IC-P-030 CONNECTIVITY OF THE LEFT FRONTAL CORTEX ATTENUATES DETRIMENTAL EFFECTS OF CSF-TAU ON MEMORY IN PRECLINICAL AND CLINICAL ALZHEIMER'S DISEASE

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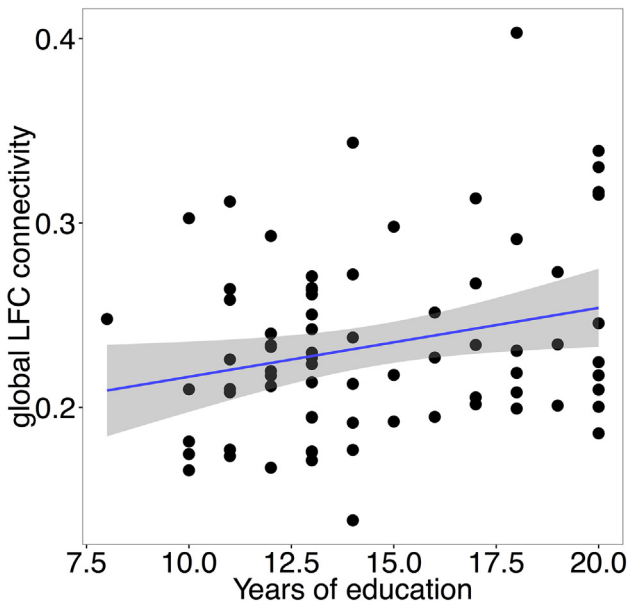
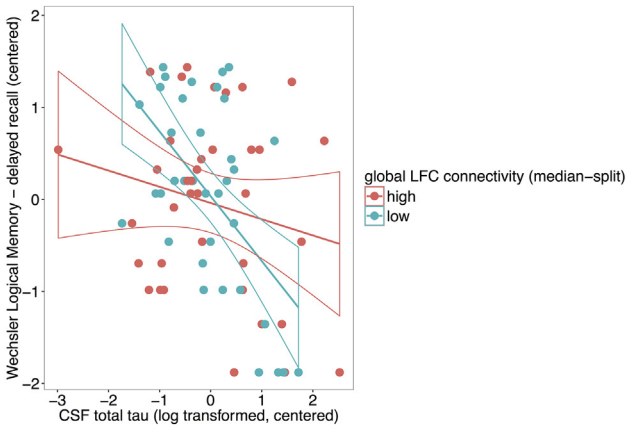
Background: Cognitively normal (CN) subjects with subjective cognitive decline (SCD) and emerging amyloid pathology are at increased risk of Alzheimer's disease (AD). The ability to maintain cognition in the face of beginning neurodegeneration (ie. cognitive reserve) may be critical for the clinical progression in subjects at increased risk of AD. The aim here was was to test functional network characteristics that confer higher reserve across the early clinical spectrum of AD. Specifically, based on our previous findings in prodromal AD showing that global functional connectivity of a left frontal cortex hub (gLFC-connectivity) was associated with higher reserve (Franzmeier, Neurology, in press) we hypothesized that: 1) higher education, a protective factor, is associated with higher gLFC-connectivity 2) higher gLFC-connectivity attenuates detrimental effects of tau pathology on memory performance in preclinical and clinical stages of AD. **Methods:** We included 75





