

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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## 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.

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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 cognition<sup>1-4</sup>. 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<sup>5,6</sup>, resting-state functional magnetic resonance imaging<sup>7</sup> (rsfMRI) captures  
6 spontaneous intrinsic brain activity<sup>8</sup>. 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<sup>6,9,10</sup>. 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<sup>6,11</sup>.

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 networks<sup>12-14</sup>.  
16 Among these RSNs, the central executive, default mode, and salience networks are  
17 three core neurocognitive networks that support efficient cognition<sup>15-17</sup>. 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<sup>16,18</sup>. Supporting this model, differences in RSNs have  
21 been detected in multiple neurological and psychiatric disorders<sup>19</sup> relative to  
22 neurotypical controls, such as Alzheimer's disease<sup>20</sup>, Parkinson's disease<sup>21</sup>, and major  
23 depressive disorder (MDD)<sup>22</sup>.

24

25 Twin and family studies have largely reported a low to moderate degree of genetic  
26 contributions to intrinsic brain activity<sup>23-29</sup>. For example, the family-based heritability  
27 estimates of major RSNs ranged from 20% to 40% in the Human Connectome Project  
28 (HCP)<sup>30</sup>. In a previous study using about 8,000 UK Biobank (UKB) individuals<sup>31</sup>, the SNP  
29 heritability<sup>32</sup> 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*<sup>33</sup> and *KIBRA*<sup>34</sup>), currently only one genome-wide association study (GWAS)<sup>31</sup>  
32 has been successfully performed on rsfMRI<sup>23</sup> ( $n \approx 8000$ ). This is likely due to both

1 insufficient sample size for GWAS discovery and weaker genetic effects on brain  
2 function than structure<sup>31,35-39</sup>. 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 effects<sup>40</sup> (e.g., image acquisition, processing  
5 procedures, and software) may cause additional technical variability in rsfMRI  
6 analyses<sup>41</sup>, 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.

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11 To address these challenges, here we collected individual-level rsfMRI data from four  
12 independent studies, including the UK Biobank<sup>42</sup>, Adolescent Brain Cognitive  
13 Development (ABCD<sup>43</sup>), Philadelphia Neurodevelopmental Cohort (PNC<sup>44</sup>), and HCP<sup>45</sup>.  
14 We harmonized rsfMRI processing procedures by following the unified UKB brain  
15 imaging pipeline<sup>9,46</sup>. Functional brain regions and corresponding functional connectivity  
16 were characterized via spatial Independent Component Analysis (ICA)<sup>47,48</sup> for 44,190  
17 individuals from multiple ancestries, including 37,339 from UK Biobank. As in previous  
18 studies<sup>9,31,49</sup>, two parcellations with different dimensionalities<sup>13,50</sup> (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-artifactual<sup>9</sup>. 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 traits<sup>31</sup>. 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 atlas<sup>51</sup> and were mapped onto major functional networks defined in Yeo, et al.<sup>14</sup> and  
30 Finn, et al.<sup>12</sup>. 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 GCTA<sup>52</sup>. 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 psychopathology<sup>16</sup>.  
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  $6.3 \times 10^{-11}$ , 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  $1.9 \times 10^{-26}$ ). 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 results<sup>31</sup>, 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 tracts<sup>53</sup> and 40% for regional brain volumes measuring brain morphometry<sup>37</sup>.  
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  $2.8 \times 10^{-11}$  ( $5 \times$   
7  $10^{-8}/1,777$ , i.e., the standard GWAS threshold, Bonferroni-adjusted for the 1,777 traits),  
8 FUMA<sup>54</sup> 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 GWAS<sup>31</sup>,  
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 disorders<sup>18</sup>.

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  $8.2 \times 10^{-5}$  (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 scores<sup>55</sup> (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 ( $197 \times 4$  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 = ( $1.1 \times 10^{-24}$ ,  $4 \times 10^{-13}$ )). 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 ( $197 \times 4$  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 catalog<sup>56</sup>, 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 disease<sup>57-59</sup>,  
26 frontotemporal dementia<sup>60</sup>, cerebral amyloid angiopathy<sup>61</sup>, cognitive decline<sup>62</sup>,  
27 cognitive impairment test score<sup>63</sup>, as well as many biomarkers of Alzheimer's disease,  
28 such as neurofibrillary tangles<sup>61</sup>, neuritic plaque<sup>61</sup>, cerebral amyloid deposition<sup>64</sup>,  
29 cerebrospinal fluid protein levels<sup>63</sup>, and cortical amyloid beta load<sup>65</sup>. Altered amplitude  
30 activity has been widely reported in patients of cognitive impairment and Alzheimer's  
31 disease<sup>66,67</sup>. The brain degeneration related to Alzheimer's disease may begin in the  
32 frontoparietal regions<sup>68</sup> and was associated with dysfunction of multiple RSNs,



