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ARTICLE

Dissociable influences of *APOE* ε4 and polygenic risk of AD dementia on amyloid and cognition

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Abstract

Objective

To investigate the effects of genetic risk of Alzheimer disease (AD) dementia in the context of β-amyloid (Aβ) accumulation.

Methods

We analyzed data from 702 participants (221 clinically normal, 367 with mild cognitive impairment, and 114 with AD dementia) with genetic data and florbetapir PET available. A subset of 669 participants additionally had longitudinal MRI scans to assess hippocampal volume. Polygenic risk scores (PRSs) were estimated with summary statistics from previous large-scale genome-wide association studies of AD dementia. We examined relationships between *APOE* ε4 status and PRS with longitudinal Aβ and cognitive and hippocampal volume measurements.

Results

APOE ε4 was strongly related to baseline Aβ, whereas only weak associations between PRS and baseline Aβ were present. *APOE* ε4 was additionally related to greater memory decline and hippocampal atrophy in Aβ+ participants. When *APOE* ε4 was controlled for, PRS was related to cognitive decline in Aβ+ participants. Finally, PRSs were associated with hippocampal atrophy in Aβ− participants and weakly associated with baseline hippocampal volume in Aβ+ participants.

Conclusions

Genetic risk factors of AD dementia demonstrate effects related to Aβ, as well as synergistic interactions with Aβ. The specific effect of faster cognitive decline in Aβ+ individuals with higher genetic risk may explain the large degree of heterogeneity in cognitive trajectories among Aβ+ individuals. Consideration of genetic variants in conjunction with baseline Aβ may improve enrichment strategies for clinical trials targeting Aβ+ individuals most at risk for imminent cognitive decline.

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Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found in the coinvestigators list at links.lww.com/WNL/A406.

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CN** = clinically normal; **GWAS** = genome-wide association studies; **LMM** = linear mixed-effects model; **MCI** = mild cognitive impairment; **PRS** = polygenic risk score; **SNP** = single nucleotide polymorphism.

Common genetic variants explain a large proportion of the heritability of sporadic Alzheimer disease (AD) dementia.[1,2] However, the mechanisms underlying these genetic risk factors are unclear, and it is likely that multiple pathways are involved. Previous work has identified limited associations between genetic risk and β-amyloid (Aβ) accumulation[3,4] and has suggested mechanistic pathways not directly linked to abnormal Aβ accumulation such as inflammatory pathways.[5–7] Thus, genetic risk variants associated with AD dementia may not solely confer risk by promoting Aβ aggregation but may make an individual more likely to decline when faced with Aβ accumulation.

A synergistic effect between genetic risk and Aβ is consistent with a framework in which Aβ may be necessary but insufficient for clinical symptoms of AD dementia[8] and may offer an explanation for the presence of clinically normal (CN) older individuals who have high levels of Aβ.[9] Along these lines, it is known that although Aβ+ CN individuals show group-level reductions in cognitive performance over time,[3,10–12] many Aβ+ individuals remain cognitively normal even after extended follow-up.[13] Heterogeneity in cognitive decline has also been reported in symptomatic patients with AD dementia, which may be related to differences in genetic risk factors. For instance, although the *APOE* ε4 allele is consistently associated with abnormal accumulation of Aβ,[14] Aβ+ individuals without dementia who are also *APOE* ε4 carriers show faster rates of cognitive decline than Aβ+ individuals who are *APOE* ε4 noncarriers.[15,16] A similar effect modification has been shown for the *BDNF* gene such that Aβ+ individuals with the *BDNF* Met allele show faster cognitive decline than Aβ+ individuals without the Met allele.[17] Given that these a priori genetic risk factors have been shown to influence cognitive decline among Aβ+ individuals, it is possible that other established genetic risk factors have a similar influence.

The overall goal of the present study was to investigate whether *APOE* ε4 and polygenic risk of AD dementia influence Aβ, cognition, and hippocampal volume measurements and to determine whether their associations with cognition and hippocampal volume are modified by Aβ status.

