Proportion of PIB positive Cognitively Normal Participants by Individual Characteristics and percent change in number needed to screen by age group

	Age 70-80		Age 80-90		Age 70-80		Age 80-90	
Characteristic	% PIB >1.4	N Needed to Screen (% change)	% PIB >1.4	N Needed to Screen (% change)	% PIB >1.5	N Needed to Screen (% change)	% PIB >1.5	N Needed to Screen (% change)
All subjects	34.9	287 (base)	56.7	177 (base)	22.7	441 (base)	44.9	223 (base)
Female gender	34.0	295 (+3%)	61.5	163 (-8%)	21.1	474 (+7%)	52.3	192 (-14%)
Family history of AD/dementia	46.4	216 (-25%)	64.2	156 (-12%)	34.8	288 (-35%)	50.9	197 (-12%)
Subjective memory complaint (≥3 points)	42.2	237 (-17%)	65.1	154 (-13%)	35.9	279 (-37%)	52.4	191 (-14%)
APOE e4 positive	55.4	181 (-37%)	83.3	121 (-29%)	43.4	231 (-48%)	66.7	150 (-33%)
Global z-score <0.13	39.7	252 (-12%)	68.4	147 (-17%)	29.3	342 (-22%)	54.4	184 (-17%)

into a clinical trial with PIB>1.4 or >1.5 was determined based on the desired sample size divided by sample proportions in the MCSA data. **Results:** Of 483 CN individuals, 151 (31%) had PIB>1.5 and 211 (44%)>1.4. In univariate and multivariate models, discrimination was modest (AUROC ~0.6-0.7). Multivariately, age and APOE best predicted odds of PIB>1.4 and >1.5. For PIB>1.5, the addition of all factors resulted in a PPV of 60% and NPV of 74%, and reduced the number needed to screen from 320 to 166 to enroll 100 individuals into a pre-clinical AD trial requiring brain amyloidosis. The predictability of some factors varied with age. For example, based on PIB>1.5, information on APOE genotype alone reduced the number needed to screen by 48% in persons aged 70-79 and 33% in those aged 80-89. **Conclusions:** Age and APOE genotype are useful predictors of amyloid accumulation, but discrimination is modest. Nonetheless, these results suggest that inexpensive and non-invasive measures could significantly reduce the number of CN individuals needed to screen with amyloid PET imaging or a lumbar puncture for CSF to identify a given number of amyloid positive subjects.

O2-06-04 IMPACT OF DIFFERENT PET IMAGE QUANTIFICATION METHODS, REGIONS-OF-INTEREST AND RISK FACTORS ON THE POWER TO DETECT A SLOWING IN BETA-AMYLOID DEPOSITION IN PRESYMPTOMATIC ALZHEIMER'S DISEASE TRIALS

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Background: We recently demonstrated an association between apolipoprotein E (APOE) ε4 gene dose (reflecting three levels of genetic risk for Alzheimer's disease (AD)) and two-year increases in PiB PET measurements of fibrillar amyloid-β (Aβ) deposition in cognitively normal 54-72 year-old adults. In this study, we sought to characterize and compare the effects of using distribution volume ratios (DVR), standard uptake value ratios (SUVRs) and different cerebral and reference regions-of-interest (ROIs) on the estimated number of 54-72 year-old ε4 homozygotes or heterozygotes needed to detect a slowing of fibrillar Aβ deposition in 24-month presymptomatic AD trials. **Methods:** 90-min dynamic PiB PET scans were acquired during baseline and approximately 24-month follow-up visits in 7 ε4 homozygotes, 8 heteroyzgotes, and 12 non-carriers 64 ± 5 (range 54-72) years of age. Cerebral-to-reference region DV's were computed using the 35-90 min frames and the Logan method; cerebral-to-reference region SUVRs were computed using the 40-70 min frames; in each case, measurements were computed using automatic anatomically labeled frontal, posterior cingulate/precuneus, lateral temporal, lateral parietal, basal ganglia, and mean parietal ROIs and several different, automatically generated cerebellar or pontine ROIs. **Results:** Depending on the use of DVR or SUVR and the combination of cerebral and reference ROIs, we estimate the need for 92-160 homozygotes 54-62 years old or 225-669 heterozygotes 58-72 year-old to detect a 25% treatment effect in a 24-month presymptomatic AD trials, as will be detailed and compared in our presentation. **Conclusions:** The sample sizes needed to detect a slowing in fibrillar Aβ deposition in presympomatic AD trials can be tailored to the person's risk factor, age, clinical trial duration, and amyloid PET ligand, as well as technical variables such as the imaging frames, DVRs or SUVRs, and cerebral or reference ROIs employed.

