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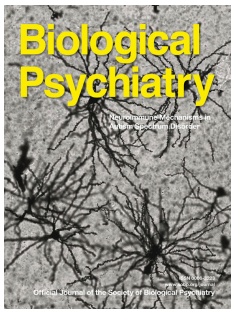

Accelerated Cortical Thinning in Schizophrenia is Associated With Rare and Common Predisposing Variation to Schizophrenia and Neurodevelopmental Disorders

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Accelerated Cortical Thinning in Schizophrenia is Associated With Rare and Common Predisposing Variation to Schizophrenia and Neurodevelopmental Disorders

Authors: Javier González-Peñas (1,2,3)*, Clara Alloza (1,2,3)*, **Rachel** Brouwer (4,5), Covadonga M. Díaz-Caneja 1,2,3,6), Javier Costas (7), Noemí González-Lois (1,2), Ana Guil Gallego (1,2), Lucía de Hoyos (1,2), Xaquín Gurriarán (1,2,3), Álvaro Andreu-Bernabeu (1,2,3), Rafael Romero-García (8,9), Lourdes Fañanas (3,10), Julio Bobes (3,11), Ana González Pinto (3,12), Benedicto Crespo-Facorro (3,13), Lourdes Martorell (3,14), Manuel Arrojo (7), Elisabet Vilella (3,14), Alfonso Guitiérrez-Zotes (3,14), Marta Perez-Rando (15,16), María Dolores Moltó (3,16,17), CIBERSAM group (**), Elizabeth Buimer (4), Neeltje van Haren (4,18), Wiepke Cahn (4,19), Michael O'Donovan (20), René S. Kahn (4,21), Celso Arango (1,2,3,6), Hilleke Hulshoff Pol (4), Joost Janssen (1,2,3,4±) & Hugo Schnack (4±).

[1] Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[2] Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain

[3] CIBERSAM, Centro Investigación Biomédica en Red Salud Mental, Madrid, Spain

[4] Department of Psychiatry, UMCU Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands

[5] Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus. Amsterdam, VU University Amsterdam, Amsterdam, The Netherlands.

[6] School of Medicine, Universidad Complutense, Madrid, Spain

[7] Instituto de Investigación Sanitaria (IDIS) de Santiago de Compostela, Complexo Hospitalario Universitario de Santiago de Compostela (CHUS), Servizo Galego de Saúde (SERGAS), Santiago de Compostela, Galicia, Spain

[8] Department of Psychiatry, University of Cambridge UK

[9] Department of Medical Physiology and Biophysics, Instituto de Biomedicina de Sevilla (IBiS), HUVR/CSIC/Universidad de Sevilla/CIBERSAM, ISCIII, Sevilla, Spain

[10] Department of Evolutionary Biology, Ecology and Environmental Sciences, Faculty of Biology, University of Barcelona, Barcelona, Spain

[11] Faculty of Medicine and Health Sciences - Psychiatry, Universidad de Oviedo, ISPA, INEUROPA. Oviedo, Spain

[12] BIOARABA Health Research Institute, OSI Araba, University Hospital, University of the Basque Country, Vitoria, Spain

[13] Hospital Universitario Virgen del Rocío, Department of Psychiatry, Universidad de Sevilla, Sevilla, Spain

[14] Hospital Universitari Institut Pere Mata, Institut d'Investigació Sanitària Pere Virgili-CERCA, Universitat Rovira i Virgili, Reus, Spain

[15] Fundación Investigación Hospital Clínico de Valencia, INCLIVA, Valencia, Spain

[16] Unidad de Neurobiología, Instituto de Biotecnología y Biomedicina (BIOTECMED), Universitat de València,Valencia, Spain.

[17] Department of Genetics, Universitat de València, Campus of Burjassot, Valencia, Spain

[18] Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre, Rotterdam, The Netherlands

[19] Altrecht Mental Health Institute, Altrecht Science, Utrecht, The Netherlands

[20] MRC Centre for Neuropsychiatric Genetics and Genomics and Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, United Kingdom

[21] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, United States

* Equal contribution

± Equal contribution

(**) **CIBERSAM group:** Javier González-Peñas (1,2,3), Covadonga M. Díaz-Caneja (1,2,3,4), Javier Costas (5), Xaquín Gurriarán (1,2,3), Álvaro Andreu-Bernabeu (1,2,3), Lourdes Fañanas (3,6), Araceli Rosa de la Cruz (3,6), Bárbara Arias (3,6), Julio Bobes (3,7), Ana González Pinto (3,8), Crespo-Facorro B. (3,9), Martorell L. (3,10), Elisabet Vilella (3,10), Gerard Muntané (3,10), María Dolores Moltó (3,11,12), María José Escartí (13), Olga Rivero (14), Mara Parellada (1,2,3,6), Carmen Moreno (1,2,3,6), Celso Arango (1,2,3,4).

[1] Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[2] Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain

[3] CIBERSAM, Centro Investigación Biomédica en Red Salud Mental, Madrid, Spain

[4] School of Medicine, Universidad Complutense, Madrid, Spain

[5] Instituto de Investigación Sanitaria (IDIS) de Santiago de Compostela, Complexo Hospitalario Universitario de Santiago de Compostela (CHUS), Servizo Galego de Saúde (SERGAS), Santiago de Compostela, Galicia, Spain

[6] Department of Evolutionary Biology, Ecology and Environmental Sciences, Faculty of Biology, University of Barcelona, Barcelona, Spain

[7] Faculty of Medicine and Health Sciences - Psychiatry, Universidad de Oviedo, ISPA, INEUROPA. Oviedo, Spain

[8] BIOARABA Health Research Institute, OSI Araba, University Hospital, University of the Basque Country, Vitoria, Spain

[9] Hospital Universitario Virgen del Rocío, Department of Psychiatry, Universidad de Sevilla, Sevilla, Spain

[10] Hospital Universitari Institut Pere Mata, Institut d'Investigació Sanitària Pere Virgili-CERCA, Universitat Rovira i Virgili, Reus, Spain

[11] Unidad de Neurobiología, Instituto de Biotecnología y Biomedicina (BIOTECMED), Universitat de València,Valencia, Spain.

[12] Department of Genetics, Universitat de València, Campus of Burjassot, Valencia, Spain

[13] Department of Psychiatry, Hospital Clínico Universitario de Valencia, School of Medicine, Universitat de València, Valencia, Spain

[14] Fundación Investigación Hospital Clínico de Valencia, INCLIVA, Valencia, Spain

Author information

Corresponding author

Correspondence to González-Peñas J.

javier.gonzalez@iisgm.com

Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Madrid, Spain

CIBERSAM, Centro Investigación Biomédica en Red Salud Mental, Spain

Calle Ibiza, 43

28009 Madrid (Spain)

Phone: +34 662051044

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ABSTRACT

Background: Schizophrenia is a highly heritable disorder characterized by increased cortical thinning throughout the lifespan. Studies have reported a shared genetic basis between schizophrenia and cortical thickness. However, no genes whose expression is related to abnormal cortical thinning in schizophrenia have been identified.

Methods: We conducted linear mixed models to estimate the rates of accelerated cortical thinning across 68 regions from the Desikan-Killiany atlas in individuals with schizophrenia compared to healthy controls from a large longitudinal sample (N_{Cases} = 169 and $N_{Controls}$ = 298, aged 16-70 years). We studied the correlation between gene expression data from the Allen Human Brain Atlas and accelerated thinning estimates across cortical regions. We finally explored the functional and genetic underpinnings of the genes most contributing to accelerated thinning.

Results: We described a global pattern of accelerated cortical thinning in individuals with schizophrenia compared to healthy controls. Genes underexpressed in cortical regions exhibiting this accelerated thinning were downregulated in several psychiatric disorders and were enriched for both common and rare disrupting variation for schizophrenia and neurodevelopmental disorders. In contrast, none of these enrichments were observed for baseline cross-sectional cortical thickness differences.

Conclusions: Our findings suggest that accelerated cortical thinning, rather than cortical thickness alone, serves as an informative phenotype for neurodevelopmental disruptions in schizophrenia. We highlight the genetic and transcriptomic correlates of this accelerated cortical thinning, emphasizing the need for future longitudinal studies to elucidate the role of genetic variation and the temporal-spatial dynamics of gene expression in brain development and aging in schizophrenia.

INTRODUCTION

Schizophrenia (SZ) is a complex and heterogeneous disorder with variable clinical and neurobiological phenotypic expression (1,2). From the genetic perspective, SZ is a highly heritable and polygenic disorder (3,4), influenced by the cumulative effects of common genetic variants (5,6) as well as rare structural (7,8) and protein-truncating mutations (9,10) distributed across the genome. This genetic variation predominantly impacts genes associated with neuronal and synaptic functions (6,9,11). Furthermore, substantial genetic and transcriptomic overlap with other mental disorders has been established (12,13).

Magnetic resonance imaging (MRI) studies have consistently reported deficits in cortical thickness (CT) in cross-sectional analyses (14). While some longitudinal studies have observed increased rates of cortical thinning over time in multiple brain regions among subjects with SZ (15,16), others have reported no progressive cortical changes in SZ patients (17,18), or have limited such changes to patient subgroups with worse functional outcomes (19). Some of these studies have correlated cortical thinning with clinical severity (20,21) and cognitive impairments associated with SZ (16,22).

Heritability analyses have recently reported a shared genetic basis between SZ and brain anatomy, including CT (23,24). The genetic basis of longitudinal changes in regional cortical volumes among typically developing individuals (i.e., individuals without neurological or psychiatric disorders or controls) has been also studied, with heritability (h^2) estimates ranging from 16 to 42% (25). Intriguingly, the genetic contribution to these longitudinal cortical volumetric changes appears to be distinct, showing minimal overlap with the genetic

contribution to the interindividual variability of cross-sectional (i.e. static) regional cortical volumes (25). The ENIGMA Plasticity working group's recent genome-wide association study (GWAS), the largest of its kind, encompassed approximately 15,000 healthy individuals across various ages. This pivotal study aimed to identify the common genetic variation that predisposes individuals to longitudinal brain structure changes. The study revealed a significant correlation between cortical thinning and common genetic variation that predisposes to SZ in the general population (26). Also, genes implicated in neurodevelopmental disorders, astrocytic metabolic processes during neurodevelopment, and aging-related neuronal and synaptic changes have been related with longitudinal brain changes. (27,28).

At the transcriptome level, a high conservation of gene expression across individuals and cortical regions has been reported (29,30). By integrating CT and brain gene expression profiles (31), Romero-García et al identified gene expression correlates of CT differences in autism spectrum disorders (ASD). Genes associated with CT abnormalities were enriched for processes related to synaptic transmission (31).

Collectively, these findings point to a genetic contribution to longitudinal change in CT in several mental disorders, but, to date, no genes have been identified whose expression is related to abnormal cortical thinning in SZ. Here we aimed to study the differences in the cortical thinning profiles observed in SZ patients and healthy controls (HC) using data from Utrecht Schizophrenia project and the GROUP consortium, to explore the correlation structure between these cortical thinning differences and gene expression across brain cortex using data from Allen Human Brain Atlas (AHBA), and to study the biological underpinnings of the genes contributing to this correlation with a comprehensive analytical pipeline (**Figure 1,** Supplemental Information (**SI**)).

MATERIALS AND METHODS

Participants

Participants comprised 169 participants with schizophrenia (SZ) and 298 healthy controls (HC), aged 16-70 years (Utrecht, The Netherlands). Exclusion criteria included an IQ below 80, medical or neurological conditions and history of head trauma. Only SZ participants with DSM-IV diagnosis of a non-affective psychotic disorder and HC without lifetime mental disorders were included. The final dataset consisted of participants with a minimum of two MRI scans, totaling 168 SZ (22% females) and 293 HC (43% females), yielding 922 scans post-quality control, with sex distribution mirroring the broader dataset. Genotyped data from an independent cohort from CIBERSAM (Spain) comprising 1,927 DSM-IV diagnosed SZ spectrum individuals (65% males) and 1,561 HC (55% males), was used for polygenic score (PGS) predictions. Further information can be found in (16,32,33) and in **SI**.

