Mapping sleep's phenotypic and genetic links to the brain and heart: a systematic analysis of multimodal brain and cardiac images in the UK Biobank

Running title: Imaging genetics for sleep

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Abstract

Sleep is essential for the health of the brain and heart. Although sleep has been identified as a factor in a few specific clinical outcomes, a systematic analysis of the relationship between sleep and brain/heart and their genetic underpinnings is lacking. Medical images can provide useful clinical endophenotypes for organ structures and functions. Here we present a systematic genetic investigation of sleep-brain/heart connections using multi-modal brain and cardiac images from over 40,000 subjects in the UK Biobank. We identified novel phenotypic and genetic links between sleep and a wide range of imaging traits, such as brain structures, white matter integrity, brain activities, as well as cardiac structures and functions. We prioritized a number of imaging modalities and traits for specific sleep conditions, such as the resting brain function measures in the somatomotor network with narcolepsy. Sleep and imaging had overlapping genetic influences in 39 genomic loci, some of which showed evidence of shared causal genetic variants. In conclusion, large-scale imaging genetic data illuminate the implications of sleep on brain and cardiac health and their genetic links. An interactive web browser (www.ig4sleep.org) has been developed to facilitate exploring our results.

Keywords: Brain Imaging; Brain Health; Cardiac Imaging; Heart Health; Sleep; UK Biobank.

A growing body of evidence suggests that poor sleep is a risk factor for physical, cognitive, and mental health problems[1]. Sleep traits (such as sleep quality and duration) and disorders (such as insomnia and narcolepsy) are associated with various cardiovascular diseases and brain disorders. For example, rapid eye movement sleep behavior disorder was found to be a strong predictor for the development of neurodegenerative diseases such as dementia and Parkinson's disease[2,3]. Sleep dysregulation and short sleep duration in midlife were consistently linked to higher risk of Alzheimer's disease and other dementias[4]. In addition, both insufficient and excess sleep duration may cause a higher incidence of cardiovascular outcomes, including coronary heart disease[5-7], hypertension[8], atrial fibrillation[9,10], and stroke[11,12]. Individuals with sleep disturbance were also more likely to have mental and psychiatric disorders[13], such as anxiety[14], post-traumatic stress disorder[15], schizophrenia[16], bipolar disorder, major depressive disorder (MDD), and attention-deficit/hyperactivity disorder (ADHD)[17,18].

Magnetic resonance imaging (MRI) provides noninvasive and comprehensive measures of the structure and function of the human organs, including the brain and heart. Imaging traits generated from brain and cardiac MRI are well-established clinical endophenotypes and have been widely used in early prediction and detection of cardiovascular, neurological, and neuropsychiatric outcomes[19-22]. Using MRI data, several studies have examined the sleep-related structural and functional alterations in the brain and heart[23-30]. Two major limitations of most existing studies have been i) the limited study sample size, which was usually less than a few hundred; and ii) focusing on one single MRI modality (or trait) and/or one sleep trait, such as hippocampal atrophy[25] and sleep duration[30-32]. It is known, however, that large sample sizes are needed for MRI studies to detect small effect sizes[33] and produce reproducible findings, especially for brain functional MRI (fMRI) data[34]. In addition, distinct MRI modalities and sleep conditions may be relevant to different diseases and health-related complex characteristics[21]. Therefore, a systematic analysis of multi-modal MRI data and multiple sleep conditions in a large cohort would provide a more comprehensive understanding of sleep-related changes in brain and heart structures and functions.

Genome-wide association studies (GWAS) have shown that sleep disorders and traits are heritable and have a polygenic genetic architecture[35-45]. The sleep-associated genetic variants are enriched for genes expressed in the brain and for metabolic and psychiatric pathways[44]. Genetic correlations between sleep traits and brain-related disorders (such as depression and schizophrenia) have been discovered, suggesting their shared neurogenetic basis[46]. On the other hand, both brain and cardiac MRI traits are also heritable and hundreds of associated genetic loci have been identified in recent GWAS[47-58]. However, few studies have ever integrated the multi-organ MRI measures and sleep conditions to explore the genetic interactions among sleep behavior, brain and cardiac structure/function, and related clinical endpoints.

To overcome these challenges, here we examined the phenotypic and genetic sleep-brain/heart connections using multi-modal cardiac and brain MRI data from more than 40,000 subjects in the UK Biobank (UKB) study[59]. We included three major brain MRI modalities: 1) brain anatomical and neuropathological structures from structural MRI, including regional brain volumes[54] and cortical thickness traits[60]; 2) white matter microstructures from diffusion MRI, including multiple diffusion tensor imaging (DTI) parameters[56]; and 3) intrinsic and extrinsic functional organizations of the cerebral cortex from resting and task fMRI, including functional connectivity and amplitude traits[58]. For heart, we used 82 traits extracted from short-axis, long-axis, and aortic cine cardiac MRI[61], including global and regional measures of 4 cardiac chambers (the left ventricle, right ventricle, left atrium, and right atrium), as well as 2 aortic sections (the ascending aorta and descending aorta). We mainly examined 7 self-reported sleep-related conditions in the UKB study: sleep duration, getting up in the morning, chronotype (morning/evening person), daytime nap, insomnia (sleeplessness), snoring, and narcolepsy (daytime sleepiness/dozing). Detailed information on these imaging and sleep data can be found in the Methods section. A series of phenotypic, genetic, and predictive analyses were conducted to understand the health implications of sleep. The overview of our study is presented in **Figure 1** and our results can be explored via the interactive web browser at www.ig4sleep.org.

RESULTS

An atlas of sleep associations with multi-modal brain and cardiac MRI traits

We examined the phenotypic associations between 7 sleep conditions and a wide range of brain and cardiac MRI traits, including 101 regional brain volumes[54], 63 cortical thickness measures[60], 110 DTI parameters[56], 92 parcellation-based network-level traits in resting and task fMRI[58], respectively, as well as 82 heart imaging traits[60,61] (**Table S1**). We performed regression analysis with unrelated white British subjects (average n = 29,025, Methods). Among the 3,780 (7×540) association pairs, 395 associations were significant at the false discovery rate (FDR) level of 5% (by the Benjamini-Hochberg procedure) and 92 of them further passed the more stringent Bonferroni significance level ($P < 1.32\times10^{-5}$, 0.05/3780) (**Figs. 2A**, **S1**, and **Table S2**). Significant associations were observed for all the 7 sleep conditions and 6 groups of imaging traits. Below we highlight the associations survived the Bonferroni multiple testing adjustment.

Resting fMRI showed the strongest sleep associations among all 6 groups of imaging traits, which were mostly related to sleep duration, narcolepsy, and getting up. Specifically, sleep duration had widespread negative associations with resting fMRI traits (including both functional connectivity and amplitude[62] measures) in multiple functional networks (β range = [-0.062, -0.036], $P < 1.02\times10^{-5}$), with the strongest association in the somatomotor network (β = -0.062, $P = 3.11\times10^{-13}$). Somatomotor function was important in multiple sleep stages and poor sleep quality and shorter duration have been linked to increased somatomotor functional connectivity in young samples[63-65]. In addition, resting fMRI traits positively correlated with easy getting up (β range = [0.036, 0.048], $P < 1.28\times10^{-5}$) and were mostly positively associated with narcolepsy (β range = [-0.051, 0.064], $P < 1.27\times10^{-5}$). Narcolepsy patients have been found to have alerted functional organizations, although previous sample sizes were usually small, making conclusions inconclusive[66,67]. In our analysis, decreased functional connectivity was mainly found in the default mode network, as well as between the auditory and orbito-affective as well as ventral-multimodal networks[68]. Functional connectivity in most of other networks had positive associations with narcolepsy (**Fig. S2**). Compared to resting fMRI, task fMRI had much weaker signals, with only two associations with getting up remaining after Bonferroni correction (β range = [-0.039, 0.042], $P < 1.07\times10^{-5}$).

To uncover detailed spatial association patterns and pinpoint sleep-related brain regions, we further performed area-level resting fMRI analysis with 64,620 (360 × 359/2) functional connectivity measures among 360 brain functional areas in 12 networks[68,69]. These high-resolution fMRI traits provided fine-grained information on the functional organization of the cerebral cortex. At the Bonferroni significance level ($P < 7.74\times10^{-7}$, 0.05/64,620), sleep duration had negative associations with most functional areas in the somatomotor and auditory networks, as well as some areas of the visual (visual1 and visual2), cingulo-opercular, and language networks (**Fig. 2B**). In contrast, most of the positive associations with sleep duration were related to the areas of the default mode network. Furthermore, we partitioned the default mode network into seven clusters[58], showing that sleep duration was predominantly related to the hippocampal and visual subclusters (**Fig. S3A**). As compared to long sleep duration, self-reported shorter sleep duration was associated with lower functional connectivity in the default mode network[70-72]. The default mode network is an active network that integrates information[73] and plays an important role in the awake brain[74]. In addition to previous evidence that shorter sleep duration was related directly to higher levels of Amyloid-θ[75], our findings provided further evidence that reducing sleep duration had a significant impact on brain functioning. For narcolepsy, positive associations were mainly in the somatomotor network and the connections between the somatomotor and visual networks (**Fig. 2C**). In contrast, negative associations with narcolepsy were found in the default mode network, most of which were related to the visual subcluster (**Fig. S3B**). For getting up and daytime nap, most of their associations were related to the visual and somatomotor networks (**Figs. S4A-S4B**). Overall, these results showed that functional connectivity of the somatomotor and visual networks had substantial connections with sleep conditions. In the default model network, narcolepsy and sleep duration were associated with brain functional activity differently than in other networks.

Our area-level analysis also identified related functional areas for snoring, insomnia, and chronotype. Particularly, snoring was linked to resting functional connections in the frontoparietal network, especially the left and right 13l areas in the posterior orbital gyrus (**Fig. S4C**). The functional connectivity between the left/right 13L areas and frontoparietal, visual, cingulo-opercular, and dorsal attention networks was increased in snoring, while

the functional connectivity with the default mode network decreased. Reduced functional connectivity was also observed within the default mode network (**Fig. S3C**). Associations with chronotype were mainly detected among cognitive networks, especially between the cingulo-opercular and default mode networks (**Figs. S3D** and **S4D**). In addition, insomnia was found to be negatively associated with resting functional connections within the somatomotor network (**Fig. S4E**). In summary, sleep-related brain functional variations were uncovered in specific brain areas, prioritizing related fMRI biomarkers for future sleep research.

Next, we observed significant associations between DTI parameters and multiple sleep conditions, especially chronotype (**Figs. 2A** and **S5**). Being an evening person was associated with higher mean diffusivity (MD) and axial diffusivity (AD) in multiple brain white matter tracts, such as the anterior corona radiata, body of corpus callosum, retrolenticular part of internal capsule, anterior limb of internal capsule, and superior corona radiata (β range = [0.042, 0.048], $P < 1.23\times10^{-5}$). Increased MD and AD may indicate abnormalities and healthy aging in glial tissue, in which the glial cells were involved in the regulation of circadian rhythms[76]. It has been reported that evening chronotype exhibited increased level of white matter changes[77]. In addition, we observed significant associations between snoring and the radial diffusiviy (RD) in the corticospinal tract (β = 0.040, $P = 1.32\times10^{-6}$), and between daytime nap and the AD of the body of corpus callosum tract (β = 0.042, $P = 1.14\times10^{-5}$). Compared to resting fMRI and DTI parameters, structural MRI traits (regional brain volumes and cortical thickness) had less phenotypic associations with sleep. Associations survived at the Bonferroni significance level were all related to daytime nap, which was associated with reduced right cerebellum white matter volume (β = -0.048, $P = 1.30\times10^{-5}$) and smaller cortical thickness of the left pars triangularis and right insula (β range = [-0.041, -0.039], $P < 4.29\times10^{-5}$).

