Schizotypy-related magnetization of cortex in healthy adolescence is co-located with expression of schizophrenia risk genes

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Abstract

Genetic risk is thought to drive phenotypic variation on a spectrum of schizophrenia-like social and cognitive personality traits; but the intermediate phenotype of brain structural variation that mechanistically links sequence variation to schizotypal experience and behavior is unclear. We assessed schizotypy through a self-reported questionnaire, and measured magnetization transfer (MT), as a putative MRI marker of intra-cortical myelination, in 68 brain regions, in 248 healthy young people (aged 14-25 years). We found that magnetization was positively correlated with schizotypy scores in bilateral regions of posterior cingulate cortex and precuneus (FDR-corrected $P < 0.05$). Meta-analysis of prior normative functional MRI data indicated that this area of schizotypy-related magnetization is specialized for memory and social cognitive functions that are impaired in schizophrenia. Using prior data from case-control studies of human brain gene transcription post mortem, we found that schizotypy-related magnetization was significantly correlated with transcriptional dysregulation in schizophrenia. The proteins coded by genes that were both positively weighted on schizotypy-related magnetization and significantly down-regulated in schizophrenia formed a dense, complex network of interactions for neuronal signaling. We conclude that intra-cortical magnetization - putatively a marker of myelinated neurons - is a plausible brain phenotype of schizotypy and represents some genetic risks for schizophrenia.

Keywords: Schizophrenia, Allen Human Brain Atlas, adolescence, partial least squares, default mode network, magnetization transfer

Introduction

Schizophrenia is a heritable, potentially disrupting syndrome of psychotic symptoms, cognitive impairment, and social impoverishment. The genetic architecture of schizophrenia assumes many independent allelic variations, each of small effect, that can contribute to the probability of diagnosis. Individuals with the greatest accumulation of genetic risk have the more severe psychotic disorder; individuals with a lower genetic risk may have less severe, non-psychotic schizotypal personality disorder, characterized by social eccentricity and unusual beliefs [1,2].

The genetic risk for schizophrenia, and putatively schizotypy, has been resolved more clearly by recent genome-wide association studies (GWAS) and by post mortem human brain transcriptional studies [3,4]. However, it remains unclear how variation in the sequence or expression of these schizophrenia risk genes might be related to intermediate brain imaging phenotypes of schizotypy.

Macro-structural magnetic resonance imaging (MRI) studies – which measure anatomical parameters like cortical thickness or striatal volume by combining data from several voxels – have collectively provided robust evidence for reduced volume or thickness in a network of inter-connected cortical areas in patients with schizophrenia [5–7]. There have been fewer MRI studies of schizotypy in non-psychotic samples, and the pattern of macro-structural results has not been consistent across studies [8–15] (**Table S1**).

Micro-structural MRI provides information about the composition of tissue within a voxel [16]. For example, magnetization transfer (MT) images [17], and “myelin maps” derived from the ratio of conventional T2- and T1-weighted images [18], are sensitive to the proportion of fatty (mostly myelinated) brain tissue represented by each voxel.. Schizophrenia has been associated with reduced MT in frontal, temporal and insular cortex [19–21]. It has also been shown that risk genes for schizophrenia are highly expressed in association cortical areas that show high rates of increasing magnetization during healthy adolescence [22].

Here we measured schizotypy, using the Schizotypal Personality Questionnaire (SPQ), and intra-cortical magnetization transfer by MRI, in a sample of 248 healthy young people (14-25 years) (**Table S2**). We tested three key hypotheses in a logical sequence. (*i*) if that intra-cortical MT was correlated with SPQ total score, *ii*) if this cortical pattern of schizotypy-related magnetization was topographically similar to gene expression maps of all genes in the genome, and *iii*) if risk genes for schizophrenia were specifically enriched in the gene set associated with schizotypy-related magnetization.

Methods

Sample

2135 healthy young people, aged 14-25 years, were recruited from schools, colleges, NHS primary care services and direct advertisement in north London and Cambridgeshire, UK. This primary cohort was stratified into 5 contiguous age-related strata, balanced for sex and ethnicity [23]. A secondary cohort of N=297 was sub-sampled from the primary cohort for structural MRI scanning at one of the following sites: (1) Wellcome Trust Centre for Neuroimaging, London; (2) Medical Research Council Cognition and Brain Sciences Unit, Cambridge and (3) Wolfson Brain Imaging Centre, Cambridge.

After quality control checks, 11 participants were excluded because of poor quality MRI data and 38 subjects were excluded due to incomplete behavioral assessment. Complete data were available for analysis on 248 subjects (19.11 ± 2.93 years [mean ± standard deviation], 123 females).

Written informed consent was provided by all participants as well as written parental assent for participants less than 16 years old. The study was ethically approved by the National Research Ethics Service and was conducted in accordance with NHS research governance standards.

Schizotypy assessment

The Schizotypal Personality Questionnaire (SPQ) [24] is a self-report scale comprising 74 dichotomous items that are grouped on 9 subscales. Participants completed the SPQ on two occasions, separated by 6-18 months, and the total SPQ score of each participant was estimated by the proportion of positively endorsed items on average over both testing sessions.

MRI data acquisition

Structural MRI scans were acquired on one of three identical 3T MRI systems in London or Cambridge, UK (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany; VB17 software version). The multi-parametric mapping (MPM) protocol [17] yielded 3 multi-echo fast low angle shot (FLASH) scans with variable excitation flip angles. By appropriate choice of repetition time (TR) and flip angle α, acquisitions were predominantly weighted by T1 (TR=18.7ms, α=20°), proton density (PD) or magnetization transfer (MT) (TR=23.7ms, α=6°). Other acquisition parameters were: 1 mm^3 voxel resolution, 176 sagittal slices and field of view (FOV) = 256 x 240 mm. MT images from this sample have been previously reported in [22] and T1 images have been reported in [25,26]. A pilot study demonstrated satisfactory levels of between-site reliability in MPM data acquisition [17].

MRI reconstruction, cortical parcellation and estimation of schizotypy-related magnetization

We used a standard automated processing pipeline for skull stripping, tissue classification, surface extraction and cortical parcellation (http://surfer.nmr.mgn.harvard.edu) applied to longitudinal relaxation rate (R1) maps (R1=1/T1). Expert visual quality control ensured accurate segmentation of pial and grey/white matter boundaries. Regional MT values were estimated at each of 68 cortical regions for each subject, resulting in a (248 x 68) regional MT data matrix.

A simple linear model of age-related change in MT was used to estimate baseline MT at 14 years, and age-related rates of change in the period from 14 to 24 years old (ΔMT), for each region using data from all participants, as previously described [22]. Effects of age on MT were controlled by regression before estimating the correlation of the age-corrected MT residuals with total SPQ.

Estimation of regional gene expression

We used the Allen Human Brain Atlas (AHBA), a whole genome expression atlas of the adult human brain created by the Allen Institute for Brain Sciences (http://human.brain-map.org) [27]. The AHBA dataset includes six donors aged 24-57 years. Each tissue sample was assigned to an anatomical structure using the MRI data provided by the AHBA for each donor. Regional expression levels were compiled to form a (68 × 20,647) regional transcription matrix, as previously described [28]. The code for estimating this matrix (https://github.com/RafaelRomeroGarcia/geneExpression_Repository) and the gene expression data [29] are publicly available. Cortical surface representations were plotted using BrainsForPublication v0.2.1 (https://doi.org/10.5281/zenodo.1069156). See details in **SI Appendix**.

Schizotypy-related magnetization and human brain gene expression

We used a multivariate method to explore the relationships between the MRI-derived phenotype of schizotypy-related magnetization and gene expression measured in the same set of 68 regions. The dimension-reducing technique of partial least squares (PLS) was used to explore the association between regional schizotypy-related magnetization and all 20,647 genes in the transcriptome [30]. The first PLS component (PLS1) is the linear sum of weighted genes that has the cortical expression map that is most correlated with the cortical map of the MRI phenotype. We tested the null hypothesis that PLS1 explained no more SRM variance than expected by chance using a permutation test. We used a bootstrapping procedure to test each gene's weight on PLS1 under the null hypothesis of zero weight with false discovery rate (FDR) of 5% to correct for the multiple comparisons in testing all genes [31].