Imaging processing

All participants had their baseline and follow-up MRI scan on a Philips 1.5T scanner. Anatomical CT information for each individual was obtained through the FreeSurfer analysis suite (34,35) across 68 cortical regions from Desikan-Killiany atlas (36). Accelerated cortical thinning (ACT) in SZ and CT differences at baseline (BCTD) between SZ and HC were studied using linear mixed models (LMM) and linear regression models, respectively. All analyses were performed in R and Matlab (v2018a). Detailed information about the image acquisition protocols, processing pipeline and sensitivity analyses performed are fully described in **SI**.

Biological correlates of accelerated cortical thinning in SZ

Partial least squares regression (PLSR) models were performed to study the relationships between standardized estimates of ACT ($\beta_{age*diagnosis}$) and brain anatomically patterned gene expression matrix (20,647 genes x 68 cortical regions). We used brain gene expression data

from the Allen Human Brain Atlas (AHBA; https://human.brain-map.org/ (29,30). We used permutation testing based on 10,000 spherical rotations of the cortical regions (p_{spin}) and assessed whether the first PLS component explained more variance than expected by chance (38). PLS weights for each gene were z-transformed (based on standard errors obtained from bootstrapping) and FDR-adjusted (37). Genes positively and negatively weighted on the first PLS component ($p_{FDR} < 0.05$) were named PLS+ and PLS- genes, respectively. Additional PLSR analyses performed to explore the gene expression correlates with regional BCTD estimates. The method is based on the one described by Romero-Garcia et al. (39) (described in **SI)**.

We used Metascape (40) to calculate Gene Ontology (GO) enrichments and hierarchical functional for PLS genes using a background gene list of 15,209 consistently brain-expressed genes (41,42). Overrepresentation of PLS genes in synaptic GO terms from SynGO database v1.1(43) was also tested.Transcriptional profiling of PLS genes across 13 adult brain regions from Genotype-Tissue Expression project (GTEx v8) (44) and across 7 developmental timepoints from Brainspan (30) was performed with FUMA (https://fuma.ctglab.nl/ (45). Up or downregulation across each GTEx brain region was assessed with one-sample t-tests. Differences in prenatal vs postnatal gene expression values were assessed with two sample t-tests. Furthermore, overrepresentation of PLS genes across cell-type specific genes (46) was assessed by resampling procedure (real overlap against 10,000 simulations). See **SI** for a detailed methodological description.

Genetic relationship between ACT and SZ and other related disorders

We studied the overrepresentation of PLS genes among differentially expressed genes (DEG) in SZ and related psychiatric disorders (47) by a resampling procedure, comparing real enrichment against enrichment distribution from 10,000 randomly selected brain-expressed gene lists. We assessed enrichment of PLS gene sets in common predisposing variation for

SZ and other related disorders with MAGMA v1.10 (48) (GWAS data described in **Supp Data 4**). Additionally, we calculated gene set-based polygenic scores (PGS) in a Spanish case-control sample (Cibersam Consortium(49); N_{SZ} = 1,927; N_{HC} = 1,561) using data from the latest SZ GWAS (6). SZ-PGS were calculated for PLS- and PLS+ gene sets with PRSet function in PRSice v2.3.5, following developer's recommendations, and significance was evaluated using logistic regression. Furthermore, we used logistic models to assess the overrepresentation of PLS genes among genes impacted by rare disruptive variation in SZ and neurodevelopmental disorders. Significance was determined through 10,000 random permutations of PLS genes.Corrected-p_{FDR} < 0.05 was considered in any case. See **SI** for comprehensive methodological information.

RESULTS

Accelerated cortical thinning trajectories in SZ.

We assessed whether the average cortical thinning in the SZ group (N = 168) was different from that in the HC group (N = 293) by regressing the effect of the age*diagnosis interaction on longitudinal CT measures across 68 brain regions with linear mixed models (see **Methods**). Positive values of $\beta_{age*diagnosis}$ represent brain regions with greater cortical thinning in SZ (SZ patients coded as "0") in comparison with the less pronounced thinning observed in HC (HC coded as "1"). Overall, we describe significantly accelerated cortical thinning (ACT) in the SZ group relative to the HC group (**Figure 2A**) for both the right and left cortex (standardized estimates for right cortex: β = 0.108, *p* = 0.041, and left cortex: β = 0.103, *p* = 0.050; **SI**). Although none of the brain regions reached statistical significance at the individual level, most of the 68 brain regions showed a positive ACT estimate (61 out of 68; one sample-t test = 11.442, p = 2.066 x 10^{-17}; **Figure 2B**; **Supp Data 1**), reflecting widespread ACT in SZ patients relative to HC. Sensitivity analyses revealed unbiased consistency of the results (**SI**).

Association between cortical gene expression and ACT in SZ

We used PLS regression to identify the correlation structure between ACT in SZ and anatomically patterned brain gene expression (N_{Genes} = 20,647), using data from the AHBA (**Figure 2C**). The first PLS component (PLS1) explained 41.54% of the variance in the regional estimates of ACT in SZ, which was higher than expected by chance (p_{spin} = 0.0023, 10,000 spherical rotation permutations).

Regional PLS1 scores (sum of the regional gene expression scores weighted by PLS1) were positively correlated with regional ACT estimates (r = 0.50, p = 1.2 x 10^{-5}; **Figure 2C)**. Genes significantly weighted on PLS1 (either positively or negatively) were associated with ACT in SZ in terms of their regional patterns of gene expression (**Figure 2D-F**), so that genes with positive and negative PLS1 weights are overexpressed and underexpressed in those brain regions with stronger ACT in SZ, respectively. After FDR-adjusting, a total of 1,373 genes were associated with regional ACT in SZ (p_{FDR} < 0.05; -3.97 < Z < 3.97; 677 positively correlated (PLS+ genes) and 696 negatively correlated (PLS- genes); See **Supp Data 2** for a complete list of PLS genes).

Biological signatures of genes related to ACT in SZ.

PLS- genes were overrepresented for ionic transport terms (GO0098662: inorganic cation transmembrane transport, p_{FDR} = 1.4 x 10^{-7}), densely connected through protein-protein interactions (PPI) networks and enriched for both presynaptic (p_{FDR} = 8.53 x 10^{-3}) and postsynaptic (p_{FDR} = 0.043) membrane potential terms (**Figure 3A**). Across PLS+ genes, we found PPI networks enriched for the G-Protein Coupled Receptors' (GPCR) signaling pathway (R-HSA-500792: GPCR ligand binding, p_{FDR} = 1 x 10^{-23}) (See **Supp Data 2** for complete results).

Across 13 adult brain regions from GTEx v8 data, both PLS- and PLS+ were enriched in genes highly expressed in cortical tissue (PLS- genes: normalized gene expression (95%CI) = 0.39 (0.29;0.49), p_{FDR} = 2.35 x 10^{-12}; PLS+ genes: normalized gene expression (95%CI) = 0.27 (0.16;0.38), p_{FDR} = 7.98 x 10^{-6}; **Figure 3B**). However, we also observed clear differences between both gene sets across the rest of brain regions. For instance, while only PLS- genes were upregulated in the cerebellum (gene expression (95%CI) = 0.81 (0.7;0.92), p_{FDR} = 1.86 x 10^{-37}), only PLS+ genes were upregulated in the hypothalamus (gene expression (95%CI) = 0.25 (0.15;0.35), p_{FDR} = 5.64 x 10^{-6}). Furthermore, different gene expression trajectories across 7 human brain developmental stages from Brainspan were observed for PLS- and PLS+ genes. Higher gene expression at postnatal vs prenatal stages was observed only for PLS- (two sample-t = -2.80, p = 0.009) (**Figure 3C**). See **Supp Data 3** for complete results.

We explored the overrepresentation of PLS genes across genes enriched in seven canonical brain cell types (50,51): excitatory neurons, inhibitory neurons, microglia, endothelial cells, oligodendrocytes, astrocytes, and oligodendrocyte precursors (OPCs). PLS- genes were enriched in genes highly expressed in both excitatory (OR = 3.14; p_{FDR} = 5.1 x 10^{-4}) and inhibitory (OR = 2.96; p_{FDR} = 5.1 x 10^{-4}) neuronal cell types, while PLS+ genes were overrepresented in astrocyte-related genes (OR = 3.30; p_{FDR} = 5.1 x 10^{-4}) (**Figure 3D-E**; **Supp Data 3**).

Relationship between ACT and gene expression profiles in SZ and related psychiatric disorders

Given the correlation structure between cortical gene expression and ACT in SZ, we explored the enrichment of PLS genes in genes dysregulated in SZ and other psychiatric disorders (**Figure 4A**) from post-mortem studies (47). Genes upregulated in SZ were enriched for PLS+ genes (OR(CI95%) = 3.25 (2.53;4.16); p_{FDR} < 0.00001) while genes downregulated in SZ were enriched for PLS- genes (OR(CI95%) = 2.38 (1.94;2.92); p_{FDR} < 0.00001), suggesting

315 contribution of brain cortical gene expression patterns towards steeper cortical thinning in SZ.
316 This association was also found when using independent RNAseq data from the PsychEncode
317 Consortium (47,52) (**Figure 4A**).

318 Moreover, these enrichments were extended to genes dysregulated in bipolar disorder (BD),
319 autism spectrum disorders (ASD), or alcohol abuse disorder (AAD), consistent with the shared
320 transcriptomic profiles across the psychiatric spectrum (47) (**Figure 4A).** However, while
321 enrichments across genes dysregulated in ASD and BD were due to a set of genes that
322 significantly overlap with genes dysregulated in SZ, the enrichment in AAD genes was found
323 to be independent of SZ related genes (**Supp table 3, supp figure 4**). Also, no enrichments
324 were found for major depression (MDD) either across PLS- or PLS+ genes, establishing a
325 clear difference in relation to the significant gene expression correlation across both disorders
326 at the genome wide level (47). See **Supp Data 3** for complete results.

327

328 **Association of common and rare genetic predisposing variation with ACT in SZ**

329 We then explored the enrichment of PLS- and PLS+ gene sets for genetic risk variation to SZ
330 and other psychiatric disorders or traits. Regarding common predisposing variation for SZ and
331 related phenotypes, PLS- genes were described to be significantly enriched in SZ (MAGMA
332 OR(CI95%) = 1.16 (1.05;1.29); p_{FDR} = 0.048; **Figure 4B**). By performing polygenic score
333 (PGS) predictions on an independent Spanish case-control cohort (N_{SZ} = 1,927, N_{HC} = 1,561;
334 See **Methods**), we confirmed the genetic contribution to SZ from PLS- (competitive-p =
335 0.0099; **Figure 4C**). Interestingly, no significant enrichments for predisposing variation to
336 cortical thinning and other longitudinal brain morphology measures in the neurotypical
337 population were found.

338 Furthermore, in relation to rare risk genetic variation (53), PLS- genes were enriched for 32
339 genes harboring protein truncating variants (PTVs) that confer risk to SZ (4 PLS- genes out of
340 32 SZ genes: *GRIN2A*, *NR3C2*, *RB1CC1* and *PREP*; OR(CI95%) = 3.39 (1.16;9.89); p_{perm} =

0.01; **Figure 4D**). This pattern of enrichment across rare coding variation was also observed for neurodevelopmental disorders. Using recent data derived from whole exome sequencing (WES) studies (54), we found that PLS- genes were enriched for genes harboring *de novo* PTVs in subjects with developmental disorders (DD) (34 PLS- genes out of 477 DD genes; OR(CI95%) = 1.75 (1.22;2.52); p_{perm} = 0.002; **Figure 4D**; **Supp Data 4**), thus suggesting that the impact of early neurodevelopment on the onset of SZ might phenotypically manifest as age-related CT decline.

PLS+ genes showed no enrichment for common or rare genetic predisposing variation to SZ and other phenotypes. Furthermore, no significant enrichments for predisposing variation to height, used as a brain-unrelated phenotype, were found, thus reinforcing the specificity of the association identified with schizophrenia.

