Supplementary material

Pittsburgh Sleep Quality Index

The sleep quality was computed as the sum of 7 analyzed components including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction; the sleep quantity was assessed by asking the participant what was the average number of hours of actual sleep per night in the past month, not counting time falling asleep and getting out of bed.

Genome-Wide Association Analysis

Genome-wide single nucleotide polymorphisms (SNPs) genotyping was performed in 831/897 participants with useable blood or saliva-based genetic material. For this study, we used only samples processed with one custom microarray chip consisting of the Illumina Mega Chip (2 million multiethnic SNPs). Clinical and demographic data, PVS measurements, and SNPs were combined to yield a single data set for every individual. Genotype information was available for 2,119,803 typed SNPs across 831 individuals with clinical data and PVS measurements. The high number of SNPs available allowed us to perform a stringent SNP-level filtering: we filtered out SNPs for which the minor allele frequency was less than 1%, in order to ensure adequate power to infer a statistically significant relationship between the SNP and the PVS. After this step, 471,068 typed SNPs across 831 individuals persisted and underwent further pre-processing steps. We subsequently performed a sample-level filtering: a call rate of 100% was applied in order to include only participants' samples with 100% of genetic data available; additionally, we excluded samples exhibiting deviations from the Hardy-Weinberg equilibrium with an

inbreeding coefficient higher than 0.1, since excess heterozygosity across typed SNPs within an individual may be an indication of poor sample quality[1]. For ancestry filtering, we first applied linkage disequilibrium pruning using a threshold value of 0.2, which eliminates a large degree of redundancy in the data and reduces the influence of chromosomal artifacts[2,3]. Then, we used the Method of Moments procedure to calculate the identity by descent (IBD) kinship coefficient: pairwise IBD distances were computed to search for sample relatedness and participants with the highest number of pairwise kinship coefficients >0.1, which typically suggest relatedness, duplicates, or sample mixture, were iteratively removed[3]. This resulted in the exclusion of 455 samples. Among non-twin and twin siblings included in this study, all but one member of each biologically independent sibship was filtered out at this step. At the end of the pre-processing procedure, 471,068 typed SNPs across 376 individuals were considered in the final genome-wide association analysis. A Bonferonni-corrected genome-wide significance threshold of 5×10^{-8} and a suggestive association significance threshold of 5×10^{-6} were adopted[3].

Supplementary references

1. Wright S. Coefficients of Inbreeding and Relationship. Am Nat 1922; 56: 330–338.
2. Laurie CC, Doheny KF, Mirel DB, et al. Quality control and quality assurance in genotypic data for genome-wide association studies. Genet Epidemiol 2010; 34: 591–602.
3. Reed E, Nunez S, Kulp D, et al. A guide to genome-wide association analysis and post-analytic interrogation. Stat Med 2015; 34: 3769–3792.
4. Van Essen DC, Ugurbil K, Auerbach E, et al. The Human Connectome Project: A data acquisition perspective. Neuroimage 2012; 62: 2222–2231.
5. Van Essen DC, Smith SM, Barch DM, et al. The WU-Minn Human Connectome Project: An overview. Neuroimage 2013; 80: 62–79.

Supplementary Figure Legends

Supplementary figure 1. 3D rendering of the white matter regions with more than 5% of the total PVS volume (**a**), and with PVS over white matter volume ratios higher than 3% (**b**).

Supplementary figure 2. Scatterplots showing the relationship between the difference in body mass index (BMI) and the difference in perivascular space (PVS) in each couple of monozygotic twins (**a**), dizygotic twins (**b**), non-twin siblings (**c**). Spearman's rank correlation coefficient.

Supplementary figure 3. Scatterplots showing the relationship of years of education with body mass index (BMI) (**a**) and perivascular space (PVS) ratio (**b**). Spearman's rank correlation coefficient.

Supplementary Tables

Supplementary Table 1. Inclusion and exclusion criteria for the participants enrolled in the Human Connectome Project (S900 release)[4].