Schizophrenia-related and other disorder-related genes

We used three, partially overlapping lists of risk genes for schizophrenia, previously defined by sequence variation (DNA) or brain expression (RNA): (*i*) the list of genes reported by Gandal et al (2018) as up-regulated (845 genes) or down-regulated (1175 genes) in post-mortem brain tissue from a large sample of people with schizophrenia and non-psychotic comparison subjects; (*ii*) the Psychiatric Genomics Consortium (PGC) list of 310 genes (at 108 loci) identified by the largest GWAS to date, with 36,989 cases of schizophrenia and 113,075 controls [4] (**Table S3**); and (*iii*) the DISEASE list [32] of 130 schizophrenia-related genes was based on data-mining of GWAS studies and text-mining for disease-gene links in biomedical abstracts (**Table S4, Table S5**).

From the DISEASE database [32], we additionally identified a list of 196 genes associated with Alzheimer's disease, 101 genes associated with Parkinson's disease, and 224 genes associated with multiple sclerosis. We also used a list of 33 genes previously associated with bipolar disorder [33,34], [35] (**Table S6**).

Enrichment analysis

We explored the cellular affiliation of the SRM gene set according to prior criteria for four cell types: neuron, astrocyte, microglia or oligodendroglia [36]. The affiliation score was calculated for each gene that was significantly (positively or negatively) weighted on PLS1. We used a data resampling procedure to test the null hypothesis that SRM positive or negative genes were randomly assigned to different cell types.

We used a similar resampling procedure to test the hypothesis that the SRM gene list included more schizophrenia risk genes (defined by the prior Gandal, PGC or DISEASE lists) than expected by chance. For each of 10,000 random permutations of "risk gene" labels across the whole genome, we counted the number of randomly re-labelled risk genes that were included in the SRM gene list. The 95th percentile of the resulting permutation distribution provided the critical value for a one-tailed test with $P < 0.05$. We used identical procedures to test the related null hypotheses that the SRM gene list was not enriched for genes conferring risk for bipolar and other disorders.

Protein-protein interaction network

We used the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING [37]; http://string-db.org) to determine the network of known protein-protein interactions between proteins coded by down-regulated schizophrenia genes that were also positively weighted on PLS1.

Results

Schizotypy and magnetization transfer

Schizotypal personality scores in this healthy (non-psychotic) sample followed a positively skewed distribution (mean=0.23, median=0.20) that was normalized by square root transformation prior to statistical analysis. There was no significant effect of age *($R^2 < 10^{-3}$, P=0.69)*, sex *($R^2 < 10^{-3}$; P=0.77)* or age-by-sex *($R^2 < 10^{-3}$; P=0.82)* on SPQ total score or subscale scores; see **Figure S1**.

Over all 248 participants, total SPQ score was modestly positively correlated with global magnetization transfer (on average over all 68 regions; R^2 = 0.02; P = 0.015; **Figure S2**). Total SPQ was more strongly, positively correlated with age-corrected regional MT in 4 out of 68 regions separately tested (R^2 > 0.04, P < 0.05, FDR corrected; **Figure 1A**, **Figure 1B** and **Table S7)**. The 4 cortical areas where MT was significantly correlated with total SPQ (left isthmus cingulate, left posterior cingulate, left precuneus and right isthmus cingulate) comprised a spatially contiguous zone of schizotypy-related magnetization. These medial posterior cortical regions had high MT signals at age 14 (MT_{14}) and relatively slow rates of increase in MT over the period 14-25 years (ΔMT) (**Figure 1C**).

To assign normative functions to this region of schizotypy-related magnetization, we used a large database of published fMRI studies to identify experimental task conditions that were most robustly associated with its functional activation ((http://neurosynth.org; [38]). The medial posterior cortical regions with significant schizotypy-related magnetization were enriched for cognitive ontology terms related to memory, social cognition or theory of mind, and executive functions (**Figure 1D**). This area of posterior cingulate and medial parietal cortex was also ontologically enriched for default mode network.

There was no regional association between SPQ subscales and MT that survived correction for multiple comparisons (**Figure S3)**. Cortical thickness was negatively correlated with SPQ in some regions but not significantly after correction for multiple comparisons (**Figure S4)**.

Schizotypy-related magnetization and gene expression

Partial least squares (PLS) was used to identify transcriptional profiles of the 20,647 genes that were significantly associated with schizotypy-related magnetization. The first PLS component (PLS1) explained 40% of the schizotypy-related magnetization, significantly more than expected by chance (permutation test, P=0.012; **Figure 2A**). This means that there was a linear combination of genes that had a cortical pattern of expression that was anatomically similar to the cortical pattern of schizotypy-related magnetization.

Multiple univariate *Z*-tests were used to test the null hypothesis that the weight of each gene was equal to zero. We found that this null hypothesis was refuted for 1,932 positively weighted genes and for 2,153 negatively weighted genes (P < 0.05, FDR corrected for whole genome testing at 20,647 genes; **Figure 2B**). Positively weighted genes were significantly over-expressed, and negatively weighted genes were under-expressed, in cortical areas with high schizotypy-related magnetization. We will refer to these 4,085 genes as the set of schizotypy-related magnetization (SRM) genes.

Enrichment analysis of schizotypy-related myelination gene set

The positive or negative weighting of each SRM gene was highly correlated with its dysregulation in association with schizophrenia. Positively weighted SRM genes were enriched for neuronal (but not glia) and had reduced expression in schizophrenia (negative differential expression post mortem). Negatively weighted SRM genes were enriched for

genes expressed by neurons, astrocytes and microglia (but not oligodendroglia) and increased expression in schizophrenia (positive differential expression post mortem; **Figure 2C**).

Positively weighted SRM genes included 213 out of the 1175 genes previously identified as down-regulated in post mortem examination of brain tissue from people with schizophrenia [3]. This was a significantly larger number of down-regulated schizophrenia genes than expected by chance (permutation test, $P<10^{-4}$; **Table S8**). Positively weighted SRM genes were not significantly enriched for up-regulated schizophrenia genes. Conversely, the negatively weighted SRM genes included 172 up-regulated schizophrenia genes, which was significantly more than expected by chance (permutation test, $P<10^{-4}$; **Table S9**). Negatively weighted SRM genes were not significantly enriched for down-regulated schizophrenia genes.

We analysed the network of known protein-protein interactions (PPI) between proteins coded by the 213 down-regulated schizophrenia genes that were also positively weighted SRM genes. The network was significantly enriched for neuronal function terms by GO analysis and there were significantly more interactions (edges) between proteins coded by these genes than expected by chance (**Figure 3**; permutation test, $P<10^{-5}$). Topologically, the network comprised several clusters of densely interconnected and functionally specialised proteins. The biggest cluster was enriched for synaptic terms and centred around CAMK2G and PVALB. CAMK2G was also the most connected “hub” protein in the network (with 14 connections) and was also one of the most strongly negatively weighted genes on PLS1 (in the bottom 0.1% of the ranked list of gene weights; **Table S8**).

The positively weighted SRM genes also included 42 of the 310 schizophrenia risk genes reported by the PGC GWAS, significantly more than expected by chance (permutation test, $P<0.005$, **Figure 4A**; **Table S8);** and 22 of the 114 schizophrenia risk genes reported by the DISEASE study, significantly more than expected by chance (permutation test, $P<0.005$, **Figure 4A**; **Table S8)**. The negatively weighted SRM genes were not enriched for schizophrenia risk genes in either the PGC or DISEASE lists.

We repeated the enrichment analysis of positively weighted SRM genes for gene sets associated with risk for several other psychiatric and neurological conditions: bipolar disorder, Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis. In each case, we found that the risk genes for these other disorders were *not* significantly over-represented among the SRM gene set (**Figure 4B**).