Differences between longitudinal and cross-sectional cortical thickness comparison in SZ

To assess whether our results were driven uniquely by diagnostic differences in the dynamic change of CT and not by diagnostic differences in static CT we assessed the main effect of diagnosis at baseline for the same regions. We found greater CT in HC relative to SZ in most brain regions (55 out of 68; one sample-t = 87.32, p = 2.71 x 10^{-9}; **Figure 5**; See **Supp Data 5** for a detailed description of each region). However, we found no correlation between baseline CT differences (BCTD; $\beta_{diagnosis}$) and ACT ($\beta_{age*diagnosis}$) estimates (r = 0.025, *p* = 0.838, **Supp Data 1**), thus suggesting anatomical differences between cross-sectional and longitudinal profiles of cortical abnormalities in SZ (**Figure 5**).

For the BCTD model, the first PLS component explained 32% of variance in the response variable (p = 0.052, 10,000 permutations). After FDR-adjustment, a total of 1,035 genes were associated with regional BCTD in SZ (342 positively correlated (BCTD-PLS+ genes) and 693

366 negatively correlated (BCTD-PLS- genes)). No significant overlap was found between ACT-
367 PLS and BCTD-PLS significant genes (either PLS- or PLS+; **Figure 5**).

368 BCTD-PLS+ genes were strongly enriched in synaptic markers and upregulated in most brain
369 tissues and cell-types. However, no enrichment across either common or rare risk variation to
370 SZ and related traits was found (**Supp Data 5**).

371

372 **DISCUSSION**

373 In this study, using a large longitudinal sample, we described a general pattern of accelerated
374 cortical thinning (ACT) in SZ patients compared to HC across the lifespan. Using PLS
375 regression, we reported that gene expression across 68 cortical brain regions is correlated
376 with age-related cortical thinning observed in SZ patients relative to HC. We described a PLS
377 component (PLS1) that explains a significant proportion (41.54%) of variance for ACT in SZ
378 and identified the genes positively (PLS+) and negatively (PLS-) weighted on PLS1. PLS+
379 genes, which refer to genes overexpressed across cortical regions showing ACT in SZ
380 patients, are enriched for G protein-coupled receptors' signaling and neurodegeneration,
381 overrepresented in astrocyte-related genes, and upregulated in SZ, BD, and ASD. PLS-
382 genes, underexpressed across cortical regions showing ACT in SZ, are enriched for ionic
383 transport and synaptic functionality, upregulated in postnatal brain developmental stages and
384 in the cerebellum, overrepresented in neuronal cell types and downregulated in SZ, BD, ASD,
385 and AAD. Moreover, we described enrichment of PLS- genes for both predisposing common
386 and rare disrupting variation for SZ. To the best of our knowledge, the association between
387 ACT and risk genetic variation has not been described before in SZ.

388 We found that participants with SZ showed reduced CT compared to HC and progressive
389 cortical thinning, consistent with results from previous studies (14). This supports that
390 progressive cortical thinning may constitute a core phenotype of SZ (15,16), which has been
391 associated with both positive (55) and negative symptomatology (21,56), that may even

392 precede psychosis onset (15,57). Nevertheless, our findings diverge from other studies that
393 have documented the absence of ACT in SZ (17,18,58). A plausible explanation for these
394 conflicting results may be the underlying clinical heterogeneity, as delineated in certain studies
395 (19). In fact, a recent study has reported steeper cortical thinning as a factor to differentiate
396 clinical high risk subjects who transition to psychosis from those who do not (59).

397 Our study underscores the critical role of 592 PLS+ and 624 PLS- genes in ACT in SZ, with
398 PLS- genes notably enriched in neuronal, synaptic, and ionic channel functions, aligning with
399 GWAS (6,11) and whole exome sequencing (WES) (10,53,60) findings in SZ. Among these,
400 potassium channels emerged as a significant enrichment, previously linked to deficits of white
401 and gray matter in SZ (61–64). Ion channel alterations, impacting neuronal activity and brain
402 homeostasis, may contribute to cortical thinning and neurodegeneration, often seen in aging
403 brains (65). For instance, the *CACNA1C* gene's rs1006737 A allele, associated with SZ (6),
404 has been implicated in age-related cortical thinning in bipolar disorder (BD) (66), illustrating
405 potential pleiotropic genetic influences on psychiatric conditions by ACT. Additionally, PLS-
406 genes show heightened expression in the cerebellum, consistent with recent SZ research
407 highlighting cerebellar dysfunction associated with neurological soft signs and negative
408 symptoms of SZ (67,68) and with studies describing genetic enrichment of cerebellum related
409 genes in SZ (6,69,70). In line with our findings, other studies have also reported that patients
410 with SZ who had more neurological signs at baseline had greater gray matter loss in the brain
411 during a 2-year follow-up (71). Our findings also reveal significant enrichment of PLS+ genes
412 in astrocytic markers, G protein-coupled receptor (GPCR) signaling, and neurodegeneration
413 pathways, emphasizing GPCRs' role in disease mechanisms and therapeutic targets (72),
414 given their relevance in antipsychotic drug action (73). Moreover, GPCRs signaling pathway
415 has been described to be enriched for genes related to neuroanatomical variation in psychosis
416 (42).

417 PLS- and PLS+ genes were found to be downregulated and upregulated, respectively, in SZ,
418 thus supporting that gene expression dysregulation in the disorder may underlie ACT. A similar

pattern was observed for differentially expressed genes in BD, ASD and AAD. Analyzing these enrichments further, however, we described that the overlaps observed between PLS genes and genes dysregulated in SZ, BD and ASD were due to sets of genes shared across disorders, unlike what was observed in the enrichments with AAD, which were due to independent genes. These results are in line with the shared transcriptional profiles across SZ, BD and ASD (47,74). However, despite a high significant transcriptional correlation previously reported between MDD and SZ (47), no enrichment was found for differentially expressed genes in MDD. This suggests that the differences at the transcriptional or genetic level may be partially responsible for the discrepancies in the cortical thinning patterns observed in SZ and MDD.

Moreover, we report PLS- genes' enrichment for common predisposing variation to SZ, but not to other psychiatric disorders. To ensure the robustness of our association from MAGMA GSEA, common predisposing variation enrichment was replicated by gene set based-PGS predictions. Unlike our study, previous works reporting genes whose expression was correlated with other brain morphology measures across psychiatric disorders did not show enrichment for genetic predisposing variation (42,51,75). Interestingly, we found no association between genetic variation to longitudinal changes in brain morphology in neurotypical population, including CT decline (26), and genes related with ACT in SZ (**Supp Data 4**), thus suggesting that the genetic mechanisms for the accelerated cortical decline in SZ may differ from those underlying cortical decline across the lifespan in the general population. In fact, none of the 6 genome-wide significant genes related with structural brain changes across lifespan (26) overlapped with any of PLS- or PLS+ genes described here.

Rare disrupting variation conferring risk to SZ and neurodevelopmental disorders was also enriched for PLS- genes, highlighting the described genetic overlap at this type of rare genetic variation between SZ and neurodevelopmental pathologies (53,76,77). In this sense, rare genetic variation conferring risk to SZ has been described to be associated with alterations in cortical thickness and cortical thinning trajectories in people with SZ (78,79).

We have also assessed the functional characteristics of genes significantly correlated with baseline CT differences in SZ compared to HC. Intriguingly, the 342 BCTD-PLS+ genes described, which denote genes overexpressed across cortical regions showing decreased baseline CT in SZ patients relative to HC, displayed notable functional relevance. These genes were upregulated across most brain tissues, exhibited a strong enrichment for synaptic markers and were overrepresented among neuronal, oligodendrocyte, and astrocyte-specific genes. Nonetheless, BCTD-PLS+ genes did not exhibit differential expression in any psychiatric disorder nor were they enriched for predisposing genetic variation to SZ and related phenotypes. This underscores the notion that longitudinal instead of baseline differences in CT may hold greater significance in improving our understanding of the genetic underpinnings of SZ.

Our study acknowledges several limitations. The use of 1.5 T rather than 3 T MRI may limit statistical power. Despite software updates, the absence of detailed information on these updates leaves potential effects on statistical power unaddressed. However, the mixed scanning of patients and controls likely minimizes any group effects on cortical thickness changes. Moreover, Our reliance on gene expression data from healthy donors limits inferences about CT changes and gene expression in SZ. Additionally, gene expression varies with age (80,81) and may be influenced by the course of illness and treatment (82). Post-mortem brain samples, despite their value, face limitations like accessibility, susceptibility to degradation, and complex interpretation due to reverse causality and pleiotropic effects (83). Moreover, insufficient statistical power may have precluded identification of associations. Future studies in larger cohorts are warranted to gain enough statistical power to identify specific brain regions of interest. Furthermore, our data are not suited to reliably extrapolate these rates of cortical thinning beyond the age scan interval used in the study. In this sense, a recent meta-analysis reported a progressively increasing rate of cortical thinning over age in SZ patients (84). Therefore, our results may not be extrapolated to younger or first episode psychosis subpopulations. In addition, the use of other approaches to model the non-linear

relationships between CT and age could improve knowledge of this issue. Finally, although no direct link was found between genetic predisposition and baseline cortical deficits in SZ, this may partially be due to the limited variance explained (32%) by the PLS component related to baseline thickness. Further studies with comparable variance are needed to explore the relationship between a broader set of genes and SZ.

In conclusion, our results suggest that PLS- and PLS+ genes may contribute to the ACT pattern observed in SZ, with PLS- genes harboring both rare and common predisposing variation to SZ that may influence this particular acceleration in cortical decline. Taken together, our data demonstrate that accelerated cortical thinning, rather than cortical thickness *per se*, may be used as an informative phenotype of neurodevelopmental disruptions in SZ, with clear genetic and transcriptomic correlates. Future longitudinal studies using larger cohorts and deep clinical and neurobiological phenotyping are needed to clarify the role of genetic variation and the temporo-spatial dynamics of gene expression in brain development in SZ and other neurodevelopmental disorders.

Author Contributions

JGP, CA, JJ and HS contributed to the conception and design of the study. JGP and CA were involved in data analysis, with contributions from NGL, AG, LDH. JGP wrote the paper with major contributions from CDC, CA, JJ and HS. The rest of authors were involved in patient recruitment, data collection and results discussion. All the authors have reviewed and approved the final version of the manuscript.

Data availability

GWAS summary datasets used in this study have been downloaded from the following repositories: PGC (https://www.med.unc.edu/pgc/download-results/), ENIGMA

(https://enigma.ini.usc.edu/research/download-enigma-gwas-results/), UK Biobank (http://www.nealelab.is/uk-biobank), SSGAC (http://www.thessgac.org/data), and .Gene expression data from brain developmental trajectories (http://www.brainspan.org/) and adult brain (https://gtexportal.org/home/) were downloaded from FUMA platform (https://fuma.ctglab.nl/)). Individual genotype data for the CIBERSAM consortium samples (Spain, https://www.cibersam.es/en) used here and analytic code are available from the corresponding author upon reasonable request, since deposit of this data to a public repository is not allowed due to ethical and legal requirements at the participating centers.

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FIGURE AND TABLE LEGENDS

Figure 1. Overall workflow of the study. Differences in longitudinal change in cortical thickness (CT) between schizophrenia (SZ) and healthy controls (HC) were studied across the 68 brain cortical regions of the Freesurfer's Desikan-Killiany atlas in 168 SZ patients and 293 HC. **A)** The differential cortical thinning pattern in SZ vs HC was estimated by linear mixed models (*lme4* R package) across the 68 cortical regions, in which we modeled the effect of the age*diagnosis interaction on CT. Age, sex, and scanner (as fixed effects) and participant identification (as a random effect) were entered as covariates. We observed accelerated cortical thinning (ACT) in SZ patients relative to HC. **B)** Partial least squares regression (PLSR) was used to study whether gene expression was associated with regional ACT standardized estimates ($\beta_{age*diagnosis}$). We used brain gene expression data provided by the Allen Institute for Brain Science (AIBS) of the adult human brain (https://human.brain-map.org/). **C)** Genes positively and negatively weighted on the first PLS component ($p_{FDR} < 0.05$) (PLS+ and PLS- genes, respectively) were studied for pathway enrichment, transcriptional profiling across the human brain, and predisposing genetic variation enrichment. All independent analyses were corrected for multiple testing.

