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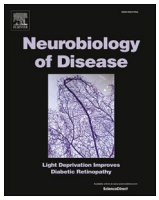

Charting the shared genetic architecture of Alzheimer's disease, cognition, and educational attainment, and associations with brain development

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ABSTRACT

The observation that the risk of developing Alzheimer's disease is reduced in individuals with high premorbid cognitive functioning, higher educational attainment, and occupational status has led to the 'cognitive reserve' hypothesis. This hypothesis suggests that individuals with greater cognitive reserve can tolerate a more significant burden of neuropathological changes before the onset of cognitive decline. The underpinnings of cognitive reserve remain poorly understood, although a shared genetic basis between measures of cognitive reserve and Alzheimer's disease has been suggested. Using the largest samples to date and novel statistical tools, we aimed to investigate shared genetic variants between Alzheimer's disease, and measures of cognitive reserve; cognition and educational attainment to identify molecular and neurobiological foundations. We applied the causal mixture model (MiXeR) to estimate the number of trait-influencing variants shared between Alzheimer's disease, cognition, and educational attainment, and condFDR/conjFDR to identify shared loci. To provide biological insights loci were functionally characterized. Subsequently, we constructed a Structural Equation Model (SEM) to determine if the polygenic foundation of cognition has a direct impact on Alzheimer's disease risk, or if its effect is mediated through established risk factors for the disease, using a case-control sample from the UK Biobank. Univariate MiXeR analysis (after excluding chromosome 19) revealed that Alzheimer's disease was substantially less polygenic (450 trait-influencing variants) compared to cognition (11,100 trait-influencing variants), and educational attainment (12,700 trait-influencing variants). Bivariate MiXeR analysis estimated that Alzheimer's

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid β; COG, cognition; condFDR, conditional false discovery rate; conjFDR, conjunctional false discovery rate; EDU, educational attainment; FUMA, Functional Mapping and Annotation; GWAS, genome-wide association studies; LD, linkage disequilibrium; LDSR, linkage disequilibrium score regression; MHC, major histocompatibility complex; MiXeR, causal mixture model; PGS, polygenic score; SEM, Structural Equation Model; WebCSEA, Web-based Cell-type-Specific Enrichment Analysis of Genes.

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disease shared approximately 70 % of trait-influencing variants with cognition, and approximately 40 % with educational attainment, with mixed effect directions. Using condFDR analysis, we identified 18 loci jointly associated with Alzheimer's disease and cognition and 6 loci jointly associated with Alzheimer's disease and educational attainment. Genes mapped to shared loci were associated with neurodevelopment, expressed in early life, and implicated the dendritic tree and phosphatidylinositol phosphate binding mechanisms. Spatiotemporal gene expression analysis of the identified genes showed that mapped genes were highly expressed during the mid-fetal period, further suggesting early neurodevelopmental stages as critical periods for establishing cognitive reserve which affect the risk of Alzheimer's disease in old age. Furthermore, our SEM analysis showed that genetic variants influencing cognition had a direct effect on the risk of developing Alzheimer's disease, providing evidence in support of the neurodevelopmental hypothesis of the disease.

1. Introduction

The risk of developing Alzheimer's disease (AD) is reduced in individuals with high premorbid cognitive functioning, higher educational attainment (EDU) and occupational status, as well as among those engaged in cognitively stimulating activities (Wilson et al., 2002; Scarmeas et al., 2001; Evans et al., 1997; Stern et al., 1994; Valenzuela and Sachdev, 2006). These observations led to the 'cognitive reserve' hypothesis, which argues that individuals with greater cognitive resources tolerate a greater burden of neuropathological changes before cognitive decline sets in, possibly reflecting the activation of preexisting or compensatory brain mechanisms (Stern, 2012).

Various proxies of cognitive reserve have been proposed, and premorbid general cognition (COG) and EDU are the most established indicators (Ko et al., 2022; Xu et al., 2015). Premorbid COG seems to moderate the relationship between AD-type brain hypometabolism (Ko et al., 2022), temporal tau deposits (Rentz et al., 2017), and precuneus amyloid β (Aβ) deposits (Rentz et al., 2010). Similarly, EDU moderates the relationship between AD-type brain hypometabolism (Ko et al., 2022), Aβ plaques (Bennett et al., 2005) and cerebrospinal fluid Aβ (Yaffe et al., 2011) with COG. While the underpinnings of cognitive reserve remain poorly understood, processes associated with environmental enrichment (e.g., synaptic plasticity, neurogenesis), as well as brain resistance to withstand the effects of disease, repair responses to insults, and an atypical compensatory pattern of brain network activation have been suggested (van Praag et al., 2000; Grady et al., 2003; Lesuis et al., 2018; Valenzuela and Sachdev, 2006; Xu et al., 2015). Recently, genetic variation has emerged as a promising instrument to study cognitive reserve in large population-based samples (Savage et al., 2018; Okbay et al., 2016; Seyedsalehi et al., 2023; Thorp et al., 2022; Wang et al., 2023).

The recent large genome-wide association studies (GWAS) of AD, COG, and EDU have provided new opportunities to investigate their shared genetic underpinnings (Archer et al., 2023; Lahti et al., 2022; Gao et al., 2022). COG, EDU, and AD are known to be complex traits, with heritability estimated in twin studies to be 0.4–0.6 (Haworth et al., 2010), 0.3–0.7 (Colodro-Conde et al., 2015), and 0.6–0.8 (Gatz et al., 2006), respectively. Despite similar heritabilities, AD is substantially less polygenic than COG and EDU, and the APOE risk variants explain a large proportion of AD's heritability (Bahrami et al., 2021; Fominykh et al., 2023; Hope et al., 2023). To identify shared genetic architecture, genetic overlap can be investigated in the entire genome or at individual genetic loci, genes, or genetic variants (Smeland et al., 2020; Frei et al., 2019). At the genome-wide level, the genetic correlation of effect sizes across common variants after controlling for linkage disequilibrium (LD) can be estimated. There are negative genetic correlations between AD and COG ($rg = -0.27$) (Savage et al., 2018), as well as between AD and EDU ($rg = -0.20$) (Okbay et al., 2016). On the level of individual genetic loci, recent GWAS meta-analyses of verbal short-term memory and verbal learning in healthy adults have identified AD-linked genetic loci (Lahti et al., 2022; Archer et al., 2023). Moreover, the *DCDC2* gene, which affects microtubule polymerization, has been implicated in both COG and long-term changes in memory functioning (Archer et al., 2023; Gao et al., 2022). Finally, mendelian randomization analysis, which tests for genetic evidence of causal relationships between two phenotypes, has suggested a protective effect of COG against AD ($OR = 0.65$) (Savage et al., 2018). Still, the shared genetic architecture underlying AD, COG, and EDU is yet to be fully characterized.

Applying an integrative study design, we combined genetic data, transcriptomic data, and novel statistical genetic approaches to gain molecular insights into the cognitive reserve model of AD (Fig. 1). To this end, we applied analyses to the largest pertinent GWAS of AD and the proxy measures of cognitive reserve, COG and EDU. First, we evaluated genome-wide genetic overlap between AD, COG, and EDU beyond genetic correlations by applying the bivariate causal mixture model (MiXeR), which estimates the total number of shared genetic variants irrespective of the effect direction. MiXeR has revealed extensive genetic overlap even in scenarios of weak or absent genetic correlation (Frei et al., 2019). Next, we identified shared genetic loci using the conjunctional false discovery (conjFDR) approach and performed gene-set analyses for genes mapped to discovered loci (Andreassen et al., 2013; Smeland et al., 2020). Finally, we investigated gene expression of putative shared genes across distinct neurodevelopmental periods and brain structures to characterize how variants jointly associated with AD and COG and EDU are linked to brain development.