Discussion

We have shown that the scores of a sample of healthy young people on a questionnaire measure of schizotypy (SPQ) were significantly correlated with magnetization transfer (MT) measured by microstructural MRI in medial posterior regions of cortex. These regions are key components of the default mode network (as defined by functional MRI studies [39]) and functionally specialised for memory, social cognitive and theory-of-mind functions that are known to be abnormal in patients with schizophrenia [40–42]. This macroscopic imaging "endophenotype", putatively a biomarker of schizotypy-related intra-cortical myelination, seems plausible. However, any biomarker must be biologically validated in some way, if it is to be anchored mechanistically.

We found a cortical map of weighted gene transcription that was approximately co-located with the cortical map of schizotypy-related magnetization. This novel set of schizotypy-related magnetization (SRM) genes was ontologically enriched for neuronal functions, included significantly more risk genes for schizophrenia (specifically) than expected by chance.

What does schizotypy-related magnetization mean?

Magnetization transfer is a magnetic resonance imaging (MRI) measurement that is approximately equivalent to the ratio of fatty and watery tissue represented by each element (voxel) of the image. High MT indicates a high proportion of fatty tissue and, in the brain, most of the fat is myelin. Recent advances in structural neuroimaging have used MT not just for its stark contrast between the cortex and the central white matter but for its more nuanced variations across different cortical areas and layers [43]. Overall, intra-cortical measurements of MT in humans have been validated as micro-structural MRI markers of myelination [44,45]. We interpret our finding of schizotypy-related magnetization to mean that higher schizotypy is associated with greater myelination of these medial posterior cortical areas.

We also found that SRM areas had high levels of magnetization at the age of 14 years and there was no significant subsequent change in magnetization over the period 14-25 years. This contrasts with areas of lateral association cortex, which have a low level of MT at 14 years but significant increase in MT over the course of adolescence [22]. We interpret this as indicating that the medial posterior cortical areas, where schizotypy-related myelination is strongest, were myelinated in a pre-adolescent wave of cortical development [46]. This is compatible with the stable trait-like properties of schizotypal personality in these data and in other studies. But there is still some uncertainty about what this intra-cortical myelination signal represents at a cellular level.

Partly in an effort to resolve the cellular interpretation of schizotypy-related myelination, we combined the MT dataset on 248 healthy young people (aged 14-25) with a prior dataset on whole genome expression post mortem in 6 adults (aged 34-54). We used partial least squares regression to find the weighted combination of genes whose cortical expression map was most strongly correlated with the cortical map of schizotypy-related magnetization. The most positively weighted genes were highly enriched for neuronal, but not glial, cellular affiliations. The negatively weighted genes were enriched for neuronal and some glial terms. But there was no enrichment for oligodendrocyte genes. We interpret this to mean that a voxel level increase in SRM is more likely to represent an increased amount of myelin, rather than an increased number of myelin-making cells per voxel.

Schizotypy-related magnetization and genetic risks for schizophrenia

Hypothetically, if schizotypy and schizophrenia are genetically related [47], and if schizotypy-related myelination is a marker of genetic risk, then the gene set associated with schizotypy-related MT should be enriched for genes associated with schizophrenia. We found supportive evidence for this prediction: schizophrenia risk genes defined by three prior lists were significantly over-represented among the set of genes most positively weighted on schizotypy-related magnetization.

The PPI network representing biochemical interactions between the 213 genes that were both dysregulated post mortem and positively weighted on schizotypy-related myelination was enriched for neuronal and synaptic terms, as well as the term “myelin sheath”. The network comprised multiple clusters or modules of densely interacting proteins which shared a specialist function in common, as well as a number of highly interactive “hub” protein. For example, calcium/calmodulin dependent protein kinase II gamma (CAMK2G) and parvalbumin (PVALB) were hub proteins, with up to 14 known biochemical interactions with other proteins in the network. CAMK2G is one of a family of serine/threonine kinases that mediate many of the second messenger effects of Ca^{2+} that are crucial for plasticity at glutamatergic synapses. PVALB is a calcium-binding albumin protein that is expressed particularly by a class of prefrontal cortical interneurons. PVALB is a calcium-binding albumin protein that is expressed particularly by a class of GABAergic interneurons and that is known to be down-regulated in patients with schizophrenia, particularly in layers III and IV [48]. Taken together, our results point to both white matter abnormalities and selective dysfunction of cortical parvalbumin neurons, the two most widely reported cellular-level abnormalities in schizophrenia. Intriguingly, abnormal myelination of fast-spiking parvalbumin interneurons has previously been proposed as a parsimonious, convergent model for the pathophysiology of schizophrenia [49].

Limitations

Several methodological limitations must be acknowledged. First, gene expression and imaging data has been acquired from different samples. The AHBA dataset is based on five male donors and one female, with a mean age of 42.5 years [27], whereas MT data was collected from 248 healthy gender-balanced subjects with a mean age of 19.1 years. As gene expression of the cerebral cortex changes with age, an adult cohort may be not suitable for testing hypotheses associated with neurodevelopmental conditions [50]. Secondly, tissue samples used for RNA sequencing were not homogenously distributed across the cortex. As a result, each cortical region included a different number of AHBA samples. Finally, there is currently no whole-brain data on gene expression changes in brain tissue from schizophrenic patients analogous to the AHBA in healthy brains. The Gandal dataset of up/down regulated genes in schizophrenia is therefore an average across multiple samples in the prefrontal cortex and parietal cortex, making the sign of expression changes difficult to interpret in the wider context of whole-brain MRI changes studied here.

Conclusions

In summary, using transcriptomic and MT imaging data, we found a strong inter-regional correlation between the expression of schizophrenia-related genes and schizotypy-related magnetization (measured as the correlation between regional MT and SPQ). This effect was particularly profound in the cingulate cortex and the isthmus. These results suggest that MT may represent a promising intermediate endophenotype to link the genetic and molecular underpinning of schizophrenia with the cognitive and behavioural traits that characterize this condition.

CONFLICTS OF INTEREST

ETB is employed half-time by the University of Cambridge and half-time by GlaxoSmithKline (GSK); he holds stock in GSK.

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FIGURES

Figure 1. Schizotypy-related magnetization: association between intra-cortical magnetization transfer (MT) and schizotypal personality questionnaire (SPQ) score. (a) Cortical surface maps highlighting areas where total SPQ score was significantly positively correlated with regional MT after controlling for age by regression: pink regions had nominally significant schizotypy-related magnetization (SRM) (two-tailed $P < 0.05$); red regions had significant SRM controlled for multiple comparisons over 68 cortical regions tested (FDR < 0.05). (b) Scatterplot of SPQ total score for each participant versus mean MT in regions of significant schizotypy-related magnetization ($R^2 = 0.04$, P = 0.002, df = 246); each dot represents one of 248 healthy people aged 14-25 years. (c) Scatterplots of SRM versus magnetization transfer at age 14 years (MT_{14}) (left; $R^2 = 0.34$, $P < 10^{-6}$, df = 67) and SRM versus change in magnetization aged 14-25 years (ΔMT) (right; $R^2 = 0.28$, $P < 10^{-5}$, df = 67). Each point represents a cortical region and colored points represent regions with significant schizotypy-related magnetization (pink, $P < 0.05$; red, FDR < 0.05). (d) Word cloud representing ontological terms most frequently associated with functional activation of the medial posterior cortical area of significant schizotypy-related magnetization.

