

1 ***Common variants contribute to intrinsic human brain functional networks***

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3 **Running title: GWAS of intrinsic brain function**

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5 Bingxin Zhao^{1,14}, Tengfei Li^{2,3,14}, Stephen M. Smith⁴, Di Xiong¹, Xifeng Wang¹, Yue Yang¹,
6 Tianyou Luo¹, Ziliang Zhu¹, Yue Shan¹, Nana Matoba^{5,6}, Quan Sun¹, Yuchen Yang⁵, Mads
7 E. Hauberg^{7,8,10,11}, Jaroslav Bendl⁷⁻⁹, John F. Fullard⁷⁻⁹, Panagiotis Roussos^{7-10,12}, Weili
8 Lin^{2,3}, Yun Li^{1,5,13}, Jason L. Stein^{5,6}, and Hongtu Zhu^{1,3*}

9

10 ¹Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

11 ²Department of Radiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

12 ³Biomedical Research Imaging Center, School of Medicine, University of North Carolina at Chapel Hill,
13 Chapel Hill, NC, USA

14 ⁴Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical
15 Neurosciences, University of Oxford, Oxford, UK

16 ⁵Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

17 ⁶UNC Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

18 ⁷Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

19 ⁸Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

20 ⁹Department of Genetics and Genomic Science and Institute for Multiscale Biology, Icahn School of
21 Medicine at Mount Sinai, New York, NY, USA

22 ¹⁰iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark

23 ¹¹Centre for Integrative Sequencing (iSEQ), Aarhus University, Aarhus, Denmark

24 ¹²Mental Illness Research, Education, and Clinical Center (VISN 2 South), James J. Peters VA Medical
25 Center, Bronx, NY, USA

26 ¹³Department of Computer Science, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

27 ¹⁴These authors contributed equally to this work.

28

29 **Corresponding author:*

30 Hongtu Zhu

31 3105C McGavran-Greenberg Hall, 135 Dauer Drive, Chapel Hill, NC 27599.

32 E-mail address: htzhu@email.unc.edu Phone: (919) 966-7250

1 **Abstract**

2 The human brain remains active in the absence of explicit tasks and forms networks of
3 correlated activity. Resting-state functional magnetic resonance imaging (rsfMRI)
4 measures brain activity at rest, which has been linked with both cognitive and clinical
5 outcomes. The genetic variants influencing human brain function are largely unknown.
6 Here we utilized rsfMRI from 44,190 individuals of multiple ancestries (37,339 in the UK
7 Biobank) to discover and validate the common genetic variants influencing intrinsic
8 brain activity. We identified hundreds of novel genetic loci associated with intrinsic
9 functional signatures ($P < 2.8 \times 10^{-11}$), including associations to the central executive,
10 default mode, and salience networks involved in the triple network model of
11 psychopathology. A number of intrinsic brain activity associated loci colocalized with
12 brain disorder GWAS (e.g., Alzheimer's disease, Parkinson's disease, schizophrenia) and
13 cognition, such as 19q13.32, 17q21.31, and 2p16.1. Particularly, we detected a
14 colocalization between one (rs429358) of the two variants in the *APOE* $\epsilon 4$ locus and
15 function of the default mode, central executive, attention, and visual networks. Genetic
16 correlation analysis demonstrated shared genetic influences between brain function and
17 brain structure in the same regions. We also detected significant genetic correlations
18 with 26 other complex traits, such as ADHD, major depressive disorder, schizophrenia,
19 intelligence, education, sleep, subjective well-being, and neuroticism. Common variants
20 associated with intrinsic brain activity were enriched within regulatory element in brain
21 tissues.

22

23 **Keywords:** Amplitude; Functional connectivity; Intrinsic brain activity; GWAS;
24 Resting-state fMRI; Triple network model; UK Biobank.

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1 The human brain is a complex system where functional organization and communication
2 between brain networks are necessary for behavior and cognition¹⁻⁴. The human brain
3 remains active in the absence of explicit tasks or stimuli, resulting in an intrinsic
4 functional architecture. Utilizing changes in blood oxygen level-dependent (BOLD)
5 signal^{5,6}, resting-state functional magnetic resonance imaging⁷ (rsfMRI) captures
6 spontaneous intrinsic brain activity⁸. Specifically, the spontaneous neural activity and
7 non-neural physiological processes within each functional region are quantified by the
8 amplitude of low frequency fluctuations (ALFF) in BOLD time series^{6,9,10}. Moreover, the
9 inter-regional correlations in spontaneous neuronal variability are used to construct a
10 functional connectivity matrix, which measures the magnitude of temporal synchrony
11 between each pair of brain regions^{6,11}.

12

13 rsfMRI has led to the discovery of multiple resting-state networks (RSNs) present in
14 neurotypical human brains, including the default mode, central executive (i.e.,
15 frontoparietal), attention, limbic, salience, somatomotor, and visual networks¹²⁻¹⁴.
16 Among these RSNs, the central executive, default mode, and salience networks are
17 three core neurocognitive networks that support efficient cognition¹⁵⁻¹⁷. Accumulating
18 evidence suggests that the functional organization and dynamic interaction of these
19 three networks underlie a wide range of mental disorders, resulting in the triple
20 network model of psychopathology^{16,18}. Supporting this model, differences in RSNs have
21 been detected in multiple neurological and psychiatric disorders¹⁹ relative to
22 neurotypical controls, such as Alzheimer's disease²⁰, Parkinson's disease²¹, and major
23 depressive disorder (MDD)²².

24

25 Twin and family studies have largely reported a low to moderate degree of genetic
26 contributions to intrinsic brain activity²³⁻²⁹. For example, the family-based heritability
27 estimates of major RSNs ranged from 20% to 40% in the Human Connectome Project
28 (HCP)³⁰. In a previous study using about 8,000 UK Biobank (UKB) individuals³¹, the SNP
29 heritability³² of amplitude and functional connectivity traits can be higher than 30%.
30 Although there were multiple candidate gene studies for intrinsic brain activity (such as
31 for *APOE*³³ and *KIBRA*³⁴), currently only one genome-wide association study (GWAS)³¹
32 has been successfully performed on rsfMRI²³ ($n \approx 8000$). This is likely due to both

1 insufficient sample size for GWAS discovery and weaker genetic effects on brain
2 function than structure^{31,35-39}. It is also known that functional connectivity traits in
3 rsfMRI are typically noisier than brain structural traits measured in other neuroimaging
4 modalities. In addition, imaging batch effects⁴⁰ (e.g., image acquisition, processing
5 procedures, and software) may cause additional technical variability in rsfMRI
6 analyses⁴¹, making GWAS meta-analysis and independent replication particularly
7 challenging. Therefore, genetic variants influencing intrinsic brain activity have
8 remained largely undiscovered and their shared genetic influences with other complex
9 traits and clinical outcomes are unknown.

10

11 To address these challenges, here we collected individual-level rsfMRI data from four
12 independent studies, including the UK Biobank⁴², Adolescent Brain Cognitive
13 Development (ABCD⁴³), Philadelphia Neurodevelopmental Cohort (PNC⁴⁴), and HCP⁴⁵.
14 We harmonized rsfMRI processing procedures by following the unified UKB brain
15 imaging pipeline^{9,46}. Functional brain regions and corresponding functional connectivity
16 were characterized via spatial Independent Component Analysis (ICA)^{47,48} for 44,190
17 individuals from multiple ancestries, including 37,339 from UK Biobank. As in previous
18 studies^{9,31,49}, two parcellations with different dimensionalities^{13,50} (25 and 100 regions,
19 respectively) were separately applied in spatial ICA and we focused on the 76 (21 and
20 55, respectively) regions that had been previously confirmed to be non-artifactual⁹. Two
21 group of neuroimaging phenotypes were then generated: the first group contains 76
22 (node) amplitude traits reflecting the regional spontaneous neuronal activity; and the
23 second group includes 1,695 (i.e., $21 \times 20/2 + 55 \times 54/2$) (edge) functional connectivity
24 traits that quantify the inter-regional co-activity, as well as 6 global functional
25 connectivity measures summarizing all of the 1,695 pairwise functional connectivity
26 traits³¹. These 1,777 traits were then used to explore the genetic architecture of intrinsic
27 brain activity. To aid interpretation of GWAS results, the functional brain regions
28 characterized in ICA were labelled by using the automated anatomical labeling (AAL)
29 atlas⁵¹ and were mapped onto major functional networks defined in Yeo, et al.¹⁴ and
30 Finn, et al.¹². Our GWAS results can be easily explored and downloaded through the
31 Brain Imaging Genetics Knowledge Portal (BIG-KP) <https://bigkp.org>.

