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Corresponding Author:
Chunhui Chen
chenchunhuichina@bnu.edu.cn

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RESEARCH

Genome-wide association study of brain functional and structural networks

Ruonan Cheng[1,2], Ruochen Yin[1], Xiaoyu Zhao[1], Wei Wang[1], Gaolang Gong[1], Chuansheng Chen[3], Gui Xue[1], Qi Dong[1], and Chunhui Chen[1]

[1]State Key Laboratory of Cognitive Neuroscience and Learning, and IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China
[2]Education Science Institute, Jilin Engineering Normal University, Jilin, China
[3]Department of Psychological Science, University of California, Irvine, CA, USA

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ABSTRACT

Imaging genetics studies with large samples have identified many genes associated with brain functions and structures, but little is known about genes associated with brain functional and structural network properties. The current genome-wide association study examined graph theory measures of brain structural and functional networks with 497 healthy Chinese participants (17–28 years). Four genes (*TGFB3, LGI1, TSPAN18*, and *FAM155A*) were identified to be significantly associated with functional network global efficiency, and two (*NLRP6* and *ICE2*) with structural network global efficiency. Meta-analysis of structural and functional brain network property confirmed the four functional-related genes and revealed two more (*RBFOX1* and *WWOX*). They were reported to be significantly associated with regional brain structural or functional measurements in the UK Biobank project; and showed differential gene expression level between low and high structure–function coupling regions according to Allen Human Brain Atlas gene expression data. Taken together, our results suggest that brain structural and functional networks had shared and unique genetic bases, consistent with the notion of many-to-many structure–function coupling of the brain.

AUTHOR SUMMARY

Genome-wide association studies on brain were often conducted with regional measurements of the brain (e.g., regional volume, thickness) rather than whole-brain properties. Here we associated whole genome to whole-brain structural and functional network properties (global efficiency, local efficiency, small-worldness), and identified four genes (*TGFB3, LGI1, TSPAN18*, and *FAM155A*) associated with functional brain network and two genes (*NLRP6* and *ICE2*) with structural network. Two more genes (*RBFOX1* and *WWOX*) were identified by meta-analysis. These genes were reported to be associated with brain regional measurements in the UK Biobank project, and they showed differential gene expression level between low and high structure–function coupling regions, suggesting shared and unique genetic bases for functional and structural brain networks.

INTRODUCTION

Genome-wide association studies (GWAS):
Associate each genetic variation on the genome to a phenotype to identify significantly associated ones.

Imaging genetics, a field that investigates the association between genes and the brain, has been advancing rapidly over the past decade. The important role genes play in brain function and structure has been supported by twin studies, which revealed moderate to high heritability of brain function and structure (Kochunov et al., 2016; Thompson et al., 2001); candidate gene studies, which implicated specific genes (Bigos & Weinberger, 2010); and genome-wide association studies (GWAS). The ENIGMA Consortium (https://enigma.ini.usc.edu/) has assembled data from around the world and enabled meta-analyses of brain GWAS with tens of thousands of subjects. Such analyses have identified many genes that contribute to brain structure and function (Grasby et al., 2020; Medland et al., 2022; Satizabal et al., 2019; Thompson et al., 2013, 2014, 2017, 2022). Other large-scale projects include the UK Biobank, the Adolescent Brain Cognitive Development (ABCD) Study, and the Human Connectome Project, all of which have collected multimodality brain imaging data and genomic data and have conducted GWAS on thousands of brain regional measurements (e.g., regional volume, surface area, thickness, white matter fractional anisotropy, and functional activation; see results online at https://open.win.ox.ac.uk/ukbiobank/big40/ and https://bigkp.org/; Elliott et al., 2018; Smith et al., 2021; Zhao et al., 2021, 2022). However, these GWAS have focused on independent regional measurements of brain structure and function, and relatively little is known about genes that contribute to the network properties of the brain networks.

Brain network:
The brain was segmented into many regions, then connected according to the connectivity between pairs of regions to form a network, many indices can be estimated to describe the network.

The brain can be understood as a "small-world" network at the structural and functional level, characterized as a combination of local connectivity and global integration (Bassett & Bullmore, 2006; Bullmore & Sporns, 2009; Sporns, 2013; van den Heuvel & Hulshoff Pol, 2010). Brain network measures reflect whole-brain characteristics that are not captured by regional measurements. In addition, the use of network measures is an effective way of dimensionality reduction of brain imaging data and thus reduces the problem of multiple comparisons.

Just like its regional structure and function, the brain's network measurements have also been shown to be subject to genetic influence (Arnatkeviciute et al., 2021) with a moderate level of heritability (Thompson et al., 2001, 2013). For example, graphological indicators of structural brain networks are significantly heritable ($h2 > 0.5$; Bohlken et al., 2014). Several whole-brain topological properties of resting-state fMRI networks, such as measures of global efficiency, clustering coefficient, path length, and cost efficiency, exhibit heritability ranging from 0.2 to 0.9 (Fornito et al., 2011; Sinclair et al., 2015; van den Heuvel et al., 2013). Another study showed that more than 50% of the variation of functional connectivity can be explained by genetic factors (Ge et al., 2017). Finally, Z. Gu et al. (2021) found that the coupling of brain structure with brain function is highly heritable, even more heritable than structural or functional connectivity. However, these studies were behavior genetics studies that could not have identified specific gene(s).

Thus far, to the best of our knowledge, only one GWAS study has explored which genes contribute to the brain network features (Foo et al., 2021). Based on the UK Biobank sample of 18,445 subjects, Foo et al. performed a GWAS analysis on 18 functional brain network measures, including global efficiency, characteristic path length, modularity, transitivity, and network strength. They found that *SLC25A33, TMEM201*, and *ZEB1* were associated with global efficiency and characteristic path length, and that *SH2B3* and *ATXN2* were associated with the default mode network's strength. Foo et al., however, did not study structural network properties. Given the close connection between brain structure and function, it would be informative to directly compare their relevant genes to identify both shared and unique sets of genes for brain structure and function.

Researchers have discussed the nature of the relation between brain structure and function (Honey et al., 2010; Ponten et al., 2010; Rubinov et al., 2009). On the one hand, brain structure is the physiological basis of function, which means functional networks are limited by structural connections. Confirming such an intuitive view, studies have indeed shown that the presence of a direct structural link between two brain regions is associated with stronger functional interactions between them (Hermundstad et al., 2013; Honey et al., 2007, 2009; Rubinov et al., 2009), that functional configuration of the cerebral cortex reflects underlying anatomical connections (Cohen et al., 2008; Koch et al., 2002; Passingham et al., 2002; Rykhlevskaia et al., 2008; Vincent et al., 2007), and that brain function can be predicted from the structural connection via machine learning (Sarwar et al., 2021).

On the other hand, structure-function mapping is not one-to-one. Studies have found functional connections that have few or no corresponding direct anatomical connections (Damoiseaux & Greicius, 2009; Honey et al., 2007). The structure-function correspondence may be even weaker at the macroscopic scale (Honey et al., 2009). It is believed that the mapping from structure to function is in the form of many-to-many (Suárez et al., 2020), with the same structure being linked to different functions and the same function being supported by different structures (Park & Friston, 2013). Therefore, it is necessary to explore both shared and unique genetic bases of brain structure and function network properties.

The current study is a GWAS of global and local brain network measurements with a sample of healthy Chinese adults. We directly compared genes associated with functional and structural networks to identify their shared and unique genes.

MATERIALS AND METHODS

Participants

Participants were 497 healthy Chinese college students (251 males and 246 females, age range from 17 to 28 years) recruited from Beijing, China. Of them, 485 had both structural and functional brain image data and were included in the structure–function coupling analysis; 484 had both genetic and functional brain image data; and 472 had both genetic and structural brain image data. Participants with missing data typically missed diffusion tensor imaging (DTI) or genetic data. All subjects were Han Chinese, had normal or corrected-to-normal vision, and reported no history of psychiatric diseases, head injuries, or stroke/seizure. The study was approved by the Institutional Review Board of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, China. Written informed consent was obtained from each participant after a complete description of the study procedures.

Diffusion tensor imaging (DTI): An MRI technique that uses anisotropic diffusion to estimate the axonal (white matter) organization of the brain.