Inclusion criteria - Age between 22-37 - No prior history of psychiatric disorders, substance abuse, neurological or cardiovascular diseases, as indicated by no report of medical diagnosis, no hospitalization, and no pharmacologic or behavioral treatment. **Exclusion criteria** - Any genetic disorder - Current use of chemotherapy or immunomodulatory agents - History of radiation or chemotherapy that could affect the brain - Sickle cell disease - Thyroid hormone treatment within 12 months before the enrollment - Treatment for diabetes - Head injury followed by neurological symptoms, such as loss of consciousness for more than 30 minutes or amnesia or change in mental status for more than 24 hours, and/or CT findings consistent with traumatic brain injury. - Ineligible to undergo an MRI scan: pregnancy, metal or devices in the body not compatible with MRI (e.g., cardiac pacemaker, cochlear implant, aneurism clip), and/or suffering moderate to severe claustrophobia were reasons for being excluded from the study. - Non-twins born prior to 37 weeks of gestation and twins born prior to 34 weeks of gestation have been excluded since preterm birth has been shown to perturb the development of the brain.[5]

Supplementary Table 2. Perivascular space ratio in each region of interest (ROI), obtained by dividing the perivascular space volume computed in the ROI by the white matter volume of the same ROI. For each ROI, the first row represents the sum of the PVS ratio computed in the two hemispheres, while the PVS ratio of each side is reported in the second and third row (right and left side, respectively). Data are mean ± standard deviation (range: minumum-maximum value). The adjusted p-values refer to the Wilcoxon matched-pairs signed rank test performed to compare the PVS ratio on the right side of each ROI with the corresponding contralateral side. The adjusted p-values that are not significant after controlling for the false discovery rate are reported in red.

ROI	Side	Male (n=394)	Female (n=503)	Overall (n=897)	Adjusted p-value
Bankssts		2.11 ± 1.08 (0.24-7.13)	2.06 ± 0.96 (0.29-5.71)	2.08 ± 1.01 (0.24-7.13)	
	Right	1.17 ± 0.67 (0.02-4.61)	1.14 ± 0.58 (0.05-3.42)	1.15 ± 0.62 (0.02-4.61)	2.50E-30
	Left	0.94 ± 0.52 (0-3.19)	0.92 ± 0.53 (0-2.72)	0.93 ± 0.53 (0-3.19)	
Caudalanteriorcingulate		3.55 ± 2.02 (0.28-9.96)	2.74 ± 1.56 (0.17-9.98)	3.09 ± 1.82 (0.17-9.98)	
	Right	1.7 ± 1.08 (0.14-5.14)	1.31 ± 0.83 (0.03-5.42)	1.48 ± 0.96 (0.03-5.42)	2.00E-11
	Left	1.85 ± 1.03 (0.13-5.31)	1.43 ± 0.84 (0.05-4.86)	1.61 ± 0.95 (0.05-5.31)	
Caudalmiddlefrontal		2.39 ± 1.26 (0.18-6.75)	2.08 ± 1.07 (0.29-6.15)	2.22 ± 1.17 (0.18-6.75)	
	Right	1.05 ± 0.63 (0.08-3.33)	0.93 ± 0.52 (0.07-2.82)	0.98 ± 0.57 (0.07-3.33)	1.60E-70
	Left	1.34 ± 0.69 (0.05-3.67)	1.15 ± 0.6 (0.09-3.33)	1.24 ± 0.65 (0.05-3.67)	
Cuneus		0.55 ± 0.54 (0-4.81)	0.46 ± 0.46 (0-2.77)	0.5 ± 0.5 (0-4.81)	
	Right	0.29 ± 0.31 (0-3.17)	0.23 ± 0.27 (0-1.62)	0.26 ± 0.29 (0-3.17)	0.24
	Left	0.26 ± 0.29 (0-1.82)	0.22 ± 0.24 (0-1.2)	0.24 ± 0.26 (0-1.82)	
Entorhinal		0.5 ± 0.6 (0-3.48)	0.24 ± 0.33 (0-2.2)	0.35 ± 0.48 (0-3.48)	
	Right	0.15 ± 0.26 (0-1.86)	0.08 ± 0.16 (0-1.39)	0.11 ± 0.21 (0-1.86)	2.40E-30
	Left	0.34 ± 0.45 (0-2.91)	0.16 ± 0.27 (0-2.06)	0.24 ± 0.37 (0-2.91)	
Fusiform		1.56 ± 0.81 (0.12-5.16)	1.46 ± 0.78 (0.12-6.88)	1.51 ± 0.8 (0.12-6.88)	
	Right	0.8 ± 0.45 (0.06-2.72)	0.77 ± 0.44 (0.02-3.76)	0.78 ± 0.44 (0.02-3.76)	6.40E-08