32

1 RESULTS

2 Genetics of the intrinsic brain functional architecture.

3 SNP heritability was estimated for the 1,777 intrinsic brain activity traits via GCTA⁵². The
4 mean heritability (h^2) estimate was 27.2% (range = (10%, 36.5%), standard error = 6.0%)
5 for the 76 amplitude traits, all of which remained significant after adjusting for multiple
6 comparisons by using the Benjamini-Hochberg procedure to control false discovery rate
7 (FDR) at 0.05 level (1,777 tests, **Fig. 1a** and **Supplementary Table 1**). Among the 1,701
8 functional connectivity traits, 1,230 had significant (again at 5% FDR) heritability with
9 estimates varying from 3% to 61% (mean = 9.6%, standard error = 5.8%). Ten functional
10 connectivity traits had heritability higher than 30%, including 4 global functional
11 connectivity measures (**Supplementary Fig. 1**) and 6 pairwise functional connectivity
12 traits (**Fig. 1b**). These most heritable traits were most related to the central executive,
13 default mode, and salience networks in the triple network model of psychopathology¹⁶.
14 To examine whether intrinsic brain activity within the triple network in general had
15 higher heritability, we classified the 76 amplitude traits into two categories 1) fully or
16 partially within the triple network and 2) outside the triple network. Correspondingly,
17 the 1,695 pairwise functional connectivity traits were classified into 1) within the triple
18 network, 2) outside the triple network, and 3) between the triple and non-triple
19 networks. We found that amplitude traits within the triple network had significantly
20 higher heritability than those outside the triple network (mean = 30.5% vs. 22.3%, $P =$
21 6.3×10^{-11} , two-sided Wilcoxon rank test) (**Fig. 1c**). Similarly, functional connectivity
22 traits within the triple network had higher heritability than interactions outside the
23 triple network or between the triple and non-triple networks (mean = 12.5% vs. 7%, $P =$
24 1.9×10^{-26}). These results indicate that the level of genetic control might be higher in
25 core neurocognitive networks. The range of heritability estimates was consistent with
26 previous results³¹, suggesting that common genetic variants had a low to moderate
27 degree of contributions to inter-individual variability of intrinsic brain activity. The
28 overall genetic effects on both amplitude and functional connectivity were lower than
29 those on brain structure. For example, the average heritability was reported to be 48.7%
30 for diffusion tensor imaging (DTI) traits of brain structural connectivity in white matter
31 tracts⁵³ and 40% for regional brain volumes measuring brain morphometry³⁷.
32 Nevertheless, as shown below, intrinsic brain activity may be more functionally relevant

1 with stronger genetic connections to brain disorders than brain structure, such as
2 Alzheimer's disease.

3

4 Genome-wide association discovery was carried out for 1,777 intrinsic brain activity
5 traits using UKB individuals of British ancestry ($n = 34,691$, Methods). The Manhattan
6 and QQ plots can be found in the BIG-KP server. At the significance level 2.8×10^{-11} ($5 \times$
7 $10^{-8}/1,777$, i.e., the standard GWAS threshold, Bonferroni-adjusted for the 1,777 traits),
8 FUMA⁵⁴ identified 264 lead independent variants (linkage disequilibrium [LD] $r^2 < 0.1$),
9 and then characterized 606 significant locus-trait associations for 197 traits (75
10 amplitude and 122 functional connectivity (**Supplementary Tables 2-3, Supplementary**
11 **Fig. 2**, Methods). The amplitude traits typically had multiple associated variants and a
12 number of variants were widely related to the amplitude in different brain regions, such
13 as rs429358 (nearest gene *APOE*), rs2274224 (*PLCE1*), and rs1133400 (*INPP5A*). In
14 addition, rs2279829 (*ZIC4*), rs62158211 (*AC016745.1*), and rs115877304 (*NR2F1-AS1*)
15 were associated with multiple functional connectivity traits. Global and pairwise
16 functional connectivity traits that had at least 5 significant variants were again most
17 related to the central executive, default mode, and salience networks (**Supplementary**
18 **Fig. 3**). Of the 14 associated variants that had been identified in the previous GWAS³¹,
19 12 were in LD ($r^2 \geq 0.6$) with our significant variants, most of which were associated
20 with amplitude traits. In summary, our analyses identify many novel variants associated
21 with intrinsic functional signatures and illustrate the global genetic influences on
22 functional connectivity across the whole brain. The degree of genetic control is higher in
23 the central executive, default mode, and salience networks, whose cross-network
24 interactions closely control multiple cognitive functions and affect major brain
25 disorders¹⁸.

26

27 **Replication and the effect of ancestry.**

28 We aimed to replicate our results in UKB British GWAS using other independent
29 datasets. First, we repeated GWAS on UKB individuals of White but Non-British ancestry
30 (UKBW, $n = 1,970$) and three non-UKB European-ancestry cohorts, including ABCD
31 European (ABCDE, $n = 3,821$), HCP ($n = 495$), and PNC ($n = 510$). We meta-analyzed the
32 four European GWAS (total $n = 6,796$) and checked whether the locus-trait associations

1 detected in UKB British GWAS can be replicated. For the 606 significant associations,
2 101 (16.7%) passed the 8.2×10^{-5} (i.e., 0.05/606) Bonferroni significance level in this
3 validation GWAS, and 599 (98.8%) were significant at FDR 5% level. Next, we performed
4 GWAS on four non-European validation datasets: the UKB Asian (UKBA, $n = 446$), UKB
5 Black (UKBBL, $n = 232$), ABCD Hispanic (ABCDH, $n = 768$), and ABCD African American
6 (ABCDAA, $n = 1,257$). We meta-analyzed these four non-European GWAS (total $n = 2,703$)
7 and found that 39 (6.4%) passed the Bonferroni significance level and 601 (99.2%) were
8 significant at FDR 5% level. Some associations with rs3781658 (*ANO1*), rs7083220
9 (*PWWP2B*), rs9373978 (*FHL5*), rs11187838 (*PLCE1*), and rs35124509 (*EPHA3*) were
10 replicated in both European and non-European datasets at the stringent Bonferroni
11 significance level. Moreover, we performed a third meta-analysis to combine all of the
12 eight validation datasets, after which the number of replicated associations moved up to
13 136 (22.4%) and 602 (99.3%) at Bonferroni and FDR significance levels, respectively.
14 These results are summarized in **Supplementary Table 4**. Overall, our results suggest
15 that the associated genetic loci discovered in UKB British GWAS have high
16 generalizability in independent rsfMRI studies, despite the fact that these studies may
17 use different imaging protocols/MRI scanners and recruit participants from different age
18 groups. The strong homogeneity of GWAS results likely benefit, in part, from the
19 consistent rsfMRI processing procedures that we applied to these datasets.

20

21 In addition, we utilized polygenic risk scores⁵⁵ (PRS) derived from UKB British GWAS for
22 further evidence of replication (Methods). For the 197 traits that had significant
23 variants, 168 had significant PRS in at least one of the four European validation GWAS
24 datasets at FDR 5% level (197×4 tests, **Supplementary Table 5**), illustrating the
25 significant out-of-sample prediction power of polygenic influences from our discovery
26 GWAS results. The largest incremental R-squared (after adjusting the effects of age, sex,
27 and ten genetic principal components) were observed on the 2nd, 3rd, 4th, and 6th
28 global functional connectivity measures in UKBW and HCP datasets, which were larger
29 than 5% (range = (5.1%, 5.7%), P range = (1.1×10^{-24} , 4×10^{-13})). To evaluate the
30 consistency across ancestry, PRS was also constructed on the four non-European
31 validation datasets. UKBA had the best validation performance among the four datasets,
32 with 86 PRS being significant at FDR 5% level (197×4 tests, **Supplementary Table 6**).

1 The number of significant PRS was reduced to 59, 39, and 31 in ABCDH, ABCDA, and
2 UKBBL, respectively. In summary, these PRS results illustrate the overall consistency of
3 genetic effects in European cohorts and also show that there may be population specific
4 influences on brain function in other cohorts, though much smaller sample sizes and
5 difficulty in conducting cross ancestry PRS strongly limit the interpretability of these
6 analyses. More efforts are required to identify causal variants associated with functional
7 brain in global diverse populations and perform better cross-population PRS predictions.

8

9 **The shared genetic loci with brain-related complex traits and disorders.**

10 To evaluate the shared genetic influences between intrinsic brain activity and other
11 complex traits, we carried out association lookups for independent significant variants
12 (and their LD tags, i.e., variants with LD, $r^2 \geq 0.6$) detected in UKB British GWAS
13 (Methods). In the NHGRI-EBI GWAS catalog⁵⁶, our results tagged many variants reported
14 for a wide range of complex traits in different trait domains, such as neurological and
15 psychiatric disorders, cognitive performance, education, bone mineral density, sleep,
16 smoking/drinking, brain structure, and anthropometric traits. Below we highlighted
17 colocalizations in a few selected genomic regions.

18

19 The index variants rs429358 (*APOE*), rs34404554 (*TOMM40*), rs157582(*TOMM40*), and
20 rs157592 (*APOC1*) in the 19q13.32 region (**Fig. 2a, Supplementary Fig. 4**) had genetic
21 effects on the amplitude of many functional brain regions that were most in the default
22 mode, central executive (i.e., frontoparietal), attention, and visual networks. It is well
23 known that 19q13.32 is a risk locus of Alzheimer's disease and rs429358 is one of the
24 two variants in the *APOE* $\epsilon 4$ locus. In this region, we tagged variants associated with
25 dementia and decline in mental ability, including Alzheimer's disease⁵⁷⁻⁵⁹,
26 frontotemporal dementia⁶⁰, cerebral amyloid angiopathy⁶¹, cognitive decline⁶²,
27 cognitive impairment test score⁶³, as well as many biomarkers of Alzheimer's disease,
28 such as neurofibrillary tangles⁶¹, neuritic plaque⁶¹, cerebral amyloid deposition⁶⁴,
29 cerebrospinal fluid protein levels⁶³, and cortical amyloid beta load⁶⁵. Altered amplitude
30 activity has been widely reported in patients of cognitive impairment and Alzheimer's
31 disease^{66,67}. The brain degeneration related to Alzheimer's disease may begin in the
32 frontoparietal regions⁶⁸ and was associated with dysfunction of multiple RSNs,

1 especially the default mode network²⁰. Our findings suggest the shared genetic
2 influences between intrinsic neuronal activity and brain atrophy of Alzheimer's disease.

