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Alzheimer's disease family history impacts resting state functional connectivity

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Abstract

Objective—Offspring whose parents have Alzheimer's disease (AD) are at increased risk for developing dementia. Patients with AD typically exhibit disruptions in the default mode network (DMN). The aim of this study was to investigate the effect of a family history of late-onset AD on DMN integrity in cognitively normal individuals. In particular, we determined whether a family history effect is detectable in apolipoprotein E (APOE) ε4 allele non-carriers.

Method—We studied a cohort of 348 cognitively normal participants with or without family history of late-onset AD. DMN integrity was assessed by resting state functional connectivity magnetic resonance imaging.

Results—A family history of late-onset AD was associated with reduced resting state functional connectivity between particular nodes of the DMN, namely the posterior cingulate and medial temporal cortex. The observed functional connectivity reduction was not attributable to medial temporal structural atrophy. Importantly, we detected a family history effect on DMN functional connectivity in APOE ε4 allele non-carriers.

Interpretation—Unknown genetic factors, embodied in a family history of late-onset AD, may affect DMN integrity prior to cognitive impairment.

Introduction

Alzheimer's disease (AD) is the most common dementing illness in older individuals, affecting more than 13% aged 65 years and older and 43% aged 85 years and older ¹. Genetic factors influence the risk of developing AD. A twin study has reported that heritability contributes up to 79% of the risk for developing AD ². Rare variations in genes encoding amyloid precursor protein and presenilin 1 and 2 ³ account for less than 1 percent of AD cases ⁴. Apolipoprotein E (APOE) is a well-established risk factor for developing late-onset AD (age at onset ≥ 65 years) ⁵. However, APOE accounts for less than 50 percent of genetic susceptibility ⁶. Investigations of additional genetic risk factors for late-onset AD are in the early stages ^{7,8}.

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Although late-onset AD traditionally is referred to as sporadic, familial clusters have frequently been observed⁹. Previous epidemiological studies have demonstrated that biological relatives of AD patients are at increased risk for developing dementia^{10, 11}. Studies of offspring whose parents were affected by late-onset AD could therefore be informative. It remains uncertain whether the contribution of family history of AD is independent of the APOE ϵ 4 allele¹² as both strongly co-occur¹³.

Neuroimaging studies have demonstrated structural, functional, and metabolic changes associated with a family history of late-onset AD. Cognitively normal adults whose parents have late onset AD exhibit atrophy in the medial temporal lobe (MTL), precuneus, and lateral frontal regions¹⁴⁻¹⁶. Functional magnetic resonance imaging (fMRI) experiments have shown that individuals with a family history of AD have altered responses to memory tasks in the MTL, posterior cingulate cortex (PCC), and precuneus^{17, 18}. More recently, positron emission tomography (PET) studies have reported reduced glucose metabolism and increased amyloid deposition in multiple regions, including the PCC and precuneus, of cognitively normal individuals with a family history of late-onset AD^{19, 20}. Interestingly, observed changes from these diverse imaging modalities have primarily converged upon the default mode network (DMN)^{21, 22}. Resting state functional connectivity MRI (rs-fcMRI) studies have demonstrated abnormalities in AD^{23, 24}. However, it remains uncertain whether a family history of late-onset AD impacts DMN integrity in cognitively normal individuals.

Here, in a large sample of cognitively normal individuals, we investigated the effect of a family history of late-onset AD on DMN integrity using rs-fcMRI. We hypothesized that a family history of AD would decrease functional connectivity within the DMN of asymptomatic offspring of AD patients. In addition, we assessed whether family history effects are detectable in APOE ϵ 4 allele non-carriers.

Materials and Methods

Participants

Participants (n=348) were community-dwelling volunteers enrolled in longitudinal studies of memory and aging through the Knight Alzheimer's Disease Research Center (ADRC) at Washington University in Saint Louis. Detailed information regarding recruitment has been previously published²⁵. The definition of a family history of late-onset AD has been described in a previous study²⁶. Briefly, a positive family history was defined as at least one biological parent with age at onset for dementia of Alzheimer type of less than 80 years, and a negative family history was defined as both biological parents did not develop dementia and lived to age 70 or longer. Inclusion criteria for this study were: 1) either positive or negative family history of late-onset AD, 2) completion of structural and rs-fcMRI scans within six month of clinical assessment, 3) normal cognition at the clinical and neuropsychometric assessment closest to the time of MRI scanning. Participants (N=8) with mild AD and with a family history of late-onset AD were studied as a reference group (see text below). Individuals were excluded from this study if they had 1) neurological, psychiatric or systemic illness that might impact cognition or might interfere with longitudinal follow-up, 2) a known deterministic mutation for AD. All procedures were approved by the Human Research Protection Office at Washington University in Saint Louis. Written informed consent was obtained from all participants and their collateral sources (informants).

