Interrogating Associations Between Polygenic Liabilities and Electroconvulsive Therapy Effectiveness

Supplementary Information

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Primary samples information

Ireland

Enhancing the Effectiveness of Electroconvulsive Therapy in Severe Depression (EFFECT-Dep) was a pragmatic, randomized, non-inferiority trial where patients were independently randomly assigned to bitemporal (BT) or high-dose right unilateral (RUL) ECT (1). In the present study, both BT and high-dose RUL ECT patients were included and Semkovska et al. (1) showed that twice-weekly high-dose RUL was noninferior to BT ECT for severe depression. Patients were recruited from 2008 until 2012 from St. Patrick's Mental Health Services, Dublin, Ireland. Inclusion criteria were age ≥18 years, referral for ECT, a diagnosis of major depressive episode (unipolar or bipolar) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria and a score ≥21 on the 24-item HDRS (2). Exclusion criteria were history of schizophrenia, schizoaffective disorder, or neurodegenerative or other neurological disorder; ECT or substance abuse in previous 6 months; involuntary status; and lack of consent. Diagnosis including presence of psychotic features was based on the structured clinical interview for the DSM-IV (3). ECT was administered twice weekly in accordance with Royal College of Psychiatrists' guidelines (4), using Mecta 5000M device and the seizure threshold was established by dose titration. The HDRS-24 was administered one to two days before the start of the ECT course and two to four days after the last ECT. The study was approved by the hospital's research ethics committee.

Belgium

Patients recruited from the University Psychiatric Hospital of Duffel, Belgium, between 2015 and 2017, participated in a prospective longitudinal study (5). Inclusion criteria were a diagnosis of major depressive disorder (MDD) or a severe depressive episode in bipolar disorder (BD) according to the DSM-IV-TR version and with confirmation by the Mini International Neuropsychiatric Interview (MINI) (6). The presence of psychotic features was determined in the same manner. Also, a score of ≥17 on the 17-item Hamilton Depression Rating Scale (HDRS-17) was required for inclusion (2). Patients with a history of substance abuse (<6 months ago) or a primary diagnosis psychotic or schizoaffective disorder were excluded. ECT was administered twice weekly in accordance with recent guidelines (7), using the Thymatron System IV. The stimulus dose was established by the age method for RUL and the half-age estimation method for bilateral (BL) ECT. An ECT course started with RUL electrode

placement, bifrontal (BF) or BT when a fast antidepressant effect was needed (8). Switching from RUL ECT to BF ECT was applied if no clinical improvement was observed after six RUL treatments. The HDRS-17 was administered on the last weekday prior to the first ECT session and approximately one week after the last ECT session. The study was approved by the Ethics Committee of the University Hospital of Antwerp.

The Netherlands

Subjects were included from three different sites in the Netherlands where ECT was administered twice weekly in accordance with Dutch guidelines (7), using the Thymatron System IV and the seizure threshold was established by dose titration. First, from 2011 until 2013 subjects aged 55 years and over eligible for ECT have been included from the Mood Disorders in Elderly treated with ECT (MODECT) study, a naturalistic longitudinal cohort study at GGZ inGeest, Amsterdam, the Netherlands (9). MDD and presence of psychotic features were diagnosed by a psychiatrist according to the DSM-IV criteria and confirmed by the MINI (6). Patients with a DSM-IV diagnosis other than unipolar depressive disorder (e.g. bipolar disorder, schizoaffective disorder) were excluded. Another exclusion criterium was a major neurological illness (including Parkinson's disease, dementia and stroke). An ECT course started with RUL ECT and switching to BL ECT was applied when the clinical condition worsened or when no clinical improvement was observed after six RUL treatments. The primary outcome measure was the Montgomery–Åsberg Depression Rating Scale (MADRS) score (10), administered one week before the first ECT session and one week after the last ECT session. The MODECT study was approved by the Ethical Review Board of the VU University Medical Center. Second, patients recruited from the Maastricht University Medical Center (Maastricht UMC+), the Netherlands, in 2010 and 2011 participated in a longitudinal study (11). Patients were diagnosed by a psychiatrist with unipolar or bipolar depressive episodes and with or without presence of psychotic features according to the DSM-IV criteria and with confirmation of the MINI (6). All patients were 'treatment-resistant' as they failed to improve significantly after at least two trials with antidepressant medications from different pharmacologic classes. Exclusion criteria were: age <18 years, illiteracy and major medical or psychiatric conditions (including cancer, cerebrovascular disorders, organic psychiatric syndromes, active drug abuse, mental retardation, dementia, neurodegenerative disorders, presence of an inflammatory condition, regular use of immune-modulating medications). All patients

were treated with BL ECT and the HDRS-17 was administered as primary outcome measure in the week prior to the first ECT sessions and one to 17 days after the last ECT session (2). The study was approved by the Medical Ethics Committee of Maastricht UMC+.

Third, in a longitudinal case-controlled study, patients were recruited at the department of psychiatry in the University Medical Center (UMC) Utrecht, the Netherlands (12). Patients indicated for ECT were aged ≥18 years and were diagnosed with unipolar or bipolar depression according to the DSM-IV-TR criteria and confirmed by the MINI (6). The presence of psychotic features was determined in the same manner. Exclusion criteria were: pregnancy and/or lactation; brain pathology (e.g. cerebrovascular accident); history of stroke; any major medical condition (e.g. diabetes, coronary heart disease, chronic obstructive pulmonary disease); and ECT in the previous 6 months. All patients were treated with BL ECT and the HDRS-17 was administered as primary outcome measure one week before the first ECT session and one week after the last ECT session (2). The study was approved by the Medical Ethical Board of the UMC Utrecht.

Genotyping and quality control (QC)

Quality control procedures were performed using PLINK v1.9 according to established methods (13, 14). SNPs and samples with call rates below 95% (n=3,658) and 98% (n=3), respectively, were removed. A strict SNP QC only for subsequent sample quality control steps was conducted. This involved a minor allele frequency (MAF) threshold >10% and a Hardy-Weinberg equilibrium (HWE) p-value>1e-05, followed by linkage disequilibrium (LD) based SNP pruning (R^2<0.2). This resulted in ~73K SNPs to assess sex errors (n=7), heterozygosity (F<3 standard deviation (SD); n=1), homozygosity (F>3SD; n=0) and relatedness by pairwise identity by descent (IBD) values (n=0; all participants had IBD pihat values <0.01). After removing all failing samples, a regular SNP QC was performed (SNP call rate >98%, HWE p>1e-06, MAF>1%). After principle components analysis (PCA) with Hapmap Phase 3 individuals to check ethnicity, samples that deviated more than 3 standard deviations from Hapmap 3 European cohorts (n=1) and within our own dataset (n=4) were removed. In addition, the first 20 genetic PCs of passed quality controlled samples were generated using the strict SNP QC list in EIGENSTRAT.(15) Next, strand ambiguous (n=2,537) and duplicate SNPs (n=2,541) were removed. Then, missingness check (2% threshold) for samples (n=0) and SNPs (n=2,102) was

conducted. In the end, 272 individuals and 473,763 genotyped SNPs passed these above-mentioned QC steps. Details of QC steps are also shown in Supplementary Table 1.