Figure 2. Accelerated cortical thinning (ACT) described in schizophrenia from longitudinal case-control data. A) Cortical thinning (CT) measures from the left and right brain hemisphere in SZ patients (red dots) and HC (blue dots). **B)** Difference in CT change rate between SZ and HC across the 68 brain regions of the Freesurfer's Desikan-Killiany atlas. Linear mixed models (LMM) with age*diagnosis interaction, age, diagnosis (SZ = 0; HC = 1), sex, and scanner variables (as fixed effects) and participant identification (as a random effect) were performed. Standardized betas for the interaction term ($\beta_{age*diagnosis}$) were used to determine differences in cortical thinning rates in SZ compared to HC per region. Regions shown in red represent greater cortical thinning in SZ compared to HC, describing a widespread pattern of ACT in SZ. **C)** Pipeline for the estimation of gene expression weights on PLS1. The most strongly weighted genes (positively - red, and negatively - blue) are displayed. **D)** Brain cortical map of regional PLS1 scores across the 68 brain cortical regions, estimated as the regional sum of the 20,647 gene expression values weighted by PLS1. **E)** Genes positively weighted on PLS1 (e.g., *LY6H*) are positively correlated with regional ACT in SZ, while genes negatively weighted on PLS1 (e.g., *LYPD5*) are negatively correlated with regional ACT in SZ. **F)** Scatterplot of regional PLS1 across

the 68 brain cortical regions vs standardized $\beta_{age*diagnosis}$ (ACT estimates). Pearson correlation is displayed.

Figure 3. Functional and transcriptional profiling of genes related to ACT in SZ. A) The first 3 clusters among PLS- and PLS+ genes, based on protein-protein interaction (PPI) from physical interactions (STRING and BioGrid) in Metascape, are displayed. The most enriched pathways across each cluster are represented. The size of the circle represents the number of genes involved in a given term. See **Methods** and **Supplementary Data 2** for a complete description. **B)** Up and down-regulation of PLS- and PLS+ genes across GTEx v8 brain regions. The average normalized gene expression across PLS- and PLS+ genes is shown. "*" represents significantly higher or lower gene expression compared to background genes assessed by one-sample t test. **C)** Up and down-regulation of PLS- and PLS+ genes across 7 developmental stages from Brainspan. The average normalized gene expression across PLS- and PLS+ genes is shown. "*" represents significant differences in prenatal vs postnatal gene expression values (two sample t-test). **D)** Enrichment of PLS- and PLS+ genes across 7 canonical brain cell-types (excitatory neurons, inhibitory neurons, microglia, endothelial cells, oligodendrocytes, astrocytes, and oligodendrocyte precursors (OPCs))(51). Enrichment OR from Fisher's exact tests are represented. "*" represents FDR-corrected significant enrichment after a resampling procedure to test enrichment of PLS gene sets in cell-type specific genes by comparing each gene set against 10,000 randomly selected gene lists selected from background genes. All analyses were performed using brain expressed genes (15,209) as background(41). **E)** Regional gene expression maps of significant cell types from enrichment analysis. Gene expression maps of excitatory/inhibitory neuronal and astrocytic genes overlapping with PLS- and PLS+ genes, respectively, are represented. ACG = Anterior cingulate cortex, AMY = Amygdala, CB = Cerebellum, CB.HEM = Cerebellum hemisphere, CBG = Caudate basal ganglia, CTX = Brain cortex, FCTX = Frontal cortex, HYPOT = Hypothalamus, HIPPOC = Hippocampus, NAC.BG = Nucleus accumbens basal ganglia, P.BG = Putamen basal ganglia, S.NIG = Substantia nigra, SC = Spinal cord cervical; Astro = Astrocytes, Endo = Endothelial, Micro = Microglia, Neuro-Ex = Excitatory neurons, Neuro-In = Inhibitory neurons, Oligo = Oligodendrocytes, OPC = Oligodendrocyte precursor cells.

Figure 4. Enrichment of differentially expressed genes (DEG) and predisposing variation to psychiatric disorders across genes related with ACT in SZ. A) Overrepresentation of PLS+ and PLS- gene sets across genes previously described to be up- and downregulated ($p < 0.05$) in SZ and other disorders (47) (i.e., bipolar disorder (BD), major depression (MDD), autism spectrum disorders (ASD), alcohol abuse disorder (AAD), and inflammatory bowel disease (IBD)). DEG in SZ from RNA-seq data were also used. "*" represents FDR-corrected significant enrichment after a resampling procedure to test enrichment of PLS gene sets (OR) in DEG genes by comparing against 10,000 randomly selected gene lists selected from brain-expressed background genes (N =15,209). **B)** Enrichment of PLS- and PLS+ genes in predisposing common variation from SZ and related disorders/traits. Enrichment was assessed with MAGMA v1.10 using a one-tailed competitive test, with brain-expressed genes (N =15,209) as background genes. Genetic variation within gene boundaries of 35 kb upstream and 10 kb downstream of the gene bodies was included. Summary data used for analyses is described in **Supp Data 4**. **C)** Gene-set based SZ-polygenic score (PGS) predictions in an independent SZ-HC case-control sample (N_{SZ} = 1,927, N_{HC} = 1,561). Liability-based R^2 (%) explained by PGS comprising common variation across PLS- and PLS+ genes was compared against a distribution of 10,000 R^2s from PGS predictions using the same number of randomly selected genes from brain-expressed background genes (N =15,209). **D)** Enrichment of PLS- and PLS+ genes in rare disruptive variation from SZ and ASD whole exome sequencing (WES) studies. Overrepresentation of PLS genes across 32 SZ-risk genes with $p_{FDR} < 0.05$ (Singh et al., 2022), and 185, 477, and 635 risk genes (TADA-$p_{FDR} < 0.05$) for ASD, developmental disorder (DD), and Neurodevelopmental disorder (NDD, considering ASD and DD together) was evaluated with logistic regression models using gene length as a covariate. Data used for analyses is described in **Supp Data 4**. Only brain-expressed background genes (N =15,209) were used. ADHD = Attention deficit and hyperactivity disorder, OCD = obsessive compulsive disorder, TS = Tourette syndrome, ALC = Alcohol use disorder, CUD = Cannabis use disorder, NEUR = Neuroticism, COG = Cognition, EA = Educational attainment, CROSS = Psychiatric cross disorder.

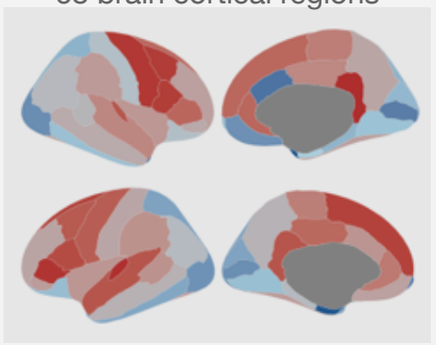
Figure 5. Differences between ACT and BCTD. A) Difference in CT change rate (ACT) and in baseline CT (BCTD) between SZ and HC across the 68 brain regions of the Freesurfer's Desikan-Killiany atlas.

For ACT, linear mixed models (LMM) with age*diagnosis interaction, age, diagnosis (SZ = 0; HC = 1), sex, and scanner variables (as fixed effects) and participant identification (as a random effect) were fitted. Standardized betas for the interaction term ($\beta_{age*diagnosis}$) were used to determine differences in cortical thinning rate in SZ compared to HC per region. For BCTD, linear regression models with diagnosis, age, sex, and scanner variables were fitted. Standardized betas for diagnosis ($\beta_{diagnosis}$) were used to evaluate baseline CT in SZ compared to HC per region, using cross-sectional data from the initial visit only. Regions shown in red represent greater cortical thinning or baseline CT in SZ compared to HC. **B)** Overlap across PLS+ and PLS- significant genes from both ACT and BCTD analyses was studied using a resampling procedure to test if the real overlap observed was higher than expected by comparing real overlap in each case against simulated overlap after 10,000 random permutations. The number of real overlapped genes (dashed lines) and from random permutations (violin plots) is displayed. C) Number of overlapped and non-overlapped genes between PLS, PLS- and PLS+ genes from ACT and BCTD models. See **Supp Data 4** for detailed information.

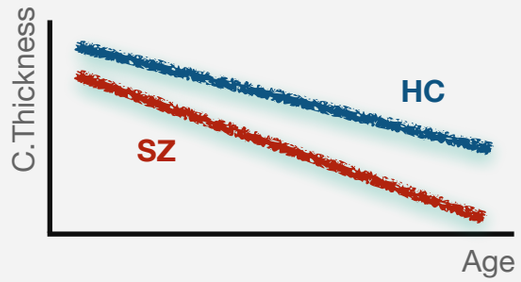
IMAGING DATA

A)

68 brain cortical regions

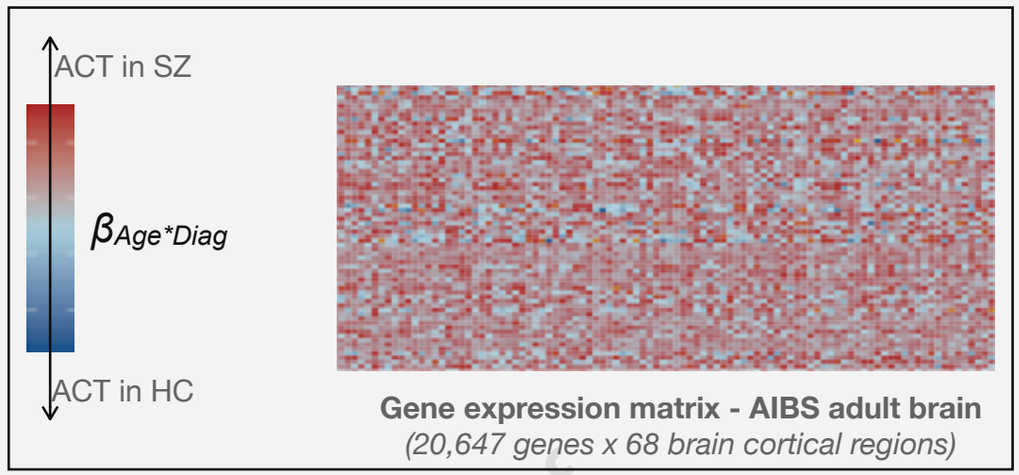


*Cortical Thickness ~ Age*Diag*



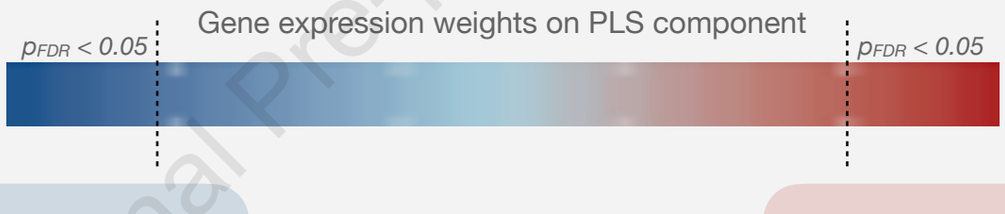
B)

Partial Least Squares Regression (PLSR)



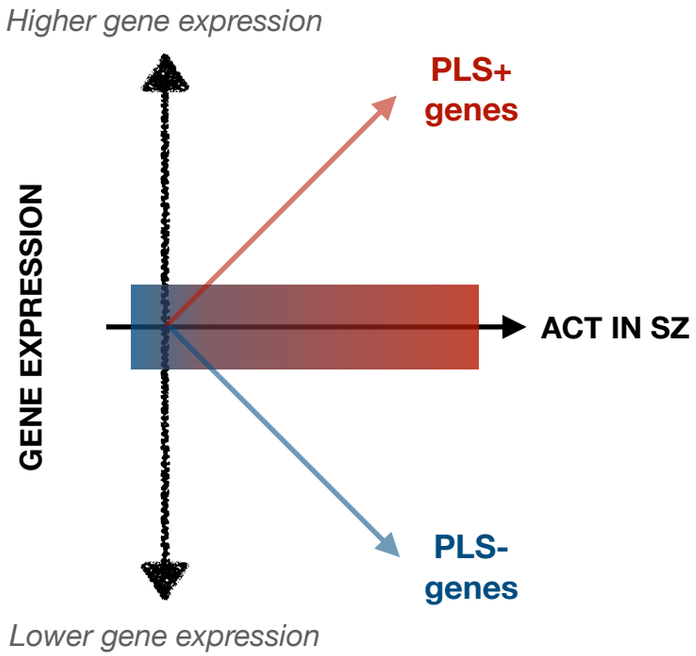
Gene expression matrix - AIBS adult brain
(20,647 genes x 68 brain cortical regions)