O2-06-05 A VOXEL-BASED MORPHOMETRY STUDY OF VOLUMETRIC MRI IN FAMILIAL ALZHEIMER'S DISEASE

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Background: DIAN (Dominantly Inherited Alzheimer's Network) is an international longitudinal study of autosomal dominant Alzheimer's disease that involves serial clinical, imaging and biomarker studies of individuals at risk of disease and those already mildly affected. Understanding the patterns of atrophy associated with the disease will be important for studies and trials tracking atrophy progression in these cohorts. **Methods:** 158 participants from the DIAN cohort were included of whom 55 were non carriers (NC); 59 were asymptomatic carriers (aMut+) with a Clinical Dementia Rating (CDR) of 0; and 44 were symptomatic carriers (sMut+) with CDR >0. Voxel based morphometry (VBM) of baseline MR imaging was used to investigate differences in grey matter (GM) and white matter (WM) between the different groups. Tissue segmentation and spatial normalization of volumetric T1-weighted images were performed using the VBM8 toolbox of SPM8. One participant was excluded due to severe WM hyperintensities. Images were smoothed using a 6mm full-width-half-maximum Gaussian kernel. Statistical parametric maps were generated of the GM and WM differences between groups, controlling for total intracranial volume (TIV), gender, acquisition site, and APOE genotype. An interaction term between group and the expected age of onset (current age - parental age of onset) was included. **Results:** Significant clusters (P <0.05

Family-Wise Error corrected) in the GM were observed between groups in the thalamus, precuneus, putamen, and amygdala. Most clusters were primarily driven by differences between the sMut+ and NC group (see Figure). No significant clusters were observed between the aMut+ and NC groups. There were also clusters in the parahippocampal/hippocampal regions. WM differences between groups were observed in the fornix superior to the thalamus, the cingulum inferiorly adjacent to the hippocampus, the splenium adjacent to the cingulate and areas adjacent to the precuneus. **Conclusions:** Symptomatic subjects show widespread differences in GM volume including deep grey structures (e.g. thalamus and putamen) and the precuneus; notable white matter changes included the fornix and the cingulum. The deep grey changes are of interest as PIB PET findings suggest early amyloid deposition in these structures.

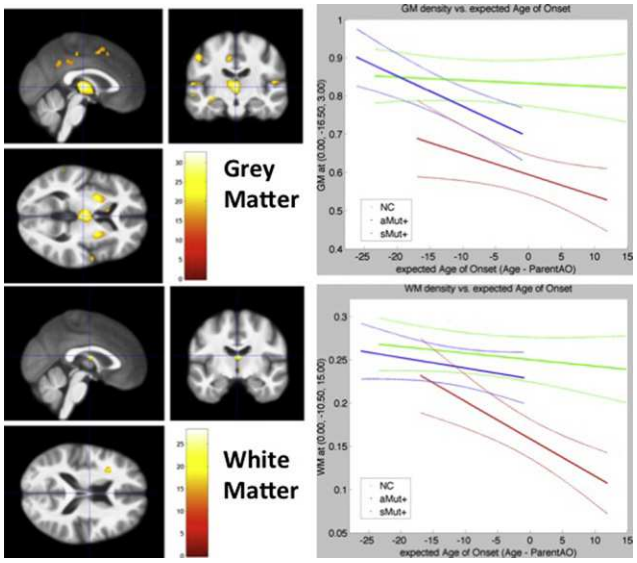

Figure. Summary of VBM study. Left column: centered on a significant cluster in the thalamus. A significant cluster in the putamen can also be seen. Right: significant cluster in the fornix. The plots below are the linear fit (with 95% confidence interval) of the tissue densities with respect to expected age at onset.