Genome-wide association analyses and results with gene-set and cell-type enrichment analyses

Statistical analyses were conducted using PLINK and R version 3.2.2 (14 Aug 2015; http://www.r-project.org/) software packages. GWAS was conducted using linear regression for our main quantitative outcome (ΔHDRS) and logistic regression for our main binary outcomes (remission and response) with age, sex, and the first 3 genetic-ancestry principal components (PCs) as covariates. We also applied the extended model outlined in the PRS Methods section for ΔHDRS with covariates age, sex, three PCs and ECT application mode. Genome-wide significance was set at $p<5x10^{-8}$ and suggestive significance at $p<5x10^{-6}$. No genome-wide significant SNPs were identified for either of the traits studied (QQ plots are shown in Supplementary Figures 1-4A, with no lambdas giving rise to suspicion of inflation of the test statistics; Manhattan plots are shown in Supplementary Figures 1-4B). The top SNP in the GWAS of ΔHDRS was rs12277346, an intronic variant nearby the OSBPL5 gene ($p=1.67x10^{-6}$). The top SNP in the GWAS of remission was rs11217522, an intergenic variant between RP11 and 215D10.1. The top SNP in the GWAS of response was rs13374658.
We used FUMA (Functional Mapping and Annotation of Genome-Wide Association Studies) to obtain gene-level summary statistics from our binary and quantitative GWAS summary statistics and perform gene-set and cell/tissue type enrichment analysis (16, 17). Then, gene-level summary statistics were used to perform differentially expressed genes analysis (DEG; GTEx v8 and BrainSpan data) and generate an expression heatmap. The only genome-wide significant gene was ZNF792 ($p=1.26x10^{-6}$; Supplementary Figure 2C) from the GWAS of ΔHDRS in the extended model. This gene was partly validated using the base model as the significance slightly diminished to $p=1.56x10^{-5}$ (Supplementary Figure 1C). No gene or gene-set passed the genome-wide significance threshold in our gene-based test in the GWASs of response and remission (Supplementary Figures 3C and 4C). The top prioritized gene was RAX for response and remission. Enriched DEG sets were detected in the hypothalamus and hippocampus for both down- and up- regulated DEG sites (Supplementary Figure 1-3D). Tissue enrichment analysis did not yield any consistently associated tissues (Supplementary Figure 1-3E).

Polygenic risk score gene-set analysis

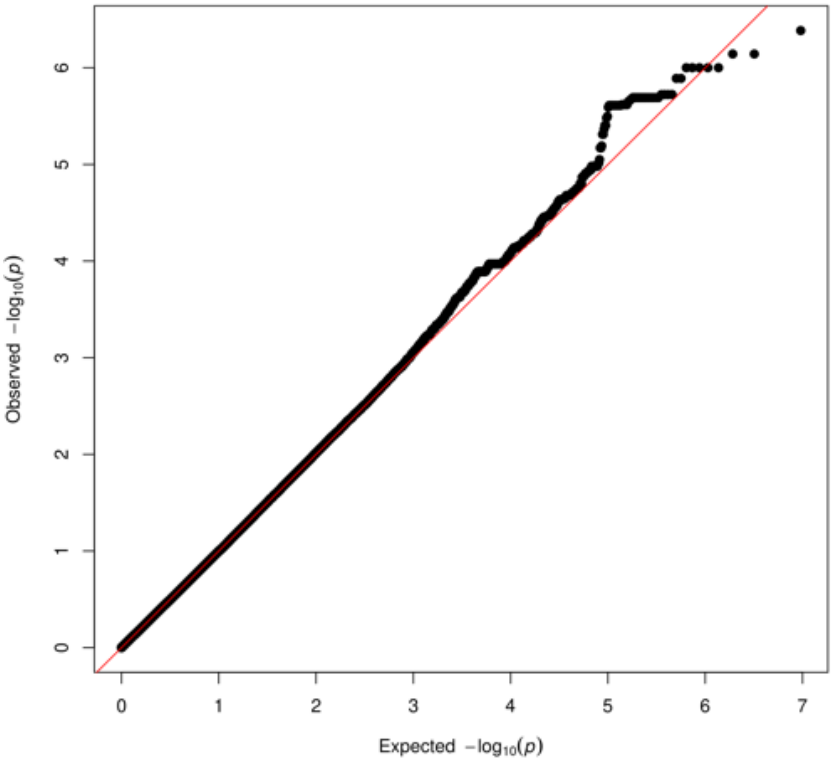
To explore if the weighted gene-set PRS may play a role in our outcome of interest, we selected the gene set with the strongest association with the risk of schizophrenia in a previous study, the TCF4 gene set (18). The TCF4 gene set was created on the basis of the differential expression of genes in neuroblastoma cells after knockdown of TCF4 (19)(expressional data are accessible through GEO Series accession number GSE48367; http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE48367). A total of 1052 autosomal genes demonstrating differential expression were included in the gene set. The genic SNPs (n=5192) were defined within the gene or <1 kb away from the gene. After extracting the genic SNPs, the generation of the PRSs was performed using the same protocol as mentioned in the main methods section using PRSice-2.

The PRS-SCZ_TCF4 was not associated with any of the outcomes in the entire cohort. When analyzing the data per country, the PRS-SCZ_TCF4 was weakly associated with remission in the Irish cohort (optimal P_t=0.05, R^2=5.72%, beta=0.542, SE= 0.232, p=0.019).

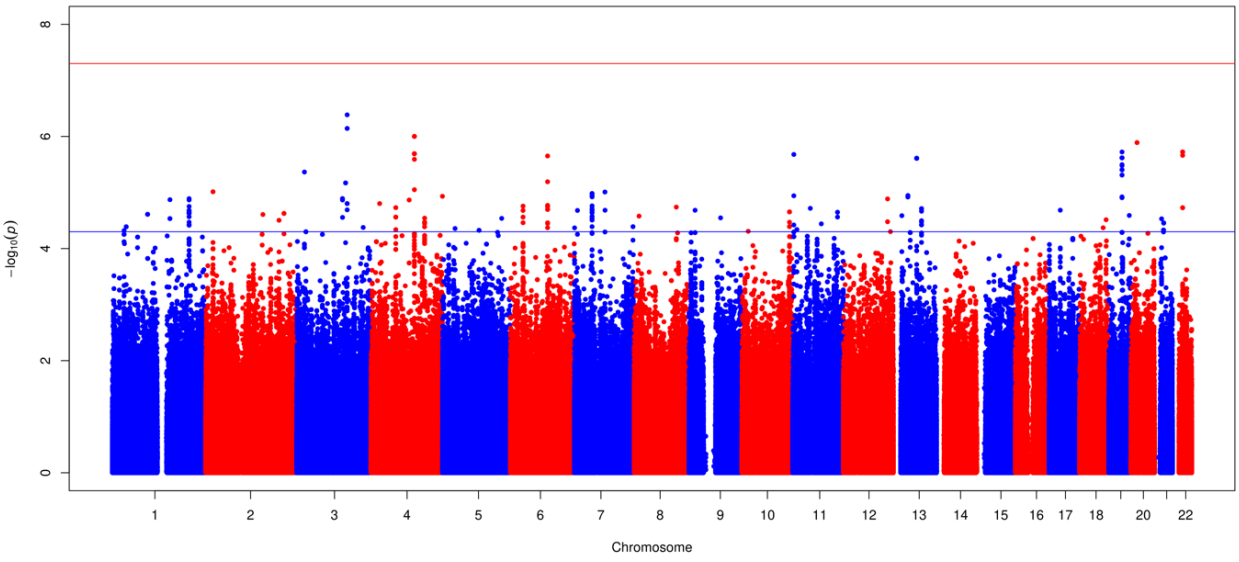
Although no significant associations between PRS-SCZ_ TCF4 and the outcomes were detected in the entire cohort, the effect directions were similar to the PRS-SCZ association test results. Given that the PRS-SCZ_TCF4 explained only 0.6% of the variance of the risk of schizophrenia in the Rammos study (18), PRS-SCZ_TCF4 cannot serve as a proxy for PRS-SCZ and no further gene sets were analyzed in the context of an omnigenic model.

