



Metabolic Vs Inflammatory Profiles Distinguish Amnestic And Atypical Alzheimer's Disease: Insights From The Orexinergic System

Abhijit Satpati¹, Felipe L. Pereira¹, Alexander V. Soloviev², Ana Moreno Arnas¹, Gowoon Son¹, Mihovil Mladinov², Song Li Hua², Alexander J. Ehrenberg², Renata E. P. Leite³, Claudia K. Suemoto³, Roberta D. Rodriguez³, Vitor R. Paes³, Christine Walsh², Salvatore Spina², William W. Seeley², Carlos A. Pasqualucci³, Wilson Jacob Filho³, Thomas C. Neylan², and Melissa Murray¹, Lea T. Grinberg^{1,3}
1. Mayo Clinic Florida, Jacksonville, FL, USA; 2. University of California, San Francisco, CA, USA; 3. University of São Paulo Medical School, São Paulo, Brazil

Background

- Alzheimer's disease (AD) is a heterogeneous disorder, most commonly presenting as **progressive cognitive decline (amnestic AD)**; however, **~10% of patients exhibit non-amnestic symptoms (atypical AD)**.
- These atypical syndromes include posterior cortical atrophy (PCA), logopenic variant of primary progressive aphasia (lvPPA), frontal variant (fvAD), behavioral or dysexecutive variant (bvAD), and ideomotor apraxia (IMA). Atypical AD is typically characterized by an earlier onset (≤ 65 years) and a lower *APOE* $\epsilon 4$ carriage.
- Despite clinical differences, both variants share similar pathological features, including extracellular amyloid- β accumulation and intracellular p-tau aggregation. However, **these variants differ in the regional p-tau distribution and patterns of neuronal loss**.
- This divergence provides a human model for studying selective neuronal vulnerability, linking molecular pathology to network-level susceptibility and disease progression.
- Wake-promoting orexinergic neurons are among the earliest and most vulnerable populations in AD, highlighting the sleep/wake circuitry as a key yet underappreciated **site of early disease expression**.
- Given that existing animal models rarely recapitulate authentic AD pathology, this natural heterogeneity of AD subtypes offers a valuable framework for dissecting mechanisms of selective vulnerability and enhancing translational relevance.

Aim and Hypothesis

Aim - Define the mechanisms driving AD subtype-specific vulnerability of orexinergic neurons, the earliest affected neuronal population that regulates the sleep/wake cycle, appetite, and neuroinflammation.

Hypothesis - Pathological tau accumulation in orexin neurons and linked changes in the orexin microenvironment induce AD-variant-specific compensatory responses that shape differential circuit vulnerability.