Sleep also correlated significantly with cardiac MRI traits of the left ventricle, right ventricle, and right atrium (**Figs. 2A** and **S6**). Specifically, snoring was positively linked to both left and right heart structures, including the left/right ventricular end-diastolic volume (LVEDV and RVEDV), right atrium maximum and stroke volumes, and right ventricular end-systolic volume (RVESV) (β range = [-0.047, 0.064], $P < 1.20\times10^{-5}$). Snoring

may affect the cardiac function and increase the risk of cardiovascular disease especially in women[24,78]. In addition, getting up had widespread associations with the LVEDV, left ventricular end-systolic volume (LVESV), left ventricular myocardial mass (LVM), RVEDV, RVESV, and right ventricular stroke volume (RVSV) (β range = [0.045, 0.072], $P < 1.70\times10^{-6}$). Furthermore, negative associations with RVEDV were found for daytime nap and chronotype (β range = [-0.0613, -0.0610], $P < 1.30\times10^{-7}$). Human health is closely related to sleep chronotypes[45], which are behavioral manifestations of circadian rhythms[79]. In perspective studies, early chronotype is often regarded as a sign of healthy sleep behavior[80,81]. Individuals with an early chronotype are typically at a reduced risk of developing cardiovascular diseases[82] and heart failure[81]. Circadian and cardiovascular diseases, however, remain elusive in terms of their underlying mechanisms. The present study established a clear physiologic relationship between early chronotype and cardiac health. Overall, we mapped phenotypic links between the brain and cardiac MRI traits and sleep characteristics. These imaging endophenotypes may aid in future clinical research and applications to better understand sleep's role in brain and heart-related clinical outcomes.

In the phenotypic analysis above, UKB subjects who had both imaging and sleep data were considered, whereas more than 80% UKB subjects had only sleep data and thus were excluded. In order to include these non-imaging UKB subjects in our study, we developed polygenic risk scores (PRS) by using GWAS summary statistics of imaging traits from previous studies[54,56,58,60]. These genetically predicted imaging traits allowed us to repeat the above sleep-imaging association analysis in non-imaging UKB unrelated white British subjects (average n = 217,254, removing relatives of imaging subjects, Methods). In this PRS analysis, 276 significant associations were identified at the FDR 5% level, covering all the 7 sleep conditions and 6 groups of imaging PRS. Among these 276 associations, 35 further passed the stringent Bonferroni significance level ($P < 1.32\times10^{-5}$) (**Table S3** and **Figs. S7-S8**). The results of phenotypic and PRS analyses were largely consistent, indicating that the sleep-imaging associations discovered by a small proportion of UKB imaging subjects had good generalizability in the whole UKB cohort. For example, similar to the phenotypic analysis, resting fMRI traits also had the largest proportion of significant associations (97/276 at FDR 5% level and 25/35 at the Bonferroni level) in PRS analysis.

Furthermore, considering that imaging PRS were predicted with genetic information, genetic factors may play an important role in influencing sleep-imaging associations. In the following sections, we will examine these underlying genetic influences in more detail.

Characterizing sleep-imaging genetic overlaps in 39 genomic loci.

To understand the genetic co-architecture underlying sleep-imaging associations, we characterized the genetic pleiotropy between sleep conditions and multi-modal brain and cardiac MRI traits at their jointly significant GWAS loci. Briefly, we searched for sleep-significant genetic variants reported in the NHGRI-EBI GWAS catalog[83] (version 2022-07-09). Then we identified those variants (and variants in linkage disequilibrium [LD] with them, $r^2 \geq 0.6$) that were also significant in GWAS of brain and cardiac MRI traits (Methods). We found that a total of 39 genomic loci showed shared genetic influences on both sleep and imaging traits, covering regional brain volumes[54], DTI parameters[56], whole brain independent component analysis (ICA)-based resting fMRI traits[53,55,84], parcellation-based resting and task fMRI traits[58], and cardiac MRI traits[60] (**Table S4**). We tagged previous GWAS for a wide range of sleep conditions, including insomnia[39], chronotype[85,86], daytime nap[39], depressive symptom (sleep problems)[87], getting up[39], hypersomnia[88], sleep duration[37,89], and snoring[90] (**Fig. 3** and **Table S5**). Additionally, we estimated the probability that sleep-imaging trait pairs shared causal genetic variants using the Bayesian colocalization test[91]. We considered pairs with a probability of shared causal variant (PPH4) greater than 0.8 to be colocalized[91,92]. Below we summarized the results for each imaging modality group.

There were 14 genomic loci where sleep-significant variants were associated with DTI parameters (LD $r^2 \geq 0.6$). For example, shared genetic components between DTI parameters and chronotype[93] were found in 7 loci, including 1q25.2 (sleep index variant rs975025, tagged many DTI parameters, such as AD of the splenium of corpus callosum), 19p13.11 (rs9636202, mode of anisotropy (MO) of the external capsule), 3p12.3 (rs7429614, MO of the corticospinal tract), 6p22.2 (rs766406, MD of the inferior fronto-occipital fasciculus), 17q21.31 (rs72828815, MD of the anterior corona radiata), 11p15.5 (rs9795439, MO of the cingulum), 8p23.1 (rs2979256, FA of the inferior fronto-occipital fasciculus) (**Figs. 4A-4B** and **S9-S12**). The 1q25.2, 19p13.11, and 11p15.5 regions had

strong evidence of shared causal genetic variants between chronotype and DTI parameters (PPH4 > 0.976). Multiple sleep index variants were expression quantitative trait loci (eQTLs) in brain tissues, such as rs975025 (for *FAM163A* and *FAM20B*), rs72828815 (for *DBF4B* and *MEIOC*), and rs9795439 (*KRTAP5-4*)[94]. For sleep duration[37], we found shared genetic influences in three loci, including 10p12.31 (rs12246842, MD of the fornix), 6p22.1 (rs34556183, MD of the superior corona radiata), and 17q21.31 (rs1991556, MD of the anterior corona radiata) (**Figs. S13-15**). Colocalization was detected in 10p12.31 (PPH4 = 0.836), and the sleep index variants rs34556183 and rs1991556 were brain eQTLs of multiple genes such as *ZSCAN31* and *ARL17A*.

In addition, DTI-insomnia[42] genetic overlaps were found in 6 loci, including 3p21.31 (rs10865954, FA of the fornix-stria terminalis), 16q12.1 (rs1544637, AD across the whole brain), 15q26.1 (rs176647, FA of the posterior limb of internal capsule), 17q21.31 (rs2239923, MD of the anterior corona radiata), 9q22.31 (rs10156602, FA of the body of corpus callosum), and 10p12.31 (rs12246842, MD of the fornix) (**Figs. S16-S19**). The sleep-significant variant rs10865954 was a brain eQTL for multiple genes such as *NCKIPSD*, *WDR6*, and *GMPPB*. We also tagged daytime nap, snoring, and getting up in 17q21.31 (rs57222984, mean AD of the sperior fronto-occipital fasciculus). Hypersomnia had genetic overlaps with MO of the cingulum (hippocampus) in 2p16.1 (rs359268) (**Figs. S20**). Among these sleep-DTI regions, we also found shared genetic influences with well-being spectrum, neuroticism, depression, risk-taking tolerance, autism spectrum disorder, cognitive traits (e.g, intelligence, math ability, reaction time, and education), life satisfaction, smoking, hypertension, and coronary artery disease, which might be a cause or consequence of white matter changes in the brain. Overall, these results suggested that sleep conditions were genetically associated with white matter integrity across multiple genomic regions, where they also overlapped with neuropsychiatric disorders, cognitive traits, and cardiovascular risk factors.

For resting fMRI, we found the shared genetic influences with sleep in 9 genomic regions. Insomnia genetic loci were in LD ($r^2 \geq 0.6$) with resting fMRI traits in 4 regions, including 2q14.1 (rs62158170, such as the somatomotor network), 2p16.1 (rs12713372, the frontoparietal and posterior-multimodal networks), 4q24 (rs11097861, the default mode,

central executive, and salience networks), as well as 19q13.32 (rs429358, the default mode network) (**Figs. 4C** and **S21-S23**). ICA-based[84] and parcellation-based[58] resting fMRI traits showed similar overlaps. Strong colocalizations between insomnia and resting fMRI were identified in 2q14.1, 4q24, and 19q13.32 (PPH4 > 0.951). The sleep index variant rs62158170 (2q14.1) was a brain eQTL of *PAX8*. As one of the two variants in the *APOE* ε4 locus, rs429358 (19q13.32) contributed to Alzheimer's disease risk. In rs429358, insomnia also had shared genetic influences with task fMRI traits of the visual network (**Fig. S24**). Snoring was genetically linked to resting fMRI traits in 12q14.3 (rs10878269, PPH4 = 0.976), 3p11.1 (rs145367119), and 17q21.31 (rs57222984), all of which tagged the triple networks of psychopathology (the default mode, central executive, and salience networks)[95] (**Fig. S25-S27**).

In 2q14.1, 2p16.1, and 17q21.31, we observed shared genetic influences with sleep duration, daytime nap, depressive symptom (sleep problems), and getting up (**Figs. S28-S29**). Chronotype-resting fMRI overlaps were found in 11q24.1 (rs3867239, the central executive, salience, default mode, and attention networks, PPH4 = 0.975) and 2p16.3 (rs17396357, the central executive, salience, default mode, and attention networks) (**Figs. S30-S31**). The rs17396357 was a brain eQTL of *GTF2A1L, FOXN2, MSH6, STON1-GTF2A1L, STON1,* and *LHCGR*. In these regions, we also found genetic links (LD r^2 ≥ 0.6) with cognitive traits (e.g, cognitive decline, math ability and education), myocardial infarction, type 2 diabetes, mental health (e.g., depression, schizophrenia, autism spectrum disorder, and neuroticism), neurological disorders (e.g., Alzheimer's disease and Parkinson's disease), and blood pressure.