Clinical assessment of participants

Experienced clinicians conducted separate semi-structured interviews with the participant and with an informant²⁵. The clinician then determined whether dementia was present or absent based on the principle of intra-individual cognitive decline relative to previously attained function. The clinician's judgment was operationalized with the Clinical Dementia Rating (CDR)²⁷, in which CDR 0, 0.5, 1, 2, and 3 corresponded to no dementia (i.e., cognitively normal), very mild, mild, moderate, and severe dementia, respectively. An etiologic diagnosis of dementia (i.e., CDR > 0.5) was made in accordance with standard criteria²⁸. This clinical assessment alone enables the detection of very mild cognitive decline at the CDR 0.5.

Genotyping

DNA was extracted from peripheral blood samples using standard procedures. APOE genotyping was performed as previously described²⁹.

Image acquisition and pre-processing of rs-fcMRI data

We collected resting state functional MRI as well as high-resolution structural MRI data for each participant. The functional MRI data were preprocessed, and underwent quality assurance procedures. Details of the data acquisition, preprocessing and quality assurance are provided in Supplementary materials.

Definition of regions of interest

Regions of interest (ROIs) within the DMN were identified in a separate group of mild AD and control participants (none used in the main analyses). fMRI data were analyzed from eight mild AD participants (CDR 1) (3 male, ages 64 to 88) with a family history of late-onset AD and eight randomly selected cognitively normal participants (CDR 0) without a family history of late-onset AD (2 male, ages 46 to 82). A 6-mm-radius sphere centered on the PCC (MNI coordinates: -2, -54, 16) was used as the seed. Functional connectivity maps were conventionally computed as the correlation between the time course extracted from the PCC seed and all other brain voxels. Correlation maps were converted to *z*-maps using Fisher's transformation. In the following, we denote Fisher *z*-transformed Pearson correlations as *z*(*r*). Averaged PCC correlation maps were obtained for the mild AD and cognitively normal groups. A group difference map was produced by subtracting the averaged map of mild AD participants from cognitively normal individuals. This map was thresholded at *z*(*r*) 0.25 and cluster size 10 voxels. Mild AD participants showed reduced functional connectivity between the PCC and retrosplenial cortex extending to the precuneus, the left and right inferior parietal lobules (IPL), the left and right medial temporal lobe (MTL), and medial prefrontal cortex (MPFC) (Figure 1). Peak foci were identified in the difference map by automated peak search (Supplementary Table S1) and 6mm radius spherical ROIs were centered on these peaks for use in the main analysis that compared cognitively normal individuals (CDR 0) with a family history of late-onset AD to those with no family history of late-onset AD.

Investigation of the effect of family history of late-onset AD on DMN integrity in the entire cognitively normal sample

Inter-regional correlation coefficients were computed between the PCC seed and each of the ROIs as described above. The six pairwise correlations (i.e., PCC-RSC, PCC-LIPL, PCC-RIPL, PCC-MPFC, PCC-LMTL and PCC-RMTL) at the subject level were analyzed separately as a function of family history (yes or no), age, sex, and APOE genotype ($\epsilon 4$ allele present or absent) by an Analysis of Covariance (ANCOVA). The interactive effects between family history and other factors were first tested and reported if confirmed.

Otherwise, the independent effect of family history was reported after adjusting for age, sex, and APOE4. All statistical comparisons were based on appropriate F - or t -tests from the ANCOVA with a statistical threshold for significance of $p < 0.05$, uncorrected for multiple comparisons. All statistical analyses were performed using SPSS 19.0 (Chicago, IL).

Investigation of the effect of family history of late-onset AD according to APOE genotype

We further assessed functional connectivity in two participant subsets: APOE $\epsilon 4$ allele non-carriers ($N=226$) and carriers ($N=116$). In each participant subset, the family history effects on inter-regional correlation coefficients were investigated by an ANCOVA after adjusting for age and sex.

