The number of CMBs in CMB(+) subjects also correlated significantly with reduced metabolism in the medial temporal lobe ($p<0.05$). Subjects with CMBs were significantly more likely to have deficits on the Clinical Dementia Rating scale (χ 2 p-value = 0.0015). Neither the presence nor number of CMBs was found to be significantly associated with [11 C]PiB SUVR or hippocampal volume. **Conclusions:** In this cohort of very elderly NCs, CMBs are associated with reduced cerebral blood flow, reduced cerebral metabolism, and mild deficits on the CDR scale. Our findings suggest that the small vessel disease associated with CMBs can independently contribute to impaired cognition and functional status, a process likely mediated by chronic hypoperfusion and hypometabolism.

IC-02-06 LONGITUDINAL CHANGES IN BRAIN MRI AND NEUROPSYCHOLOGICAL MEASURES IN ASYMPTOMATIC AND SYMPTOMATIC FAMILIAL FRONTOTEMPORAL LOBAR DEGENERATION WITH MUTATIONS IN MAPT

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Background: As disease modifying therapies for familial frontotemporal lobar degenerations (f-FTLD) move into both the symptomatic and asymptomatic patient populations, it will be necessary to develop robust biomarkers that are sensitive to disease progression in both of these populations. In this study we investigated the longitudinal change in brain MRI and neuropsychological measures in asymptomatic and symptomatic carriers of microtubule associated protein tau (MAPT) mutations. **Methods:** All available neuroimaging and neuropsychological data on MAPT mutation carriers (symptomatic = +m CDR≥0.5 and asymptomatic = +m CDR=0) evaluated at Mayo Clinic were analyzed; non-mutation carrier family members (-m CDR=0) were used as controls (Table 1). Longitudinal structural brain MRI scans for each subject were processed using the Symmetric Diffeomorphic Image Normalization method for normalization of serial scans to obtain Tensor Based Morphometry (TBM-SyN) maps. We also compared baseline and longitudinal data on the Controlled Oral Word Association Test (COWAT), Trailmaking Test B (TMT B), Boston Naming Test (BNT) and Category Fluency (Cat Fl). We used linear mixed models with random slopes and intercepts to analyze longitudinal clinical and imaging data with years from baseline as the time scale. **Results:** The +m CDR≥0.5 subjects had non-zero rates of decline in annual % change in all regions analyzed with TBM-SyN. These rates were significantly different from both +m CDR=0 and -m CDR=0 family members (Figure 1a). The +m CDR=0 subjects had a non-zero rate of decline in the temporal ROI ($p = 0.009$) and trends in the composite frontotemporal region ($p = 0.08$) and the ventricular volume ($p = 0.08$). There was no significant difference when comparing the rates between +m CDR=0 and -m CDR=0. A similar pattern was also observed for all neuropsychological measures without any evidence for non-zero rates of change in +m CDR=0 (Figure 1b). **Conclusions:** Regional brain MRI volumes and neuropsychological measures longitudinally decline in +m CDR≥0.5 subjects and may be useful as biomarkers in this phase of the disease. TBM-SyN analysis of +m CDR=0 subjects identified a non-zero rate of temporal lobe change in this relatively young group, which may indicate that brain MRI is a suitable biomarker in the asymptomatic phase of the disease.

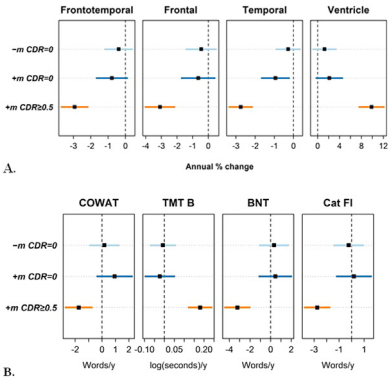

Figure 1. Mean and 95% confidence intervals of annual change in a) frontotemporal regions of interest and ventricular volume and b) neuropsychological measures per group.

Table 1Demographics table of asymptomatic and symptomatic familial FTLD subjects with mutations of MAPT.