3

4 Next, the variant rs62061845 (*KANSL1*) in the 17q21.31 region (**Supplementary Fig. 5**)
5 was associated with functional connectivity over the inferior frontal, middle frontal,
6 superior frontal, middle temporal, and supplementary motor area regions in the default
7 mode and salience networks. Variants in LD with rs62061845 have been frequently
8 reported to be associated with Parkinson's disease studies⁶⁹⁻⁷³. As a system-level
9 progressive neurodegenerative disorder⁷⁴, Parkinson's disease not only leads to motor
10 abnormalities, but also has non-motor symptoms such as temporal perception
11 abnormalities⁷⁵ and impaired connectivity among frontal regions⁷⁶. Cognitive
12 dysfunction and disrupted coupling between default mode and salience networks were
13 commonly reported in Parkinson's disease¹⁷. In addition to Parkinson's disease, the
14 17q21.31 region was widely related to other complex traits, including neurological
15 disorders (e.g., Alzheimer's disease⁷⁷, corticobasal degeneration⁷⁸, progressive
16 supranuclear palsy⁷⁹), psychiatric disorders (e.g., autism spectrum disorder⁸⁰, depressive
17 symptoms⁸¹), educational attainment⁸², psychological traits (e.g., neuroticism⁸¹),
18 cognitive traits (cognitive ability⁸³), sleep⁸⁴, heel bone mineral density⁸⁵, alcohol use
19 disorder⁸⁶, subcortical brain volumes³⁸, cortical surface area and thickness³⁶, and white
20 matter microstructure⁵³.

21

22 In addition, the 2p16.1 (**Fig. 2b, Supplementary Fig. 6**) and 5q15 (**Supplementary Fig. 7**)
23 regions were mainly associated with interactions among the central executive, default
24 mode, and salience networks. We observed colocalizations with psychiatric disorders
25 (e.g., schizophrenia⁸⁷, MDD⁸⁸, depressive symptoms⁸⁹, autism spectrum disorder⁹⁰),
26 psychological traits (e.g., neuroticism⁸¹, well-being spectrum⁹¹), sleep⁹², cognitive traits
27 (e.g., intelligence⁹³), and educational attainment⁸². Dysregulated triple network
28 interactions were frequently reported in patients of schizophrenia⁹⁴, depression⁹⁵, and
29 autism spectrum disorder⁹⁶. Similarly, the 2q24.2 (**Supplementary Fig. 8**) and 10q26.13
30 (**Supplementary Fig. 9**) regions had genetic effects on functional connectivity traits
31 involved in the central executive, default mode, salience, and limbic networks. In these
32 two regions, our identified variants tagged those that have been implicated with

1 schizophrenia⁹⁷, educational attainment⁸², cognitive traits (e.g., cognitive ability⁸³),
2 smoking/drinking (e.g., smoking status⁹⁸, alcohol consumption⁹⁹), hippocampus subfield
3 volumes¹⁰⁰, and heel bone mineral density⁸⁵. We also observed colocalizations in some
4 other genomic regions, such as in 2q14.1 region (**Fig. 2c, Supplementary Fig. 10**) with
5 sleep traits (e.g., sleep duration⁸⁴, insomnia⁹²), in 3p11.1 (**Supplementary Fig. 11**) with
6 cognitive traits (e.g., intelligence¹⁰¹, math ability⁸²), and in 5q14.3 (**Supplementary Fig.**
7 **12**) with cognitive traits⁸³ and educational attainment⁸². All of these results are
8 summarized in **Supplementary Table 7**. In summary, intrinsic brain function has wide
9 genetic links to a large number of brain-related complex traits and clinical outcomes,
10 especially neurological and psychiatric disorders and cognitive traits. Integration of
11 GWAS of brain function with these clinical outcomes may help to explain the underlying
12 brain functional mechanisms leading to risk for these disorders.

13

14 **Genetic correlations with brain structure, brain disorders, and cognition.**

15 The intricate brain neuroanatomical structure is fundamental in supporting brain
16 function. To explore whether genetically mediated brain structural changes were
17 associated with brain function, we examined pairwise genetic correlations (gc) between
18 1,777 intrinsic brain activity traits and 315 brain structure traits via LDSC¹⁰² (Methods),
19 including 100 regional brain volumes³⁷ and 215 DTI traits of brain structural connectivity
20 in white matter tracts¹⁰³. There were 151 significant pairs between 94 intrinsic brain
21 functional traits and 73 brain structural traits at FDR 5% level ($315 \times 1,777$ tests, $|gc|$
22 range = (0.22, 0.61), P range = (1.2×10^{-21} , 1.5×10^{-5}), **Supplementary Table 8**).

23

24 We found significant genetic correlations between regional brain volumes and
25 functional connectivity strengths ($|gc|$ range = (0.22, 0.61), P range = (1.2×10^{-21} , $1.2 \times$
26 10^{-5}), **Supplementary Fig. 13**). Most of the observed correlations were related to higher
27 order brain functional networks, particularly the attention, default mode, salience, and
28 central executive networks. For example, the insula has been widely implicated to be
29 associated with multiple functions, including but not limited to emotion, addiction, and
30 cognition through extensive connections to neocortex, the limbic system, and
31 amygdala¹⁰⁴. We observed genetic correlations¹⁰⁴ between insula volumes and the
32 connection strengths of multiple pairs of brain regions ($|gc|$ range = (0.22, 0.27), $P < 1.2$

1 $\times 10^{-5}$, **Fig. 3a-b**), which were largely in the default mode and central executive
2 networks, including the angular and the inferior and superior frontal regions. Similarly,
3 left inferior parietal lobule volume exhibited strong genetic correlations with
4 connectivity strengths over multiple pairs of brain regions that were known to be a part
5 of the default mode, visual, attention, and salience networks ($|gc|$ range = (0.34, 0.49),
6 $P < 9.7 \times 10^{-6}$, **Supplementary Fig. 14a**). Interestingly, however, the above identified
7 genetic correlations appeared to be more specific to the left but not right. The inferior
8 parietal has been implicated to be associated with language function and is connected
9 with the Broca's region via the superior longitudinal fasciculus (SLF)¹⁰⁵⁻¹⁰⁷. Considering
10 language processing is left-lateralized in about 95% of right-handers and 75% of
11 left-handers¹⁰⁸⁻¹¹¹, the observed associations of the left inferior parietal are consistent
12 with the results reported in the literature. In addition, we observed spatial
13 colocalizations between regional brain volumes and their genetically correlated
14 functional connectivity traits in multiple brain regions. For instance, left pericalcarine
15 volume was genetically correlated with the connectivity strengths among its
16 neighboring regions, such as the calcarine, superior occipital, cuneus, precuneus, and
17 lingual, which were largely in the visual, default mode, and central executive networks
18 (**Fig. 3c**). More spatial overlap/proximity examples included the associations between
19 right precuneus volume and functional connectivity pairs over the precuneus, angular,
20 inferior parietal, and middle temporal regions (**Supplementary Fig. 14b**); and the
21 associations between postcentral volumes and functional interactions among the
22 postcentral, inferior and superior parietal, supramarginal, and precuneus regions
23 (**Supplementary Fig. 14c**).

24

25 Significant genetic correlations were also observed between brain structural
26 connectivity and functional connectivity ($|gc|$ range = (0.25, 0.49), P range = (5.5×10^{-10} ,
27 1.3×10^{-5}), **Supplementary Fig. 15**). Many of the white matter tracts, in particular the
28 SLF and corpus callosum, manifested a strong genetic correlation with the interactions
29 of functional networks (**Fig. 4a**). These results provided genetic evidence on how these
30 distributed networks communicate across large distances. The SLF has been widely
31 documented connecting brain regions in temporal, parietal, and frontal lobes¹¹².
32 Functionally, SLF has been reported associated with a wide array of brain functions,

1 including working memory¹¹³, attention^{114,115}, and language functions^{116,117}. We
2 observed significant genetic correlations between SLF and connectivity strengths over
3 multiple pairs of brain regions including the frontal, parietal, and temporal regions ($|gc|$
4 range = (0.33, 0.49), $P < 2.4 \times 10^{-6}$, **Fig. 4b**). For example, a significant association
5 between insula and temporal connection and SLF was observed. This finding is
6 consistent with the well documented broad functions of insula, including attention and
7 salience processes¹⁰⁴. Furthermore, parietal and frontal connections most likely
8 reflected attention and executive control networks. Moreover, the splenium of corpus
9 callosum (SCC) is located in the most posterior part of the corpus callosum and connects
10 brain regions in the temporal, posterior parietal, and occipital lobes. Our results show
11 that SCC was genetically associated with brain regions within the parietal lobe ($|gc|$
12 range = (0.34, 0.48), $P < 6.5 \times 10^{-6}$, **Fig. 4c**). In particular, multiple regions connected to
13 the precuneus were observed, such as the inferior parietal, supramarginal, and occipital
14 regions. The precuneus has been shown to connect multiple cortical and subcortical
15 regions. Functionally, the precuneus is one of the critical areas of the default mode
16 network and has also been implicated to be associated with attention as well as
17 memory functions¹¹⁸. Our findings suggest that these connections may be genetically
18 mediated by the SCC. Besides functional connectivity traits, amplitude traits also had
19 significant genetic associations with regional brain volumes and white matter tracts
20 (**Supplementary Figs. 16-17, Supplementary Note**). Overall, our results uncover the
21 genetic links between intrinsic brain function networks and the associated structural
22 substrates. As illustrated, a few pairs of the genetically correlated brain functional and
23 structural traits show high congruity in spatial location and the involved functions. There
24 has been growing interest to understand how brain topography interacts with brain
25 functional networks¹¹⁹. To our knowledge, our results are the first to indicate that
26 genetic changes in brain structure may also impact brain function.

