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METHODS

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- The diagram illustrates the localization of Homer1 to the Drosophila neuromuscular junction. The top part shows a neuron with a box indicating the region of interest. An arrow labeled 'HOMER1' points to the bottom part, which shows a detailed view of the neuromuscular junction. SNAP25 is shown in vesicles, and NPTX1 is shown on the presynaptic membrane. Homer1 is shown as a red dot at the active zone.

The diagram illustrates the integration of two data sources for 438 participants:

- ROSMAP Neuropathology**: Includes images of brain sections showing various pathologies such as Amyloid, tau, Lewy Bodies, TDP-43, CAA, Arteriosclerosis, Atherosclerosis, and Infarcts.
- Synaptic Proteomics**: Shows a workflow starting with a sample, followed by a bar chart of protein abundance, and then a mass spectrometer image. It notes that 206 synaptic peptides were quantified using Selected Reaction Monitoring (SRM).

The data from these sources is analyzed to identify **Protein associations** (represented by colored circles) and their **Overlap with cognitive function proteins** (represented by overlapping circles). This analysis leads to the **Biological Structure and Function Analysis**, which includes a detailed diagram of a cell with various organelles and proteins.

HIGHLIGHTS

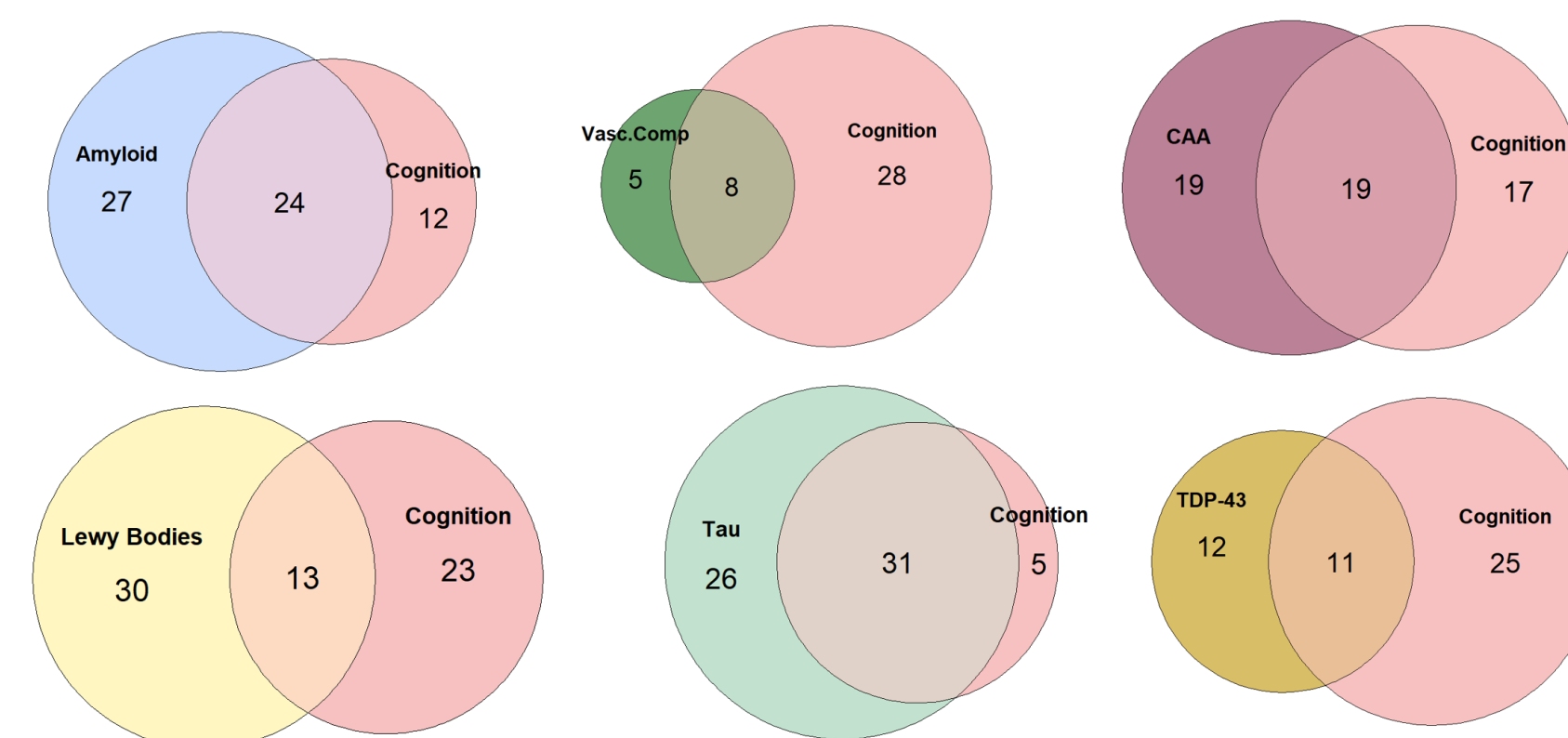


Figure 3: Intersection of synaptic peptides (nominal $p < 0.05$) across neuropathology outcomes and cognition. Tau and amyloid showcase the largest number of raw associations.