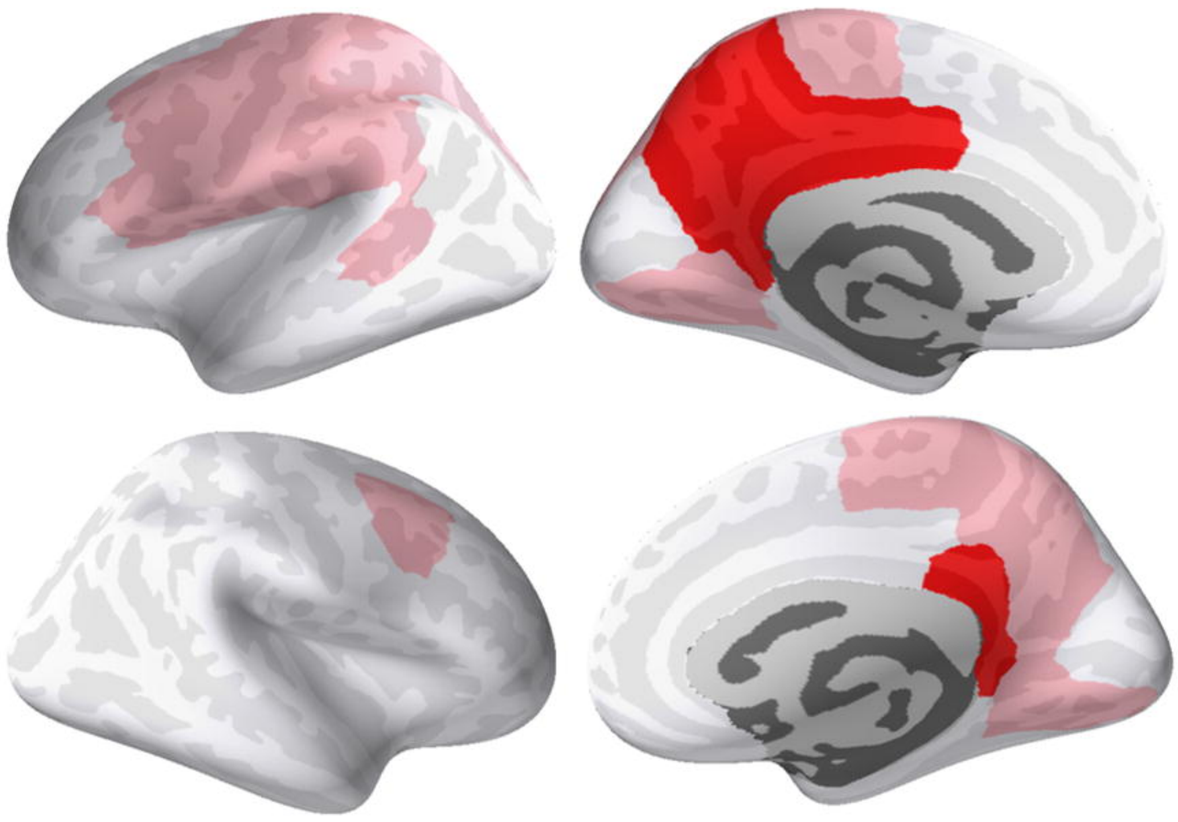
Figure 2. Gene expression and schizotypy-related magnetization (a) (left) The first partial least squares component (PLS1) defined a linear combination of genes that had a similar cortical pattern of expression to the cortical pattern of schizotypy-related magnetization (c.f., **Figure 1A**). (center) Scatterplot of PLS1 scores versus schizotypy-related magnetization; each point is a cortical region. (right) The combination of genes defined by PLS1 explains more of the variance in schizotypy-related magnetization (dotted line) than expected by chance (histogram of permutation distribution) (b) Illustrative example of the weights assigned to representative genes on PLS1. Genes with the highest positive weights are colored in pink, non-significantly weighted genes are shown in white, and the genes with the lowest negative weights are colored in blue. Tables summarise *P*-values by permutation testing for enrichment analysis by four lists of genes affiliated to specific cell types and four lists of genes associated with schizophrenia: Gandal up-reg is a list of genes transcriptionally up-regulated post mortem in schizophrenia; Gandal down-reg is a list of genes transcriptionally down-regulated in schizophrenia; PGC is a list of genes defined by the largest single GWAS of schizophrenia; DISEASE is a list of genes defined by data-

mining of GWAS results on schizophrenia. Scatterplots and cortical maps illustrate that positively weighted genes, like *ANK1*, are over-expressed in cortical regions with high levels of schizotypy-related myelination; whereas negatively weighted genes, like *PTPRC*, are under-expressed in regions with high levels of SRM. (c) The weight of each gene on the first PLS component was significantly negatively correlated with differential gene expression post mortem [3]. This was true for the subset of 473 schizotypy-related magnetization genes that were both significantly weighted on PLS1 and significantly dysregulated in schizophrenia post mortem (left panel; Spearman's rank correlation, $R^2 = 0.31$, P = 0, df = 472) and for all genes in the genome (right panel; Spearman's rank correlation, $R^2 = 0.03$, $P < 10^{-65}$, df = 11111).

Figure 3. Protein-protein interaction network for a set of 213 proteins coded by genes associated with both schizotypy-related magnetization and post mortem brain transcription in schizophrenia. Nodes represent genes that were both (i) down-regulated in brain tissue from 159 patients with schizophrenia; and (ii) positively weighted on the PLS component most strongly associated with schizotypy-related myelination in 290 healthy adolescents. Edges represent known protein-protein interactions and weights are proportional to the STRING confidence score > 0.4 [37]. Proteins are colored by their participation in the most highly enriched GO cellular component terms; all *P*-values are reported after FDR correction.

Figure 4. Schizotypy-related magnetization (SRM) genes are enriched specifically for schizophrenia GWAS risk genes. (a) The number of risk genes for schizophrenia included in the SRM list was greater than the 95th percentile of the null distribution (grey histogram) for both the PGC GWAS (left) and the DISEASE (right) lists of schizophrenia risk genes. (b) The number of DISEASE risk genes for multiple sclerosis, Alzheimer's disease, bipolar disorder, or Parkinson's disease, that were included in the SRM gene list was less than the 95th percentile of the null distribution.

A



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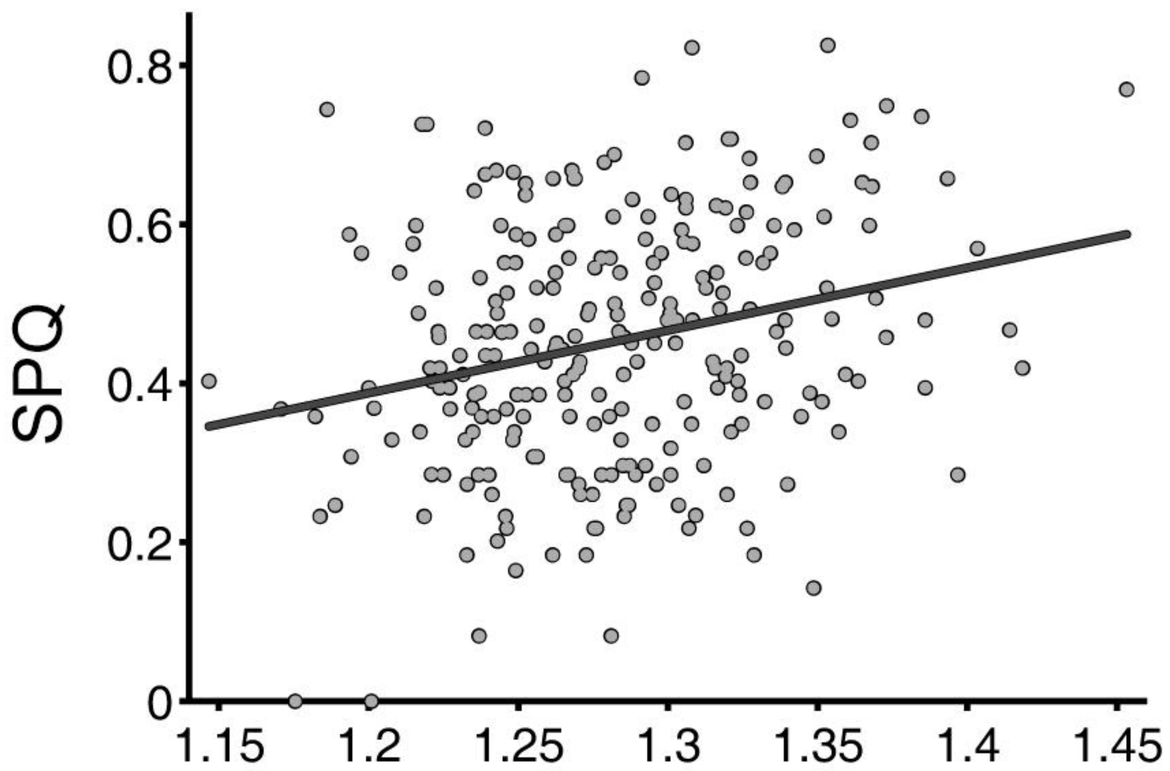