2. Materials and methods

2.1. Samples

2.1.1. Genome-wide association studies

We used GWAS summary statistics results for AD, COG and EDU. We employed the latest GWAS summary statistics for AD from the Psychiatric Genomics Consortium (PGC) (Jansen et al., 2019). To avoid sample overlap with the GWAS of COG and EDU, we excluded samples from the 23andMe, UK Biobank, deCODE, and HUNT from the AD GWAS. Data on COG were based on 269,867 people from 14 cohorts, mostly from the UK Biobank (n = 195,653) (Savage et al., 2018). We also used GWAS summary statistics results for EDU including 293,723 individuals, and a replication study in an independent sample of 111,349 individuals from the UK Biobank (Okbay et al., 2016).

2.1.2. Case control sample

Our analysis was conducted on a sample of 269,362 (3188 AD cases, 266,174 controls; Supplementary Fig. 1) unrelated (with a kinship coefficient estimate below 0.05), white British participants, all aged 65 or over, from the UK Biobank (https://www.ukbiobank.ac.uk/; accession number 27412).

2.1.3. Consent statement

GWASs investigated in the study were approved by the ethics committees, and informed consent was obtained from all participants. The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee and all participants provided written informed consent to participate in the UK Biobank study. The Regional Committee for Medical Research Ethics (REC) has approved the study. The use of individual data for the study of genetics of dementia and cognition is approved by REC (2014/631, 2009/2485) including the use

of UK Biobank data (accession number 27412). The REC evaluated the research protocol that only included GWAS summary statistics data and found that no additional institutional review board approval was necessary as no individual data were used. The HUSKment study was approved by the Regional Committee for Medical Research Ethics Western Norway (REK Vest 10279 (2018/915)).

2.2. Gaussian causal mixture modeling method (MiXeR) analysis

We estimated genetic correlations between AD, COG, and EDU using linkage disequilibrium score regression (LDSR) (Bulik-Sullivan et al., 2015a, 2015b). Subsequently, we used MiXeR to estimate polygenic overlap between AD, COG, and EDU (Frei et al., 2019). MiXeR employs a univariate causal mixture model to estimate the proportion of non-null SNPs (polygenicity) and the variance of the effect size of non-null SNPs for each phenotype. Specifically, the model estimates two key parameters: the proportion of SNPs with non-zero effects (polygenicity) and the variance of effect sizes among these SNPs. For our analysis, we used default settings for these parameters, including the assumption of normality for the distribution of effect sizes and a grid search method to optimize the likelihood function.

Subsequently, a bivariate causal mixture model is used to estimate the total number of shared and specific trait-influencing variants between two phenotypes. This model extends the univariate approach by simultaneously modeling two traits, estimating the overlap in polygenicity and the degree of shared genetic architecture between them. The bivariate model also estimates the genetic correlation and provides the proportion of shared SNPs with non-zero effects between the traits.

To visualize the results, MiXeR presents a Venn diagram illustrating the unique and shared polygenic components across traits. For the visualization, the model outputs the estimated number of unique and shared variants for each pair of traits, which are then depicted in the diagram to highlight the genetic overlap and specificity between AD, COG, and EDU. We excluded the major histocompatibility complex (MHC) region due to its complex LD, as recommended (Fernandes et al., 2023; Fominykh et al., 2023). Additionally, we followed the analytic setup from Holland et al. (Holland et al., 2020) and analyzed chromosome 19 independently from the other chromosomes because of the large effect of the APOE region in AD (Fominykh et al., 2023; Holland et al., 2020).

2.3. Conditional and conjunctional false discovery rate (condFDR and conjFDR) analyses

We implemented the conditional and conjunctional false discovery rate (condFDR and conjFDR) analyses to improve the identification of common variants associated with AD, COG, and EDU (condFDR) and detect shared genomic loci (conjFDR) (Smeland et al., 2020; Andreassen et al., 2013). The condFDR analysis allows to control for false discoveries more accurately by incorporating information from multiple traits and considering the pleiotropic effects of genetic variants on different phenotypes. Furthermore, we utilized the conjFDR method, which considers the joint FDR across two traits simultaneously to identify shared loci between two traits. Cross-trait enrichment of SNP associations between AD and each of COG and EDU was visualized using conditional QQ plots. The condFDR value of each SNP was computed for AD conditional on COG and EDU and vice versa. We ran the analysis after omitting SNPs from the extended MHC (hg19 position chr 6:25119106-33854733), 8p23.1 (hg19 location chr 8:7242715-12483982) and AOPE (hg 19 position chr19:44000000-47000000) regions to prevent possible biases due to genomic regions with complex LD.

We attempted to validate the identified lead SNPs for AD using results from an independent GWAS (Supplementary materials).

2.4. Genomic loci definition and functional annotation

We used the Functional Mapping and Annotation (FUMA) protocol to characterize identified genetic loci (Watanabe et al., 2017). In this step, we considered SNPs having a condFDR < 0.01 and at $r2 < 0.6$ with each other as independent significant SNPs and a fraction of independent significant SNPs in approximate linkage equilibrium with each other at $r2 < 0.1$ as lead SNPs. If two or more lead SNPs were located within one

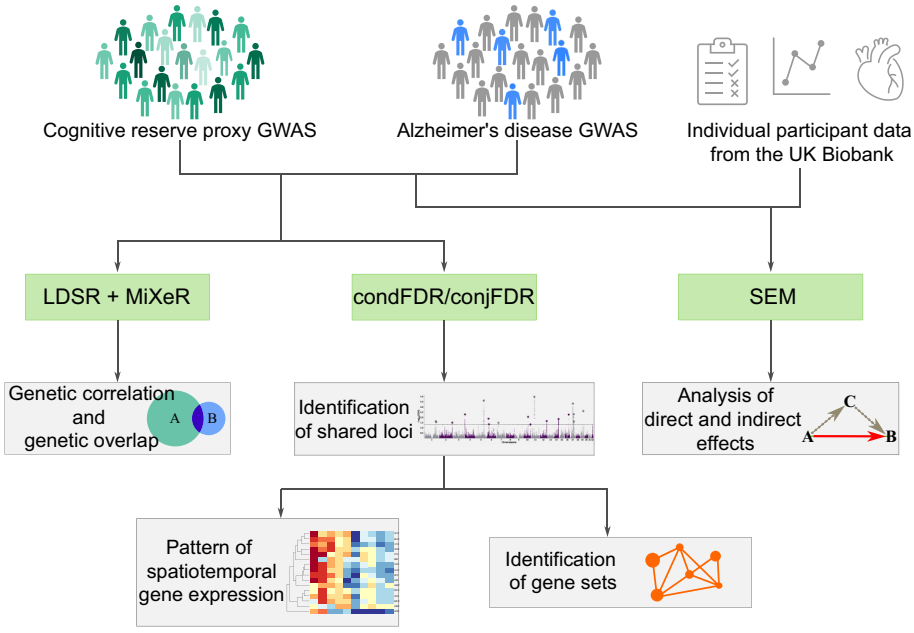

Fig. 1. Schematic overview of the study design. The linkage disequilibrium score regression (LDSR) and the causal mixture model (MiXeR) were applied to the results of the largest genome-wide association studies (GWAS) for cognitive reserve proxies (cognition and educational attainment) and Alzheimer's disease (AD) to calculate genetic correlation and genetic overlap. Subsequently, the conditional/conjunctional false discovery rate (condFDR/conjFDR) approach was applied to the same summary statistics to identify genomic loci shared between traits of interest, followed by the analysis of spatiotemporal expression and gene set identification for genes mapped to the shared loci. Finally, structural equation models (SEM) were applied to the UK Biobank data along with summary statistics for the traits of interest to analyze the direct and indirect effects of the polygenic architecture of cognitive reserve proxies on the diagnosis of AD.

