Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

Supplemental Material for

Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex

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Methods

Participants

In this cohort study, bipolar disorder patients were recruited in the framework of the St. Göran project, which is a long-term follow-up program at the affective disorder outpatient unit at the Northern Stockholm psychiatric clinic, Stockholm, Sweden. Details on exclusion and inclusion criteria and diagnostic tools can be found in [1, 2]. In brief, a clinical diagnosis of bipolar disorder was established according to the DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID) included in the structured interview instrument Affective Disorder Evaluation (ADE)[3]. Educational achievement was categorized into 1: pre-high school, 2: high school, 3: university (< 3 years), and 4: university (3 years or longer). To screen for comorbid psychiatric conditions, we used the Mini International Neuropsychiatric Interview (M.I.N.I.). Diagnostic decision was made by a consensus panel of experienced board-certified psychiatrists specialized in BD. The majority of patients were in an euthymic state at scan day as defined by Montgomery Åsberg Depression Rating Scale (MADRS) [4] and Young Ziegler Mania Rating Scale (YMRS) [5] scores of < 14. Thirteen patients had MADRS scores >14, but all patients were in stable mood, i.e., not depressed or (hypo)manic. Statistics Sweden randomly selected age and sex matched healthy controls (HC). Details of the

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recruitment, in- and exclusion criteria can be found elsewhere [6, 7]. Eligible persons were scheduled for a personal examination by a psychiatrist using M.I.N.I. and selected parts of the ADE. In brief, exclusion criteria were: any current psychiatric disorder, a family history of schizophrenia or bipolar disorder in first-degree relatives, drug or alcohol abuse, and neurological conditions. This study included patients with bipolar disorder type 1 (BDI) and type 2 (BDII). Patients and controls underwent same procedures. Prior to analysis, data from 21 participants (6 patients and 15 controls) were excluded. Reasons for exclusions were detected pathology, consent withdrawal, technical errors during image acquisition, or motion artifacts that led to failed FreeSurfer segmentations. Participants who provided both genetic and sufficient structural brain imaging data at baseline investigation were included in this cross-sectional study, yielding a final sample size of N=179. This is a subsample of the cohort (N=225) previously analysed concerning case-control differences in cortical brain structure [8].

MRI image processing

Structural MRI

For each participant, measures for regional cortical volume, thickness and surface area of 34 regions of interest per hemisphere (Desikan atlas[9]) were obtained from structural T1-weighted images using the semi-automated cortical surface reconstruction and parcellation methods provided by FreeSurfer[10-14]. The procedure includes intensity normalization, removal of non-brain tissue, segmentation of cortical grey, subcortical white, deep grey matter volumetric structures, as well as triangular tessellation of the grey/white matter interface and white matter/cerebrospinal fluid boundary (pial surface). Before data extraction, reconstruction of

the surfaces were visually inspected and, if necessary, corrected manually using editing tools provided by FreeSurfer. More details can be found in our previous publication on case-control differences[8]. As we had no hypothesis regarding laterality differences, we combined measures of left and right hemispheres by averaging thickness and summing area and volume measures. Our hypothesis-driven approach focussed on areas which have consistently been reported to be affected in BD patients[8, 15-17]. These included regions involved in the core symptoms of BD according to current disease models[18], and known to be structurally influenced by genetic factors[19-21]. This resulted in the investigation of 16 cortical regions: 11 frontal, four temporal and insular cortex, listed in Tables S2-S4. The ROI approach was also chosen to increase statistical power, and to provide better comparability to numerous previous studies that used the same parcellation method, including large-scale multi-center ENIGMA studies in the field of BD[15] and across disorders[22]. However, we also tested the relationships between PRS and brain structure a) in ROIs outside our hypothesis (Tables S5-S7), and b) on a vertex-level across the whole brain. For vertex-wise analyses, individual reconstructed surfaces were smoothed (fwhm = 20 mm), transformed and resampled onto a common standard space (fsaverage) using the -qcache command.

Resting state functional MRI (rs-fMRI)

rs-fMRI preprocessing was performed using FMRIPREP version 1.0.11 [23]. Each T1w (T1-weighted) volume was corrected for INU (intensity non-uniformity) using *N4BiasFieldCorrection* v2.1.0[24]. Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c was performed through nonlinear registration with the

antsRegistration tool of ANTs v2.1.0[25], using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray matter (GM) was performed on the brain-extracted T1w image using *FAST*[26] of the FMRIB Software Library (FSL, https://www.fmrib.ox.ac.uk, v5.0.9). Functional data was motion corrected using MCFLIRT. This was followed by co-registration to the corresponding T1w image using boundary-based registration with 9 degrees of freedom, using *FLIRT*. Motion correcting transformations, BOLD-to-T1w transformation and T1w-to-template (MNI) warp were concatenated and applied in a single step, using *antsApplyTransforms* (ANTs v2.1.0) and Lanczos interpolation. Physiological noise regressors were extracted, applying CompCor[27]. Principal components were estimated for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). For aCompCor, six components were calculated within the intersection of the subcortical mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run. Frame-wise displacement[28] was calculated for each functional run using the implementation of Nipype. Eighteen movement regressors (6 extracted motion regressors and corresponding first and second derivatives), global signal, framewise displacement and 6 aCompCorr regressors were regressed out from the fMRI data. Time series of 400 regions of interest following the Schaeffer parcellation[29] were extracted by averaging over voxels in each brain regions. A bandpass filter was applied between 0.01 and 0.1 Hz. Each node was assigned to one of 7 brain networks from the Yeo 7-network template. Post-fmriprep preprocessing was done using *nilearn* (**v0.5.0**)[30] and *teneto* (v0.4.4)[31].

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Computation of polygenic risk scores (PRS)

The individual-genotype data for BD was based on the Swedish Bipolar Collection study (SWEBIC) as part of the Bipolar Disorder Working Group of PGC[32]. Cases of this study were adults diagnosed according to the DSM-IV-TR with BD type 1, BD type 2, BD not otherwise specified, or schizoaffective disorder bipolar type, mostly recruited via the Swedish Quality Register for BD (BipoläR). Participants provided blood samples for genotyping, which was conducted at the Broad Institute of Harvard and MIT. Genotyping was conducted using Affymetrix 6.0 (wave 1) (Affymetrix, Santa Clara, CA, USA), Illumina OmniExpress (wave 2) chips (Illumina, San Diego, CA, USA) and PsychChip array with HumanCore, Human Exome, and custom psych content (Illumina, San Diego, CA, USA). We followed the Ricopili pipeline for QC and pre-imputation processing[33]. We used the Sanger imputation service to conduct the imputation using the Haplotype Reference Consortium (HRC) reference panel and the PBWT (Positional Burrows-Wheeler Transform) imputation algorithm. For each individual, a single score reflecting the aggregated polygenic risk for BD (PRS-BD) was generated using the largest genome-wide association study on BD to date, performed by the Psychiatric Genomic Consortium (PGC), as a "discovery" set[32]. Since the original GWAS included the participants from the St. Göran Bipolar Project (target set), the GWAS analysis was re-run to exclude the sample under investigation to remove sample overlap between discovery and target sets. The PRS-BD was computed using PLINK v1.9 as the sum of the imputed SNP dosages weighted by the allele effect from the discovery set across all SNPs under a GWAS p-value of p=0.1. This threshold was previously identified to best predict case-control status[34] and was a good balance between variance explained and SNP inclusion[32,

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[35]. For consistency and to reduce the multiple testing burden, only one threshold was investigated. Variants with minor allele frequency <0.1 were excluded, so were those with an imputation score of <0.9 or ambiguous strand. To avoid correlation between investigated SNP's, linkage disequilibrium (LD) clumping was performed at r^2<0.1 in a 500kb window[36]. BD and schizophrenia share symptoms and at least half of their genetic risk[37, 38]. Also, GWAS for schizophrenia have included larger samples than for BD conferring greater accuracy for the main results and PRS. Therefore, a risk score for schizophrenia (PRS-SCZ) was computed using the Psychiatric Genomics Consortium schizophrenia GWAS results after excluding the shared controls between discovery and target sets using a p-value threshold of 0.10 and was tested against the same cortical regions[35]. The total numbers of SNPs left for PRS generation were 30,131 for BD and 29,830 for SCZ. GWAS used to create polygenic risk scores were performed with individuals of European ancestry (excluding genetically identified non-Europeans; 6 standard deviation from PC means based on the 1000 Genomes Project European samples[39]), best predicting bipolar disorder status in other European samples, such as the cohort investigated.

