retrosplenial cortex after adjusting for global cortical PiB retention in DLB. **Conclusions:** Patients with DLB are characterized by increases in the anterior DMN and decreases in the posterior DMN and PVN. This reciprocal change in the anterior and posterior DMN identified in patients with DLB closely resemble the DMN changes observed in AD. Although β - amyloid load modifies the decreases in the middle and posterior cingulate regions in the posterior DMN, connectivity abnormalities in DLB persist even after controlling for β - amyloid load. The pattern of posterior DMN and PVN connectivity decreases sparing the middle and posterior cingulate gyri after adjusting for β - amyloid load is consistent with the pattern of regional hypometabolism typically observed in DLB.

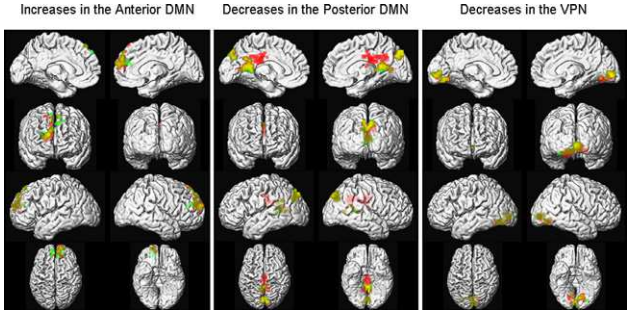

Figure. Within-network connectivity differences between DLB (n = 24) and controls (n = 48) ($p<0.05$ corrected for multiple comparisons at the cluster level). Red: differences un-adjusted for global cortical PiB retention; Green: differences adjusted for global cortical PiB retention; Yellow: differences common to both global cortical PiB adjusted and un-adjusted analyses. Posterior cingulate and middle cingulate gyri decreases in the posterior DMN normalize after adjusting for global cortical PiB retention in DLB (middle panel).

IC-P-136 MATHEMATICAL AND STATISTICAL METHODS TO MODEL THE TRAJECTORY AND ESTIMATE THE AGE AT ONSET OF ALZHEIMER'S DISEASE BIOMARKER CHANGES

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Background: We have been using cross-sectional brain imaging, cerebrospinal fluid (CSF) and other measurements to characterize and compare the age-dependent trajectory of different Alzheimer's disease (AD) biomarker changes associated with the preclinical and clinical stages of AD in PS1 E280A mutation carriers and non-carriers from the world's largest early-onset AD kindred. To help in this endeavor, we have developed statistical methods to model the preclinical trajectory and estimate the age at onset of AD biomarker changes. **Methods:** Florbetapir PET and volumetric MRI images were acquired in 31 asymptomatic and symptomatic PS1 E280A mutation carriers 20-56 years of age. Mean cortical-to-pontine florbetapir PET standard uptake value ratios (SUVRs) were used to characterize amyloid plaque deposition. the FreeSurfer algorithm was used to characterize hippocampal-to-total intracranial volumes, and the data were inverted to depict smaller hippocampal volumes with higher numerical values, corresponding to greater volume reduction. In order to characterize the age at onset of amyloid plaque deposition, we introduced a mathematical expression corresponding to a trajectory associated with an initial floor effect at the youngest ages, followed by an age-dependent increase, and culminating in a ceiling effect. In order to characterize the age at onset of hippocampal volume reduction, we introduced a mathematical expression associated with an initial floor effect, followed by a slow rate followed by a higher rate of volume reduction. A computer-simulation based statistical procedure with the fitted curve and estimated variances at different ages was developed to characterize and statistically compare the duration of the different biomarker floor effects, the age at onset of different biomarker changes. **Results:** Using this approach, PS1 E280A mutation carriers had an age of about 28 at the onset of amyloid plaque deposition (about 1 7 years before the kindred's average age at MCI onset), an average age of about 3 7 at the onset of the hippocampal volume reduction (about 8 years before the average age at MCI onset), significantly later than amyloid plaque deposition. **Conclusions:** The onset of different AD biomarkers changes can be mathematically expressed and statistically analyzed. The methods introduced here may help in the characterization of preclinical AD.

