

Striatal Tau Burden in Autopsy-Confirmed FTLD-tau and Relationship to Neuropsychiatric Symptoms

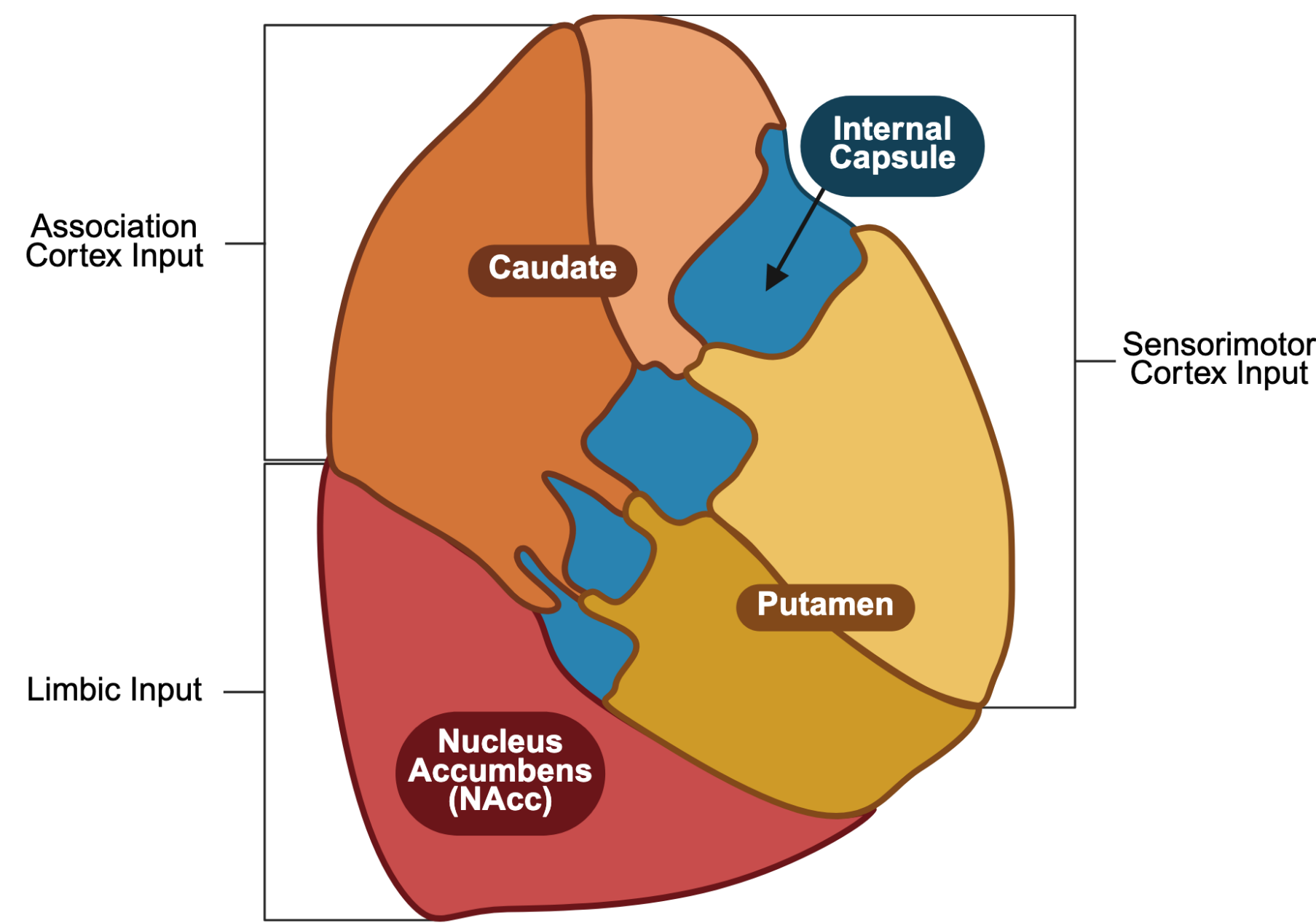
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INTRODUCTION

- Neuropsychiatric symptoms are common in primary progressive aphasia (PPA) or behavioral variant frontotemporal dementia (bvFTD) due to frontotemporal lobar degeneration with tau pathology (FTLD-tau) of the 3R or 4R species.^{1,2}
- The **striatum** is implicated in neuropsychiatric symptoms and is differentially vulnerable to FTLD.^{4,5}

Figure 1. Striatum Anatomy and Afferent Connectivity⁶



Objective: To examine the relationship between tau species, striatal tau burden, and neuropsychiatric symptoms in PPA and bvFTD due to 3R vs. 4R FTLD-tau.