Methods

Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI; adni.loni.usc.edu) as of March 25, 2017. This study used 702 ADNI-GO/2 participants (221 CN, 367 with mild cognitive impairment [MCI], and 114 with AD dementia) of European ancestry who had florbetapir PET images, longitudinal neuropsychological assessment, and genome-wide single nucleotide polymorphisms (SNPs). Of the 702 participants, 669 additionally had longitudinal brain MRI scans that passed quality control. Given that florbetapir PET was introduced midstudy, longitudinal neuropsychological and hippocampal volume measurements taken >1 year before the baseline PET scan were discarded from the analyses.

Standard protocol approvals, registrations, and patient consents

Institutional review boards approved study procedures across ADNI participating sites. Written informed consent for research was obtained from all participants.

Aβ imaging

Global standardized uptake value ratio florbetapir index values were averaged across 4 large bilateral regions (frontal, cingulate, parietal, and lateral temporal) and normalized by the whole cerebellum.[18,19] A 1.11 cutoff of the baseline standardized uptake value ratio value was used to classify participants as Aβ+ and Aβ−.[18,20]

Neuropsychological assessments

Composite scores of memory[21] and executive function[22] were developed previously by using sophisticated neuropsychometric approaches (confirmatory factor analyses and item response theory) to account for different distributions and formats of individual scores, missing items, and different versions of neuropsychological tests.

Structural MRI

The 3T T1 structural brain MRI scans were processed with the FreeSurfer version 5.3 longitudinal pipeline and used to define bilateral hippocampal volume.[23] We processed the MRI scans locally rather than using the imaging measurements from the ADNI website because this led to more longitudinal time points and the use of a more recent FreeSurfer version.

Processing of genetic data

Genome-wide SNP data from 793 ADNI-GO/2 participants were processed following standard pipelines.[24] Non-European participants, population outliers, and closely related participants were removed. Genotype imputation was performed with the MaCH software.[25] SNPs that had poor imputation quality, high missing rate (>2%), low minor allele frequency (<1%), or significant deviation from Hardy-Weinberg equilibrium ($p < 1e{-}6$) and participants who had

a high missing genotype rate (>2%) were filtered out. Seven hundred sixteen participants with 7,694,586 autosomal SNPs remained after quality control. Of the 716 participants, 702 had florbetapir PET and longitudinal neuropsychological assessments.

Calculation of polygenic risk score

Polygenic risk score (PRS) was computed on the basis of the summary statistics from the stage 1 analysis of the International Genomics of Alzheimer's Project, the largest-to-date case-control genome-wide association studies (GWAS) (17,008 cases with AD and 37,154 CN controls) of AD dementia diagnosis,[26] with the software package PRSice.[27] Specifically, imputed genome-wide SNPs were pruned by use of p value informed clumping. PRS was computed as the sum of individual SNPs below a p value threshold, weighted by the log of the odds ratio estimated by the GWAS. PRS thus summarizes genetic effects among an ensemble of variants spanning the genome that may not individually achieve GWAS-level significance. A range of p value thresholds from $p < 1e{-}7$ to $p < 1e{-}2$ were used in this study.

Statistical analysis

The influences of *APOE* ε4 status and PRS on baseline florbetapir values and binary Aβ+/− groups were examined in the whole sample with linear regression and logistic regression, respectively, with adjustment for top 4 principal components of the genotype data, baseline diagnosis, baseline age, sex, and education. When assessing the effect of PRS, we included *APOE* ε4 status in the model.

The influences of *APOE* ε4 status and PRS on the baseline and longitudinal change in florbetapir values, neuropsychological composite scores, and hippocampal volume measurements were examined with longitudinal linear mixed-effects models (LMMs). All models included an intercept, time from baseline, top 4 genotype principal components, baseline diagnosis, baseline age, sex, education, and the interactions between baseline diagnosis, baseline age, sex, education, and time (i.e., baseline diagnosis × time, baseline age × time, etc) as fixed-effect covariates. Throughout the article, the calculation of PRS included the *APOE* ε4 allele, but when assessing the association between PRS and longitudinal change, we included *APOE* ε4 and its interaction with time in the model to assess the effect of PRS above and beyond *APOE* ε4 status. When analyzing hippocampal volume, we additionally adjusted for intracranial volume and its interaction with time as covariates. Random intercept and slopes were included in each LMM. All analyses were repeated in Aβ+ and Aβ− participants separately. All p values reported in this article are 2-sided uncorrected p values.