IC-P-137 MILD COGNITIVE IMPAIRMENT OF FRONTOTEMPORAL LOBAR DEGENERATION SUBTYPES: CLINICAL AND IMAGING CHARACTERISTICS

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Background: Although many investigators believe that the majority of neurodegenerative dementias have an initial symptomatic phase consistent with mild cognitive impairment (MCI), there has been relatively little study of non-Alzheimer forms of MCI. We set out to investigate the frequency and characteristics of a recognizable clinical phase of MCI in patients with a diagnosis of Frontotemporal Lobar Degeneration (FLTD) and to investigate the clinical, psychometric, and structural MRI predictors of conversion to dementia in this population. **Methods:** A consecutive series of patients with a clinical diagnosis of FTLD were evaluated comprehensively, including functional assessment, to determine whether their overall clinical status was best defined as MCI or dementia. Cortical thickness analysis was employed to measure regional atrophy. **Results:** Of the 124 patients in our FTLD cohort, 43 were classified as having a clinical status of MCI at initial presentation; the remainder (81) were classified as having a clinical status of dementia. Nearly half (20) of the patients who presented with MCI have since converted to dementia. The majority of patients (34) with MCI clinical status had one of the primary progressive aphasia phenotypes, with the remainder (9) having a behavioral variant FTLD (bvFTLD) phenotype. All but 1 of the bvFTLD patients converted to dementia. All MCI-FTLD patients demonstrated atrophy detectable on quantitative MRI, with distinct "signature" imaging findings for each phenotypic subtype. **Conclusions:** Analysis to date of our FTLD cohort suggests that it is relatively more common for aphasic than behavioral variant FTLD to present in a prodromal clinical phase consistent with MCI. MCI of the FTLD type usually has specific recognizable syndromic clinical characteristics and structural MRI changes that are often distinct from MCI due to Alzheimer's disease. Additional analyses are in progress to identify the best predictors of conversion to dementia.

IC-P-138 BRAIN AND HIPPOCAMPAL RATES OF ATROPHY IN FAMILIAL ALZHEIMER'S DISEASE MUTATION CARRIERS: PRELIMINARY FINDINGS FROM THE DIAN STUDY

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Background: The Dominantly Inherited Alzheimer Network (http://dian-info.org/) study is an international clinical, biomarker and multimodality imaging study of individuals at risk for autosomal dominant Alzheimer's disease and those already mildly affected. This prospective study of these individuals provides an opportunity to follow these individuals through different stages of the disease process, starting several years before symptoms are evident. We report here the first longitudinal analyses of cerebral and hippocampal atrophy rates from the DIAN cohort. **Methods:** All DIAN participants have T1-weighted volumetric MRI scanning at baseline. We analysed data from the first 22 participants with a follow-up MRI scan (mean ± sd interval 12.7 ± 0.9 months). Seventeen subjects were symptomatic mutation carriers (sMut+) with Clinical Dementia Rating (CDR) scores >0 aged 46.4 ± 9.6 years; three were asymptomatic carriers (aMut+) with CDR = 0; and two were non-carriers (NC). The aMut+ and NC were combined into one group for this initial analysis (age: 34.5 ± 5.4 years). The whole brain and hippocampi were first delineated using an automated procedure. Annualized atrophy rates were measured by volumetric difference as well as the Boundary Shift Integral (BSI). Two sample t-tests assuming unequal variances were performed between the annualized atrophy rates of the sMut+ group and the combined NC/aMut+ group. **Results:** Brain BSI atrophy rates were higher (see Table) in the symptomatic subjects (1.9% vs. 0%/year; $P = 0.003$). However, the difference in hippocampal atrophy rates was not statistically significant (2.5% vs. 0.5%/year; $P = 0.057$ for volumetric). **Conclusions:** Initial analysis of atrophy rates from this cohort indicates that brain atrophy rates are higher in symptomatic mutation carriers than in asymptomatic carriers or non-carriers. The lack of a detectable difference in hippocampal atrophy rates may reflect the small sample size and that these preliminary analyses included presymptomatic mutation carriers in the control group who may have already had increasing rates of hippocampal atrophy. Over 200 subjects will be followed longitudinally, so as more data are acquired, we will separately analyze atrophy rates in asymptomatic carriers and non-mutation carriers, estimate sample sizes for trials and assess the relationship between atrophy rates and symptom onset.