Image Acquisition and Preprocessing

All subjects were scanned on a Siemens Trio 3 Tesla MR system in the Brain Imaging Center of Beijing Normal University. During data collection, subjects were required to lie still in the MRI machine, with head movement constrained by a foam pad. They were asked to close their eyes, but remain awake, breathe steadily, relax their minds, and avoid thinking about anything in particular.

The DTI data were acquired using a twice-refocused spin-echo EPI sequence with the following parameters: TR/TE = 8,000 ms/89 ms; matrix = 128 × 128; FOV = 282 × 282 mm; number of slices = 62; voxel size = 2.2 × 2.2 × 2.0 mm^3; 1 b0 volume and 30 directions with b = 1,000 s/mm^2. This procedure was repeated once and images were averaged from the two

Resting-state functional image: Functional MRI scanning during which subjects just have a rest without any specific task to do.

scans for subsequent analyses. Resting-state functional images were acquired with single-shot T2*-weighted gradient-echo EPI sequence, with the following parameters: TR/TE = 2,000 ms/30 ms; flip angle = 90°; FOV = 200 × 200 mm; matrix = 64 × 64; number of slices = 33; voxel size = 3.1 × 3.1 × 3.5 mm^3. A series of 200 images were acquired. A high-resolution 3D anatomical image was acquired for normalization purpose using T1-weighted, three-dimensional, gradient-echo pulse sequence. Parameters for this sequence were as follows: TR/TE/flip angle = 2,530 ms/3.39 ms/7°, field of view = 256 × 256 mm, matrix = 256 × 256, slice thickness = 1.33 mm. A total of 144 sagittal slices were acquired to cover the whole brain.

Resting-state functional images were processed as described before (Feng et al., 2020). Steps included removing first 10 volumes, slice timing correcting, realignment, coregistering and normalizing to the standardized MNI space, linear detrending, nuisance regression, and temporal band-pass filtering (0.01∼0.08 Hz). DTI data were preprocessed using PANDA toolbox default settings (Cui et al., 2013). Standard steps include skull stripping, eddy-current correction, tensor fitting, and the calculation of diffusion tensor metrics as well as spatial normalization.

Brain Network Construction and Analysis

Brainnetome Atlas (Fan et al., 2016) excluding the cerebellum was used to define nodes (246 brain regions); connectivity between pairs of nodes were defined as edges of structural and functional networks. Functional connectivity was measured as the Pearson correlation between mean time courses for each pair of nodes. Structural connectivity between regions was estimated as connection probability calculated by probabilistic tractography. The probabilistic diffusion tractography is used because of the evidence that the heritability estimates of graph theoretic metrics are higher with probabilistic algorithms than with deterministic algorithms (Zhan et al., 2015).

The functional and structural connectivity matrices of all subjects were fed into the GRETNA v2.1 toolbox for graph theoretical network analysis (Wang et al., 2015). The structural connectivity matrices were binarized at a threshold of 0, that is, having or not having a connection. Sparsity of the functional network was set to 0.5 so that it would be comparable to that of the structural network (0.5816). The following graph theory measures were calculated: clustering coefficient (C_p), local efficiency (E_{loc}), and normalized clustering coefficient (γ), which all represent the local characteristics of the network; shortest path length (L_p), global efficiency (E_g), and normalized shortest path length (λ), which all represent the global characteristics of the network; and small-worldness (σ), which represents small-world characteristics.

Genotyping

The genotyping procedures for this dataset were previously reported in detail in Chen et al. (2020). Briefly, DNA was extracted from blood samples and genotyped using Infinium chips (Illumina, San Diego, CA, USA). The resulting data were then imputed using the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html) with the 1000G Phase 3 EAS population as a reference. To ensure high-quality data, the imputed data were further cleaned by only keeping single-nucleotide polymorphisms (SNPs) with an imputation quality of r2 > 0.8, a minor allele frequency of MAF > 0.05, and a Hardy-Weinberg equilibrium of HWE > 1E−6, resulting in a total of 4,856,474 SNPs.

Statistical Analysis

Structure–function coupling was measured as the Pearson correlation between the corresponding functional and structural network measures, as well as for each edge across subjects. The significant edges were classified as within or between subnetworks. The seven subnetworks of Yeo (Yeo et al., 2011) were used, resulting in 28 categories (seven within-subnetwork connectivity and 21 between-subnetwork connectivity). Enrichment patterns among subnetworks were calculated as described in a previous article (Feng et al., 2022). First, enrichment fold was calculated as the ratio of the actual observed number of coupling edges within the category and the expected number (the number of significant edges times the number of edges within a category divided by the number of total edges). Significance level was then estimated by permutation, that is, randomly selecting the same number of significant edges and calculating enrichment fold, and repeating the procedure 10,000 times to obtain a null distribution.

Genome-wide association analyses were performed using linear regression models in PLINK1.9 (https://www.cog-genomics.org/plink/1.9/), with genetic markers as predictors and each of the graph theory measures as the dependent variable; age, gender, and 10 principal components of the genomes were included as covariates. The results of the whole genome analysis of each graph theory measure were presented in a Manhattan plot. Next, the summary statistics from the GWAS were input into MAGMA (de Leeuw et al., 2015). The gene definition was obtained from the MAGMA website (https://ctg.cncr.nl/software/magma) using the NCBI37.3 version, resulting in 17,285 genes. The SNP-level statistical significance threshold was set to $p < 5E{-}8$, and the gene-level threshold was set (after Bonferroni correction) at $p < 2.89E{-}6$ (0.05/17,285).

To identify genes that were associated with both brain structural and functional characteristics, a meta-analysis was conducted using METAL (https://www.sph.umich.edu/csg/abecasis/metal/; Willer et al., 2010). GWAS summary statistics of each measurement of the structural and functional networks were meta-analyzed. The resulting GWAS results were fed to MAGMA for gene-level analysis.

To further confirm the effects of the identified genes on brain structure and function, we searched the UK Biobank Oxford Brain Imaging Genetics Server (https://open.win.ox.ac.uk/ukbiobank/big40/), which contains the GWAS results for almost 4,000 imaging-derived phenotypes from the multimodal brain imaging data in the UK Biobank (with 40,000 subjects, based on the imaging data release from early 2020). The discovery sample size was 22,138 and the replication sample size was 11,086. Chromosomes 1:22 and X were all included, and the resulting number of SNPs was 17,103,079.

Finally, we explored the gene expression data of the identified genes using the Allen Human Brain Atlas (https://human.brain-map.org; Hawrylycz et al., 2012), which includes brain-wide gene expression data from six postmortem brains (one female, ages 24.0~57.0, 42.50 ± 13.38). We downloaded and processed the data with the abagen toolbox (version 0.1.3; https://github.com/rmarkello/abagen; Arnatkeviciute et al., 2019; Markello et al.,

Table 1. Coupling of brain network indices between structural and functional networks.

	C_p	L_p	λ	γ	σ	E_{loc}	E_g
r	−0.08	0.11	−0.09	−0.11	−0.09	0.07	0.10
p	0.09	0.02	0.04	0.02	0.04	0.12	0.03

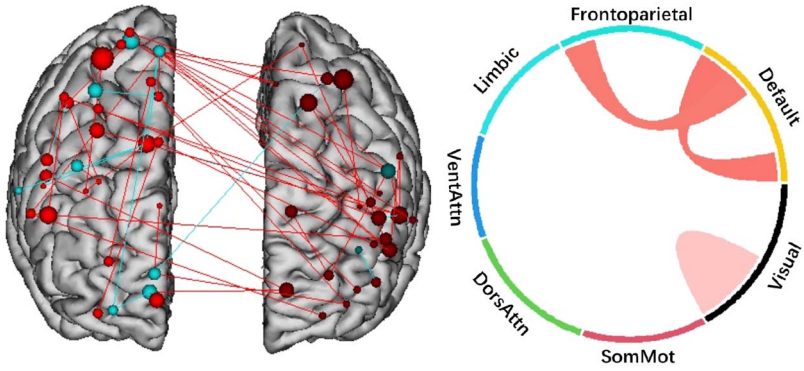

Figure 1. Significant structure–function coupling edges and their enrichment within/between subnetworks.