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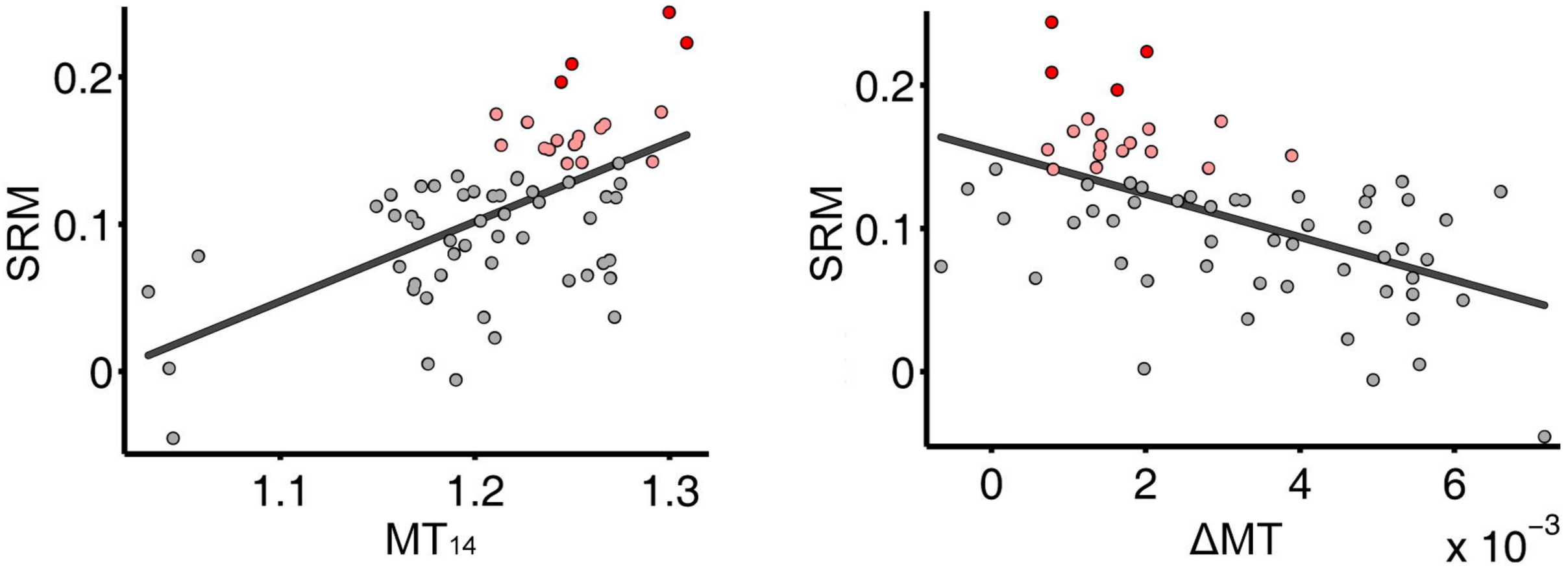

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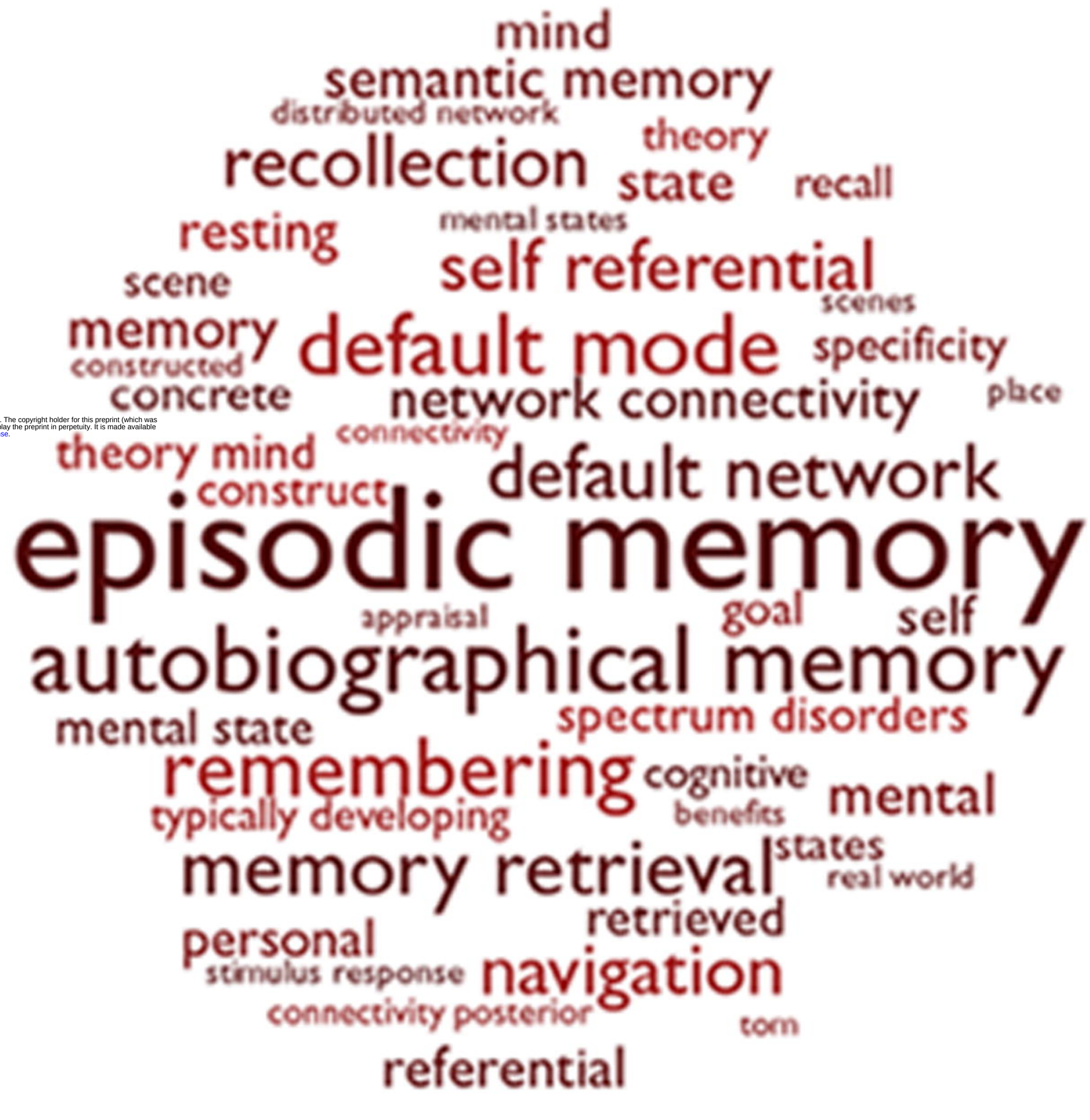