Methods

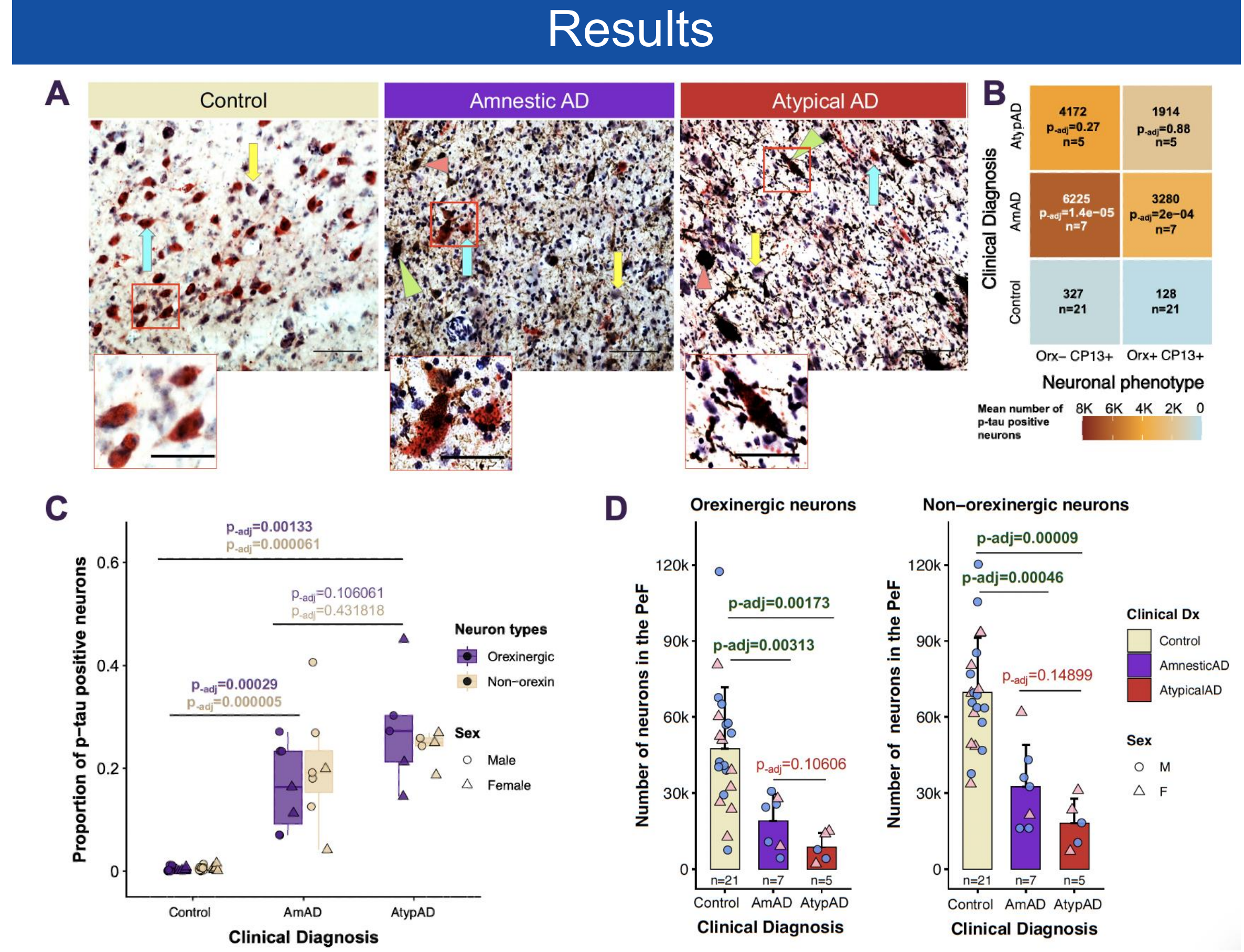