	Non-carrier MAPT family members n = 11	Asymptomatic MAPT mutation carriers n = 9	Symptomatic MAPT carriers n = 21
No. of males (%)	4 (36%)	2 (22%)	12 (57%)
Age (y)	39 (9)	35.0 (6.9)	50 (12)
Education (y)	15 (2)	15 (2)	14 (2)
No. of ε4 carriers (%)	3 (27%)	4 (44%)	4 (19%)
Scan interval (y)	4.2 (1.7)	5.2 (2.1)	5.3 (4.0)

Mean (SD) for continuous variables
Count (%) for categorical variable

SATURDAY, JULY 12, 2014
ALZHEIMER'S IMAGING CONSORTIUM (IC)
IC-03
NEW DEVELOPMENTS

IC-03-01 IMAGING OF TAU PATHOLOGY IN PATIENTS WITH NON-ALZHEIMER'S DISEASE TAUOPATHIES BY [11C]PBB3-PET

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Background: [11 C]PBB3 has been recently developed as a tau imaging PET ligand.The preclinical studies showed high affinity and selectivity of this ligand for tau deposits. Our initial PET study with [11 C]PBB3 demonstrated high [11 C]PBB3 binding in the cerebral cortex including medial temporal lobes in patients with Alzheimer's disease (AD) compared with age-matched controls. The aim of this study is to test the hypothesis that [11 C]PBB3 PET is a sensitive in vivo imaging method for detecting tau lesions in non-AD tauopathies such as progressive supranuclar palsy (PSP) and corticobasal degeneration (CBD). **Methods:** Ten patients with PSP, five patients with corticobasal syndrome (CBS), and 18 age-matched healthy controls (HCs) participated in this study. Sequential PET scans were performed for 70 min following intravenous injection of [11 C]PBB3. PET images were anatomically normalized to the Montreal Neurological Institute space using T1 weighted MRI, and standardized uptake value ratio (SUVR) was calculated using the cerebellar cortex as reference region. One-way ANOVA test was performed among PSP, CBS patients, and HCs using statistical parametric mapping software (SPM 8). Statistical threshold was set to 0.01 with extent threshold of 50 voxels without correction for multiple comparisons. Cerebral beta-amyloid depositions were also estimated using

SUVR images at 50-70 min after [11 C]Pittsburgh compound B injection in all patients and HCs. **Results:** All patients and HCs were PIB-negative except one PIB-positive patient with CBS and one HC. SPM analysis showed high [11 C] PBB3 binding in globus pallidus, putamen, thalamus, subthalamus, midbrain, pons, and peri-rolandic areas in PSP patients compared with HCs. PIB-negative CBS patients (n=4) showed high [11 C]PBB3 binding in peri-rolandic areas, supplementary motor area, subthalamus, and midbrain compared with HCs. SUVR images of one PIB-positive patient with CBS showed high [11 C] PBB3 binding in the whole cerebral cortex including limbic cortex like advanced AD patients. **Conclusions:** The distribution of [11 C]PBB3 binding in the patients was in accord with the known distribution of tau pathology in PSP and CBD. The present study supports the utility of [11 C]PBB3-PET for detecting tau deposition in non-AD tauopathies including PSP and CBD.

IC-03-02 MODELING LONGITUDINAL FLORBETAPIR CHANGE ACROSS THE DISEASE SPECTRUM

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Background: Limited availability of longitudinal amyloid PET measurements has made it difficult to examine the pattern of amyloid deposition over the entire course of disease. Of particular importance is determining the early period during which amyloid accumulates up to a maximum. This period is a critical window for disease-modifying treatments. PiB-PET studies have begun to model trajectories of longitudinal amyloid change, but it is unclear how these models generalize to other amyloid PET tracers, such as florbetapir, and other methodological factors such as reference region. **Methods:** We used longitudinal florbetapir PET measurements obtained at a two year interval in cognitively normal (N=68), Early MCI (N=84), Late MCI (N=28), and AD participants (N=15; 195 total) from the Alzheimer's Disease Neuroimaging Initiative. In particular, we focused on examining characteristics of normal individuals with subthreshold florbetapir retention. We also examined the influence of several methodological factors such as reference region selection on estimated trajectories across the entire range of amyloid measurements. **Results:** Average annual absolute florbetapir change was consistent across diagnostic groups (1-2%) but was highly variable across individuals (SD=1%). Of cognitively normal individuals, 52/68 (76%) were florbetapir negative at baseline. Of this group, 21 (40%) decreased during followup (-1 +/- 1% annual SUVR decrease), indicating absence of AD-related pathology. The remaining 60% had a 2 +/- 1% annual SUVR increase), suggesting that some of these individuals are on a trajectory to AD. Of the 16/68 normals (24%) who were amyloid positive at baseline, 13 increased at approximately the same rate as the amyloid negative normals (2 +/- 2%). Plotting florbetapir change as a function of baseline status in accumulating normal and the patient groups resulted in an inverted-U shaped function. This allowed us to estimate a 6-7 year window of accumulation between the threshold for amyloid positivity and the peak of amyloid deposition. **Conclusions:** Longitudinal florbetapir measurements are highly variable in subthreshold individuals. Amyloid deposition that occurs between the positivity threshold and the peak of accumulation may represent an optimal window for therapeutic intervention.

