

Discriminate Pathologic Correlates of Apathy and Disinhibition in Behavioral vs. Aphasic Dementia due to Pick Disease

Rachel Keszycki, PhD, Allegra Kawles, BS, Caroline Nelson, BS, Grace Minogue, BS, Antonia Zouridakis, BS, Alyssa Macomber, BS, Sandra Weintraub, PhD, M.-Marsel Mesulam, PhD, Rudolph Castellani, MD, Pouya Jamshidi, MD, Changiz Geula, PhD, and Tamar Gefen, PhD

Mesulam Institute for Cognitive Neurology and Alzheimer's Disease, Feinberg School of Medicine, Northwestern University, Chicago, IL

INTRODUCTION

- Apathy** and **disinhibition** are common symptoms in patients with primary progressive aphasia (PPA) and behavioral variant frontotemporal dementia (bvFTD).
- Frontotemporal lobar degeneration with tau pathology (FTLD-tau), such as **Pick disease**, commonly leads to PPA or bvFTD.^{1,2}
- The **frontal lobe** and **amygdala**, implicated in apathy and disinhibition, are severely affected by tau and microglial activation in Pick disease.

Objective: To quantify tau and microglial activation in the frontal cortex and amygdala in bvFTD and PPA in Pick disease and their associations with apathy and disinhibition.

METHODS

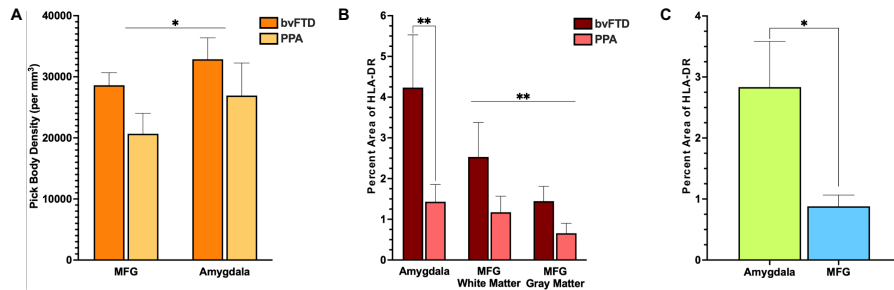
- 17 cases with PPA (n=8) or bvFTD (n=9) due to autopsy-confirmed Pick disease were identified from the **Northwestern Alzheimer's Disease Research Center Brain Bank** (see **Table 1**).

Table 1. Participant demographics

PPA	8
bvFTD	9
Sex (% female)	8 (47.06%)
Education (years)	15.82 (±2.92)
Age at Onset (years)	59.35 (±6.31)
Age at Death (years)	69.59 (±5.91)
Disease Duration (years)	10.63 (±2.68)
Postmortem Interval (hours)	15.77 (±12.86)
Brain Weight (grams)	986.24 (±128.46)

- Apathy and disinhibition were assessed annually via the **Neuropsychiatric Inventory Questionnaire (NPI-Q)**.
- Unilateral amygdala (11 left, 6 right) and bilateral **middle frontal gyrus (MFG)** sections were stained for phosphorylated tau (AT-8) and activated microglia (HLA-DR).
- Pick body density** was quantified using unbiased stereology.
- HLA-DR percent area** was measured via digital analysis (HALO, Indica Labs).
- Mixed regressions covarying for hemisphere examined regional differences between bvFTD and PPA and associations with apathy and disinhibition at final research visit before death.