Ab+ individuals in different AD stages (25 CN, 23 SCD, 14 Mild Cognitive Impairment (MCI), 13 AD Dementia), as well as 50 Ab- individuals (24 CN, 17 SCD, 9 MCI) all recruited within the German DELCODE study on biomarker changes in AD. GLFC-connectivity was computed as the average resting-state fMRI-connectivity between an 8mm spherical LFC-ROI (BA6/44) and each grey matter voxel. Using linear regression stratified by Ab-status, we tested whether education predicted higher gLFC-connectivity. Next, we tested whether gLFC-connectivity moderates the association between CSF-tau and the Wechsler Logical Memory delayed recall score. All regression models were controlled for age, gender and diagnosis. **Results:** Greater education predicted higher gLFC-connectivity in Ab+ (p=0.031; Figure 1) but not Ab-. The interaction gLFC-connectivity x CSF-tau was significant (p=0.027) in Ab+, such that at higher gLFC-connectivity the association between higher CSF-tau and memory impairment was attenuated (Figure 2). When tested separately in preclinical (CN-Ab+ & SCD-Ab+) and clinical (MCI-Ab+ & AD dementia) groups, the interaction remained at trend level significance (preclinical: p=0.067; clinical: p=0.059), suggesting compensatory effects of gLFC-connectivity on Tau pathology already in preclinical AD. No interaction was found in Ab- participants. **Conclusions:** Higher connectivity gLFC-connectivity is a neural substrate of CR that allows compensating detrimental effects of tau pathology on memory already in CN and SCD participants.

IC-P-031 INTRINSIC CONNECTIVITY NETWORKS IN POSTERIOR CORTICAL ATROPHY: A ROLE FOR THE PULVINAR?

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Background: Amnestic Alzheimer's disease (AD) is characterized by disrupted default mode network (DMN) connectivity with corresponding increased salience network (SN) connectivity. Posterior

cortical atrophy (PCA) is an uncommon AD variant presenting with progressive visuospatial symptoms, and the relationships between functional networks in PCA are unknown. We hypothesized that PCA patients would show early decreased integrity within the visual network, with corresponding increases in SN connectivity, despite relative preservation of DMN. As the medial and lateral pulvinar are anatomically interconnected with SN, DMN, and visual structures, we further hypothesized that the pulvinar nucleus might play a key role in these networks. **Methods:** 26 individuals diagnosed with PCA (all amyloid-positive or with AD-consistent CSF) and 64 matched controls were recruited through UCSF Memory and Aging Center research programs. Each completed a standardized neuropsychological battery, structural imaging, and task-free fMRI. We used voxel-based morphometry (VBM) to assess structural atrophy. For fMRI, time series from seeds for networks of interest were regressed across the whole brain and fitted to a second-level regression model for group effects analysis. Functional data analyses were atrophy-corrected using the BPM toolbox. **Results:** PCA patients show relatively preserved memory in the early stages of illness despite poor visuospatial performance; like others with AD, they also show preserved social sensitivity. As expected, VBM revealed highly significant parieto-occipital atrophy (Figure 1). PCA patients showed widespread decreased connectivity within the visual network, increased connectivity between some structures in SN, and increased connectivity between key nodes of the DMN compared to controls. Medial pulvinar connectivity mirrored SN connectivity, while lateral pulvinar connectivity mirrored DMN connectivity (Figure 2). **Conclusions:** Individuals with PCA show relatively preserved connectivity in SN and DMN despite widespread parietooccipital atrophy and decreased visual network connectivity. The striking similarity of medial and lateral pulvinar-derived connectivity maps to SN and DMN suggests an important role for the pulvinar within these networks, particularly given the close anatomic relationship between medial pulvinar and SN, and lateral pulvinar and DMN and visual regions. Thalamic subnuclei are well-poised to serve as network switches, and different subnuclei may be differentially implicated in different subtypes of AD.

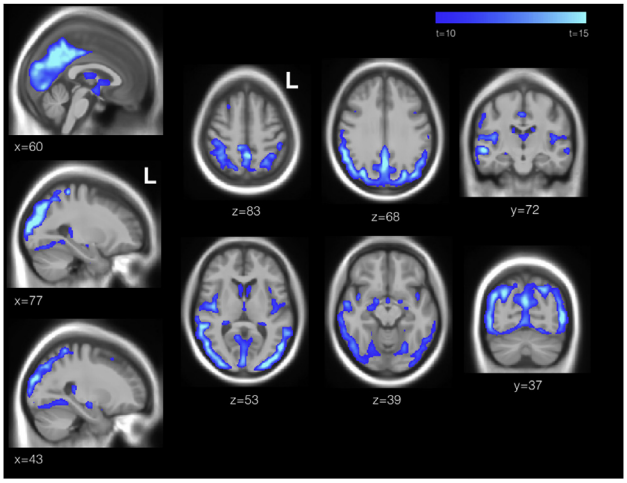

Figure 1. VBM, gray matter mask, PCA <HC.

