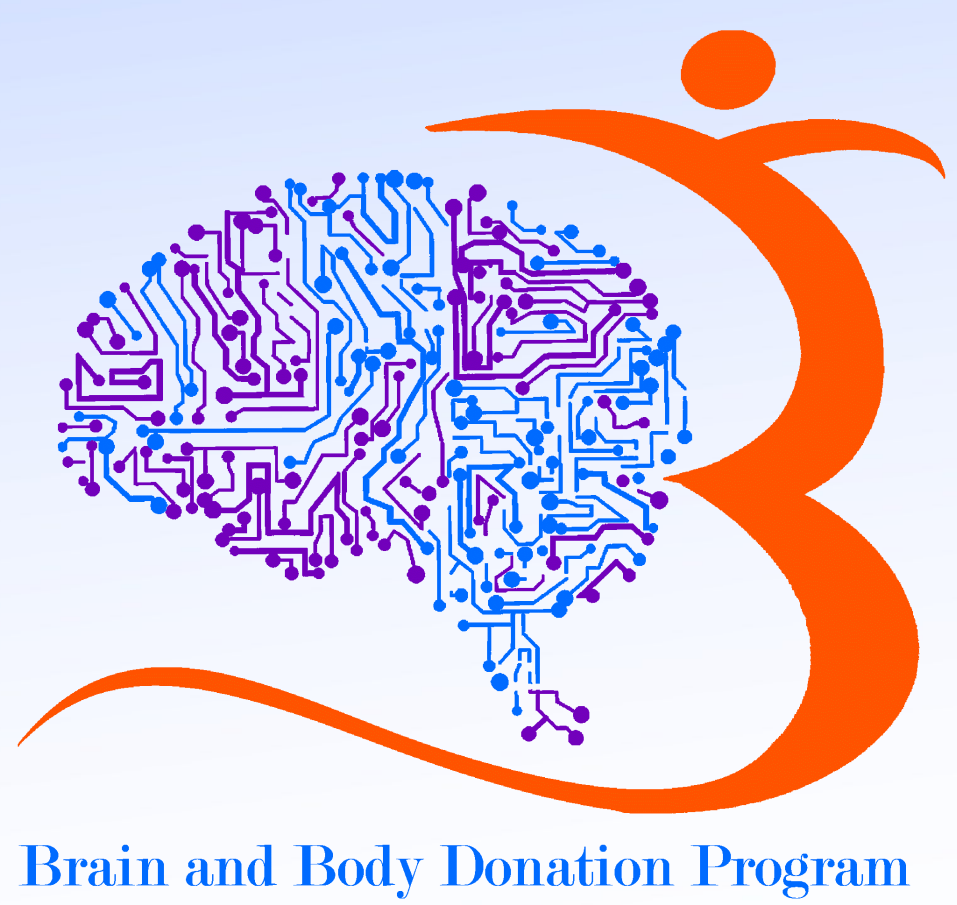


[18F]SynVesT-1 SV2A Synaptic PET Clinical-Biomarker Characterization in Cognitively Unimpaired and Early AD/ADRD

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Introduction

Synaptic dysfunction, degeneration, and loss may represent a converging final common pathway through which Alzheimer's disease (AD) and related disorders (ADRD) produce cognitive and behavioral impairment. There is a critical need for robust biomarkers of synaptic density that, along with other biomarkers, inform prognosis and therapeutic responses in AD/ADRD. This synaptic vesicle glycoprotein-2A (SV2A) PET-autopsy validation study is part of a larger proof-of-concept study funded by the Foundation for the National Institutes of Health (FNIH) - that integrates plasma biomarkers, in vivo SV2A-PET, ex vivo brain tissue measurements (e.g. radioligand binding and electron microscopy) and subsequent autopsy validation to assess the potential of SV2A-PET as a robust biomarker of synaptic density across the clinical spectrum of cognitively unimpaired (CU)-MCI mild dementia with AD/ADRD

Methods

Participants were recruited from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), a community-based longitudinal biomarker and brain donation program. The target sample size is N = 75 older adults spanning the clinical spectrum, including cognitively unimpaired (CU), mild cognitive impairment (MCI), and mild dementia due to Alzheimer's disease or related dementias (AD/ADRD).

