Selective Vulnerability of the Locus Coeruleus in Tau versus TDP Proteinopathies

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Background

- The locus coeruleus is a nucleus of noradrenergic cells located in the brainstem that plays a major role in arousal, cognition, and stress responses[1]. Previous studies have suggested that the locus coeruleus is susceptible to degeneration in patients diagnosed with Parkinson's disease and Alzheimer's disease, but its vulnerability in frontotemporal lobar degeneration (FTLD) is not well understood[2].
- FTLD is comprised of two main types of proteinopathies: tauopathies (FTLD-tau) and transactive response DNA-binding protein of 43kDa (FTLD-TDP), and an accurate identification of these neuropathologies in living patients is necessary for clinical trials that plan to target these abnormal protein aggregates.
- Staging studies[3,4,5] suggest that the distribution of pathology in the locus coeruleus of FTLD-Tau patients occurs at the early stages of disease progression, whereas the locus coeruleus of FTLD-TDP patients remains mostly intact.
- Understanding the differential progression of FTLD-TDP and FTLD-Tau pathology in specific brain regions, such as the locus coeruleus, could guide the development of biomarkers for the early detection of these disorders and possibly allow us to influence their progression.

The purpose of this project is to determine if the locus coeruleus is more vulnerable in FTLD-tau compared to FTLD-TDP by measuring tau and TDP burden and other markers of neurodegeneration.

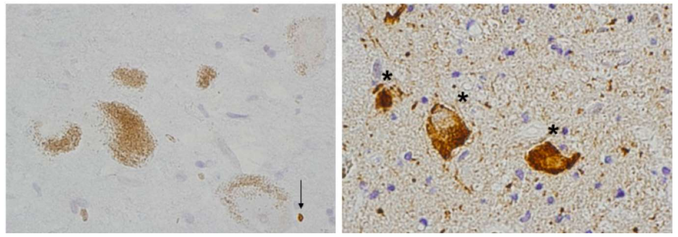

Figure 1. The locus coeruleus displayed more tau neuropathology than TDP neuropathology.
A) TDP inclusions (arrow) were rare and typically accumulated outside magnocellular LC neurons, while B) tau inclusions (asterisks) were more frequent and high depigmentation in the locus coeruleus.

Methods

- Preliminary evidence derived from queries of the Integrated Neurodegenerative Disease Database (INDD) suggested that the locus coeruleus is more vulnerable to pathology and neurodegeneration in FTLD-Tau compared to FTLD-TDP.
- Patients with a primary neuropathologic diagnosis of either FTLD-Tau (n=48) or FTLD-TDP (n=48) were selected based on available tissue.
- One postmortem section of the locus coeruleus per case was stained with hematoxylin (a histochemical stain for cell nuclei).
- TDP and tau inclusion burden, in addition to the extent of neurodegeneration of the locus coeruleus , were assessed microscopically and assigned ordinal scores ranging from 0-3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Inclusion burden was evaluated based on the presence of magnocellular inclusions and non-magnocellular inclusions. Neurodegeneration was evaluated by the degree of cellular loss, vacuolation, depigmentation, and extracellular pigmentation.
- Digital imaging was used to quantify differences in pigmentation of the FTLD-Tau and FTLD-TDP subsample groups (Fig. 4).

Results

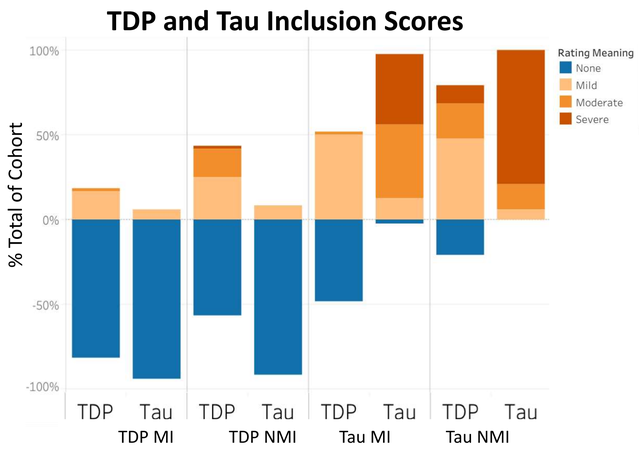

Figure 2. Ratings for tau and TDP burden in magnocellular inclusions (MI) and non-magnocellular inclusions (NMI) of FTLD-Tau and FTLD-TDP cases.
Scores for magnocellular inclusions were higher in tau than TDP ($p < 0.05$).
Scores for non-magnocellular inclusions were higher in tau than TDP ($p < 0.05$).