27

28 Next, we examined the genetic correlations between 1,777 intrinsic brain activity traits
29 and 30 other complex traits, mainly focusing on brain disorders and cognition
30 (**Supplementary Table 9**). We found 176 significant pairs between 26 complex traits and
31 102 intrinsic brain activity traits at FDR 5% level ($30 \times 1,777$ tests, P range = (8.6×10^{-12} ,
32 2.3×10^{-3}), **Supplementary Table 10**). Particularly, functional connectivity strengths

1 were genetically correlated with a few brain disorders, including attention deficit
2 hyperactivity disorder (ADHD), schizophrenia (SCZ), major depressive disorder (MDD),
3 and cross disorder (five major psychiatric disorders¹²⁰) ($|gc|$ range = (0.18, 0.37), $P < 1.2$
4 $\times 10^{-4}$, **Fig. 5a**). For example, we observed a significant genetic correlation between
5 ADHD and functional interactions among the precentral, supplementary motor area,
6 superior frontal, putamen, and caudate regions, which were largely in the attention,
7 salience, motor, and subcortical-cerebellum networks (**Fig. 5b**). These brain regions
8 have been widely implicated with ADHD in previous studies. ADHD patients have been
9 observed to have stronger connectivity across the supplementary motor area,
10 precentral, and superior frontal regions¹²¹. These regions are also associated with
11 difficulties in performing some fine motor skills¹²². In addition, the putamen and
12 caudate regions compose the dorsal striatum, one largest part of the basal ganglia,
13 which is important in controlling motor functions^{123,124}. Moreover, significant genetic
14 correlations were observed between SCZ and connection strengths over the precentral,
15 postcentral, precuneus, frontal, and superior parietal regions (**Fig. 5c**); and between
16 MDD and the interactions among the middle temporal, angular, and superior and
17 middle frontal regions (**Fig. 5d, Supplementary Note**).

18

19 In addition, many genetic correlations were observed between functional connectivity
20 and cognitive traits studied in previous GWAS, including intelligence, cognitive
21 performance, general cognitive function, and numerical reasoning. For example,
22 intelligence had genetic correlations with connection strengths over multiple brain
23 regions ($|gc|$ range = (0.11, 0.34), $P < 1.8 \times 10^{-4}$, **Fig. 5e**). The strongest correlation
24 located at the superior and middle frontal regions in the central executive and salience
25 networks. It is known that the frontal lobe is associated with higher level cognitive skills,
26 such as problem solving, thinking, planning, and organizing¹²⁵. Wang, et al. ¹²⁶ revealed a
27 general intelligence network for logical-math, general intelligence, and linguistic skills,
28 which widely included frontal, parietal, occipital, temporal, and limbic regions.
29 Furthermore, significant genetic correlations were broadly observed on subjective
30 well-being, education, neuroticism, sleep, risk tolerance, automobile speeding, manual
31 occupation, BMI, high blood pressure, and behavioral factors (drinking and smoking)

1 **(Supplementary Figs. 18-19)**. More details and interpretations can be found in
2 **Supplementary Note**.

3

4 **Gene-level association analysis and biological annotations.**

5 Gene-level association was tested via MAGMA¹²⁷ (Methods), which detected 970
6 significant gene-trait associations ($P < 1.5 \times 10^{-9}$, adjusted for 1,777 phenotypes) for 123
7 genes **(Supplementary Fig. 20, Supplementary Table 11)**. In addition, we applied
8 FUMA⁵⁴ to map significant variants ($P < 2.8 \times 10^{-11}$) to genes via physical position,
9 expression quantitative trait loci (eQTL) association, and 3D chromatin (Hi-C)
10 interaction, which yielded 197 more associated genes that were not discovered in
11 MAGMA (276 in total, **Supplementary Table 12**). For the 320 genes associated with
12 intrinsic brain activity in either MAGMA or FUMA, 84 had been linked to white matter
13 microstructure¹⁰³, 48 were reported to be associated with regional brain volumes³⁷, and
14 42 were related to both of them **(Supplementary Table 13)**. These triple overlapped
15 genes were also widely associated with other complex traits, such as Parkinson's disease,
16 neuroticism, stroke, alopecia, handedness, and intelligence **(Supplementary Table 14)**,
17 providing more insights into the genetic overlaps among brain structure, brain function,
18 and other brain-related traits. For example, *MAPT*, *NSF*, *WNT3*, and *LRRC37A3* were risk
19 genes of Parkinson's disease, which were also associated with pallidum volumes³⁷, white
20 matter microstructure¹⁰³, and intrinsic functional connectivity in central executive,
21 default mode, and salience networks. These complementary neuroimaging traits had all
22 been used to study the pathophysiology of Parkinson's disease¹²⁸⁻¹³⁰. Similarly, *CDKN2C*
23 and *FAF1* were associated with ischemic stroke¹³¹ as well as multiple neuroimaging
24 traits of brain structure and function. In addition, 4 of our intrinsic brain activity
25 associated genes (*CALY*, *SLC47A1*, *CYP2C8*, and *CYP2C9*) were targets for 11 nervous
26 system drugs¹³², such as 4 psycholeptics (ATC code: N05) to produce calming effects, 2
27 anti-depressants (N06A) to treat MDD and related conditions, 2 anti-migraine (N02C),
28 and one anti-dementia (N06D) **(Supplementary Table 15)**.

29

30 It is of particular interest to study the functional connectivity dysfunction in Alzheimer's
31 disease and identify the overlapped genes^{20,133}. Our gene-level analysis replicated *APOE*
32 and *SORL1*, which were frequently targeted in Alzheimer's disease-candidate gene

1 studies of functional connectivity^{23,134}. More importantly, we uncovered more
2 overlapped genes between intrinsic brain activity and Alzheimer's disease, such as
3 *PVRL2*, *TOMM40*, *APOC1*, *MAPK7*, *CLPTM1*, *HESX1*, *BCAR3*, *ANO3*, and *YAP1*
4 (**Supplementary Table 16**). Interestingly, through the BIG-KP server, we found that
5 these genes had much stronger associations with intrinsic brain function than brain
6 structure. We also observed many pleiotropic genes associated with serum metabolite,
7 low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglyceride,
8 type II diabetes mellitus, and blood protein measurements, all of which might be related
9 to the Alzheimer's disease^{135,136}. These results expand the overview of the shared
10 genetic components among metabolic dysfunction, blood biomarkers, brain function in
11 Alzheimer's disease research, suggesting the potential value of integrating these traits in
12 future studies.

13

14 To identify the tissues and cell types in which genetic variation yields differences in brain
15 functional connectivity, we performed partitioned heritability analyses¹³⁷ for tissue type
16 and cell type specific regulatory elements¹³⁸ (Methods). We focused on the 10
17 functional connectivity traits that had heritability higher than 30%. At FDR 5% level, the
18 most significant enrichments of heritability were observed in active gene regulation
19 regions of fetal brain tissues, neurospheres, and neuron/neuronal progenitor cultured
20 cells (**Supplementary Fig. 21, Supplementary Table 17**). We also tried to further identify
21 brain cell type specific enrichments using chromatin accessibility data of two main gross
22 brain cell types¹³⁹ (i.e., neurons (NeuN+) and glia (NeuN-)) and multiple neuronal and
23 glial cell subtypes, including oligodendrocyte (NeuN-/Sox10+), microglia, and astrocyte
24 (NeuN-/Sox10-), as well as GABAergic (NeuN+/Sox6+) and glutamatergic neurons
25 (NeuN+/Sox6-). Although enrichments were observed in some cell types, few of them
26 remained significant after adjusting for multiple testing (**Supplementary Fig. 22,**
27 **Supplementary Table 18**). Next, we performed MAGMA tissue-specific gene property¹²⁷
28 analysis for 13 GTEx¹⁴⁰ (v8) brain tissues (Methods). We found that genes with higher
29 expression levels in human brain tissues generally had stronger associations with
30 intrinsic brain activity, particularly for tissues sampled from cerebellar hemisphere and
31 cerebellum regions ($P < 1.9 \times 10^{-5}$, **Supplementary Fig. 23, Supplementary Table 19**).

32

1 Among the associated variants of intrinsic brain activity, a few resided in frequently
2 interacting regions (FIREs) and topologically associating domain (TAD) boundaries in
3 brain tissues^{141,142} (**Supplementary Table 20**). Partitioned heritability analysis also
4 provided suggestive evidence of heritability enrichment in these FIREs and TAD
5 boundaries (**Supplementary Fig. 24, Supplementary Table 21**). We performed
6 additional gene mapping using 14 recent Hi-C datasets of brain tissue and cell
7 types¹⁴¹⁻¹⁴⁵ (Methods). This Hi-C gene mapping prioritized 29 genes, 14 of which were
8 not identified by the Hi-C analysis in FUMA⁵⁴ (**Supplementary Table 22**). Many of the
9 newly mapped genes have been reported for brain-related disorders/conditions, sleep,
10 and intelligence, including *APOE*, *HSPG2*, *APOC1*, *UFL1*, *NR2F1*, *NPM1*, *FAM172A*, *FADD*,
11 *FHL5*, and *EPHA3*. Finally, MAGMA¹²⁷ gene-set analysis was performed to prioritize the
12 enriched biological pathways (Methods). We found 59 significantly enriched gene sets
13 after Bonferroni adjustment ($P < 1.8 \times 10^{-9}$, **Supplementary Table 23**). Multiple
14 pathways related to nervous system were detected, such as “go neurogenesis” (GO:
15 0022008), “go neuron differentiation” (GO: 0030182), “go regulation of nervous system
16 development” (GO: 0051960), “go regulation of neuron differentiation” (GO: 0045664),
17 “go cell morphogenesis involved in neuron differentiation” (GO: 0048667), and “go
18 neuron development” (GO: 0048666).

