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Background

- ❖ Approximately 15-40% of clinical dementia cases diagnosed as Alzheimer's disease (AD) do not have elevated amyloid deposition despite presenting with clinical and cognitive symptoms concordant with AD dementia.
- ❖ Memory decline is closely associated with the development of amyloid pathology. Thus, the etiology of memory decline in the absence of amyloid is less clear.
- ❖ Characterizing factors contributing to amyloid- and non-amyloid-related memory decline is critical to deconstructing the complexity of clinical dementia.
- ❖ Here, we perform the largest study to date investigating the genetic architecture of memory performance stratified by the presence of amyloid pathology.

Methods

- ❖ Data from ten cohorts of aging and AD were included: the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study; the Adult Changes in Thought (ACT) study; the Alzheimer's Disease Neuroimaging Initiative (ADNI); Knight AD Research Center (Knight ADRC); the National Alzheimer's Coordinating Center (NACC); the National Institute on Aging Alzheimer's Disease Family Based Study (NIA-AD FBS); the 3 harmonized cohorts of the Religious Orders Study and the Rush Memory and Aging Project (ROS/MAP); the Wisconsin Registry for Alzheimer's Prevention (WRAP) study; the Biomarkers of Cognitive Decline Among Normal Individuals (BIOCARD) study; and the Baltimore Longitudinal Study of Aging (BLSA). Except the last two, these studies are a part of the AD Sequencing Project – Phenotype Harmonization Core (ADSP-PHC).

- ❖ Participants were ages 50+, of European ancestry, and with cognitive assessments available <5 years ante-mortem for autopsy cohorts.

- ❖ Amyloid positivity definitions were drawn from cerebrospinal fluid (CSF) amyloid- β 42 positivity, positive amyloid positron emission tomography (PET) scan, or presence amyloid pathology (CERAD moderate to severe) at neuropathological examination.

- ❖ Memory scores were harmonized across cohorts to be on the same scale.

- ❖ GWAS on cross-sectional memory performance were run in amyloid positive and negative sets while SNP*amyloid status interaction models assessed statistical differences between the sets for observed associations.

- ❖ Covariates included age, sex, years of education, amyloid source, and the first 5 principal components.

- ❖ GNOVA (GeNetic cOVariance Analyzer) was used to assess what phenotypes had shared genetic structure with amyloid-related and non-amyloid-related decline using summary statistics from GWAS on 65 other phenotypes.

Table 1. Participant Characteristics

	Amyloid-	Amyloid+	P-value	Total
	(N=5663)	(N=6287)		(N=11950)
Age	77 (± 9.9)	79 (± 9.9)	<0.001	79 (± 10)
Sex (# (%)) Female	3143 (56 %)	3346 (53 %)	0.0132	6489 (54 %)
Education	16 (± 2.9)	16 (± 3.0)	<0.001	16 (± 2.9)
Diagnosis				
CU	4129 (73 %)	2038 (32 %)	<0.001	6167 (52 %)
MCI	796 (14 %)	900 (14 %)		1696 (14 %)
AD	725 (13 %)	3311 (53 %)		4036 (34 %)
Harmonized Memory	0.46 (± 0.82)	-0.52 (± 1.1)	<0.001	-0.056 (± 1.1)

Continuous variables are presented in mean (standard deviation). Categorical variables are presented in N (%). CU: cognitively unimpaired; MCI: mild cognitive impairment; AD: Alzheimer's disease.