To compute a metric of variance explained, we extended the classic adjusted R^2 statistic in multiple regression analysis to the context of LMM. Specifically, we assume that the unbiased estimate of the variance of the random slope in the full LMM is V_{full} and the unbiased estimate of the variance of the random slope in a reduced model without genetic risk factors (*APOE* ε4 or PRS) is V_{reduced}. The reduced model contained all covariates and their interactions with time. Then, variation in the rate of decline explained by each genetic risk factor is defined as $R^2_{\text{slope}} = 1 - V_{\text{full}}/V_{\text{reduced}}$. R^2_{slope} measures the proportion of interparticipant variation in the slope that can be explained by adding the genetic risk factor into the model. R^2_{slope} was calculated for *APOE* ε4 by adding *APOE* ε4 to the reduced model. PRS was then added to this model to estimate R^2_{slope} for PRS. Variance explained in baseline measurements by genetic factors can be defined similarly.

Data availability

All imaging, genetic, demographics, and neuropsychological composite scores used this article are publicly available and were downloaded from the ADNI website (adni.loni.usc.edu). Structural MRI data and GWAS data were downloaded and used to derive the measurements used here (hippocampus volume and PRS). The authors will provide a list of ADNI participant identifications on request for replication purposes.

Results

PRS, baseline Aβ, and clinical diagnosis

Table 1 summarizes the participant characteristics. In general, PRS was greater in the Aβ+ compared to the Aβ− group (2-sample t test $p < 0.05$ across diagnosis and PRS thresholds; figure 1). However, the associations between PRS and baseline Aβ were weak, regardless of whether Aβ is treated as a continuous variable or as a binary variable (table e-1, links.lww.com/WNL/A405). For instance, the most significant relationship between PRS and continuous Aβ explained only 0.75% of the Aβ variation ($p = 0.013$). As expected, *APOE* ε4 was strongly associated with elevated continuous Aβ at baseline, explaining 17.94% of the variance.

PRS was associated with clinical diagnosis, even in the Aβ+ group (PRS was higher in Aβ+ patients with MCI and Aβ+ patients with AD compared to Aβ+ controls; figure 1). This pattern was present for the majority of PRS thresholds (1-way analysis of variance $p < 0.05$). There were no significant diagnostic difference in PRS among the Aβ− group (figure 1). Diagnosis and its interaction with time were controlled for in all subsequent analyses to ensure that results related to cognitive decline were independent of diagnosis.

Genetic risk factors and Aβ accumulation

We next examined the associations between genetic risk factors and longitudinal accumulation of Aβ over time. Given the slow rates of Aβ accumulation, longitudinal Aβ was treated as a continuous variable and examined separately in the Aβ− and Aβ+ groups (defined at baseline). We found that Aβ− *APOE* ε4 carriers had faster Aβ accumulation over time than Aβ− noncarriers ($p = 0.005$). There was no effect of *APOE* ε4 on Aβ accumulation in the Aβ+ group. PRS had no influence on

Table 1 Participant demographics

	Neuropsychological		Neuroimaging		Aβ	
	Aβ+	Aβ−	Aβ+	Aβ−	Aβ+	Aβ−
Sample size, n	380	322	355	314	380	322
Baseline CN/MCI/AD, n	78/202/100	143/165/14	71/191/93	137/164/13	78/202/100	143/165/14
Baseline age (range), y	73.9 (55.1–90.3)	71.5 (55.1–91.5)	73.5 (55.1–90.1)	71.3 (55.0–91.4)	73.9 (55.1–90.3)	71.5 (55.1–91.5)
Female, n (%)	181 (47.6)	138 (42.9)	172 (48.5)	134 (42.7)	181 (47.6)	138 (42.9)
Education (range), y	16.0 (8–20)	16.6 (12–20)	16.0 (8–20)	16.6 (12–20)	16.0 (8–20)	16.6 (12–20)
***APOE* ε4+, n (%)**	250 (65.8)	68 (21.1)	237 (66.8)	66 (21.0)	250 (65.8)	68 (21.1)
Measurements (range), n	4.16 (1–8)	4.71 (1–8)	3.92 (1–7)	4.25 (1–7)	1.71 (1–3)	2.11 (1–3)
Follow-up, mean/median (interquartile range), y	2.50/2.03 (1.02–4.01)	3.22/3.93 (2.02–4.05)	1.52/1.25 (1.00–2.08)	1.77/2.04 (1.03–2.12)	1.44/1.94 (0.00–2.04)	2.29/2.04 (1.92–3.97)