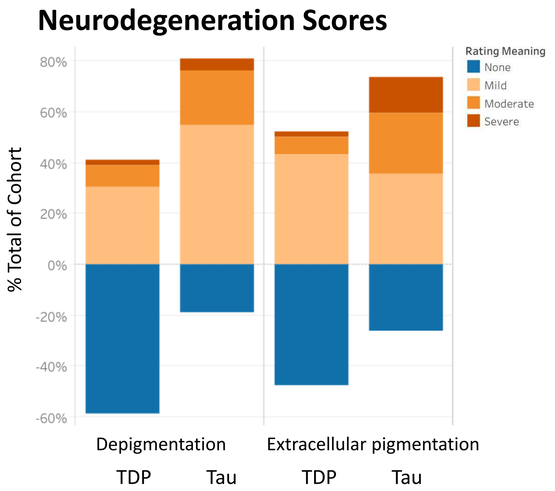

Figure 3. Neurodegeneration scores for FTLD-Tau and FTLD-TDP cases.
Depigmentation was greater in tau than TDP ($Z = -3.6$, $p < 0.001$).
Extracellular pigment was greater in tau than TDP ($Z = -3.1$, $p < 0.002$).

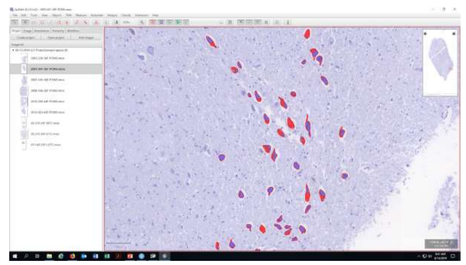

Figure 4. QuPath analysis
Digital quantitation of percent area occupied of healthy melanin.

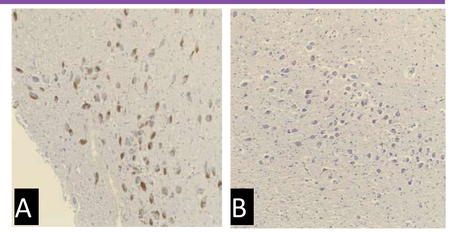

Figure 5. Depigmentation in FTLD- Tau
Higher amounts of magnocellular melanin-positive cells in FTLD-TDP (A) than in FTLD-Tau (B). Magnification = 10X

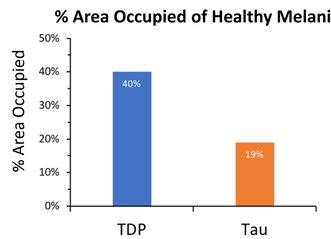

Figure 6. Percent area occupied by healthy melanin in locus coeruleus cells of FTLD-TDP and FTLD-tau subsample groups.

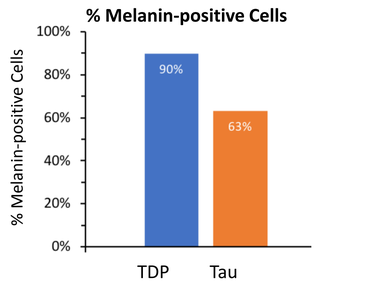

Figure 7. Number of melanin-positive cells (melanin amount > 0) out of total cells in locus coeruleus tissue of FTLD-TDP and FTLD-tau subsample groups.

Conclusions and Future Directions

- **FTLD-Tau had noticeably more extracellular pigmentation and depigmentation compared to FTLD-TDP in the selected cohort.**
- **Magnocellular tau burden in FTLD-Tau was significantly higher than magnocellular TDP burden in FTLD-TDP** (Fig. 2)**,** which is consistent with previous findings from the integrated neurodegenerative disease database at Penn.
- Locus coeruleus **cells in FTLD-TDP had a higher percent area occupied by healthy melanin** (Fig. 6) **and a higher number of melanin-positive cells than the FTLD-Tau group** (Fig. 7)**,** suggesting a higher depigmentation of the locus coeruleus in FTLD-Tau.

- Converging evidence from these independent measures suggests that the locus coeruleus appears more diseased in FTLD-Tau than FTLD-TDP. These findings could be implemented in clinical settings by using MRIs to detect depigmentation in the locus coeruleus and obtain a more accurate diagnosis.

- Our cohort will be expanded in order to obtain more representative data.
- Healthy locus coeruleus tissue will be used as a control to develop better parameters for the digital imaging software.
- We will use additional markers, including glial and tyrosine hydroxylase stains, to better detect the type of cells where pathological inclusions are located.

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References

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