Results

Figure 1. Genetic Associations with Memory Stratified by Amyloid Status

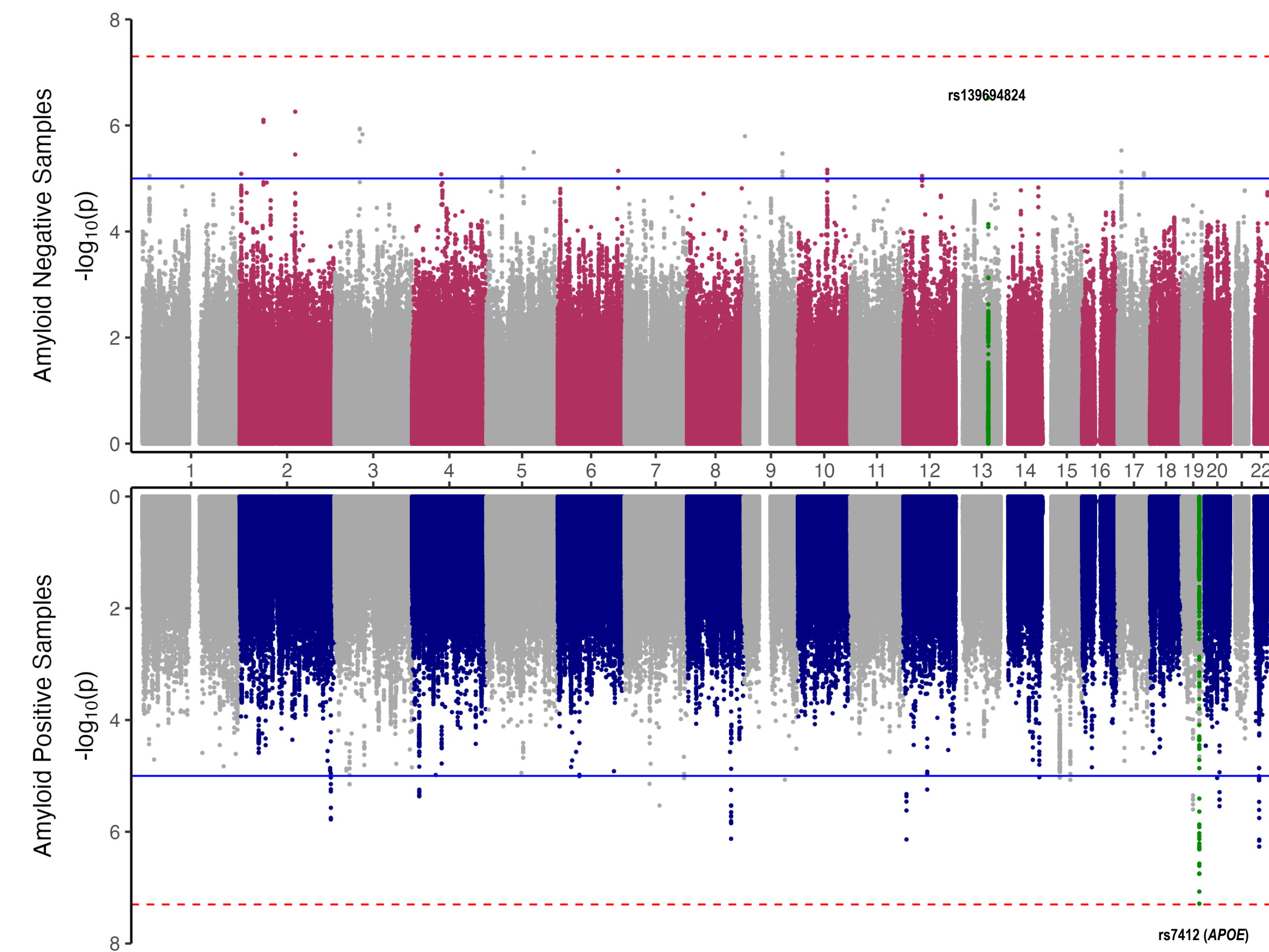


Figure 1 legend. Each point represents a variant with the x axis indicating genomic location and the y axis indicating significance level. The top panel presents associations in the amyloid negative analysis while the bottom presents the amyloid positive one. The top signals in each group are highlighted in green and labeled with the most significant variant.