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Statistical Analyses

Whole-brain analyses

Regression analyses, as described for the main analysis, were also performed on regions located outside the 16 ROIs described previously. Results are listed in (Table S4-6). We also performed whole-brain vertex-wise analyses to investigate the focal nature of the correlations observed in the main analysis with higher regional resolution. Analyses testing the effects of both PRS-BD and PRS-SCZ on cortical thickness (dependent variable) at the vertex-level were performed using QDEC with a surface-based smoothing of FWHM=20mm, and age and sex as covariates. Analyses were performed in the combined cohort, and repeated while correcting for case-control status, as well as in patients and controls separately. Although this was a secondary analysis, we performed correction for multiple comparisons using a Monte Carlo cluster-wise simulation approach with a cluster forming threshold of 0.05.

Sensitivity analyses to test for potential confounding effects

We tested for potential confounding effects by other demographic (BMI, etc.) or clinical variables (e.g., comorbidities, medication use) listed in Table 1 by entering those variables separately as additional covariates in the statistical model in SPSS (one at a time). In further tests, where the number of participants with a specific comorbidity/medication was low (<10), we repeated the analysis when excluding those individuals. For each testing variable, this was done in a separate test. Finally, to limit the possibility that differences in ancestry could influence the results, regression analyses were also performed while adjusting for six

principal components (PCs) derived from LD-pruned genome-wide data to account for population substructure[40]. Detailed results of such tests are not shown due to the large number of sensitivity tests performed.

vmPFC functional hub strength (DMN-hubiness) and associations with PRS

Case-control differences in vmPFC DMN-hubiness were computed using a univariate analysis of variance (ANOVA) with the rs-fMRI measure as the dependent variable and group as fixed factor. The main effect of group was also tested when adjusting for age and sex using ANCOVA. Pearson correlations were calculated between left and right vmPFC DMN-hubiness and PRS (SPSS). In addition, partial correlations were performed correcting for age and sex, and for age, sex and group status. Correlations were also performed in patients and controls separately.

VmPFC DMN-hubiness and correlations with mOFC/vmPFC thickness

We correlated vmPFC DMN-hubiness to mOFC/vmPFC thickness using Pearson correlation and performed partial correlations correcting for age and sex, as well as for age, sex and patient status. We further explored the relationship between vmPFC DMN-hubiness and cortical thickness in a vertex-wise covariation analysis (QDEC) using cortical thickness as the dependent variable and vmPFC DMN-hubiness as covariate of interest, while correcting for

age and sex. We also re-run the analyses when additionally correcting for case-control status, and within patients and controls separately.

Results

Effects of demographic and clinical variables (controlling for potential confounding factors)

Sensitivity analyses controlling for BMI, bipolar subtype (BDI vs. BDII), smoking/snuff-use, education, MADRS, YMRS, intracranial volume, any psychiatric comorbidity or medical treatment did not change the results nor conclusions drawn. The same is true when rerunning the analyses excluding patients with ADHD, OCD, post-traumatic stress disorder (PTSD), or drug and alcohol misuse. However, the predictive effect of PRS-BD on mOFC/vmPFC thickness became weaker when controlling for history of psychosis ($p_{PRS\text{-}BD}$ =0.105, t=-1.628, beta=-0.112; R2=0.227, F(4,172)=12.623, p_model<0.001). Note that 48% of patients had a history of psychosis, thus results when controlling for it potentially disguise relationships of interest, similar to results obtained when correcting for patient status.

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Correcting for genetic principal component (PCs, controlling for ancestry differences) did not change the results or conclusions.

Whole brain analysis on vertex-level

Whole brain analyses on vertex-level confirmed the results obtained in the main analysis. PRS-SCZ predicted cortical thickness in vmPFC (most significant vertex was observed in right vmPFC; p=0.00005; MNI coordinates: [11, 54, -6]) (Figure 2, main text). Significant clusters were also observed in lateral prefrontal cortex including ventrolateral PFC and lateral OFC (Figure S1). As observed in the main analysis, PRS-BD also predicted lateral and medial OFC thickness on vertex level, which, however, did not survive Monte Carlo cluster-wise correction. See Figure S2 for detailed results of the vertex-wise analysis. Similar results were obtained when correcting for group status (Figure S3), and when analyzing patients and controls separately (Figures S1 and S2).

Whole brain analysis (ROI approach)

Analyses of additional ROIs outside our hypothesis are shown in Tables S5-S7. The whole brain ROI approach revealed that higher PRS-SCZ also predicted lower cortical thickness of fusiform and posterior cingulate cortex. Higher PRS-BD predicted lower thickness of lingual and pericalcarine cortex (visual brain areas).

VmPFC DMN-hubiness and correlations with mOFC/vmPFC thickness

Using the ROI approach, left, but not right, vmPFC DMN-hubiness correlated positively mOFC/vmPFC thickness (partial r=0.23, p=0.028, n=90, df=86) correcting for age and sex.

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This correlation became weaker when controlling for age, sex and patient status (partial r=0.198, p=0.066). As significant correlation between left vmPFC DMN-hubiness and its thickness were observed in patients (partial r=0.34, p=0.025, n=45, df=41), but not in controls (partial r=-0.04, p=0.801, n=45, df=41). Further, exploring this relationship in patients using a vertex-wise whole-brain analysis showed significant associations between left vmPFC DMN-hubiness and right vmPFC and lateral prefrontal cortex thickness. Interestingly, although at a somewhat lower significance level, it also correlated with other key regions of the default mode network (precuneus, middle temporal, temporoparietal junction), as well as and anterior insula cortex (Figure S4).

