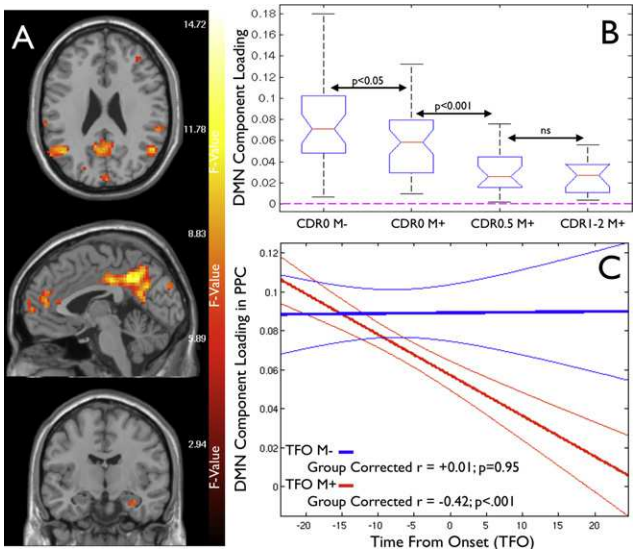
Table 1
Demographic information for DIAN cohort groups.

	CDR0 M-	CDR0 M+	CDR0.5 M+	CDR1-2 M+
N	37	44	24	15
	25 PS1; 5 PS2; 7 APP	35 PS1; 3 PS2; 6 APP	20 PS1; 2 PS2; 2 APP	13 PS1; 0 PS2; 2 APP
Age	38.9 (9.7)	34.6 (8.04)	44.5 (11.7)	49.3 (9.7)
Estimated Time From Age of Onset	-7.7 (12.1)	-12.4 (7.3)	-2.6 (8.6)	2.3 (8.1)

older subjects, suggesting network dysconnection may be an early marker of AD-related synaptic failure. The Dominantly Inherited Alzheimer Network (DIAN) cohort offers a unique opportunity to probe AD related network dysfunction in a much younger cohort, including presymptomatic carriers of presenilin-1 (PS-1), presenilin-2 (PS-2), and amyloid precursor protein (APP) mutations, and to model DMN connectivity as a function of proximity to the observed age of disease onset in these families (time from onset = TFO). **Methods:** A total of 120 subjects, including 83 mutation carriers (PS-1M+ n = 68; PS-2M+ n = 5; APPM+ n = 10) and 37 non-mutation carriers (M-) from the same families, underwent functional MRI during resting state (5.3 min scan). Subjects were then classified into 4 groups based on the Clinical Dementia Rating Scale (CDR) and carrier status (collapsing across mutations; see Table 1 for demographics): CDR0M- (n = 37); CDR0M+ (n = 44); CDR 0.5M+ (n = 24); CDR1-2M+ (n = 15). Functional connectivity MRI (fc-MRI) analyses were conducted with group-independent component analysis using SPM8 and GIFT. **Results:** Whole-brain map ANOVA revealed group differences throughout nodes of the DMN, with the strongest effect in the Precuneus/Posterior Cingulate (PPC; F(3,116) = 14.72, P <0.0001; Fig-A). Post-hoc comparison showed significantly decreased fc-MRI in asymptomatic CDR0M+ compared to CDR0M- in the PPC (P <0.05; Fig-B), right lateral parietal (P <0.01), left lateral temporal (P <0.0001), and medial temporal regions (P <0.001). We observed a negative correlation between DMN connectivity in the PPC and TFO across all mutation carriers (r = -.42; P <0.001), whereas no relationship



A. Whole brain ANOVA across the 4 groups: threshold = P<0.001; F = 5.8. **B**. Box Plots of four groups from the peak voxel in the PPC. **C**. DMN functional connectivity in the PPC (single voxel) by estimated Time from Age of Onset (Unadjusted data shown). Regression model including CDR as covariate revealed significant differences between M- and M+ group sloped (P<0.01).

was observed among non-carriers (r = .01;P = 0.95). The difference in mutation group slopes remained significant when controlling for CDR (difference in slopes P <0.01; Fig-C). **Conclusions:** Impaired connectivity among multiple nodes of the DMN was observed with advancing clinical decline in familial AD, similar to reports in sporadic AD. Presymptomatic mutation carriers demonstrated subtle evidence of DMN dysfunction compared to non-carriers. A strong linear relationship between decreasing DMN integrity and increasing proximity to the expected age of symptom onset suggests that fc-MRI may be useful for tracking disease progression in the preclinical phases of AD.