Investigation of the specificity of the family history effect on resting state networks

Additional analyses were performed using seed regions within the motor, visual and auditory systems. ROIs were selected based upon previous work: motor (MNI coordinates: left motor cortex: -40, -23, 53, right motor cortex: 41, -22, 48, supplemental motor area: 1, -18, 49), visual (MNI coordinates: left V1: -8, -83, 0, right V1: 7, -83, 0) and auditory (MNI coordinates: left A1: -64, -28, 13 right A1: 62, -24, 13)³⁰. We calculated mean correlation coefficients between three region pairs in the motor network, or correlation coefficients between one region pair in each of the visual and auditory networks. The effect of family history of AD on correlation coefficients was assessed by an ANCOVA after adjusting for age and sex.

Investigation of the effect of family history of late-onset AD on MTL volumetrics

Previous studies have reported MTL atrophy in cognitively normal individuals with a family history of late-onset AD¹⁴⁻¹⁶. We investigated the possibility that observed functional connectivity changes were merely attributable to MTL atrophy. High-resolution structural MRI scans were processed to obtain entorhinal cortical thickness and hippocampal volumes. Details of structural MRI data processing are provided in Supplementary Material. These two MTL volumetric measures were analyzed as a function of family history (yes or no), age, sex, and APOE genotype ($\epsilon 4$ allele present or absent) by an ANCOVA. The interactive effects between family history and other factors were first tested and reported if confirmed. Otherwise the independent effect of family history, after adjusting for age, sex, and APOE4, was reported.

Results

Demographic variables of cognitively normal participants

Demographic information for these participants is provided in Table 1. Participants with a family history of late-onset AD ($N=196$) were more likely to be younger ($p < 0.05$), female ($p < 0.05$), and have at least one APOE $\epsilon 4$ allele ($p < 0.001$) compared to those without a family history ($N = 152$). No significant group differences were found in education levels or Mini-Mental State Examination (MMSE) scores.

Effects of family history of late-onset AD on DMN integrity for the entire cohort

Inter-regional correlation coefficients were computed between the PCC and DMN ROIs defined *a priori* by an analysis of a separate participant sample (see Methods). We compared correlation coefficients, measured in DMN node pairs, between participants with and without a family history of late-onset AD. In general, cognitively normal individuals with a family history of late-onset AD had reduced correlations between the PCC and other DMN nodes. However, statistically significant decreases were observed only between the PCC and MTL ($p < 0.05$ bilaterally), after adjusting for age, sex, and presence of APOE $\epsilon 4$ allele

(Figure 2A) (Supplementary Table S2 and Table S3). The effect of APOE $\epsilon 4$ allele on functional connectivity between the PCC and other DMN regions was not significant (all $p > 0.14$, after adjusting for age, sex, and family history of AD). In addition, a significant interaction effect was observed only between family history and age for functional connectivity between the PCC-retrosplenial cortex (RSC) node pair ($p < 0.05$). Specifically, correlations between the PCC-RSC showed a significant age-dependent decrease in individuals with a family history of late-onset AD, but not in those without a family history (Figure 2D).

Effects of family history on DMN integrity in APOE 4 allele non-carriers

To test whether the observed family history effect was observed in APOE $\epsilon 4$ non-carriers, we restricted our analyses to a subset of participants who did not have this allele. A similar pattern of functional connectivity loss was seen in APOE $\epsilon 4$ negative individuals with a family history of late-onset AD ($n=112$) compared to those without a family history of AD ($n=114$). Significant correlation decreases were again seen only for the PCC-left MTL and the PCC-right MTL (both $p < 0.05$, after adjusting for age and sex) (Figure 2B and Supplementary Table S3).

Effects of family history on DMN integrity in APOE 4 allele carriers

To assess the influence of the presence of APOE $\epsilon 4$ allele on the expression of a family history of late-onset AD, we restricted our analyses to individuals with at least one APOE $\epsilon 4$ allele. This included 81 participants with a family history of late-onset AD and 35 participants without a family history of late-onset AD. We observed no significant differences in inter-regional correlation coefficients between any of the DMN regions (all $p > 0.28$, after adjusting for age and sex) (Figure 2C and Supplementary Table S3).

Control analysis for possible contribution of MTL volumetric changes

Entorhinal cortical thickness and standardized hippocampal volumes were not significantly different between participants with and without a family history of late-onset AD (both $p > 0.56$, after adjusting for age, sex, and the presence of APOE $\epsilon 4$ allele) (Figure 3).