LD block (in 250 kb), we merged them into a single genomic risk locus. To accurately associate significant SNPs with their respective genes, we employed the variant-to-gene tool from Open Targets Genetics (Ghoussaini et al., 2021; Mountjoy et al., 2021). This tool prioritizes causal variants and identifies possible causative genes linked to a variety of phenotypes and diseases. The mapping of lead SNPs to their corresponding genes is performed by integrating data from several sources. Specifically, the tool utilizes positional information, such as the physical distance between the SNP and the canonical transcription start site (TSS) of genes, along with functional genomics data, including expression quantitative trait loci (eQTLs), protein quantitative trait loci (pQTLs), and splicing QTLs. Additionally, it incorporates epigenomic data that reveal chromatin state and DNA accessibility, as well as computational functional predictions that assess the impact of variants on gene function. By combining these diverse datasets, Open Targets Genetics systematically identifies the most likely gene or genes associated with each locus, providing a robust framework for understanding the genetic basis of complex traits. After mapping SNPs to genes, we performed gene-set analysis based on the gene ontology classification system using FUMA. FUMA performs gene-set enrichment analysis using predefined biological pathways and gene sets. The analysis identifies pathways that are significantly overrepresented among the prioritized genes, highlighting potential biological processes involved in the trait under study. Using BrainSpan RNA sequencing data, we also created spatiotemporal heat maps of gene-expression levels across 11 brain tissues at 11 developmental time points using the R package *cerebroViz* (Miller et al., 2014; Bahl et al., 2017). Utilizing unsupervised hierarchical cluster analysis, expression was clustered across brain tissues. We utilized the WebCSEA (Web-based Cell-type-Specific Enrichment Analysis of Genes) tool to examine the context-specific expression of mapped genes shared between COG, EDU and AD (Dai et al., 2022). WebCSEA is an online tool that comprises 1355 tissue-cell types from 111 scRNA-seq panels drawn from a variety of human tissues and organ systems. Additionally, we identified the cell-specific expression of each shared gene mapped independently in the human cerebral cortex, including neurons, foetal and adult astrocytes, oligodendrocytes, microglia/macrophages, and endothelial cells (Y. Zhang et al., 2016).

2.5. Structural Equation Model (SEM)

To determine if the polygenic foundation of COG has a direct impact on AD risk or if its effect is mediated through established risk factors for AD, which is essential for interpreting the primary outcomes of our study, we constructed a Structural Equation Model (SEM) using the R package *lavaan* (Rosseel, 2012) and analyzed the case-control sample from the UK Biobank.

First, we evaluated associations between previously identified risk factors for AD (Livingston et al., 2020) and polygenic score (PGS) for COG. To this end, we applied PRSice, version 2.3.3 (Choi and O'Reilly, 2019) to calculate PGS (*p*-value thresholds = 5e-8, 1e-7, 1e-6, 1e-5, 1e-4, 1e-3, 1e-2, 5e-2, 1e-1, 5e-1, 1) for COG from a GWAS (Davies et al., 2018). We extracted the first principal component for COG PGS across all *p*-value thresholds, following a widely applied method (Coombes et al., 2020). We employed logistic regression models with the hospital diagnosis of AD (field 41,280), and the specified risk factor, as a binary outcome variable, and PGS for cognition, as a predictor. Models included the first 10 genetic principal components, age, sex, and genetic array as covariates. We analyzed the following risk factors that were previously identified (Livingston et al., 2020) and are available in the UK Biobank: head injury (field 41,280: ICD-10 diagnosis of S02.0, S02.1, S02.7 - S02.9, S06, S07 or S09), alcohol use disorder (field 41,280: ICD-10 diagnosis of F10.1 - F10.4), smoking status (field 20,116), hearing loss (fields 2247 and 3393), high blood pressure (field 4080; systolic blood pressure equal or above 140 mmHg), BMI equal or above 30 (field 21001), loneliness (field 2020), inactivity (field 904; if no vigorous physical activity in typical week).

Subsequently, we constructed a SEM mediation model to assess the direct effect of PGS for COG, as well as the indirect effect mediated by the risk factors identified in the previous step on AD diagnosis. In the proposed model, the presence of alcohol use disorder was coded as present only if an ICD-10 diagnosis within the range of F10.1 to F10.4 had been assigned at least one year prior to the diagnosis of AD. Potential confounders included in the model were age, sex, genetic array, and the first 10 genetic principal components.

We also constructed a similar SEM on educational attainment (Supplementary materials).

3. Results

3.1. Quantifying trait-influencing variants and genetic overlap

Using LDSR, we found a significant negative genetic correlation between AD and COG ($rg = -0.181$, $SE = 0.0635$, $p = 0.004$) and a weak, non-significant genetic correlation between AD and EDU ($rg = -0.094$, $SE = 0.05$, $p = 0.06$).

Using MiXeR, we found that AD was substantially less polygenic than EDU and COG, as previously reported (Bahrami et al., 2021; Fominykh et al., 2023; Hope et al., 2023). The number of trait-influencing variants was estimated to be approximately 12,700 ($SD = 300$) variants for EDU, 11100 ($SD = 300$) for COG, and 450 ($SD = 100$) for AD (Fig. 2). Bivariate MiXeR analysis showed polygenic overlap after excluding chromosome 19. The predicted number of shared trait-influencing variants between AD and COG (Fig. 2) was approximately 300 ($SD = 50$). The fraction of AD polygenicity shared with COG was estimated at 67.51 %. Similarly, the predicted number of shared trait-influencing variants between AD and EDU was approximately 200 ($SD = 50$). The fraction of AD polygenicity shared with EDU was estimated at 41.61 %.

3.2. ConjFDR analysis identifies shared genomic loci between AD and COG and EDU

The conditional QQ plots demonstrate bidirectional cross-trait enrichment between AD and each of COG, EDU (Fig. 3). This is illustrated by a consistent leftward deflection from the dashed line (representing no enrichment) for subsets of variants with higher significance in the conditional trait.

Using condFDR analysis at FDR < 0.01, we identified 50, and 31 loci associated with AD conditionally on COG and EDU, respectively (Supplementary Tables 1 and 2).