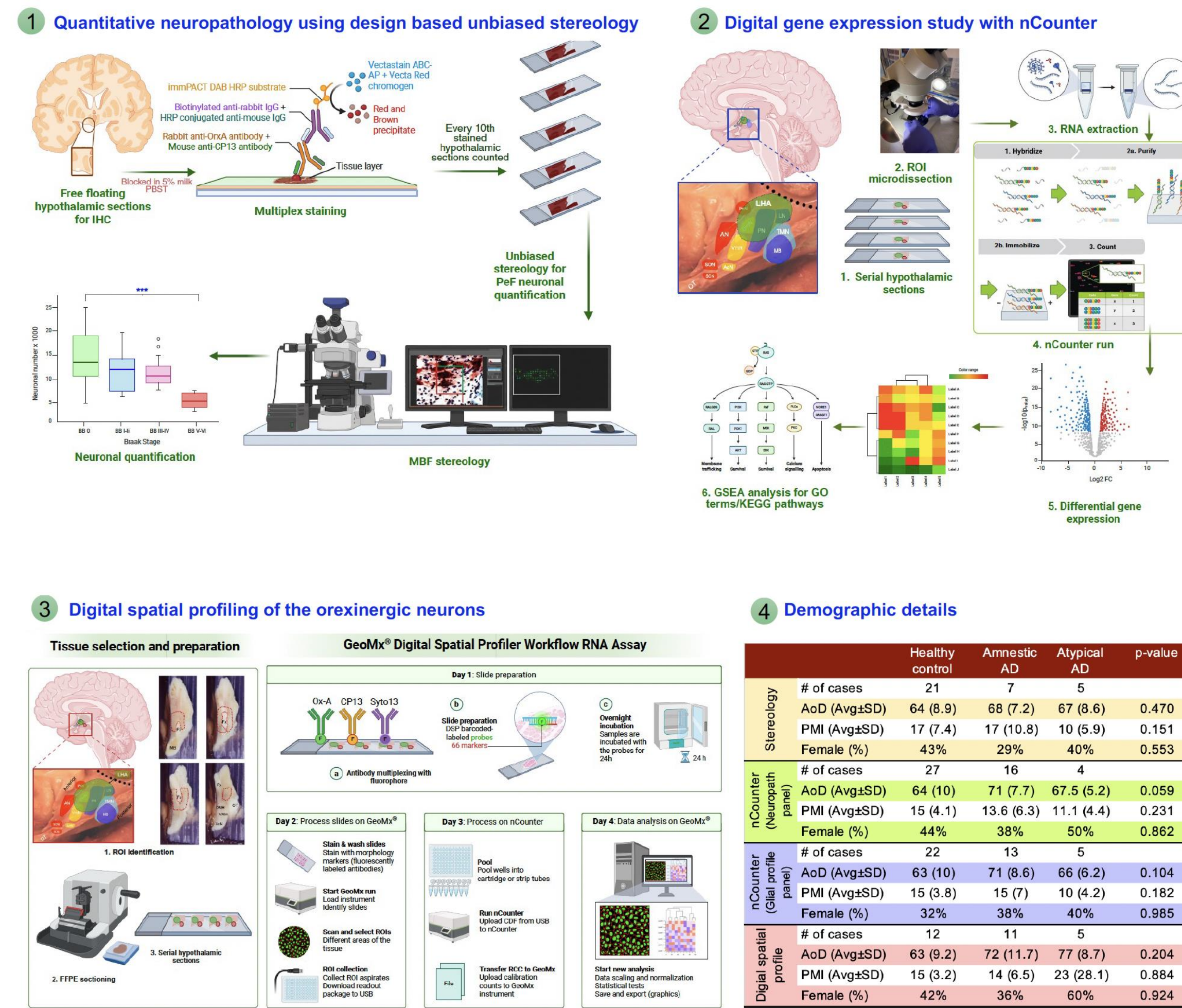