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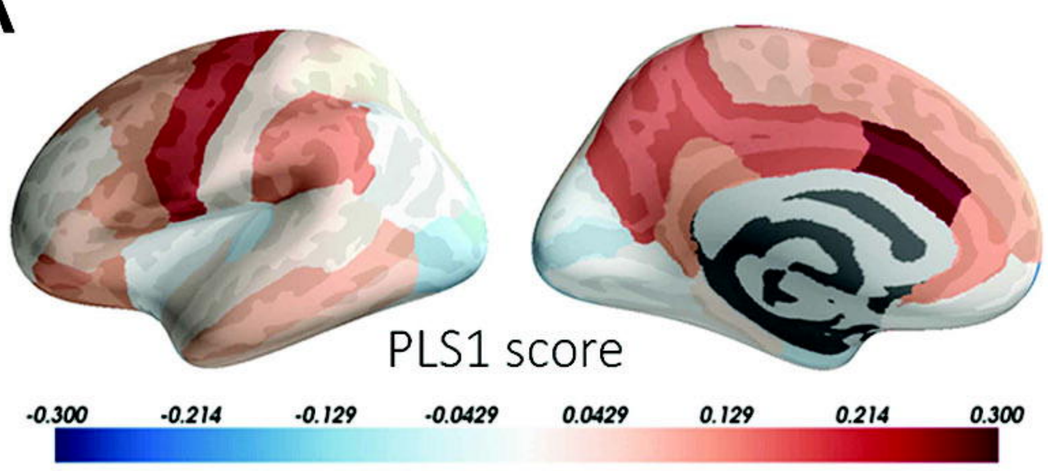
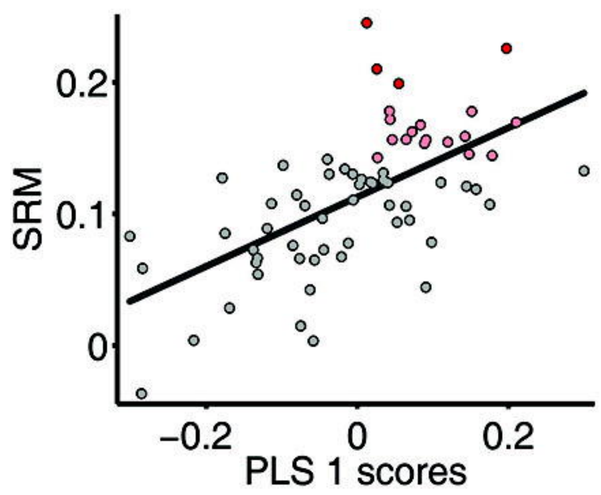
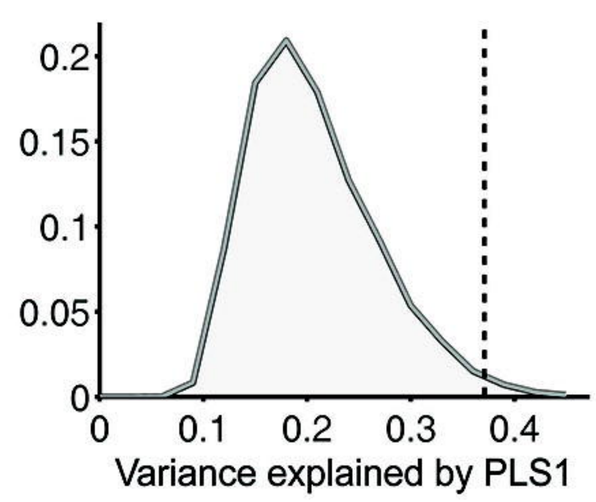






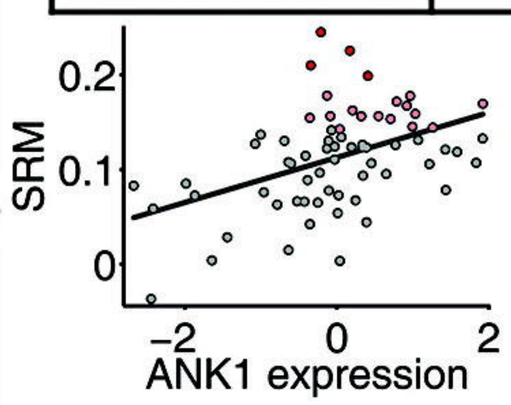
B

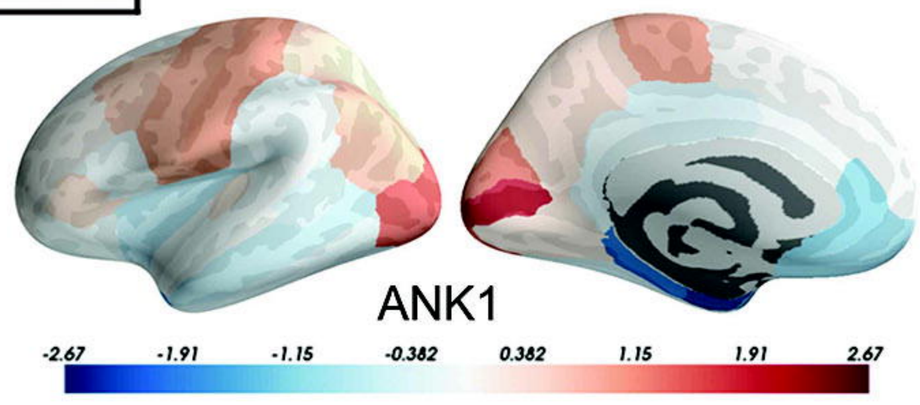
Gene name	PLS1 weight	FDR adjusted p-value
PPP1R28	6.64	$<10^{-5}$
IER2	6.55	$<10^{-5}$
RET	6.53	$<10^{-5}$
TMEM81	6.52	$<10^{-5}$
PPARGC1A	6.50	$<10^{-5}$
KCNC1	6.49	$<10^{-5}$
ANK1	6.47	$<10^{-5}$
...	...	...
ENOSF1	0.15	0.848
ADCY7	0.15	0.848
CD300LD	0.15	0.849
C6orf94	0.15	0.849
VAX2	0.15	0.849
TEF	0.15	0.849
ZBTB40	0.15	0.849
...	...	...
PTPRC	-6.22	$<10^{-5}$
NKAIN2	-6.22	$<10^{-5}$
CCDC90B	-6.26	$<10^{-5}$
ACY3	-6.29	$<10^{-5}$
C6orf173	-6.32	$<10^{-5}$
RBP4	-6.34	$<10^{-5}$

Positively weighted

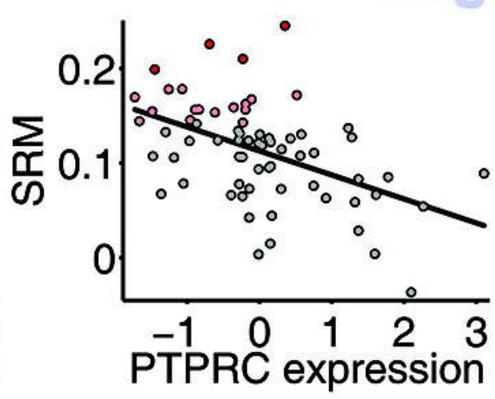
Cellular affiliation	*P*-value
Astrocyte	1
Oligodendrocyte	0.96
Microglia	0.99
Neuron	$<10^{-4}$

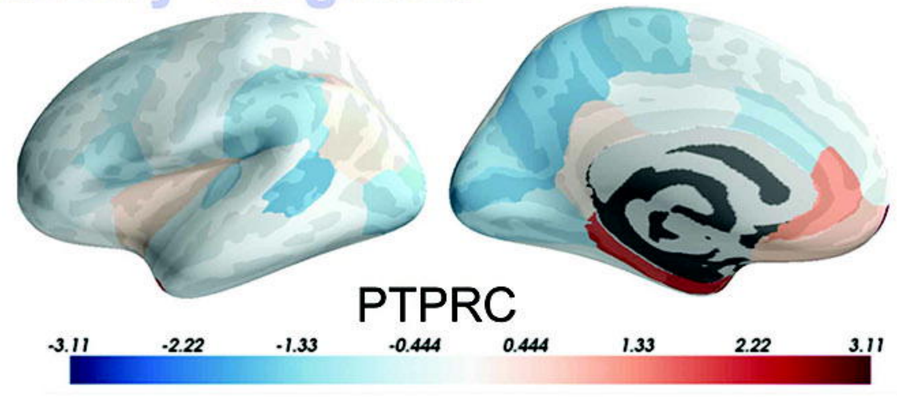
Disease enrichment	*P*-value
Gandal Up-Reg	1
Gandal Down-Reg	$<10^{-4}$
PGC	0.008
DISEASE	0.005