ConjFDR analysis at FDR < 0.05 showed 18 and 6 shared loci between AD and each of COG and EDU, respectively (Tables 1 and 2, Fig. 4). Two loci were identified across both analyses while they had different lead SNPs. Furthermore, 72 % of lead SNPs (13/18) had the

Fig. 2. The bivariate MiXeR analysis after excluding chromosome 19. Venn diagrams illustrate the number of shared (dark blue) and trait-specific 'causal' variants in cognition (COG; purple), Alzheimer's disease (AD; light blue), and educational attainment (EDU; green). The number of trait-specific and shared variants is expressed in thousands, with standard deviations in brackets. The circles' size represents the traits' polygenicity. The genome-wide genetic correlation of shared variants (rg) is depicted below. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

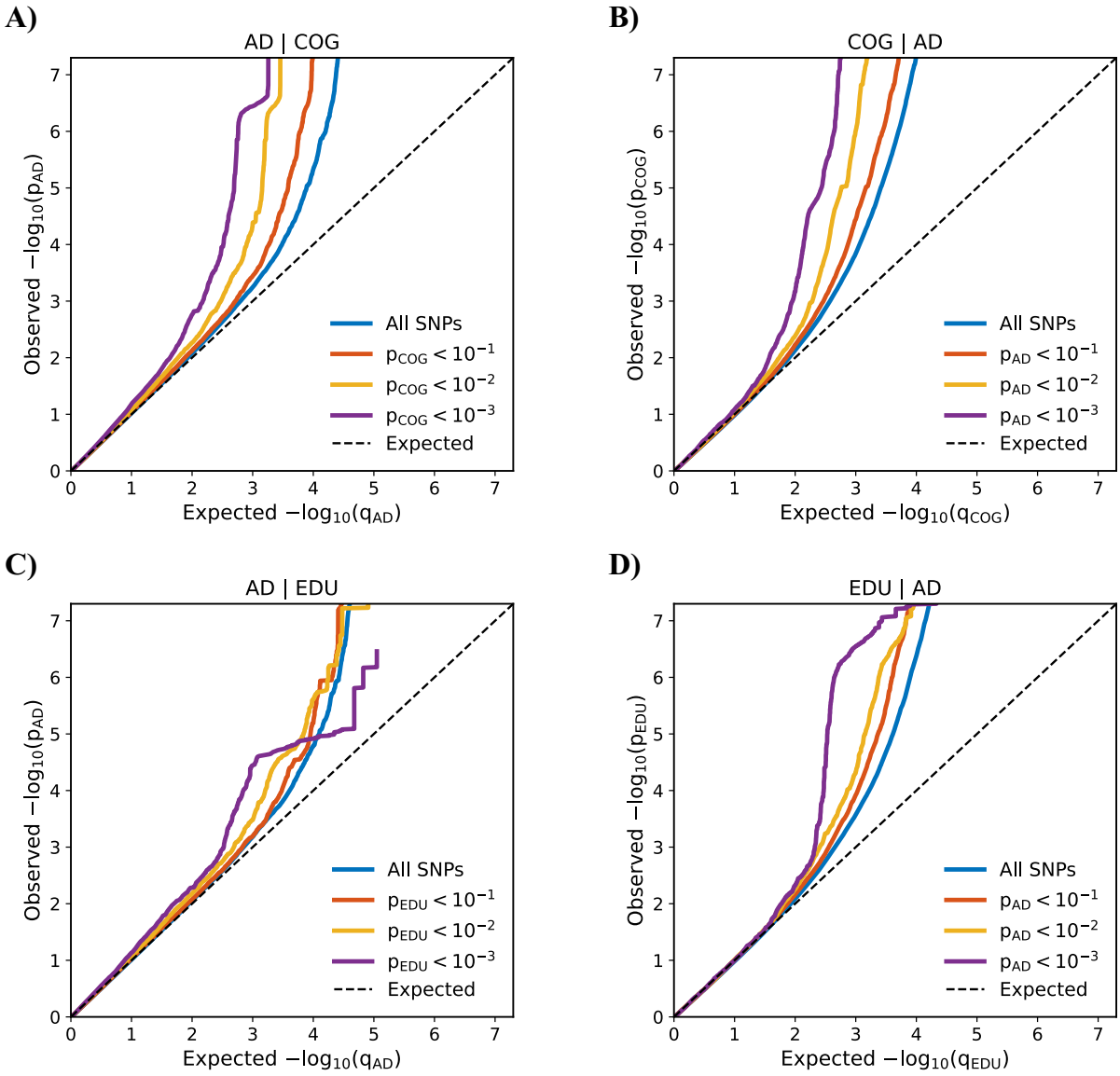

Fig. 3. Conditional QQ plots illustrating cross-phenotype polygenic enrichment between (A-B) Alzheimer's disease (AD) and cognition (COG), and (C—D) AD and educational attainment (EDU). The plots show the observed vs. expected −log10 *p*-values (corrected for inflation) for the trait of interest, below the standard genome-wide association study threshold of $p < 5 \times 10^{-8}$, as a function of the significance of association with the conditional trait at levels of $p \leq 0.1$ (red lines), $p \leq 0.01$ (orange lines), and $p \leq 0.001$ (purple lines). The blue lines indicate all single nucleotide polymorphisms. The dashed lines indicate the null hypothesis. (A) AD is the trait of interest and is conditioned on COG. (B) COG is the trait of interest and is conditioned on AD. (C) AD is the trait of interest and is conditioned on EDU. (D) EDU is the trait of interest and is conditioned on AD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

opposite effect direction on AD and COG compared to 50 % for AD and EDU (3/6), consistent with the negative genetic correlation between AD and COG and minimal negative genetic correlation between AD and EDU.

Validation results of the identified lead SNPs for AD using results from an independent GWAS are available in the Supplementary materials.

3.3. Functional annotation of identified genetic loci

We used FUMA to functionally annotate all SNPs within loci associated with AD and each of COG and EDU in LD ($r2 \geq 0.6$) with a significant independent SNP and with conjFDR <0.1. We found 54 % and 73 % of the SNPs jointly associated with AD and each of COG and EDU to be intronic, respectively. For more details see Supplementary Tables 3 and 4.

Using the Open Targets Genetics portal, we mapped a total of 18 genes to lead SNPs jointly associated with AD and COG (Supplementary Table 3) and 6 genes for AD and EDU (Supplementary Table 4). Three of the lead SNPs (rs11168036, rs9381037, and rs77804065) for the shared loci between AD and COG had a CADD score above 12.37, suggesting high deleteriousness. These SNPs were mapped to *SRA1*, *APOBEC2*, and *MAPT* genes respectively.

We conducted gene-set analyses using gene ontology terms on each set of mapped genes jointly associated with AD and each of COG and EDU. For genes mapped to AD and COG we identified two gene sets related to the molecular functions ("GO PHOSPHATIDYLINOSITOL BISPHOSPHATE BINDING", "GO PHOSPHATIDYLINOSITOL PHOSPHATE BINDING"), and for genes mapped to AD and EDU we identified one gene set related to cellular components ("GO DENDRITIC TREE").

We also present spatiotemporal gene-expression analyses, using normalized BrainSpan RNA sequencing data (Fig. 5), for genes mapped

Table 1
Genomic loci jointly associated with Alzheimer's disease (AD) and cognition (COG) at conjunctional FDR < 0.05.