Figure 2. rs7412 (*APOE*) Association with Memory In Amyloid Positive But Not Amyloid Negative Samples

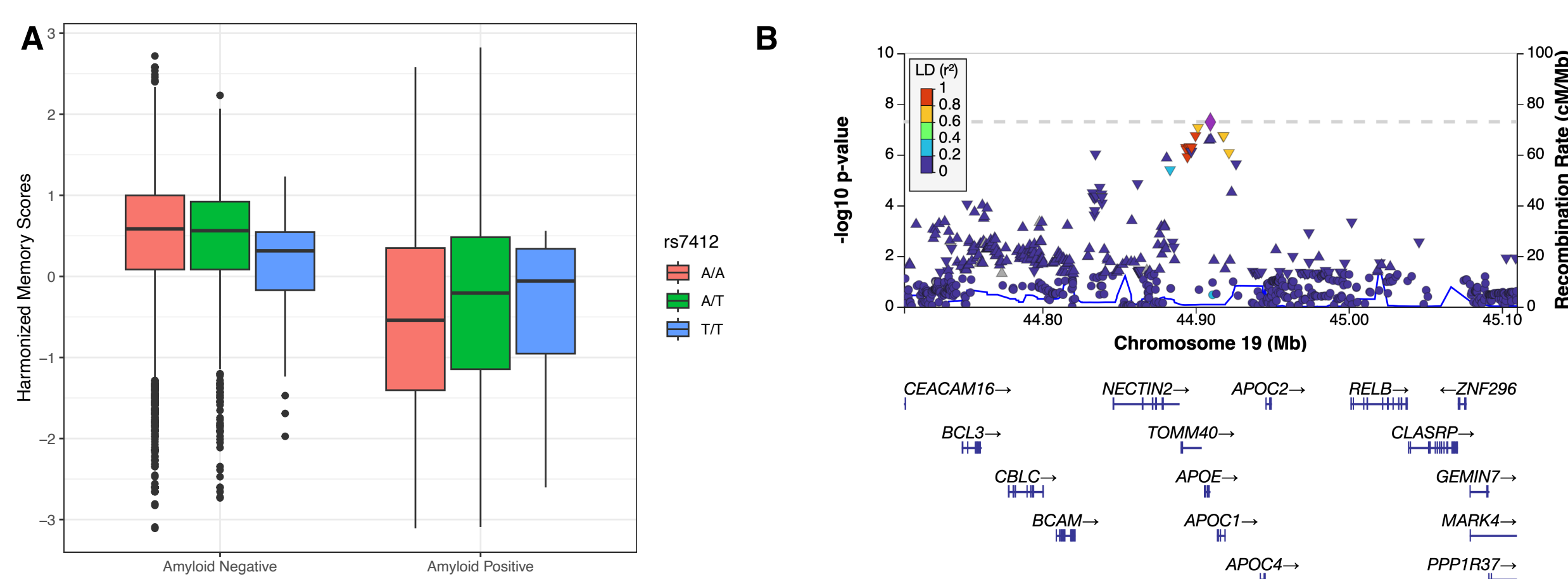


Figure 3. rs139694824 Association with Memory In Amyloid Negative But Not Amyloid Positive Samples