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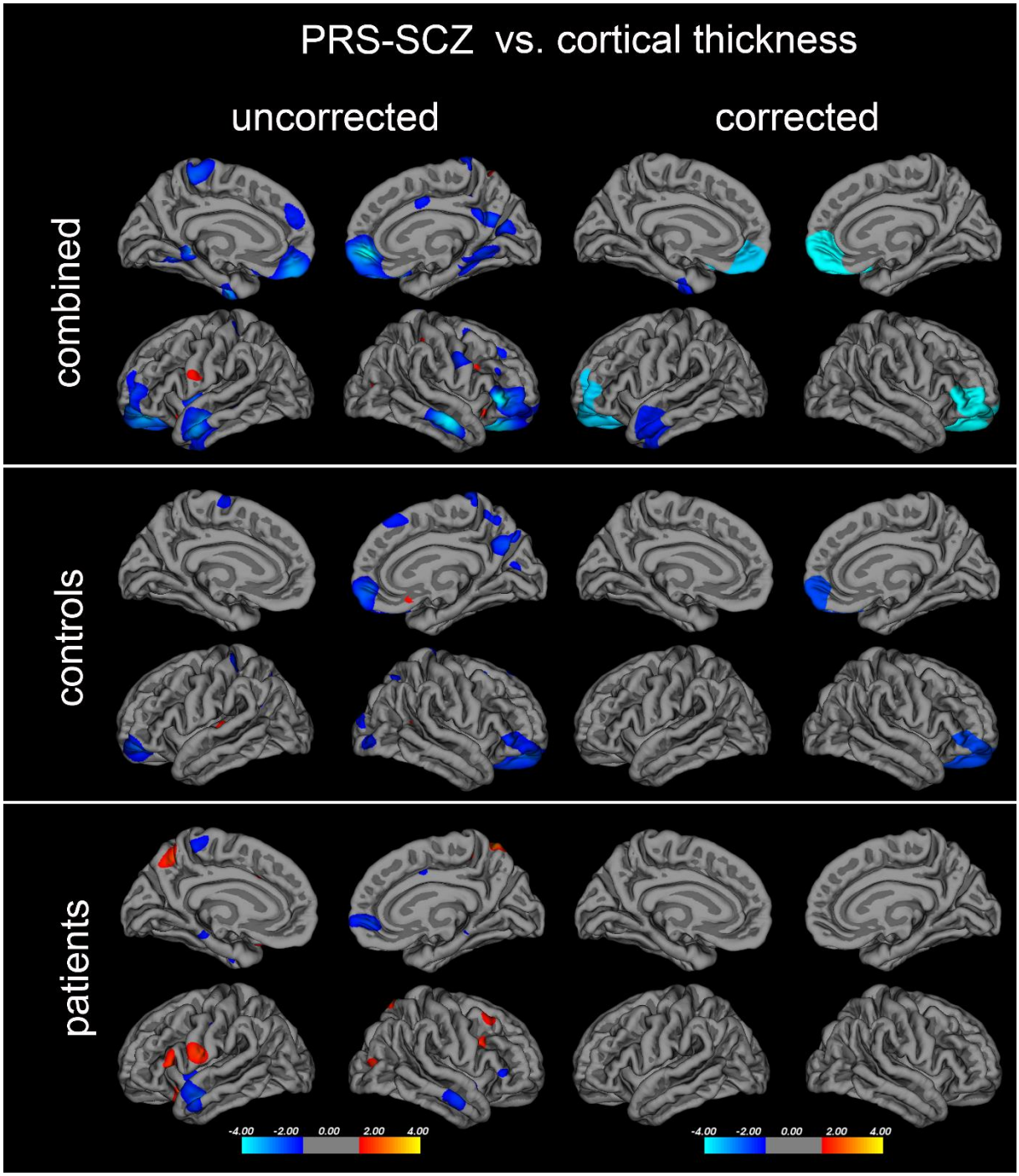
Figure S1.



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Whole-brain analyses on vertex-level. Correlations between PRS-SCZ and cortical thickness in the combined cohort (top), in controls (middle), and patients (bottom). Colored areas represent brain regions in which significant correlations were observed. Results are displayed with a significance threshold of p=0.05 (uncorrected, left panel) and after correcting for multiple comparisons using Monte Carlo cluster-wise correction (corrected, right panel). Cold colors represent negative correlations. After correction for multiple comparison, no positive (warm colors) correlations were observed. Significance is displayed on a -log(p) scale. Right vmPFC showed the most significant PRS-thickness association in the combined cohort, which was also present in controls and with a somewhat lower significance in patients. The lower significance in separate groups may arise from smaller subsample sizes or potential flooring effects in patients. In the combined group, PRS and thickness ranges may also be increased which can help identify correlations.

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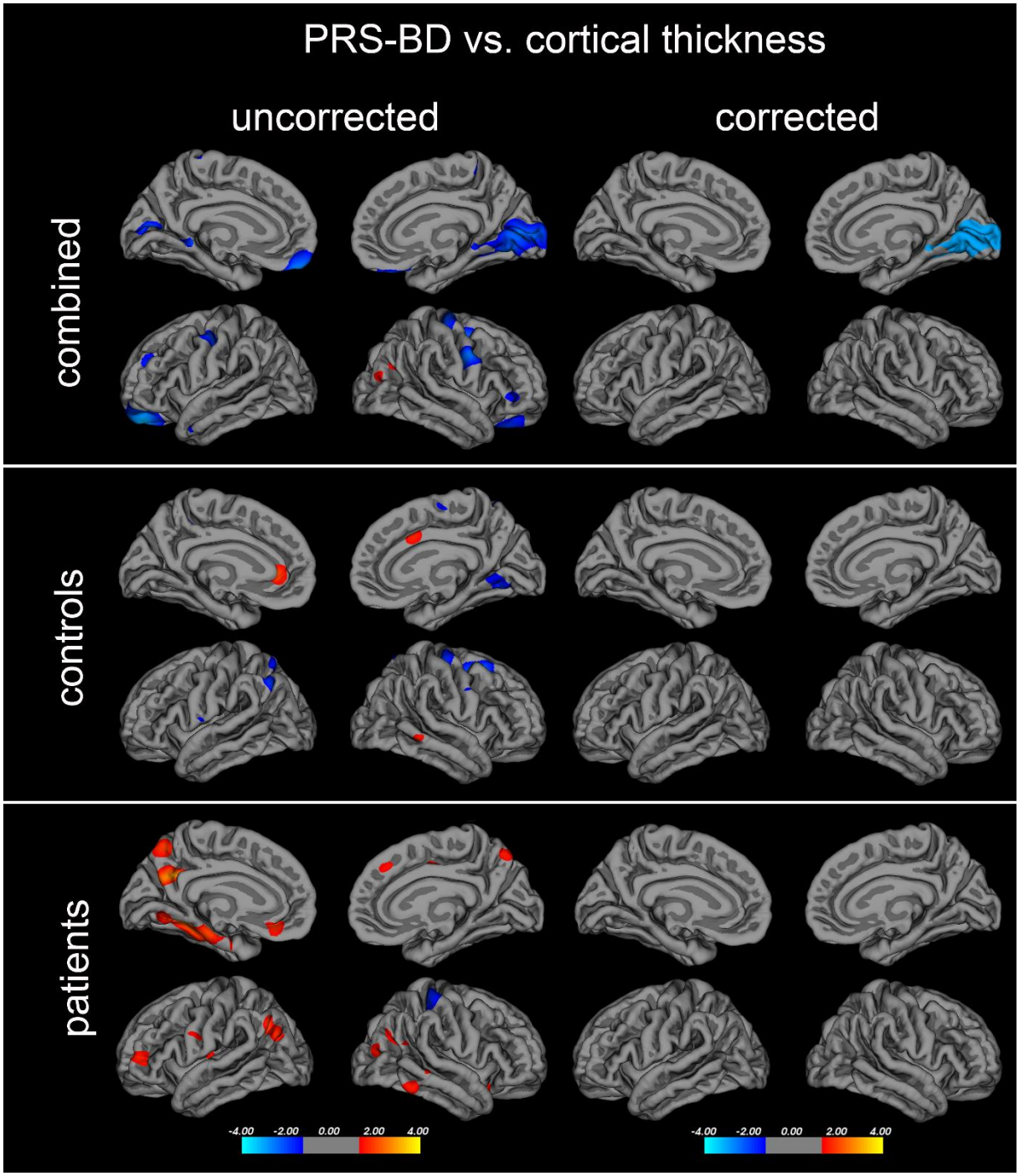
Figure S2.