Chr	Lead SNP	BP	A1	A2	FDR	Z value AD	Z value COG	Top gene by Open Targets
1	rs374827	200,874,327	C	T	2.44E-02	2.71	−4.15	*INAVA*
1	rs34386700	207,767,671	T	C	2.86E-02	−3.89	4.65	*CR1*
2	rs4663811	238,857,869	A	G	3.25E-02	3.22	−4.06	*UBE2F*
4	rs2269495	2,744,087	A	G	5.22E-03	3.35	−4.66	*TNIP2*
5	rs11168036	139,707,439	G	T	2.50E-04	−3.51	6.06	*SRA1*
6	rs204883	32,032,743	A	G	1.35E-02	−4.15	−4.35	*TNXB*
6	rs9381037	41,073,638	A	G	4.68E-02	−4.77	3.92	*APOBEC2*
7	rs10264306	28,239,466	G	A	3.36E-02	−3.61	−4.04	*JAZF1*
10	rs6586030	82,254,047	G	A	9.02E-03	3.96	−4.48	*TSPAN14*
10	rs2421017	124,148,167	G	A	4.72E-02	−4.54	4.46	*PLEKHA1*
11	rs11605348	47,606,483	A	G	1.08E-04	−4.79	−5.74	*MTCH2*
12	rs4275659	123,447,928	T	C	2.30E-02	−2.04	5.88	*MPHOSPH9*
14	rs45441198	104,002,611	C	T	1.45E-02	−3.32	4.78	*MARK3*
16	rs55900782	70,737,892	G	A	5.40E-03	−2.11	4.64	*MTSS2*
17	rs77804065	43,810,896	T	C	4.83E-04	−4.35	−5.35	*MAPT*
17	rs7208590	56,960,385	A	G	5.01E-03	−3.08	7.00	*TEX14*
17	rs9898829	60,554,275	G	T	2.52E-02	−1.53	4.14	*MRC2*
19	rs7260359	45,814,908	T	C	2.51E-03	−3.78	−5.22	*CKM*

The most strongly associated SNPs in independent genomic loci shared between AD and COG at conjFDR <0.05. Chromosomal position (Chr), lead SNP, base pair position (BP). Z value for AD and COG from original summary statistics. The effect allele is A1.

Table 2
Genomic loci jointly associated with Alzheimer's disease (AD) and educational attainment (EDU) at conjunctional FDR < 0.05.

Chr	Lead SNP	BP	A1	A2	FDR	Z value AD	Z value EDU	Top gene by Open Targets
2	rs6757645	161,891,382	G	A	1.78E-02	1.40	−5.00	*TANK*
4	rs10004140	66,240,703	G	A	3.42E-02	0.39	4.00	*EPHA5*
6	rs9274536	32,634,634	T	C	8.31E-03	−4.26	−4.33	*HLA-DQA1*
11	rs7104832	12,786,489	G	A	1.67E-02	1.93	−4.33	*TEAD1*
15	rs3098205	50,742,977	T	G	3.31E-02	−4.14	−5.00	*USP8*
17	rs113856644	43,932,277	A	G	5.27E-03	−4.31	−5.67	*MAPT*

The most strongly associated SNPs in independent genomic loci shared between AD and EDU at conjFDR <0.05. Chromosomal position (Chr), lead SNP, base pair position (BP). Z value for AD and EDU from original summary statistics. The effect allele is A1.

using the Open targets data. Global expression of mapped genes for both AD and COG and AD and EDU were generally down regulated after early childhood.

Using WebCSEA, we found enrichment in the lymphatic system and the digestive system (Supplementary Fig. 2). The top enriched cell types were mostly related to the digestive and innate immune systems (epithelial cells and monocytes) (Supplementary Fig. 2).

We also found that the mapped genes expressed in the brain have cell-type-specific expression patterns in the main cell types of the human cerebral cortex (Supplementary Fig. 3).

3.4. Mediation analysis of direct and indirect effects of PGS for COG on the diagnosis of AD

Logistic regression analyses revealed negative associations between PGS for COG and BMI equal or above 30 ($\beta = -0.07$; 95 %CI, −0.08, −0.06; $p = 3.44 \times 10^{-58}$), smoking ($\beta = -0.06$; 95 %CI, −0.07, −0.05; $p = 7.92 \times 10^{-19}$), loneliness ($\beta = -0.05$; 95 %CI, −0.06, −0.04; $p = 2.32 \times 10^{-18}$), alcohol use disorder ($\beta = -0.03$; 95 %CI, −0.06, −0.005; $p = 0.02$), high blood pressure ($\beta = -0.03$; 95 %CI, −0.04, −0.02; $p = 9.02 \times 10^{-13}$) (Supplementary Fig. 5).

The SEM model revealed a negative direct effect of PGS for COG on the diagnosis of AD ($\beta = -0.03$; 95 %CI, −0.044, −0.015; $p = 4.53 \times 10^{-5}$) (Fig. 6). Moreover, our analysis revealed that the part of the association between COG and AD is mediated through loneliness ($\beta = -0.001$; $p = 0.001$).

The SEM model on EDU (Supplementary materials) similarly revealed a direct negative effect of PGS for EDU on the diagnosis of AD ($\beta = -0.022$; 95 %CI, −0.037, −0.006; $p = 0.007$). Furthermore, as with COG, the analysis demonstrated that part of the association between EDU and AD is mediated through loneliness ($\beta = 0.001$; $p = 0.021$).

4. Discussion

We utilized large-scale genome-wide datasets and applied MiXeR, which revealed extensive shared genetic architecture between AD and both COG and EDU, two measures of cognitive reserve. We used conjFDR and identified a total of 24 shared genetic loci between AD and the cognitive reserve measures. Among mapped genes for shared loci, we identified *UBE2F* and *PLEKHA1*, both of which are involved in the development and plasticity of the nervous system. Gene sets analysis implicated phosphatidylinositol phosphate binding and the dendritic tree. Spatiotemporal gene expression analysis showed that mapped genes were highly expressed during the mid-fetal period, further implicating the role of neurodevelopment and supporting the neurodevelopmental hypothesis of AD. Functional gene sets assessment showed involvement in processes that shape the structure and activity of neural networks. Finally, we used SEM which showed that genetic variants of COG appear to have mainly a direct effect on AD risk, while some is mediated through loneliness, but not any of the other tested modifiable risk factors. Taken together, we demonstrate that the genetic risk for AD is in part overlapping with the genetic underpinnings of COG and EDU, supporting the 'cognitive reserve' hypothesis. The putative causal genes and gene sets we identified indicate the direction for future research. Follow-up studies should clarify the role of the identified genes, their spatiotemporal expression, their common and rare genetic variants, as well as the fate of their protein products, including the sets they form and how they may interact with the environment, in the pathoetiology of AD. This can improve our understanding of the mechanisms involved in the protective effects of 'cognitive reserve' in AD. Our MiXeR analysis demonstrated that both COG and EDU are polygenic traits, while AD has substantially fewer trait-influencing variants.