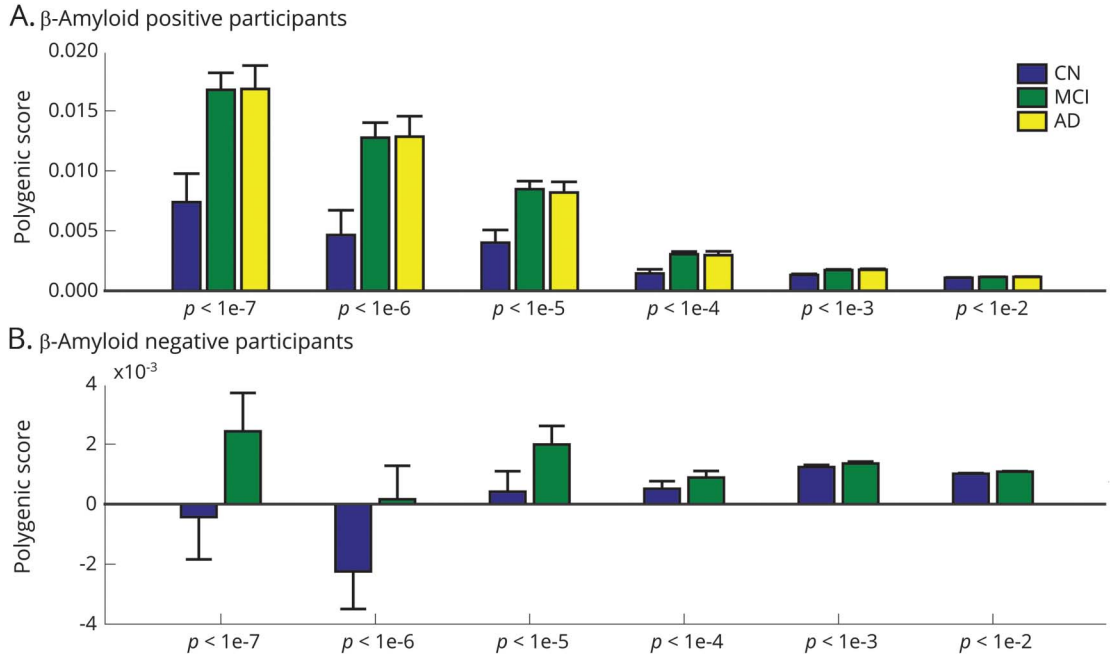
Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; CN = clinically normal; MCI = mild cognitive impairment.
Characteristics of the Aβ+ and Aβ− participants from the Alzheimer's Disease Neuroimaging Initiative.

Aβ accumulation in either the Aβ+ or Aβ− group (figure 2 and tables e-2 and e-3, links.lww.com/WNL/A405).