METHODS

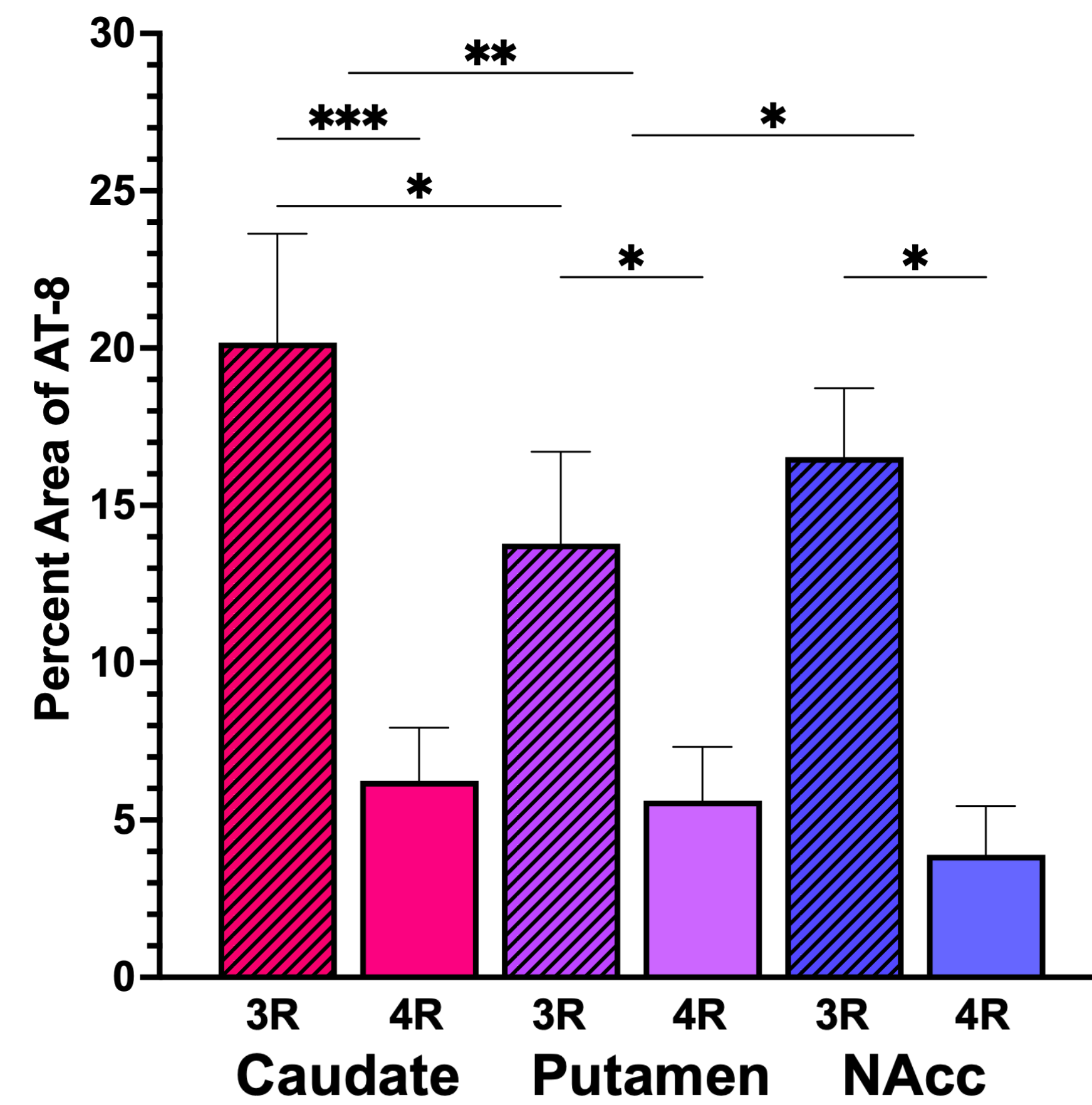
- 16 cases with agrammatic PPA (n=8) or bvFTD (n=8) due to autopsy-confirmed 3R (n=8) or 4R (n=8) FTLD-tau were identified from the **Northwestern Alzheimer's Disease Research Center Brain Bank** (see **Table 1**).
- Level of **neuropsychiatric symptoms** (e.g., apathy, irritability) at the final visit was quantified via the Neuropsychiatric Inventory Questionnaire (NPI-Q).
- Unilateral striatum (14 left, 2 right) was sectioned and stained with AT-8 for phosphorylated tau. %AT-8 immunopositivity was digitally quantified via QuPath.
- We used mixed-effects linear regression to compare regional phosphorylated tau burden between tau species (3R, 4R), dementia diagnosis (bvFTD, PPA), and relationship to neuropsychiatric symptoms at the final visit before death.