Control analysis focusing on other resting state networks

To test whether the presently observed rs-fcMRI effects were specific to the DMN, we compared functional connectivity between regions comprising the motor, visual, and auditory systems. No significant differences were found in functional connectivity between the two groups for each of these regions (motor: $p = 0.46$; visual: $p = 0.19$; auditory: $p = 0.92$) (Supplementary Table S4).

Discussion

Prior work has shown that DMN functionality is disrupted in AD^{23, 24} as well as in cognitively normal individuals at increased risk for developing AD (i.e., individuals having at least one APOE $\epsilon 4$ allele or participants with amyloid plaques using Pittsburgh Compound B (PiB))³¹⁻³³. In the present work, we demonstrate reduced functional connectivity within specific regions of the DMN (PCC-MTL) in asymptomatic individuals whose parents have late-onset AD. This effect was detectable in non-carriers of the APOE $\epsilon 4$ allele. Observed decreases in functional connectivity were not attributable to structural MTL atrophy. In addition, other networks were not affected (i.e., motor, visual, and auditory). Disruption of PCC-MTL functional connectivity may be an early pathophysiological marker of AD reflecting unknown genetic factors.

Previous studies using neuronal tract tracing techniques have described anatomical connections between the PCC and MTL in non-human primates^{34, 35}. Diffusion tensor imaging studies of humans have identified structural connectivity (the cingulum bundle) between the two regions^{36, 37}. Recent work using rs-fcMRI has demonstrated PCC-MTL functional connections in humans²³ that might be relevant for episodic memory³⁸. The present result, that is, selective reduction in the PCC-MTL connectivity in asymptomatic individuals, is consistent with a model in which pathology (neurofibrillary tangles) initially appears within transentorhinal regions and subsequently spreads within the limbic system³⁹. Furthermore, prior work has shown that symptomatic AD patients have reduced functional connectivity not only between the PCC and MTL, but also between the PCC and other regions of the DMN^{23, 24, 40}. Hence, the available data suggest that reduced functional connectivity in AD progresses in an orderly manner, the earliest changes occurring between the PCC-MTL, with subsequent spread to other DMN regions. Longitudinal studies tracking the effects of AD progression on functional networks and identifying pathological basis of functional network disruption are therefore needed.

An age-related increase in amyloid deposition has been previously observed in individuals with a family history of AD but not in individuals without a family history of AD²⁶. Similarly, the present work found an age-dependent decrease in the PCC-RSC functional connectivity only within individuals with a family history of AD but not in those without. Prior work has related functional abnormalities in the PCC and RSC to the increase of amyloid burden⁴¹. Thus, it is possible that the decreased functional connectivity may be related to amyloid deposition in an age-dependent fashion in individuals with a family history of AD. Future work assessing the relationships between family history of AD, amyloid deposition, and resting state networks is needed.

We observed that the effect of family history of late-onset AD was significant in APOE ϵ 4 non-carriers but not in APOE ϵ 4 carriers. The biological mechanisms underlying this differential influence of APOE genotype on the expression of the family history remain unclear. It is possible that the negative results seen in APOE ϵ 4 carriers are a consequence of insufficient statistical power; the smallest group of participants were those who did not have a family history but had at least one APOE ϵ 4 allele (N=35). Further studies are required to determine whether gene-gene interactions impact DMN integrity.

Previous investigations of APOE ϵ 4 effects on the DMN typically studied individuals in relatively narrow age ranges^{33, 42-45}. It has been reported that, relative to APOE ϵ 4 non-carriers, functional connectivity in carriers is increased in young adulthood (mean age 28 years)⁴², unchanged in middle adulthood (mean age 46 years)⁴⁴, decreased³³ or increased⁴⁵ (mean age 59 and 63 years respectively) in middle age, and decreased in old age (median age 78 years)⁴³. These discrepancies are difficult to reconcile and may reflect differences in the ages of the study samples and experimental strategies (i.e., seed-based vs. independent component analysis). Our study cohort was 68 years old on average, ranging from 45 to 91 years. The possibility of a non-linear relationship between age and APOE ϵ 4 related changes in DMN functional connectivity was assessed but not observed (data not shown). Further work investigating a lifespan cohort that includes sufficient sample sizes in each age range is needed to reveal the trajectory of APOE ϵ 4 related changes in functional connectivity.