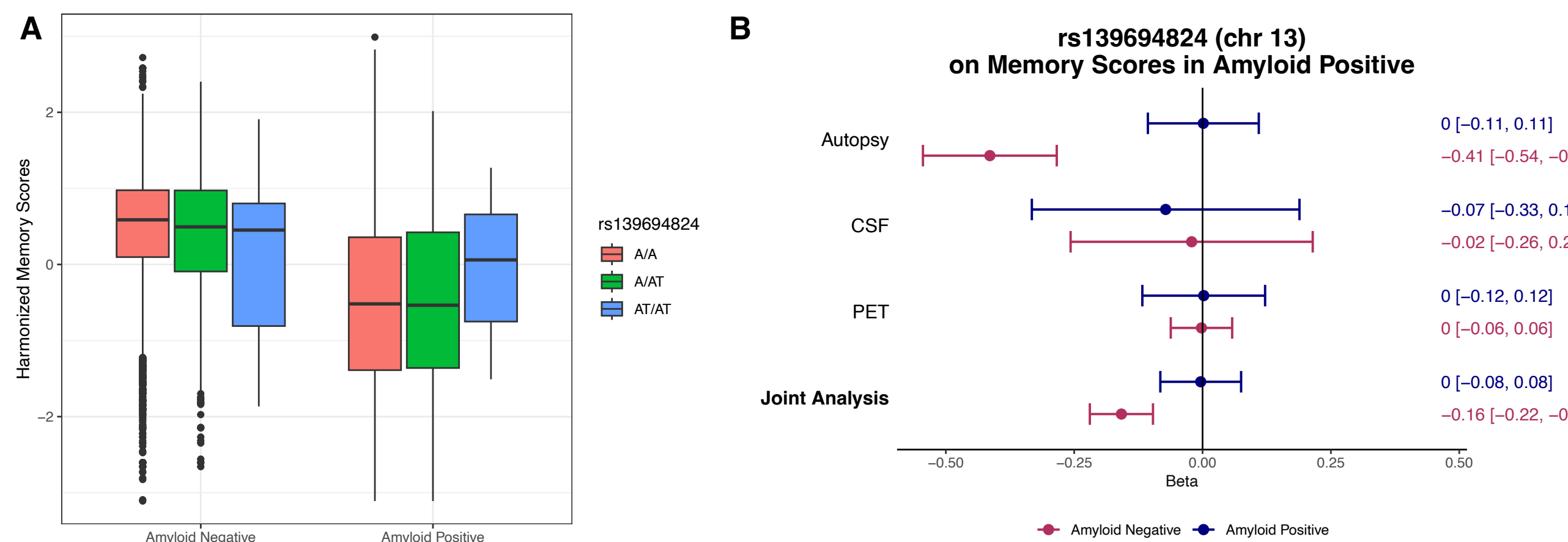
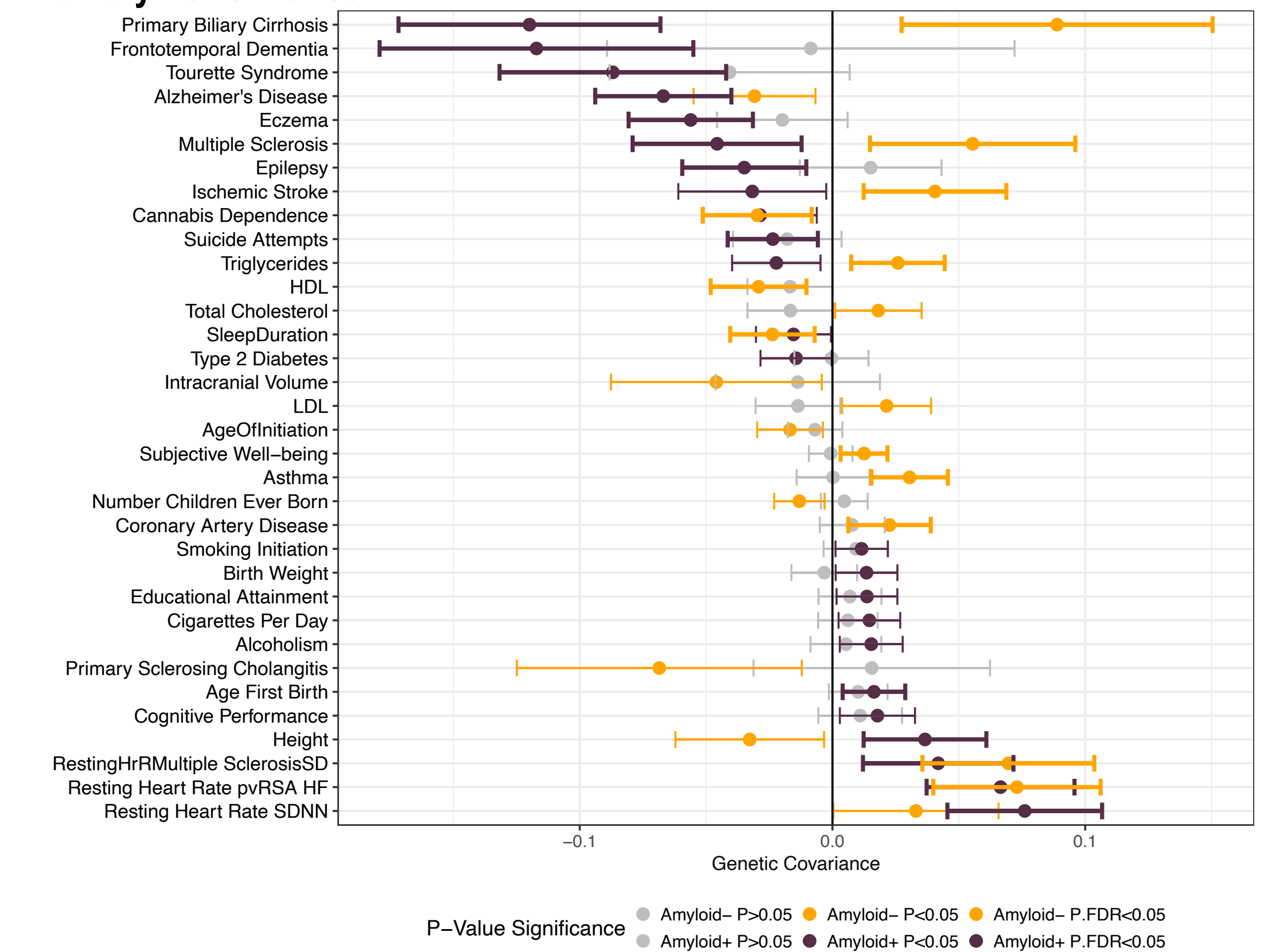