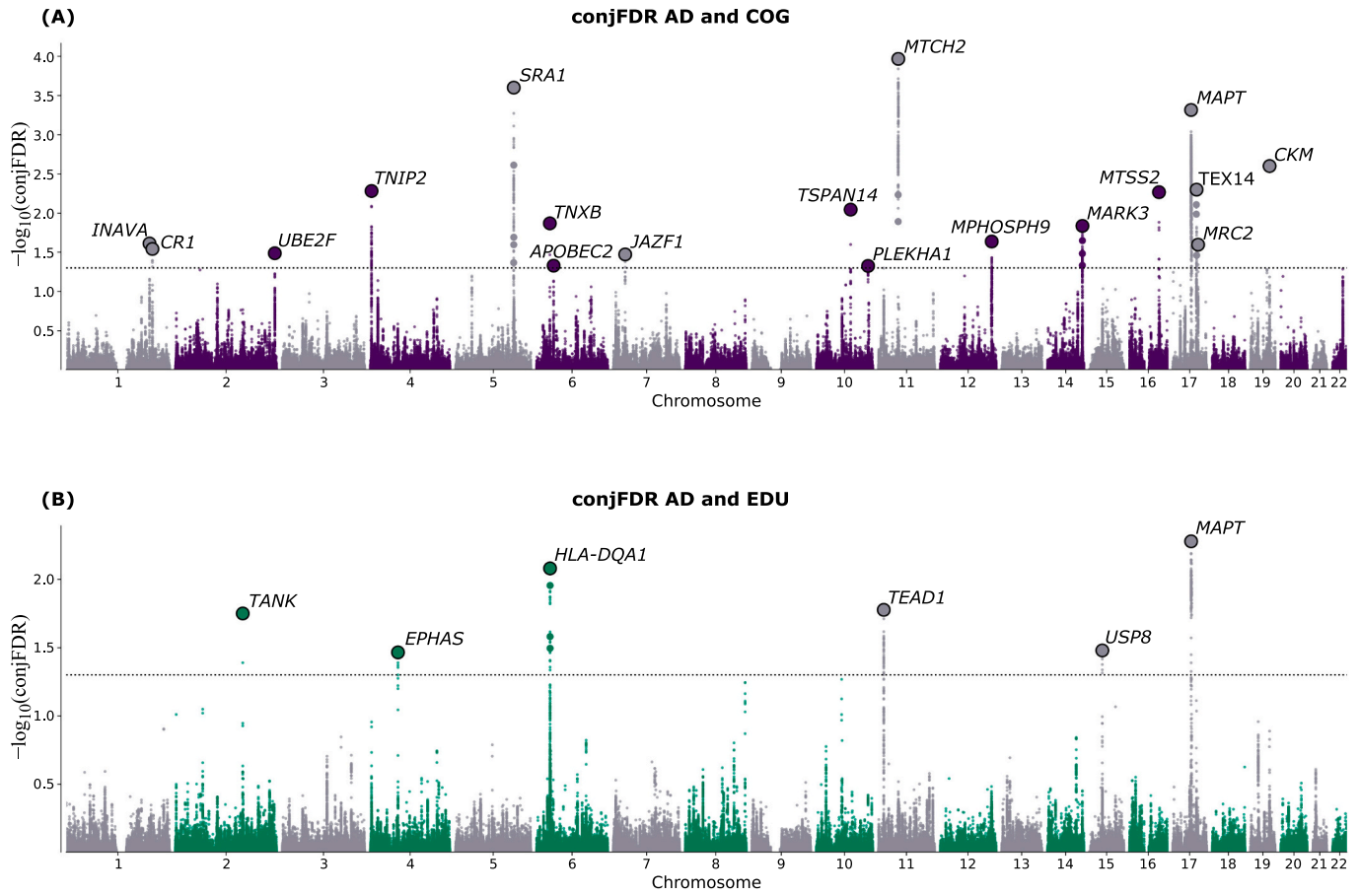

Fig. 4. The "ConjFDR Manhattan plots" illustrate common genetic variants that are jointly associated with (A) Alzheimer's disease (AD) and cognition (COG), and (B) AD and educational attainment (EDU) at conjunctional false discovery rate (conjFDR) < 0.05. The y-axis shows the −log10 transformed conjFDR. Chromosomal position is presented along the x-axis. The threshold for significant shared associations (conjFDR <0.05) is represented by the horizontal dotted line. Independent SNPs are indicated by a black perimeter.

The use of MiXeR, which, unlike most currently used tools, estimates the total number of shared genetic variants irrespective of their effect direction, allowing the identification of genetic overlap even in the absence of genetic correlation. Our results extend previous observations from smaller samples (Fominykh et al., 2023). Furthermore, AD was found to share ~70 % of its trait-influencing variants with COG, despite a genome-wide genetic correlation estimated at −0.12. Similarly, 72 % of SNPs shared between AD and COG had the opposite effect direction (Table 1). This indicates that most causal variants influencing AD also influence COG, and variants associated with increased COG tend to be associated with decreased risk for AD, consistent with the 'cognitive reserve' hypothesis. The proportion of AD variants shared with EDU is smaller (~40 %), with a smaller, non-significant negative genetic correlation and a balanced mixed effect direction of identified SNPs (Fig. 2, Table 2). Taken together, these observations indicate that the biological determinants of AD are related to the cognitive reserve measures COG and EDU, with somewhat bigger overlap with COG.

The analysis of spatiotemporal gene expression of the genes mapped in the conjFDR analysis revealed a pattern of higher expression in early life. Furthermore, among genes mapped to loci jointly associated with AD and each of COG and EDU, *UBE2F, PLEKHA1, MTSS2, EPHA5, TEAD1*, and *USP8* all play roles in development. *UBE2F* is involved in neddylation, a posttranslational protein modification process, that has been linked with neurodevelopment, neuroplasticity (e.g. long-term potentiation), and neural apoptosis (D. T. Huang et al., 2009; He et al., 2022). Furthermore, previous studies indicated that dysfunctional neddylation associated with amyloid precursor protein-binding protein 1, is involved in the pathogenesis of AD (Y. Chen et al., 2012). *PLEKHA1* encodes a plasma membrane protein involved in brain development and signal transduction (Yamada et al., 2012). Interestingly, whole-exome sequencing analysis has revealed an association between a de novo mutation within *PLEKHA1* and autism accompanied by intellectual disability (W. X. Chen et al., 2022). It has been demonstrated that a variant of *MTSS2* is associated with neurodevelopmental disorders characterized by intellectual disability (Y. Huang et al., 2022; Corona-Rivera et al., 2023). *EPHA5* regulates embryonic and postnatal development, particularly of the central nervous system. Animal studies have shown that knockout of *Epha5* results in disturbed axon guidance, aberrant morphology of spines, and distortion of spatial learning (Das et al., 2016). Moreover, *EPHA5* has been identified as one of the genes associated with early-onset familial AD (Hooli et al., 2014). *TEAD1* encodes TEA domain transcription factor 1 (TEAD1) that plays a central role in the Hippo signaling pathway. A mutation within *TEAD1* has been linked with Aicardi syndrome, a congenital neurodevelopmental disorder (Schrauwen et al., 2015). Of note, *TEAD1* has previously been identified in a GWAS of EDU (Okbay et al., 2016). *USP8* encodes Ubiquitin specific peptidase 8 (USP8), an endosomal enzyme that regulates the ubiquitination and lysosomal degradation. A germline 22-kb deletion within *USP8* has been linked with severe developmental delay (Sakamoto et al., 2024). USP8 regulates the level of SHANK3 protein, which has also been linked with a neurodevelopmental and intellectual disability (Campbell and Sheng, 2018). The depletion of USP8 reduces levels of BACE1, which is accompanied by a decrease in BACE1-mediated amyloid precursor protein cleavage and amyloid-β levels. Moreover, it has been suggested that enhancing BACE1 degradation could present a potential therapeutic avenue for AD, and BACE1