We found no evidence that the decreased PCC-MTL functional connectivity is attributable to MTL atrophy. This observation is consistent with previous studies reporting that reduced DMN functional connectivity associated with risk factors for AD in general is not attributable to atrophy³¹⁻⁴³. Collectively, these findings suggest that rs-fcMRI may be more sensitive than structural MRI for the detection of group differences at preclinical stages of AD.

The present work has several limitations. It is possible that some participants whose parents had neurodegenerative dementias other than AD were included, as inclusion was based on reports of the offspring (i.e., the participants) and parental diagnoses generally were not confirmed by neuropathological examination. Moreover, it is also possible that some of our participants with no family history of AD have parents who will eventually develop AD. Inclusion of such participants would have reduced the sensitivity of our analyses. In addition, our study is cross-sectional in design. Additional longitudinal studies are required to determine if decreased functional connectivity remains restricted to PCC-MTL, or if additional DMN regions are disrupted. The present results show that rs-fcMRI measures are affected by unknown genetic factors embodied in a family history of late-onset AD. Future research is warranted to determine the extent to which specific genetic factors, such as novel AD susceptibility genes identified by recent genome-wide association studies ⁴⁶, account for the observed changes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Localization of regions of interest for subsequent analysis of cognitively normal participants.

Using a seed (red sphere) placed in the posterior cingulate cortex (PCC), functional connectivity maps were constructed for eight mild Alzheimer's disease (AD) participants with a family history of late-onset AD and eight cognitively normal participants without a family history of late-onset AD. A group difference map was produced by subtracting the averaged map of mild AD patients from that of cognitively normal individuals.

Regions (yellow) comprising of at least 10 voxels that exhibited significant differences (exceeding a threshold of $z(r) = 0.25$) between the two groups (cognitively normal minus AD) are overlaid on axial anatomic images. The MNI coordinates of peak loci for these regions are listed in Supplementary Table S1. Left in the images refers to anatomical orientation.

Figure 2.

The effect of a family history of late-onset AD on resting state functional connectivity in cognitively normal individuals

Bar graphs (A-C) display covariates-adjusted means (y axis) of correlation coefficients for participants without a family history (FH-) and with (FH+) a family history of late-onset AD. Data are presented for the entire sample (A), apolipoprotein E $\epsilon 4$ (APOE $\epsilon 4$) non-carriers (B), and APOE $\epsilon 4$ carriers (C) respectively. *: $p < 0.05$, adjusting for age, sex and the presence of APOE $\epsilon 4$ allele in (A), and adjusting for age and sex in (B) and (C). Error bars in A-C represent one standard error of the mean. Statistical analyses for the data in A are presented in Supplementary Table S2. Correlation coefficients between the PCC and RSC (y axis) are plotted against age (x axis) and family history of AD in (D). An age-related decrease in functional connectivity is present in individuals with a family history of AD (FH

+) (Pearson $r = -0.25$, $p < 0.001$) but not in those without a family history of AD (FH-) (Pearson $r = 0.07$, $p = 0.41$).

PCC: posterior cingulate cortex, LIPL: left inferior parietal lobule, RIPL: right inferior parietal lobule; MPFC: medial prefrontal cortex; LMTL: left medial temporal lobe; RMTL: right medial temporal lobe, RSC: retrosplenial cortex.

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Figure 3.

MTL volumetric measures for cognitively normal individuals with and without a family history of late-onset AD

Bar graphs show covariates-adjusted means (y axis) of the entorhinal cortical thickness (A) and standardized hippocampal volume (B). Both $p = 0.56$ after adjusting for age, sex, and the presence of APOE $\epsilon 4$ allele.

ERC: entorhinal cortex, HF: hippocampal formation.

Table 1

Demographics of cognitively normal participants

Participants	FH- (n=152)	FH+ (n=196)	<i>p</i>
Mean age (SD), years old	70 (9)	68 (10)	< .05
Age range, years old	45-87	45-91	
Sex, (% Male)	43	30	< .05
Mean Education (SD), years	16 (3)	16 (3)	0.2
Mean MMSE score (SD)	29 (1)	29 (1)	0.77
<i>APOE</i> genotype, % ε4+	24 ^a	42 ^b	< .001

FH-: participants without a family history of late-onset AD, FH+: participants with a family history of late-onset AD, MMSE: minimal mental state examination, APOE: apolipoprotein E,

^a data available from 149 participants

^b data available from 193 participants