Genetic risk factors and cognition

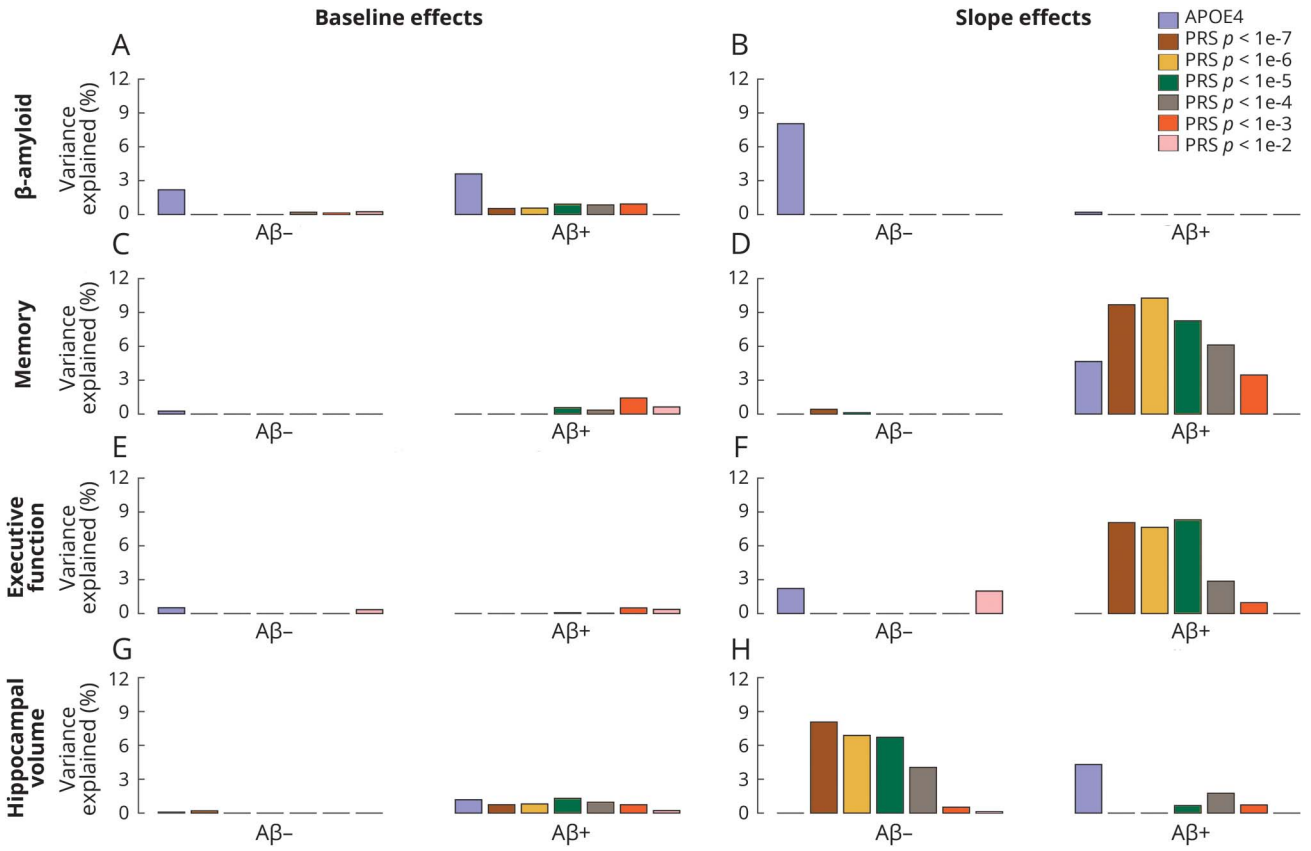
Aβ+ *APOE* ε4 carriers had faster memory decline than noncarriers ($p = 0.015$). There was no effect of *APOE* ε4 on memory in the Aβ− group. *APOE* ε4 was weakly associated with executive function decline in the Aβ− group ($p = 0.049$) but not the Aβ+ group. Furthermore, controlling for *APOE* ε4, higher polygenic risk was strongly associated with higher rates of decline in memory and executive function in Aβ+ individuals across a range of PRS p value thresholds. These associations explained approximately 8% to 10% of the variation in the rate of cognitive decline across Aβ+ participants. PRSs were not associated with cognitive decline in Aβ− participants or baseline cognitive scores in either Aβ group (figures 2 and 3 and tables e-2 and e-3, links.

Figure 1 PRSs of AD dementia by diagnosis and Aβ status



Mean and standard error of the polygenic risk score (PRS) of Alzheimer disease (AD) dementia by diagnosis among (A) β-amyloid (Aβ)–positive and (B) Aβ-negative participants across PRS p value thresholds are shown. CN = clinically normal; MCI = mild cognitive impairment.