Sleep traits and regional brain volumes had shared genetic influences (LD r^2 ≥ 0.6) in 20 genomic regions. Many brain regions were affected by 9 insomnia-related genomic loci (10q24.32, 12q24.31, 4q24, 2q33.3, 5q14.3, 11q14.1, 12q14.3, 10p12.31, and 18q21.2), such as the left/right basal forebrain (rs12411886), cerebellar vermal lobules I-V (rs28576953), left/right accumbens area (rs6855246 and rs13135092), cerebellar vermal lobules VIII-X (rs55772859), left/right putamen (rs16903122, rs667730, and rs375051009), total brain volume (rs61921611), and left/right lateral ventricle (rs12251016) (**Figs. S32-S36**). Colocalizations between insomnia and regional brain volumes were identified in

10q24.32 and 11q14.1 (PPH4 > 0.853). Insomnia has previously been associated with shrinking subcortical volumes and smaller cortical surface areas[96,97]. These findings may suggest the genetic basis of brain structure-insomnia connections. Chronotype also overlapped genetically with the left/right putamen in 5q14.3 (rs12657776), as well as other brain regions in 5 more loci, including 16q12.2 (rs4784256, such as brain stem), 9q22.2 (rs3138490, left amygdala), 11p15.5 (rs9795439, white matter), and 3q13.11 (rs34967119, right cuneus), and 2p11.2 (rs11681299, brain stem) (**Figs. S37-S39**). We observed colocalization between sleep and chronotype in 9p22.2, 11p15.5, and 2p11.2 (PPH4 > 0.856). Furthermore, we found genetic overlaps for daytime nap in 5 additional genomic loci: 1p31.1, 7p22.2, 17q21.31, 11q12.2, and 5q22.2. Daytime nap was genetically linked to the cerebellar vermal lobules VIII-X (rs10782582), left/right lateral ventricle (rs4557589), total brain volume (rs57222984), left/right cerebellum exterior (rs174541), and left/right cerebellum white matter (rs2099810) (**Figs. S40-S42**). Both 11q12.2 and 5q22.2 had strong evidence of shared causal genetic variants between daytime nap and regional brain volumes (PPH4 > 0.923). In addition, 17q21.31, 11q12.2, and 4q24 (rs13109404, left accumbens area) regions contributed to the genetic links between sleep duration and regional brain volumes. Similarly, 12q14.3, 14q32.2, and 17q21.31 were associated with both snoring and multiple regions, including the right inferior parietal (rs10878269), left thalamus proper (rs2664299), right fusiform (rs4792897), and total brain volume (rs57222984) (**Figs. 4D and S43**). We found colocalization between snoring and regional brain volumes in 12q14.3 and 14q32.2 (PPH4 > 0.956). There were also genetic overlaps with getting up in 3 of the above loci: 17q21.31, 4q24, and 11q12.2.

Genetic pleiotropy ($r^2 \geq 0.6$) was observed between sleep and cardiac MRI traits in 5 regions. Chronotype-heart overlaps were observed in 8p23.1 (rs11992186, regional peak circumferential strain), 22q13.1 (rs139911, ascending aorta maximum area), 11p11.2 (rs11605348, global myocardial-wall thickness), and 17q21.32 (rs11992186, RVEDV) (**Figs. S44-S45**). Shared genetic influences were found in 11p11.2 with insomnia (rs10838708, global myocardial-wall thickness) and in 17q21.31 with sleep duration, snoring, getting up, as well as daytime nap (rs1991556 and rs57222984, regional myocardial-wall thickness) (**Figs. S46-S47**). We also found genetic overlaps with mental health (e.g.,

neuroticism) and heart diseases (e.g., atrial fibrillation and coronary artery disease) in these loci. In summary, sleep had substantial genetic links with brain and heart structural and functional variations. Different sleep conditions, such as insomnia and daytime nap, may have genetic overlaps with the brain and heart in different genomic regions. Integrating imaging and sleep GWAS results may provide insight into sleep-related brain and heart health mechanisms.

Genome-wide and local genetic correlation patterns

We quantified the genome-wide genetic similarity between sleep conditions and imaging traits by genetic correlations (GC) estimated from cross-trait LD score regression[98]. We collected 19 sets of publicly available sleep GWAS summary statistics (**Table S6**) and screened them with GWAS summary statistics of multi-modal imaging traits (Methods). At 5% FDR level, significant genetic correlations were observed between sleep and all imaging modalities (**Fig. 5A** and **Table S7**). We reported below the top-ranking significant brain and cardiac MRI traits associated with sleep after applying the FDR correction ($P < 6.18\times10^{-4}$).

There were many resting fMRI traits associated genetically with sleep conditions in agreement with our phenotypic association analysis. Particularly, sleep duration and narcolepsy were genetically associated with the functional connectivity of multiple brain networks, such as the somatomotor, visual, language, cingulo-opercular, and frontoparietal (GC range = [-0.472, 0.508], $P < 6.18\times10^{-4}$). Other sleep traits were also genetically correlated with more specific brain networks. For example, snoring was genetically associated with functional connectivity between the default mode and orbito-affective networks, as was daytime napping with functional connectivity between the cingulo-opercular and frontoparietal networks (GC range = [-0.286, 0.250], $P < 6.00\times10^{-4}$). Besides functional connectivity traits, resting amplitude traits[62,99,100] were linked to sleep duration and narcolepsy, as well as snoring, with more area-level information revealed (**Fig. S48**). For example, amplitude results consistently demonstrated that narcolepsy was genetically associated with brain functional activity in the somatomotor and secondary visual areas (GC range = [0.183, 0.418], $P < 6.00\times10^{-4}$). In addition, sleep duration had negative genetic correlations with brain functional activity in the auditory, cingulo-

opercular, dorsal-attention, somatomotor, and visual areas (GC range = [-0.240, -0.149], $P < 6.00\times10^{-4}$). Snoring was positively correlated with brain functional areas in the default mode, frontoparietal, and orbito-affective networks (GC range = [0.137, 0.234], $P < 6.00\times10^{-4}$). Genetic links between sleep and brain functions were also observed in task fMRI (GC range = [-0.315, 0.488], $P < 6.00\times10^{-4}$, **Fig. S49**). Overall, sleep and brain function were genetically correlated throughout brain functional networks, with specific patterns confined to certain areas.

For DTI parameters, significant negative genetic correlations were consistently observed between snoring and the multiple DTI-derived metrics (AD, MD, and RD) of the corticospinal tract (GC range = [-0.202, -0.123], $P < 1.03\times10^{-4}$, **Fig. S50**). The corticospinal tract is a major neuronal pathway carrying movement-related information from the cerebral cortex to the spinal cord. Impaired corticospinal tract was observed in poor cognitive performance and patients with obstructive sleep spnea[101]. A few genetic correlations were also observed between regional brain volumes and sleep conditions, especially insomnia (**Fig. S51**). Specifically, insomnia was genetically correlated with increased brain volume in the left and right caudate (GC range = [0.138, 0.170], $P < 7.02\times10^{-5}$) as well as decreased total brain volume (GC = -0.132, $P < 2.15\times10^{-5}$). The caudate is a well-known functional region for sleep and modulates multiple sleep stages[102]. Additionally, we found genetic correlations between left ventricle and chronotype, as well as between left atrium and snoring (GC range = [-0.192, 0.166], $P < 6.00\times10^{-4}$, **Fig. S52**). The left atrium has been reported to be associated with obstructive sleep apnea in coronary artery disease[103].

In the above genome-wide genetic correlation analyses, sleep-imaging traits are assumed to be genetically similar throughout the genome. To examine local patterns of shared genetic basis between sleep and imaging and to localize coheritability in specific genomic regions, we partitioned the genome into thousands of regions and performed local genetic correlations analysis using LAVA[104] and SUPERGNOVA[105] pipelines. In both LAVA and SUPERGNOVA, local genetic correlations were found at the FDR 5% level ($P < 1.87\times10^{-4}$ for LAVA, $P < 5.89\times10^{-5}$ for SUPERGNOVA) for all sleep conditions, and fMRI traits contributed the largest proportion of significant findings (**Figs. 5B, S53,** and **Tables S8-S9**).

In comparison with LDSC, both methods revealed more genetic correlations with task fMRI. For example, among the 777 significant local genetic correlations identified by LAVA, 46.98% (365/777) were related to task fMRI traits. More than 10% (39/365) of the task fMRI-sleep local genetic correlations were located in the 19q13.32 region, which was the locus identified in our association lookup analysis for task fMRI. In addition to 19q13.32, other top-ranking putative pleiotropic regions for task fMRI were 16q12.2, 14q11.2, 7p15.1, and 15q26.2. Moreover, sleep-imaging genetic connections can vary across genomic regions or even be opposites. For example, chronotype had a positive local genetic correlation with left MBelt area task amplitude in 1p13.2 (GC = 0.574, $P = 1.10\times10^{-4}$), but negative correlation in 16q12.2 (GC = -0.466, $P = 1.87\times10^{-4}$). These results demonstrate the complex genetic co-architecture of sleep and imaging traits.

Causal genetic relationships detected by Mendelian randomization.

To investigate the causal genetic links between sleep and imaging traits, we performed Mendelian randomization (MR) analyses with their GWAS summary statistics (Methods). At the Bonferroni significance level ($P < 3.67\times10^{-5}$), we found strong evidence of genetic causal effects from brain structures to sleep conditions (**Table S10**). For example, increased left ventral DC volume had genetic causal effects on being a morning person (β = -0.102, SE = 0.021, $P = 1.71\times10^{-6}$). All of the MR methods tested indicated the same causal genetic effects direction, and two of them were able to survive the Bonferroni multiple testing procedure. In addition, larger subcortical volumes were causally related to increased risk of daytime nap (β = 0.046, SE = 0.01, $P = 3.81\times10^{-6}$ for the left accumbens area, and β = 0.038, SE = 0.009, $P = 1.14\times10^{-5}$ for the right hippocampus). By balancing adenosine and dopamine activity, the accumbens played an important role in regulating sleep-wake patterns[106,107]. Furthermore, there was a significant genetic causal relationship between larger total brain volume and longer sleep duration (β = 0.055, SE = 0.01, $P = 1.08\times10^{-5}$). For DTI parameters, we found a causal link between higher MO of the external capsule tract and being an evening person (β = -0.085, SE = 0.02, $P = 6.04\times10^{-6}$). All these results were summarized in **Figure S54.** There was no evidence of a causal relationship in another direction (in which sleep traits was the exposure and brain structural traits was the outcomes) after Bonferroni correction.

More genetic causal effects from brain structures to sleep were found at the FDR 5% level (*P* range = [1.71×10^{-6}, 2.09×10^{-3}]). In total ,73 imaging-sleep causal pairs were identified, most of which were related to DTI parameters (42/73) and regional brain volumes (29/73). DTI parameters from multiple white matter tracts showed genetic causal effects on sleep conditions, such as sleep duration, daytime nap, and chronotype. More volumetric traits were found to have causal effects on sleep. For example, several MR methods have consistently demonstrated that total brain volume has a causal genetic influence on insomnia (β < -0.044, $P < 1.93\times10^{-4}$). In summary, our MR analysis suggested a causal genetic pathway from brain structures to sleep conditions.

Sleep and mental health predictions by integrating multiple data types

According to our imaging genetics analyses, genetic data and multimodal brain and cardiac images could possibly be combined to predict sleep conditions. In clinical and epidemiological studies, sleep has also been reported to be affected by environmental factors, behaviors, biomarkers, and disease status, which makes it desirable to develop sleep prediction models that incorporate imaging genetics and other forms of data. In this section, we performed sleep predictions based on a variety of data types. Our goal is to understand the contributions made by these types of data and their relative performance in predicting different sleep disorders and traits. Our analysis focused on multi-modality brain and cardiac MRI traits, sleep polygenic risk score (PRS), biomarkers, disease status, and 6 categories of environmental variables, including lifestyle and environment, psychosocial factors, physical measures, local environments, and early life factors (**Table S11**). We used a training, validation, and testing design, where all model parameters were tuned on validation data, and prediction performance was assessed on independent testing data. Detailed information on model training and adjusted covariates can be found in the Methods section.