IC-03-03 COMPARISON OF MEASUREMENTS OF CEREBRAL BLOOD FLOW BY EARLY FRAMES OF 11C-DEUTERIUM-L-DEPRENYL (11C-DED) AND 11C-PIB PET TRACERS AT DIFFERENT STAGES OF ALZHEIMER'S DISEASE

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Background: The pathophysiological mechanisms of Alzheimer's disease (AD) are complex and there is evidence that neuroinflammatory and neurovascular changes may precede β -amyloid (A β) plaque deposition in AD. Reactive astrocytes seem to play an important role in neuroprotective or neurotoxic mechanisms at different stages of AD, and are also involved in neurovascular dysfunction. The PET tracer 11 C-deuterium-L-deprenyl (11 C-DED), which binds to monoamine oxidase B (MAO-B) and a marker of astrocytosis, was applied together with 11 C-PIB and 18 F-FDG in a multi-tracer study. Here we wanted to compare 11 C-DED and 11 C-PIB early frames as measures of cerebral blood flow (CBF) at different stages of Alzheimer's disease. **Methods:** 11 C-DED, 11 C-PIB and 18 F-FDG PET scans were performed in 64 subjects including sporadic AD (n=8), sporadic MCI with or without fibrillar A β deposition (n=16), healthy controls (n=14), and members of families with known AD mutations (n=26). Mean target-to-pons regional values were obtained for 11 C-PIB and 18 F-FDG, while a modified reference (cerebellum gray matter) Patlak model was applied to 11 C-DED. **Results:** In this study, the 1-4 minute early frames of 11 C-DED (eDED) and 11 C-PIB (ePIB) were compared as estimates of CBF at different stages of AD as well as in controls. CBF as measured by eDED was found to be significantly decreased in MCI PIB-positive patients compared to healthy controls in most cortical regions and in the putamen. In contrast, no significant CBF changes were detected in presymptomatic familial AD (FAD) mutation carriers when compared to age-matched non-carriers. However, CBF in presymptomatic FAD carriers declined in time when approaching estimated age of onset. CBF changes as measured by ePIB were compared to the estimates using eDED as well as the 18 F-FDG uptake in the same study groups. **Conclusions:** The use of early frames of 11 C-DED and 11 C-PIB tracers as measures of CBF in addition to binding data in the late frames offers the advantage of obtaining dual physiological (CBF) and pathological information from a single PET scan. The measurement of CBF from these tracers contributes to the understanding of the time course and regional brain changes at different stages in AD.

IC-03-04 PATIENTS SHOW SIGNIFICANT DISTURBANCE IN WATER INFLUX INTO CSF SPACE, STRONGLY SUPPORTING BETA-AMYLOID CLEARANCE HYPOTHESIS

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Background: Recent studies on cerebrospinal fluid (CSF) homeostasis emphasize the importance of water influx through the peri-capillary (Virchow-Robin) space for both CSF production and reabsorption (Oreskovic and Klarica hypothesis). CSF influx through the water channel aquaporin-4 (AQP-4) is likely to play a role as the brain's equivalent of lymphatic drainage, and is believed to be critical for proper b -amyloid clearance. Using mice genetically modified for precursor protein (APP) overproduction (APP overproduction Alzheimer disease model) and [17O]H 2 O JJ vicinal coupling proton exchange (JJVCPE) MRI imaging, we discovered that APP overproduction alone was not sufficient to form senile plaque. An additional condition is necessary: a significant reduction of water influx into the CSF space, the condition which presumably represents a significant disturbance in b -amyloid clearance. **Methods:** Six young volunteers (young control, 21-24 years old), seven senior volunteers (senior control, 60-78 years old, MMSE $\geqq$ 26), and six Alzheimer's disease (AD) patients (study group, 59-84 years old, MMSE: 13-19) were included in this study. All AD patients were diagnosed by experienced neurologists based on DSM-IV criteria. CSF dynamics were analyzed using positron emission tomography (PET) following an intravenous injection of 1,000 MBq [15O]H2O synthesized on-site. **Results:** Water influx into CSF space in AD patients expressed as influx ratio (0.761 $\pm$ 0.009) was significantly reduced ($p < 0.001$) compared to young controls (1.329 $\pm$ 0.218). Senior controls showed a large range of influx ratio (0.599-1.442) suggesting that reduction in water influx into CSF represents one of the "aging" processes. **Conclusions:** Reduction in water influx into the CSF and clearance rate of b -amyloid is the necessary, if not sufficient, factor in the pathogenesis of AD. Cohort studies for assessing dynamical indices of the balance between production and clearance of b -amyloid in various patient populations, including mild cognitive impairment (MCI) patients, will be critical for our proper understanding of the pathogenesis of AD.