2021) using the 246-region Brainnetome Atlas in the MNI space. We selected the "centroids" option to deal with brain regions that were not assigned any sample from any donor. For all other settings, we used the default. This resulted in a matrix of expression level of 15,633 genes within 246 brain regions. The 246 brain regions were divided into two groups: low (n = 96 regions) and high (n = 150 regions) structure–function coupling regions. A two-sample test was then used to compare the expression level of each gene between these two groups of regions.

RESULTS

Structure–Function Coupling

Table 1 shows Pearson correlations between the measures of structural and functional brain networks. They were all nonsignificant after Bonferroni correction. Of the total 30,135 edges, however, 476 were significantly correlated at $p < 0.01$. These significant edges were enriched within the visual network and the default mode network, as well as between the frontoparietal network and the default mode network (Figure 1). These results indicate that the structure–function coupling was not captured by whole-brain connectivity patterns but was evident for some subnetworks.

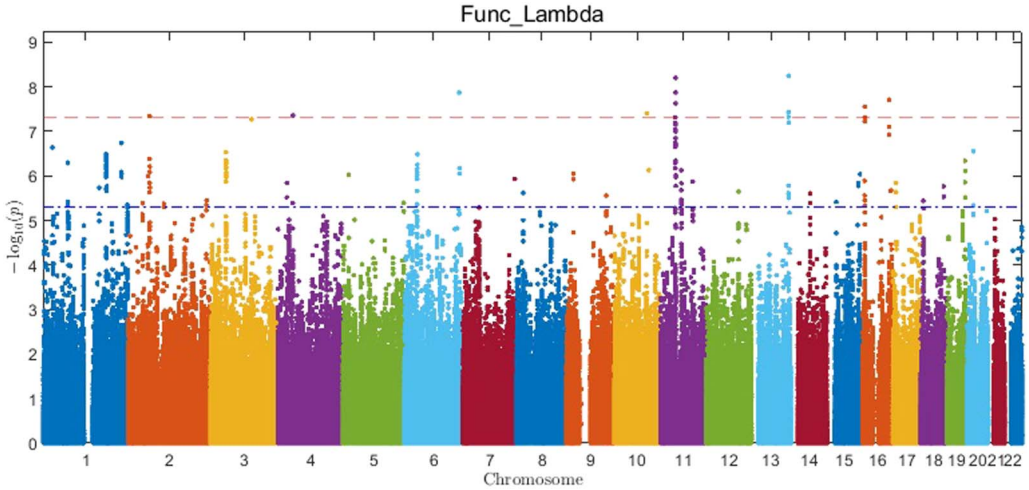

Figure 2. Manhattan plot for λ of the functional brain network, with the blue dotted line representing suggestive threshold p = 5E−6 and the red dotted line representing genome-wide significant results p = 5E−8.

Table 2. Loci significantly associated with λ of the functional network.

CHR	Leading SNP	BP	A1	Beta	*SE*	*Z*	*P*	Total number of significant SNPs	Region of SNPs (bp)	Gene
2	rs4671567	64598021	G	6.68E−06	1.20E−06	5.56	4.55E−08	1	64598021	–
4	rs142920507	44605055	T	6.98E−06	1.26E−06	5.57	4.40E−08	1	44605055	–
6	rs6923410	162105755	A	6.77E−06	1.17E−06	5.78	1.34E−08	1	162105755	*PRKN*
10	rs7099034	95545378	C	7.10E−06	1.27E−06	5.59	3.89E−08	1	95545378	*LGI1*
11	rs7928632	44873126	T	7.72E−06	1.31E−06	5.92	6.25E−09	7	44855750–44873126	*TSPAN18*
13	rs7336849	108230531	A	8.10E−06	1.36E−06	5.94	5.58E−09	4	108230531–108248045	*FAM155A*
16	rs79153854	79112865	T	7.26E−06	1.27E−06	5.72	1.93E−08	4	7420635–79112865	*WWOX*

GWAS of Functional Brain Network Measures

Of the seven brain network indices investigated, only λ showed genome-wide significant results ($p < 5E{-}8$; see Figure 2). Both linkage disequilibrium score regression intercept (1.0026 ± 0.0071) (Bulik-Sullivan et al., 2015) and Q-Q plot genome control (0.9515) showed no inflation. These significant SNPs are located on chromosomes 2, 4, 6, 10, 11, 13, and 16. Detailed information of the significant loci with leading SNPs and mapped genes are shown in Table 2. Gene effects on other brain network indices were weaker, with some SNPs showing effects of $p < 5E{-}6$, but none reached genome-wide significance of $p < 5E{-}8$ (Figure S1 in the Supporting Information).

MAGMA gene-based analysis confirmed the effect of SNPs on chromosomes 10, 11, and 13 on λ of the functional network (see Table 3). The genes with significant effects included *LGI1, TSPAN18*, and *FAM155A*. In addition, *TGFB3*, located on chromosome 14, showed a

Table 3. Significant genes for functional and structural network indices identified by MAGMA.

Gene	Graph theory measures	CHR	Start	Stop	Function		Structure	
					Z	*P*	*Z*	*P*
TGFB3	E_g	14	76424440	76449334	4.91	4.62E−7*	−0.64	0.61
TGFB3	L_p	14	76424440	76449334	5.36	4.06E−8*	−0.69	0.63
LGI1	λ	10	95517566	95557916	4.14	6.62E−7*	−0.64	0.63
TSPAN18	λ	11	44748731	44953978	4.82	7.10E−7*	−1.51	0.88
FAM155A	λ	13	107820879	108519460	4.43	2.16E−7*	−0.46	0.45
NLRP6	λ	11	278570	285388	0.94	0.14	4.81	7.56E−7*
ICE2	λ	15	60711808	60771359	2.93	1.72E−03	4.71	1.24E−6*

* Significant after Bonferroni correction ($p < 2.89e{-}6$).