Genome-wide association study (GWAS) and post-GWAS visualization of change in the 17-item Hamilton Depression Rating Scale (ΔHDRS) score in the base model.

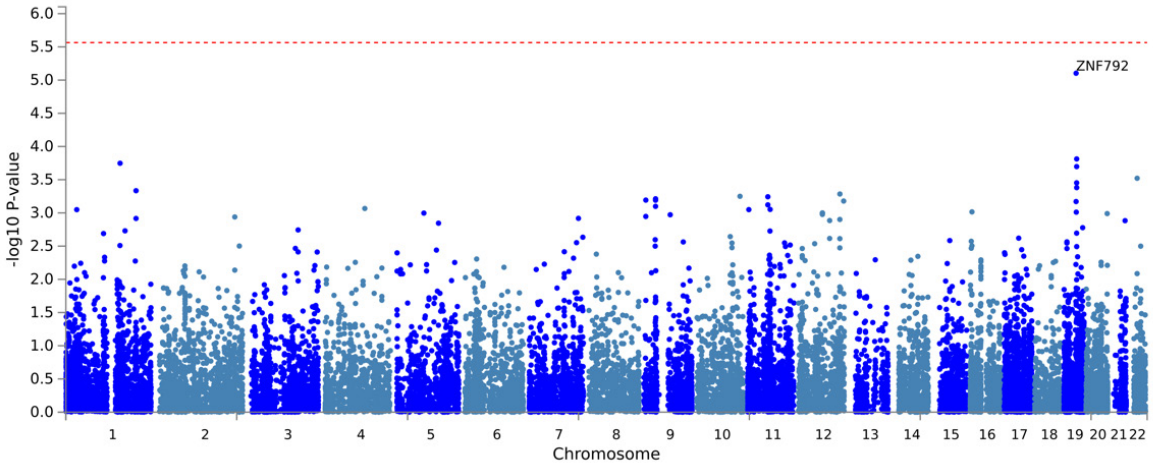
Supplementary Figure S1A. QQ plot of the genome-wide association study (GWAS) of the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score.



Supplementary Figure S1B. Manhattan plot of the genome-wide association study (GWAS) of the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score.

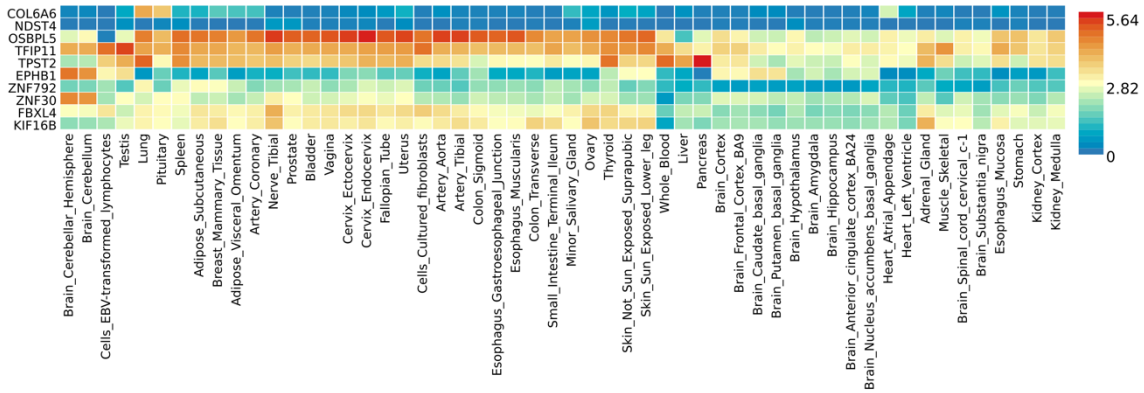


Supplementary Figure S1C. Gene-based test as computed in MAGMA based on the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score from genome-wide association study (GWAS) summary statistics.



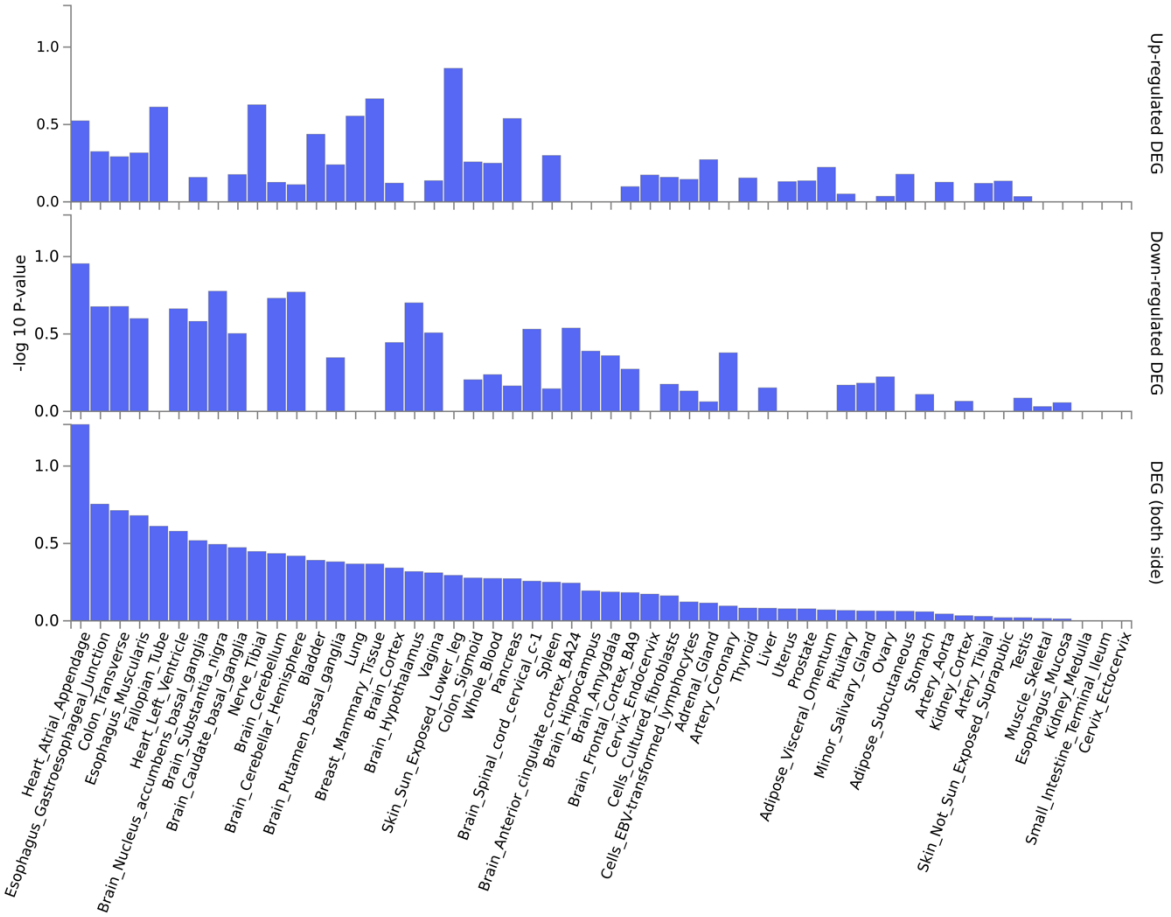
Input SNPs were mapped to 18347 protein coding genes. Genome wide significance, defined by the red dashed line, was defined at p=0.05/18347=2.73x10^{-6}.

Supplementary Figure S1D. Heatmap plot using 54 tissues from GTEx for the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score.