Figure 2 Associations between genetic risk factors and Aβ, cognition, and hippocampal volume



Variance explained by *APOE* ε4 and polygenic risk scores (PRSs) of Alzheimer disease dementia across longitudinal linear mixed effects models predicting (A and B) β-amyloid (Aβ), (C and D) memory, (E and F) executive function, and (G and H) hippocampal volume.

lww.com/WNL/A405). All results remained similar when the analysis was restricted to participants without dementia (CN and MCI combined; table e-4 and figure e-1, links.lww.com/WNL/A404). The effects of PRS on cognitive decline among Aβ+ participants remained strong if we additionally controlled for baseline hippocampal volume and its interaction with time in the model (table e-5).

Genetic risk factors and hippocampal volume

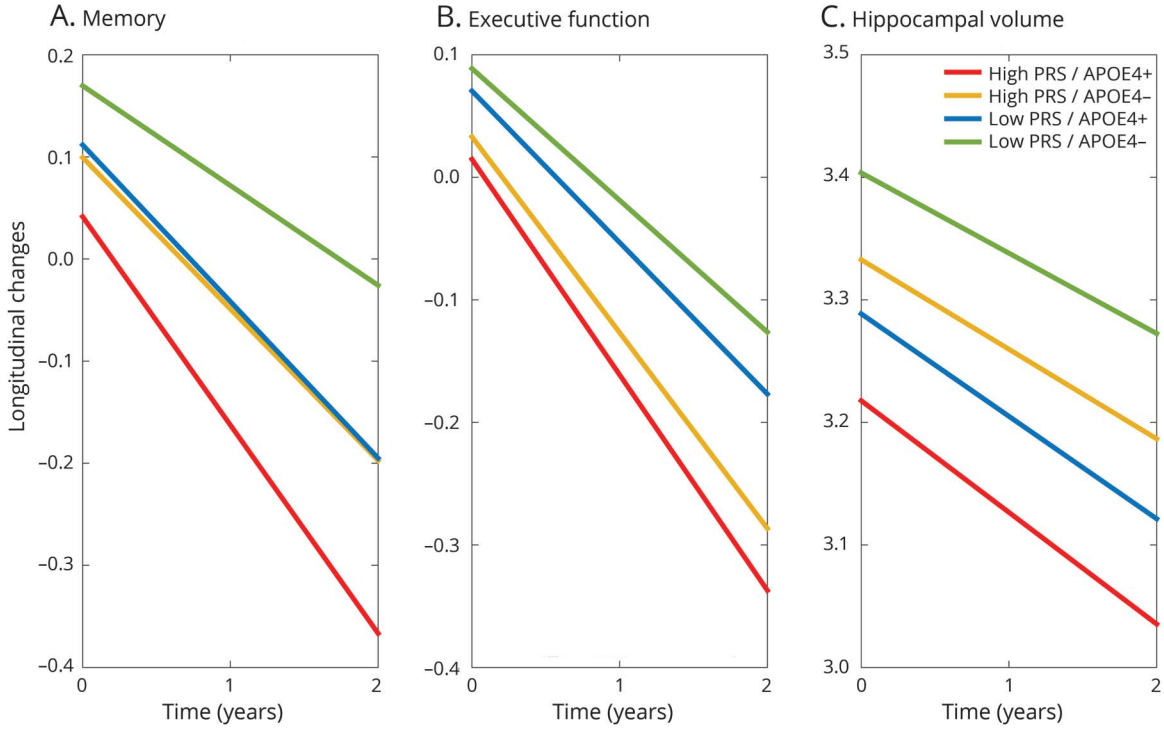
Among Aβ+ participants, both *APOE* ε4 status and polygenic risk were associated with baseline hippocampal volume. However, these effects on baseline hippocampus volume were small, accounting for <2% of the variance. Among Aβ−, PRS was strongly associated with longitudinal change in hippocampal volume but not hippocampal volume at baseline. PRS using the strictest threshold explained 8% of the variance in hippocampal atrophy in the Aβ− group (figures 2 and 3 and tables e-2 and e-3, links.lww.com/WNL/A405).

