: stage 1 + hippocampus and/or entorhinal/transentorhinal cortex
  - Stage 3: stage 2+ middle frontal gyrus

Cohort

	LATE Positive (n=13)	LATE Negative (n=27)
Age (Mean ± SD) (years)	83.54 ± 9.94	76.67 ± 12.00
Sex (% Female)	46.15%	40.74%
Last MMSE Score (mean ± SD)	17.9 ± 8.07	14.8 ± 8.09
Dementia Duration (mean ± SD) (years)	11.65 ± 3.03	9.09 ± 3.40
Postmortem interval (mean ± SD) (hours)	7.48 ± 3.82	9.77 ± 5.80
Brain weight (mean ± SD) (grams)	1104.61 ± 192.01	1240.59 ± 128.09

Results

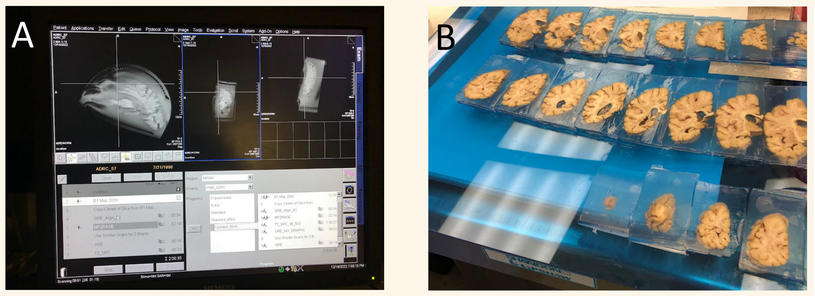

Figure 1: Postmortem Brain preparation. Brain is embedded in agar inside 3D printed container and is prepared for MRI scanning (A). Afterwards, brain is sectioned and aligned for tissue analysis (B).

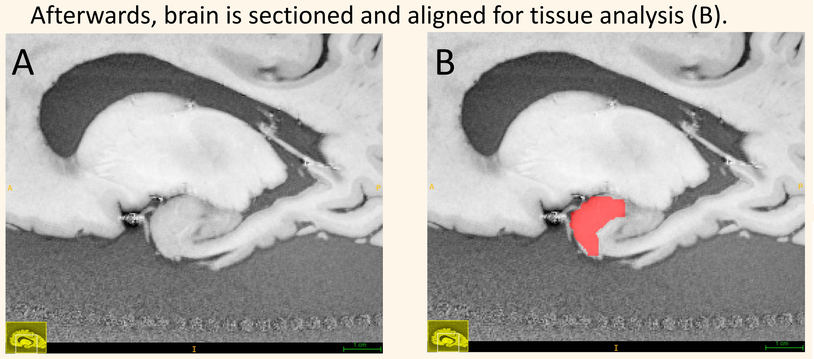

Figure 2: Image Segmentation. Amygdala is shown before (A) and after (B) manual segmentation

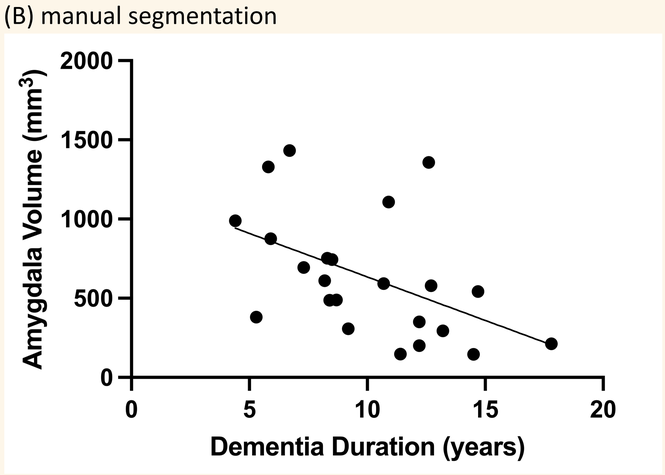

Figure 3: Dementia Duration vs Amygdala Volume. Longer disease duration was associated with smaller amygdala volume (p=0.0193)