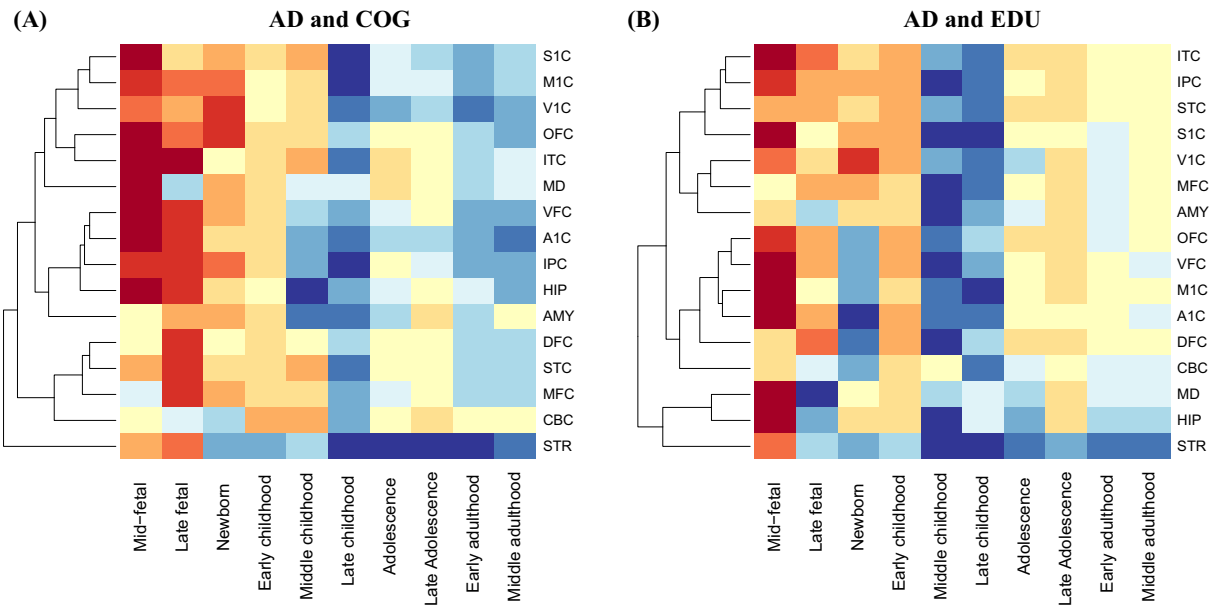

Fig. 5. Spatiotemporal gene expression of all mapped genes. Dendrogram and heat map showing spatiotemporal gene expression of all mapped genes for (A) Alzheimer's disease (AD) and cognition (COG) and (B) AD and educational attainment (EDU) using RNA sequencing data from BrainSpan over 11 developmental periods (columns) and 16 brain regions (rows). Gene expression is indicated from high (red) to low (blue); amygdala (AMY), cerebellum (CBC), dorsolateral prefrontal cortex (DFC), hippocampus (HIP), inferior parietal cortex (IPC), medial prefrontal cortex (MFC), superior temporal cortex (STC), striatum (STR), auditory cortex (A1C), primary sensory (S1C), primary motor (M1C), primary visual (V1C), inferior temporal (ITC), ventrolateral prefrontal (VFC), orbitofrontal cortices (OFC), thalamus (THA). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

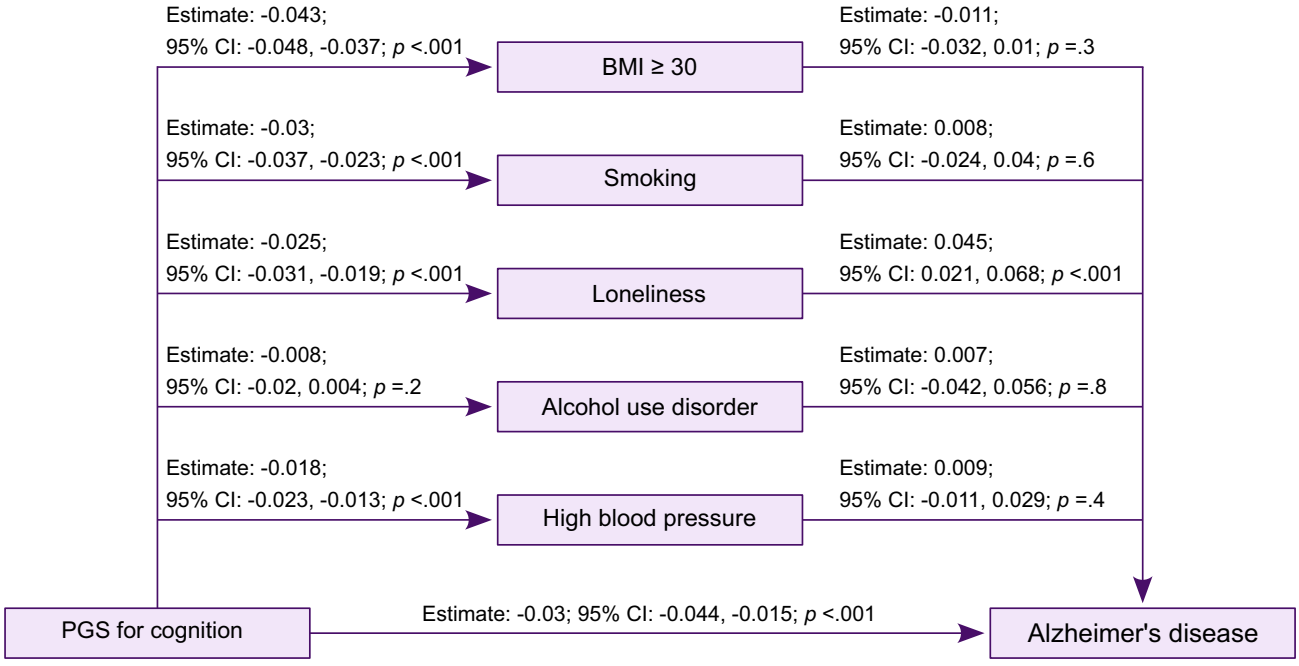

Fig. 6. Structural Equation Model for the direct and mediated effects of polygenic score (PGS) for cognition on Alzheimer's disease diagnosis (2951 cases, 248,416 controls). The figure illustrates the estimates (95 % CIs) of the structural equation model, representing the associations between the PGS for cognition, a BMI ≥ 30, smoking, loneliness, alcohol use disorder, high blood pressure, and the diagnosis of Alzheimer's disease. All associations were adjusted for age, sex, the first ten genetic principal components, and the genetic array.

inhibitors are under investigation in clinical trials (Yeates, 2016).