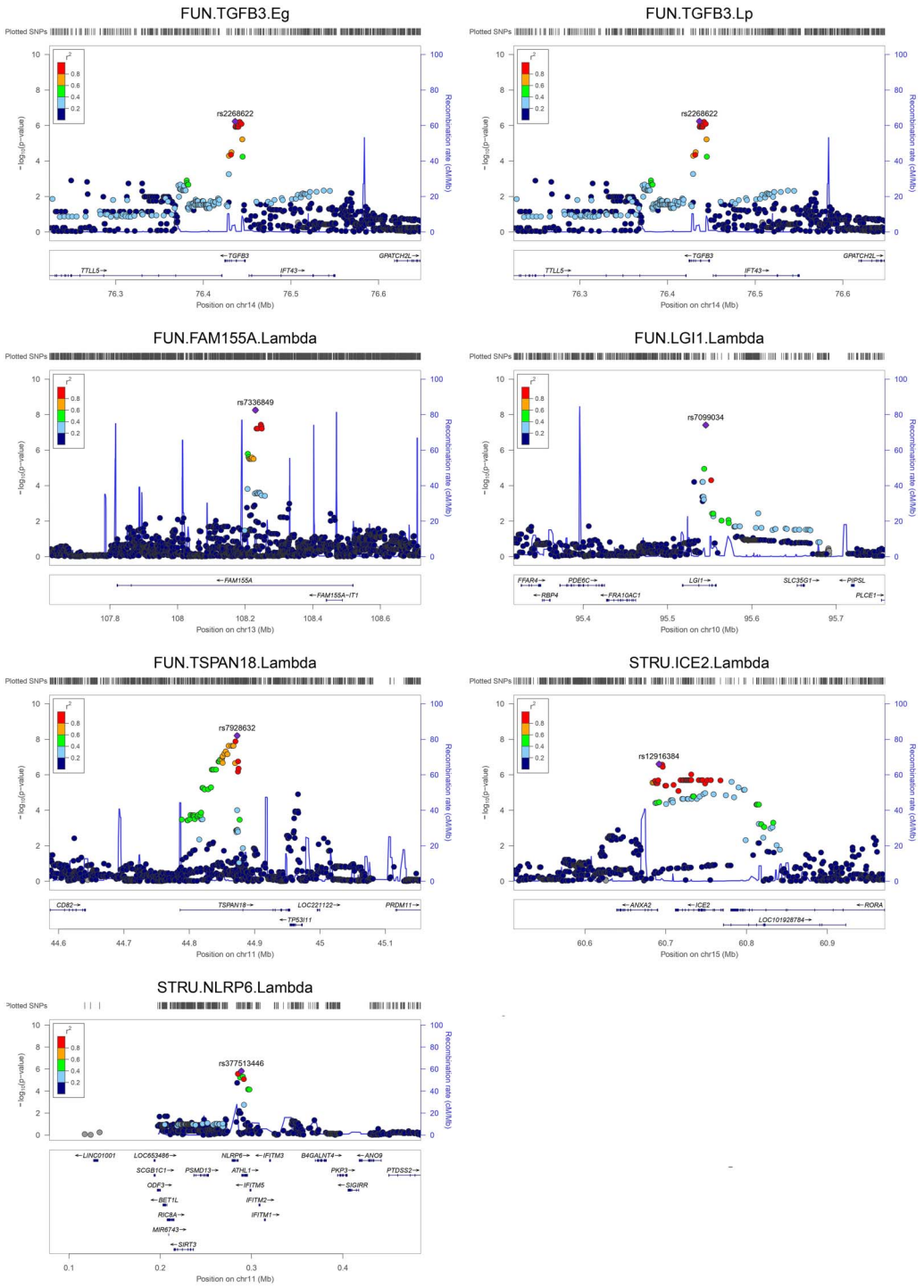

Figure 3. Regional gene effects on network measurements for each gene identified by MAGMA, plotted by LocusZoom.

significant effect on L_p and E_g of the functional network at the gene level (see Table 3). Details of regional genetic effects of these genes are shown in Figure 3 with LocusZoom (Pruim et al., 2010). Many SNPs in the gene regions showed relatively large effects, supporting the idea that their cumulative effects at the gene level are strong.

Table 4. Significant genes based on the meta-analysis identified by MAGMA.

Gene	Graph theory measures	CHR	Start	Stop	*Z*	*P*
TGFB3	E_g	14	76424440	76449334	5.11	1.61E−7*
TGFB3	L_p	14	76424440	76449334	5.14	1.38E−7*
LGI1	λ	10	95517566	95557916	4.64	2.88E−8*
TSPAN18	λ	11	44748731	44953978	4.94	3.88E−7*
FAM155A	λ	13	107820879	108519460	4.28	4.36E−7*
RBFOX1	λ	16	5289469	7763342	4.32	2.54E−6*
WWOX	λ	16	78133310	79246567	3.99	2.50E−6*

* Significant after Bonferroni correction ($p < 2.89e–6$).

GWAS of Structural Brain Network Measures

Gene effects on structural brain network measures were weaker compared with those on functional network measures. No SNP had an effect on structural indices reaching genome-wide significance. Nevertheless, many SNPs showed suggestive effects (Figure S2 in the Supporting Information). MAGMA gene-based analysis captured some of these effects, with λ of the structural network being significantly associated with *NLRP6* and *ICE2* (Table 3). LocusZoom showed that many SNPs within these regions, including some other genes close to *NLRP6*, had moderate effects, suggesting a strong cumulative effect at the gene level (Figure 3). Table 3 also seems to suggest that there is a certain degree of double disassociation between genes associated with function and structure brain network measurements, suggesting differential genetic mechanisms on brain structure and function.

Meta-Analysis of GWAS Results on the Functional and Structural Networks

The meta-analysis of GWAS results on structural and functional network indices showed that only λ was significantly associated with some SNPs ($p < 5e−8$) (Supporting Information Figure S3). MAGMA analysis identified six significant genes for λ (Table 4), including *LGI1, TSPAN18, FAM155A, RBF0X1*, and *WW0X*. The meta-analysis on E_g and L_p also revealed a significant effect of *TGFB3* (Table 4). These results were highly similar to those based on the functional network (except for the newly identified *RBF0X1* and *WW0X*), suggesting that these meta-analysis results were to some extent driven by those of the functional network GWAS.

Validation With Data From the UK Biobank

Although the phenotypes we used in this study (brain network measures) were different from those in the UK Biobank database (regional measurements derived from multimodal neuroimaging data), it would be informative to explore whether there was converging evidence. Results showed that for the genes identified in our study, each was associated with multiple regional measurements (Supporting Information Table S1). Specifically, *TGFB3* was associated with some DTI measurements; *LGI1, FAM155A*, and *ICE2* were associated with resting-state functional connectivity; *TSPAN18* and *RBFOX1* were associated with the area and volume of many regions; and *NLRP6* was associated with DTI and resting-state fMRI indices. These results confirmed the contribution of these genes to brain structure and function.

Table 5. Gene expression difference between high and low structure–function coupling subnetworks.

Gene	*t*	*df*	*p*
TGFB3	−1.50	244	0.13
LGI1	−1.77	244	0.08
TSPAN18	−4.21	244	3.53E−5
FAM155A	3.25	244	1.30E−3
RBFOX1	4.50	244	1.04E−5
WWOX	−4.06	244	6.51E−5
ICE2	−3.55	244	4.71E−4
*NLRP6**			

* Data were not available in the processed Allen Human Brain Atlas database.

Validation With Data From the Allen Human Brain Atlas

Because the edges with high structure–function coupling were mainly enriched within the visual network and the default mode network, as well as between the frontoparietal network and the default mode network, we explored the identified genes' expression patterns in these subnetworks as compared with those in the other brain regions. The Allen Human Brain Atlas gene expression data showed that *TSPAN18, WWOX*, and *ICE2* showed lower levels of expression in these high structure–function coupling subnetworks than in the low structure–function coupling regions, whereas *FAM155A* and *RBFOX1* showed the opposite pattern (i.e., higher levels of expression in these regions). See Table 5.

DISCUSSION

The current study for the first time explored genes that are commonly or specifically associated with brain functional and structural network properties. Overall, we identified eight significant genes. *TGFB3, LGI1, TSPAN18*, and *FAM155A* were significantly associated with functional network global efficiency; and *NLRP6* and *ICE2* were significantly associated with structural network global efficiency. The meta-analysis combining structural and functional brain network properties further identified *RBFOX1* and *WWOX* in addition to confirming the four genes associated with functional network global efficiency mentioned above. Most of these genes have been associated with regional brain measures according to the published UK Biobank database. These genes also showed significantly higher or lower expression levels in high structure–function coupling subnetworks than in low structure–function coupling subnetworks. In the following paragraphs, we will discuss these genes and their roles in neuron growth or mental disorders.

The *TGFB3* gene is expressed as transforming growth factor beta 3 (TGFB3) in the developing and adult brain. This protein plays a role in the development and function of the nervous system and has been implicated in various processes including neural development, axon guidance, synapse formation, and plasticity (Hao et al., 2008). A study demonstrated that TGFB3 also plays a role in promoting axon outgrowth and guidance in the developing and injured nervous system (Watabe & Miyazono, 2009).

LGI1 is expressed in the brain and is thought to play a role in brain development and neurological disorders. Mutations in the *LGI1* gene have been associated with a number of

neurological disorders, including epilepsy and encephalitis (Cowell, 2014). A data-driven study that combines resting-state fMRI and DTI investigated the neural mechanisms of anti-LGI1 encephalitis associated with the *LGI1* gene, and found that compared with the control group, the functional connectivity of brain regions related to memory, cognition, and motor is decreased in subjects with anti-LGI1 encephalitis, indicating that the *LGI1* gene may be involved in widespread changes in brain connectivity and microstructure (Qiao et al., 2020). Some studies have also suggested that *LGI1* may be involved in the development of gliomas (W. Gu et al., 2005). A study on mouse brains also demonstrates that *LGI1* may be an important player in cerebellar and cortical development (Su et al., 2015).

TSPAN18 encodes a transmembrane protein that plays an important role in cell membranes. In the nervous system, tetraspanin-18 (TSPAN18) may be involved in the calcium-signaling pathway linked to dopamine-induced apoptosis of cortical neurons, and it is considered to be an important mechanism in the pathogenesis of schizophrenia (Noy et al., 2019). Tspan18 may be involved in regulating the formation and maintenance of neuronal connections (cranial neural crest), that is, the formation and function of brain networks (Fairchild & Gammill, 2013). Studies suggest that *TSPAN18* expression in glial cells may be associated with brain development and may play a role in neurodegenerative diseases (L. Wu et al., 2016).