Figure 6A summarized the results of 7 different sleep conditions using different types of brain imaging data. All sleep conditions were significantly predicted by resting fMRI (prediction correlation β range = [0.040, 0.121], *P* range = [9.82×10^{-4}, 4.05×10^{-23}]). The ICA-based and parcellation-based resting fMRI traits, as well as the amplitude and functional connectivity traits, showed similar trends, although their relative performance

may vary depending on the sleep characteristics being predicted. Each of the regional brain volumes, DTI parameters, and task fMRI traits can significantly predict at least five sleep conditions (**Table S12**). As for sleep duration, chronotype, and insomnia, adding these additional imaging types will not improve prediction performance over and above resting fMRI, suggesting that resting fMRI is largely responsible for the prediction power of other imaging modalities. As an example, both regional brain volumes and task-related fMRI traits were marginally significant in predicting sleep duration (β range = [0.030, 0.042], P range = [2.47×10^{-2}, 7.28×10^{-4}]). Using regional brain volumes, task fMRI traits, and resting fMRI traits together did not result in a better performance than using resting fMRI alone (β = 0.116 vs. 0.120). These results suggest that among the imaging modalities tested in this study, resting fMRI showed the strongest correlation with the three sleep traits, and it may be the most effective imaging modality to predict insomnia.

In the case of getting up, snoring, daytime nap, and narcolepsy, it will be beneficial to integrate multiple imaging modalities rather than using one type of data. For example, task fMRI had the best prediction performance in predicting snoring across different imaging modalities (β range = [0.068, 0.085], P = [2.81×10^{-7}, 1.55×10^{-10}]). Snoring can also be significantly predicted by DTI parameters, regional brain volumes, and resting fMRI traits (β range = [0.040, 0.063], P range = [1.25×10^{-3}, 2.23×10^{-7}]). When all these imaging types were combined, the prediction accuracy increased to 0.103 (P = 1.68×10^{-14}), suggesting that each imaging type contributes additionally to the prediction of snoring. In another example, when combining DTI parameters, regional brain volume, and resting fMRI traits, the prediction performance moved up to 0.109 (P = 1.14×10^{-18}) for nap during day.

Next, we evaluated more data types in sleep prediction (**Fig. 6B**). Cardiac MRI traits were significantly predictive of 6 sleep traits, with the highest prediction accuracy observed for snoring (β = 0.067, P = 1.57×10^{-6}). Insomnia can be more accurately predicted by using brain and cardiac MRI traits jointly (β = 0.087, P = 8.39×10^{-10}, **Fig. S55**). In addition, sleep PRS were significant predictors for all sleep conditions (β range = [0.108, 0.201], P range = [2.46×10^{-15}, 1.71×10^{-49}]). Six different PRS methods were used, and all provided similar results (**Fig. S56** and **Table S12**). The combination of PRS and brain imaging data increases

prediction accuracy for all sleep traits, with narcolepsy showing the greatest improvement. PRS and imaging traits had a prediction accuracy of 0.108 ($P = 2.46\times10^{-15}$) and 0.124 ($P = 2.68\times10^{-20}$), respectively, for narcolepsy. The performance increased to 0.159 ($P = 5.15\times10^{-30}$) after combination.

Sleep conditions were also strongly predicted by biomarkers and environmental variables. The highest prediction accuracy of biomarker was observed on snoring ($\beta = 0.081$, $P = 4.98\times10^{-10}$). Environmental variables were much better at predicting insomnia and getting up than PRS and imaging traits. For example, the prediction accuracy of environmental variables was 0.226 ($P = 5.25\times10^{-68}$) for insomnia, which was largely contributed by the psychosocial factors ($\beta = 0.202$, $P = 2.15\times10^{-54}$, **Fig. S57**). More importantly, combining PRS, imaging, and environmental variables resulted in a higher level of accuracy when predicting all sleep traits. Narcolepsy and snoring were predicted similarly by the three types of data (β range = [0.108, 0.122], P range = [2.46×10^{-15}, 4.58×10^{-19}] for PRS; β range = [0.103, 0.124], P range = [1.68×10^{-14}, 2.68×10^{-20}] for brain imaging; β range = [0.113, 0.121], P range = [1.07×10^{-11}, 1.01×10^{-17}] for environmental variables), and the accuracy increased by more than 50% when they were combined (β range = [0.180, 0.198], P range = [1.17×10^{-19}, 8.01×10^{-30}]). In general, imaging, genetics, and environment all play key roles in predicting sleep variations. Integrating multiple types of data could benefit sleep prediction in clinical applications and research.

Mental health problems were highly comorbid with sleep disorders[108,109]. In order to gain a better understanding of how sleep contributes to mental health problems, we assessed the predictive power of sleep traits for three mental health traits: depression, neuroticism, and anxiety. We adjusted the same covariates as the above sleep prediction analysis and additionally examined other data types (Methods). For all three mental health traits, sleep traits and early life factors were among the top two strongest predictors (β range = [0.178, 0.316], P range = [9.24×10^{-43}, 8.21×10^{-135}], **Figs. 6C, S58,** and **Table S13**). These mental health traits were also significantly predicted by brain imaging and mental health PRS (β range = [0.034, 0.152], P range = [4.84×10^{-3}, 8.43×10^{-29}], **Figs. 6C and S58**). A combination of all predictors increased the prediction correlation to 0.413 for neuroticism, 0.353 for depression, and 0.277 for anxiety (P range = [5.65×10^{-91}, 1.83×10^{-176}]).

Furthermore, when sleep conditions were controlled as covariates, the prediction power of many traits was reduced, suggesting that sleep may partially explain their predictive power (**Figs. 6D and S58**). For example, after conditioning on sleep, electronic devices usage no longer had significant predictive power for neuroticism or depression; and alcohol, physical activity, and sun exposure did not have significant predictive power for anxiety. In addition, prediction performance of early life factors on neuroticism decreased from 0.178 ($P = 9.24\times10^{-43}$) to 0.147 ($P = 3.80\times10^{-32}$), suggesting 17.7% prediction power of early life factors on neuroticism could be mediated by sleep. The proportion of reduction was 16.1% for mental health PRS and 28.7% for disease status. Similar reduction was also found in prediction power of PRS and early life factors for depression and anxiety. In summary, sleep was an important predictor of mental health traits and may be able to mediate the influence of genetic and nongenetic risk factors on mental health.

DISCUSSION

Sleep is vital to both physical health and mental wellbeing. Understanding how sleep interacts with human health is of great interest. This study aimed to identify novel phenotypic and genetic connections between sleep-related conditions and human brain and heart health by using multimodal imaging data as endophenotypes. In our study, we found substantial links between sleep and the structure and function of the brain and the heart, some of which can be explained by shared genetic influences. We examined the genetic basis of sleep-imaging connections from a variety of perspectives, including the genetic loci that were jointly significant, the genetic covariance at the local level, and the genetic similarity across the genome. Based on MR analysis, sleep conditions have been found to be more a consequence than a cause of brain structural differences along the genetic pathway, matching the results in a recent study specially on sleep duration and brain structure[32]. Using prediction analysis, we assessed the relative contributions of genetic and imaging factors to sleep prediction and integrated them with additional environmental data to provide a more accurate prediction. Future epidemiological and clinical studies of sleep and comorbid conditions may benefit from these findings and insights.

In our study, we found that sleep and brain functions are strongly linked through multiple functional networks, including the default mode network. Several studies have shown that the default mode network activity is essential to conscious awareness[74,110,111], which may provide an opportunity to investigate the relation between sleepiness and decreased functional connectivity of the default mode network. Daytime sleepiness is generally considered a clinical symptom of sleep disorders or a consequence of insufficient sleep. The symptoms of insomnia and sleep deprivation are usually accompanied by sleepiness[112], which both have been linked to reduced connectivity in the brain's default mode network[70,113]. Narcolepsy is a rare neurological disorder characterized by daytime sleepiness and the presence, or absence, of cataplexy-like episodes[114,115]. The cause of narcolepsy is determined by both genetic and environmental factors[116], and it may lead to adverse cardiovascular events[117]. Our phenotypic and genetic results reveal possible mechanisms of default mode network brain activity that underlie these sleep disorders.

The present study has a few limitations. First, our analyses were mainly based on European subjects in the UKB study. In future studies, data from a broader range of sources could be incorporated into the imaging genetics study of sleep, and findings developed by UKB could be generalized to global populations. The current study focused on the human brain and heart, which are two important organs of the human body. Using abdominal images, such as those of the kidneys and liver[118], it would be interesting to determine how sleep is connected to more organs. Finally, we focused primarily on linear relationships in our models. Several recent studies have demonstrated that certain sleep traits may also have nonlinear phenotypic and genetic links (such as sleep duration[30,31]). In the future, advanced statistical and machine learning methods may be used to identify more comprehensive relationships and improve prediction performance.

METHODS

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

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

ACKNOWLEDGEMENTS

We thank the individuals represented in the UK Biobank for their participation and the research teams for their work in collecting, processing and disseminating these datasets for analysis. We would like to thank the University of North Carolina at Chapel Hill and Purdue University and their research computing groups for providing computational resources and support that have contributed to these research results. We gratefully acknowledge all the studies and databases that made GWAS and eQTL summary-level data publicly available. This research has been conducted using the UK Biobank resource (application number 22783), subject to a data transfer agreement.

AUTHOR CONTRIBUTIONS

B.Z. designed the study. Z.F., B.Z., J.S., X.Y., B.L., J.L., and T.L. analyzed the data. Y.L., Z.F., and B.Z. designed the website and developed online resources. Q.W., P.P., T.L., and H.Z. provide comments and interpret the results. Z.F. and B.Z. wrote the manuscript with feedback from all authors.

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COMPETETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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METHODS

Phenotypic sleep-imaging analyses.