O2-06-02 FDG METABOLISM IN THE DIAN STUDY OF AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE

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Background: Abnormal brain glucose metabolism has been reported in individuals with genetic risk factors for AD. In order to evaluate the natural history of these changes, participants in the Dominantly Inherited Alzheimer's Network (DIAN) study underwent 18F FDG PET, and we report here an initial assessment of the current baseline FDG-PET DIAN data set. Objective: To evaluate the association of FDG metabolism with age and mutation status in cognitively normal (CDR = 0) and symptomatic (CDR> = 0.5) individuals. **Methods:** FDG data sets from 91 CDR0 (47 carriers/44 non-carriers), 20 CDR0.5 (all carriers) and 13 CDR> = 1 (all carriers) subjects were spatially normalized to an MNI-space template using SPM8, resampled in regions defined by the MNI-based LONI probabilistic atlas, and scaled to cerebellum. Linear regression was used to model the associations of regional average FDG with age, time-to-familial-age-of-onset (TFAO), mutation status and group membership. **Results:** Compared to CDR0 non- carriers and controlling for age, FDG uptake was significantly lower in CDR0.5 subjects globally (P <0.01) and in AD-vulnerable regions

including angular gyrus (*P* <10-5), middle temporal (*P* <0.004), supramarginal (*P* <0.003) and precuneus (*P* <10-5) (Figure 1). Greater decreases in metabolism were seen in CDR> = 1 subjects in a similar set of regions (*P* <10-5). Significant negative associations of FDG metabolism with age, controlling for CDR group, were also seen in these regions (*P* <0.04). While lower mean regional FDG uptake in CDR0 carriers compared to non-carriers did not reach statistical significance, there was a significant inverse relation between TFAO and carrier FDG uptake measured in an AD-vulnerable aggregate region (*P* <0.05) and in the angular gyrus (*P* <0.05) (Figure 2). **Conclusions:** In symptomatic DIAN participants, FDG metabolism was reduced in a regional pattern similar to sporadic AD. In asymptomatic mutation carriers, a similar pattern of FDG hypometabolism was associated with increasing proximity to their family's median age of symptom onset.

Table

	CDR0 non-carriers	CDR0 carriers	CDR0.5 carriers	CDR>=1 carriers
N	44	47	20	13
Sex M/F	19/25	17/30	10/10	7/6
Age	41.3 ± 9.0	35.6 ± 8.6	44.0 ± 10.8	47.5 ± 8.6
Time to Familial Age of Onset	-3.9 ± 12.0	-11.6 ± 8.0	-0.8 ± 9.7	1.6 ± 7.7