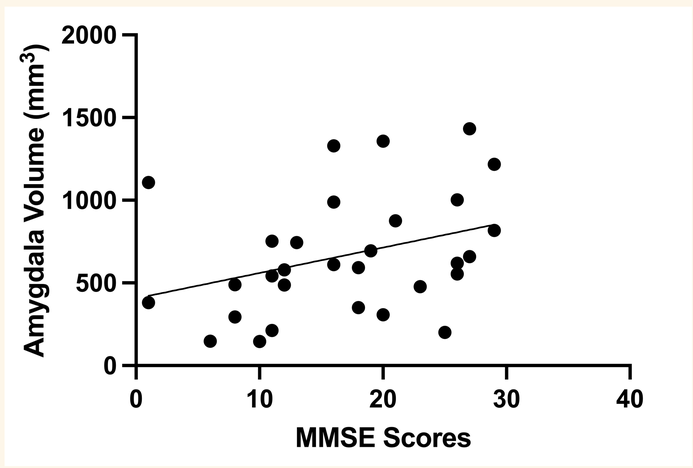

Figure 4: MMSE Scores vs Amygdala Volume. MMSE scores were shown to have a trend towards positive correlation with amygdala volume (p=0.0656)

Results

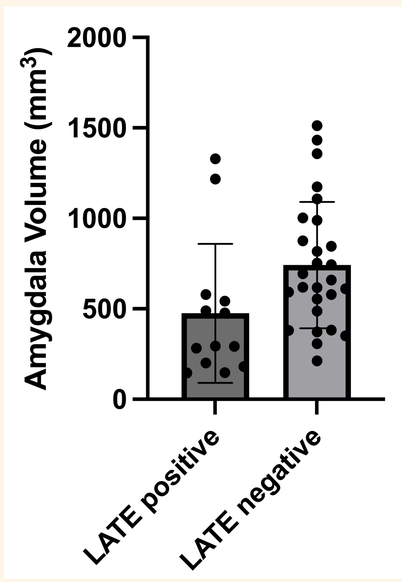

Figure 5: LATE positive vs LATE negative amygdala volume comparison. Compared to patients without LATE pathology, patients with LATE pathology have significantly lower amygdala volumes (p=0.035)

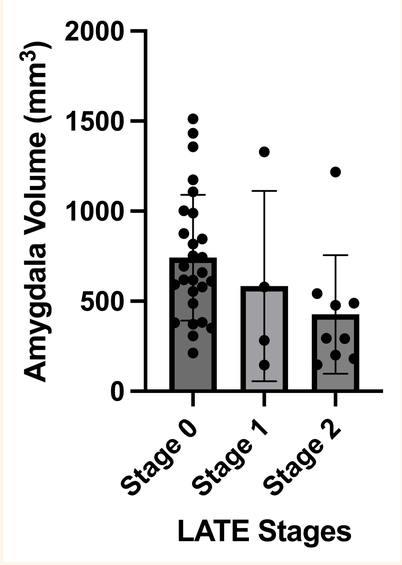

Figure 6: Amygdala Volumes with Increasing LATE Pathology. As LATE pathology progresses in stages, there is a trend towards decreasing amygdala volumes (p=0.09)

Conclusions

- LATE pathology is associated with decreased amygdala volumes, as previously seen for hippocampal volume
- Longer dementia duration is associated with smaller amygdala volumes

Future Directions

- Future studies will be needed to determine if Lewy and Alzheimer's disease pathologies have an added effect on amygdala volume.
- Due to technical limitations, we were unable to segment cases with advanced mesial temporal lobe atrophy (hippocampal sclerosis). Further technical refinements are needed to allow inclusion of these cases

Acknowledgments

Funding: NIH R56 AG074467, U19 AG068054, R01 AG069912, P30 AG066468, R01 MH111265-03S1, P30 AG025204