1 especially the default mode network<sup>20</sup>. 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 studies<sup>69-73</sup>. As a system-level  
9 progressive neurodegenerative disorder<sup>74</sup>, Parkinson's disease not only leads to motor  
10 abnormalities, but also has non-motor symptoms such as temporal perception  
11 abnormalities<sup>75</sup> and impaired connectivity among frontal regions<sup>76</sup>. Cognitive  
12 dysfunction and disrupted coupling between default mode and salience networks were  
13 commonly reported in Parkinson's disease<sup>17</sup>. 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 disease<sup>77</sup>, corticobasal degeneration<sup>78</sup>, progressive  
16 supranuclear palsy<sup>79</sup>), psychiatric disorders (e.g., autism spectrum disorder<sup>80</sup>, depressive  
17 symptoms<sup>81</sup>), educational attainment<sup>82</sup>, psychological traits (e.g., neuroticism<sup>81</sup>),  
18 cognitive traits (cognitive ability<sup>83</sup>), sleep<sup>84</sup>, heel bone mineral density<sup>85</sup>, alcohol use  
19 disorder<sup>86</sup>, subcortical brain volumes<sup>38</sup>, cortical surface area and thickness<sup>36</sup>, and white  
20 matter microstructure<sup>53</sup>.

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., schizophrenia<sup>87</sup>, MDD<sup>88</sup>, depressive symptoms<sup>89</sup>, autism spectrum disorder<sup>90</sup>),  
26 psychological traits (e.g., neuroticism<sup>81</sup>, well-being spectrum<sup>91</sup>), sleep<sup>92</sup>, cognitive traits  
27 (e.g., intelligence<sup>93</sup>), and educational attainment<sup>82</sup>. Dysregulated triple network  
28 interactions were frequently reported in patients of schizophrenia<sup>94</sup>, depression<sup>95</sup>, and  
29 autism spectrum disorder<sup>96</sup>. 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 schizophrenia<sup>97</sup>, educational attainment<sup>82</sup>, cognitive traits (e.g., cognitive ability<sup>83</sup>),  
2 smoking/drinking (e.g., smoking status<sup>98</sup>, alcohol consumption<sup>99</sup>), hippocampus subfield  
3 volumes<sup>100</sup>, and heel bone mineral density<sup>85</sup>. 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 duration<sup>84</sup>, insomnia<sup>92</sup>), in 3p11.1 (**Supplementary Fig. 11**) with  
6 cognitive traits (e.g., intelligence<sup>101</sup>, math ability<sup>82</sup>), and in 5q14.3 (**Supplementary Fig.**  
7 **12**) with cognitive traits<sup>83</sup> and educational attainment<sup>82</sup>. 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 LDSC<sup>102</sup> (Methods),  
19 including 100 regional brain volumes<sup>37</sup> and 215 DTI traits of brain structural connectivity  
20 in white matter tracts<sup>103</sup>. 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 = ( $1.2 \times 10^{-21}$ ,  $1.5 \times 10^{-5}$ ), **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 = ( $1.2 \times 10^{-21}$ ,  $1.2 \times$   
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 amygdala<sup>104</sup>. We observed genetic correlations<sup>104</sup> between insula volumes and the  
32 connection strengths of multiple pairs of brain regions ( $|gc|$  range = (0.22, 0.27),  $P < 1.2$

1  $\times 10^{-5}$ , **Figs. 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)<sup>105-107</sup>. Considering  
10 language processing is left-lateralized in about 95% of right-handers and 75% of  
11 left-handers<sup>108-111</sup>, 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 = ( $5.5 \times 10^{-10}$ ,  
27  $1.3 \times 10^{-5}$ ), **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 lobes<sup>112</sup>.  
32 Functionally, SLF has been reported associated with a wide array of brain functions,

1 including working memory<sup>113</sup>, attention<sup>114,115</sup>, and language functions<sup>116,117</sup>. 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 processes<sup>104</sup>. 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 functions<sup>118</sup>. 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 networks<sup>119</sup>. 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 = ( $8.6 \times 10^{-12}$ ,  
32  $2.3 \times 10^{-3}$ ), **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 disorders<sup>120</sup>) ( $|gc|$  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 regions<sup>121</sup>. These regions are also associated with  
11 difficulties in performing some fine motor skills<sup>122</sup>. 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<sup>123,124</sup>. 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 organizing<sup>125</sup>. Wang, et al. <sup>126</sup> 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 MAGMA<sup>127</sup> (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 FUMA<sup>54</sup> 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 microstructure<sup>103</sup>, 48 were reported to be associated with regional brain volumes<sup>37</sup>, 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 volumes<sup>37</sup>, white  
20 matter microstructure<sup>103</sup>, 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 disease<sup>128-130</sup>. Similarly, *CDKN2C*  
23 and *FAF1* were associated with ischemic stroke<sup>131</sup> 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 drugs<sup>132</sup>, 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<sup>20,133</sup>. Our gene-level analysis replicated *APOE*  
32 and *SORL1*, which were frequently targeted in Alzheimer's disease-candidate gene