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Whole-brain analyses on vertex-level. Correlations between PRS-BD and cortical thickness in the combined cohort (top), in controls (middle), and patients (bottom). Colored areas represent brain regions in which significant correlations were observed. Results are displayed with a significance threshold of p=0.05 (uncorrected, left panel) and after correcting for multiple comparisons using Monte Carlo cluster-wise correction (corrected, right panel). Cold colors represent negative correlations. After correction for multiple comparison, no positive (warm colors) correlations were observed. Significance is displayed on a -log(p) scale. The only significant cluster obtained after multiple comparison correction was in the medial occipital cortex (including cuneus, lingual, and pericalcarine) in the combined cohort. Uncorrected results indicate correlations in medial occipital (visual) cortex of controls, and in the orbitofrontal cortex in the combined cohort, similar to what was observed in the main analysis.

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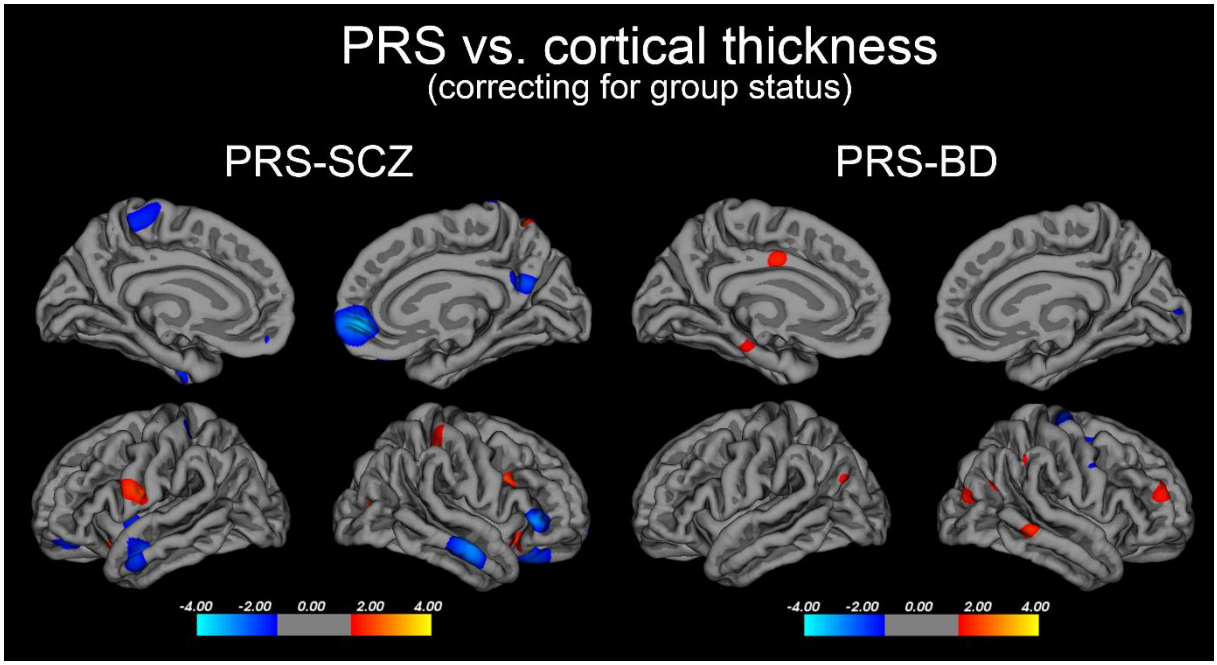
Figure S3.



Vertex-wise whole-brain analyses when correcting for patient-control (group) status. Correlations between PRS-SCZ/BD and cortical thickness in the combined cohort (top) observed when correcting for patient-control status. Color code is the same as described in Figures S1 and S2. Results are displayed with a significance threshold of p=0.05 (uncorrected). No significant associations were observed after correction for multiple comparisons. Strikingly, however, in case of PRS-SCZ, similar clusters are obtained as when group-status is not controlled for, and the vmPFC cluster is still present when correcting for group status, albeit at a lower significance level. Note, correcting for group status might disguise associations of interest, as group is highly related to genetic risk.

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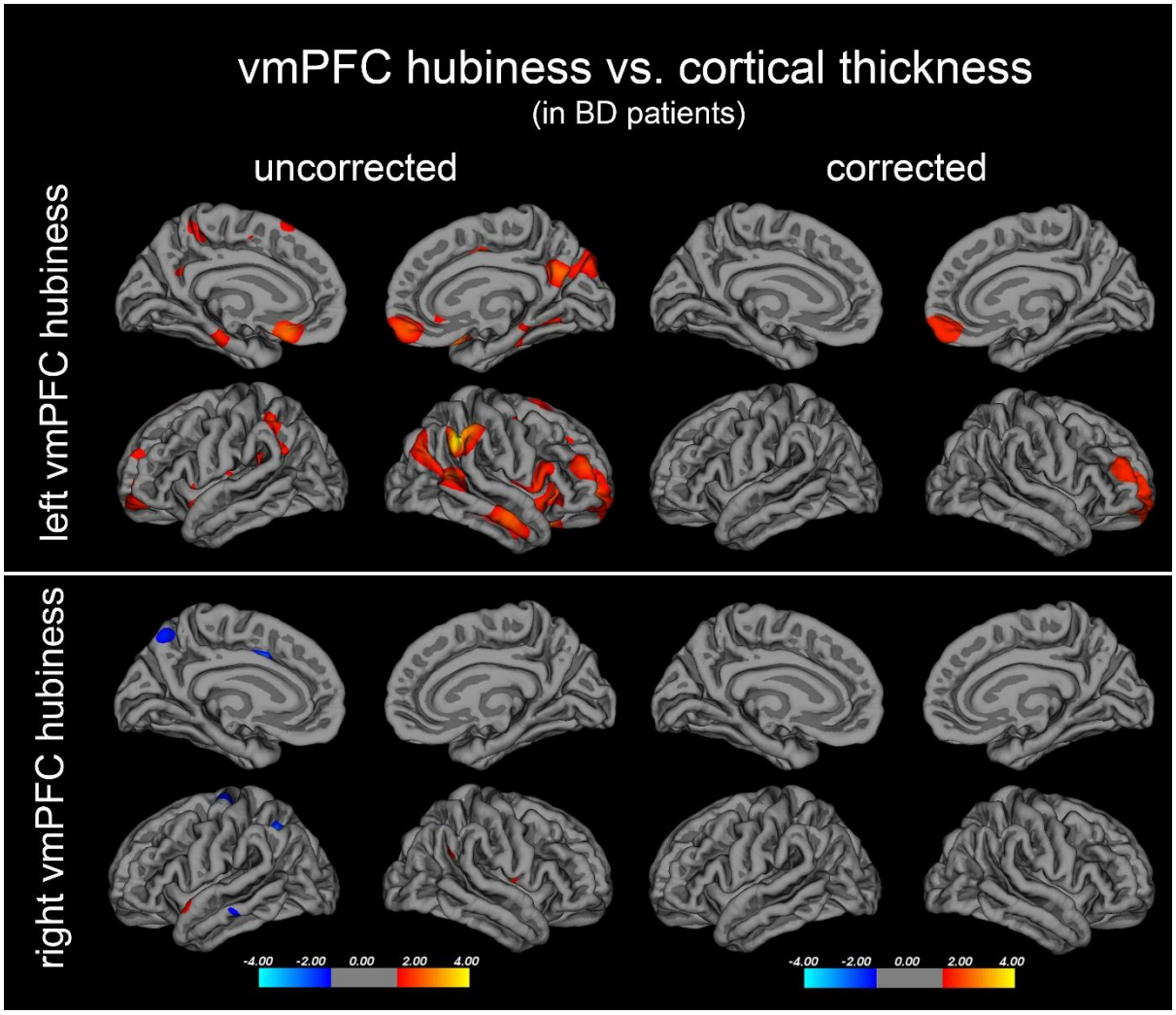
Figure S4.