	Left	0.76 ± 0.43 (0.05-2.91)	0.7 ± 0.41 (0.03-3.13)	0.72 ± 0.42 (0.03-3.13)	
Inferiorparietal		2.67 ± 1.29 (0.35-8.01)	2.58 ± 1.23 (0.26-7.29)	2.62 ± 1.25 (0.26-8.01)	
	Right	1.47 ± 0.7 (0.18-4.33)	1.4 ± 0.68 (0.2-4.07)	1.43 ± 0.69 (0.18-4.33)	2.00E-64
	Left	1.2 ± 0.63 (0.14-4.39)	1.18 ± 0.6 (0.07-3.56)	1.19 ± 0.61 (0.07-4.39)	
Inferiortemporal		1.48 ± 0.83 (0.11-5.22)	1.39 ± 0.77 (0.08-5.01)	1.43 ± 0.8 (0.08-5.22)	
	Right	0.69 ± 0.43 (0.01-2.83)	0.68 ± 0.4 (0.01-2.53)	0.69 ± 0.41 (0.01-2.83)	2.30E-07
	Left	0.78 ± 0.45 (0.01-2.74)	0.71 ± 0.43 (0-2.69)	0.74 ± 0.44 (0-2.74)	
Isthmuscingulate		3.63 ± 1.77 (0.39-10.15)	2.71 ± 1.27 (0.24-8.12)	3.11 ± 1.58 (0.24-10.15)	
	Right	1.96 ± 0.99 (0.25-5.31)	1.4 ± 0.7 (0.07-4.84)	1.65 ± 0.89 (0.07-5.31)	5.00E-30
	Left	1.67 ± 0.83 (0.12-4.84)	1.3 ± 0.63 (0.12-3.77)	1.47 ± 0.75 (0.12-4.84)	
Lateraloccipital		1.06 ± 0.73 (0.03-4.61)	1 ± 0.64 (0.03-3.89)	1.03 ± 0.68 (0.03-4.61)	
	Right	0.59 ± 0.41 (0-2.33)	0.56 ± 0.37 (0.02-2.4)	0.57 ± 0.39 (0-2.4)	3.40E-49
	Left	0.47 ± 0.36 (0.02-2.28)	0.44 ± 0.3 (0-1.63)	0.45 ± 0.33 (0-2.28)	
Lateralorbitofrontal		2.54 ± 1.44 (0.39-8.15)	2.26 ± 1.27 (0.32-8.67)	2.38 ± 1.36 (0.32-8.67)	
	Right	1.19 ± 0.71 (0.15-4.23)	1.11 ± 0.64 (0.16-4.59)	1.14 ± 0.67 (0.15-4.59)	1.60E-08
	Left	1.35 ± 0.8 (0.14-4.31)	1.15 ± 0.7 (0.12-5.29)	1.24 ± 0.75 (0.12-5.29)	
Lingual		1.06 ± 0.6 (0.07-4.29)	1 ± 0.57 (0-3.52)	1.03 ± 0.59 (0-4.29)	
	Right	0.64 ± 0.38 (0.02-2.36)	0.6 ± 0.36 (0-2.28)	0.62 ± 0.37 (0-2.36)	3.50E-69
	Left	0.42 ± 0.32 (0-2.09)	0.4 ± 0.3 (0-1.98)	0.41 ± 0.31 (0-2.09)	
Medialorbitofrontal		1.46 ± 1.09 (0.05-7.15)	1.24 ± 0.88 (0.08-6.16)	1.33 ± 0.98 (0.05-7.15)	
	Right	0.64 ± 0.61 (0-3.89)	0.55 ± 0.51 (0-3.7)	0.59 ± 0.56 (0-3.89)	1.90E-41
	Left	0.81 ± 0.54 (0-3.42)	0.69 ± 0.45 (0.03-2.78)	0.74 ± 0.49 (0-3.42)	
Middletemporal		1.51 ± 0.81 (0.11-4.78)	1.43 ± 0.76 (0.11-4.62)	1.46 ± 0.78 (0.11-4.78)	
	Right	0.73 ± 0.43 (0.02-2.7)	0.7 ± 0.4 (0.06-2.73)	0.71 ± 0.42 (0.02-2.73)	0.001
	Left	0.79 ± 0.44 (0.07-2.84)	0.73 ± 0.42 (0.02-2.66)	0.75 ± 0.43 (0.02-2.84)	
Parahippocampal		0.83 ± 0.62 (0-4.12)	0.58 ± 0.56 (0-3.76)	0.69 ± 0.6 (0-4.12)	
	Right	0.37 ± 0.32 (0-1.98)	0.28 ± 0.35 (0-2.86)	0.32 ± 0.34 (0-2.86)	0.005
	Left	0.45 ± 0.41 (0-3)	0.3 ± 0.35 (0-2.73)	0.36 ± 0.38 (0-3)	
Paracentral		1.42 ± 0.86 (0.04-5.19)	1.24 ± 0.77 (0.03-4.41)	1.32 ± 0.82 (0.03-5.19)	
	Right	0.8 ± 0.5 (0.02-3.21)	0.68 ± 0.44 (0.03-2.55)	0.73 ± 0.47 (0.02-3.21)	3.80E-35
	Left	0.62 ± 0.42 (0-2.09)	0.56 ± 0.39 (0-2.34)	0.59 ± 0.4 (0-2.34)	
Parsopercularis		1.96 ± 1.26 (0.03-7.17)	1.62 ± 1.11 (0.06-7.45)	1.77 ± 1.19 (0.03-7.45)	
	Right	0.99 ± 0.69 (0-3.75)	0.84 ± 0.6 (0-3.18)	0.91 ± 0.65 (0-3.75)	0.034
	Left	0.97 ± 0.65 (0-3.43)	0.77 ± 0.59 (0-4.28)	0.86 ± 0.63 (0-4.28)	
Parsorbitalis		0.85 ± 0.76 (0-3.9)	0.78 ± 0.71 (0-4)	0.81 ± 0.73 (0-4)	
	Right	0.41 ± 0.42 (0-2.37)	0.37 ± 0.36 (0-1.89)	0.39 ± 0.39 (0-2.37)	0.28
	Left	0.44 ± 0.44 (0-2.25)	0.41 ± 0.46 (0-2.87)	0.42 ± 0.45 (0-2.87)	
Parstriangularis		1.5 ± 1.08 (0-5.84)	1.28 ± 0.86 (0-4.81)	1.37 ± 0.96 (0-5.84)	
	Right	0.64 ± 0.53 (0-2.85)	0.57 ± 0.44 (0-2.94)	0.6 ± 0.48 (0-2.94)	2.00E-36
	Left	0.86 ± 0.62 (0-3.21)	0.71 ± 0.5 (0-3.2)	0.78 ± 0.56 (0-3.21)	

