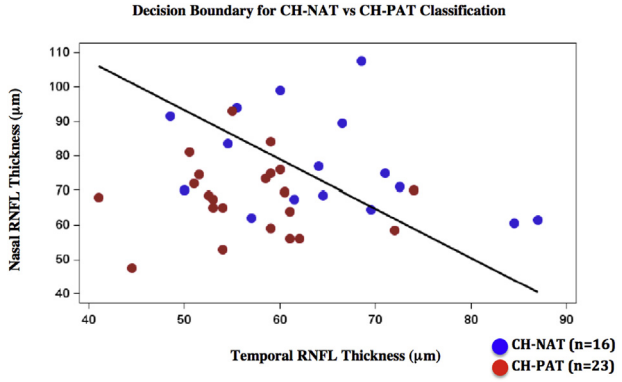
CSF amyloid/tau in a cognitively healthy group of 43 individuals. Preliminary modeling with these data yielded excellent sensitivity (87%) to predict CSF classification. These results support this methodology as a promising, noninvasive screening method for early AD pathology, prior to development of symptoms.




Predicting cognitively healthy-normal and pathological amyloid/tau (CH-NAT and CH-PAT) classification based on retinal nerve fiber layer (RNFL) thickness in the nasal and temporal quadrants.

## O5-03-06 DO ODOR IDENTIFICATION AND REMOTE ODOR MEMORY TOGETHER PREDICT CONVERSION FROM MCI TO AD IN APOE ε4 CARRIERS?

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**Background:** Like odor identification, remote odor memory, reflected in familiarity ratings, is impaired in AD (Murphy, *Nature Reviews Neurology*, 2019). We investigated the relative abilities of standard screening (MMSE), odor identification and remote odor memory to predict transitions from amnestic MCI (aMCI) to AD in a sample from the UCSD ADRC. **Methods:** The sample contained 170 controls, 210 AD, 26 aMCI converters to AD and 42 aMCI non-converters. A receiver operating characteristic (ROC) curve plots the trade-off between sensitivity and specificity. The area under the curve (AUC) indicates how well a marker discriminates patients from controls. **Results:** Analyses showed higher predictive value for converting from aMCI to AD in ApoE ε4+ carriers for odor familiarity, odor identification and for the combination than for the MMSE. ROC/AUCs for the conversion from aMCI to AD have ranged from .63 - .67 for CSF biomarkers. Odor familiarity and odor identification had similar AUC values; however, combining odor familiarity and odor identification produced an ROC/AUC value of 1.0 in ε4 carriers, appreciably higher than for MMSE alone (.58). **Conclusions:** Olfactory biomarkers show real promise as early, non-invasive indicators of disease, particularly in samples enriched with ε4 carriers. Although odor identification has been the focus of olfactory biomarker work, the results suggest that other measures of olfactory function have the potential to enhance prediction. Combining odor familiarity and odor identification produced a predictive value of 1.0 in ε4 carriers. The results warrant further investigation into the potential for enhancing drug trials and clinical screening. Supported by NIH grants R01AG004085-26 (CM) and P50AG005131 (UCSD ADRC). We thank the UCSD ADRC and particularly Drs. Douglas Galasko and David Salmon.

# ORAL SESSIONS
# O5-04
# MOLECULAR AND CELL BIOLOGY: TAU BIOLOGY, AGGREGATION AND SPREADING

## O5-04-01 TRIM46 KNOCKDOWN CAUSES NEURONAL TAU REDISTRIBUTION AND INCREASES AXOSOMATIC TAU DIFFUSION

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**Background:** Tau is enriched in the axonal compartment in healthy neurons but is mislocalized to the somatodendritic compartment in disease. This process is thought to play an important role in tauopathy pathogenesis, including Alzheimer's disease. The localization of tau in axons involves the axon initial segment (AIS), which is a specialized region of the proximal axon that acts as a retrograde diffusion barrier for tau. The process by which the AIS regulates axonal tau enrichment is not well-understood. **Methods:** Here, we examined the temporal development of AIS-specific proteins alongside the differential distribution of tau within axons of cultured hippocampal neurons. To further elucidate the effect of the AIS on axonal tau enrichment, we used shRNAs to knockdown the expression of AIS proteins: Ankyrin G (AnkG) and tripartite motif containing protein 46 (TRIM46). In addition to developmental distribution, we analyzed the diffusion behavior of tau in living hippocampal neurons by using a photo-convertible fluorescent construct. Retrograde tau diffusion was measured after knockdown of AnkG and TRIM46. Lastly, we investigated direct protein-protein interactions between tau and protein components of the AIS using proximity ligation assay (PLA), co-immunoprecipitation, and mass spectrometry. **Results:** We discovered that the development of axonal tau enrichment corresponds to the expression and localization of TRIM46, and happens before AnkG concentrates within the AIS. We show that TRIM46 plays a critical role in maintenance of the diffusion barrier in cultured hippocampal neurons, as knockdown of TRIM46 is sufficient to allow diffusion of axonal tau into the soma and reduce the relative axonal enrichment of tau. Knockdown of AnkG does not change tau localization or axosomatic distribution. Positive PLA signal between tau and TRIM46 was detected within the AIS, but we did not observe direct interactions with co-immunoprecipitation or mass spectrometry. **Conclusions:** We conclude that tau and TRIM46 do not interact directly. Instead, we identified TRIM46 interactions with several microtubule-associated and actin-associated proteins. One identified role for TRIM46 in the AIS is maintaining correct microtubule orientation, thus, we propose that TRIM46-mediated regulation of AIS cytoskeletal organization is critical for modulating axonal localization and retrograde diffusion of axonal tau.