FAM155A is a gene located on chromosome 13 and is expressed on the neuronal cell membrane. Although the function of the FAM155A protein is not fully understood, some studies suggest that it may be involved in the signaling processes on the cell membrane (Kang & Chen, 2022; Kschonsak et al., 2022). More research is needed to determine the relationship between the *FAM155A* gene and the brain or brain networks.

NLRP6 has been shown in previous studies to interact with *SP1* to enhance malignant behavior, immune evasion, and radiation resistance in glioma cells (Yu et al., 2021). Research on animals has shown that Nlrp6 also has pro-inflammatory effects in brain injury, and can improve brain damage after cerebral hemorrhage (Coe et al., 2019).

The *ICE2* (inducer of CBF expression 2) is a gene that encodes a transcription factor and is involved in plant adaptation and response to environmental stress (Cai et al., 2019; C. L. Wu et al., 2021). Guelfi et al. (2019) demonstrated that the *ICE2* gene is associated with canine blood cell neuroplasticity and has an interactive effect with the environment.

The protein encoded by the *RBFOX1* (RNA binding fox-1 homolog 1) gene is involved in the regulation of alternative splicing of pre-mRNA. Studies have found that *RBFOX1* is expressed at high levels in the brain and is involved in the regulation of the expression of several key neural development and function-related genes. For example, it plays an important role in neuronal migration and synaptic network formation during cortical development (Hamada et al., 2016). Dysregulation of *RBFOX1* has been linked to several neurodevelopmental disorders, including autism and intellectual disability (Bill et al., 2013).

The *WWOX* gene may play an important role in brain development. Studies suggest that *WWOX* may be associated with neurodevelopment in the brain and may play a role in the repair process after brain injury (Kośla et al., 2020). *WWOX* was initially found to potentially suppress tumors, but more recently it has been linked to several central nervous system disorders, including ADHD, Alzheimer's disease, and autism (Aldaz & Hussain, 2020). It has been determined that when the function of WWOX is impaired, it can lead to a range of neurodegenerative conditions (Aldaz & Hussain, 2020; Kośla et al., 2020). While the specific molecular processes behind these conditions have yet to be fully understood, it is clear that *WWOX* plays a significant role in the normal development and functioning of the central nervous system.

In summary, the genes identified in our study are usually related to brain development, the growth and development of nerve cells, and neurological disorders. L_p, E_g, and λ all represent the information transfer capacity and efficiency of the global network, suggesting that the effects of these genes on the brain are dispersive rather than focused. More broadly, our results are consistent with the evidence of high heritability of brain structure–function coupling (Z. Gu et al., 2021). Our finding of both overlapping and distinct genes associated with brain structure and function is also consistent with the notion that the coupling of brain function and structure is not one-to-one but many-to-many mapping (see Introduction). Some genes influence whole-brain functional and structural connection, which contributed to structure–function consistency, whereas other genes influence either brain function or brain structure.

Studies of the UK Biobank (Elliott et al., 2018; Smith et al., 2021) have found that regional indices of brain structure have higher heritability and show stronger gene effects than do regional indices of brain function. In contrast, we found that the functional brain's global network indices showed stronger gene effects than did structural brain's global network indices. This inconsistency may be due to at least two differences in the studies: regional versus global network indices, and Chinese versus European participants. Consistent with our results, Z. Gu et al. (2021) also found the heritability of structure–function coupling is more correlated with heritability of functional connectivity compared with that of structural connectivity with European participants. Another study of Europeans also found that gene co-expression and SNPs were consistently more strongly related to functional than to structural connectivity (Bertolero et al., 2019). They further found that the connectivity of brain network modules was primarily encoded by sets of genes that are mostly nonoverlapping for different pairs of modules.

Foo et al. (2021) performed a GWAS based on UK Biobank large-sample data for graph theory measures of resting-state functional brain networks, but they found genes that are different from ours. Several reasons could cause this result. First, there could be a population difference that different genes affect brain structural and functional organization between Easterners and Westerners. Second, since our sample size was not large, it may have lacked power to detect genes with smaller effect sizes. Third, Foo et al. constructed weighted undirected networks, but we used binarized networks. As Foo et al. pointed out, constructing weighted networks avoided setting subjective binary thresholds, but they were more affected by non-neural noise. Weighted networks may capture more information, but binary networks were more often used in other studies (Bassett & Bullmore, 2017; Q. Wu et al., 2023). We further run weighted network analysis on our dataset but failed to find any significant gene. However, both Foo et al. and the current study found stronger genetic effects on global (E_g and L_p) compared with local characteristics of the network, suggesting that genes may have widespread effects on the brain. Still, the current study was the first effort to explore the common and unique genes that influence brain functional and structural networks, and the results should be interpreted with caution.

SUPPORTING INFORMATION

Supporting information for this article is available at https://doi.org/10.1162/netn_a_00356.

AUTHOR CONTRIBUTIONS

Ruonan Cheng: Formal analysis; Writing – original draft. Ruochen Yin: Formal analysis. Xiaoyu Zhao: Methodology. Wei Wang: Formal analysis. Gaolang Gong: Funding acquisition; Project administration. Chuansheng Chen: Writing – review & editing. Gui Xue: Supervision. Qi Dong: Supervision. Chunhui Chen: Funding acquisition; Supervision; Writing – review & editing.

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REFERENCES

Aldaz, C. M., & Hussain, T. (2020). WWOX loss of Function in neurodevelopmental and neurodegenerative disorders. *International Journal of Molecular Sciences*, *21*(23), 8922. https://doi.org/10.3390/ijms21238922, PubMed: 33255508

Arnatkeviciute, A., Fulcher, B. D., & Fornito, A. (2019). A practical guide to linking brain-wide gene expression and neuroimaging data. *NeuroImage*, *189*, 353–367. https://doi.org/10.1016/j.neuroimage.2019.01.011, PubMed: 30648605

Arnatkeviciute, A., Fulcher, B. D., Oldham, S., Tiego, J., Paquola, C., Gerring, Z., Aquino, K., Hawi, Z., Johnson, B., Ball, G., Klein, M., Deco, G., Franke, B., Bellgrove, M. A., & Fornito, A. (2021). Genetic influences on hub connectivity of the human connectome. *Nature Communications*, *12*(1), 4237. https://doi.org/10.1038/s41467-021-24306-2, PubMed: 34244483

Bassett, D. S., & Bullmore, E. (2006). Small-world brain networks. *Neuroscientist*, *12*(6), 512–523. https://doi.org/10.1177/1073858406293182, PubMed: 17079517

Bassett, D. S., & Bullmore, E. (2017). Small-world brain networks revisited. *Neuroscientist*, *23*(5), 499–516. https://doi.org/10.1177/1073858416667720, PubMed: 27655008

Bertolero, M. A., Blevins, A. S., Baum, G. L., Gur, R. C., Gur, R. E., Roalf, D. R., Satterthwaite, T. D., & Bassett, D. S. (2019). The human brain's network architecture is genetically encoded by modular pleiotropy. *arXiv*. https://doi.org/10.48550/arXiv.1905.07606

Bigos, K. L., & Weinberger, D. R. (2010). Imaging genetics—Days of future past. *NeuroImage*, *53*, 804–809. https://doi.org/10.1016/j.neuroimage.2010.01.035, PubMed: 20080192

Bill, B. R., Lowe, J. K., Dybuncio, C. T., & Fogel, B. L. (2013). Orchestration of neurodevelopmental programs by RBFOX1: Implications for autism spectrum disorder. *International Review of Neurobiology*, *113*, 251–267. https://doi.org/10.1016/B978-0-12-418700-9.00008-3, PubMed: 24290388

Bohlken, M. M., Mandl, R. C. W., Brouwer, R. M., van den Heuvel, M. P., Hedman, A. M., Kahn, R. S., & Hulshoff Pol, H. E. (2014). Heritability of structural brain network topology: A DTI study of 156 twins. *Human Brain Mapping*, *35*(10), 5295–5305. https://doi.org/10.1002/hbm.22550, PubMed: 24845163

Bulik-Sullivan, B. K., Loh, P.-R., Finucane, H. K., Ripke, S., Yang, J., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Patterson, N., Daly, M. J., Price, A. L., & Neale, B. M. (2015). LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics*, *47*(3), 291–295. https://doi.org/10.1038/ng.3211, PubMed: 25642630

