O2-06-01 DISRUPTED FUNCTIONAL CONNECTIVITY IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE: PRELIMINARY FINDINGS FROM THE DIAN STUDY

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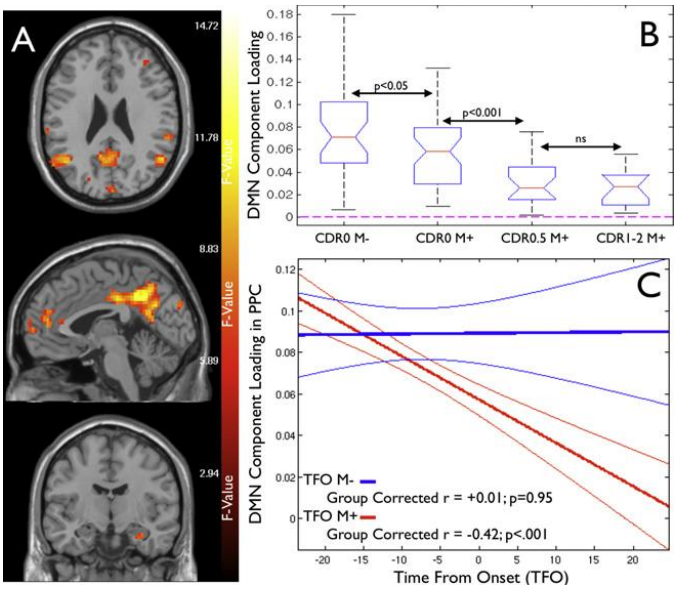
Background: Decreases in the functional connectivity of the default mode network (DMN) have been observed in sporadic, late-onset Alzheimer's Disease (AD) and in amyloid-positive clinically normal older subjects, suggesting network dysconnection may be an early marker of AD-related synaptic failure. 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 ¼ TFO). Methods: A total of 120 subjects, including 83 mutation carriers (PS-1M+ n ¼ 68; PS-2M+ n ¼ 5; APPM+ n ¼ 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 ¼ 37); CDR0M+ (n ¼ 44); CDR 0.5M+ (n ¼ 24); CDR1-2M+ (n ¼ 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

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)



A. Whole brain ANOVA across the 4 groups: threshold¼P<0.001; F¼5.8. 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 ¼ .01;P ¼ 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 symptomonset suggests that fc-MRImay be useful for tracking disease progression in the preclinical phases of AD