Table 2. Genetic Loci Associated with Memory by Amyloid Status

CHR	POS	ID	A1:A2	MAF	Int P	Amyloid +			Amyloid -		
						BETA	SE	P	BETA	SE	P
19	44908822	rs7412	T:A	0.062	8.97E-07	0.217	0.042	2.69E-07	-0.012	0.025	0.618
19	44909698	rs1081105	C:A	0.043	0.031	-0.190	0.035	5.16E-08	-0.084	0.046	0.067
13	83463770	rs139694824	AT:A	0.047	0.003	0.002	0.040	0.960	-0.163	0.032	2.99E-07

Italics indicate suggestive genome-wide effects (P<5E-06). CHR=chromosome; BP=base pair position; A1=minor allele; A2=other allele; MAF=minor allele frequency

Figure 4. Genetic Correlations with Amyloid-Related and Non-Amyloid-Related Memory Performance



Results Summary

- ❖ The *APOE* variant rs7412 on chromosome 19 was associated with memory only among amyloid positive participants, not amyloid negative (**Table 2, Figure 2**). This signal is attenuated when including an *APOE-ε4* count covariate ($p=0.01$).
- ❖ An intergenic chromosome 13 variant was negatively associated in amyloid negative participants but was not associated at all in amyloid positive ones (**Table 2, Figure 3**).
- ❖ GNOVA demonstrated that while amyloid-related and non-amyloid-related memory performance share genetic correlations with some traits (like heart function phenotypes and negatively with AD), they have divergent genetic correlations with others, particularly some immune-related phenotypes (see **Figure 4**)

Conclusions

- ❖ In this study, we explored genetic factors associated with amyloid and non-amyloid-related decline. Specifically, we observed an amyloid-specific association of *APOE* with memory decline, that corresponds to previous reports.
- ❖ Genetic correlation results observed here suggest that heterogeneity may be impacted by differing contributions of immune function to dementia in the presence and absence of amyloid.
- ❖ The current analysis has limited power due to sample size and to the relatively low frequency of the variants with observed associations. Future studies with additional studies will increase the power to detect meaningful associations.
- ❖ Accounting for amyloid heterogeneity may improve mechanistic understanding of memory decline and inform precision medicine strategies.



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