Differential Degeneration of Inhibitory Neurons in FTLD-Tau and FTLD-TDP in Behavioral Variant Frontotemporal Dementia Patients

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Background

- Previous research has studied inhibitory neurons in a wide range of psychiatric disorders and some neurological disorders such as epilepsy and Alzheimer's disease. However, detailed studies examining differences in inhibitory neuron loss between frontotemporal lobar degeneration (FTLD) subgroups, which include FTLD-tau and FTLD-TDP, are lacking.
- Using a large autopsy cohort, the goal of this project is to quantify the density and distribution of calretinin-positive inhibitory neurons across the grey matter of FTLD-Tau and FTLD-TDP patients with a clinical diagnosis of behavioral variant frontotemporal dementia by measuring density and percent area occupied of neurons in the middle frontal cortex, the orbitofrontal cortex, and the anterior cingulate cortex.

Materials and Methods

- Selected patients had an autopsy-confirmed primary neuropathological diagnosis of FTLD-Tau (n=27) or FTLD-TDP (n=44) and a clinical diagnosis of behavioral variant frontotemporal dementia with available tissue for examination.
- Age-matched healthy controls (n=21) were also selected based on available tissue.

Patient Group	Primary Neuropathological Diagnosis	Age at Death	Disease Duration
FTLD-Tau n=27	PiD = 10 CBD = 5 PSP = 4 Tau-U = 8	64.8 (13.4)	8.0 (4.1)
FTLD-TDP n=44	ALS = 6 TDP-A = 17 TDP-B = 13 TDP-C = 3 TDP-E = 5	65.5 (11.6)	11.9 (3.8)

Values= frequency counts or mean (STD). PiD = pick's disease, CBD = corticobasal disease, PSP = progressive supranuclear palsy, Tau-U = unclassifiable tauopathies and ALS = amyotrophic lateral sclerosis.

- Middle frontal cortex, orbitofrontal cortex, and anterior cingulate cortex tissue were cut into 6µm-thick sections and stained for calretinin with 3,3'-Diaminobenzidine (DAB) as the chromogen.
- Neuron densities and percent area occupied were generated using a semi-automated neuron detection pipeline developed in the lab.

Results

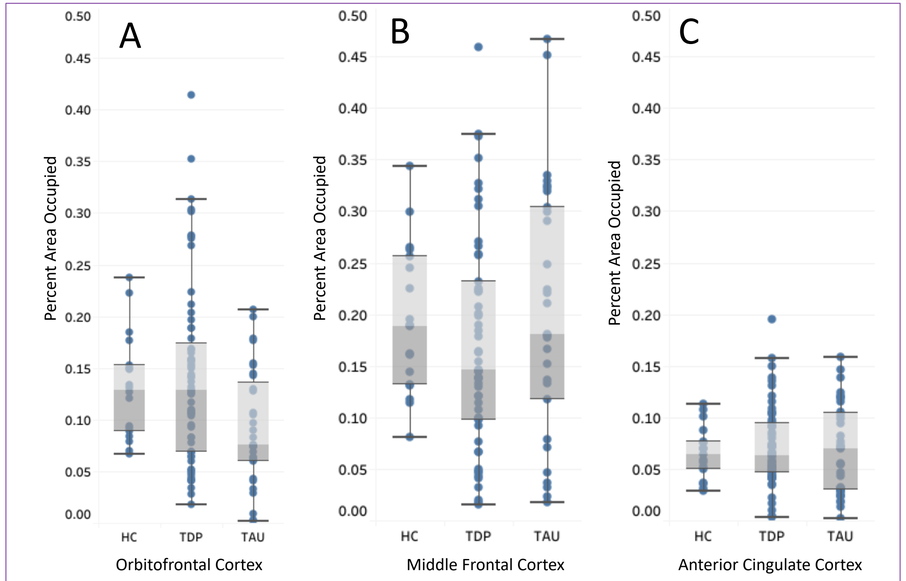

Figure 1. Percent Area Occupied Values for FTLD-Tau, FTLD-TDP and Healthy Control Cases. Percent area occupied values for Tau patients were significantly lower than for TDP patients in the orbitofrontal cortex (A) whereas values for TDP patients were lower than for Tau patients in the middle frontal cortex (B) and anterior cingulate cortex (C).