Vertex-wise correlation analyses between left and right vmPFC funtional hub strength (DMN-hubiness) and cortical thickness in patients. Colored areas represent brain regions in which significant correlations were observed. Results are displayed with a significance threshold of p=0.05 (uncorrected, left panel) and after Monte Carlo cluster-wise correction (corrected, right panel). Warm colors represent positive and cold colors negative correlations.

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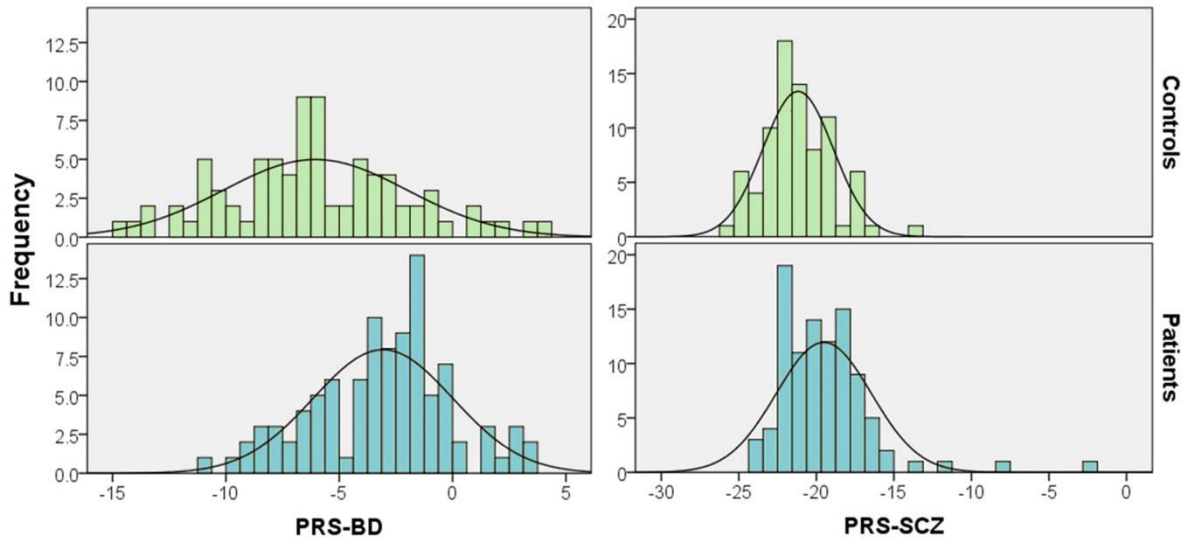
Significance is displayed on a -log(p) scale. Note: These correlations were observed despite the time difference between structural and functional MRI acquisitions.

Figure S5.



Distribution of polygenic risk scores for schizophrenia (PRS-SCZ) and bipolar disorder (PRS-BD) in patients (bottom) and controls (top) are shown to display the wide and overlapping range of PRS.

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Table S1.

	Variable; PRS-BD			Model		
Region	**p**	**t**	**β**	**R^2**	**F**	**p**
Caudal a. cingulate	0.423	-0.803	-0.058	0.109	(3, 175) = 7.118	<0.001
Caudal middle frontal	0.312	-1.01	-0.064	0.311	(3, 175) = 26.33	<0.001
Frontal pole	0.542	-0.611	-0.047	0.009	(3, 169) = 0.484	0.694
Lateral orbitofrontal	**0.025***	-2.254	-0.152	0.214	(3, 173) = 15.727	<0.001
Medial orbitofrontal	**0.014****	-2.476	-0.173	0.153	(3, 174) = 10.498	<0.001
Pars opercularis	0.506	-0.666	-0.043	0.29	(3, 175) = 23,808	<0.001
Pars orbitalis	0.219	-1.233	-0.083	0.218	(3, 175) = 16.249	<0.001
Pars triangularis	0.099	-1.656	-0.108	0.266	(3, 175) = 21.121	<0.001
Rostral a. cingulate	0.854	-0.185	-0.014	0.056	(3, 175) = 3,442	0.018
Rostral middle frontal	0.099	-1.657	-0.108	0.27	(3, 173) = 21.300	<0.001
Superior frontal	0.316	-1.005	-0.061	0.353	(3, 175) = 31.775	<0.001
Inferior temporal	0.453	-0.752	-0.053	0.15	(3, 175) = 10.283	<0.001
Middle Temporal	0.623	-0.492	-0.034	0.179	(3, 175) = 12.754	<0.001
Superior temporal	0.416	-0.815	-0.055	0.205	(3, 174) = 14.967	<0.001
Temporal Pole	0.848	0.192	0.014	0.068	(3, 174) = 4.245	0.006
Insula	0.621	-0.496	-0.033	0.237	(3, 173) = 17.922	<0.001
	Variable; PRS-SCZ			**Model**		
	p	**t**	**β**	**R^2**	**F**	**p**
Caudal a. cingulate	0.575	-0.561	-0.04	0.107	(3, 175) = 6.995	<0.001
Caudal middle frontal	0.676	0.418	0.026	0.308	(3, 175) = 25.923	<0.001
Frontal pole	0.575	-0.562	-0.043	0.008	(3, 169) = 0.446	0.707
Lateral orbitofrontal	**0.005****	-2.829	-0.19	0.227	(3, 173) = 16.931	<0.001
Medial orbitofrontal	**0.00001****	-4.55	-0.306	0.217	(3, 174) = 16.038	<0.001
Pars opercularis	0.419	0.81	0.052	0.291	(3, 175) = 23,907	<0.001
Pars orbitalis	**0.04***	-2.069	-0.138	0.23	(3, 175) = 17.415	<0.001
Pars triangularis	0.07	-1.822	-0.118	0.268	(3, 175) = 21.379	<0.001
Rostral a. cingulate	0.302	-1.034	-0.076	0.061	(3, 175) = 3,808	0.011
Rostral middle frontal	**0.026***	-2.25	-0.146	0.279	(3, 173) = 22.342	<0.001
Superior frontal	0.232	-1.2	-0.073	0.354	(3, 175) = 31.996	<0.001
Inferior temporal	0.171	-1.375	-0.096	0.156	(3, 175) = 10.801	<0.001
Middle Temporal	**0.003****	-2.964	-0.199	0.218	(3, 175) = 16.220	<0.001
Superior temporal	0.259	-1.133	-0.077	0.208	(3, 174) = 15.226	<0.001
Temporal Pole	0.545	-0.613	-0.045	0.07	(3, 174) = 4.367	<0.005
Insula	0.758	-0.309	-0.021	0.236	(3, 173) = 17.857	<0.001

Linear regression results for effects of PRS on cortical thickness (main analysis). β-coefficients (standardized), t- and p-values are given for polygenic risk scores as predictor for cortical thickness. Negative β correspond to negative associations: e.g. higher PRS are related to thinner cortices. Model column shows R^2, F-values and p-values for the overall regression model, including age- and sex as covariates. Abbreviations: PRS-BD/SCZ = polygenic risk score for bipolar disorder and schizophrenia. *Statistically significant ($p<0.05$). ** Significant after multiple comparison correction ($p<0.014$). Inter-correlation across all regions was r=0.53.

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Table S2.