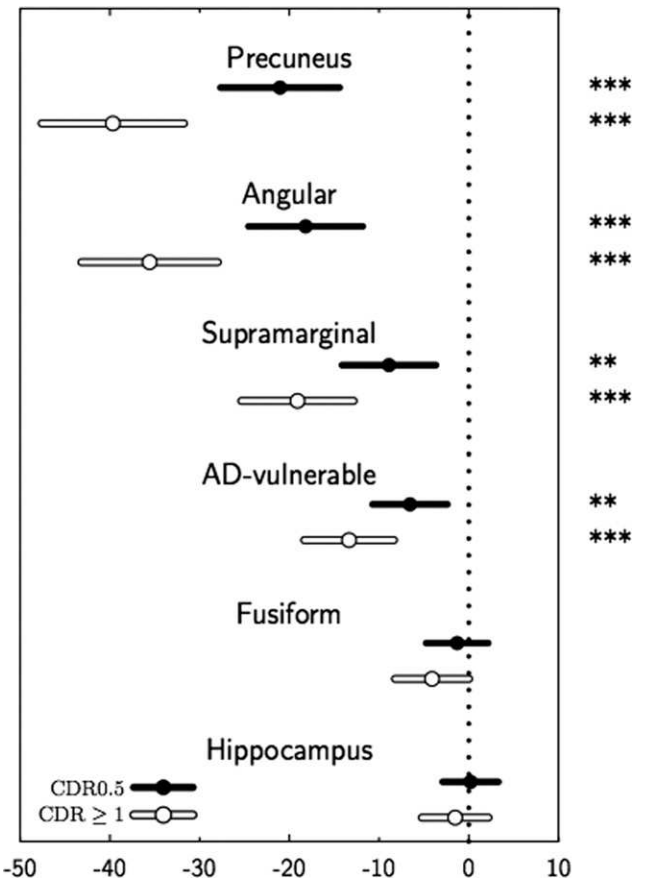

Figure 1. FDG uptake in CDR0.5 and CDR>=1 groups compared to CDR0 non-carriers controlling for age; difference*10^2 and 95% confidence interval. *P*-values: *(<0.05); **(<0.01); ***(<0.001). AD-vulnerable is an aggregate of regions typically affected in sporadic AD.

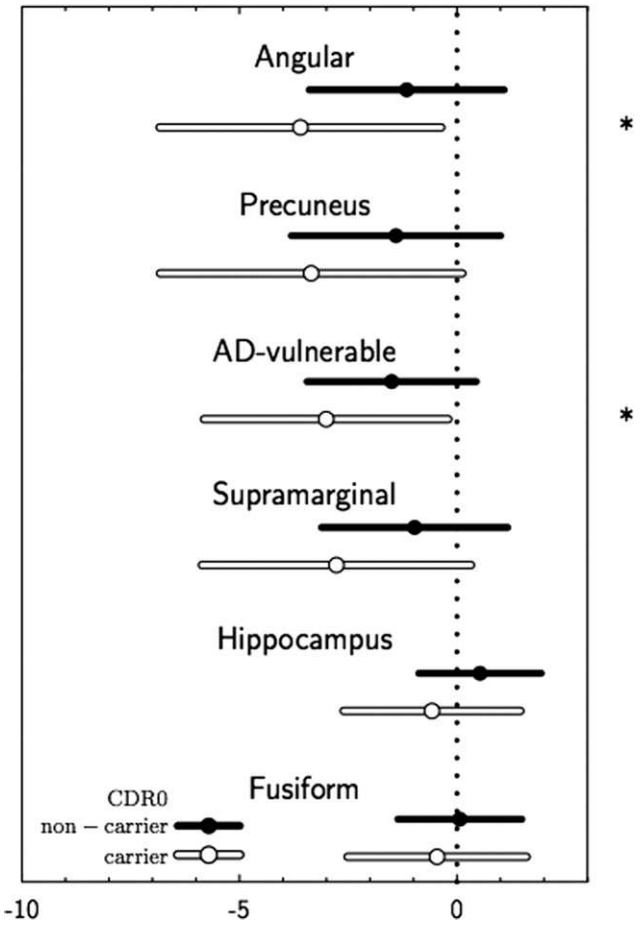

Figure 2. Association of FDG uptake and time-to-familial-age-onset in CDR0 non-carriers and carriers; regression-coefficient*10^3 and 95% confidence interval.

O2-06-03

IDENTIFICATION OF NON-INVASIVE SCREENING VARIABLES FOR THE PREDICTION OF AMYLOID ACCUMULATION IN A POPULATION-BASED STUDY OF COGNITIVELY NORMAL ELDERLY INDIVIDUALS

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Background: The design of secondary Alzheimer's disease (AD) prevention trials in preclinical subjects will likely require documentation of brain amyloidosis for enrollment. The identification of inexpensive and non-invasive screening variables that could predict which individuals have significant amyloid accumulation would reduce screening costs. **Methods:** 483 cognitively normal (CN) individuals, aged 70-92, from the population-based Mayo Clinic Study of Aging underwent PIB-PET imaging. Logistic regression was used to determine whether age, sex, APOE genotype, family history, or cognitive performance were associated with increased odds of a PIB retention ratio>1.4 and >1.5. Area under the receiver operating characteristic curve (AUROC) evaluated the discrimination between PIB positive and negative subjects. Positive (PPV) and negative (NPV) predictive value was defined based on an estimated probability >0.50 who were PIB-positive. The estimated sample size for each characteristic, by age group (70-79 and 80-89 years), needed to screen to enroll 100 participants