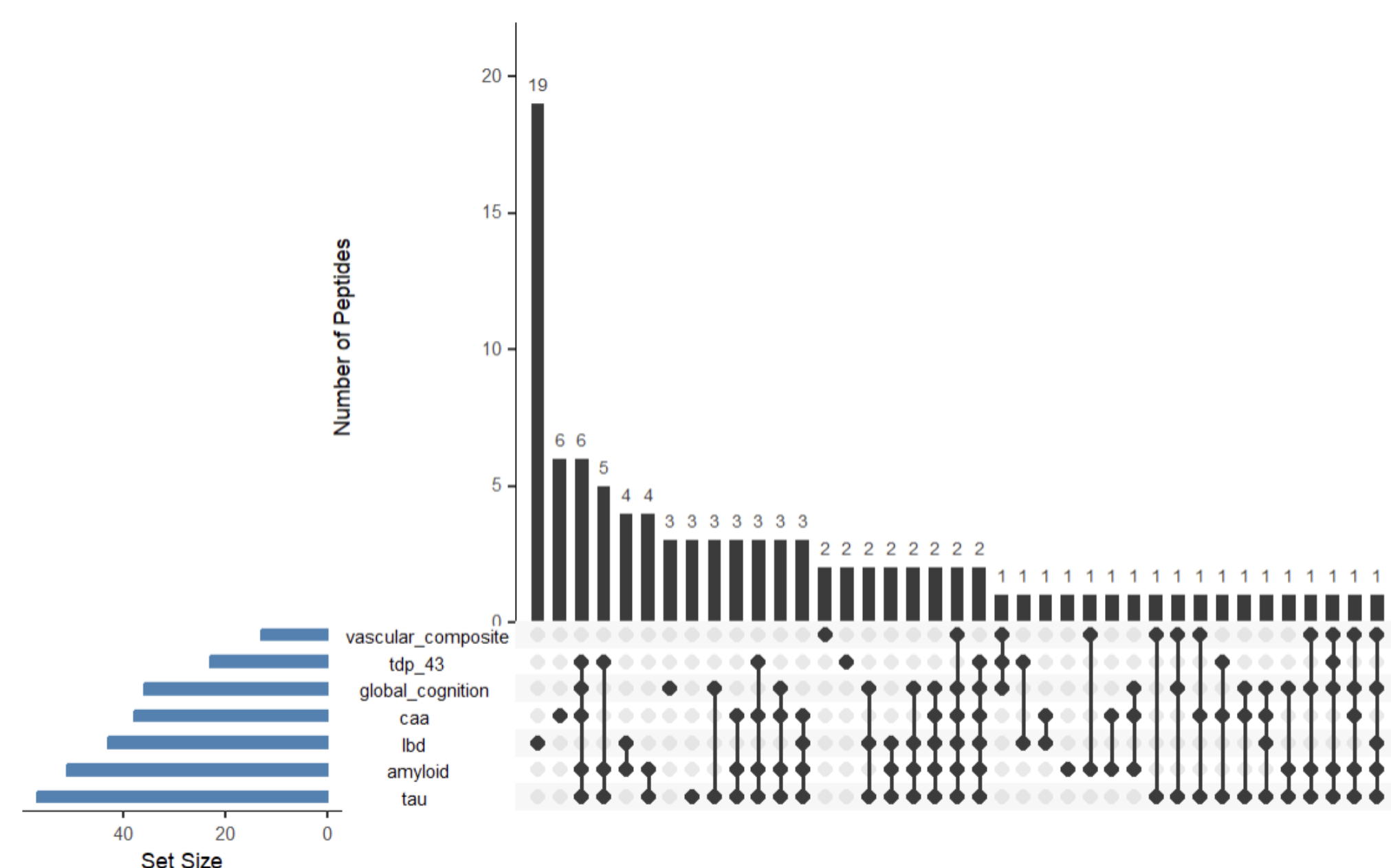


Figure 5: Intersection of nominally significant synaptic peptides ($p < 0.05$) across outcomes.

- **Early AD Hallmark:** Synaptic dysfunction is an early, central characteristic of Alzheimer's disease
- **Unique LBD Signatures:** Lewy Body Disease showed most etiology-specific synaptic peptide profile among non-AD pathologies examined
- **Attenuated Non-AD Signaling:** Signal outside AD pathways (TDP-43/Vascular) shows smaller synaptic associations
- **Drivers of Cognitive Resilience:** A subset of four neuronal pentraxin proteins explains significant cognitive variance independent of demographic covariates and neuropathology
- **Pathology-Agnostic Therapeutics:** These highly conserved, pathology-agnostic synaptic pathways highlight promising broad-spectrum therapeutic targets

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