Our observations align with previous studies that suggested a connection between genetics of development and neurodegeneration in AD and potentially provide a link between the neurodevelopmental hypothesis and the cognitive reserve hypothesis underlying the origins of AD (Shabani and Hassan, 2023; Rogers and Schor, 2010; L. Zhang et al., 2022). This requires further investigations not only in AD but also in neurodevelopmental disorders such as Rett syndrome, Aicardi syndrome, and idiopathic intellectual disability. Specific genes, such as *APP* and *PSEN1, APOE4* previously linked with AD pathogenesis, play a role in neurodevelopment (Shabani and Hassan, 2023; Rogers and Schor, 2010; Myrum et al., 2017). The role of developmental genes in AD-associated brain circular RNA network has recently been identified by multi-layered transcriptomic analysis (Piergiorge et al., 2023).

Furthermore, the pattern of functional loss observed in AD closely mirrors, in reverse order, the sequential acquisition of central nervous system functions at subsequent stages of phylogenesis and ontogenesis (Arendt et al., 2017; Reisberg et al., 2002; Douaud et al., 2014). Intriguingly, by applying a data-driven methodological approach different from ours, specifically, carrying out a structural MRI examination of the brains of people at different stages of life, a mirroring relationship between neurodevelopmental processes and brain aging was demonstrated (Douaud et al., 2014). Similarly, previous analysis of genetic variants within genes responsible for neurodevelopment has revealed their association with accelerated atrophy in specific areas of the brain (Vacher et al., 2021). The neurodevelopmental hypothesis of AD is further supported by the rare occurrence of neurofibrillary degeneration in non-primate animals and the localization of these changes principally within regions associated with the evolution of primates (Arendt et al., 2017). The involvement of the developmental period in the pathogenesis of AD has been further underscored by observations that link winter and fall births with an increased risk of AD (Mooldijk et al., 2021).

Both networks of genes identified in the gene sets analysis, namely phosphatidylinositol bisphosphate binding and dendritic tree, are closely related with the connecting nodes being synaptic activity and structure, transmembrane transport, and actin dynamics (Kulkarni and Firestein, 2012; Mandal, 2020). The formation of intricately branched dendrites, which depends on synaptic stimulation and cytoskeletal activity, plays a key role in neuronal information transmission and processing (Kulkarni and Firestein, 2012). This contributes to the development of a brain that is capable of complex operations, including learning, memory processes, and social functioning (Kulkarni and Firestein, 2012). The occurrence of dendritic tree disorganizations has been thoroughly described for neurocognitive disorders such as mental retardation, Rett syndrome, and AD (Kulkarni and Firestein, 2012). Interestingly, in the previously mentioned brain structure study, the area in which a particularly strong mirror relationship between neurodevelopmental and aging processes was observed in the transmodal cortex, characterized by the highest synaptic levels of bottom-up processing (Douaud et al., 2014).

In parallel, it has been hypothesized that the metabolism of phosphoinositides may play a central role in the decrease of functional integrity of receptor-mediated signal transduction and the cellular pathology in AD (Fowler et al., 1990; Bothmer et al., 1994; Arancio, 2008). Phosphatidylinositol bisphosphate (PIP2), a major lipid messenger, regulates ion channels and vesicular transport across membranes (Arancio, 2008). Moreover, PIP2 influences actin dynamics, a process that plays a role in intracellular transport, cell migration and cellular force generation (Mandal, 2020). This mechanism has been associated with learning and memory (Rudy, 2015), as well as AD (Mandal, 2020). PIP2 interacts with the actin network via proteins that have been linked with AD and/or COG, such as cofilin, formin (Agís-Balboa et al., 2017), gelsolin (Feldt et al., 2019), and ezrin (Vega et al., 2018). The level of PIP2 is reduced in the brains of human ApoE3 carriers. Moreover, the restoration of PIP2 levels via genetic reduction of phosphoinositide phosphatase synaptojanin 1, a PIP2-degrading enzyme, restores cognitive function in animal models (Zhu et al., 2015). Although our findings indicate an association between phosphoinositides and AD, elucidating the potential role of phosphoinositides in the pathogenesis of the disease remains an area for future research.

Our SEM analysis indicates that genetic variants that influence COG can have a direct effect on the risk of developing AD, providing indirect evidence in support of the neurodevelopmental hypothesis. The overarching concept that links developmental processes with the pathogenesis of AD encompasses two main hypotheses: the 'two hits' hypothesis, where one 'hit' happens early with a genetic or developmental basis and the second 'hit' occurs later with an environmental basis, and a second hypothesis suggesting that crucial neurodevelopmental processes persist throughout life. Therefore, disturbances in these processes at later stages may lead to the development of AD (Rogers and Schor, 2010). The results of our study, which indicate that the expression of mapped genes predominantly occurs in the early phase of life, support the first hypothesis. Taken together, it may be posited that the foundation of cognitive reserve capacity is established early in life. Therefore, increasing our understanding of the development of brain reserve may help identifying individuals at risk of AD, as well as form the foundation for develop strategies to prevent neurodegeneration.

The results obtained from novel statistical analyses of the largest GWAS of AD and the proxy measures of cognitive reserve, COG and EDU, provided evidence supporting the genetic basis for the cognitive reserve hypothesis in AD. This was supported by findings from combining genetic data with transcriptomic data, and we provided putative molecular pathways underlying the cognitive reserve model of AD.

Moreover, our findings suggest that stratification of risk groups for developing AD may be possible based on specific risk factors related to cognitive reserve measures. However, while our findings suggest increased awareness of these subgroups, more specific measures should be applied, and the direction of the effect should be established before this can be implemented in the clinic. Furthermore, our results emphasize the need to evaluate the impact of the interplay between the mapped genes and environmental factors on the risk of developing AD. Our SEM analysis highlights the importance of loneliness. However, currently available data do not allow for a detailed examination of gene-environment interplay.

4.1. *Strengths and limitations*

A strength of our study is the use of MiXeR and condFDR, which allow for exploration of genetic architecture beyond genetic correlations, unlike classical techniques. Secondly, we employed large GWAS studies, making them particularly suitable as proxies for cognitive reserve. A limitation of our study is that the analyses are restricted to individuals of European ancestry, which impedes the generalizability of the findings to populations with different ancestral backgrounds. We emphasize the need to promote genomic studies of non-European ancestries as well as the development of analytical tools for trans-ancestry genomic analysis. One of the limitations in research on cognitive reserve is the lack of direct, accessible measures, that also applies to our study. We have applied a genetic approach, and our results can be followed up in future studies when samples with more direct measures are available. When interpreting the current results, the limitations of gene expression analysis tools (i.e. BrainSpan and WebCSEA) should be considered, particularly those arising from the lack of information on the medications taken by the donors. Due to the potential sample overlap between the GWAS for EDU and the UK Biobank, we have included the results of SEM for Educational Attainment in the supplementary materials.

5. Conclusions

To conclude, we show that there is shared genetic architecture between AD and the cognitive reserve proxy measures, COG and EDU. The shared genes implicate both neurodevelopmental and neuroplastic components in the pathoetiology of AD. These findings provide evidence in support of the cognitive reserve hypothesis in AD, suggesting early neurodevelopmental stages as critical periods for establishing cognitive reserve, which affect the risk of AD in old age. Moreover, the results of our study provide a basis for further examination of the possible role of the mapped genes and their products in the pathogenesis of AD, both from a developmental perspective and in terms of their interactions with environmental risk factors. The current results can guide future directions not only in AD but also in neurodevelopmental disorders.

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Declaration of competing interest

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Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2024.106750.

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