Negatively weighted

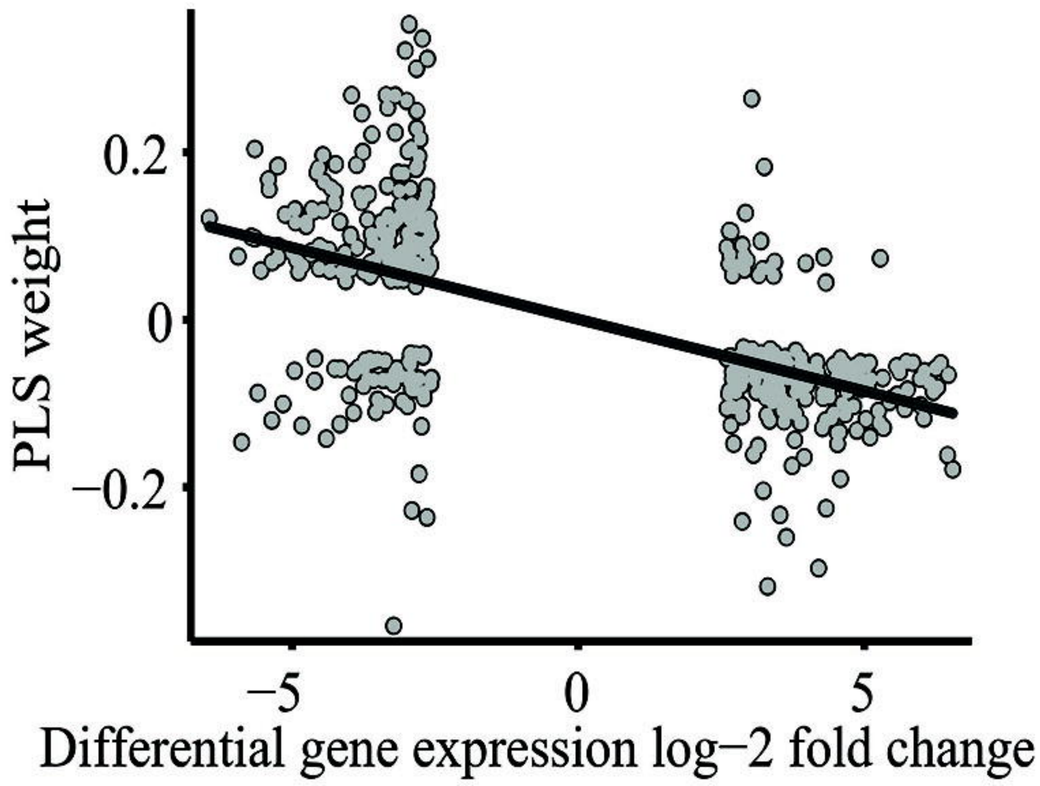


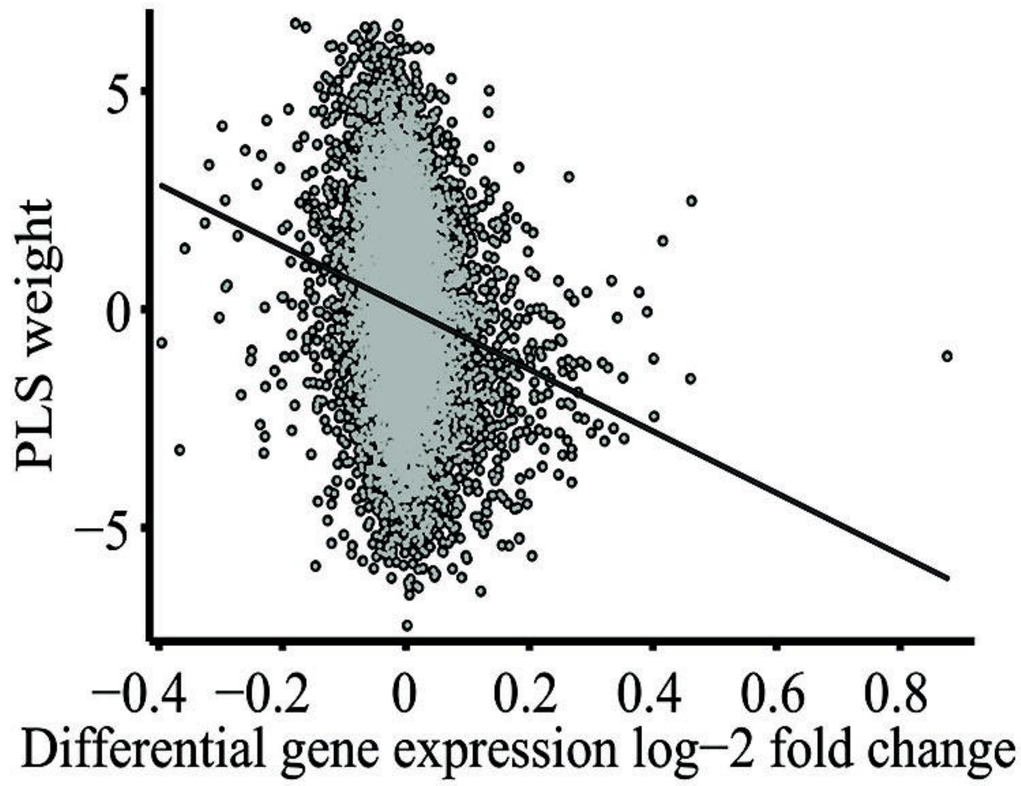


Cellular affiliation	*P*-value
Astrocyte	$<10^{-4}$
Oligodendrocyte	0.39
Microglia	$<10^{-4}$
Neuron	$<10^{-4}$

Disease enrichment	*P*-value
Gandal Up-Reg	$<10^{-4}$
Gandal Down-Reg	1
PGC	0.48
DISEASE	0.49