O2-06-06 LONGITUDINAL ANALYSIS OF CORTICAL THICKNESS IN PIB+ AND PIB- HEALTHY ELDERLY CONTROLS

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Background: Previous studies have shown that Aβ plaques are likely to exhibit local effects on cortical grey matter only at early stages of the disease, sometimes even before cognitive symptoms arise. Understanding when and where cortical neurodegeneration starts may provide insights into the pathogenesis of AD. In this study, we examined cognitively unimpaired elderly subjects, termed healthy controls (HC). While the majority of the HC present with low neocortical PiB retention, ~30% present with high PiB retention. In this abstract, we evaluate the progressive loss of cortical thickness (CTL) in HC with large and low PiB retention independently. **Methods:** As part of the Australian Imaging, Biomarker and Lifestyle study, 53 HC underwent MRI and 11C-PIB PET scans every 18 months over 3 years. PiB scans were normalised using the standardized uptake value ratio (SUVR) method. A SUVR threshold of 1.5 was use to differentiate subjects with high PiB retention (PiB+) from those with low retention (PiB-). Based on this threshold, 15 HC (28%) were classified as PiB+, while 38 HC (72%) were deemed PIB-. The cortical thickness values from the baseline and follow-ups MRI were mapped onto their associated baseline WM/GM interface surface. Cortical thickness differences were corrected for age and years of education. All baseline surfaces were registered to a common surface to generate population statistics. **Results:** While the PiB- HC group exhibited some CTL, CTL was faster in PiB+ HC than in PiB- HC especially in the temporal ($P = 0.05$), posterior cingulate, and hippocampal regions. (Fig 1) No significant CTL was observed in the frontal areas in any of the groups. When compared to the 18 month scans, CTL was more extensive at 36 months in PiB+ HC but no significant progression was observed in PiB- HC. **Conclusions:** High Aβ burden is associated with faster CTL, suggesting an early neurodegenerative effect of Aβ in asymptomatic individuals. The pattern of CTL also suggests that certain areas of the brain, e.g. the temporal lobe, might be more susceptible/vulnerable to Aβ than others.

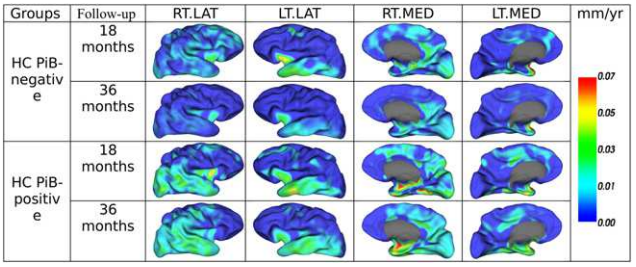

Figure 1. Progression of the cortical thickness loss (in mm/year) for elder HC PiB-negative and HC PiB-positive. The two follow-up scans were taken 18 and 36 months after the baseline ones.

ORAL SESSIONS: O2-07 SOCIAL-BEHAVIORAL AND CARE RESEARCH AND PRACTICE: FAMILY CAREGIVING

O2-07-01 CAREGIVER BURDEN AS ILLNESS PROGRESSES IN ALZHEIMER'S DISEASE (AD): ASSOCIATION WITH PATIENT DEPENDENCE ON OTHERS AND OTHER FACTORS—RESULTS FROM THE DEPENDENCE IN ALZHEIMER'S DISEASE IN ENGLAND (DADE) STUDY

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Background: Dependence on others for care needs has been recommended as a unifying construct in defining severity in AD. Understanding the drivers of caregiver burden is important if patient management in AD is to be optimized. The DADE sought to examine how perceived caregiver burden and caring time changes with increasing patient dependence. **Methods:** A multicentre, cross-sectional, observational study, in 18 UK sites was conducted. Patients in the community and institutionalized with possible/probable AD according to NINCDS/ADRDA criteria were recruited. Assessments included patient dependence (Dependence Scale; DS), caregiver burden (Zarit burden interview; ZBI), and for co-resident caregivers only, the proportion of time patients could be left alone. Multivariate analyses (GLM) were used to assess the relationship between the ZBI and the DS. **Results:** Data on 249