The UKB study (https://www.ukbiobank.ac.uk/) recruited approximately half a million participants aged between 40 and 69 years between 2006 and 2010[59]. The ethics approval of the UKB study was from the North West Multicentre Research Ethics Committee (approval number: 11/NW/0382). The UKB imaging study started in 2014 and aimed to collect multi-modal imaging data from 100,000 subjects[119]. Detailed procedures to generate brain and cardiac MRI traits used phenotypic analysis can be found in previous papers[54,56,58,60,61]. All these imaging traits were generated from the raw images in Category 100003 (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100003). Overall, we used 101 regional brain volumes and 63 cortical thickness measures from T1-weighted structural MRI image[54,60], 110 DTI parameters from diffusion MRI image[56], 92 functional activity (amplitude) and connectivity traits from resting-state and task-based fMRI image[58], respectively, as well as 82 cardiac MRI traits from the short-axis, long-axis, and aortic cine images[61]. These traits captured the structural and functional characteristics of the human brain, heart, and aorta. Briefly, the advanced normalization tools[120] (ANTs) was used to generate regional brain volumes for 98 cortical and subcortical areas, as well as 3 global brain volume measures, including the total gray matter volume,

total white matter volume, and total brain volume. Similarly, 63 global and regional cortical thickness measured were also generated by ANTs. In addition, we applied the ENIGMA-DTI pipeline[121,122] to diffusion MRI, and generated 110 tract-averaged parameters, including the fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and mode of anisotropy (MO) for 21 predefined major white matter tracts, as well as across the whole brain (5 × 22). For fMRI, we used a parcellation-based approach with the Glasser360 atlas[69] and partitioned the cerebral cortex into 360 regions in 12 functional networks[68], including the primary visual, secondary visual, auditory, somatomotor, cingulo-opercular, default mode, dorsal attention, frontoparietal, language, posterior multimodal, ventral multimodal, and orbito-affective networks. We calculated the mean amplitude of each network, the mean functional connectivity for each pair of networks (including within the same network), and the mean amplitude and mean functional connectivity of the whole cortex. As strong signals were identified in resting fMRI, we also considered the 64,620 (360 × 359/2) area-level high-resolution resting functional connectivity measures, which can provide more fine-grained details on functional organizations of cerebral cortex. The 82 cardiac MRI traits were from 6 categories, including 64 traits of left ventricle, 4 of left atrium, 4 of right ventricle, 4 of right atrium, 3 of ascending aorta, and 3 of descending aorta. See **Table S1** for the complete ID list of these traits.

We studied the sleep-imaging phenotypic relationships with 7 self-reported sleep traits: the sleep duration ("*About how many hours sleep do you get in every 24 hours? (please include naps)*", Data field 1160); getting up in morning *("On an average day, how easy do you find getting up in the morning? 1) not at all easy; 2) not very easy; 3) fairly easy; 4) very easy"*, Data field 1170); morning/evening person (chronotype, *"Do you consider yourself to be 1) definitely a 'morning' person; 2) more a 'morning' person than an 'evening' person; 3) more an 'evening' person than a 'morning' person; 4) definitely an 'evening' person?",* Data field 1180); nap during day ("*Do you have a nap during the day? 1) never/rarely; 2) sometimes; 3) usually.",* Data field 1190); sleeplessness/insomnia ("*Do you have trouble falling asleep at night or do you wake up in the middle of the night? 1) never/rarely; 2) sometimes; 3) usually.",* Data field 1200); snoring ("*Does your partner or a close relative or friend complain about your snoring?*", Data field 1210); and daytime

dozing/sleeping (narcolepsy, "*How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g. when working, reading or driving) 1) never/rarely; 2) sometimes; 3) often; 4) all of the time.",* Data field 1220). We used the data coded by the UKB study and removed the subjects with responses "do not know" or "prefer not to answer". In our phenotypic analysis, we used the white British imaging individuals in UKB phases 1 to 3 data release (released up through 2020, average *n* = 29,025, mean age range = (45,82), mean = 64.15, standard error = 7.67, and proportion of female was 51.6%). We fitted linear models for each pair of sleep and imaging traits, in which we adjusted for the effects of age (at imaging), age-squared, sex, age-sex interaction, age-squared-sex interaction, imaging site code, the top 40 genetic principal components (PCs)[123], volumetric scaling, head motion, head motion-squared, brain position, and brain position-squared[53,55]. For regional brain volumes and regional cortical thickness measures, we additionally adjusted for the total brain volume and global mean thickness, respectively, to remove the global effects. The values greater than five times the median absolute deviation from the median were removed in each imaging trait and continuous covariate variable. The *P* values from two-sided t test were reported (R version 3.6.0).

We also performed the PRS-based association analysis for the same set of imaging traits. Specifically, we used the GWAS summary statistics of these imaging traits released by previous imaging GWAS studies[54,56,58,60,61] and constructed PRS based on PRS-CS[124]. We used all default parameters in the PRS-CS software (https://github.com/getian107/PRScs) and generated the PRS for all non-imaging individuals in the UKB study (removing relatives of the UKB imaging individuals). We then used these genetically predicted imaging traits to repeat the above association analysis with the 7 sleep traits in non-imaging unrelated white British UKB subjects (average *n* = 217,254, removing relatives of imaging subjects, Methods). We adjusted for the effects of age (at baseline), age-squared, sex, age-sex interaction, age-squared-sex interaction, and the top 40 genetic PCs[123].

Genetic sleep-imaging analyses.

Our genetic analyses were mainly based on GWAS summary statistics of sleep-related traits and imaging traits from previous studies. First, we systematically looked for the genomic loci that were reported to be significant for both sleep and imaging traits. We

looked up the reported sleep-significant genetic variants in the NHGRI-EBI GWAS catalog[83] (https://www.ebi.ac.uk/gwas/, version 2022-07-09). Among these sleep-associated variants (and variants in LD with them, $r^2 \geq 0.6$), we searched for those that were also reported to be significant in previous GWAS of brain and cardiac MRI traits, including 101 regional brain volumes[54], 110 DTI parameters[56], 1,777 ICA-based resting fMRI traits[84] (76 ICA-based amplitude traits and 1,701 ICA-based functional connectivity traits), 1,985 network-level parcellation-based resting and task fMRI traits[58] (1,066 for resting and 919 for task), and 82 cardiac MRI traits[60] (**Table S4**). For the sleep-significant genetic variants, we also searched to see whether they were reported brain eQTLs on MetaBrain (https://www.metabrain.nl/)[94]. Finally, we tested for whether the sleep and imaging traits had shared causal genetic variants using the Bayesian colocalization test[91].

We examined genetic correlation analysis between sleep and imaging traits via LDSC[125] (https://github.com/bulik/ldsc/, version 1.0.1). We collected and used 19 set of publicly available GWAS summary statistics for sleep traits (**Table S6**). For imaging traits, we screened the 101 regional brain volumes[54], 110 DTI parameters[56], 1,985 network-level parcellation-based resting and task fMRI traits[58] (1,066 for resting and 919 for task), and 82 cardiac MRI traits[60]. To provide more details of the brain functional organization, we also examined the amplitude traits in each of the 360 brain regions for resting and task fMRI, respectively. The LD scores were calculated by LDSC and were based on the 1000 Genomes European data. We used the default setups of LDSC, in which the HapMap3[126] variants and the variants in the major histocompatibility complex region were removed.

Local genetic correlation analyses between sleep and imaging traits were performed separately using LAVA[104] (https://github.com/josefin-werme/LAVA) and SUPERGONA[105] (https://github.com/qlu-lab/SUPERGNOVA). We tested the same sets of GWAS summary statistics as used in the above LDSC analysis. We followed the tutorials of the two methods and used the default setups. In SUPERGONA, we removed all single nucleotide polymorphisms (SNPs) with missing values in GWAS summary statistics and minor allele frequency (MAF) less than 0.05. We used the provided 1000 Genomes European reference panel and the genome partition file. In LAVA, we input the GWAS summary statistics, the 1000 Genomes European reference genotype data file, and the provided

locus definition file. Within each locus, LAVA processed these input files and converted the marginal GWAS summary statistics to locus-specific joint effects. LAVA first performed univariate tests on all traits and loci to select those with sufficient local genetic signals. Bivariate tests were then performed on the selected loci and traits to examine their local genetic correlations.

We performed MR analyses using multiple methods in the two-sample MR package (https://mrcieu.github.io/TwoSampleMR/), including MR Egger, simple median, weighted median, panelized weighted median, and inverse variance weighted[127]**.** Bidirectional MR analyses were performed using GWAS summary statistics between each pair of sleep conditions and imaging traits, including 101 regional brain volumes[54], 110 DTI parameters[56], 92 network-level parcellation-based resting fMRI traits[58] (the same traits as in the phenotypic analysis), and 82 cardiac MRI traits[60]. GWAS summary statistics of sleep conditions were obtained from the IEU GWAS database (https://gwas.mrcieu.ac.uk/). To select independent strong genetic instrumental variables, exposure GWAS summary statistics were clumped by using Plink[128] (v1.9) with *P*-value significance threshold being 5×10^{-8} (p1) and the secondary significance threshold for clumped genetic variants was also set to be 5×10^{-8} (p2). Physical distance threshold for clumping was kb = 1,000, LD threshold for clumping was r^2 = 0.01, and we used the 1000 Genomes European reference panel. Genetic variants of the exposure remained were extracted from the outcome dataset via the *extract_outcome_data()* function with default parameters. Harmonization was further performed to ensure the effects of each genetic variant on exposure and outcome were corresponding to each other, which was done by the *harmonise_data function()* with level of strictness in dealing with SNPs action = 2. Sleep-imaging pairs with number of SNPs less than 10 were discarded. MR was then conducted with the *mr()* function with the above methods.

Integrative prediction models for sleep and mental health traits.

We developed prediction models for sleep by using genetic variants, imaging traits, and a wide range of other data types, such as biomarkers, disease status, and 6 categories of environmental variables, including lifestyle and environment, psychosocial factors, physical measures, local environments, early life factors, and cognitive functions (**Table**

S11). First, we considered performance of the following imaging predictors: 101 regional brain volumes[54], 110 DTI parameters[56], 1,777 ICA-based resting fMRI traits[84], 1,985 network-level parcellation-based resting and task fMRI traits[58], 720 area-level parcellation-based resting and task fMRI amplitude traits (360 each), and 82 cardiac MRI traits[60]. We focused on the unrelated white British subjects and randomly divided the data into three independent parts: training (average *n* = 20270), validation (average *n* = 6790), and testing (average *n* = 6764). We estimated the effect sizes of these imaging traits by ridge regression in the glmnet[129] package (R version 3.6.0). The same set of the covariates as in the phenotypic association analysis were controlled. Model parameters were tuned on validation data, and prediction performance was evaluated on testing data by calculating the correlation between predicted and observed sleep traits. Next, we examined the performance of genetic PRS for sleep traits. Data from all UKB white British subjects were used as training data, except for those in the above validation and testing data (and their relatives). We adjusted for the effects of age (at baseline), age-squared, sex, age-sex interaction, age-squared-sex interaction, and the top 40 genetic PCs. We developed using 6 different methods, including pruning and thresholding (P + T), lassosum[130], LDpred2[131], LDpred-funct[132], DBSLMM[133], and PRSCS[124]. The above validation dataset was used to tune the parameters. We also used other data types as predictors with ridge regressions. To help interpret and identify the top-ranking predictors from each category, we also performed phenotypic associations between these variables and sleep traits and shred the results in **Table S14** and our website. The performance was evaluated on the subjects with all these data types in the testing dataset. Similar prediction models were also developed on three mental health traits, where sleep traits were added as predictors.

Code availability

We made use of publicly available software and tools. The codes are available upon reasonable request.

Data availability

GWAS summary statistics of brain and cardiac MRI traits can be freely downloaded at BIG-KP https://bigkp.org/ and Heart-KP https://heartkp.org/. GWAS summary statistics of

sleep conditions used in this study are publicly available and the links can be found in Table S6. The individual level UK Biobank data used in this study can be obtained from https://www.ukbiobank.ac.uk/. We have built an interactive web browser to share our results at www.ig4sleep.org.