	Variable; PRS-BD			Model		
Region	**p**	**t**	**β**	**R^2**	**F**	**p**
Caudal a. cingulate	0.815	0.188	0.013	0.168	(3, 175) = 11.739	<0.001
Caudal middle frontal	0.264	1.12	0.074	0.247	(3, 175) = 19.084	<0.001
Frontal pole	0.391	0.86	0.06	0.185	(3, 169) = 12.801	<0.001
Lateral orbitofrontal	0.646	-4.61	-0.029	0.329	(3, 173) = 28.335	<0.001
Medial orbitofrontal	0.48	-0.708	-0.045	0.291	(3, 174) = 23,759	<0.001
Pars opercularis	0.847	-0.194	-0.014	0.146	(3, 175) = 9.992	<0.001
Pars orbitalis	0.771	-0.291	0.018	0.362	(3, 175) = 33,050	<0.001
Pars triangularis	0.683	0.41	0.028	0.201	(3, 175) = 14.641	<0.001
Rostral a. cingulate	0.919	-0.102	-0.007	0.175	(3, 175) = 12.417	<0.001
Rostral middle frontal	0.888	0.141	0.009	0.287	(3, 173) = 23, 247	<0.001
Superior frontal	0.862	-0.174	-0.011	0.315	(3, 175) = 26. 834	<0.001
Inferior temporal	0.665	-0.434	-0.029	0.228	(3, 175) = 17.179	<0.001
Middle Temporal	0.912	-0.111	-0.007	0.208	(3, 175) = 15.348	<0.001
Superior temporal	0.775	0.287	0.019	0.231	(3, 174) = 17.389	<0.001
Temporal Pole	0.503	-0.671	-0.048	0.098	(3, 174) = 6.285	<0.001
Insula	0.415	0.817	0.054	0.262	(3, 173) = 20.421	<0.001
	Variable; PRS-SCZ			**Model**		
	p	**t**	**β**	**R^2**	**F**	**p**
Caudal a. cingulate	0.355	0.927	0.064	0.171	(3, 175) = 12.069	<0.001
Caudal middle frontal	0.65	0.454	0.03	0.242	(3, 175) = 18.624	<0.001
Frontal pole	0.985	-0.019	-0.001	0.182	(3, 169) = 12.500	<0.001
Lateral orbitofrontal	0.934	0.082	0.005	0.329	(3, 173) = 28.233	<0.001
Medial orbitofrontal	0.679	-0.414	-0.027	0.289	(3, 174) = 23,605	<0.001
Pars opercularis	0.528	-0.632	-0.044	0.148	(3, 175) = 10.133	<0.001
Pars orbitalis	0.391	0.86	0.052	0.364	(3, 175) = 33,392	<0.001
Pars triangularis	0.322	-0.993	-0.067	0.204	(3, 175) = 14.982	<0.001
Rostral a. cingulate	0.109	1.612	0.11	0.188	(3, 175) = 13,463	<0.001
Rostral middle frontal	0.3	1.039	0.067	0.292	(3, 173) = 23,743	<0.001
Superior frontal	0.43	-0.791	-0.5	0.137	(3, 175) = 27.124	<0.001
Inferior temporal	0.933	0.085	0.006	0.227	(3, 175) = 17.101	<0.001
Middle Temporal	0.643	0.465	0.031	0.209	(3, 175) = 15.433	<0.001
Superior temporal	0.389	0.863	0.058	0.234	(3, 174) = 17.676	<0.001
Temporal Pole	0.84	-0.202	-0.015	0.096	(3, 174) = 6.134	0.001
Insula	0.391	0.86	0.056	0.262	(3, 173) = 20.453	<0.001

Linear regression results for effects of PRS on cortical surface area (complementary). β-coefficients

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

(standardized), t- and p-values are given for polygenic risk scores as predictor for surface. Model column shows R^2, F-values and p-values for the overall regression model, including age- and sex as covariates. Abbreviations: PRS-BD/SCZ = polygenic risk score for bipolar disorder and schizophrenia. No significant PRS associations were observed. Inter-correlation across all regions was r=0.61.

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

Table S3.

	Variable; PRS-BD			Model		
Region	**p**	**t**	**β**	**R^2**	**F**	**p**
Caudal a. cingulate	0.866	0.169	0.012	0.149	(3, 175) = 10.192	<0.001
Caudal middle frontal	0.603	0.521	0.033	0.305	(3, 175) = 25.616	<0.001
Frontal pole	0.415	0.817	0.059	0.128	(3, 169) = 8.283	<0.001
Lateral orbitofrontal	0.18	-1.346	-0.077	0.434	(3, 173) = 44.248	<0.001
Medial orbitofrontal	0.074	-1.797	-0.108	0.373	(3, 174) = 34.477	<0.001
Pars opercularis	0.657	-0.445	-0.029	0.244	(3, 175) = 18.815	<0.001
Pars orbitalis	0.522	-0.642	-0.039	0.351	(3, 175) = 31.572	<0.001
Pars triangularis	0.861	-0.176	-0.011	0.265	(3, 175) = 20.992	<0.001
Rostral a. cingulate	0.793	-0.263	-0.018	0.233	(3, 175) = 17.675	<0.001
Rostral middle frontal	0.522	-0.641	-0.039	0.349	(3, 173) = 30.965	<0.001
Superior frontal	0.481	-0.706	0.042	0.376	(3, 175) = 35.134	<0.001
Inferior temporal	0.672	-0.425	-0.028	0.263	(3, 175) = 20.808	<0.001
Middle Temporal	0.985	0.019	0.001	0.262	(3, 175) = 20.725	<0.001
Superior temporal	0.974	-0.033	-0.002	0.232	(3, 174) = 17.484	<0.001
Temporal Pole	0.648	-0.457	-0.032	0.131	(3, 174) = 8.747	<0.001
Insula	0.572	0.567	0.036	0.309	(3, 173) = 25.756	<0.001
	Variable; PRS-SCZ			**Model**		
	p	**t**	**β**	**R^2**	**F**	**p**
Caudal a. cingulate	0.358	0.922	0.064	0.153	(3, 175) = 10.514	<0.001
Caudal middle frontal	0.637	0.473	0.03	0.305	(3, 175) = 25.593	<0.001
Frontal pole	0.984	0.02	0.001	0.125	(3, 169) = 8.028	<0.001
Lateral orbitofrontal	0.368	-0.903	-0.052	0.431	(3, 173) = 43,668	<0.001
Medial orbitofrontal	**0.014****	-2.484	-0.148	0.383	(3, 174) = 36.01	<0.001
Pars opercularis	0.803	-0.25	-0.016	0.243	(3, 175) = 18.7555	<0.001
Pars orbitalis	0.721	-0.357	-0.022	0.35	(3, 175) = 31.426	<0.001
Pars triangularis	0.143	-1.473	-0.95	0.274	(3, 175) = 21.962	<0.001
Rostral a. cingulate	0.403	0.839	0.056	0.235	(3, 175) = 17.950	<0.001
Rostral middle frontal	0.984	-0.02	-0.001	0.348	(3, 173) = 30.755	<0.001
Superior frontal	0.143	-1.472	-0.088	0.382	(3, 175) = 36.023	<0.001
Inferior temporal	0.853	-0.186	-0.012	0.262	(3, 175) = 20.742	<0.001
Middle Temporal	0.381	-0.879	-0.057	0.265	(3, 175) = 21.074	<0.001
Superior temporal	0.78	0.279	0.019	0.232	(3, 174) = 17.518	<0.001
Temporal Pole	0.659	-0.442	-0.031	0.131	(3, 174) = 8.742	<0.001
Insula	0.464	0.733	0.047	0.31	(3, 173) = 20.86	<0.001

Linear regression results for effects of PRS on cortical volume (complementary). β-coefficients

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

(standardized), t- and p-values are given for polygenic risk scores as predictor for cortical volume. Model column shows R^2, F-values and p-values for the overall regression model, including age- and sex as covariates. Abbreviations: PRS-BD/SCZ = polygenic risk score for bipolar disorder and schizophrenia. *Statistically significant ($p<0.05$). ** Significant after multiple comparison correction ($p<0.014$). Inter-correlation across all regions was $r=0.62$.