Pericalcarine		2.1 ± 1.28 (0-6.57)	2.14 ± 1.26 (0-7.37)	2.12 ± 1.27 (0-7.37)	
	Right	1.03 ± 0.69 (0-3.45)	1.05 ± 0.7 (0-3.42)	1.04 ± 0.69 (0-3.45)	1
	Left	1.07 ± 0.86 (0-4.81)	1.09 ± 0.88 (0-4.65)	1.08 ± 0.87 (0-4.81)	
Postcentral		1.61 ± 0.96 (0.06-5.82)	1.4 ± 0.82 (0.06-4.88)	1.49 ± 0.89 (0.06-5.82)	
	Right	0.79 ± 0.49 (0.02-3.07)	0.69 ± 0.42 (0.02-2.53)	0.73 ± 0.45 (0.02-3.07)	0.017
	Left	0.83 ± 0.53 (0.03-3.56)	0.71 ± 0.45 (0-2.6)	0.76 ± 0.49 (0-3.56)	
Posteriorcingulate		2.6 ± 1.32 (0.33-6.97)	2.11 ± 1.07 (0.34-6.47)	2.33 ± 1.21 (0.33-6.97)	
	Right	1.35 ± 0.71 (0.15-3.77)	1.08 ± 0.58 (0.15-3.36)	1.2 ± 0.65 (0.15-3.77)	3.30E-06
	Left	1.25 ± 0.65 (0.12-3.61)	1.03 ± 0.55 (0.1-3.46)	1.13 ± 0.61 (0.1-3.61)	
Precentral		2.23 ± 1.2 (0.23-7.12)	1.98 ± 1.06 (0.25-6.68)	2.09 ± 1.13 (0.23-7.12)	
	Right	1.11 ± 0.62 (0.12-3.8)	0.98 ± 0.53 (0.06-3.06)	1.04 ± 0.58 (0.06-3.8)	0.57
	Left	1.11 ± 0.61 (0.11-3.78)	1 ± 0.55 (0.05-3.62)	1.05 ± 0.58 (0.05-3.78)	
Precuneus		2.65 ± 1.11 (0.37-7.24)	2.45 ± 1.06 (0.52-6.35)	2.54 ± 1.09 (0.37-7.24)	
	Right	1.47 ± 0.61 (0.24-3.85)	1.33 ± 0.59 (0.28-3.69)	1.39 ± 0.61 (0.24-3.85)	5.10E-74
	Left	1.18 ± 0.55 (0.13-3.39)	1.11 ± 0.52 (0.22-3.3)	1.14 ± 0.53 (0.13-3.39)	
Rostralanteriorcingulate		3.15 ± 2.05 (0.3-13.05)	2.53 ± 1.61 (0.15-11.6)	2.8 ± 1.84 (0.15-13.05)	
	Right	1.57 ± 1.1 (0.07-6.04)	1.25 ± 0.86 (0-5.88)	1.39 ± 0.99 (0-6.04)	0.57
	Left	1.58 ± 1.05 (0.09-7.26)	1.28 ± 0.84 (0-5.72)	1.41 ± 0.95 (0-7.26)	
Rostralmiddlefrontal		1.97 ± 1.26 (0.09-7.52)	1.81 ± 1.06 (0.15-6.13)	1.88 ± 1.16 (0.09-7.52)	
	Right	0.84 ± 0.59 (0.03-3.67)	0.8 ± 0.51 (0.04-3.39)	0.82 ± 0.55 (0.03-3.67)	2.50E-96