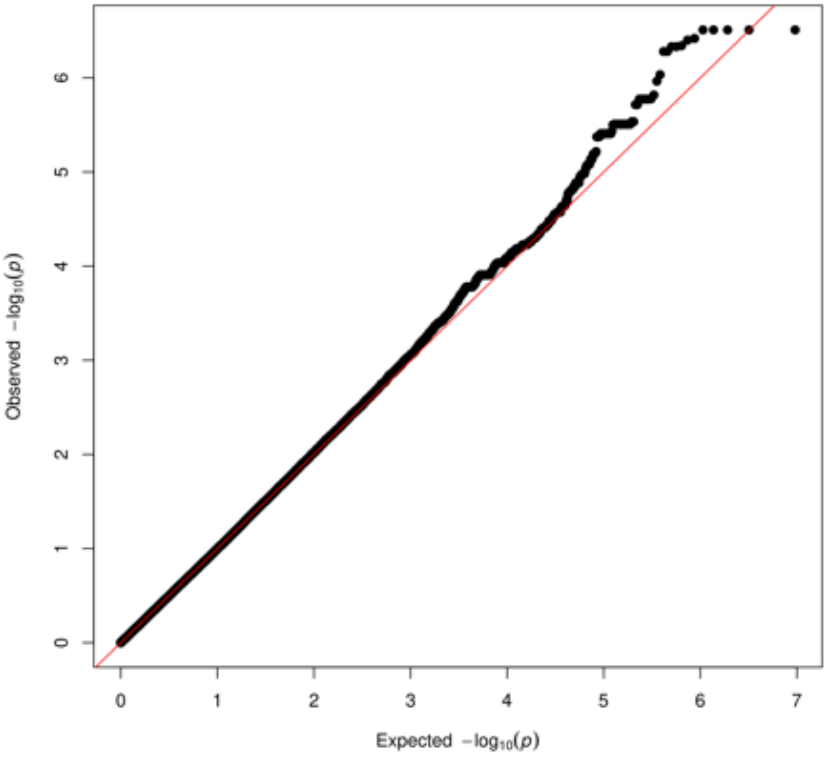
The expression values were the average of normalized expression per label (with a mean of zero across samples).

Supplementary Figure S1E. Tissue specificity results for the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score in the base model: enrichment test results of differentially expressed genes (DEG) sets for user-selected expression datasets.

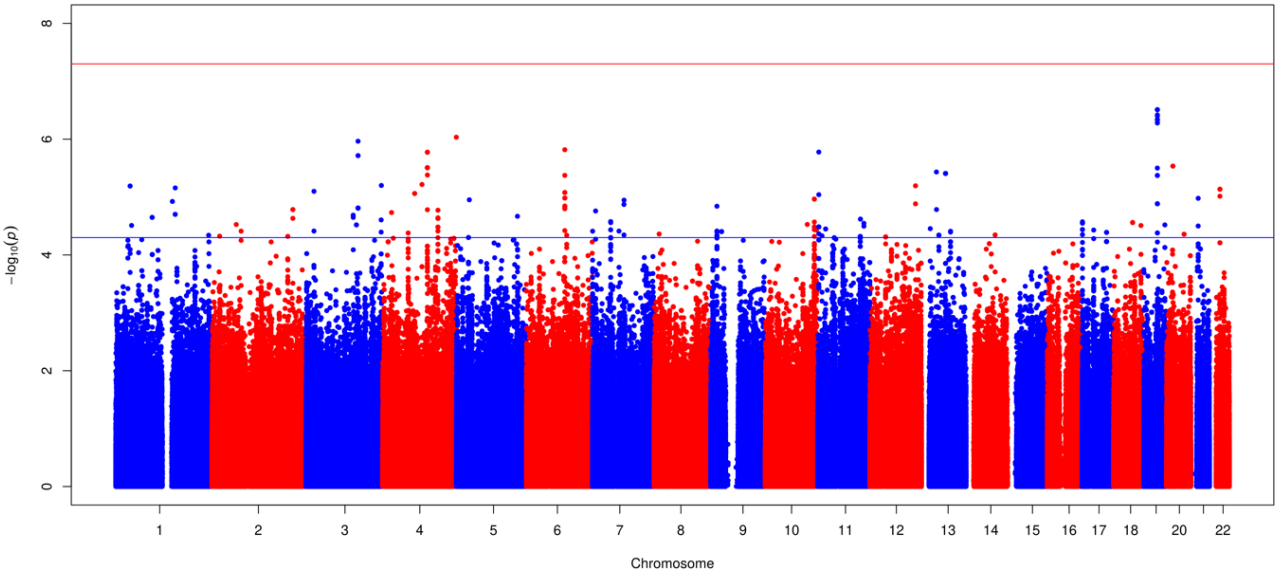


Genome-wide association studie (GWAS) and post-GWAS visualization of change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score in the extended model.

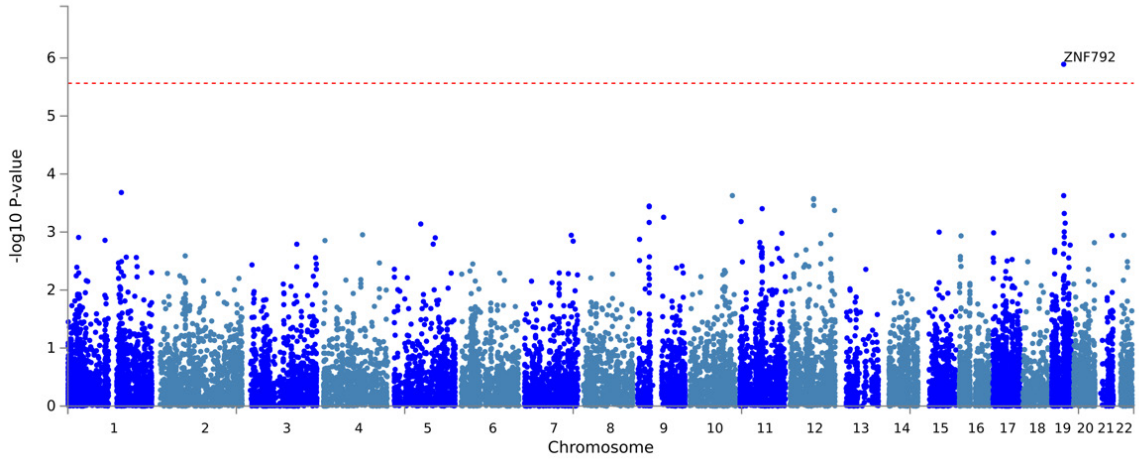
Supplementary Figure S2A. QQ plot of the genome-wide association study (GWAS) of the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score.



Supplementary Figure S2B. Manhattan plot of the genome-wide association study (GWAS) of the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score.

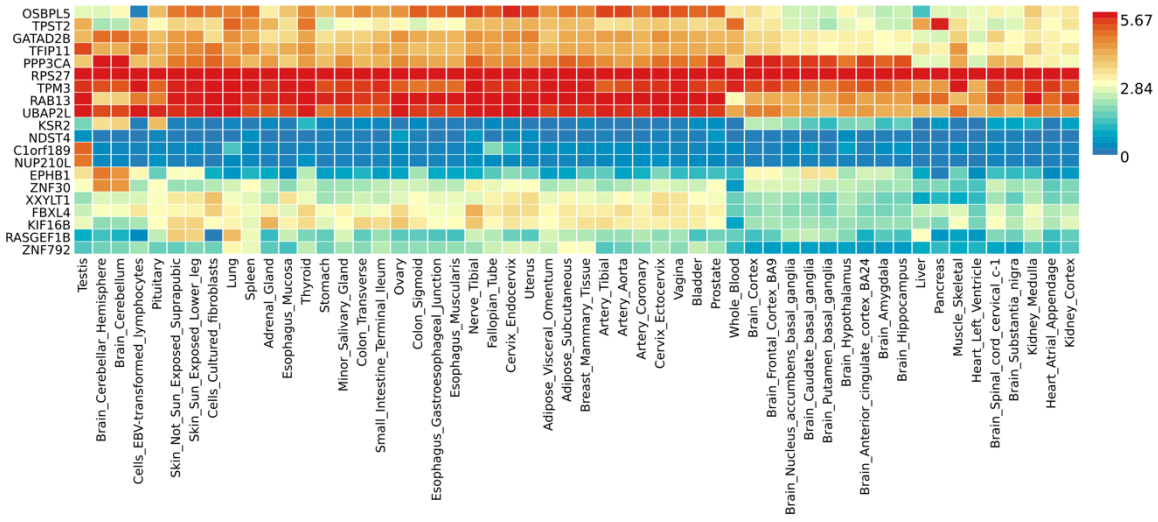


Supplementary Figure S2C. Gene-based test as computed in MAGMA based on the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score from genome-wide association study (GWAS) summary statistics.