C)



PLS- genes

PLS+ genes



Functional enrichment

- Gene set enrichment analysis (GSEA) for biological processes / pathways
- Protein-protein interaction (PPI) clusters (Metascape MCODE algorithm)
- GSEA for Synaptic GO (SynGO) database v1.1

Transcriptional profiling

- Up / Down-regulation across 13 brain adult tissue (GTEx v8)
- Up / Down-regulation across developmental brain stages (BrainSpan)
- Gene expression enrichment across 7 brain cell-types (Li et al., 2022)
- Enriched across differentially expressed genes (DEG) in psychiatric disorders (Gandal et al., 2018)

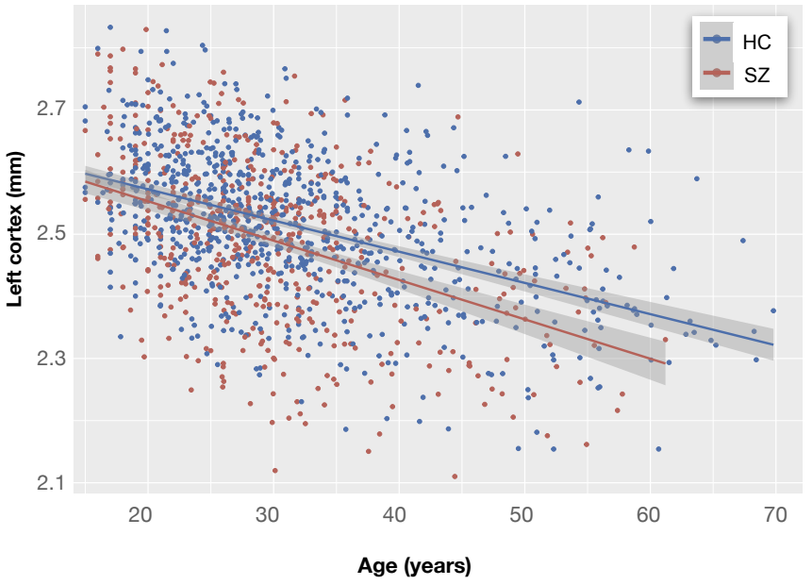
Genetic variation enrichment

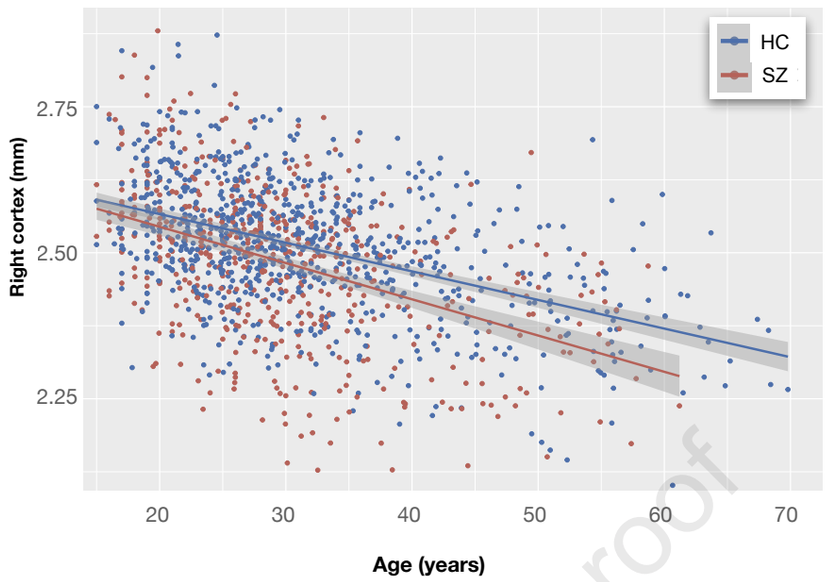
- Common predisposing variation to SZ and related phenotypes (MAGMA v1.10)
- Gene set-based SZ-Polygenic score (PGS) predictions
- Rare disrupting variation across SZ, ASD, and neurodevelopmental disorders

IMAGING - GENETICS

BIOLOGICAL CHARACTERIZATION

A) **Longitudinal cortical thinning trajectories**





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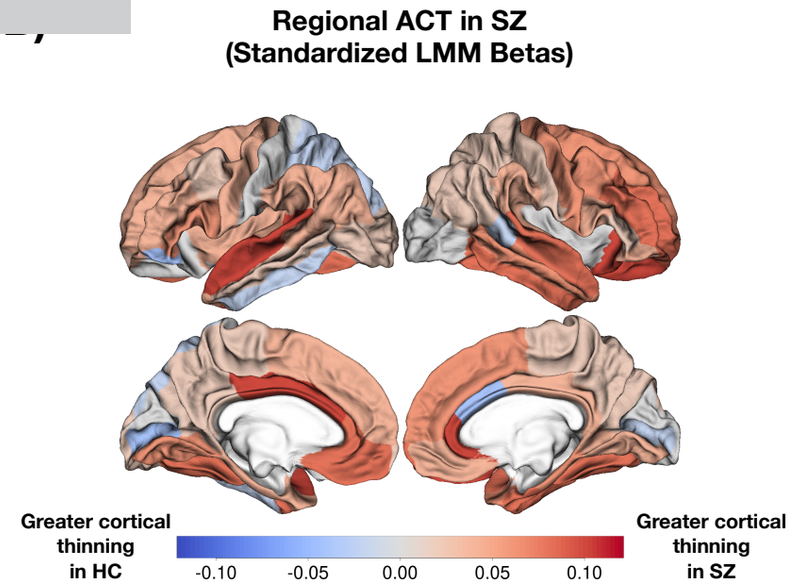

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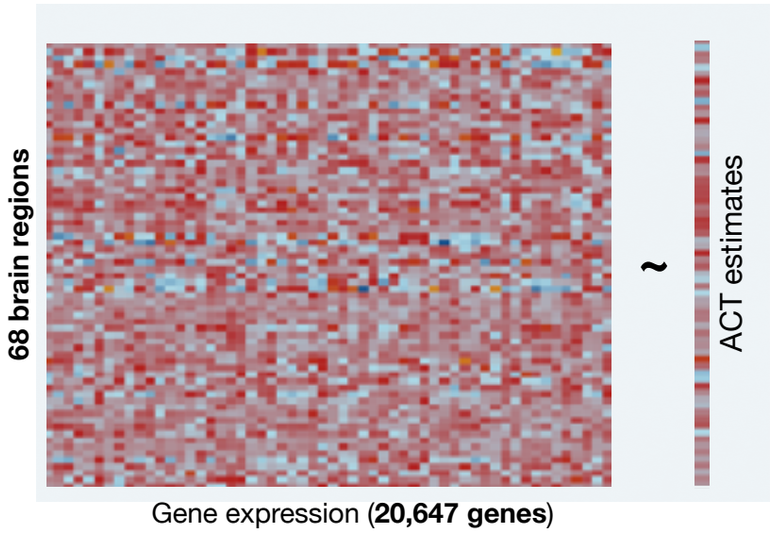
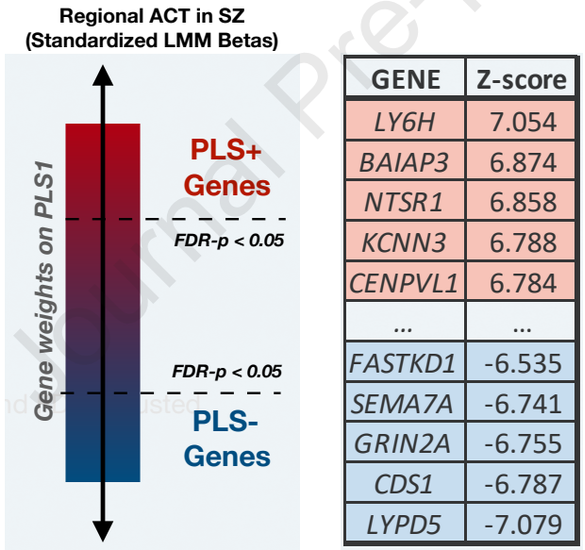
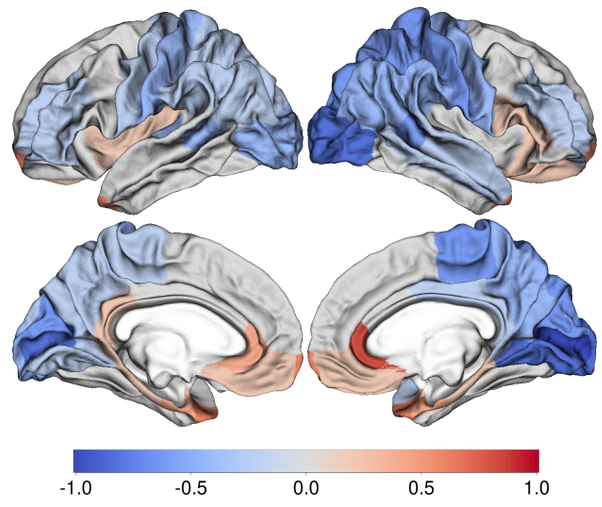




GENE	Z-score
LY6H	7.054
BAIAP3	6.874
NTSR1	6.858
KCNN3	6.788
CENPVL1	6.784
...	...
FASTKD1	-6.535
SEMA7A	-6.741
GRIN2A	-6.755
CDS1	-6.787
LYPD5	-7.079

D)



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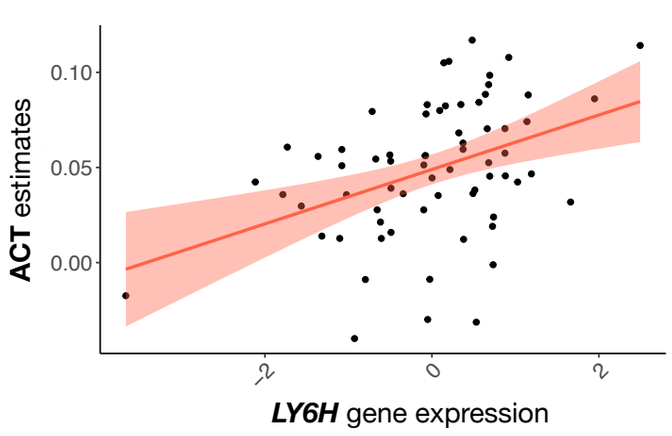