Figure legends

Fig. 1 Overview of our imaging genetics studies for sleep.

Multimodal brain and cardiac imaging were used to investigate the relationship between sleep and brain and heart health. We covered a full spectrum of imaging modalities, including T1-weighted structural MRI, diffusion MRI, resting-state and task-based fMRI, as well as short-axis, long-axis, and aortic cine images of cardiac MRI. Seven sleep conditions were examined, including sleep duration, getting up in the morning, chronotype, daytime nap, insomnia, snoring, and narcolepsy. Sleep-imaging connections can be explained in part by shared genetic factors. A variety of analyses were conducted throughout the paper in order to uncover the overlapping genetic influences, including polygenic risk scores, identification of shared genetic risk loci and colocalization, genome-wise and local genetic correlations, Mendelian randomizations, and integrated predictions.

Fig. 2 Phenotypic sleep-imaging associations.

(A) The -log10(p-value) of phenotypic correlations between 7 sleep traits and 6 groups of imaging, including 101 regional brain volumes, 63 cortical thickness measures, 110 DTI parameters, 92 resting fMRI traits, 92 task fMRI traits, and 82 heart imaging traits. See Table S1 for more information of these imaging traits. The red and black dashed lines indicate the Bonferroni significance level ($P < 1.33 \times 10^{-5}$) and the false discovery rate at 5%, respectively. Each sleep condition is labeled with a different color. **(B)** and **(C)** Significant correlations between area-level resting functional connectivity traits and narcolepsy (in B) and sleep duration (in C). We show the correlations that passed the Bonferroni significance level ($P < 7.74 \times 10^{-7}$). Correlation estimates are indicated by the color. Visual1, the primary visual network; and Visual2, the secondary visual network.

Fig. 3 Jointly significant genomic loci for sleep conditions and imaging traits.

(A) In the NHGRI-EBI GWAS catalog (https://www.ebi.ac.uk/gwas/, version 2022-07-09), we found shared genetic influences between sleep and imaging traits in 39 genomic loci (names are in black color). That is, sleep and imaging GWAS reported significant variants in these loci and the index variants were in linkage disequilibrium (LD, $r^2 \geq 0.6$). Each imaging modality is labeled with a different color. We tagged a wide range of reported sleep traits and grouped them into chronotype (e.g., morningness and morning person), insomnia (e.g., insomnia and insomnia symptoms), sleep duration (e.g., sleep duration long sleep and short sleep), and others, such as snoring, hypersomnia, getting up, and daytime nap. **(B)** We further summarized the results into a table, where the *x*-axis represents the 39 genomic regions and *y*-axis displays the sleep traits. Each imaging modality is labeled with a different color and the orange color is used when more than one imaging modalities are observed in the locus.

Fig. 4 Selected genetic loci that were associated with both sleep conditions and imaging traits.

(A) In 1q25.2, we observed colocalization between chronotype (index variant rs975025) and the mean axial diffusivity of the splenium of corpus callosum tract (SCC AD, index variant rs755699529). The posterior probability of Bayesian colocalization analysis for the shared causal variant hypothesis (PPH4) is 0.976. **(B)** In 19p13.11, we observed colocalization between chronotype and the mean mode of anisotropy of the external capsule (EC MO, shared index variant rs9636202, PPH4 = 0.992). In this region, chronotype was also in LD ($r^2 \geq 0.6$) with reaction time, life satisfaction, smoking, hypertension, and coronary artery disease. **(C)** In 4q24, we observed colocalization between insomnia (index variant rs11097861) and functional connectivity among the triple networks of psychopathology (the default mode, central executive, and salience networks, index variant rs4417974, PPH4 = 0.952). **(D)** In 14q32.2, we observed colocalization between snoring and volume of the left thalamus proper (shared index variant rs2664299, PPH4 = 0.997). We also observed the shared associations (LD $r^2 \geq 0.6$)

with self-reported math ability, cognitive performance, smoking initiation, and educational attainment.

Fig. 5 Genetic correlations between sleep and imaging traits.

(A) We illustrated the pattern of significant genome-wide genetic correlation estimates (at the 5% false discovery rate level by LDSC, $P < 6.18\times10^{-4}$) between various groups of imaging traits (left upper panel) and sleep conditions (left lower panel). We listed the number of significant pairs for each imaging group and sleep condition on the right side. **(B)** We illustrated pattern of significant local genetic correlation estimates (at the 5% false discovery rate level, $P < 1.87\times10^{-4}$) between various groups of imaging traits (left upper panel) and sleep conditions (left lower panel) by LAVA. We listed the number of significant pairs for each imaging group and sleep condition on the right side.

Fig. 6 Integrative prediction analysis for sleep conditions and mental traits.

(A) Predicting 7 sleep conditions using multimodal brain imaging traits, including DTI parameters, region brain volumes, ICA-based resting fMRI traits (resting ICA), parcellation-based network and area-level resting and task fMRI traits (resting g360 network, resting g360 area, task g360 network, and task g360 area), and all modalities (joint of all brain MRI traits). **(B)** Predicting 7 sleep conditions using multiple data types. PRS, sleep polygenic risk scores of genetic variants, Brain imaging, multimodal brain imaging traits. **(C)** The accuracy of neuroticism prediction analysis using different types of data. PRS, neuroticism polygenic risk scores of genetic variants, Brain imaging, multimodal brain imaging traits. **(D)** The accuracy of different data types in neuroticism prediction analysis before (marginal) and after controlling sleep traits (conditional on sleep).