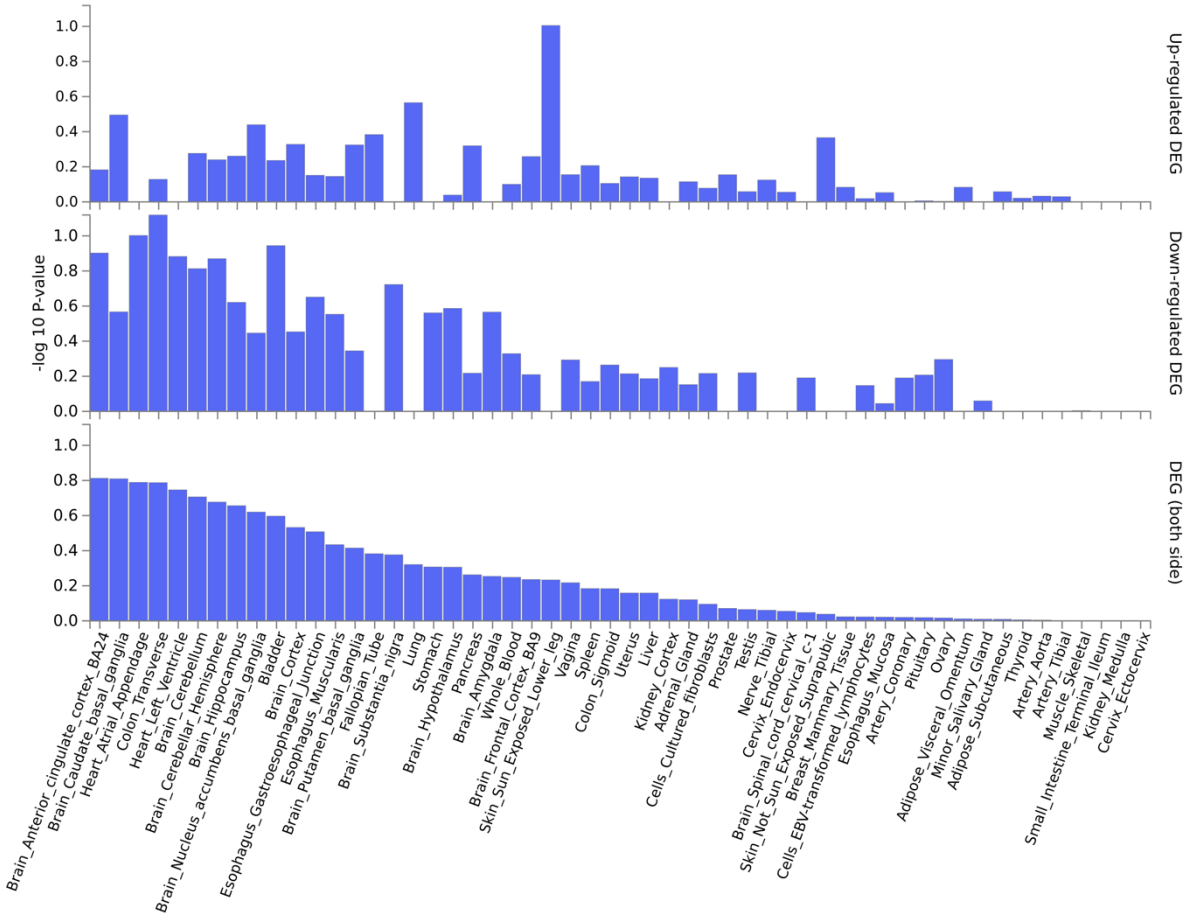
Input SNPs were mapped to 18347 protein coding genes. Genome wide significance, defined by the red dashed line, was defined at $p=0.05/18347=2.73x10^{-6}$.

Supplementary Figure S2D. Heatmap plot using 54 tissues from GTEx for the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score.



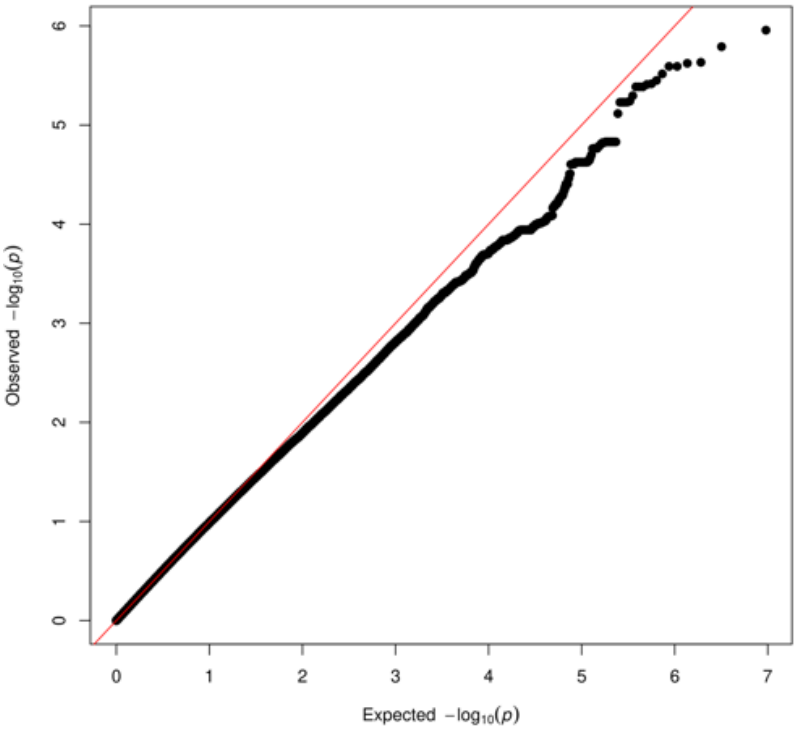
The expression values were the average of normalized expression per label (with a mean of zero across samples).

Supplementary Figure S2E. Tissue specificity results for the change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score in the extended model: enrichment test results of differentially expressed genes (DEG) sets for user-selected expression datasets.