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

Table S4.

	Variable; PGRS-BD			Model		
Region	**p**	**t**	**β**	**R^2**	**F**	**p**
Whole cortex	0.255	-1.142	-0.072	0.305	(3, 175) = 25.556	<0.001
Banks sup. temporal	0.464	0.733	0.051	0.166	(3, 175) = 11.577	<0.001
Cuneus	0.303	-1.034	-0.072	0.153	(3, 175) = 10.51	<0.001
Entorhinal	0.169	-1.381	-0.104	0.015	(3, 175) = 0.914	0.435
Fusiform	0.113	-1.593	-0.112	0.142	(3, 175) = 9.644	<0.001
Inferior parietal	0.306	1.026	0.07	0.2	(3, 175) = 14.583	<0.001
Isthmus cingulate	0.688	-0.402	-0.027	0.228	(3, 175) = 17.223	<0.001
Lateral occipital	0.542	-0.611	-0.046	0.054	(3, 172) = 3,247	0.023
Lingual	**0.024***	-2.277	-0.154	0.202	(3, 175) = 14.809	<0.001
Paracentral	0.207	-1.267	-0.86	0.192	(3, 175) = 13,851	<0.001
Pericalcarine	**0.001***	-3,362	-0.233	0.184	(3, 171) = 12.877	<0.001
Parahippocampal	0.640	0.469	0.036	0.002	(3, 175) = 0.12	0.948
Postcentral	0.531	-0.628	-0.041	0.265	(3, 175) = 21.03	<0.001
Posterior cingulate	0.151	-1.443	-0.104	0.093	(3, 175) = 6.002	0.001
Precentral	**0.067**	-1.841	-0.116	0.315	(3, 175) = 26.886	<0.001
Precuneus	0.785	0.273	0.019	0.146	(3, 175) = 9.989	<0.001
Superior parietal	0.923	0.097	0.007	0.122	(3, 175) = 8.093	<0.001
Supramarginal	0.835	0.209	0.013	0.292	(3, 175) = 24.023	<0.001
Transverse temporal	0.761	-0.304	-0.02	0.222	(3, 175) = 16.632	<0.001
	Variable; PGRS-SCZ			**Model**		
	p	**t**	**β**	**R^2**	**F**	**p**
Whole cortex	0.169	-1.38	-0.087	0.307	(3, 175) = 25.842	<0.001
Banks sup. temporal	0.255	-1.143	-0.079	0.169	(3, 175) = 11.883	<0.001
Cuneus	0.203	-1.279	-0.089	0.155	(3, 175) = 10.733	<0.001
Entorhinal	0.209	-1.262	-0.095	0.014	(3, 175) = 0.809	0.491
Fusiform	**0.029***	-2.205	-0.154	0.153	(3, 175) = 10.535	<0.001
Inferior parietal	0.829	-0.216	-0.015	0.195	(3, 175) = 14.166	<0.001
Isthmus cingulate	0.395	-0.852	-0.057	0.233	(3, 175) = 17.467	<0.001
Lateral occipital	0.41	-0.826	-0.062	0.055	(3, 172) = 3,356	0.02
Lingual	**0.065**	-1.856	-0.126	0.195	(3, 175) = 14.102	<0.001
Paracentral	0.196	-1.299	-0.089	0.192	(3, 175) = 13,885	<0.001
Pericalcarine	0.2	-1.288	-0.092	0.139	(3, 171) = 9.181	<0.001
Parahippocampal	0.318	-1.002	-0.076	0.007	(3, 175) = 0.382	0.766
Postcentral	0.864	0.171	0.011	0.263	(3, 175) = 20.865	<0.001
Posterior cingulate	**0.043***	-2.036	-0.146	0.104	(3, 175) = 6.752	<0.001
Precentral	0.408	-0.829	-0.052	0.305	(3, 175) = 25.595	<0.001
Precuneus	0.381	-0.879	-0.061	0.15	(3, 175) = 10.261	<0.001
Superior parietal	0.914	0.108	0.008	0.122	(3, 175) = 8.094	<0.001
Supramarginal	0.643	-0.465	-0.03	0.292	(3, 175) = 24.104	<0.001
Transverse temporal	0.153	1.437	0.096	0.231	(3, 175) = 17.477	<0.001

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

Linear regression results for effects of PRS on cortical thickness in additional regions outside our hypothesis covering the whole-brain (secondary). β-coefficients (standardized), t- and p-values are given for polygenic risk scores as predictor for cortical thickness. Model column shows R^2, F-values and p-values for the overall regression model, including age- and sex as covariates. Abbreviations: PRS-BD/SCZ = polygenic risk score for bipolar disorder and schizophrenia. *Statistically significant ($p<0.05$).

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

Table S5

	Variable; PGRS-BD			**Model**		
Region	**p**	**t**	**β**	**R^2**	**F**	**p**
Whole cortex	0.950	-0.063	-0.004	0.34	(3, 175) = 30.043	<0.001
Banks sup. temporal	0.175	-1.361	-0.097	0.123	(3, 175) = 8.124	<0.001
Cuneus	0.463	0.736	0.051	0.157	(3, 175) = 10.842	<0.001
Entorhinal	0.377	0.885	0.062	0.144	(3, 175) = 9.801	<0.001
Fusiform	0.682	-0.410	-0.027	0.241	(3,175) = 18.508	<0.001
Inferior parietal	0.855	-0.185	-0.012	0.218	(3, 175) = 16.243	<0.001
Isthmus cingulate	0.649	-0.455	-0.032	0.145	(3, 175) = 9.992	<0.001
Lateral occipital	0.313	-1.013	-0.067	0.25	(3, 172) = 19.094	<0.001
Lingual	0.192	-1.309	-0.09	0.187	(3, 175) = 13,436	<0.001
Paracentral	0.895	-0.132	-0.009	0.215	(3, 175) = 15.966	<0.001
Pericalcarine	0.636	0.474	0.035	0.091	(3, 171) = 5.697	<0.001
Parahippocampal	0.867	-0.168	-0.012	0.141	(3, 175) = 9.567	<0.001
Postcentral	0.974	0.033	0.002	0.24	(3, 175) = 18.43	<0.001
Posterior cingulate	0.62	0.497	0.0325	0.145	(3, 175) = 9.919	<0.001
Precentral	0.949	0.063	0.004	0.307	(3, 175) = 25.85	<0.001
Precuneus	0.609	-0.513	-0.034	0.243	(3, 175) = 18.721	<0.001
Superior parietal	0.455	0.748	0.049	0.25	(3, 175) = 19.422	<0.001
Supramarginal	0.894	0.134	0.009	0.228	(3, 175) = 17.263	<0.001
Transverse temporal	0.413	0.821	0.058	0.14	(3, 175) = 9.526	<0.001
	Variable; PGRS-SCZ			**Model**		
	p	**t**	**β**	**R^2**	**F**	**p**
Whole cortex	0.89	0.139	0.009	0.34	(3, 175) = 30.05	<0.001
Banks sup. temporal	0.816	0.233	0.017	0.114	(3, 175) = 7.538	<0.001
Cuneus	0.278	-1.088	-0.076	0.16	(3, 175) = 11.095	<0.001
Entorhinal	**0.017***	2.405	0.167	0.168	(3, 175) = 11.74	<0.001
Fusiform	0.325	0.988	0.065	0.244	(3, 175) = 18.862	<0.001
Inferior parietal	0.859	0.178	0.012	0.128	(3, 175) = 16.242	<0.001
Isthmus cingulate	0.658	0.443	0.031	0.146	(3, 175) = 9.987	<0.001
Lateral occipital	0.45	-0.756	-0.05	0.248	(3, 172) = 18.894	<0.001
Lingual	0.244	-1.168	-0.08	0.186	(3, 175) = 13,295	<0.001
Paracentral	0.68	-0.413	-0.028	0.216	(3, 175) = 16.031	<0.001
Pericalcarine	0.691	-0.398	-0.029	0.091	(3, 171) = 5.673	<0.001
Parahippocampal	0.14	1.483	0.104	0.151	(3, 175) = 10.41	<0.001
Postcentral	0.299	1.043	0.069	0.245	(3, 175) = 18.906	<0.001
Posterior cingulate	0.485	0.7	0.069	0.147	(3, 175) = 10.014	<0.001
Precentral	0.872	0.161	0.01	0.307	(3, 175) = 25.86	<0.001
Precuneus	0.915	0.106	0.007	0.242	(3, 175) = 18.611	<0.001
Superior parietal	0.567	-0.574	-0.038	0.249	(3, 175) = 19.32	<0.001
Supramarginal	0.679	-0.415	-0.028	0.229	(3, 175) = 17.329	<0.001
Transverse temporal	0.916	0.105	0.007	0.137	(3, 175) = 9.27	<0.001