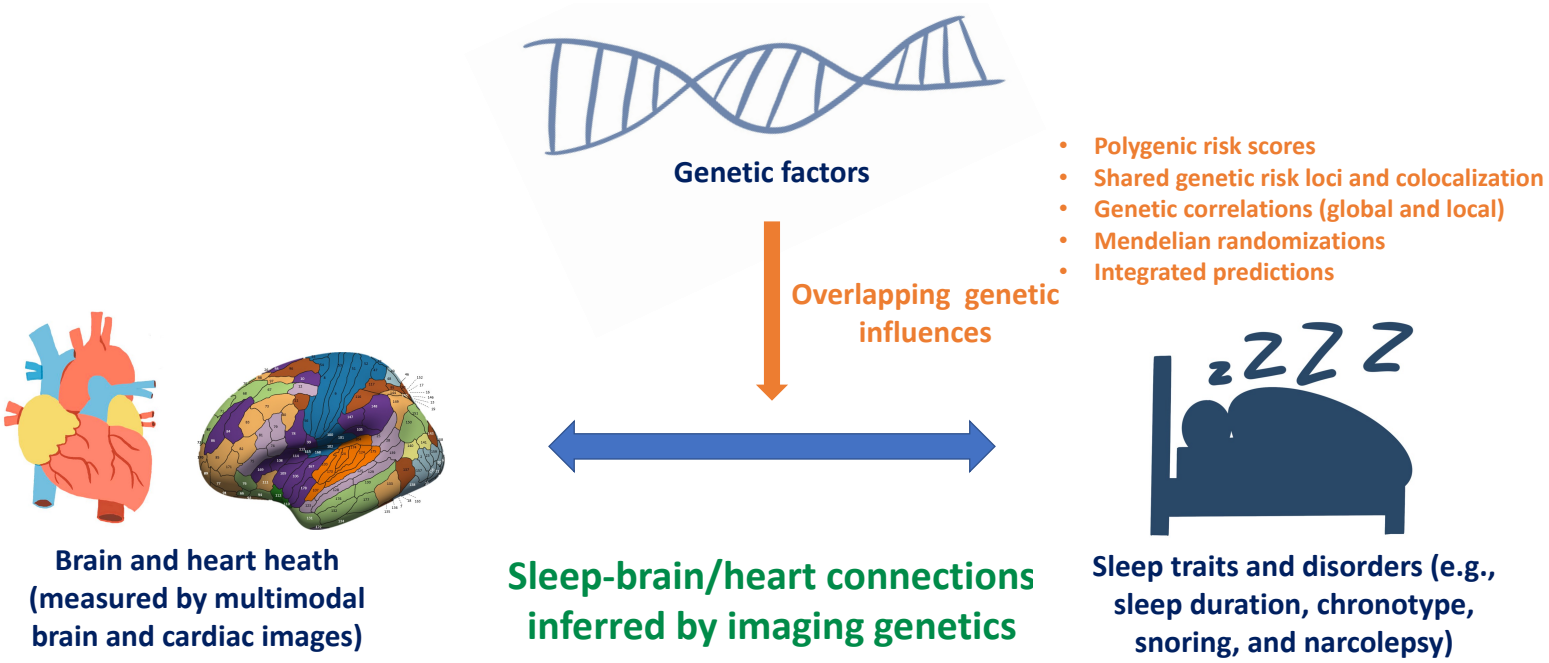


Figure 1

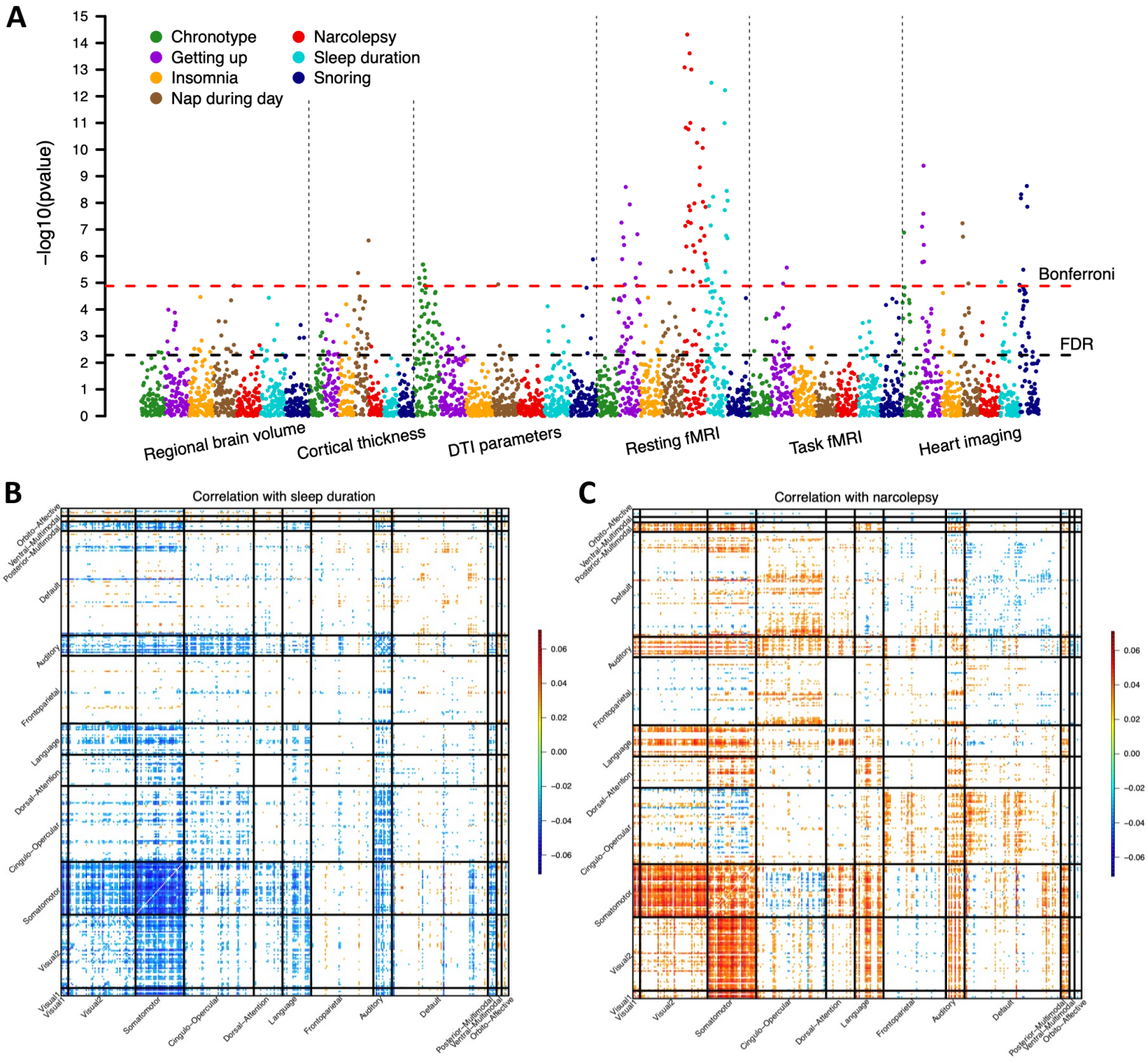
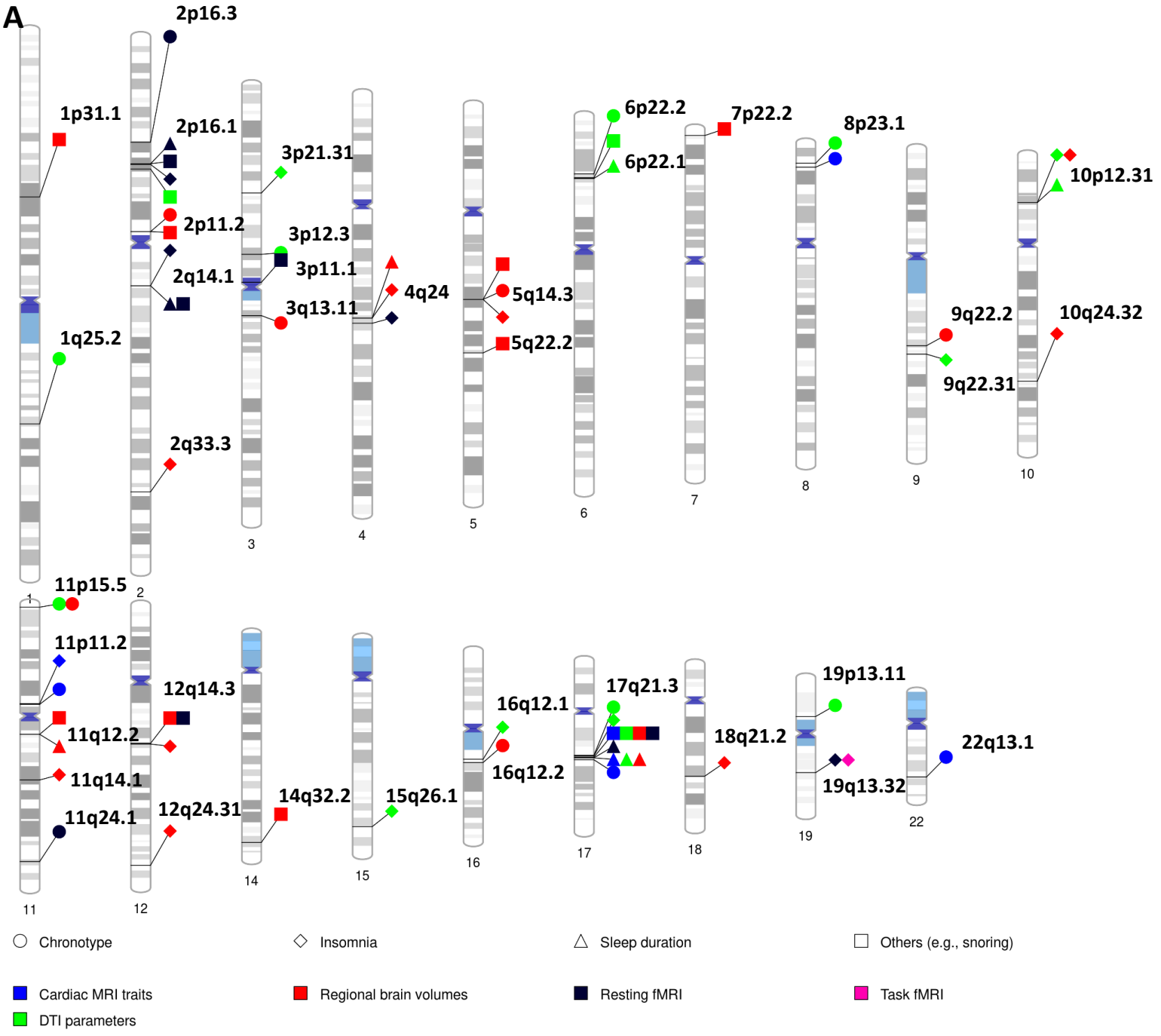


Figure 2



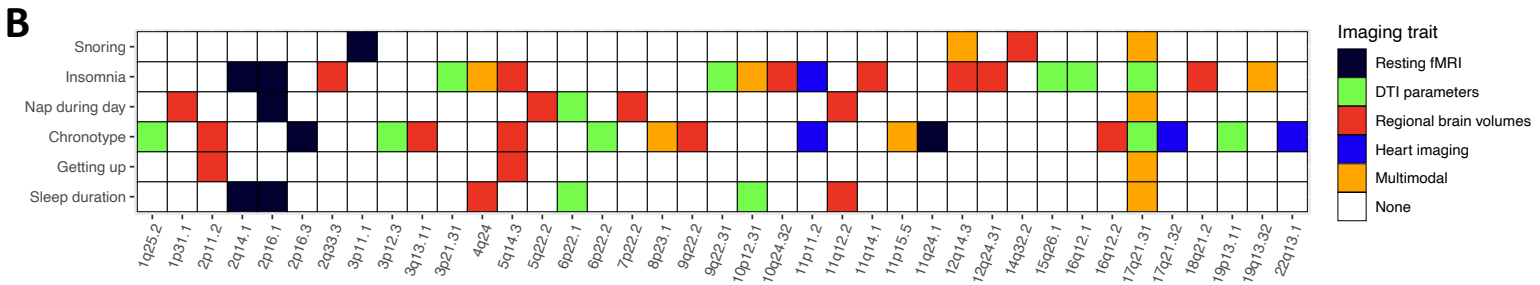


Figure 3

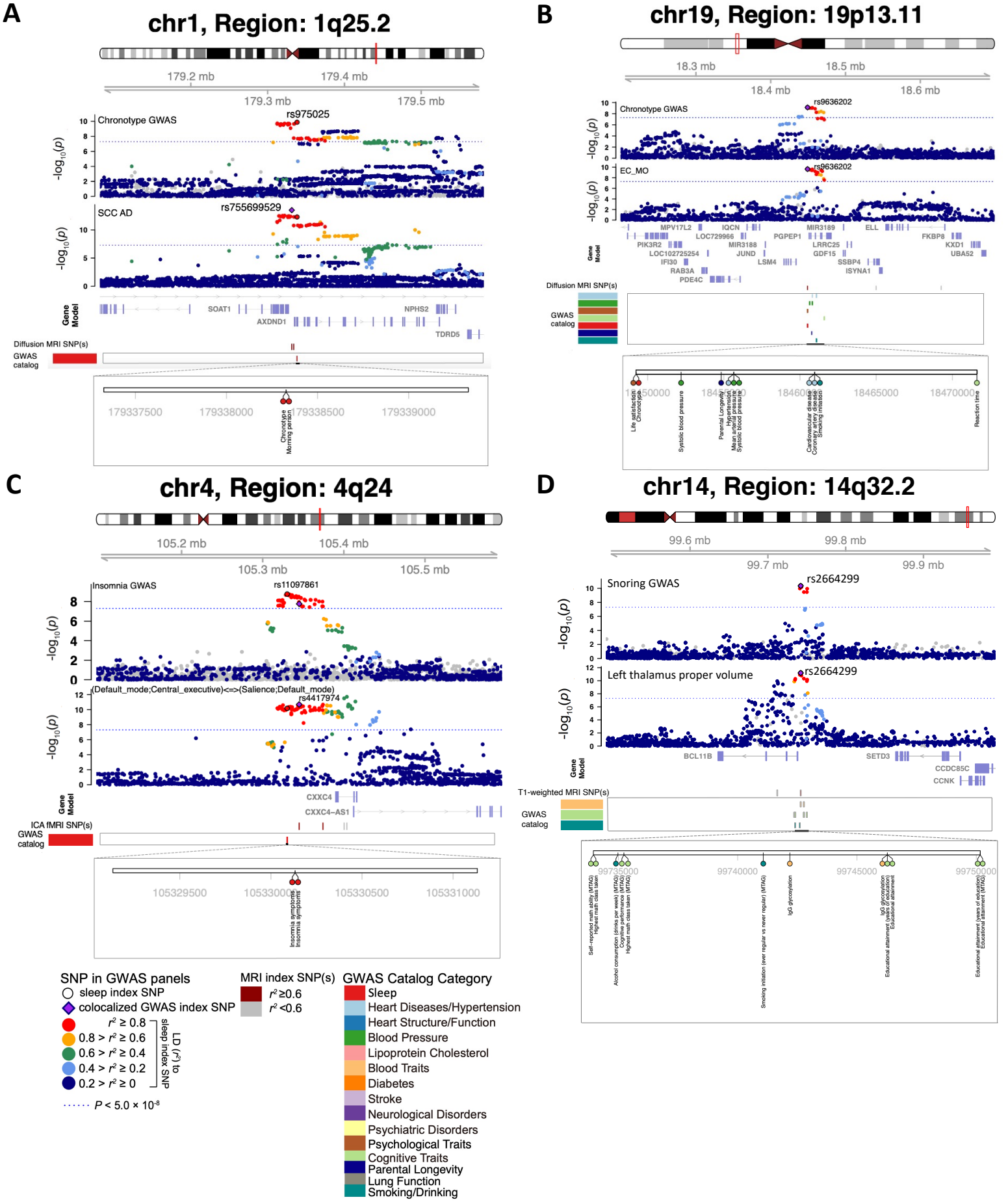
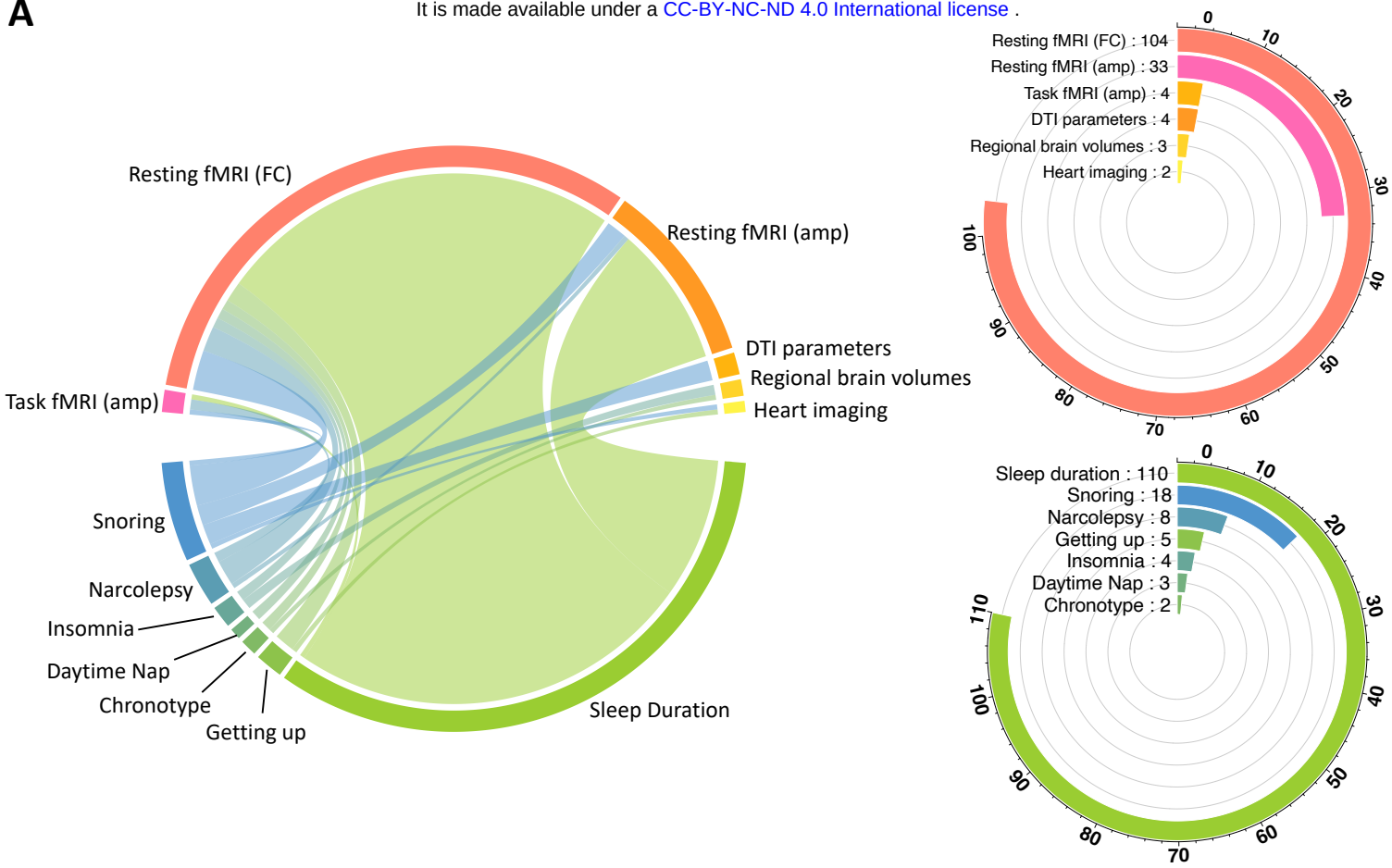