All participants undergo standardized clinical and neuropsychological assessments, along with multimodal biomarker collection, including SV2A PET imaging, structural MRI, and plasma-based AD-related biomarker profiling (including NULISA platforms). A subset (~50%) of the cohort additionally undergoes amyloid and tau PET imaging.

All participants consent to brain donation. The program maintains a median postmortem interval of approximately 3 hours. Both frozen and fixed brain tissue samples are collected at autopsy. Postmortem synaptic density measures will be quantified and compared with in vivo SV2A PET imaging metrics.

	CU	MCI	Dementia	Total
N	37	17	12	66
Female: Male	24:13	10:7	3:9	37:29
Age Mean (SDV)	85.9 (5.1)	84.7 (7.5)	82.6 (8.0)	85 (6.4)
Ed Mean (SDV)	15.9 (2.4)	15.3 (3.1)	16.1 (2.1)	15.8 (2.6)
CDR-sb Mean (SDV)	0.2 (0.4)	2.4 (2.7)	5.9 (4.1)	1.8 (3.1)
MMSE Mean (SDV)	28.5 (1.6)	25.6 (3.7)	22 (6.7)	26.5 (4.3)
MoCA Mean (SDV)	24.8 (2.9)	19.4 (4.4)	17.0 (7.0)	22.0 (5.4)
FAQ Mean (SDV)	0.1 (0.4)	5.5 (8.2)	16.3 (8.2)	4.5 (8.0)
ptau217/Aβ-42 Median (SDV)	0.02 (0.02)	0.02 (0.02)	0.04 (0.02)	0.02 (0.02)
GFAP Median (SDV)	134.6 (60.5)	125.1 (66.3)	241.1 (62.9)	138.4 (67.1)

Table 1. Participant demographics, clinical characteristics, and plasma biomarkers by diagnostic group. Data are presented by diagnostic group (cognitively unimpaired [CU], mild cognitive impairment [MCI], and with dementia) and for the total study cohort. *N*: number of participants; *SDV*: standard deviation; *ED*: education; *CDR-sb*: Clinical Dementia Rating-Sum of Boxes; *MMSE*: Mini Mental State Examination; *MoCa*: Montreal Cognitive Assessment; *FAQ*: Functional Assessment Questionnaire; *ptau*: phosphorylated tau; *Aβ*: amyloid beta; *GFAP*: Glial Fibrillary Acidic Protein.

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Case	Expired age	PMI	SV2A/ MRI years to autopsy	Cognitive diagnosis	Brain Wgt	Plaque density	Thal Phase	NFT Braak score	NIA-AA
1	≥90	4.13	1.72	Dementia, probable AD	966	frequent	Phase 5 (A3)	V	High ADNC
2	≥90	3.17	1.76	Cognitively Normal	1082	frequent	Phase 3 (A2)	IV	Intermediate ADNC
3	88	5.02	1.47	Dementia, probable AD	955	frequent	Phase 5 (A3)	V	High ADNC
4	≥90	3.72	2.13	Dementia, probable AD	1080	frequent	Phase 5 (A3)	VI	High ADNC
5	87	4.22	0.75	Non-amnestic MCI	1103	zero	Phase 0 (A0)	IV	Not AD
6	85	3.6	2.22	Cognitively Normal	1313	frequent	Phase 3 (A2)	IV	Intermediate ADNC

Table 2. Participant characteristics at autopsy, including clinical and neuropathologic measures. PMI: postmortem interval; SV2A: Synaptic Vesicle Glycoprotein 2A; MRI: Magnetic Resonance Imaging; Wgt: weight; NFT: neurofibrillary tangles.