1 studies of functional connectivity<sup>23,134</sup>. 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<sup>135,136</sup>. 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 analyses<sup>137</sup> for tissue type  
16 and cell type specific regulatory elements<sup>138</sup> (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 types<sup>139</sup> (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 property<sup>127</sup>  
28 analysis for 13 GTEx<sup>140</sup> (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<sup>141,142</sup> (**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 types<sup>141-145</sup> (Methods). This Hi-C gene mapping prioritized 29 genes, 14 of which were  
8 not identified by the Hi-C analysis in FUMA<sup>54</sup> (**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, MAGMA<sup>127</sup> 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 study<sup>31</sup> 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 study<sup>28</sup> 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 brain<sup>6</sup>. 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](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

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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 pipeline<sup>9</sup>. Details about image  
3 acquisition, preprocessing, and phenotype generation in each dataset can be found in  
4 **Supplementary Note**. Following the previous study<sup>31</sup>, 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 atlas<sup>51</sup> (**Supplementary Table 24**) and were mapped onto major functional networks  
11 defined in Yeo, et al. <sup>14</sup> and Finn, et al. <sup>12</sup> (**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 ancestry<sup>146</sup> 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. <sup>146</sup>. The  
25 ancestry in ABCD was assigned by combining the self-reported ethnicity and ancestry  
26 inference results as in Zhao, et al. <sup>103</sup>.

27

28 **GWAS discovery and validation.** Details of genotyping and quality controls can be found  
29 in **Supplementary Note**. SNP heritability was estimated by GCTA<sup>52</sup> 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 fastGWA<sup>147</sup>, while adjusting the same set  
2 of covariates as in GCTA. GWAS were also separately performed via Plink<sup>148</sup> 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 METAL<sup>149</sup>. 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,  $1 \times 10^{-3}$ ,  $1 \times$   
22  $10^{-4}$ ,  $1 \times 10^{-5}$ ,  $1 \times 10^{-6}$ ,  $1 \times 10^{-7}$ , and  $1 \times 10^{-8}$ . 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 FINDOR<sup>98</sup>. 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. LDSC<sup>102</sup> 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 HapMap3<sup>150</sup> 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 MAGMA<sup>127</sup>  
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 LDSC<sup>137</sup>. 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. <sup>103</sup>. We also performed gene property analysis for the 13 GTEx<sup>140</sup>  
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 Database<sup>151</sup> (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)<sup>143</sup>; 2) the Hi-C data of hippocampus and DLPFC<sup>141</sup>; 3) the Hi-C data from fetal  
10 and adult cortices<sup>142</sup>, 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 neurons<sup>144</sup> (cortical, hippocampal, and motor); and 5) proximity ligation assisted  
13 chromatin immunoprecipitation (PLAC-seq) data on sorted fetal neuron cells<sup>145</sup>,  
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 <sup>143</sup>, 0.05 for the  $q$ -value in Schmitt, et al. <sup>141</sup> and Giusti-Rodriguez and Sullivan <sup>142</sup>, 5 for  
17 the Chicago score in Song, et al. <sup>144</sup>, and 0.01 for the FDR in Song, et al. <sup>145</sup>.