Table 1. Participant demographics

	3R (n = 8)	4R (n = 8)
Clinical Diagnosis		
PPA	4	4
bvFTD	4	4
Sex (% female)	3 (37.5%)	5 (62.5%)
Education (years)	16.63 (±1.59)	15 (±2.14)
Age at Onset (years)	59.63 (±6.74)	62.75 (±8.84)
Age at Death (years)	70.75 (±6.14)	70 (±11.26)
Disease Duration (years)	11.13 (±3.14)	7.25 (±3.49)
Postmortem Interval (hours)	23.44 (±14.43)	23.75 (±18.49)
Brain Weight (grams)	1045.13 (±154.01)	1129.88 (±110.29)

RESULTS

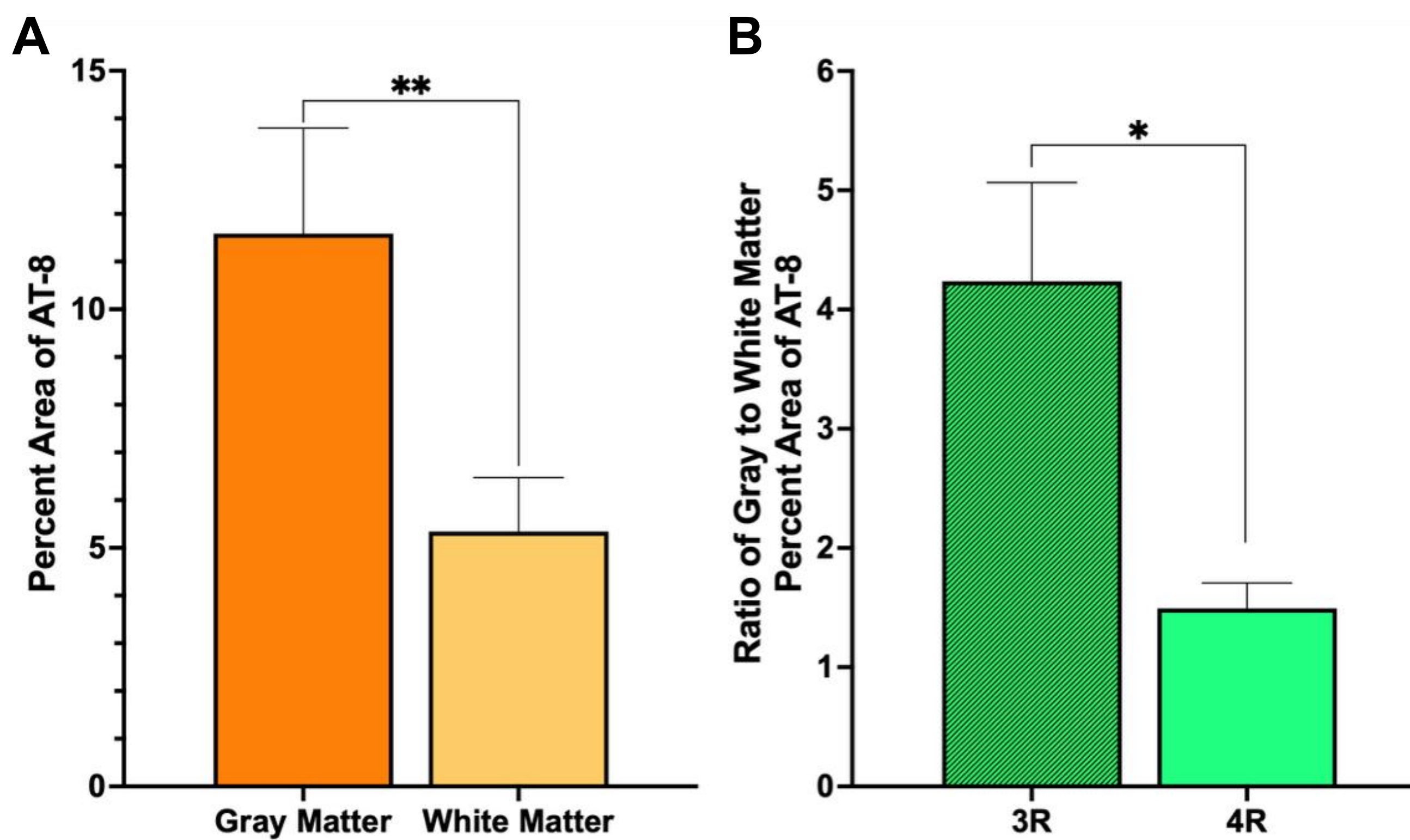
Figure 2. Regional Distribution of Tau Pathology