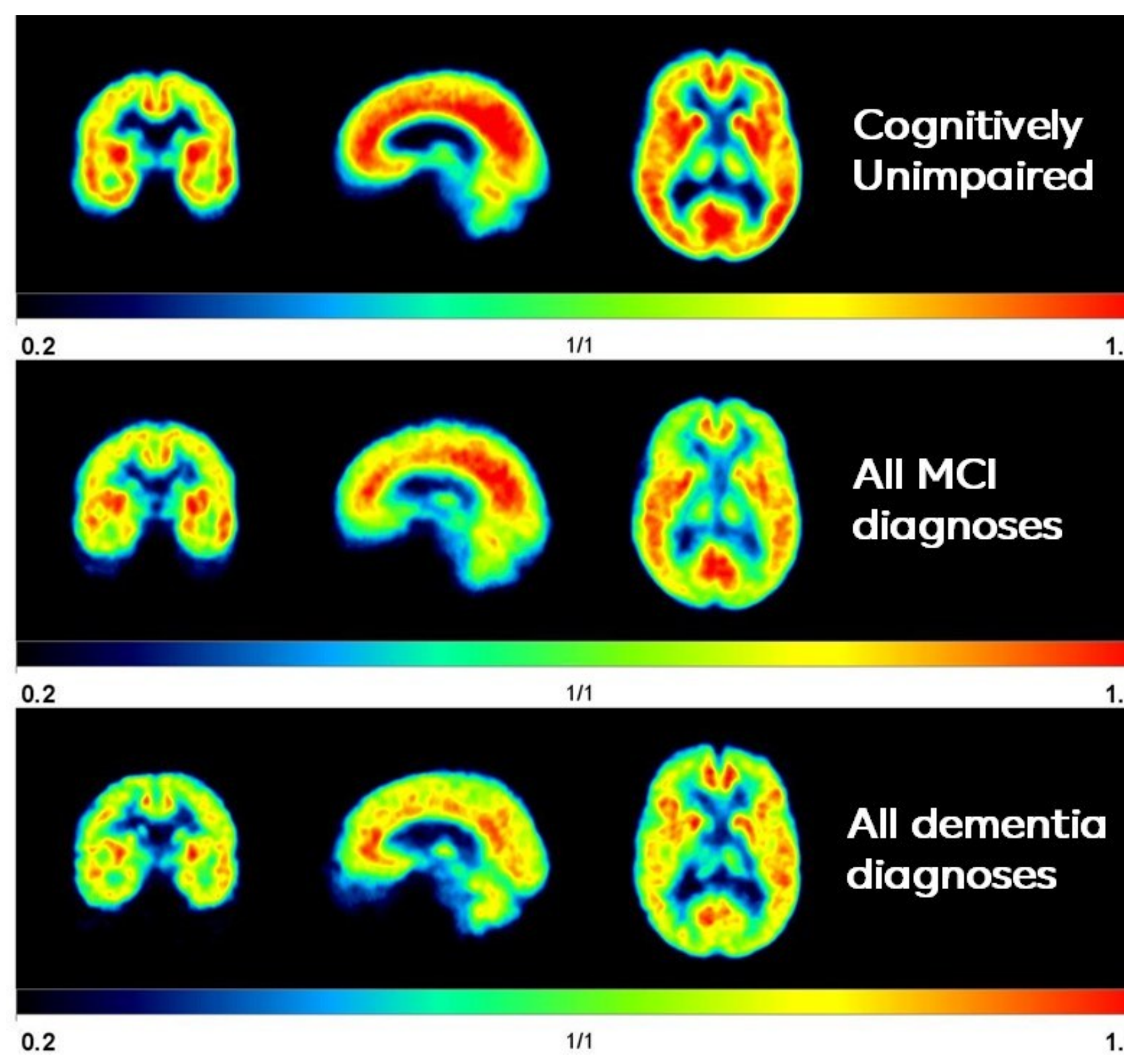


Figure 1. In vivo SV2A PET imaging of tracer activity shows progressive decline across groups from cognitively unimpaired (CU) to MCI to Dementia. Mean SUVR maps of the SV2 PET ligand in cognitively unimpaired (CU, n = 31), MCI (n = 20), and dementia (n = 13). Maps share a common intensity scale (SUVR 0.2–1.4), with colors ranging from black/dark blue (low) to red (high).