18

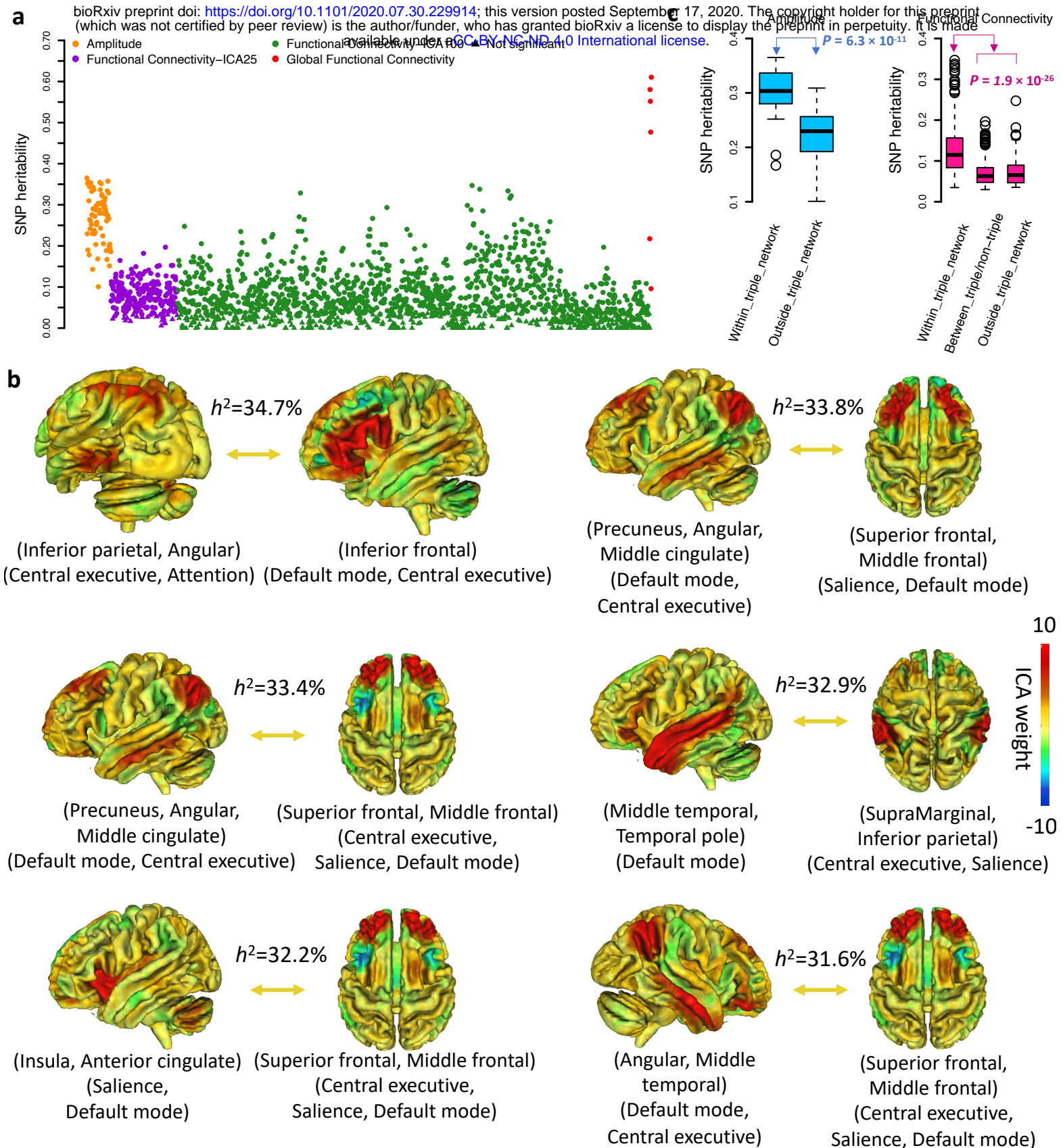
### 19 **Code availability**

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.