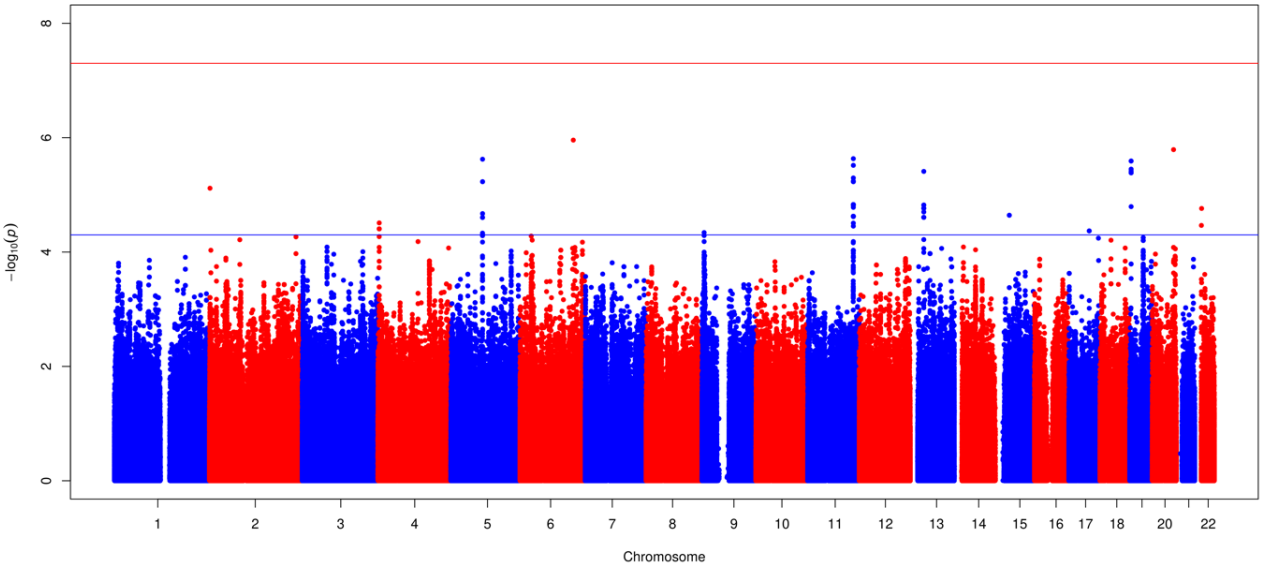


Genome-wide association study (GWAS) and post-GWAS visualization of remission after treatment with electroconvulsive therapy (ECT), defined as a 17-item Hamilton Depression Rating Scale (ΔHDRS) score of ≤7.

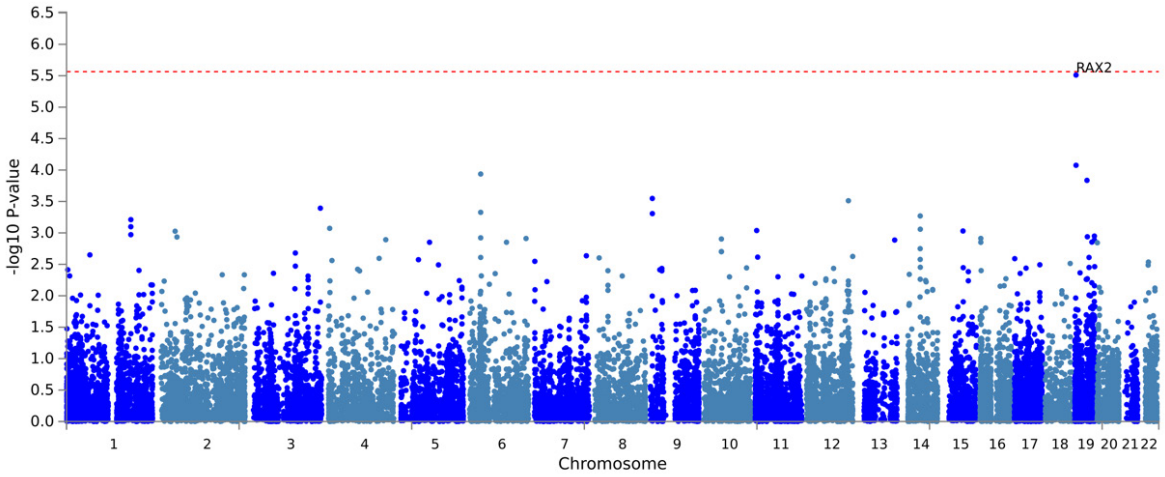
Supplementary Figure S3A. QQ plot of the genome-wide association study (GWAS) of remission.



Supplementary Figure S3B. Manhattan plot of the genome-wide association study (GWAS) of remission.

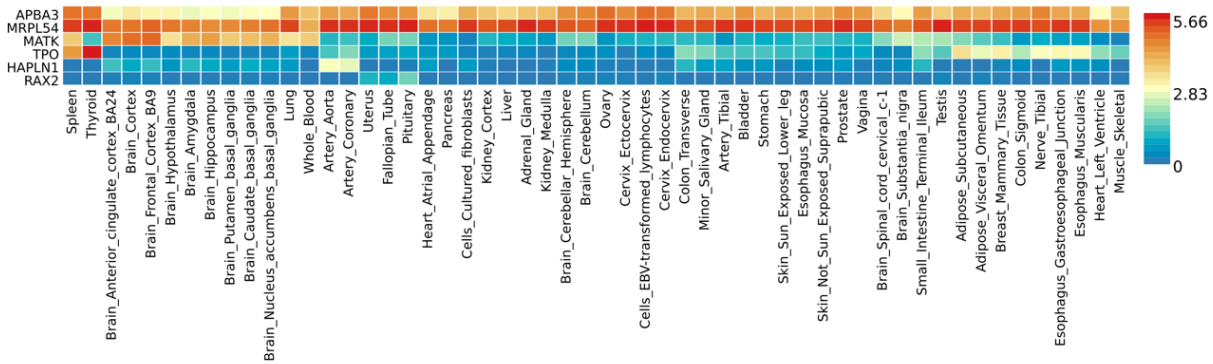


Supplementary Figure S3C. Gene-based test as computed in MAGMA based on the remission genome-wide association study (GWAS) summary statistics.



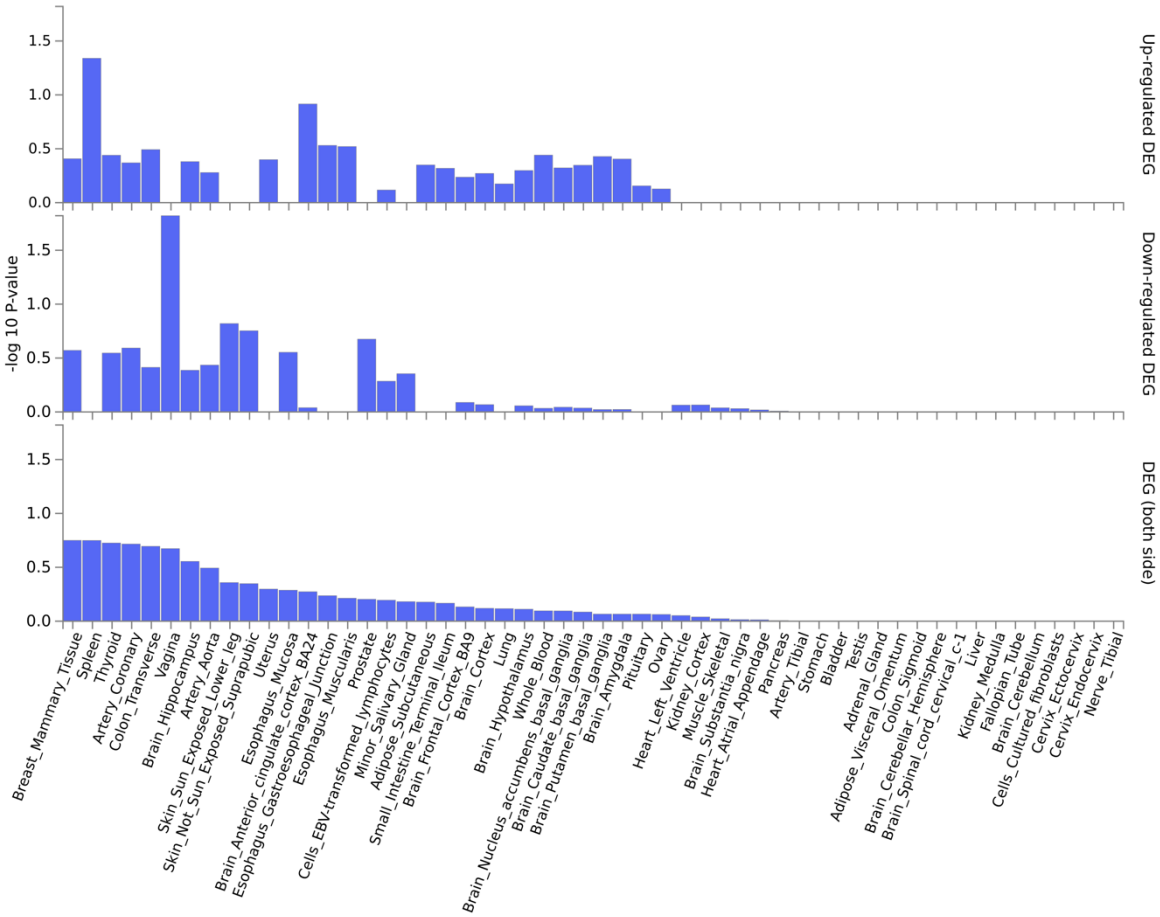
Input SNPs were mapped to 18347 protein coding genes. Genome wide significance, defined by the red dashed line, was defined at $p=0.05/18347=2.73x10^{-6}$.