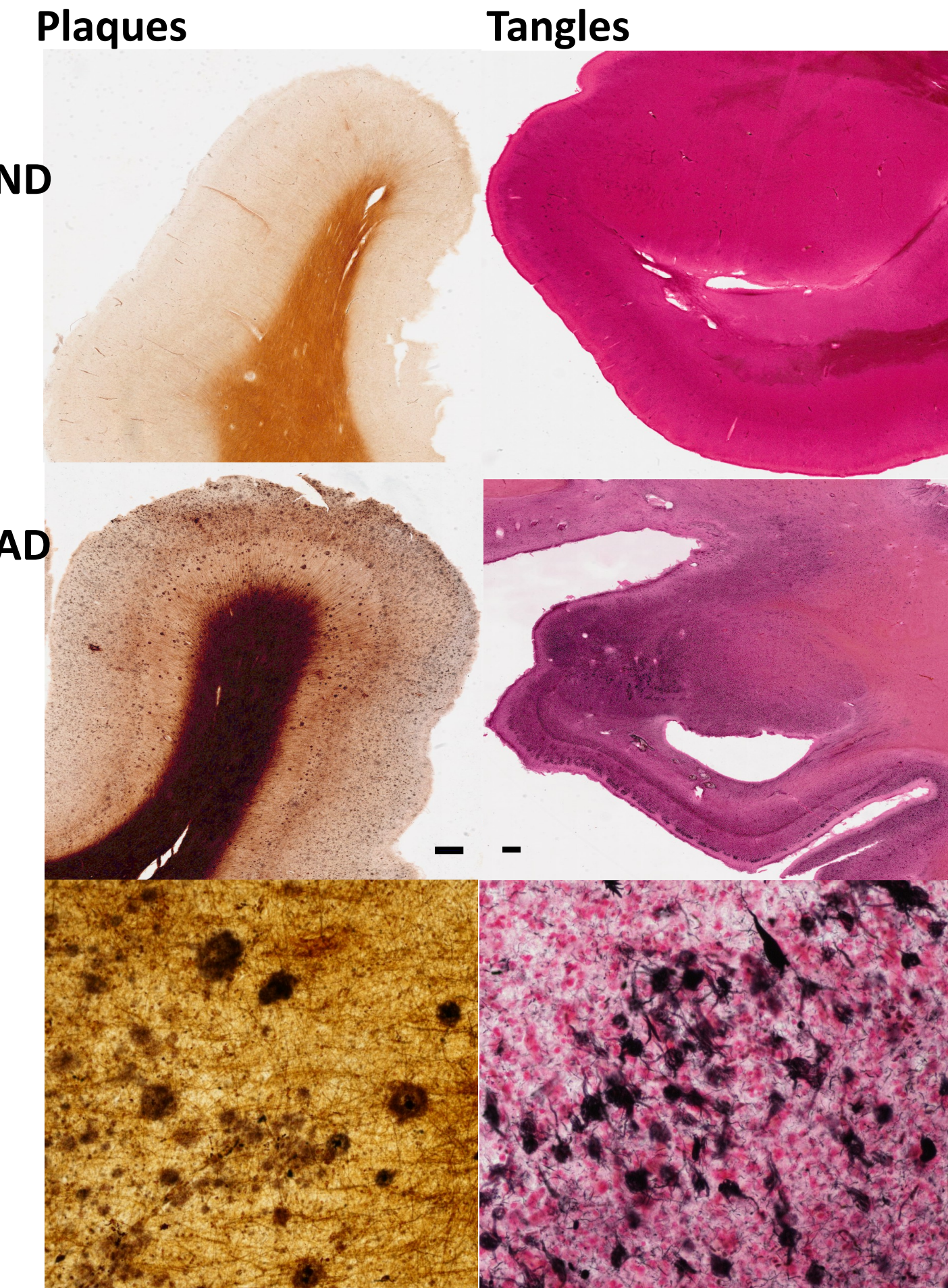


Figure 2. Pathology staging shows variable AD lesion burden in demented and non-demented cases. Silver (pyridine) staining highlights amyloid plaques (A–C), and Gallyas staining reveals neurofibrillary tangles (D–F), each graded as sparse or frequent. Scale bars = 500 μm.