Discussion

In this study, we found that *APOE* ε4 and PRS of AD dementia show different patterns of associations with AD markers. Specifically, *APOE* ε4 was related to elevated baseline Aβ and the accumulation of Aβ over time in Aβ−, whereas PRS showed minimal associations with Aβ but was strongly associated with faster cognitive decline in Aβ+ participants. The influence of PRS on longitudinal cognitive trajectories was above and beyond the effect of *APOE* ε4 status, diagnosis, and hippocampal volume, highlighting the value of a priori genetic risk factors as a predictor of short-term decline among Aβ+ individuals. Furthermore, polygenic risk was not related to rates of cognitive decline in the Aβ− group, suggesting a synergistic effect between abnormal Aβ and genetic risk on cognitive decline. Finally, polygenic risk showed associations with hippocampal volume across both the Aβ+ and Aβ− groups, suggesting that genetic risk of AD may have an effect on non-Aβ pathways that influence brain structure in regions central to AD dementia.

We did not find strong evidence that an aggregate measure of genetic risk of AD dementia was directly associated with abnormal levels of amyloid, assessed either cross-sectionally or longitudinally. However, our analyses consistently showed an association between polygenic risk and cognitive decline that was specific to the Aβ+ group. This finding is in line with previous studies that have shown that Aβ and *APOE* ε4

Figure 3 Illustration of the influences of genetic risk on cognitive decline and hippocampal atrophy in Aβ+ participants



Model-based estimation of longitudinal changes in (A) memory, (B) executive function, and (C) hippocampal volume based on *APOE* ε4 status and the polygenic risk score (PRS) of Alzheimer disease dementia computed with $p < 1e{-}5$ as the *p* value threshold in β-amyloid–positive (Aβ+) participants. High PRS refers to the upper quartile (75%) of the PRS in the sample; low PRS refers to the lower quartile (25%) of the PRS in the sample. All fixed-effect covariates (principal components, baseline diagnosis, baseline age, sex, education, and their interactions with time) were set to the sample average.

interact to accelerate cognitive decline and hippocampal degeneration in CN individuals,[16,17,28] highlighting synergistic interactions between genetic risk of AD and the presence of abnormal Aβ. Furthermore, we have previously observed that elevated PRS is associated with greater longitudinal cognitive decline in older individuals without dementia.[29] However, other studies investigating PRS of AD dementia have failed to identify an association with cognitive decline[30] or clinical progression.[31] One source of this discrepancy may be that these previous investigations of polygenic risk did not examine decline in the context of AD biomarkers. Our results indicate that elevated PRS is associated with cognitive decline only among Aβ+ individuals, suggesting that genetic risk factors and Aβ act synergistically to influence cognitive decline. Recent work from Tan et al.[32] and Desikan et al.[33] also using the ADNI dataset has reported a similar pattern: cognitive decline was greatest in individuals with both abnormal CSF AD markers (amyloid and tau) and elevated genetic risk of AD as assessed with a polygenic hazard score. Although this study implemented a different methodological strategy to aggregate genetic risk across multiple genomic loci, the consistency across our study and theirs highlights a synergistic effect between genetic risk and AD pathology on cognitive trajectories. Given that genetic risk of AD has been implicated in non-Aβ pathways such as the immune system and cytoskeletal function,[5–7] it is possible that the convergence of these non-Aβ pathways with late-life Aβ accumulation is an important predictor of subsequent decline.

Whereas polygenic risk was related to decline in both memory and executive function among Aβ+ individuals, *APOE* ε4 was specifically related to decline in memory and not executive function. This finding is consistent with analyses in patients with AD dementia that have suggested that *APOE* ε4 carriers tend to show memory impairment whereas patients with AD dementia who are *APOE* ε4 noncarriers show impairment in executive function.[34] Likewise, examination of pathologically defined subtypes of AD dementia suggests that *APOE* ε4 is associated with a limbic predominant presentation among late-onset AD cases.[35] The finding that polygenic risk influences both memory and executive function implies that polygenic risk of AD dementia may influence a more distributed set of brain regions compared to *APOE* ε4. Along these lines, we previously found that polygenic risk was associated with multiple cortical regions, including frontal, parietal, and temporal cortices,[36] which may explain the broad effect of polygenic risk on cognitive decline. Given that calculation of polygenic risk aggregates information across many genomic loci and potentially many genetic pathways, it is unclear whether there are certain subgroups of genetic risk factors that relate to more specific brain networks and would demonstrate an effect on cognition that was domain specific.