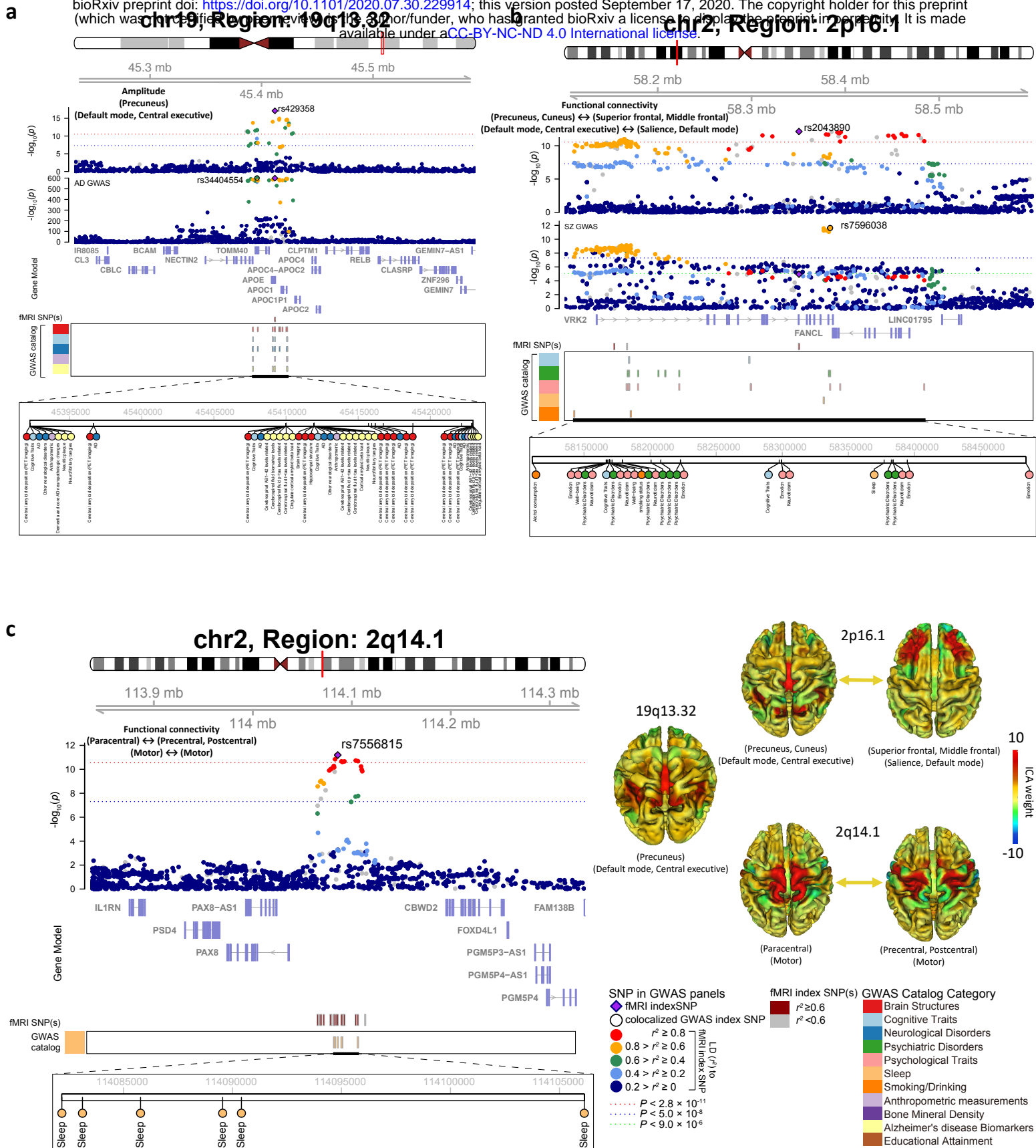
22

### 23 **Data availability**

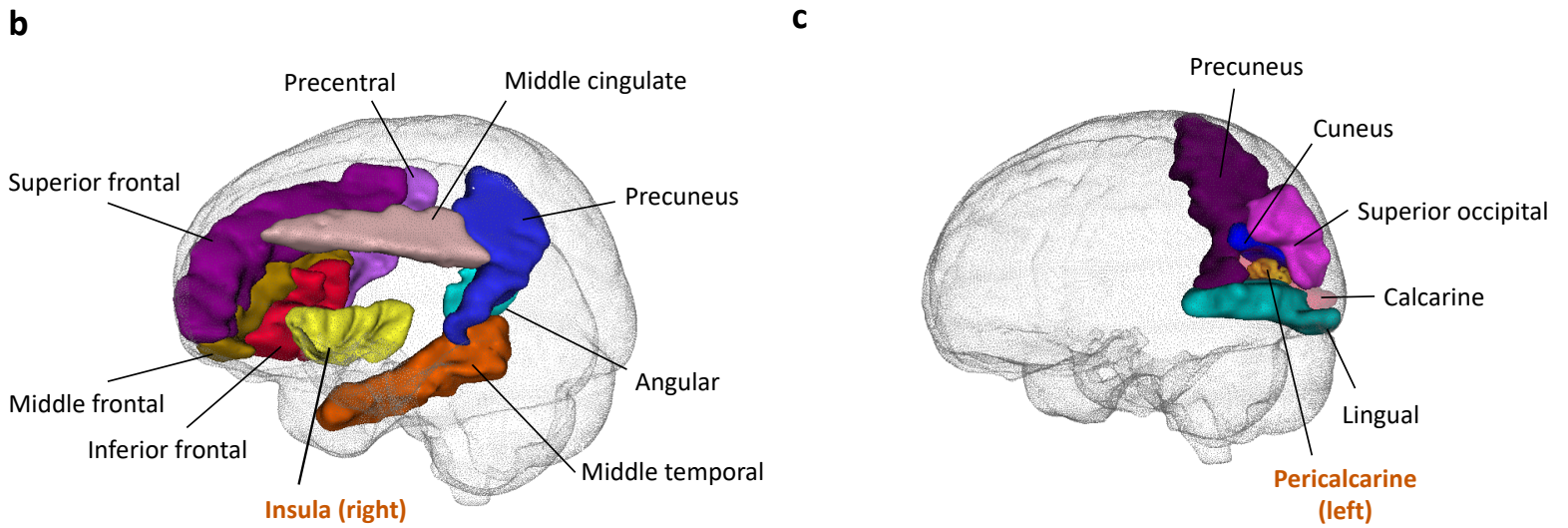
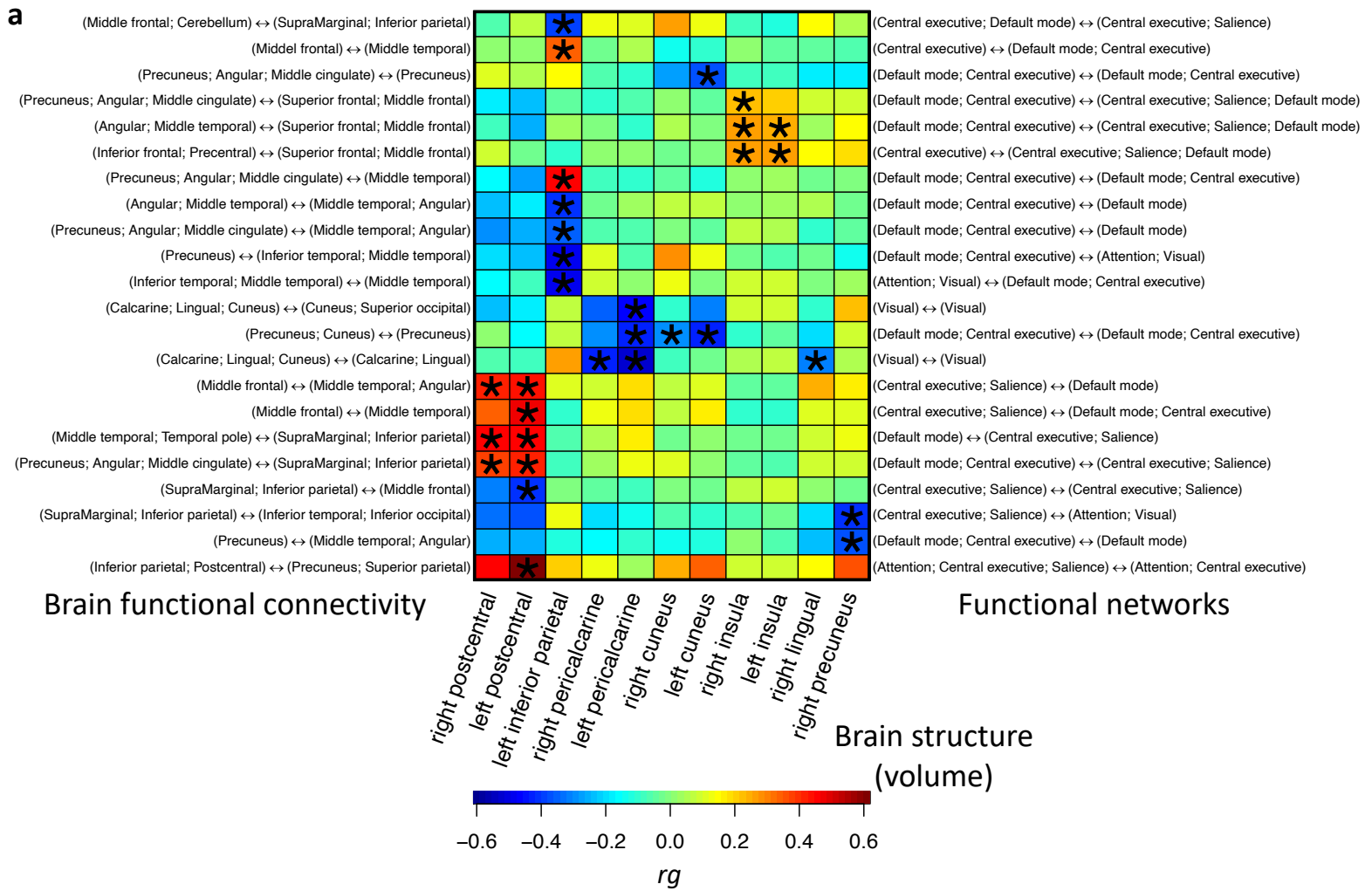
24 Our GWAS summary statistics can be downloaded at <https://github.com/BIG-S2/GWAS>.  
25 The individual-level data used in the present study can be obtained from four publicly  
26 accessible data resources: UK Biobank (<http://www.ukbiobank.ac.uk/resources/>), ABCD  
27 (<https://abcdstudy.org/>), 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/>.