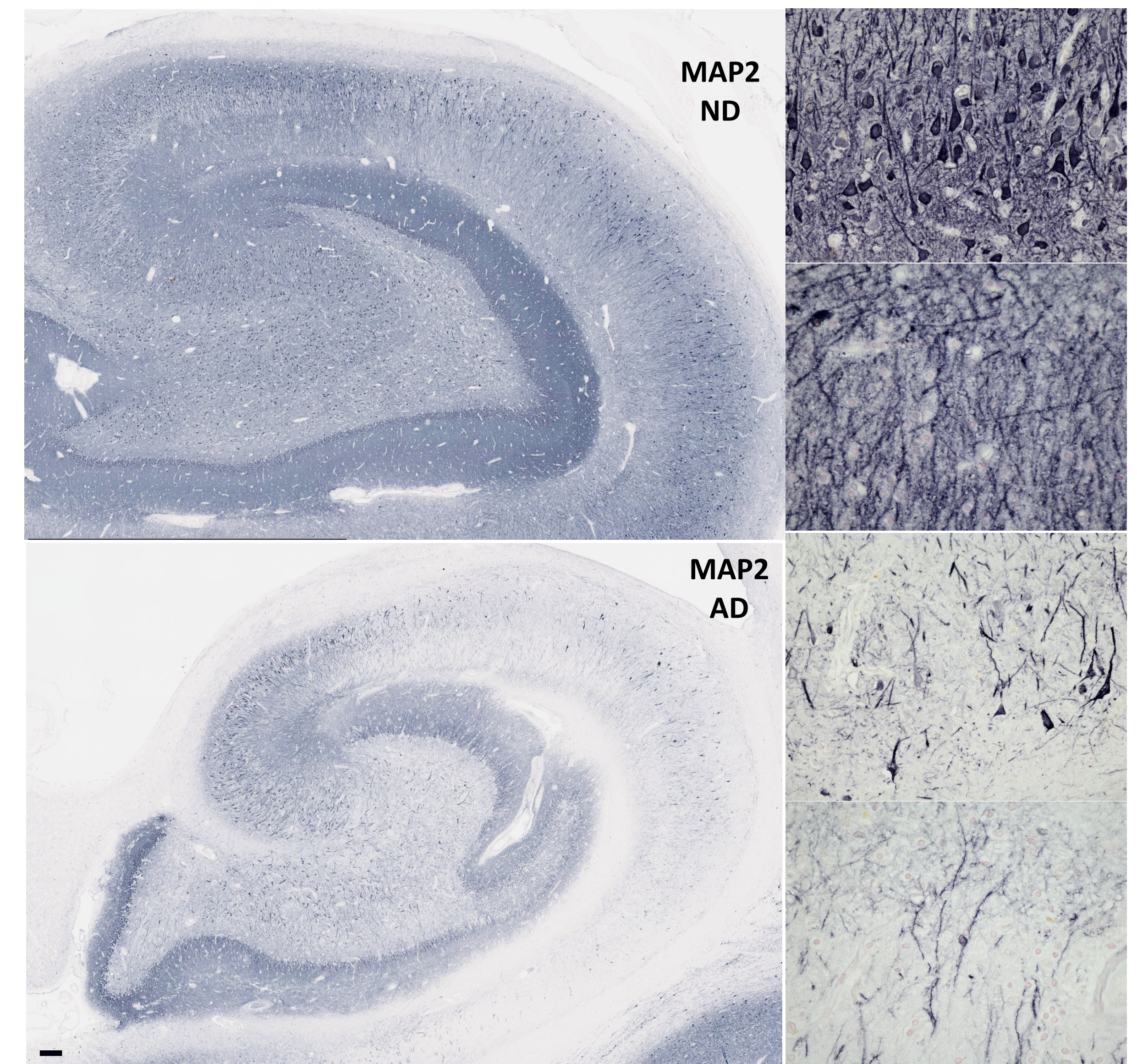


Figure 3. Microtubule-Associated Protein 2 (MAP2) immunostaining shows overall neuronal degeneration in AD compared to controls. Representative images illustrate the consistent reduction in MAP2 signal across AD cases, highlighting widespread neuronal loss. Scale bars = 200 μm.

Summary and Conclusions

- Sixty-six participants (CU, MCI, Dementia) underwent SV2A PET, MRI, and plasma biomarker assessment, with autopsy in six cases. Clinical severity increased across groups, with worsening cognition and function. SV2A PET showed a stepwise decline in tracer activity from CU to dementia, paralleled by higher pTau217/Aβ42 in dementia and variable GFAP.
- Autopsy confirmed high AD pathology in dementia, while some CU/MCI cases showed substantial pathology (≥Braak IV, intermediate ADNC). Histology demonstrated increased plaques and tangles with reduced MAP2, indicating neuronal loss in AD. Related work from the FNIH consortium (see Poster Sunday-0560) further examines correlations between SV2A PET and synaptosome measures.

***SV2A PET captures in vivo synaptic loss that tracks clinical severity and underlying AD pathology.**