19

20 **DISCUSSION**

21 In the present study, we evaluated the influences of common variants on intrinsic brain
22 functional architecture using harmonized rsfMRI data of 44,190 subjects from four
23 independent studies. Genome-wide association analysis found hundreds of novel loci
24 related to intrinsic brain activity in the UKB British cohort, which were successfully
25 replicated in independent datasets. The interactions across core neurocognitive
26 networks (central executive, default mode, and salience) in the triple network model
27 had genetic links with cognition and multiple brain disorders. Shared genetic influences
28 among functional, structural, and diffusion neuroimaging traits were also uncovered,
29 showing that brain structure and function are intimately related. Gene-level analysis
30 detected many overlapped genes between intrinsic brain activity and Alzheimer’s
31 disease. We also detected a colocalization between one of the two variants in the *APOE*
32 $\epsilon 4$ locus and function of the default mode, central executive, attention, and visual

1 networks, which may explain in part the functional mechanism underlying Alzheimer's
2 risk. The enriched tissues and biological pathways were also prioritized in bioinformatic
3 analyses. Compared to the previous study³¹ with about 8,000 subjects, this large-scale
4 GWAS much improved our understanding of the genetic architecture of functional
5 human brain.

6

7 Our study faces a few limitations. First, the samples in our discovery GWAS were mainly
8 from European ancestry. In our PRS analysis, we illustrated a relatively poor replication
9 of the European GWAS results within validation cohorts with non-European ancestry.
10 The non-European GWAS was of small sample size, so population specific influences will
11 be better understood when more data from global populations become available.
12 Second, our study focused on the brain functional activity at rest. A recent study²⁸ had
13 found that combining rsfMRI and task functional magnetic resonance imaging (tfMRI)
14 may result in higher heritability estimates and potentially boost the GWAS power. Thus,
15 future studies could model rsfMRI and tfMRI together to uncover more insights into the
16 genetic influences on brain function. In addition, we applied ICA in this study, which was
17 a popular approach to characterize the functionally connected brain⁶. It is also of great
18 interest to evaluate the performance of other popular rsfMRI approaches (such as
19 seed-based analysis) in these large-scale datasets. Finally, although we found genetic
20 links between brain function and other complex traits, future work is needed to dissect
21 the underlying mechanisms by which genetic variation leads to differences in brain
22 activity. We expect that accumulating publicly available imaging genetics data resources
23 will lead to a better understanding of specific genes involved in human brain structure
24 function relationships and how variants can alter these relationships leading to risk for
25 neuropsychiatric disorders.

26

27 **URLs.**

28 Brain Imaging Genetics Knowledge Portal (BIG-KP), <https://bigkp.org/>;

29 Brain Imaging GWAS Summary Statistics, <https://github.com/BIG-S2/GWAS>;

30 UKB Imaging Pipeline, https://git.fmrib.ox.ac.uk/falmagro/UK_biobank_pipeline_v_1;

31 PLINK, <https://www.cog-genomics.org/plink2/>;

32 GCTA & fastGWA, <http://cnsgenomics.com/software/gcta/>;

- 1 METAL, <https://genome.sph.umich.edu/wiki/METAL>;
- 2 FUMA, <http://fuma.ctglab.nl/>;
- 3 MGAMA, <https://ctg.cncr.nl/software/magma>;
- 4 LDSC, <https://github.com/bulik/ldsc/>;
- 5 FINDOR, <https://github.com/gkichaev/FINDOR>;
- 6 NHGRI-EBI GWAS Catalog, <https://www.ebi.ac.uk/gwas/home>;
- 7 The atlas of GWAS Summary Statistics, <http://atlas.ctglab.nl/>.

8

9 **METHODS**

10 Methods are available in the **Methods** section.

11 *Note: One supplementary information pdf file and one supplementary table zip file are*
12 *available.*

13

14 **ACKNOWLEDGEMENTS**

15 This research was partially supported by U.S. NIH grants MH086633 (H.Z.) and
16 MH116527 (TF.L.). We thank the individuals represented in the UK Biobank, ABCD, HCP,
17 and PNC studies for their participation and the research teams for their work in
18 collecting, processing and disseminating these datasets for analysis. We gratefully
19 acknowledge all the studies and databases that made GWAS summary data available.
20 This research has been conducted using the UK Biobank resource (application number
21 22783), subject to a data transfer agreement. Part of the data used in the preparation of
22 this article were obtained from the Adolescent Brain Cognitive Development (ABCD)
23 Study (<https://abcdstudy.org>), held in the NIMH Data Archive (NDA). This is a multisite,
24 longitudinal study designed to recruit more than 10,000 children age 9-10 and follow
25 them over 10 years into early adulthood. The ABCD Study is supported by the National
26 Institutes of Health and additional federal partners under award numbers
27 U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106,
28 U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156,
29 U01DA041174, U24DA041123, U24DA041147, U01DA041093, and U01DA041025. A full
30 list of supporters is available at <https://abcdstudy.org/federal-partners.html>. A listing of
31 participating sites and a complete listing of the study investigators can be found at
32 <https://abcdstudy.org/scientists/workgroups/>. ABCD consortium investigators designed

1 and implemented the study and/or provided data but did not necessarily participate in
2 analysis or writing of this report. This manuscript reflects the views of the authors and
3 may not reflect the opinions or views of the NIH or ABCD consortium investigators.
4 Support for the collection of the PNC datasets was provided by grant RC2MH089983
5 awarded to Raquel Gur and RC2MH089924 awarded to Hakon Hakonarson. All PNC
6 subjects were recruited through the Center for Applied Genomics at The Children's
7 Hospital in Philadelphia. HCP data were provided by the Human Connectome Project,
8 WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil;
9 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH
10 Blueprint for Neuroscience Research; and by the McDonnell Center for Systems
11 Neuroscience at Washington University.

12

13 **AUTHOR CONTRIBUTIONS**

14 B.Z., H.Z., J.L.S., S.M.S., and Y.L. designed the study. B.Z., T.F.L., D.X., X.W., Y.Y., T.Y.L.,
15 N.M., Q.S., Y.C.Y. analyzed the data. T.F. L., Z.Z., and Y.S. downloaded the datasets,
16 processed rsfMRI data, and undertook quality controls. P.R., M.E.H., J.B., and J.F.F.
17 analyzed brain cell chromatin accessibility data. B.Z. and H.Z. wrote the manuscript with
18 feedback from all authors.

19

20 **CORRESPONDENCE AND REQUESTS FOR MATERIALS** should be addressed to H.Z.

21

22 **COMPETING FINANCIAL INTERESTS**

23 The authors declare no competing financial interests.

24

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30

31 METHODS

1 **Imaging phenotypes and datasets.** The rsfMRI datasets were consistently processed
2 following the procedures in UK Biobank imaging pipeline⁹. Details about image
3 acquisition, preprocessing, and phenotype generation in each dataset can be found in
4 **Supplementary Note**. Following the previous study³¹, we generated two groups of
5 phenotypes, including 76 node amplitude traits reflecting the spontaneous neuronal
6 activity, and 1,695 pairwise functional connectivity traits quantifying co-activity for node
7 pairs, as well as 6 global functional connectivity measures to summarize all pairwise
8 functional connectivity. To aid interpretation of these phenotypes, the functional brain
9 regions characterized in ICA were labelled using the automated anatomical labeling
10 atlas⁵¹ (**Supplementary Table 24**) and were mapped onto major functional networks
11 defined in Yeo, et al. ¹⁴ and Finn, et al. ¹² (**Supplementary Figs. 25-26**). The assigned
12 location and functional networks are provided in **Supplementary Table 25**. Details of
13 our mapping procedures are provided in **Supplementary Note**. For each continuous
14 phenotype or covariate variable, values greater than five times the median absolute
15 deviation from the median value were removed. We analyzed the following nine
16 datasets separately: 1) the UKB discovery GWAS, which used data of individuals of
17 British ancestry¹⁴⁶ in the UKB study ($n = 34,691$); 2) four European validation GWAS: UKB
18 White but Non-British (UKBW, $n = 1,970$), ABCD European (ABCDE, $n = 3,821$), HCP ($n =$
19 495), and PNC ($n = 510$); 3) two non-European UKB validation GWAS: UKB Asian (UKBA,
20 $n = 446$) and UKB Black (UKBBL, $n = 232$); and 4) two non-European non-UKB validation
21 GWAS, including ABCD Hispanic (ABCDH, $n = 768$) and ABCD African American (ABCD A,
22 $n = 1,257$). See **Supplementary Table 26** for a summary of these datasets and
23 demographic information. The assignment of ancestry in UKB was based on
24 self-reported ethnicity (Data-Field 21000), which was verified in Bycroft, et al. ¹⁴⁶. The
25 ancestry in ABCD was assigned by combining the self-reported ethnicity and ancestry
26 inference results as in Zhao, et al. ¹⁰³.