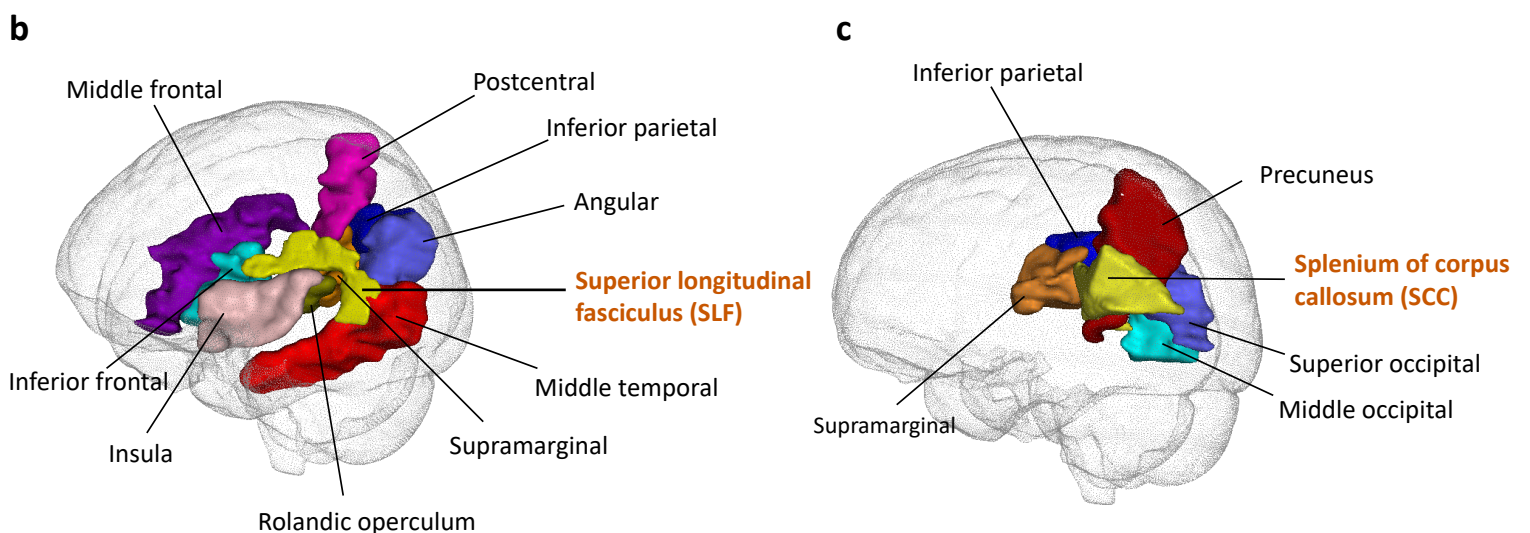
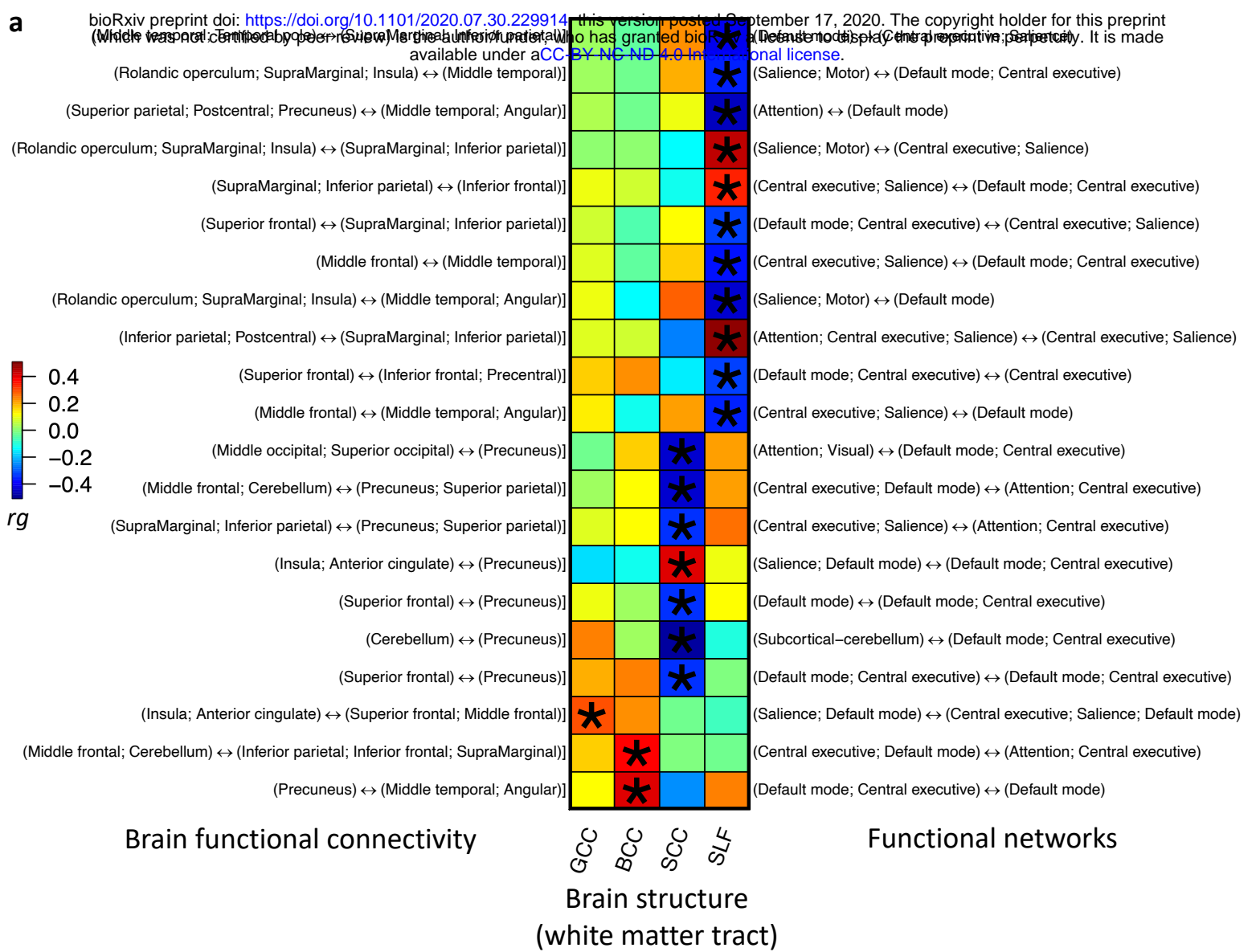
**Figure 1: SNP heritability analysis of rsfMRI traits (n = 34,691 subjects).** **a**) Heritability estimates of 1,777 rsfMRI traits of brain activity, including 76 amplitude traits, 1,695 pairwise functional connectivity traits (from two parcellations with 25 and 100 dimensionalities, respectively), 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.



