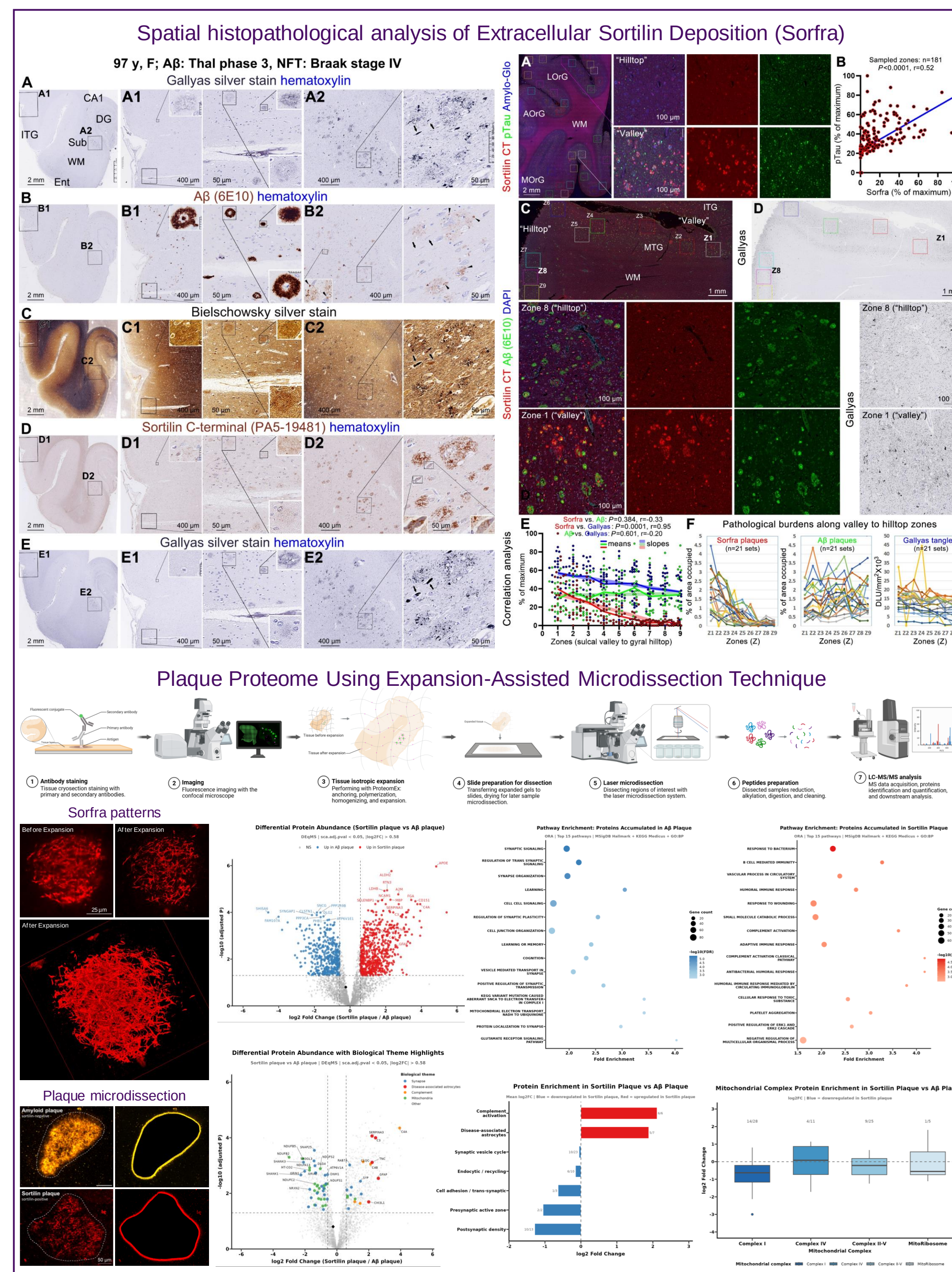


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Fragments of sortilin are extracellularly deposited as the senile plaque-like structures in the human AD cerebrum. Although sortilin deposition partially overlaps with A β plaques and shows a spatial-temporal pattern aligned with tau pathology, its neuropathological relevance to neuritic plaques remains incompletely defined. In this study, we integrated sequential histopathological staining with plaque-specific proteomic analysis to characterize the spatial and molecular architecture of extracellular sortilin deposition and to further provide insights into the mechanisms underlying cognitive impairment.

Postmortem human brain tissues were analyzed using serial-section histopathology, immunohistochemistry, and double-label immunofluorescence to characterize the spatial relationships among sortilin-positive plaques, pTau, A β deposition, and neuritic pathology. Expansion-assisted microdissection was then performed to isolate plaque regions precisely, followed by sample preparation for LC-MS/MS analysis to define the proteomic features.



Extracellular sortilin deposition (Sorfra) is detected as plaque-like morphology in the human brain. Sorfra is co-deposited but mismatched with the A β plaques, while emerging with the spatial-temporal distribution paralleling tauopathy in the cerebrum and showing concordance with the silver-stained neuritic plaques. Compared with Amyloid plaques, Sortilin plaques exhibited a distinct proteomic signature characterized by coordinated enrichment of the disease-associated astrocyte markers and complement cascade proteins, together with reduced abundance of excitatory trans-synaptic complex proteins and a selective deficit of mitochondrial complexes.

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Correlative spatial
histopathological and
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**Extracellular Sortilin
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as a promising marker
for characterizing the
pathological features
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