	Left	1.13 ± 0.7 (0.02-4.28)	1.01 ± 0.59 (0.09-4.11)	1.06 ± 0.64 (0.02-4.28)	
Superiorfrontal		2.49 ± 1.2 (0.33-7.13)	2.22 ± 1.09 (0.25-6.55)	2.33 ± 1.15 (0.25-7.13)	
	Right	1.21 ± 0.61 (0.13-3.45)	1.09 ± 0.55 (0.1-3.59)	1.14 ± 0.58 (0.1-3.59)	3.40E-09
	Left	1.27 ± 0.61 (0.13-3.73)	1.13 ± 0.57 (0.12-3.3)	1.19 ± 0.59 (0.12-3.73)	
Superiorparietal		2.62 ± 1.22 (0.52-6.31)	2.41 ± 1.07 (0.45-6)	2.5 ± 1.14 (0.45-6.31)	
	Right	1.33 ± 0.63 (0.23-3.54)	1.23 ± 0.56 (0.2-3.27)	1.27 ± 0.6 (0.2-3.54)	2.10E-05
	Left	1.29 ± 0.62 (0.28-3.4)	1.18 ± 0.54 (0.13-2.9)	1.23 ± 0.58 (0.13-3.4)	
Superiortemporal		1.44 ± 0.81 (0.11-4.2)	1.26 ± 0.74 (0.06-4.52)	1.34 ± 0.78 (0.06-4.52)	
	Right	0.59 ± 0.4 (0.02-2.45)	0.54 ± 0.38 (0.01-2.49)	0.57 ± 0.39 (0.01-2.49)	3.80E-68
	Left	0.85 ± 0.47 (0.01-2.73)	0.71 ± 0.43 (0.02-2.46)	0.77 ± 0.45 (0.01-2.73)	
Supramarginal		3.25 ± 1.58 (0.25-8.69)	2.9 ± 1.37 (0.44-7.75)	3.06 ± 1.48 (0.25-8.69)	
	Right	1.6 ± 0.8 (0.14-4.35)	1.4 ± 0.68 (0.1-3.72)	1.49 ± 0.74 (0.1-4.35)	3.10E-07
	Left	1.66 ± 0.85 (0.03-4.79)	1.5 ± 0.76 (0.19-4.16)	1.57 ± 0.8 (0.03-4.79)	
Frontalpole		0.32 ± 0.49 (0-2.96)	0.24 ± 0.4 (0-2.77)	0.28 ± 0.44 (0-2.96)	
	Right	0.17 ± 0.32 (0-1.83)	0.13 ± 0.27 (0-1.68)	0.15 ± 0.29 (0-1.83)	0.063
	Left	0.15 ± 0.32 (0-2.4)	0.11 ± 0.27 (0-2.77)	0.13 ± 0.3 (0-2.77)	
Temporalpole		0.89 ± 0.86 (0-4.32)	0.62 ± 0.71 (0-6.45)	0.74 ± 0.79 (0-6.45)	
	Right	0.36 ± 0.45 (0-3.43)	0.27 ± 0.38 (0-2.78)	0.31 ± 0.41 (0-3.43)	2.10E-12
	Left	0.53 ± 0.56 (0-3.19)	0.35 ± 0.47 (0-3.67)	0.43 ± 0.52 (0-3.67)	
Transversetemporal		1.52 ± 1.26 (0-7.15)	1.7 ± 1.37 (0-8.34)	1.62 ± 1.33 (0-8.34)	