Figure 1. AD-variant-specific vulnerability of orexin neurons; Panel A shows representative micrographs of perifornical (PeF) orexinergic neurons across Alzheimer's disease (AD) subtypes, highlighting non-orexin neurons (yellow arrow), p-tau-positive non-orexin neurons (pink arrowhead), orexinergic neurons (blue arrow), and p-tau-positive orexinergic neurons (green arrowhead), imaged at 20 $\times$ (scale bar, 100 μ m) with a 63 $\times$ inset (scale bar, 20 μ m). **Panel B** displays a heat map visualizing the distribution of p-tau-positive neurons within the PeF area; **Panel C** shows box plots indicating the proportion of p-tau-positive non-orexin and orexin neurons; and the bar plots in **Panel D** summarize PeF neuronal counts. Pairwise Wilcoxon rank-sum tests with Holm correction were applied to stereological estimates to obtain adjusted P values for comparisons between AD variants and control cases.

Results

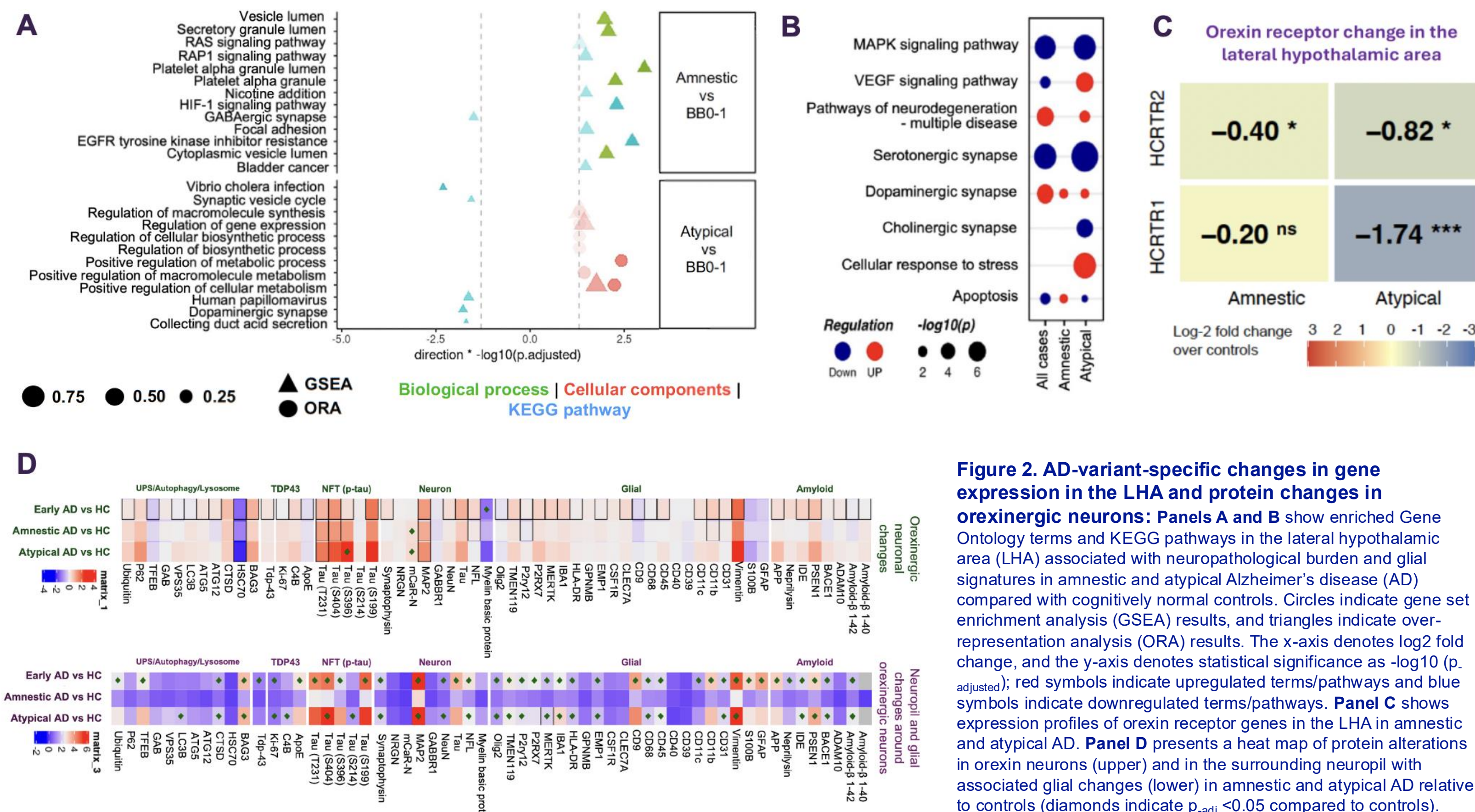


Figure 2. AD-variant-specific changes in gene expression in the LHA and protein changes in orexinergic neurons: Panels A and B show enriched Gene Ontology terms and KEGG pathways in the lateral hypothalamic area (LHA) associated with neuropathological burden and glial signatures in amnestic and atypical Alzheimer's disease (AD) compared with cognitively normal controls. Circles indicate gene set enrichment analysis (GSEA) results, and triangles indicate over-representation analysis (ORA) results. The x-axis denotes log2 fold change, and the y-axis denotes statistical significance as $-\log_{10}$ (p, adjusted); red symbols indicate upregulated terms/pathways and blue symbols indicate downregulated terms/pathways. **Panel C** shows expression profiles of orexin receptor genes in the LHA in amnestic and atypical AD. **Panel D** presents a heat map of protein alterations in orexin neurons (upper) and in the surrounding neuropil with associated glial changes (lower) in amnestic and atypical AD relative to controls (diamonds indicate p-adj < 0.05 compared to controls).

Conclusions

- Significant loss of Ox neurons was seen across AD variants compared to healthy controls, while atypical AD tends to be more severe.
- HCRT receptor 1 (HCRT1) downregulation was atypical-AD-specific, indicating a variant-specific orexin receptor vulnerability.
- Atypical AD exhibits an elevated inflammatory state with cellular stress, proteostatic compensation, gliosis, reactive neuronal remodeling, and a decline in apoptosis.
- Amnestic AD is characterized by altered cell-matrix interactions, growth/survival and RAS/RAP-1 signaling, inhibitory-excitatory imbalance, and enhanced apoptosis, indicating a signaling-linked metabolic remodeling state.
- Intrinsic proteome changes in orexin neurons indicate a similar proteostatic tuning in both variants, while p-tau burden was higher in Atypical AD.
- Peri-orexin neuropil and associated glia exhibit tau-linked proteostatic inflammatory remodeling in atypical AD, whereas extracellular stress signaling appears relatively blunted in amnestic AD.
- Differential orexin receptor expression varies across AD variants, suggesting that dual orexin receptor antagonist (DORA) responses may be variant-specific and highlighting orexin receptor status as a critical factor for therapeutic efficacy.