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, *10*(3), 186–198. https://doi.org/10.1038/nrn2575, PubMed: 19190637

Cai, X., Magwanga, R. O., Xu, Y., Zhou, Z., Wang, X., Hou, Y., Wang, Y., Zhang, Y., Liu, F., & Wang, K. (2019). Comparative transcriptome, physiological and biochemical analyses reveal response mechanism mediated by *CBF4* and *ICE2* in enhancing cold stress tolerance in *Gossypium thurberi*. *AoB Plants*, *11*(6), plz045. https://doi.org/10.1093/aobpla/plz045, PubMed: 31777648

Chen, C., Chen, C., Xue, G., Dong, Q., Zhao, L., & Zhang, S. (2020). Parental warmth interacts with several genes to affect executive function components: A genome-wide environment interaction study. *BMC Genetics*, *21*(1), 11. https://doi.org/10.1186/s12863-020-0819-8, PubMed: 32019487

Coe, B. P., Stessman, H. A. F., Sulovari, A., Geisheker, M. R., Bakken, T. E., Lake, A. M., Dougherty, J. D., Lein, E. S., Hormozdiari, F., Bernier, R. A., & Eichler, E. E. (2019). Neurodevelopmental disease genes implicated by de novo mutation and copy number variation morbidity. *Nature Genetics*, *51*, 106–116. https://doi.org/10.1038/s41588-018-0288-4, PubMed: 30559488

Cohen, A. L., Fair, D. A., Dosenbach, N. U. F., Miezin, F. M., Dierker, D., Van Essen, D. C., Schlaggar, B. L., & Petersen, S. E. (2008). Defining functional areas in individual human brains using resting functional connectivity MRI. *NeuroImage*, *41*(1), 45–57. https://doi.org/10.1016/j.neuroimage.2008.01.066, PubMed: 18367410

Cowell, J. K. (2014). LGI1: From zebrafish to human epilepsy. *Progress in Brain Research*, *213*, 159–179. https://doi.org/10.1016/B978-0-444-63326-2.00009-0, PubMed: 25194489

Cui, Z., Zhong, S., Xu, P., He, Y., & Gong, G. (2013). PANDA: A pipeline toolbox for analyzing brain diffusion images. *Frontiers in Human Neuroscience*, *7*, 42. https://doi.org/10.3389/fnhum.2013.00042, PubMed: 23439846

Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: A review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure and Function*, *213*(6), 525–533. https://doi.org/10.1007/s00429-009-0208-6, PubMed: 19565262

de Leeuw, C. A., Mooij, J. M., Heskes, T., & Posthuma, D. (2015). MAGMA: Generalized gene-set analysis of GWAS data. *PLOS Computational Biology*, *11*(4), e1004219. https://doi.org/10.1371/journal.pcbi.1004219, PubMed: 25885710

Elliott, L. T., Sharp, K., Alfaro-Almagro, F., Shi, S., Miller, K. L., Douaud, G., Marchini, J., & Smith, S. M. (2018). Genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nature*, *562*(7726), 210–216. https://doi.org/10.1038/s41586-018-0571-7, PubMed: 30305740

Fairchild, C. L., & Gammill, L. S. (2013). Tetraspanin18 is a FoxD3-responsive antagonist of cranial neural crest epithelial-to-mesenchymal transition that maintains cadherin-6B protein. *Journal of Cell Science*, *126*(6), 1464–1476. https://doi.org/10.1242/jcs.120915, PubMed: 23418345

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., Fox, P. T., Eickhoff, S. B., Yu, C., & Jiang, T. (2016). The human Brainnetome Atlas: A new brain atlas based on connectional architecture. *Cerebral Cortex*, *26*(8), 3508–3526. https://doi.org/10.1093/cercor/bhw157, PubMed: 27230218

Feng, J., Chen, C., Cai, Y., Ye, Z., Feng, K., Liu, J., Zhang, L., Yang, Q., Li, A., Sheng, J., Zhu, B., Yu, Z., Chen, C., Dong, Q., & Xue, G. (2020). Partitioning heritability analyses unveil the genetic architecture of human brain multidimensional functional connectivity patterns. *Human Brain Mapping*, *41*(12), 3305–3317. https://doi.org/10.1002/hbm.25018, PubMed: 32329556

Feng, J., Zhang, L., Chen, C., Sheng, J., Ye, Z., Feng, K., Liu, J., Cai, Y., Zhu, B., Yu, Z., Chen, C., Dong, Q., & Xue, G. (2022). A cognitive neurogenetic approach to uncovering the structure of executive functions. *Nature Communications*, *13*(1), 4588. https://doi.org/10.1038/s41467-022-32383-0, PubMed: 35933428

Foo, H., Thalamuthu, A., Jiang, J., Koch, F. C., Mather, K. A., Wen, W., & Sachdev, P. S. (2021). Novel genetic variants associated with brain functional networks in 18,445 adults from the UK Biobank. *Scientific Reports*, *11*(1), 14633. https://doi.org/10.1038/s41598-021-94182-9, PubMed: 34272439

Fornito, A., Zalesky, A., Bassett, D. S., Meunier, D., Ellison-Wright, I., Yücel, M., Wood, S. J., Shaw, K., O'Connor, J., Nertney, D., Mowry, B. J., Pantelis, C., & Bullmore, E. T. (2011). Genetic influences on cost-efficient organization of human cortical functional networks. *Journal of Neuroscience*, *31*(9), 3261–3270. https://doi.org/10.1523/JNEUROSCI.4858-10.2011, PubMed: 21368038

Ge, T., Holmes, A. J., Buckner, R. L., Smoller, J. W., & Sabuncu, M. R. (2017). Heritability analysis with repeat measurements and its application to resting-state functional connectivity. *Proceedings of the National Academy of Sciences*, *114*(21), 5521–5526. https://doi.org/10.1073/pnas.1700765114, PubMed: 28484032

Grasby, K. L., Jahanshad, N., Painter, J. N., Colodro-Conde, L., Bralten, J., Hibar, D. P., Lind, P. A., Pizzagalli, F., Ching, C. R. K., McMahon, M. A. B., Shatokhina, N., Zsembik, L. C. P., Thomopoulos, S. I., Zhu, A. H., Strike, L. T., Agartz, I., Alhusaini, S., Almeida, M. A. A., Alnæs, D., ... Enhancing NeuroImaging Genetics through Meta-Analysis Consortium (ENIGMA)—Genetics Working Group. (2020). The genetic architecture of the human cerebral cortex. *Science*, *367*(6484), eaay6690. https://doi.org/10.1126/science.aay6690, PubMed: 32193296

Gu, W., Brodtkorb, E., Piepoli, T., Finocchiaro, G., & Steinlein, O. K. (2005). LGI1: A gene involved in epileptogenesis and glioma progression? *Neurogenetics*, *6*(2), 59–66. https://doi.org/10.1007/s10048-005-0216-5, PubMed: 15827762

Gu, Z., Jamison, K. W., Sabuncu, M. R., & Kuceyeski, A. (2021). Heritability and interindividual variability of regional structure-function coupling. *Nature Communications*, *12*(1), 4894. https://doi.org/10.1038/s41467-021-25184-4, PubMed: 34385454

Guelfi, G., Casano, A. B., Menchetti, L., Bellicci, M., Suvieri, C., Moscati, L., Carotenuto, P., Santoro, M. M., & Diverio, S. (2019). A cross-talk between blood-cell neuroplasticity-related genes and environmental enrichment in working dogs. *Scientific Reports*, *9*(1), 6910. https://doi.org/10.1038/s41598-019-43402-4, PubMed: 31061480

Hamada, N., Ito, H., Nishijo, T., Iwamoto, I., Morishita, R., Tabata, H., Momiyama, T., & Nagata, K.-I. (2016). Essential role of the nuclear isoform of RBFOX1, a candidate gene for autism spectrum disorders, in the brain development. *Scientific Reports*, *6*, 30805. https://doi.org/10.1038/srep30805, PubMed: 27481563

Hao, J., Varshney, R. R., & Wang, D.-A. (2008). TGF-β3: A promising growth factor in engineered organogenesis. *Expert Opinion on Biological Therapy*, *8*(10), 1485–1493. https://doi.org/10.1517/14712598.8.10.1485, PubMed: 18774917