	Right	0.74 ± 0.81 (0-5.09)	0.88 ± 0.87 (0-4.87)	0.82 ± 0.85 (0-5.09)	1
	Left	0.78 ± 0.72 (0-3.76)	0.82 ± 0.78 (0-4.88)	0.81 ± 0.75 (0-4.88)	
Insula		3.25 ± 1.12 (0.82-7.76)	2.87 ± 0.95 (0.96-7.43)	3.04 ± 1.05 (0.82-7.76)	
	Right	1.58 ± 0.6 (0.41-4.52)	1.43 ± 0.52 (0.33-3.87)	1.5 ± 0.56 (0.33-4.52)	0.0013
	Left	1.67 ± 0.58 (0.41-3.92)	1.44 ± 0.49 (0.38-3.56)	1.54 ± 0.55 (0.38-3.92)	

Supplementary Table 3. Results of the ANCOVA model testing the effects of gender and BMI on PVS ratio after controlling for age. BMI groups: 1. BMI < 20; 2. BMI between 20 and 25; 3. BMI between 25 and 30; 4. BMI > 30. Significant p-values after controlling for the false discovery rate are marked with *.

	F-test statistic	p-value	η^2
Age	22.209	2.85E-06*	0.025
Gender	42.572	1.16E-10*	0.047
BMI groups	15.552	7.34E-10*	0.051
Gender:BMI groups interaction	2.698	0.045	0.009