Supplementary Figure S3D. Heatmap plot using 54 tissues from GTEx for remission.



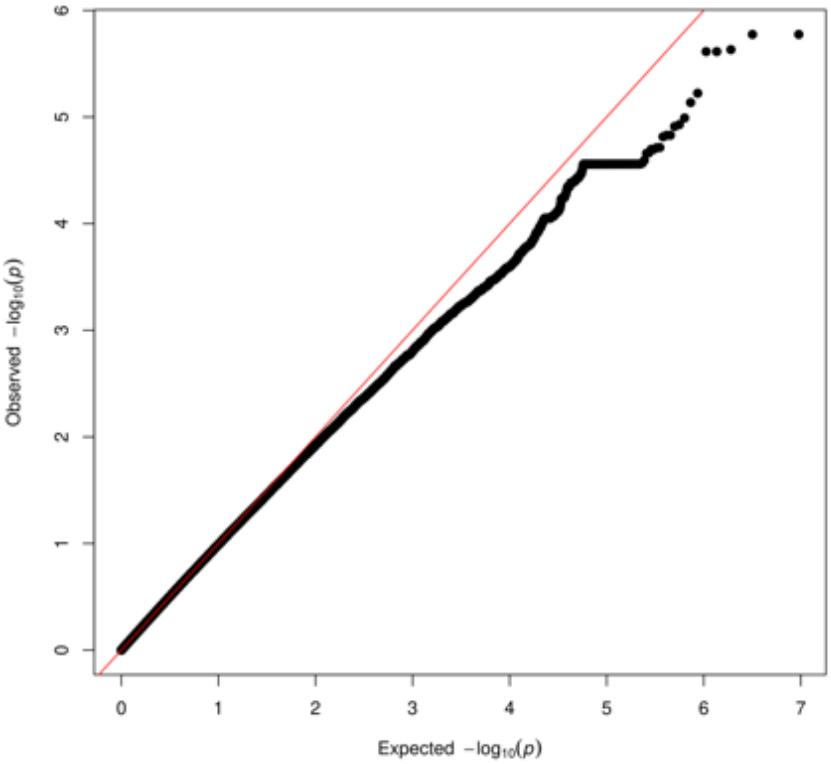
The expression values were the average of normalized expression per label (with a mean of zero across samples).

Supplementary Figure S3E. Tissue specificity results for remission: enrichment test results of differentially expressed genes (DEG) sets for user-selected expression datasets.

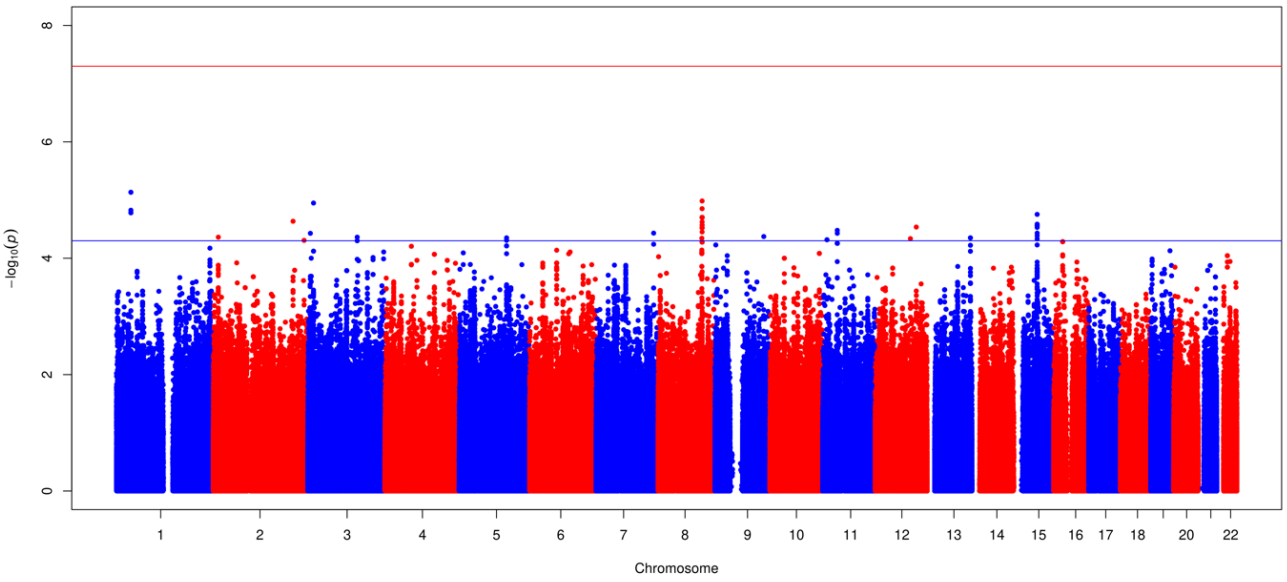


Genome-wide association study (GWAS) and post-GWAS visualization of reponse after treatment with electroconvulsive therapy (ECT), defined as a decrease of ≥50% in the 17-item Hamilton Depression Rating Scale (ΔHDRS) score.

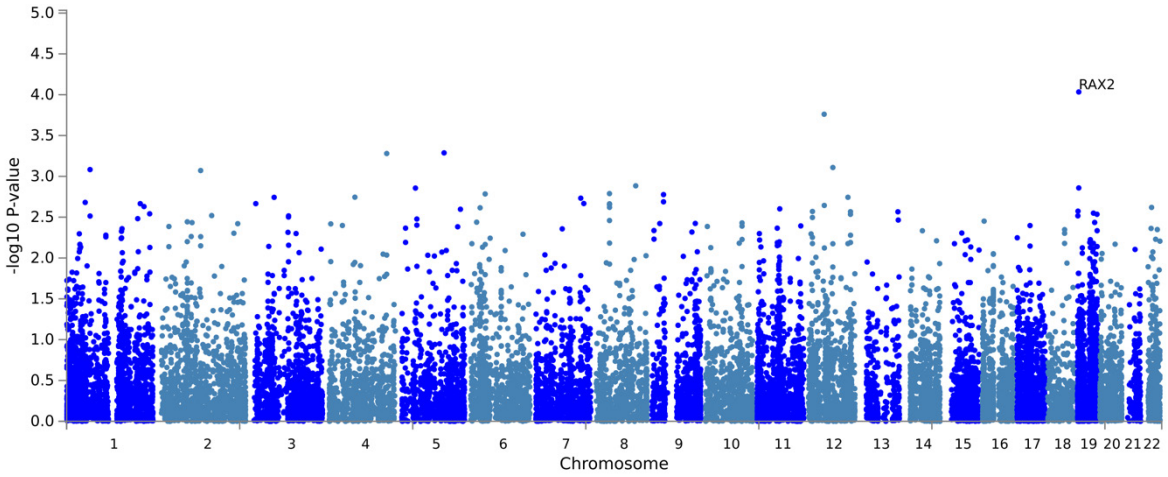
Supplementary Figure S4A. QQ plot of the genome-wide association study (GWAS) of response.