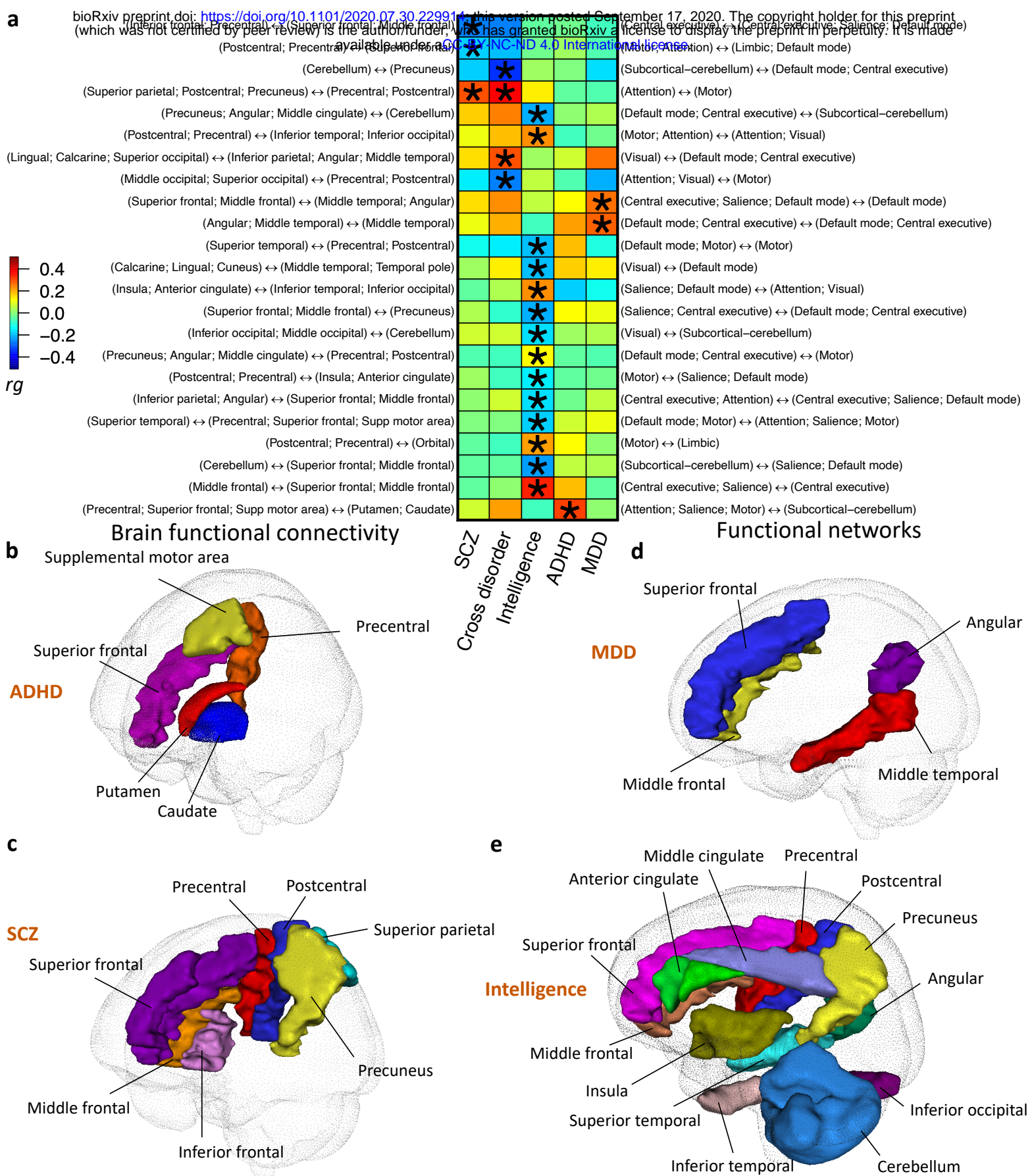
**Figure 2: Selected genetic loci that associated with both rsfMRI traits of brain activity and other brain-related complex traits and disorders.** We highlight local colocalization ( $LD\ r^2 \geq 0.6$ ) in **a**) 19q13.32 (colocalized with Alzheimer's disease); **b**) 2p16.1 (with schizophrenia); and **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 3: Selected pairwise genetic correlations between functional connectivity traits and regional brain volumes.** **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 regional brain volumes. The colors represent genetic correlations ( $rg$ ). **b**) Location of the right insula and its neighboring brain regions whose functional connectivity strengths were genetically correlated with the right insula volume. The colors describe different brain regions. **c**) Location of the left pericalcarine and its neighboring brain regions whose functional connectivity strengths were genetically correlated with the left pericalcarine volume.



**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.