Table 1
Mean (95%CI) brain and hippocampal atrophy rates as a percentage of baseline volume

Group	Age	Annualized Brain BSI % loss/year	Annualized Hippocampal Volume change % loss/year
NC/aMut+ (n = 5)	34.5 ± 5.4	0.0 ± 0.8% (-1.0,1.1)	0.5 ± 1.7% (-1.6,2.6)
sMut+ (n = 17)	46.4 ± 9.6	1.9 ± 1.3% (1.2,2.5)	2.5 ± 1.7% (1.6,3.3)
P-value	0.006	0.003	0.057

IC-P-139 IN-HOME CONTINUOUS MONITORING OF GAIT SPEED: A SENSITIVE METHOD FOR DETECTING MOTOR SLOWING ASSOCIATED WITH SMALLER BRAIN VOLUMES AND DEMENTIA RISK

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Background: Slower walking is common with advanced age, and is associated with loss of independence and increased dementia risk. Single gait speed (SGS) measures are typically obtained only at an annual visit. Continuous in-home monitoring of gait speed (CIHM-GS) derived from hundreds of walking episodes per person may provide a better measure linking real-world motor abilities and brain integrity. **Methods:** 19 dementia-free volunteers (mean MMSE 28.7) enrolled in the Intelligent Systems for Assessing Aging Change study underwent 3T brain MRI. FreeSurfer was used to determine brain, ventricular, and hippocampal volumes. Gait speed (GS) was determined: 1) at the time of the MRI, assessing the number of seconds to walk 9 meters with a stopwatch, and 2) using an in-home assessment system that continuously collected data using passive infra-red motion-activity sensors averaged over a one month period aligned with the volunteer's MRI acquisition. Regression analyses examining MRI volumetric measures adjusted for ICV were performed with the outcome of GS. **Results:** Mean SGS was 81.7 cm/sec, while CIHM-GS was 76.4 cm/sec (correlation: $R2 = 0.27$, $P = 0.02$). Slower CIHM-GS was associated with decreased total brain ($R2 = 0.29$, $P = 0.02$), increased ventricular ($R2 = 0.28$, $P = 0.02$), and decreased hippocampal ($R2 = 0.44$, $P = 0.002$) volumes. SGS measures were not associated with either brain or ventricular volumes, but were associated with hippocampal size ($R2 = 0.30$, $P = 0.02$). CIHM-GS was associated with brain ($P = 0.02$) and CSF ($P = 0.02$) in two separate step-wise regressions with age, and gender as covariates. In a step-wise regression with hippocampal volume as an outcome, and age, gender, and both SGS, and CIHM-GS as covariates, only CIHM-GS remained related to hippocampal volume (0.002). **Conclusions:** SGS measures may over-estimate walking abilities in the elderly. Compared with SGS, CIHM-GS measures were associated with smaller global and regional brain volumes, indicators of increased dementia risk. CIHM may provide a more accurate reflection of GS in dementia-free elderly gauging biologically relevant changes in motor performance associated with cognitive decline.

IC-P-140 BASELINE CLINICAL SCORES AND VOLUMETRIC MRI PARAMETERS ACROSS SUBJECTS RANDOMIZED IN MILD-TO-MODERATE (BMS CN156-013) AND PREDEMENTIA (BMS CN156-018) ALZHEIMER'S DISEASE CLINICAL TRIALS OF AVAGACESTAT

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Background: Avagacestat (BMS-708163), an oral gamma-secretase inhibitor, has been studied in two phase 2 clinical trials in mild-to-moderate (CN156-013, completed) and predementia Alzheimer's disease (PDAD) [CN156-018, ongoing]. This post-hoc analysis of MRI volumetric measures