In 3R tau cases, tau burden in the caudate was significantly greater than in the putamen ($p < 0.05$). Comparing between pathological groups, 3R cases showed higher tau immunopositivity than 4R tau cases in all gray matter regions ($p < 0.05$, $***p < 0.001$). Across the entire cohort, regional analyses indicated the greatest tau burden in the caudate, followed by the NAcc and the putamen ($p < 0.05$ vs. NAcc, $**p < 0.01$ vs. caudate).

Greater tau burden in the caudate relative to the putamen was associated with the presence of more neuropsychiatric symptoms at participants' final visit ($p < 0.05$).

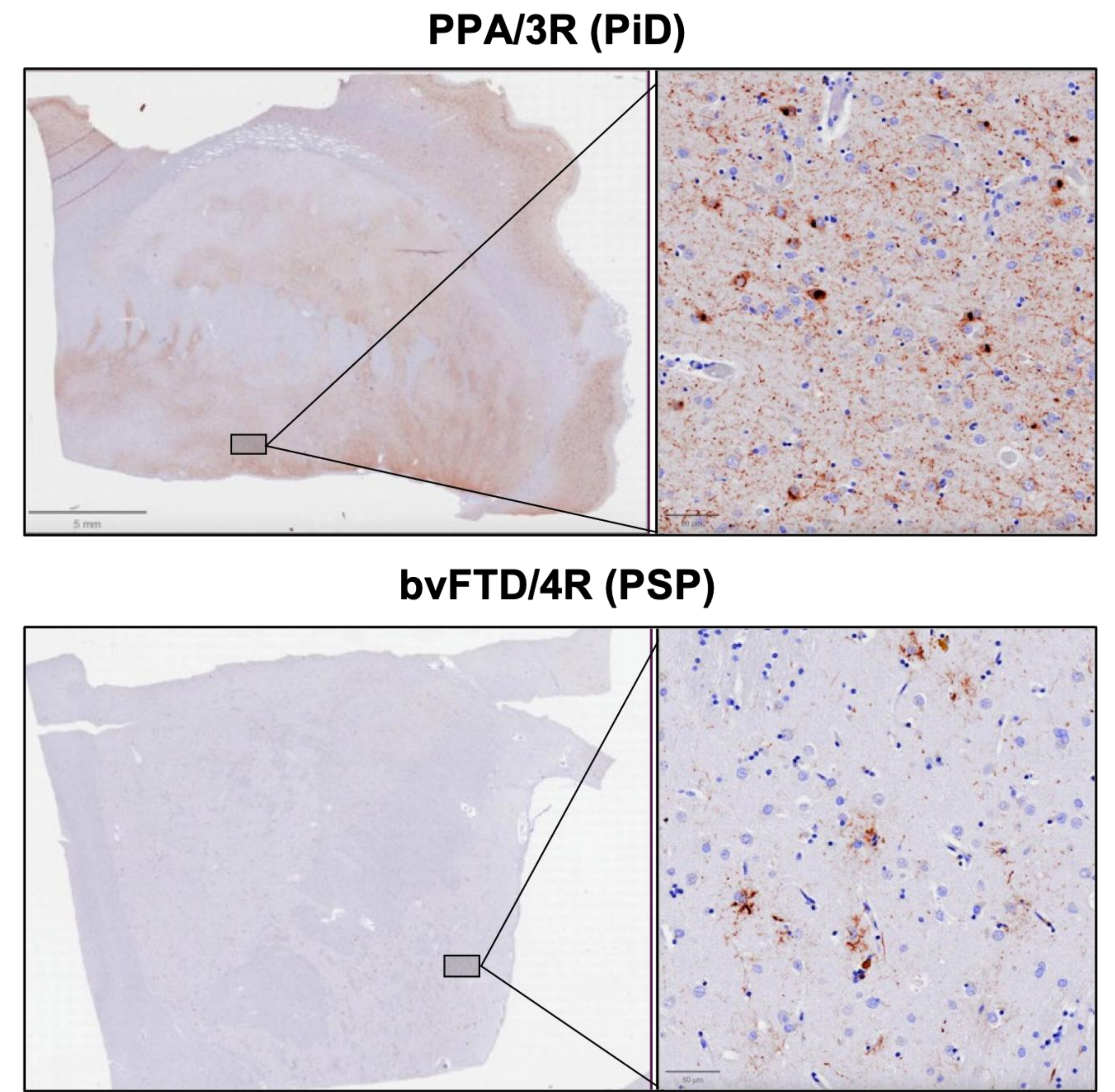
Figure 3. Gray and White Matter Tau in the Striatum