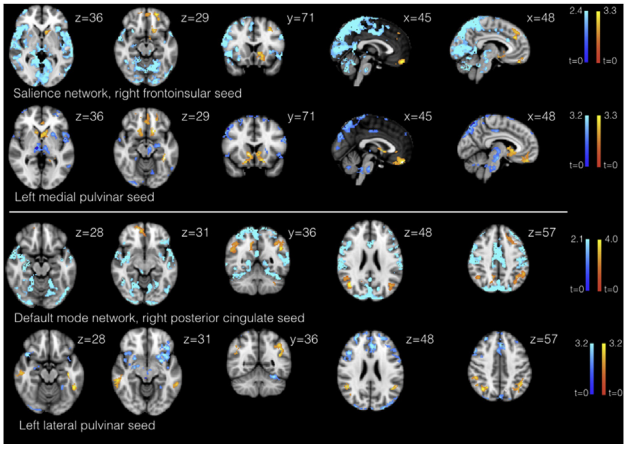

Figure 2. Seed-based analyses, PCA>HC. Joint height and extent probability threshold of $p < 0.05$, corrected at the whole brain level. BPM-corrected for voxelwise atrophy.

IC-P-032 **TRAUMATIC BRAIN INJURY EFFECTS UPON THE STRUCTURAL CONNECTOME MIRROR THOSE CAUSED BY ALZHEIMER'S DISEASE**

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Background: The extent to which mild traumatic brain injury (mTBI) modulates the risk for Alzheimer's Disease (AD) as a function of age at injury is poorly understood. In many mTBI victims, blood-brain barrier (BBB) disruption is associated with connectome reorganization, leading to neurological deterioration whose severity increases with age. *Post-mortem* histological examination of brain tissue samples collected from mTBI patients indicates that Amyloid-beta (Aβ) protein deposits are more likely to occur in regions affected by BBB disruption. **Methods:** We acquired magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) from 20 middle-aged (age: $\mu \sim 45.1$ years, $\sigma \sim 7.3$ years) and 20 older (age: $\mu \sim 68.6$ years, $\sigma \sim 8.4$ years) mTBI victims. Data were acquired both within the first few days and 6 months after injury. Multimodal MRI and DTI were combined to generate graph-theoretical representations of network models and to study their spatiotemporal dynamics. **Results:** Changes in white matter connectivity density [proportion of total tractography streamlines which connect one cortical region to the rest of the brain] are significantly and negatively correlated with the distance between cortex and the closest micro-bleeds (R^2: μ=-0.47, SEM=0.21, t_{39}=3.13, p<0.001), both in older (μ=-0.54, SEM=0.29, t_{39}=3.35, p<0.001) and younger patients (μ=-0.41, SEM=0.25, t_{39}=3.41, p<0.001). The rich club coefficients of nodes located in the vicinity of micro-bleeds were found to decrease (R^2: μ=0.44, SEM=0.19, t_{39}=3.44, p<0.001). Changes to network topology in the vicinity of micro-bleeds were found to be strongly correlated (R^2: μ=0.54, SEM=0.23, t_{39}=3.24, p<0.001) with decreases in Glasgow Outcome Score. Areas found to be associated with brain network deterioration are known to be responsible for memory formation (medial temporal lobe), personality (prefrontal cortex), cognitive control (anterior limbic areas) and language (ventromedial temporal lobe). **Conclusions:** Damage to regions often affected by AD appears to increase with age, as does the probability that brain network damage and neurological function deterioration due to mTBI is associated with these regions. Since these areas also feature substantial Aβ deposition in both AD and mTBI, this research can help to understand the relationship between AD-like