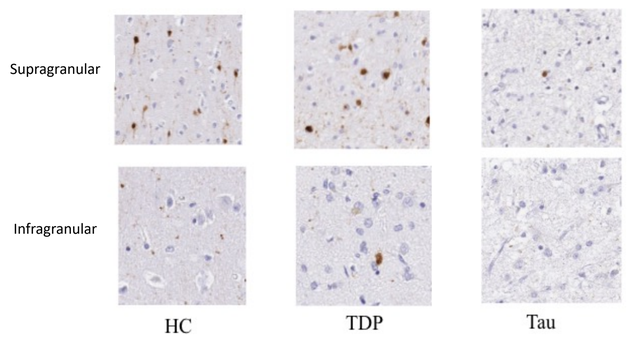

Figure 3. Representative Density of Calretinin-Immunoreactive Neurons in the Orbitofrontal Cortex. Calretinin-positive neurons were primarily found in supragranular layers. Tau patients had significantly more degeneration of inhibitory neurons than TDP patients.

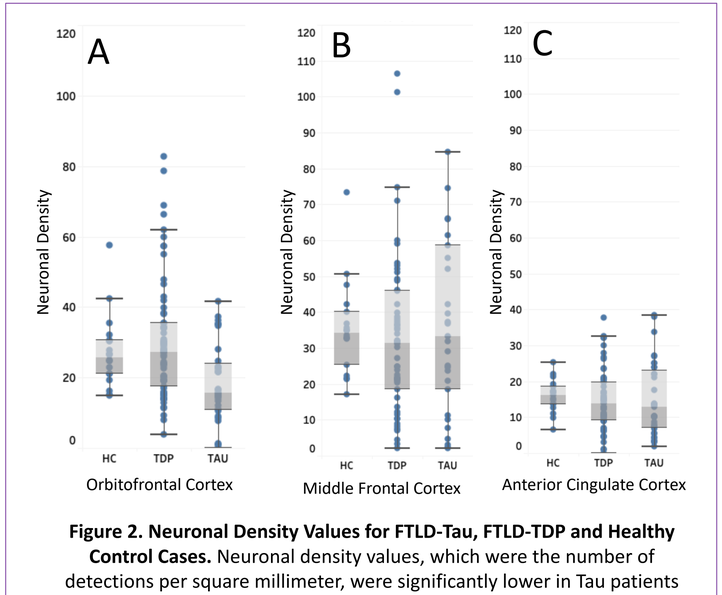

Figure 2. Neuronal Density Values for FTLD-Tau, FTLD-TDP and Healthy Control Cases. Neuronal density values, which were the number of detections per square millimeter, were significantly lower in Tau patients than in TDP patients in the orbitofrontal cortex (A) whereas values for TDP patients were lower than for Tau patients in the middle frontal cortex (B) and anterior cingulate cortex (C).

Results

- FTLD-Tau patients had lower neuronal densities and percent area occupied of inhibitory calretinin-positive neurons than FTLD-TDP patients in the orbitofrontal cortex. In contrast, FTLD-TDP patients had lower neuron densities and percent area occupied in the middle frontal cortex and anterior cingulate gyrus, although no statistically significant differences were observed.
- **These findings suggest that FTLD-Tau and FTLD-TDP may differentially target inhibitory neurons in a region-specific manner.**
- Further examination will be conducted in more regions and specific cortical layers enriched for inhibitory neurons. Additionally, soma size reduction measurements and morphological features of calretinin-positive neurons in these subgroups will be studied to elucidate the divergent vulnerabilities of neuronal populations in the FTLD spectrum.

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