RESULTS

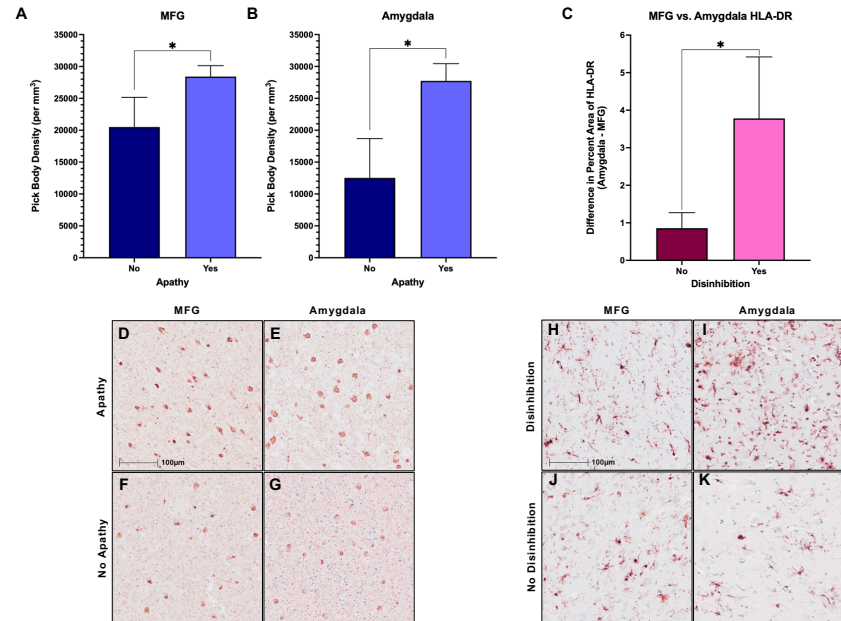


A) Mean Pick body density was higher in the amygdala vs. the MFG but did not significantly differ between clinical groups. **B)** bvFTD showed greater overall HLA-DR immunopositivity than PPA, specifically in the amygdala (** $p < 0.01$). Microglial activation (HLA-DR) was significantly higher in the MFG white matter vs. gray matter (** $p < 0.01$). **C)** HLA-DR immunopositivity was significantly higher in the amygdala vs. ipsilateral MFG gray matter (* $p < 0.05$).

RESULTS

- There was a significant, **positive association** between **tau** and **neuroinflammation** across both regions ($R^2c = 0.37$, * $p < 0.05$).
- At final visit, **71%** showed **apathy** and **41%** showed **disinhibition**.

Figure 2. Associations Between Pathology and Clinical Symptoms



A-B) Apathy at final visit was associated with increased Pick body density in both regions (both * $p < 0.05$). **C)** Disinhibition was associated with elevated microglial activation in the amygdala, particularly when this exceeded MFG levels (* $p < 0.05$). **D-I)** 10x Photomicrographs show higher frontolimbic tau burden in **D-E)** a PPA case with apathy vs. **F-G)** a PPA case without no apathy at final visit. **H-K)** 10x Photomicrographs show relatively higher amygdala vs. MFG microglial activation in **H-I)** a bvFTD cases with disinhibition vs. **J-K)** a bvFTD case without disinhibition at final visit.

CONCLUSIONS

- Distinct frontolimbic pathogenic processes were associated with behavioral symptoms in Pick disease, namely apathy with tau pathology and disinhibition with microglial activation.
- Despite similar tau burdens, PPA and bvFTD showed varying susceptibility to neuroinflammation, particularly in the amygdala.
- Future investigations examining white matter connectivity and neuronal integrity may further elucidate these relationships.

REFERENCES

- Rasovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., van Swieten, J. C., Seelaar, H., Dopper, E. G., Onyiah, 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., Pielak-Latham, C. E., Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioral variant of frontotemporal dementia. *Brain - a journal of neurology*, 134(Pt 9), 2466-2477. <https://doi.org/10.1093/brain/aww179>
 - Dickson, D. W., Kouri, N., Murray, M. E., & Josephs, K. A. (2011). Neuropathology of frontotemporal lobar degeneration-tau (FTLD-tau). *Journal of molecular neuroscience*, 45(3), 384-389. <https://doi.org/10.1007/s12031-011-9588-4>
 - Mesulam, M. M., Rogalski, E. J., Wiernke, C., Hurley, R. S., Geula, C., Bigio, E. H., Thompson, C. K., & Weintraub, S. (2014). Primary progressive aphasia and the evolving neurology of the language network. *Nature reviews. Neurology*, 10(10), 554-569. <https://doi.org/10.1038/nrn.2014.169>
- Thank you to our participants and their families for their enthusiasm and commitment to our research. This work was funded in part by: NIA/NIH (P30 AG072977, R01 NS065770, R01 NS075075, R01 AG056258, R01 AG062566, R01 AG077444, T32 AG 020506), the NIDCD/NIH (R01 DC008552), the NIH (T32 NS047987-14, F31 AG076318), a NACC New Investigator Award (U01 AG016976), the Karen Toffler Charitable Trust, and the Kathryn Piper Center for Frontotemporal Cognitive Disorders.