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Linear regression results for effects of PRS on cortical surface area in additional regions outside our hypothesis covering the whole-brain (secondary). β-coefficients (standardized), t- and p-values are given for polygenic risk scores as predictor for cortical thickness. Model column shows R^2, F-values and p-values for the overall regression model, including age- and sex as covariates. Abbreviations: PRS-BD/SCZ = polygenic risk score for bipolar disorder and schizophrenia.*Statistically significant ($p<0.05$).

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

Table S6.

	Variable; PGRS-BD			Model		
Region	**p**	**t**	**β**	**R^2**	**F**	**p**
Whole cortex	0.583	-0.55	-0.033	0.369	(3, 175) = 34.083	<0.001
Banks sup. temporal	0.469	-0.726	-0.05	0.162	(3, 175) = 11.249	<0.001
Cuneus	0.927	-0.092	-0.006	0.141	(3, 174) = 9.614	<0.001
Entorhinal	0.548	0.601	0.042	0.14	(3, 175) = 9.523	<0.001
Fusiform	0.446	-0.764	-0.05	0.251	(3, 175) = 19.556	<0.001
Inferior parietal	0.881	0.15	0.01	0.227	(3, 175) = 17.16	<0.001
Isthmus cingulate	0.582	-0.552	-0.038	0.188	(3, 175) = 13,464	<0.001
Lateral occipital	0.236	-1.19	-0.08	0.238	(3, 172) = 17.881	<0.001
Lingual	**0.013***	-2.51	-0.166	0.241	(3, 175) = 18.484	<0.001
Paracentral	0.46	-0.741	-0.049	0.245	(3, 175) = 18.949	<0.001
Pericalcarine	0.178	-1.351	-0.097	0.124	(3, 171) = 8.095	<0.001
Parahippocampal	0.717	0.363	0.026	0.114	(3, 175) = 7.538	<0.001
Postcentral	0.695	-0.393	-0.027	0.208	(3, 175) = 15.326	<0.001
Posterior cingulate	0.782	0.277	0.019	0.165	(3, 175) = 11.486	<0.001
Precentral	0.36	-0.917	-0.058	0.303	(3, 175) = 25.303	<0.001
Precuneus	0.77	-0.293	-0.019	0.271	(3, 175) = 21.641	<0.001
Superior parietal	0.684	0.408	0.027	0.235	(3, 175) = 17.914	<0.001
Supramarginal	0.827	0.219	0.014	0.277	(3, 175) = 22.358	<0.001
Transverse temporal	0.531	0.628	0.043	0.196	(3, 175) = 14.223	<0.001
	Variable; PGRS-SCZ			**Model**		
	p	**t**	**β**	**R^2**	**F**	**p**
Whole cortex	0.595	-0.533	-0.032	0.369	(3, 175) = 34.073	<0.001
Banks sup. temporal	0.945	-0.069	-0.005	0.159	(3, 175) = 11.042	<0.001
Cuneus	0.117	-1.576	-0.11	0.153	(3, 175) = 10.575	<0.001
Entorhinal	**0.036***	2.109	0.147	0.16	(3, 175) = 11.104	<0.001
Fusiform	0.695	0.392	0.026	0.249	(3, 175) = 19.365	<0.001
Inferior parietal	0.989	0.014	0.001	0.227	(3, 175) = 17.151	<0.001
Isthmus cingulate	0.874	0.159	0.011	0.186	(3, 175) = 13,35	<0.001
Lateral occipital	0.314	-1.009	-0.068	0.236	(3, 172) = 13,948	<0.001
Lingual	**0.041***	-2.054	-0.137	0.232	(3, 175) = 17.603	<0.001
Paracentral	0.264	-1.12	-0.074	0.248	(3, 175) = 19.261	<0.001
Pericalcarine	0.195	-1.3	-0.093	0.124	(3, 171) = 8.044	<0.001
Parahippocampal	0.466	0.73	0.052	0.116	(3, 175) = 7.689	<0.001
Postcentral	0.458	0.743	0.05	0.21	(3, 175) = 15.494	<0.001
Posterior cingulate	0.879	0.152	0.011	0.164	(3, 175) = 11.465	<0.001
Precentral	0.556	-0.59	-0.037	0.301	(3, 175) = 25.069	<0.001
Precuneus	0.678	-0.416	-0.027	0.271	(3, 175) = 21.680	<0.001
Superior parietal	0.387	-0.867	-0.057	0.237	(3, 175) = 18.169	<0.001
Supramarginal	0.433	-0.785	-0.051	0.279	(3, 175) = 22.619	<0.001
Transverse temporal	0.422	0.804	0.055	0.197	(3, 175) = 14.327	<0.001

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

Linear regression results for effects of PRS on cortical volume in additional regions outside our hypothesis covering the whole-brain (secondary). β-coefficients (standardized), t- and p-values are given for polygenic risk scores as predictor for cortical thickness. Model column shows R^2, F-values and p-values for the overall regression model, including age- and sex as covariates. Abbreviations: PRS-BD/SCZ = polygenic risk score for bipolar disorder and schizophrenia. *Statistically significant ($p<0.05$).

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

Table S7.

Region	HC	BD	HC vs. BD
right vmPFC DMN-hubiness	0.17 ± 0.62	-0.27 ± 0.78	p=0.004
left vmPFC DMN-hubiness	0.47 ± 0.60	0.33 ± 0.83	p=0.371
PC right	0.76 ± 0.06	0.76 ± 0.06	p= 0.496
PC left	0.73 ± 0.08	0.74 ± 0.08	p= 0.596

Means and SD of **vmPFC DMN-hubiness and participation coefficients** (PC) for healthy controls (HC) and BD patients, and p-values obtained from group comparisons are shown.

Appendix 1 to Abé C, Petrovic P, Ossler W, et al. Genetic risk for bipolar disorder and schizophrenia predicts structure and function of the ventromedial prefrontal cortex. *J Psychiatry Neurosci* 2021. doi: 10.1503/jpn.200165

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