27

28 **GWAS discovery and validation.** Details of genotyping and quality controls can be found
29 in **Supplementary Note**. SNP heritability was estimated by GCTA⁵² using all autosomal
30 SNPs in the UKB British cohort. We adjusted the effects of age (at imaging),
31 age-squared, sex, age-sex interaction, age-squared-sex interaction, imaging site, and the
32 top 40 genetic principle components (PCs). Genome-wide association analysis was

1 performed in linear mixed effect model using fastGWA¹⁴⁷, while adjusting the same set
2 of covariates as in GCTA. GWAS were also separately performed via Plink¹⁴⁸ in the eight
3 validation datasets, including UKBW, UKBBL, UKBA, ABCDA, ABCDH, ABCDE, HCP, and
4 PNC, where the effects of age, age-squared, sex, imaging sites (if applicable), scanners (if
5 applicable), age-sex interaction, age-squared-sex interaction, and top ten genetic PCs
6 were adjusted.

7

8 To validate results in the UKB British discovery GWAS, meta-analysis was performed
9 using the sample-size weighted approach via METAL¹⁴⁹. We examined whether the
10 locus-level associations detected in the British GWAS can be replicated in the 1)
11 meta-analyzed four European validation GWAS (UKBW, ABCDE, HCP, and PNC); 2)
12 meta-analyzed four non-European validation GWAS (UKBBL, UKBA, ABCDA, and ABCDH);
13 and 3) the combination of the above eight validation GWAS. Specifically, for each
14 meta-analyzed GWAS, we checked and reported the smallest *P*-value among the
15 variants within each associated locus identified in the UKB British discovery GWAS.
16 Polygenic risk scores (PRS) were constructed on eight validation datasets using Plink.
17 The BLUP effect sizes estimated from GCTA-GREML analysis in UKB British discovery
18 GWAS were used as weights in PRS construction, which accounted for the LD structures.
19 Ambiguous variants (i.e. variants with complementary alleles) were removed from
20 analysis. We tried 17 *P*-value thresholds for variant selection according to their marginal
21 *P*-values from fastGWA: 1, 0.8, 0.5, 0.4, 0.3, 0.2, 0.1, 0.08, 0.05, 0.02, 0.01, 1×10^{-3} , $1 \times$
22 10^{-4} , 1×10^{-5} , 1×10^{-6} , 1×10^{-7} , and 1×10^{-8} . The best prediction accuracy achieved by a
23 single threshold was reported for each phenotype, which was measured by the
24 additional phenotypic variation that can be explained by the polygenic profile (i.e., the
25 incremental R-squared), while adjusting for the effects of age, sex, and top ten genetic
26 PCs.

27

28 **The shared loci and genetic correlation.** The genomic loci associated with intrinsic brain
29 activity traits were defined using FUMA (version 1.3.5e). We input UKB British discovery
30 summary statistics after reweighting the *P*-values using functional information via
31 FINDOR⁹⁸. To define the LD boundaries, FUMA identified independent significant
32 variants, which were defined as variants with a *P*-value smaller than the predefined

1 threshold and were independent of other significant variants ($LD\ r^2 < 0.6$). FUMA then
2 constructed LD blocks for these independent significant variants by tagging all variants
3 in LD ($r^2 \geq 0.6$) with at least one independent significant variant and had a $MAF \geq$
4 0.0005 . These variants included those from the 1000 Genomes reference panel that may
5 not have been included in the GWAS. Moreover, within these significant variants,
6 independent lead variants were identified as those that were independent from each
7 other ($LD\ r^2 < 0.1$). If LD blocks of independent significant variants were close ($< 250\text{ kb}$
8 based on the closest boundary variants of LD blocks), they were merged into a single
9 genomic locus. Thus, each genomic locus could contain multiple significant variants and
10 lead variants. Independent significant variants and all the variants in LD with them ($r^2 \geq$
11 0.6) were searched by FUMA on the NHGRI-EBI GWAS catalog (version 2019-09-24) to
12 look for previously reported associations ($P < 9 \times 10^{-6}$) with any traits. LDSC¹⁰² software
13 (version 1.0.1) was used to estimate and test the pairwise genetic correlation. We used
14 the pre-calculated LD scores provided by LDSC, which were computed using 1000
15 Genomes European data. We used HapMap3¹⁵⁰ variants and removed all variants in the
16 major histocompatibility complex (MHC) region. The summary statistics of intrinsic brain
17 activity traits were from the UKB British discovery GWAS and the resources of other
18 summary statistics were provided in **Supplementary Table 9**.

19

20 **Gene-level analysis and biological annotation.** Gene-based association analysis was
21 performed in UKB British participants for 18,796 protein-coding genes using MAGMA¹²⁷
22 (version 1.07). Default MAGMA settings were used with zero window size around each
23 gene. We then carried out FUMA functional annotation and mapping analysis, in which
24 variants were annotated with their biological functionality and then were linked to
25 35,808 candidate genes by a combination of positional, eQTL, and 3D chromatin
26 interaction mappings. Brain-related tissues/cells were selected in all options and default
27 values were used for all other parameters in FUMA. For the detected genes in MAGMA
28 and FUMA, we performed lookups in the NHGRI-EBI GWAS catalog (version 2020-02-08)
29 to explore their previously reported gene-trait associations. We performed heritability
30 enrichment analysis via partitioned LDSC¹³⁷. Baseline models were adjusted when
31 estimating and testing the enrichment scores for our tissue type and cell type specific
32 annotations. Methods to analysis chromatin data of glial and neuronal cell subtypes can

1 be found in Zhao, et al.¹⁰³. We also performed gene property analysis for the 13 GTEx¹⁴⁰
2 v8 brain tissues via MAGMA. Specifically, we examined whether the tissue-specific gene
3 expression levels can be linked to the strength of the gene-trait association. MAGMA
4 was also used to explore the enriched biological pathways, in which we tested 500
5 curated gene sets and 9,996 Gene Ontology (GO) terms from the Molecular Signatures
6 Database¹⁵¹ (MSigDB, version 7.0). Additional gene mapping was performed using 14
7 Hi-C datasets of brain tissue and cell types from five recent studies, including 1) the
8 promoter capture Hi-C (PCHi-C) data of hippocampus and dorsolateral prefrontal cortex
9 (DLPFC)¹⁴³; 2) the Hi-C data of hippocampus and DLPFC¹⁴¹; 3) the Hi-C data from fetal
10 and adult cortices¹⁴², restricting to the high confidence interactions; 4) the PCHi-C data
11 of primary astrocytes and three types of induced pluripotent stem cell (iPSC)-derived
12 neurons¹⁴⁴ (cortical, hippocampal, and motor); and 5) proximity ligation assisted
13 chromatin immunoprecipitation (PLAC-seq) data on sorted fetal neuron cells¹⁴⁵,
14 including radial glial cells, intermediate progenitor cells, neurons, and interneurons. For
15 interaction intensity cutoffs, we used 2 for the $-\log_{10}(P)$ used in datasets of Jung, et al.
16 ¹⁴³, 0.05 for the q -value in Schmitt, et al.¹⁴¹ and Giusti-Rodriguez and Sullivan¹⁴², 5 for
17 the Chicago score in Song, et al.¹⁴⁴, and 0.01 for the FDR in Song, et al.¹⁴⁵.

18

19 **Code availability**

20 We made use of publicly available software and tools listed in URLs. Other codes used in
21 our analyses are available upon reasonable request.

22

23 **Data availability**

24 Our GWAS summary statistics can be downloaded at <https://github.com/BIG-S2/GWAS>.
25 The individual-level data used in the present study can be obtained from four publicly
26 accessible data resources: UK Biobank (<http://www.ukbiobank.ac.uk/resources/>), ABCD
27 (<https://abcdstudy.org/>), HCP (<https://www.humanconnectome.org/>), and PNC
28 (<https://www.med.upenn.edu/bbl/philadelphianeurodevelopmentalcohort.html>). Our
29 results can also be easily browsed through our knowledge portal <https://bigkp.org/>.