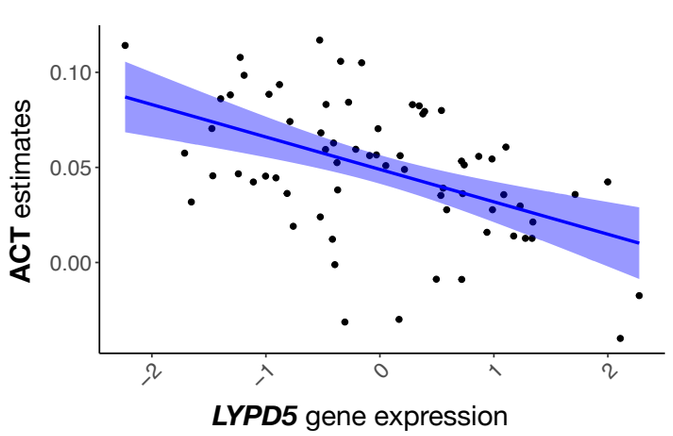

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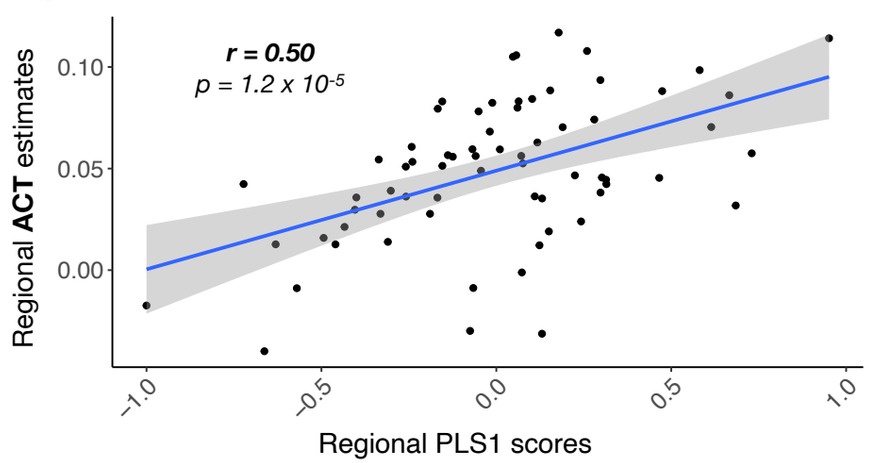
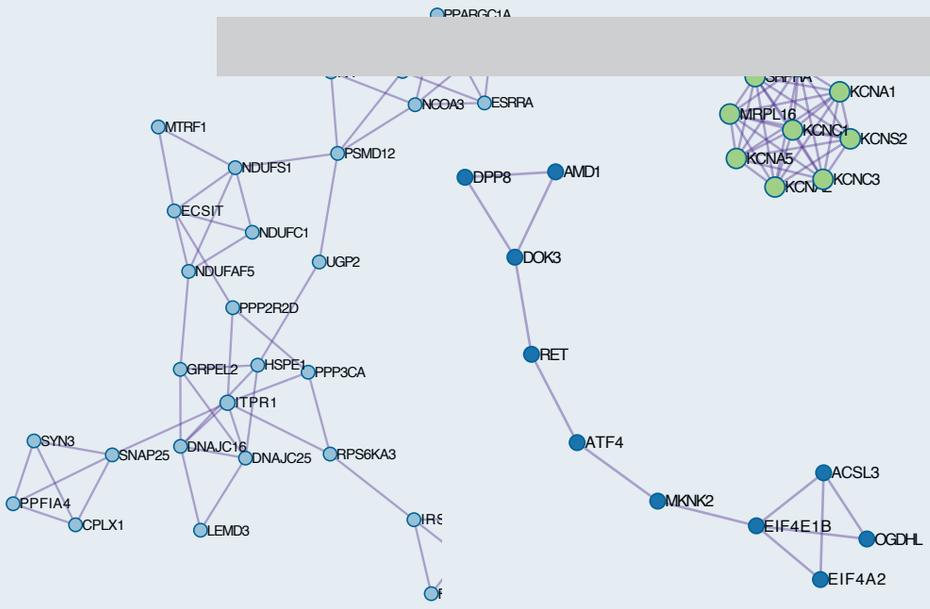


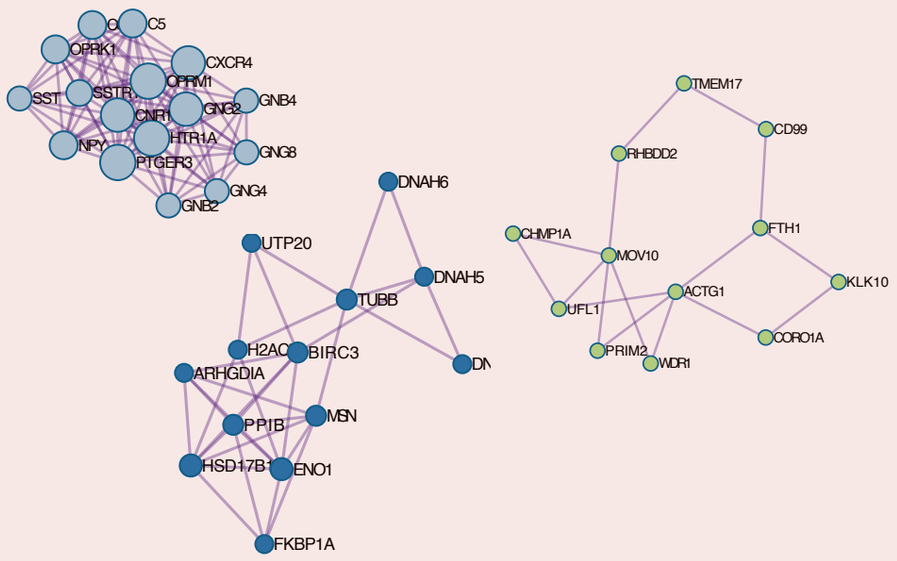
A)

MCODE PPI networks

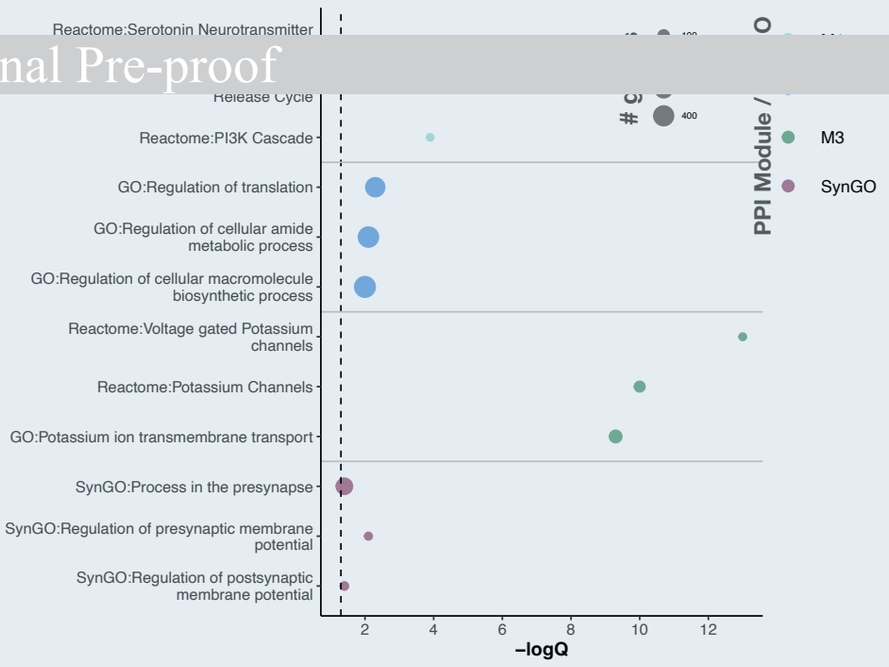
PLS- genes

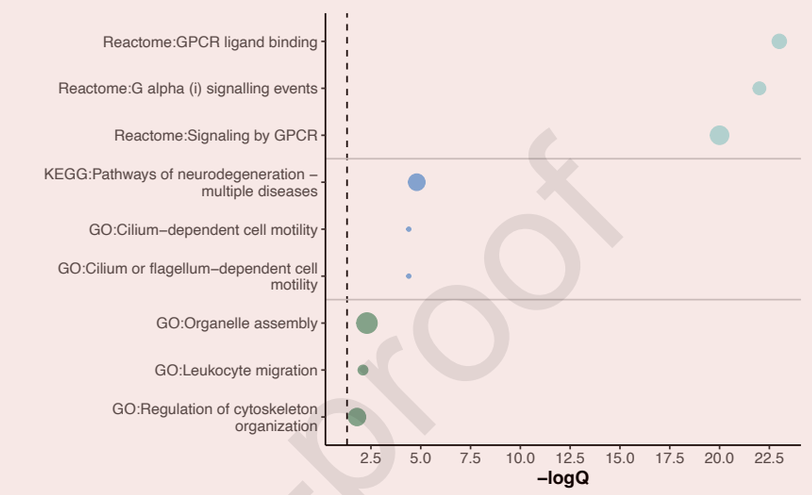


PLS+ genes

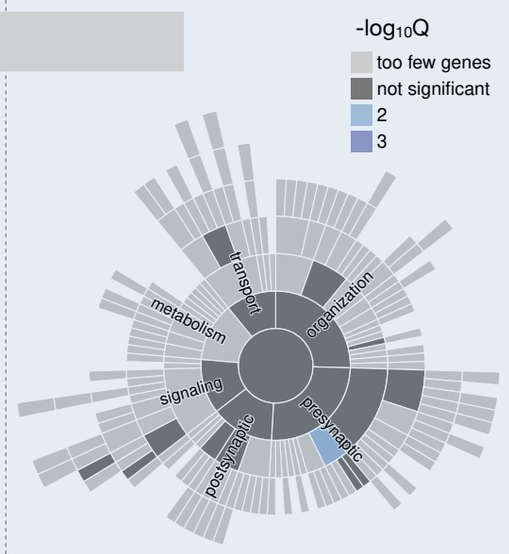


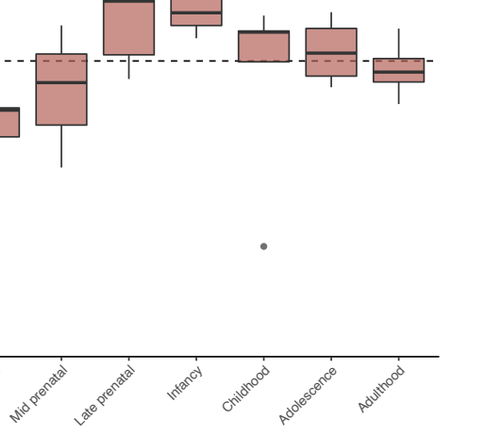
Functional enrichment (PPI networks)