A) Gray matter showed a significantly greater percent area of phosphorylated tau immunopositivity than white matter ($**p < 0.01$). B) The ratio of gray to white matter tau was significantly higher in 3R than 4R ($*p < 0.05$).

RESULTS

Figure 4. Striatal Tau Burden in FTLD-tau



Representative photomicrographs show relatively higher tau burden in a case with 3R tau (a 68-year-old female with a 7-year course of agrammatic PPA) vs. 4R tau (a 72-year-old female with a 5-year course of bvFTD). Scale bars show 5 mm (left) and 50 μ m (right).

CONCLUSIONS

- Results suggest a potential contribution of striatal tau burden, particularly the relative burden between the caudate and putamen, to neuropsychiatric symptoms in bvFTD and PPA due to FTLD-tau.
- Future analyses focused on how tau influences neuronal integrity and inflammation in this region may yield additional insights into the biological substrates underlying these symptoms.

REFERENCES

- Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., van Swieten, J. C., Seelaar, H., Dopper, E. G., Onyike, C. U., Hillis, A. E., Josephs, K. A., Boeve, B. F., Kertesz, A., Seeley, W. W., Rankin, K. P., Johnson, J. K., Gorno-Tempini, M. L., Rosen, H., Prileau-Latham, C. E., ... Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain : a journal of neurology*, 134(Pt 9), 2456–2477. <https://doi.org/10.1093/brain/awr179>
- Restrepo-Martinez, M., Ramirez-Bermudez, J., Chacon-Gonzalez, J., Ruiz-Garcia, R., Malik, R., & Finger, E. (2024). Defining repetitive behaviours in frontotemporal dementia. *Brain : a journal of neurology*, 147(4), 1149–1165. <https://doi.org/10.1093/brain/awad431>
- Kammen, A., Cavaleri, J., Lam, J., Frank, A. C., Mason, X., Choi, W., Penn, M., Brasfield, K., Van Noppen, B., Murray, S. B., & Lee, D. J. (2022). Neuromodulation of OCD: A review of invasive and non-invasive methods. *Frontiers in neurology*, 13, 909264. <https://doi.org/10.3389/fneur.2022.909264>
- Halabi, C., Halabi, A., Dean, D. L., Wang, P. N., Boxer, A. L., Trojanowski, J. Q., Dearmond, S. J., Miller, B. L., Kramer, J. H., & Seeley, W. W. (2013). Patterns of striatal degeneration in frontotemporal dementia. *Alzheimer disease and associated disorders*, 27(1), 74–83. <https://doi.org/10.1097/1097-WAD.0b013e31824a7d4e>
- Macfarlane, M. D., Jakabek, D., Walterfang, M., Vestberg, S., Velakoulis, D., Wilkes, F. A., Nilsson, C., van Westen, D., Looi, J. C., & Santillo, A. F. (2015). Striatal Atrophy in the Behavioural Variant of Frontotemporal Dementia: Correlation with Diagnosis, Negative Symptoms and Disease Severity. *PLoS one*, 10(6), e0129692. <https://doi.org/10.1371/journal.pone.0129692>
- Chuhma, N., Mingote, S., Kalmbach, A., Yelnikoff, L., & Rayport, S. (2017). Heterogeneity in Dopamine Neuron Synaptic Actions Across the Striatum and Its Relevance for Schizophrenia. *Biological psychiatry*, 81(1), 43–51. <https://doi.org/10.1016/j.biopsych.2016.07.002>

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