Hawrylycz, M. J., Lein, E. S., Guillozet-Bongaarts, A. L., Shen, E. H., Ng, L., Miller, J. A., van de Lagemaat, L. N., Smith, K. A., Ebbert, A., Riley, Z. L., Abajian, C., Beckmann, C. F., Bernard, A., Bertagnolli, D., Boe, A. F., Cartagena, P. M., Chakravarty, M. M., Chapin, M., Chong, J., ... Jones, A. R. (2012). An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature*, *489*(7416), 391–399. https://doi.org/10.1038/nature11405, PubMed: 22996553

Hermundstad, A. M., Bassett, D. S., Brown, K. S., Aminoff, E. M., Clewett, D., Freeman, S., Frithsen, A., Johnson, A., Tipper, C. M., Miller, M. B., Grafton, S. T., & Carlson, J. M. (2013). Structural foundations of resting-state and task-based functional connectivity in the human brain. *Proceedings of the National Academy of Sciences*, *110*(15), 6169–6174. https://doi.org/10.1073/pnas.1219562110, PubMed: 23530246

Honey, C. J., Kötter, R., Breakspear, M., & Sporns, O. (2007). Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proceedings of the National Academy of Sciences*, *104*(24), 10240–10245. https://doi.org/10.1073/pnas.0701519104, PubMed: 17548818

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences*, *106*(6), 2035–2040. https://doi.org/10.1073/pnas.0811168106, PubMed: 19188601

Honey, C. J., Thivierge, J.-P., & Sporns, O. (2010). Can structure predict function in the human brain? *NeuroImage*, *52*(3), 766–776. https://doi.org/10.1016/j.neuroimage.2010.01.071, PubMed: 20116438

Kang, Y., & Chen, L. (2022). Structure and mechanism of NALCN-FAM155A-UNC79-UNC80 channel complex. *Nature Communications*, *13*(1), 2639. https://doi.org/10.1038/s41467-022-30403-7, PubMed: 35550517

Koch, M. A., Norris, D. G., & Hund-Georgiadis, M. (2002). An investigation of functional and anatomical connectivity using magnetic resonance imaging. *NeuroImage*, *16*(1), 241–250. https://doi.org/10.1006/nimg.2001.1052, PubMed: 11969331

Kochunov, P., Fu, M., Nugent, K., Wright, S. N., Du, X., Muellerklein, F., Morrissey, M., Eskandar, G., Shukla, D. K., Jahanshad, N., Thompson, P. M., Patel, B., Postolache, T. T., Strauss, K. A., Shuldiner, A. R., Mitchell, B. D., & Hong, L. E. (2016). Heritability of complex white matter diffusion traits assessed in a

population isolate. *Human Brain Mapping*, *37*(2), 525–535. https://doi.org/10.1002/hbm.23047, PubMed: 26538488

Kośla, K., Kałuzińska, Ż., & Bednarek, A. K. (2020). The WWOX gene in brain development and pathology. *Experimental Biology and Medicine*, *245*(13), 1122–1129. https://doi.org/10.1177/1535370220924618, PubMed: 32389029

Kschonsak, M., Chua, H. C., Weidling, C., Chakouri, N., Noland, C. L., Schott, K., Chang, T., Tam, C., Patel, N., Arthur, C. P., Leitner, A., Ben-Johny, M., Ciferri, C., Pless, S. A., & Payandeh, J. (2022). Structural architecture of the human NALCN channelosome. *Nature*, *603*(7899), 180–186. https://doi.org/10.1038/s41586-021-04313-5, PubMed: 34929720

Markello, R. D., Arnatkeviciute, A., Poline, J.-B., Fulcher, B. D., Fornito, A., & Misic, B. (2021). Standardizing workflows in imaging transcriptomics with the abagen toolbox. *eLife*, *10*, e72129. https://doi.org/10.7554/eLife.72129, PubMed: 34783653

Medland, S. E., Grasby, K. L., Jahanshad, N., Painter, J. N., Colodro-Conde, L., Bralten, J., Hibar, D. P., Lind, P. A., Pizzagalli, F., Thomopoulos, S. I., Stein, J. L., Franke, B., Martin, N. G., Thompson, P. M., & ENIGMA Genetics Working Group. (2022). Ten years of enhancing neuro-imaging genetics through meta-analysis: An overview from the ENIGMA Genetics Working Group. *Human Brain Mapping*, *43*, 292–299. https://doi.org/10.1002/hbm.25311, PubMed: 33300665

Noy, P. J., Gavin, R. L., Colombo, D., Haining, E. J., Reyat, J. S., Payne, H., Thielmann, I., Lokman, A. B., Neag, G., Yang, J., Lloyd, T., Harrison, N., Heath, V. L., Gardiner, C., Whitworth, K. M., Robinson, J., Koo, C. Z., Di Maio, A., Harrison, P., ... Tomlinson, M. G. (2019). Tspan18 is a novel regulator of the Ca^{2+} channel Orai1 and von Willebrand factor release in endothelial cells. *Haematologica*, *104*(9), 1892–1905. https://doi.org/10.3324/haematol.2018.194241, PubMed: 30573509

Park, H.-J., & Friston, K. (2013). Structural and functional brain networks:From connections to cognition. *Science*, *342*(6158), 1238411. https://doi.org/10.1126/science.1238411, PubMed: 24179229

Passingham, R. E., Stephan, K. E., & Kötter, R. (2002). The anatomical basis of functional localization in the cortex. *Nature Reviews Neuroscience*, *3*(8), 606–616. https://doi.org/10.1038/nrn893, PubMed: 12154362

Ponten, S. C., Daffertshofer, A., Hillebrand, A., & Stam, C. J. (2010). The relationship between structural and functional connectivity: Graph theoretical analysis of an EEG neural mass model. *NeuroImage*, *52*(3), 985–994. https://doi.org/10.1016/j.neuroimage.2009.10.049, PubMed: 19853665

Pruim, R. J., Welch, R. P., Sanna, S., Teslovich, T. M., Chines, P. S., Gliedt, T. P., Boehnke, M., Abecasis, G. R., & Willer, C. J. (2010). LocusZoom: Regional visualization of genome-wide association scan results. *Bioinformatics*, *26*(18), 2336–2337. https://doi.org/10.1093/bioinformatics/btq419, PubMed: 20634204

Qiao, J., Zhao, X., Wang, S., Li, A., Wang, Z., Cao, C., & Wang, Q. (2020). Functional and structural brain alterations in encephalitis with LGI1 Antibodies. *Frontiers in Neuroscience*, *14*, 304. https://doi.org/10.3389/fnins.2020.00304, PubMed: 32317923

Rubinov, M., Sporns, O., van Leeuwen, C., & Breakspear, M. (2009). Symbiotic relationship between brain structure and dynamics. *BMC Neuroscience*, *10*, 55. https://doi.org/10.1186/1471-2202-10-55, PubMed: 19486538

Rykhlevskaia, E., Gratton, G., & Fabiani, M. (2008). Combining structural and functional neuroimaging data for studying brain connectivity: A review. *Psychophysiology*, *45*(2), 173–187. https://doi.org/10.1111/j.1469-8986.2007.00621.x, PubMed: 17995910

Sarwar, T., Tian, Y., Yeo, B. T. T., Ramamohanarao, K., & Zalesky, A. (2021). Structure-function coupling in the human connectome: A machine learning approach. *NeuroImage*, *226*, 117609. https://doi.org/10.1016/j.neuroimage.2020.117609, PubMed: 33271268

Satizabal, C. L., Adams, H. H. H., Hibar, D. P., White, C. C., Knol, M. J., Stein, J. L., Scholz, M., Sargurupremraj, M., Jahanshad, N., Roshchupkin, G. V., Smith, A. V., Bis, J. C., Jian, X., Luciano, M., Hofer, E., Teumer, A., van der Lee, S. J., Yang, J., Yanek, L. R., ... Ikram, M. A. (2019). Genetic architecture of subcortical brain structures in 38,851 individuals. *Nature Genetics*, *51*(11), 1624–1636. https://doi.org/10.1038/s41588-019-0511-y, PubMed: 31636452