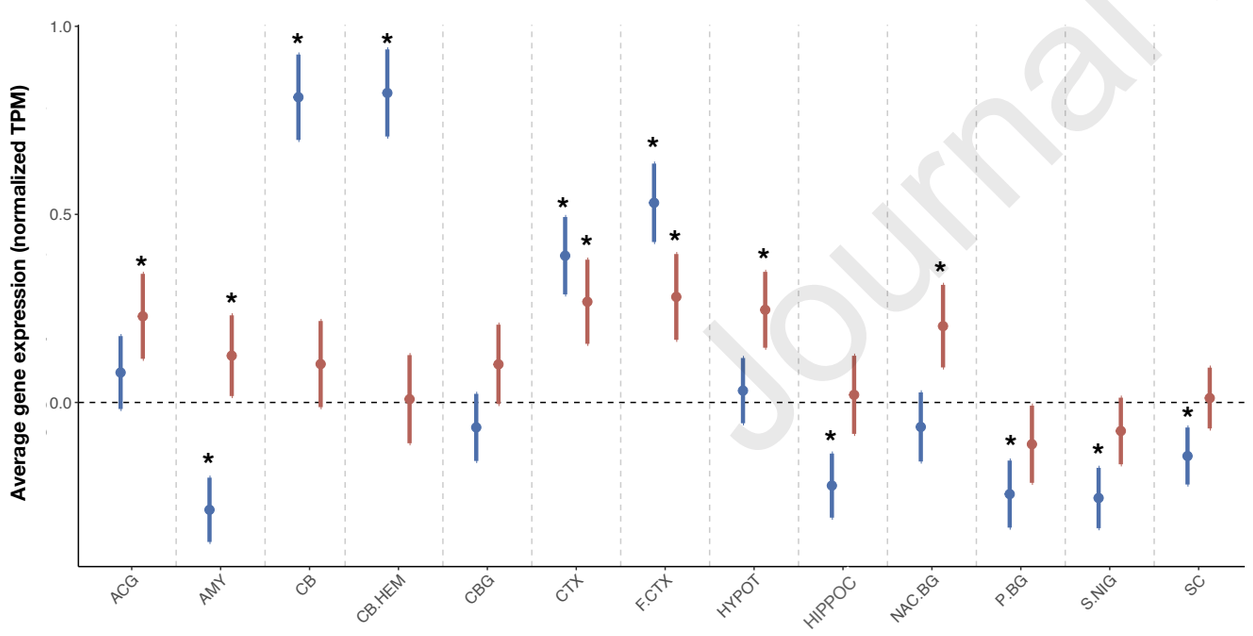


SynGO Biological Processes



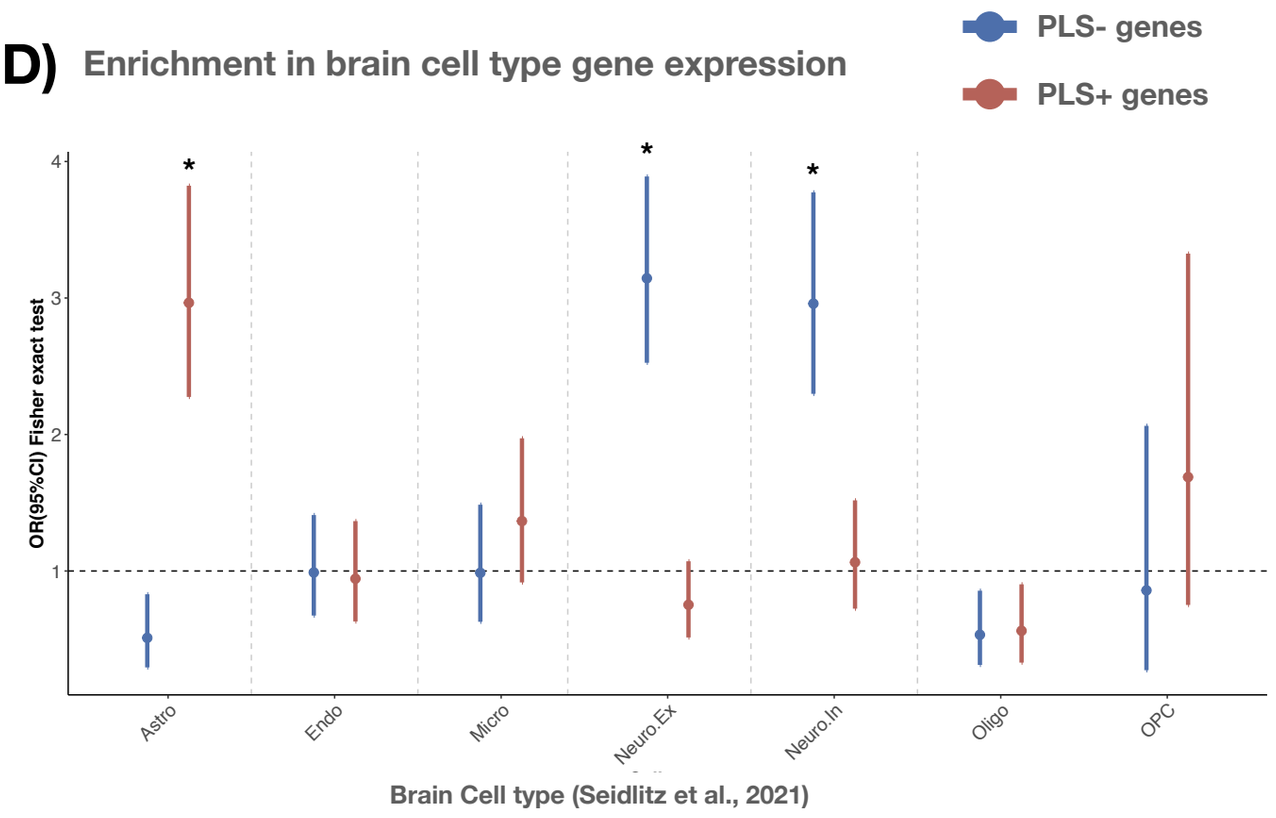


B) Gene expression across brain regions (GTEx v8)

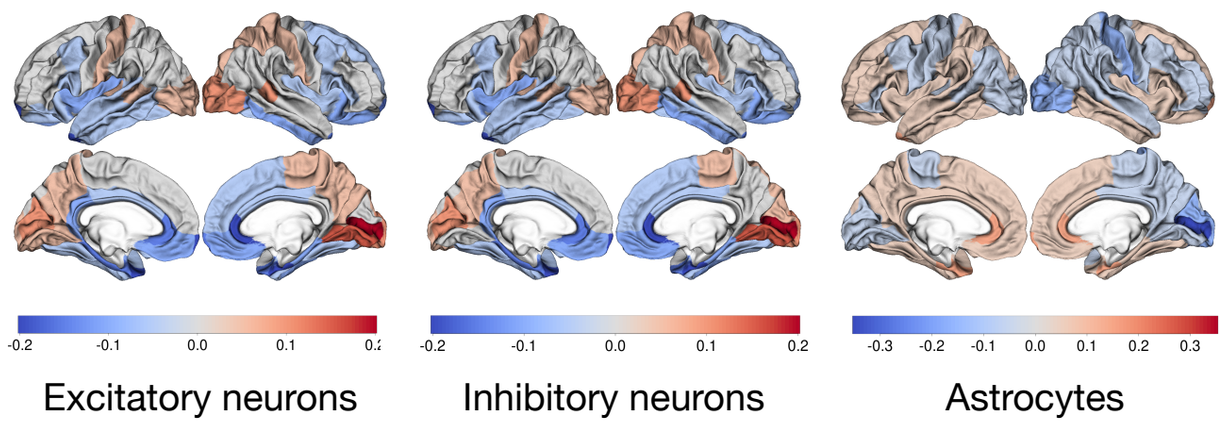


C) Gene expression across brain developmental stages (BrainSpan)

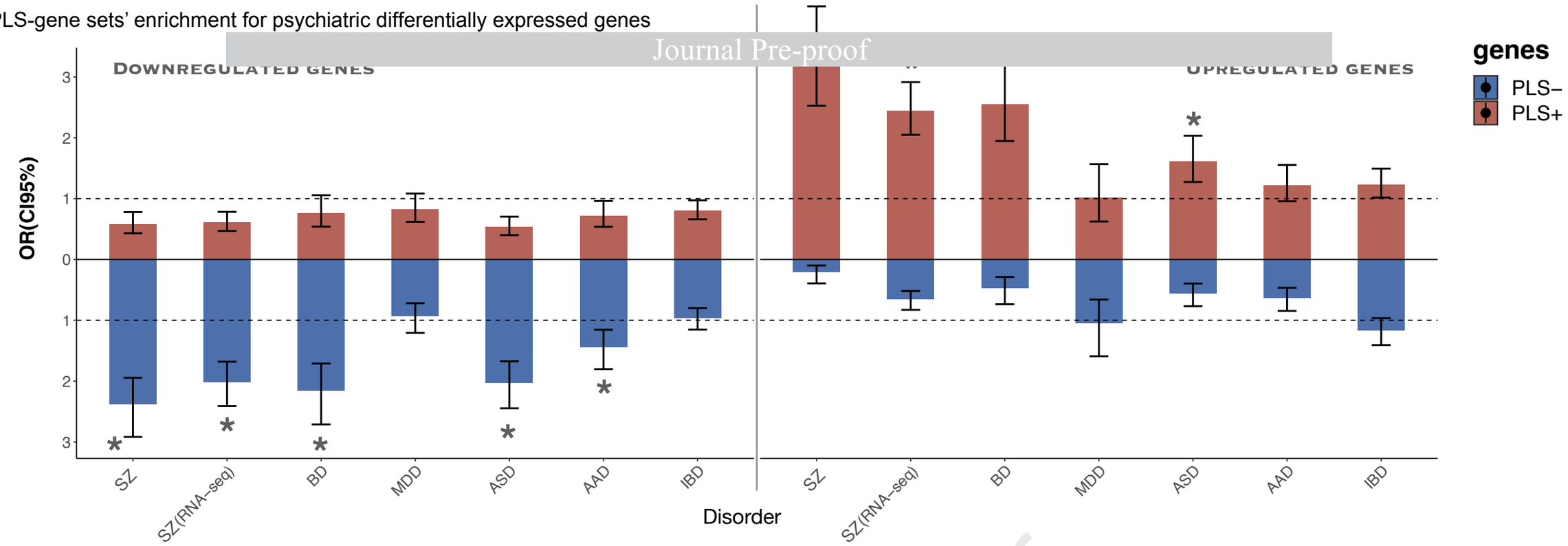
D) Enrichment in brain cell type gene expression



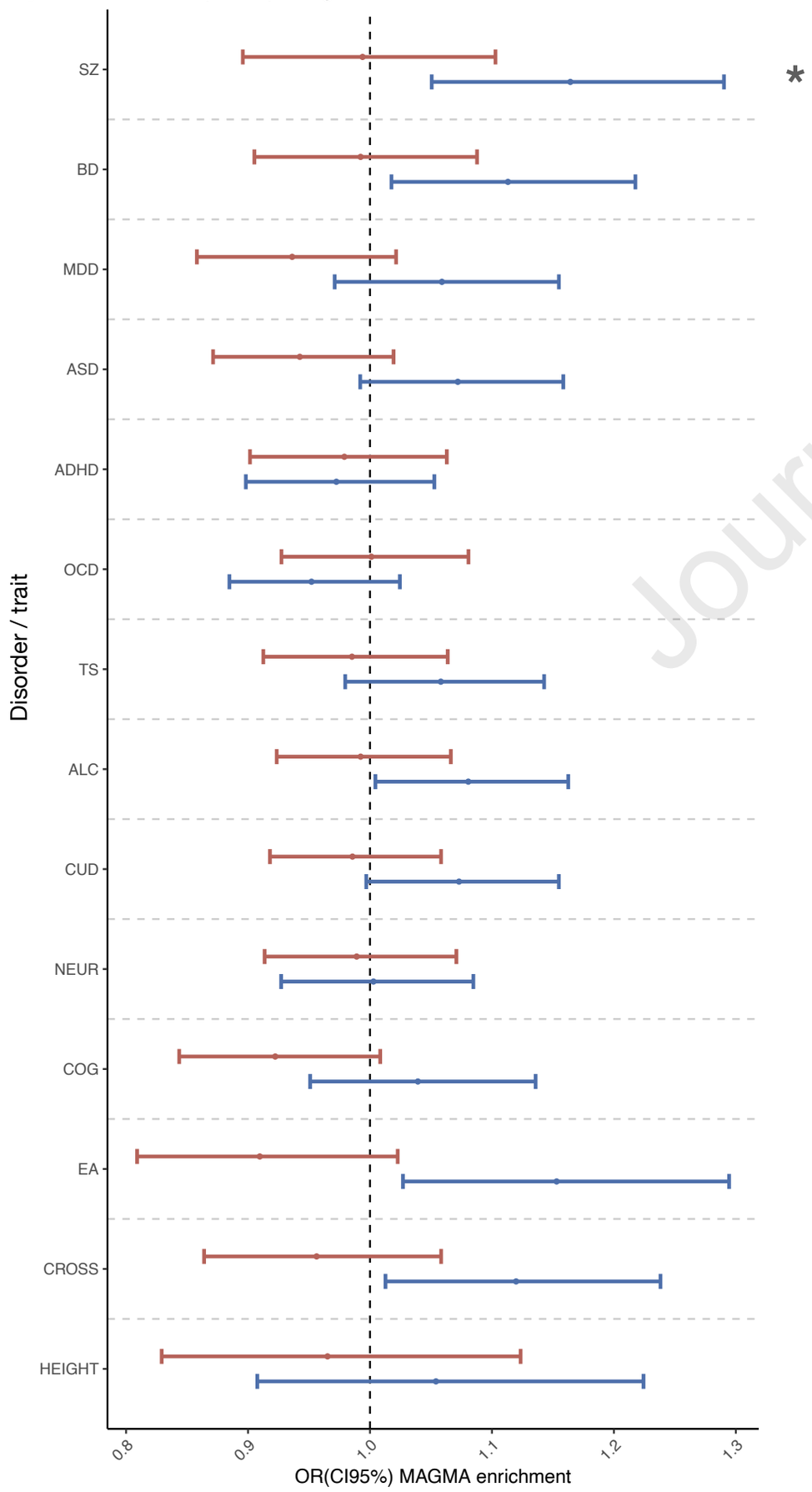
E) Cell type - regional gene expression maps