Figure 4

A



B

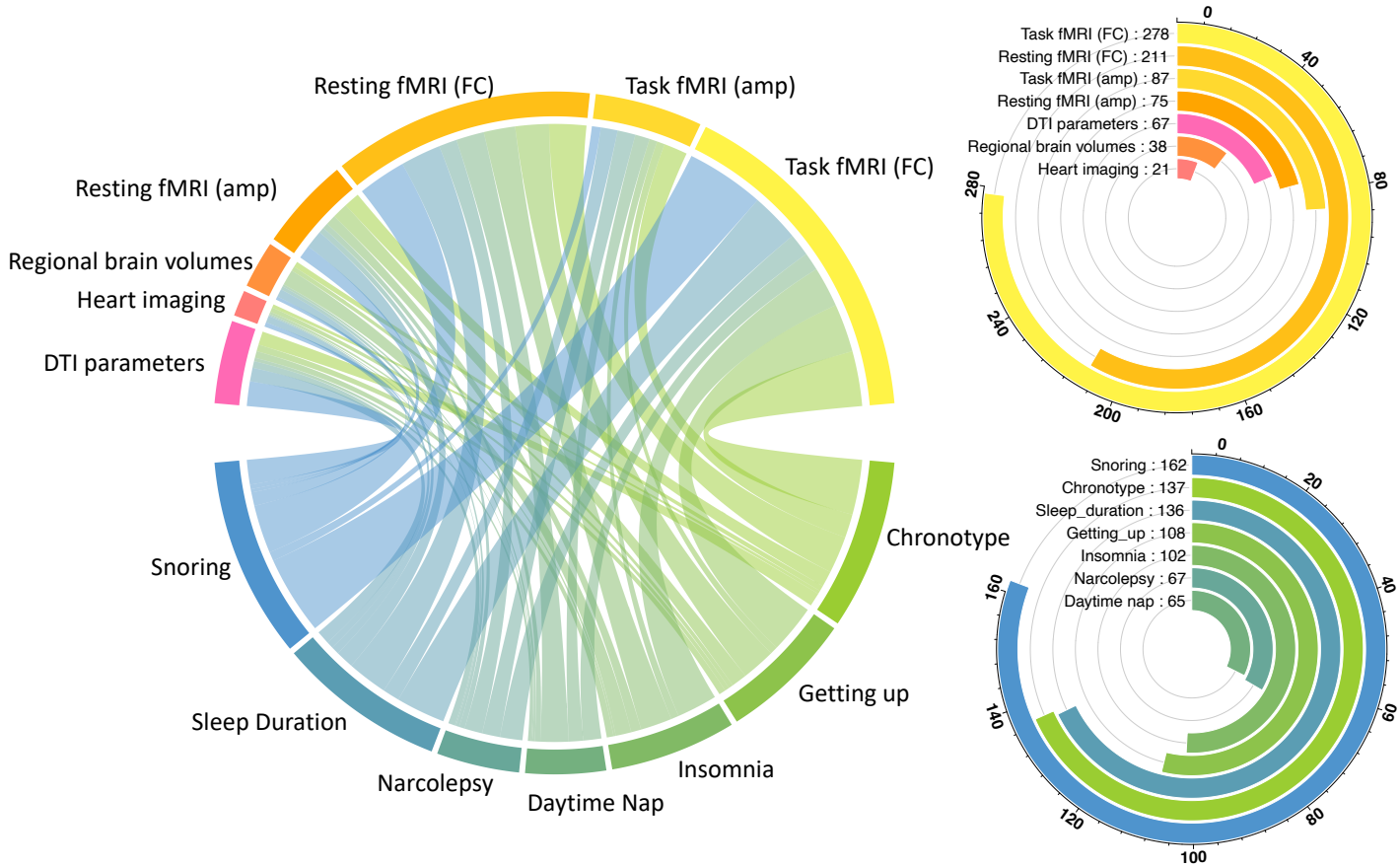


Figure 5

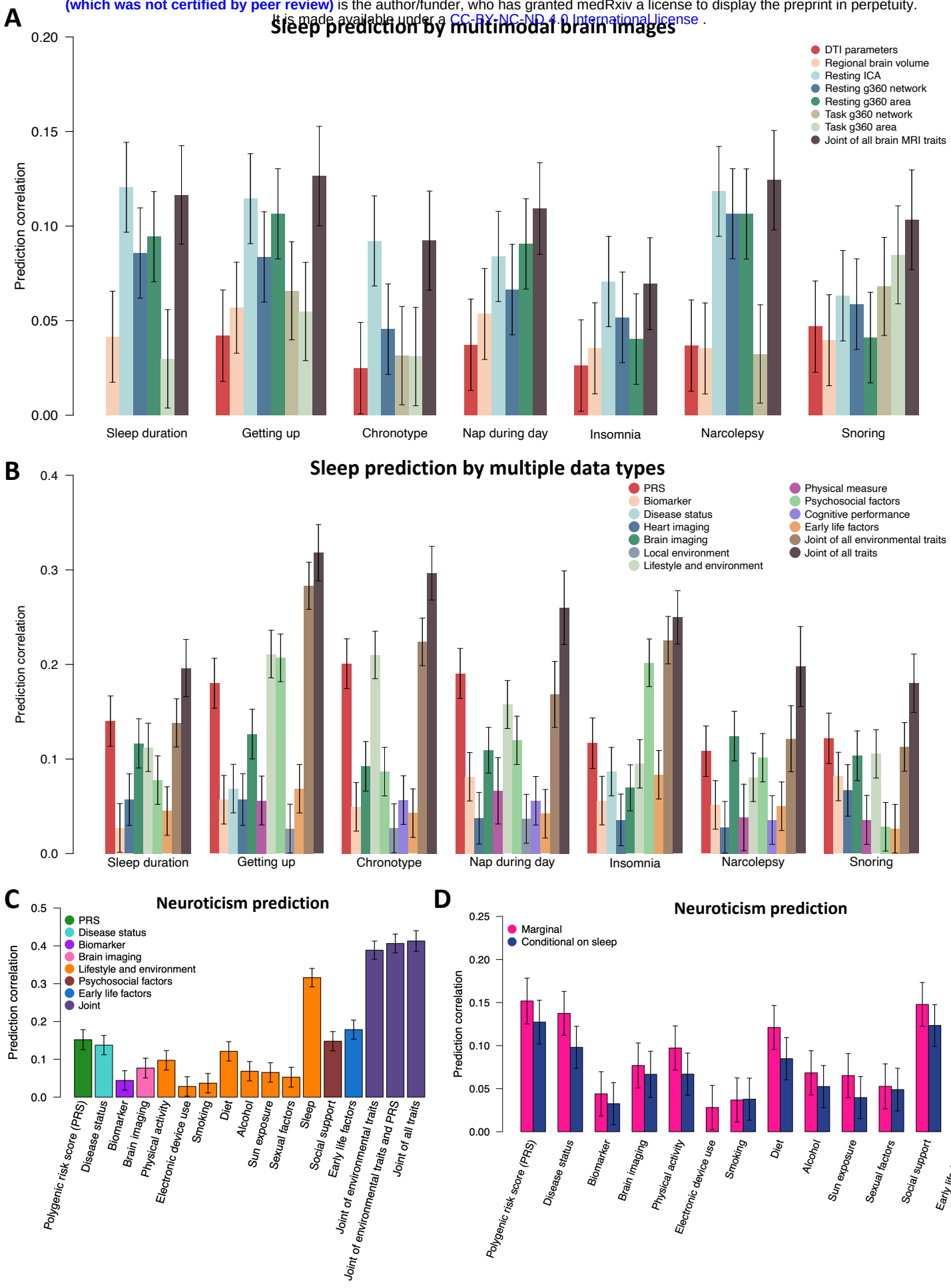


Figure 6