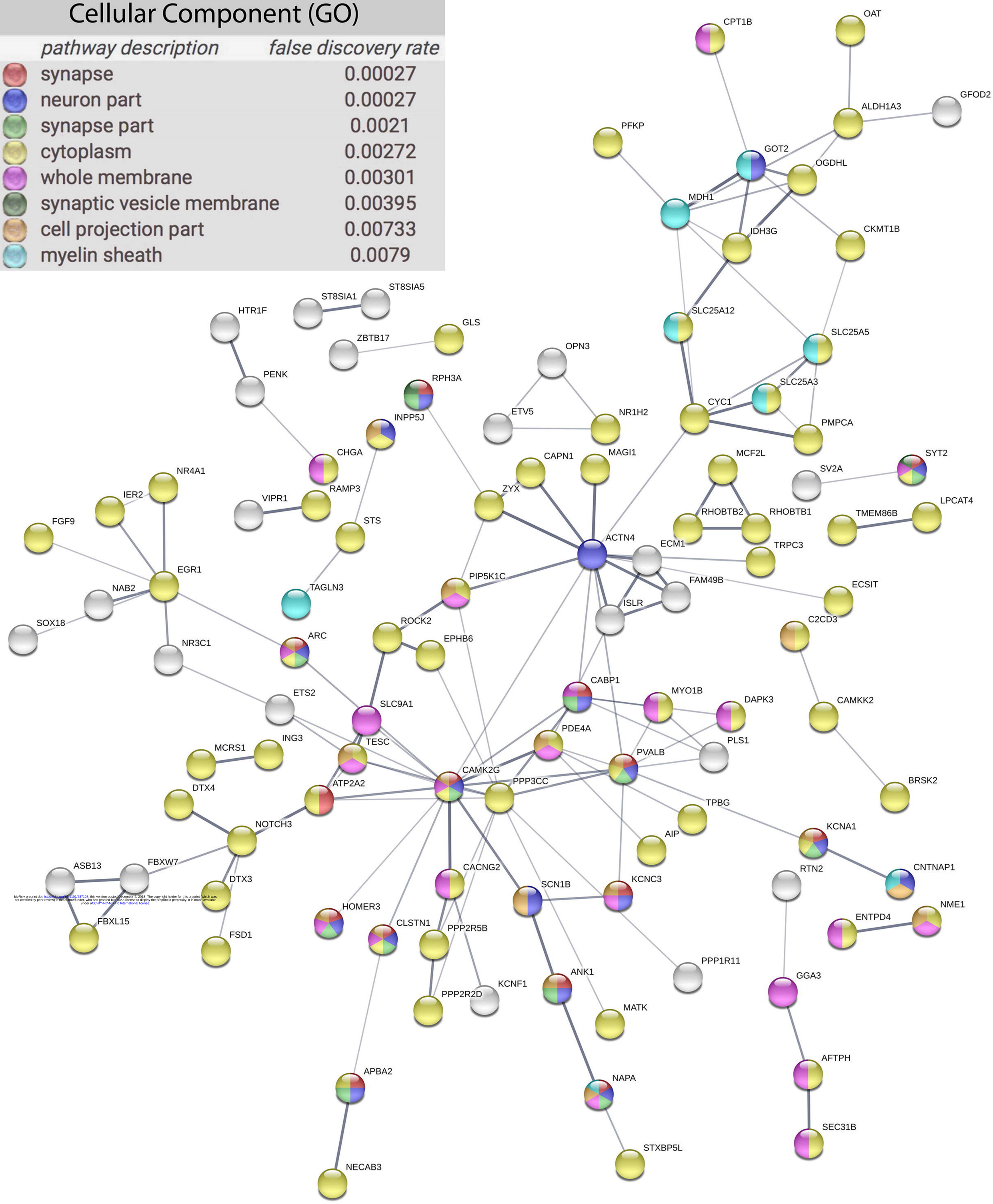
C





Cellular Component (GO)

pathway description	false discovery rate
synapse	0.00027
neuron part	0.00027
synapse part	0.0021
cytoplasm	0.00272
whole membrane	0.00301
synaptic vesicle membrane	0.00395
cell projection part	0.00733
myelin sheath	0.0079



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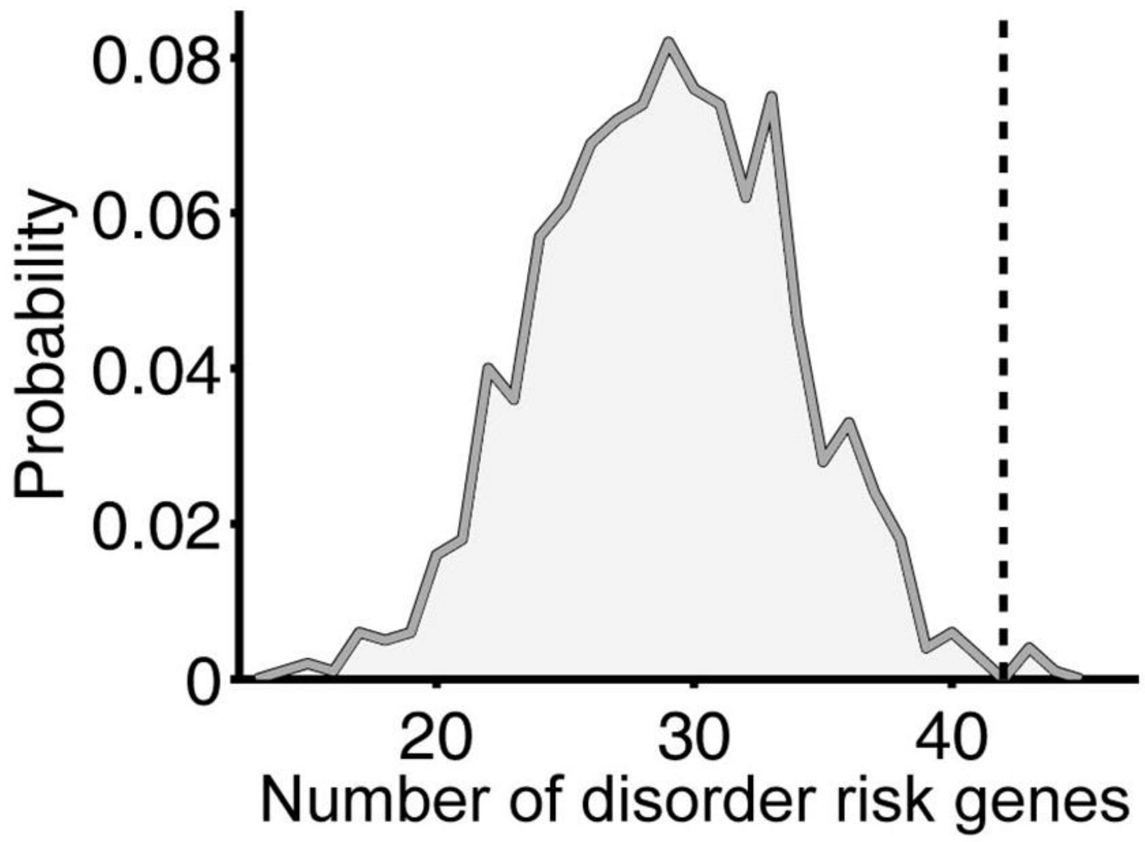

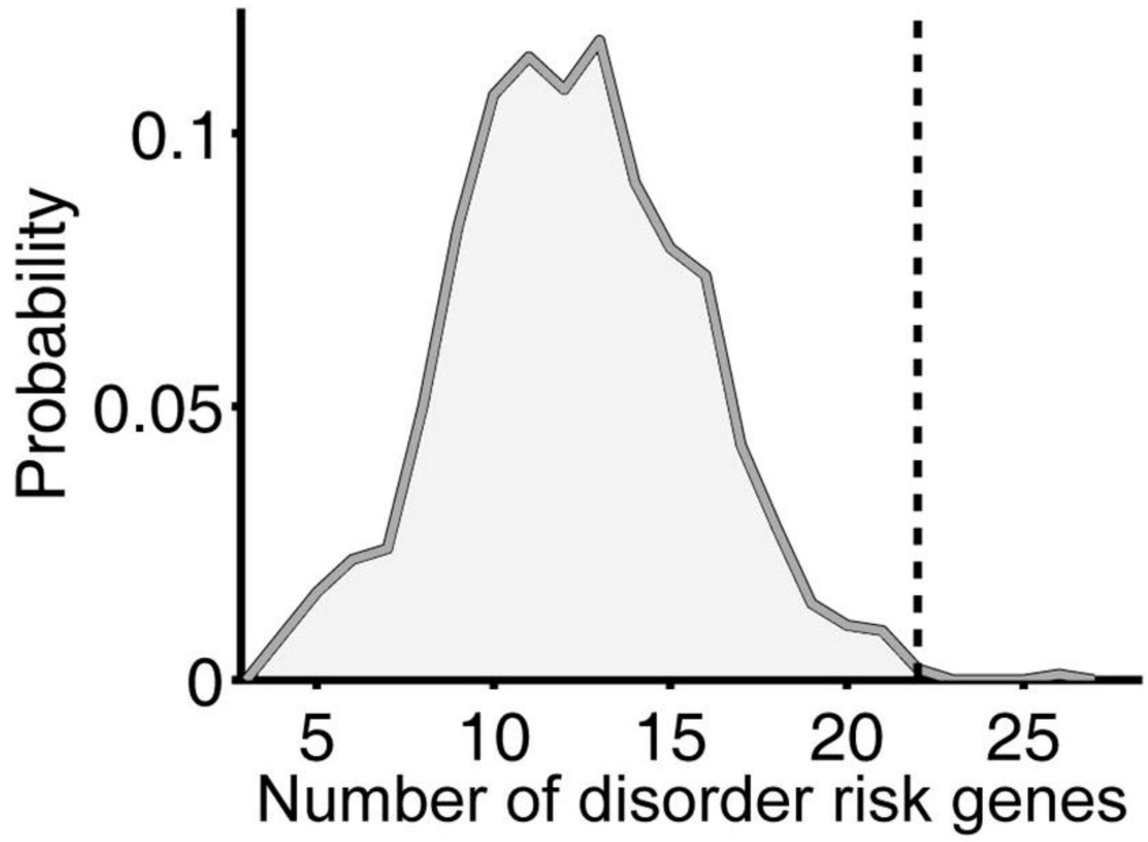

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