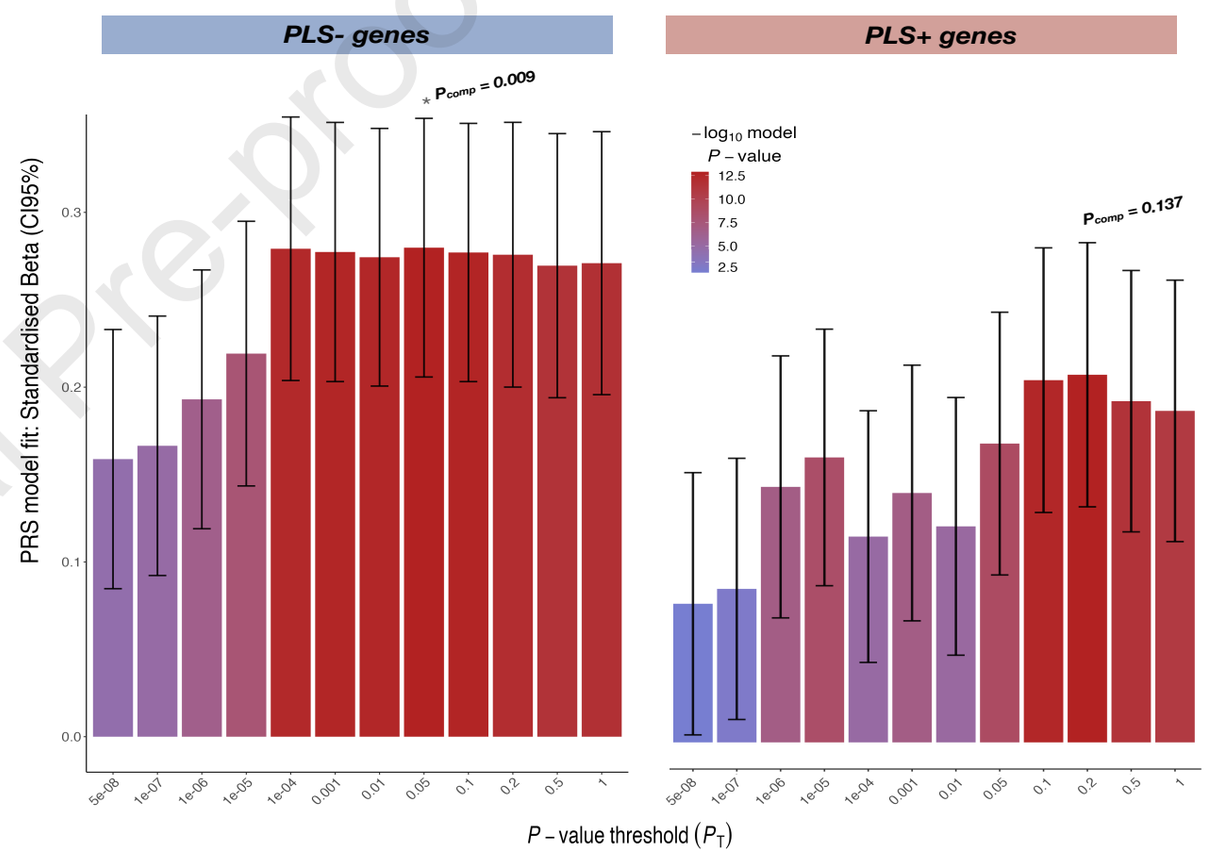
A) PLS-gene sets' enrichment for psychiatric differentially expressed genes



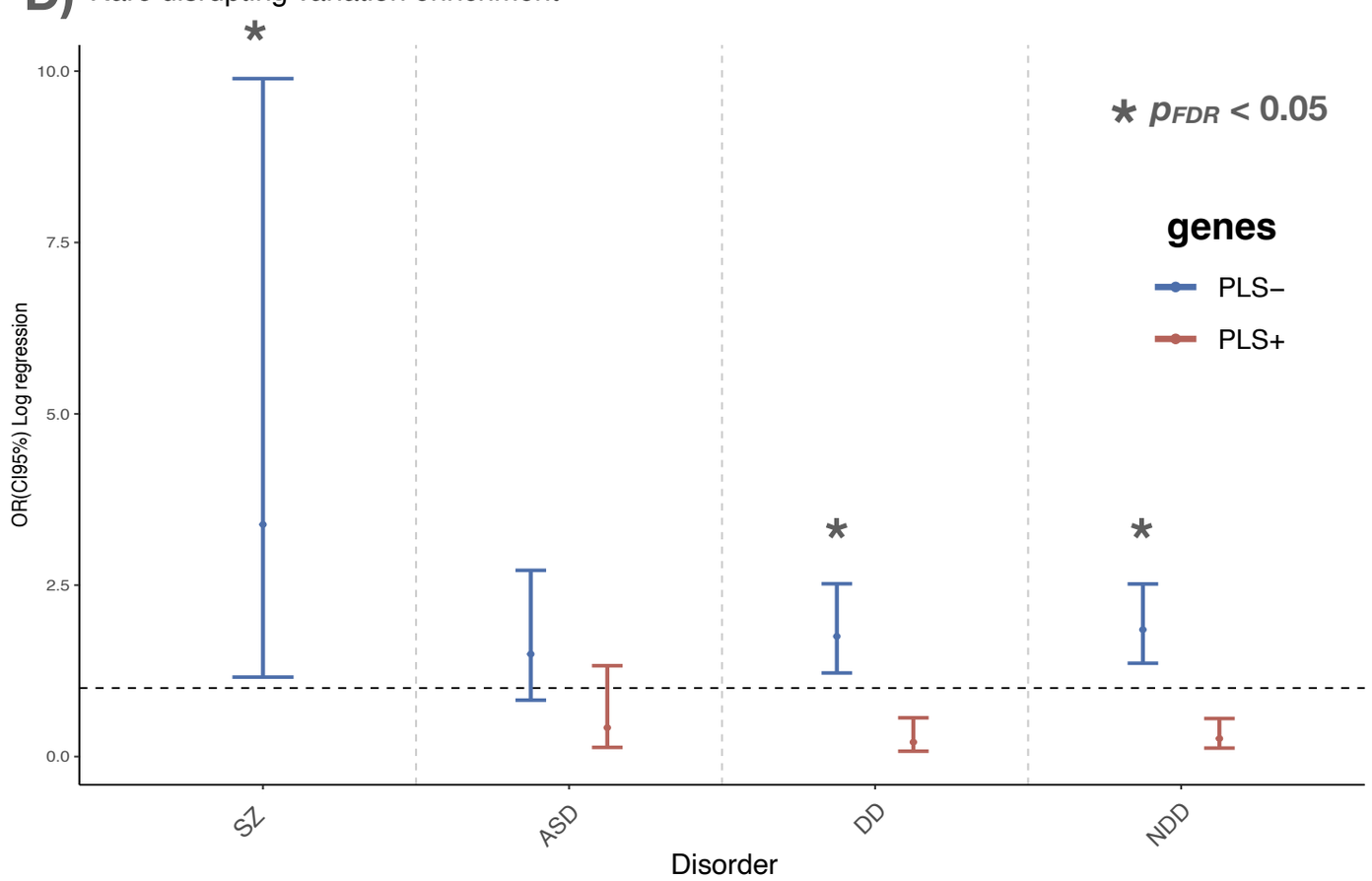
B) Common predisposing variation enrichment



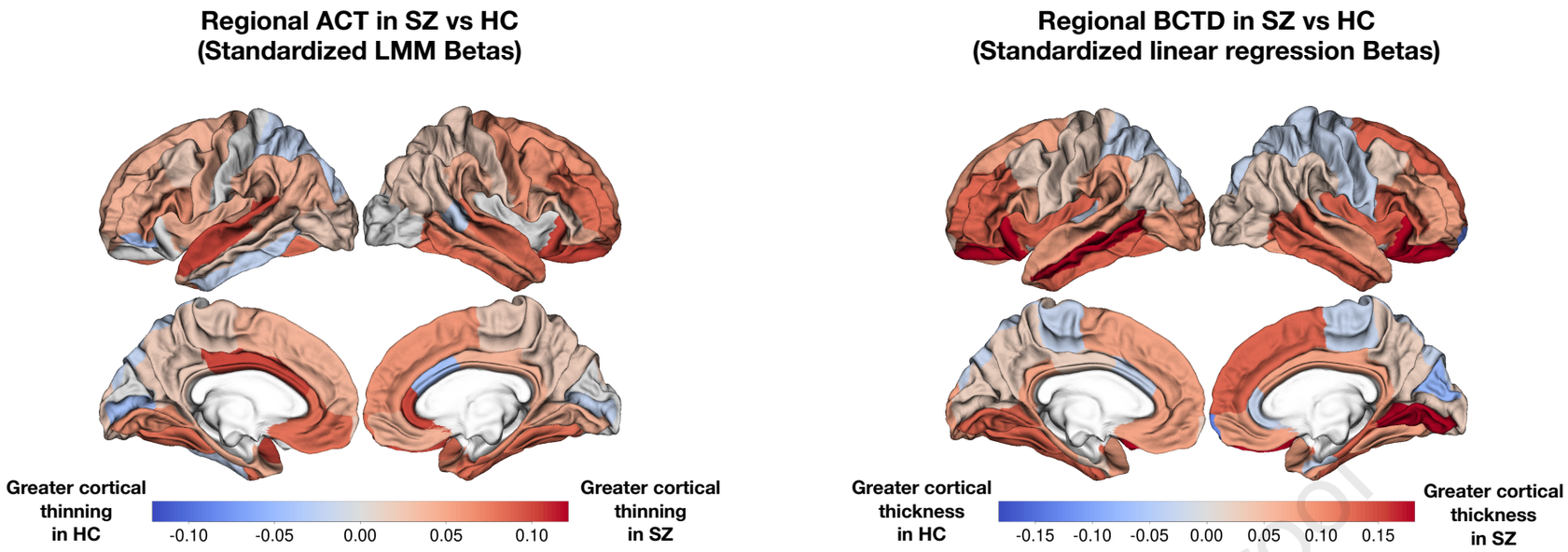
C) PLS-based polygenic score (PGS) predictions



D) Rare disrupting variation enrichment



A)



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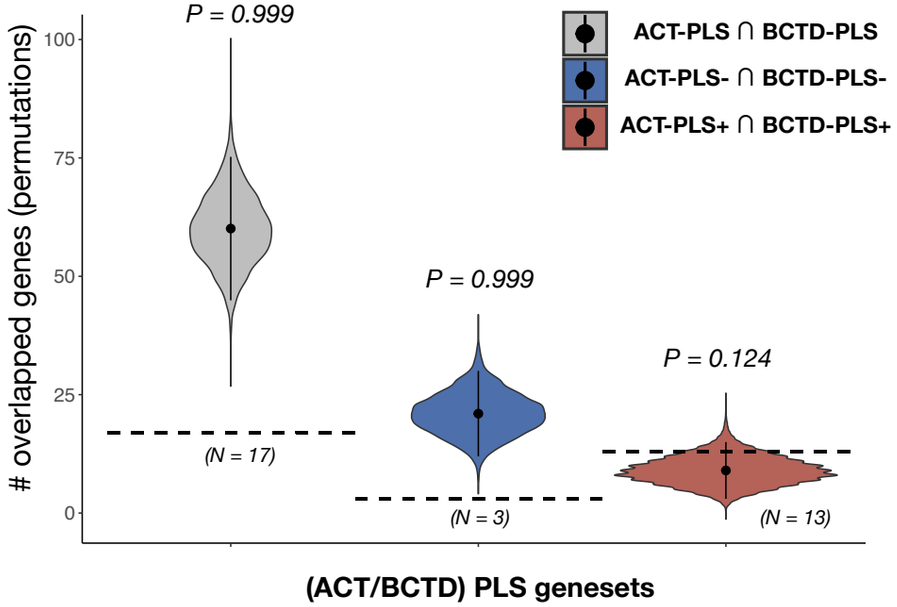

C)