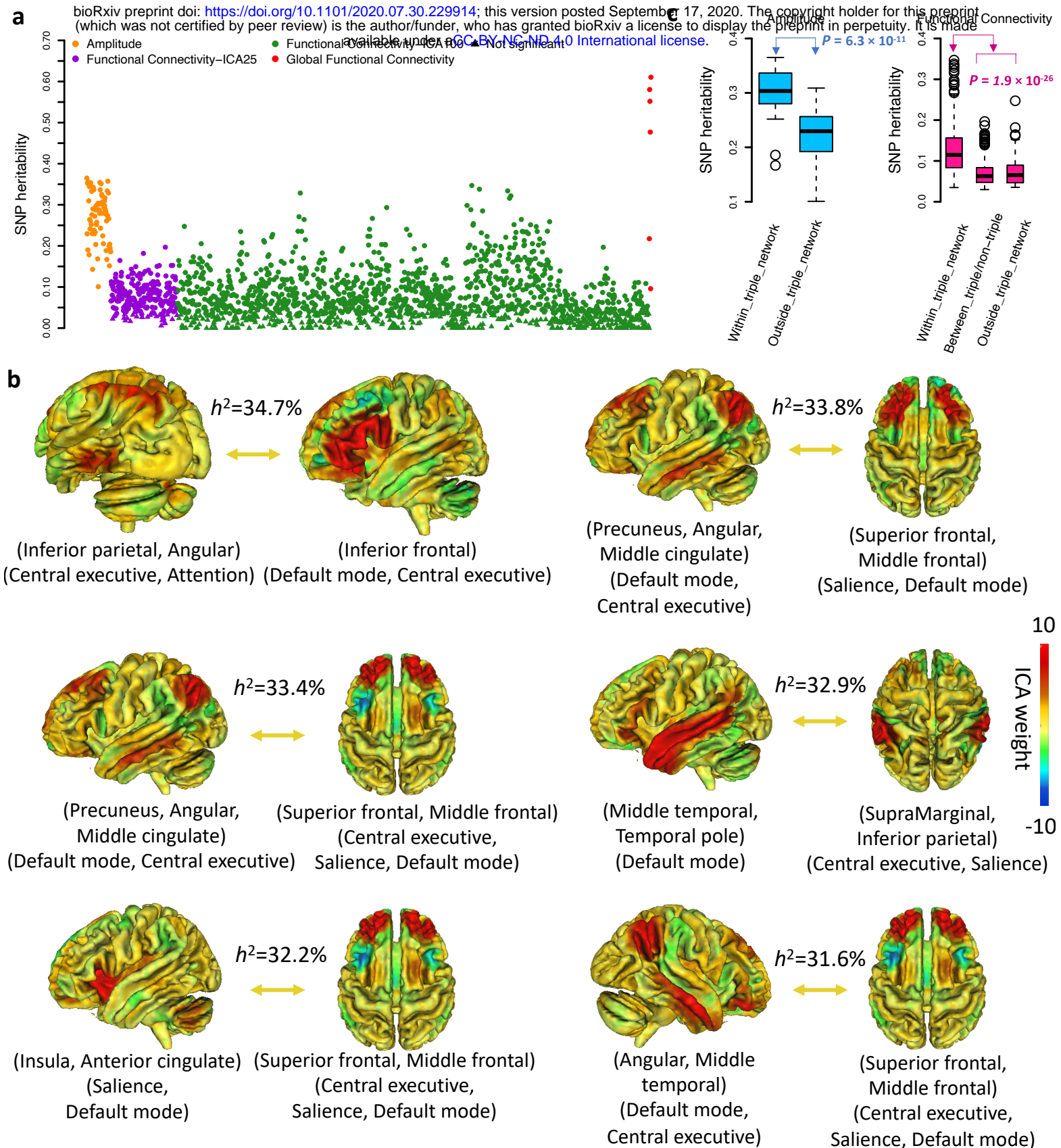


Figure 1: SNP heritability analysis of rsfMRI traits (n = 34,691 subjects). **a**) Heritability estimates of 1,777 rsfMRI traits of brain activity, including 76 amplitude traits, 1,695 pairwise functional connectivity traits (from two parcellations with 25 and 100 dimensionalities, respectively), and 6 global functional connectivity measures. **b**) Location and functional network of the pairs of functional regions (i.e., nodes) characterized by spatial independent component analysis (ICA) whose inter-regional functional connectivity had heritability (h^2) higher than 30%. The color represents the weight profile of the ICA node. For example, the functional connectivity between two ICA nodes mainly over the inferior parietal, angular and inferior frontal regions had $h^2 = 34.7\%$. **c**) Comparison of the heritability within the triple network (i.e., the three core neurocognitive networks: central executive, default mode, and salience) and the heritability outside the triple network. P -value (P) of the two-sided Wilcoxon rank test was used to evaluate the difference.

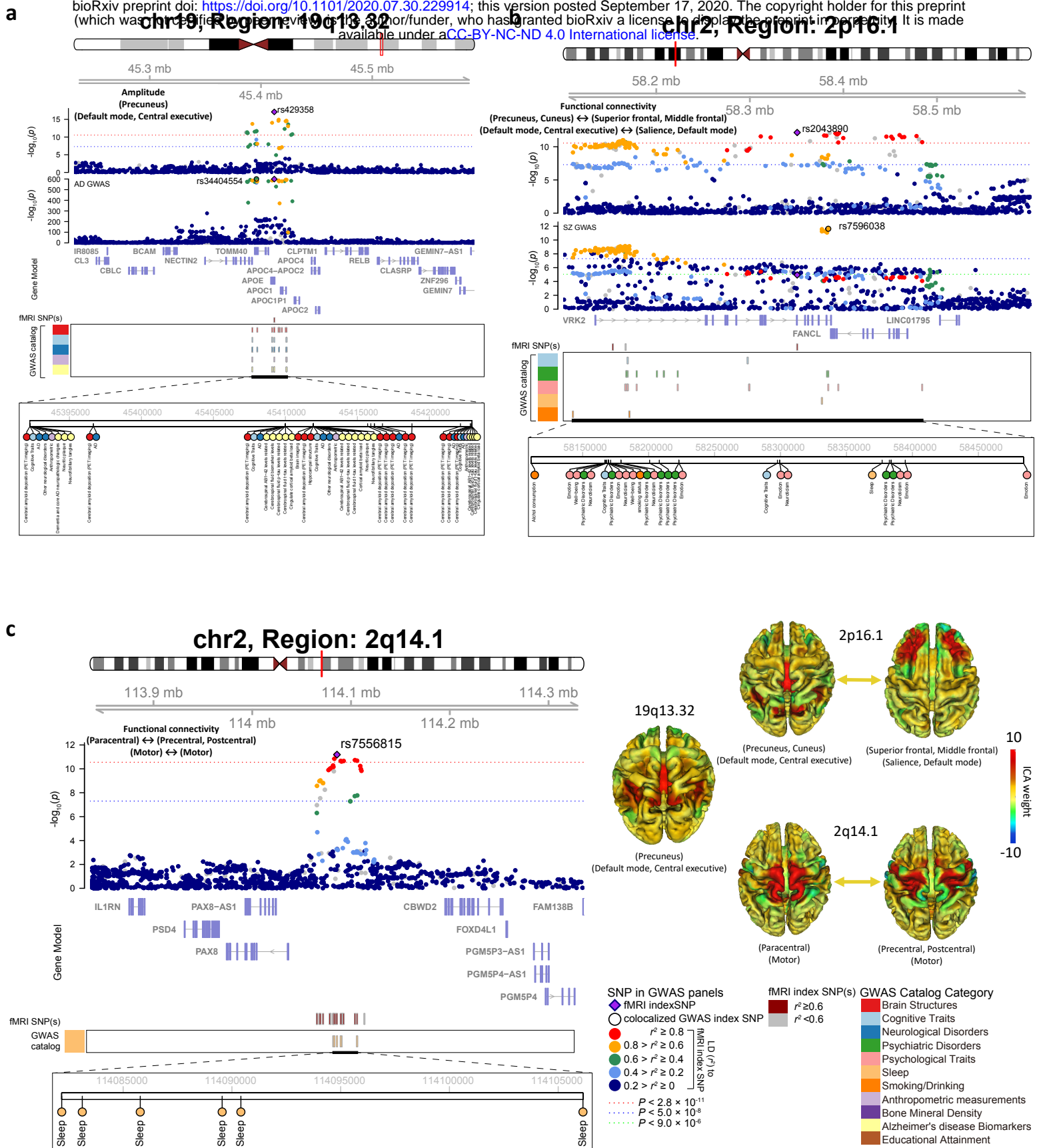


Figure 2: Selected genetic loci that associated with both rsfMRI traits of brain activity and other brain-related complex traits and disorders. We highlight local colocalization ($LD\ r^2 \geq 0.6$) in **a**) 19q13.32 (colocalized with Alzheimer's disease); **b**) 2p16.1 (with schizophrenia); and **c**) 2q14.1 (with sleep). For example, in 19q13.32, we observed colocalization between the amplitude of the precuneus region in the default mode and central executive networks with Alzheimer's disease. Location and functional network of the displayed three rsfMRI traits are illustrated on the bottom right. More examples of the shared genetic loci and the involved rsfMRI traits can be found in Supplementary Figures 4-12.