Sinclair, B., Hansell, N. K., Blokland, G. A. M., Martin, N. G., Thompson, P. M., Breakspear, M., de Zubicaray, G. I., Wright, M. J., & McMahon, K. L. (2015). Heritability of the network architecture of intrinsic brain functional connectivity. *NeuroImage*, *121*, 243–252. https://doi.org/10.1016/j.neuroimage.2015.07.048, PubMed: 26226088

Smith, S. M., Douaud, G., Chen, W., Hanayik, T., Alfaro-Almagro, F., Sharp, K., & Elliott, L. T. (2021). An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nature Neuroscience*, *24*(5), 737–745. https://doi.org/10.1038/s41593-021-00826-4, PubMed: 33875891

Sporns, O. (2013). Network attributes for segregation and integration in the human brain. *Current Opinion in Neurobiology*, *23*(2), 162–171. https://doi.org/10.1016/j.conb.2012.11.015, PubMed: 23294553

Su, L.-D., Xie, Y.-J., Zhou, L., Shen, Y., & Hu, Y.-H. (2015). LGI1 is involved in the development of mouse brain. *Cerebellum*, *14*(1), 12–14. https://doi.org/10.1007/s12311-014-0628-6, PubMed: 25471260

Suárez, L. E., Markello, R. D., Betzel, R. F., & Misic, B. (2020). Linking structure and function in macroscale brain networks. *Trends in Cognitive Sciences*, *24*(4), 302–315. https://doi.org/10.1016/j.tics.2020.01.008, PubMed: 32160567

Thompson, P. M., Andreassen, O. A., Arias-Vasquez, A., Bearden, C. E., Boedhoe, P. S., Brouwer, R. M., Buckner, R. L., Buitelaar, J. K., Bulayeva, K. B., Cannon, D. M., Cohen, R. A., Conrod, P. J., Dale, A. M., Deary, I. J., Dennis, E. L., de Reus, M. A., Desrivieres, S., Dima, D., Donohoe, G., ... ENIGMA Consortium. (2017). ENIGMA and the individual: Predicting factors that affect the brain in 35 countries worldwide. *NeuroImage*, *145*, 389–408. https://doi.org/10.1016/j.neuroimage.2015.11.057, PubMed: 26658930

Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V. P., Huttunen, M., Lönnqvist, J., Standertskjöld-Nordenstam, C. G., Kaprio, J., Khaledy, M., Dail, R., Zoumalan, C. I., & Toga, A. W. (2001). Genetic influences on brain structure. *Nature Neuroscience*, *4*(12), 1253–1258. https://doi.org/10.1038/nn758, PubMed: 11694885

Thompson, P. M., Ge, T., Glahn, D. C., Jahanshad, N., & Nichols, T. E. (2013). Genetics of the connectome. *NeuroImage*, *80*,

475–488. https://doi.org/10.1016/j.neuroimage.2013.05.013, PubMed: 23707675

Thompson, P. M., Jahanshad, N., Schmaal, L., Turner, J. A., Winkler, A. M., Thomopoulos, S. I., Egan, G. F., & Kochunov, P. (2022). The Enhancing NeuroImaging Genetics through Meta-Analysis Consortium: 10 years of global collaborations in human brain mapping. *Human Brain Mapping*, *43*(1), 15–22. https://doi.org/10.1002/hbm.25672, PubMed: 34612558

Thompson, P. M., Stein, J. L., Medland, S. E., Hibar, D. P., Vasquez, A. A., Renteria, M. E., Toro, R., Jahanshad, N., Schumann, G., Franke, B., Wright, M. J., Martin, N. G., Agartz, I., Alda, M., Alhusaini, S., Almasy, L., Almeida, J., Alpert, K., Andreasen, N. C., … Saguenay Youth Study (SYS) Group. (2014). The ENIGMA Consortium: Large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging and Behavior*, *8*(2), 153–182. https://doi.org/10.1007/s11682-013-9269-5, PubMed: 24399358

van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology*, *20*(8), 519–534. https://doi.org/10.1016/j.euroneuro.2010.03.008, PubMed: 20471808

van den Heuvel, M. P., van Soelen, I. L. C., Stam, C. J., Kahn, R. S., Boomsma, D. I., & Hulshoff Pol, H. E. (2013). Genetic control of functional brain network efficiency in children. *European Neuropsychopharmacology*, *23*(1), 19–23. https://doi.org/10.1016/j.euroneuro.2012.06.007, PubMed: 22819192

Vincent, J. L., Patel, G. H., Fox, M. D., Snyder, A. Z., Baker, J. T., Van Essen, D. C., Zempel, J. M., Snyder, L. H., Corbetta, M., & Raichle, M. E. (2007). Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*, *447*(7140), 83–86. https://doi.org/10.1038/nature05758, PubMed: 17476267

Wang, J., Wang, X., Xia, M., Liao, X., Evans, A., & He, Y. (2015). GRETNA: A graph theoretical network analysis toolbox for imaging connectomics. *Frontiers in Human Neuroscience*, *9*, 386. https://doi.org/10.3389/fnhum.2015.00386, PubMed: 26175682

Watabe, T., & Miyazono, K. (2009). Roles of TGF-β family signaling in stem cell renewal and differentiation. *Cell Research*, *19*(1), 103–115. https://doi.org/10.1038/cr.2008.323, PubMed: 19114993

Willer, C. J., Li, Y., & Abecasis, G. R. (2010). METAL: Fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*, *26*(17), 2190–2191. https://doi.org/10.1093/bioinformatics/btq340, PubMed: 20616382

Wu, C.-L., Lin, L.-F., Hsu, H.-C., Huang, L.-F., Hsiao, C.-D., & Chou, M.-L. (2021). *Saussurea involucrata* (snow lotus) *ICE1* and *ICE2* orthologues involved in regulating cold stress tolerance in transgenic *Arabidopsis*. *International Journal of Molecular Sciences*, *22*(19), 10850. https://doi.org/10.3390/ijms221910850, PubMed: 34639192

Wu, L., Chen, F., Wei, J., Shen, Y., & Xu, Q. (2016). Study of the tetraspanin 18 association with schizophrenia in a Han Chinese population. *Psychiatry Research*, *241*, 263–266. https://doi.org/10.1016/j.psychres.2016.03.057, PubMed: 27208512

Wu, Q., Lei, H., Mao, T., Deng, Y., Zhang, X., Jiang, Y., Zhong, X., Detre, J. A., Liu, J., & Rao, H. (2023). Test-retest reliability of resting brain small-world network properties across different data processing and modeling strategies. *Brain Sciences*, *13*(5), 825. https://doi.org/10.3390/brainsci13050825, PubMed: 37239297

Yeo, B. T. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011, PubMed: 21653723

Yu, Y., Cao, F., Xiong, Y., & Zhou, H. (2021). SP1 transcriptionally activates NLRP6 inflammasome and induces immune evasion and radioresistance in glioma cells. *International Immunopharmacology*, *98*, 107858. https://doi.org/10.1016/j.intimp.2021.107858, PubMed: 34147913

Zhan, L., Jahanshad, N., Faskowitz, J., Zhu, D., Prasad, G., Martin, N.G., de Zubicaray, G. I., McMahon, K. L., Wright, M. J., & Thompson, P. M. (2015). Heritability of brain network topology in 853 twins and siblings. In *2015 IEEE 12th international symposium on biomedical imaging* (pp. 449–453). https://doi.org/10.1109/ISBI.2015.7163908

Zhao, B., Li, T., Smith, S. M., Xiong, D., Wang, X., Yang, Y., Luo, T., Zhu, Z., Shan, Y., Matoba, N., Sun, Q., Yang, Y., Hauberg, M. E., Bendl, J., Fullard, J. F., Roussos, P., Lin, W., Li, Y., Stein, J. L., & Zhu, H. (2022). Common variants contribute to intrinsic human brain functional networks. *Nature Genetics*, *54*(4), 508–517. https://doi.org/10.1038/s41588-022-01039-6, PubMed: 35393594

Zhao, B., Li, T., Yang, Y., Wang, X., Luo, T., Shan, Y., Zhu, Z., Xiong, D., Hauberg, M. E., Bendl, J., Fullard, J. F., Roussos, P., Li, Y., Stein, J. L., & Zhu, H. (2021). Common genetic variation influencing human white matter microstructure. *Science*, *372*(6548), eabf3736. https://doi.org/10.1126/science.abf3736, PubMed: 34140357