If so, a participant's composition of these genetic risk factors may be predictive of the specific cognitive domain that is most vulnerable in an individual and provide an explanation for the heterogeneity in clinical expression of AD dementia that exists across individuals. Future work that refines polygenic risk to encapsulate variability across different cognitive domains may offer insights into the known heterogeneity of the clinical expression of AD.[37]

In contrast to memory and executive function, we found that in Aβ+ participants, PRS did not strongly influence longitudinal hippocampal atrophy but was associated with baseline volume, while in the Aβ− group, PRS was strongly associated with the longitudinal change in hippocampal volume but not its baseline measurements. This finding highlights that although polygenic risk influences hippocampal volume regardless of Aβ status, the time course of this effect varies. It is possible that the effect of polygenic risk on hippocampal atrophy occurs before late-life Aβ accumulation and that once abnormal levels of Aβ have occurred, there are stronger drivers of subsequent atrophy compared to polygenic risk (such as tau-mediated neurodegeneration[38]). This framework is consistent with previous work that has shown a relationship between polygenic risk of AD dementia and hippocampal volume in young participants,[29,39] well before the age at which abnormal Aβ is anticipated.[40] Thus, the effect of polygenic risk on hippocampal volume in stages preceding Aβ accumulation (as supported by findings in both younger participants[29,39] and older Aβ− participants in the current study) may ultimately make an individual more vulnerable to cognitive decline in late life when additionally faced with Aβ accumulation.

Our analyses have several limitations. First, the PRSs were calculated from summary statistics from cross-sectional case-control GWAS.[26] Therefore, the estimated effect sizes of genetic variants may not reflect their strength of influences on longitudinal change in AD markers, and the constructed PRS may thus be suboptimal for investigating the genetic basis of cognitive decline and AD progression. Conducting large-scale GWAS of longitudinal neuropsychological assessments and neuroimaging biomarkers of AD may improve genetic prediction of longitudinal decline. Second, although we focused on hippocampus volume, other MRI-derived neuroimaging markers of AD progression may also be relevant, especially given the association we identified between PRS and executive function. Third, although we report that ≈10% of the variance in cognitive decline among Aβ+ individuals can be explained by genetic risk factors, the majority of variance remains unexplained. Thus, the consideration of additional factors such as the regional deposition of tau (via PET), as well as vascular, lifestyle, and other genetic risk factors that were not captured in the International Genomics of Alzheimer's Project GWAS analysis, will be necessary to optimize our ability to predict risk at the individual participant level. Lastly, replication of the findings in this study is needed in other large cohorts with biomarker data and prospective neuropsychological follow-up.

We observed that *APOE* ε4 status and higher polygenic risk of AD dementia were associated with higher rates of decline in neuropsychological assessments of memory and executive function in Aβ+ individuals. The effect of polygenic risk on cognitive decline was above and beyond *APOE* ε4 and specific to the Aβ+ group, suggesting a synergistic effect between abnormal Aβ and genetic risk. Polygenic risk was also associated with hippocampal volume, an effect that was not dependent on Aβ status. These findings suggest that although this aggregate measure of genetic risk is not strongly associated with amyloid, it may moderate an individual's risk of decline once abnormal levels of amyloid are present, ultimately improving efforts to identify individuals at risk for cognitive decline.

Author contributions

Conception and design of the study: T.G., and E.C.M. Statistical analysis: T.G. Drafting the manuscript: T.G., and E.C.M. Interpretation of data: T.G., M.R.S., J.W.S., R.A.S., and E.C.M. Revising manuscript: T.G., M.R.S., J.W.S., R.A.S., and E.C.M.

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