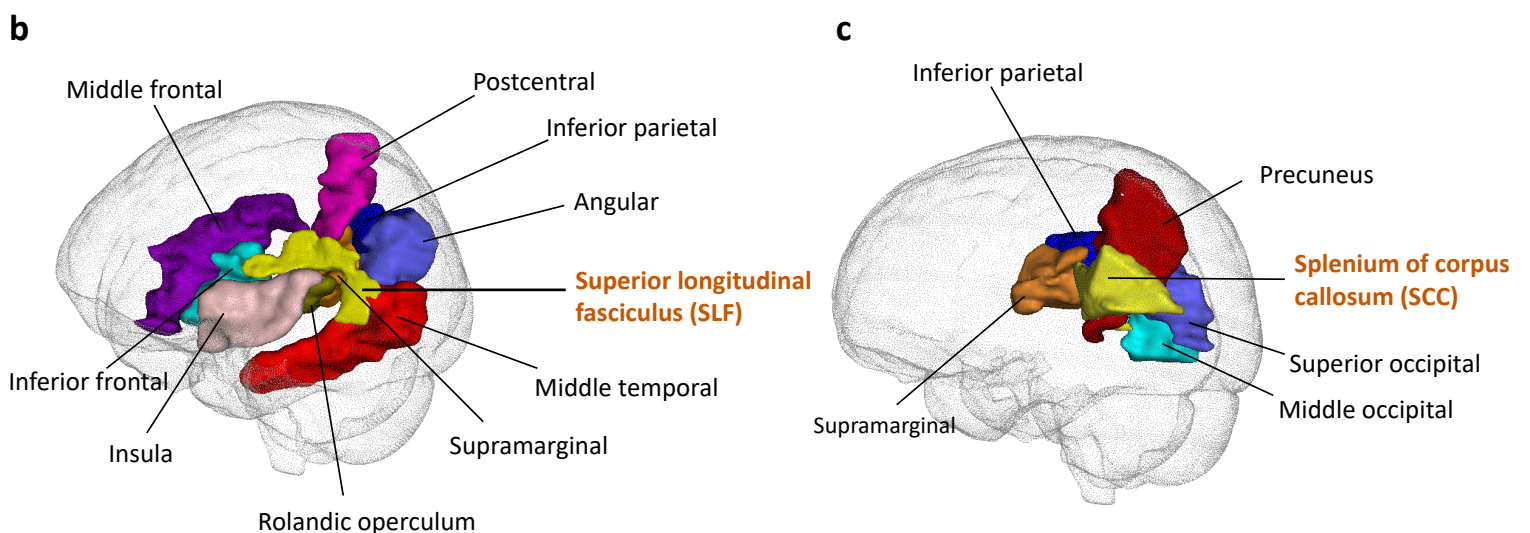
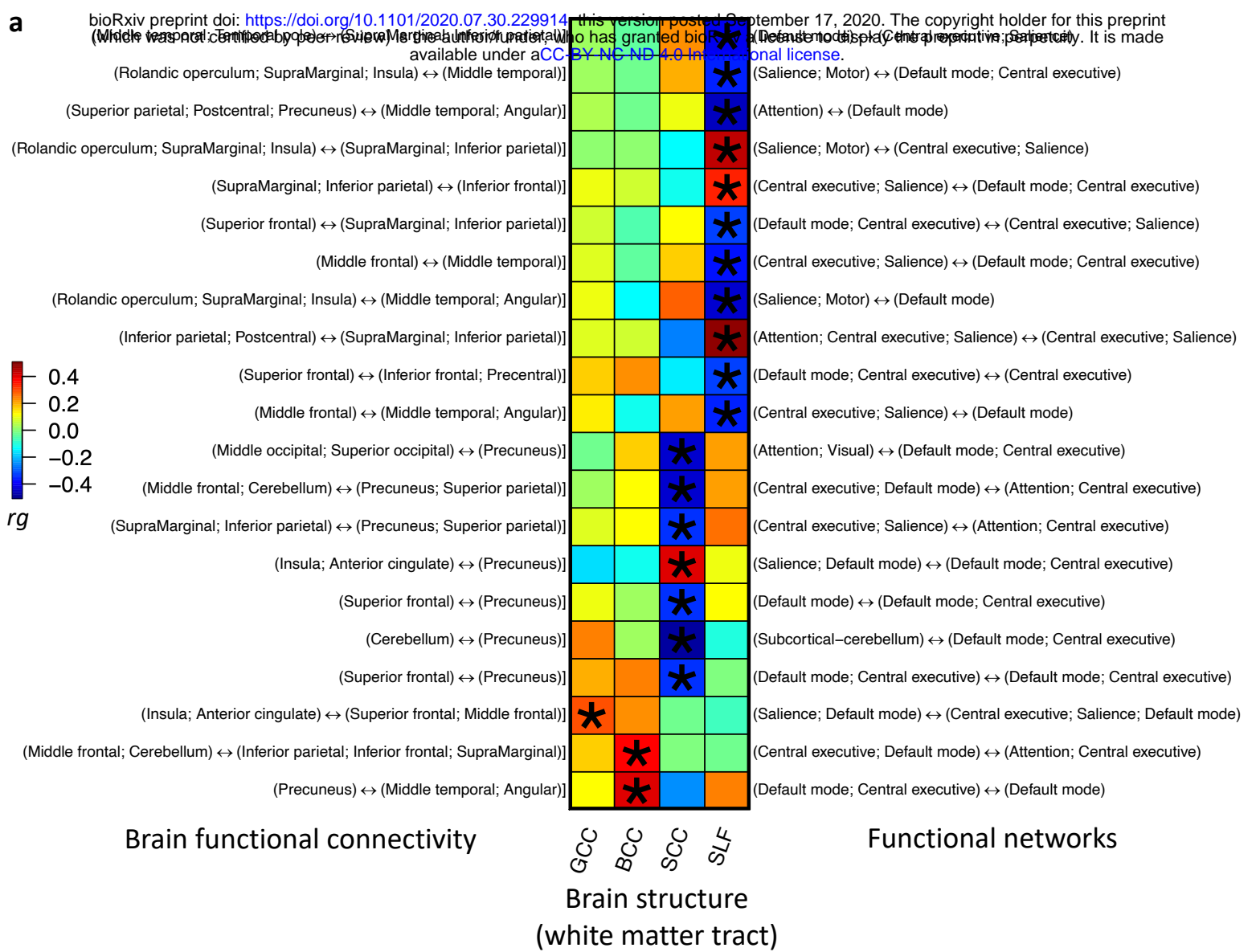


Figure 4: Selected pairwise genetic correlations between functional connectivity traits and fractional anisotropy (FA) of white matter tracts. a) The asterisks highlight significant associations after controlling the false discovery rate at 0.05 level. The left y-axis lists the location of functional connectivity traits, the right y-axis shows the associated functional networks, and the x-axis provides the name of white matter tracts. The colors represent genetic correlations (*rg*). **b)** Location of the SLF (left part) and its neighboring brain regions whose functional connectivity strengths were genetically correlated with the FA of SLF. The colors describe different brain regions. **c)** Location of the SCC (left part) and its neighboring brain regions whose functional connectivity strengths were genetically correlated with the FA of SCC.

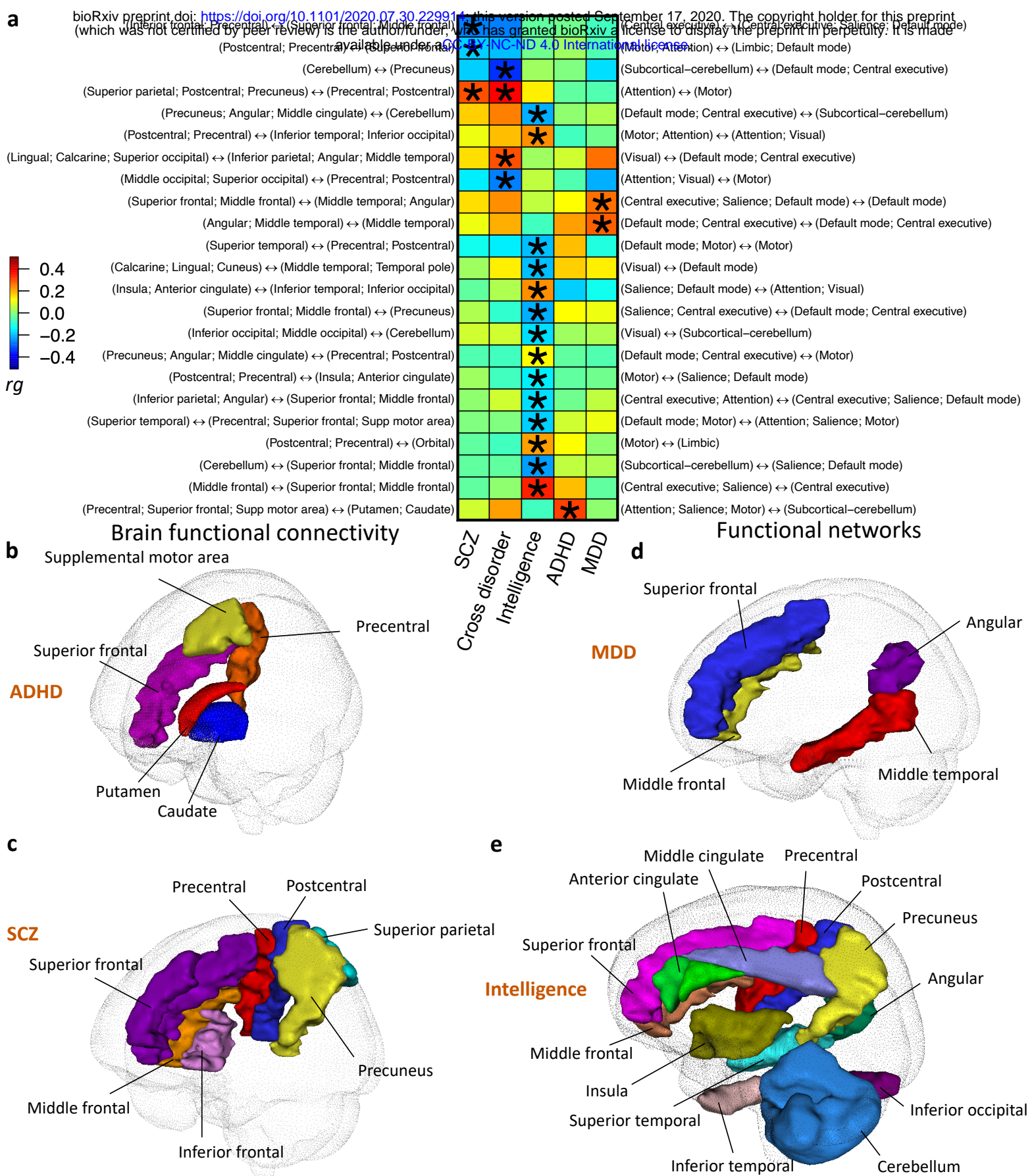


Figure 5: Selected pairwise genetic correlations between functional connectivity traits and other brain-related traits/disorders. **a**) The asterisks highlight significant associations after controlling the false discovery rate at 0.05 level. The left y-axis lists the location of functional connectivity traits, the right y-axis shows the associated functional networks, and the x-axis provides the name of other brain-related traits/disorders. The colors represent genetic correlations (rg). **b-e**) Location of the brain regions whose functional connectivity strengths were genetically correlated with **b**) attention-deficit/hyperactivity disorder (ADHD); **c**) schizophrenia (SCZ); **d**) major depressive disorder (MDD); and **e**) intelligence. The colors describe different brain regions.