Supplementary Figure S4B. Manhattan plot of the genome-wide association study (GWAS) of response.

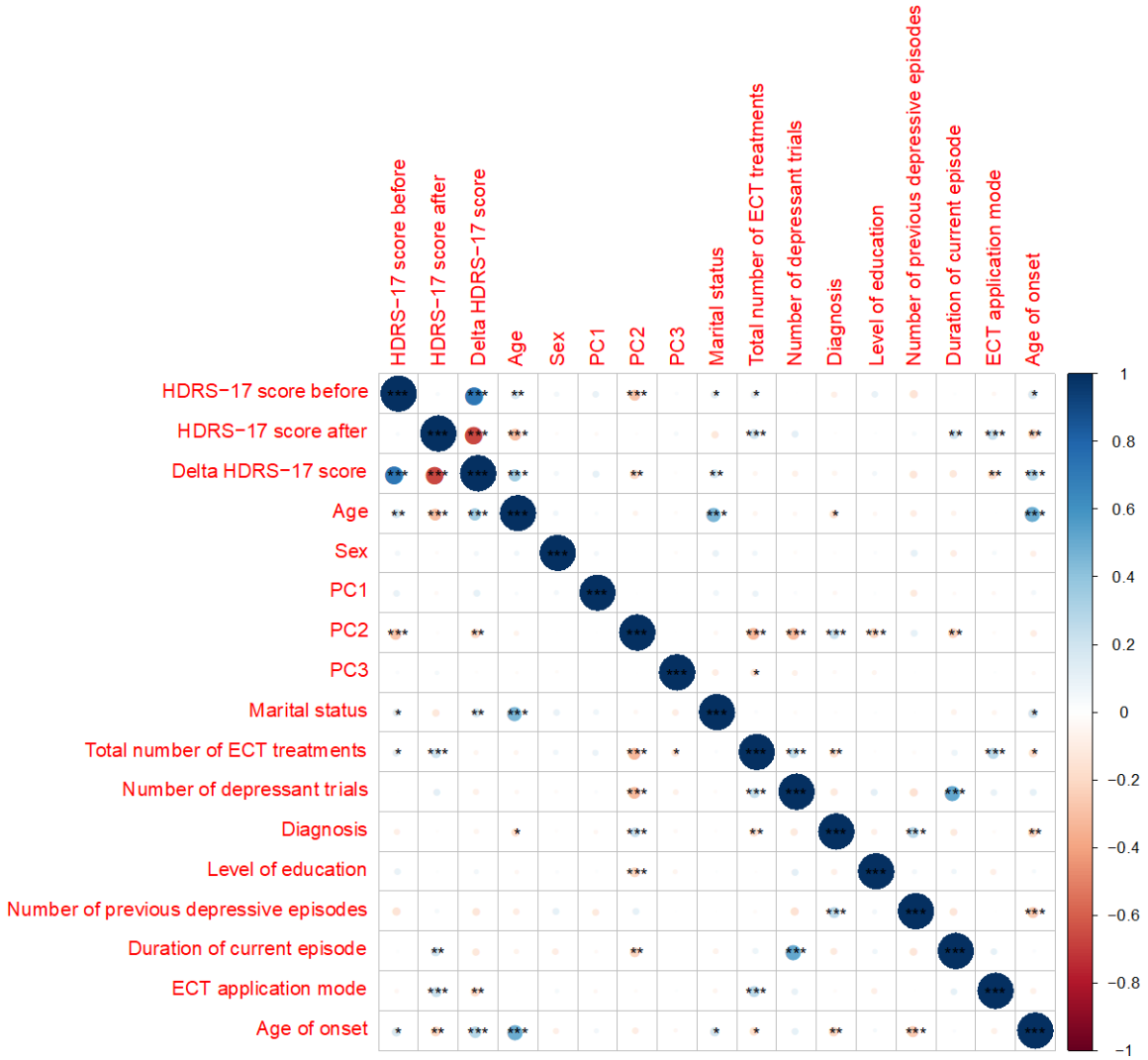


Supplementary Figure S4C. Gene-based test as computed in MAGMA based on the response genome-wide association study (GWAS) summary statistics.



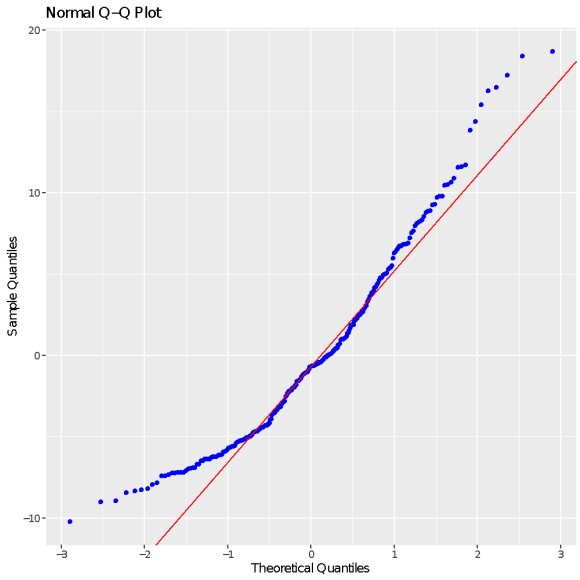
Input SNPs were mapped to 18347 protein coding genes. Genome wide significance was defined at $p=0.05/18347=2.73x10^{-6}$.

Supplementary Figure S5. Correlation matrix of outcomes and candidate covariates.

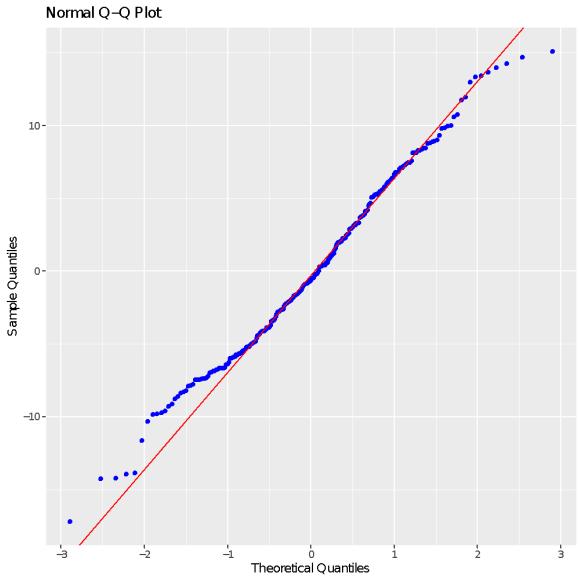


Abbreviations: HDRS-17= the 17-item Hamilton Depression Rating Scale, PC=principal components, ECT=electroconvulsive therapy. * Represents the significant level from Pearson correlation test: *p<0.05; **p<0.01 and ***p<0.001. ECT application mode was the only covariate independently (not correlated to another covariate) and nominally significantly (p<0.05) correlated with ΔHDRS. For the secondary outcomes, no independent covariates were found (in addition to age, sex and three PCs).

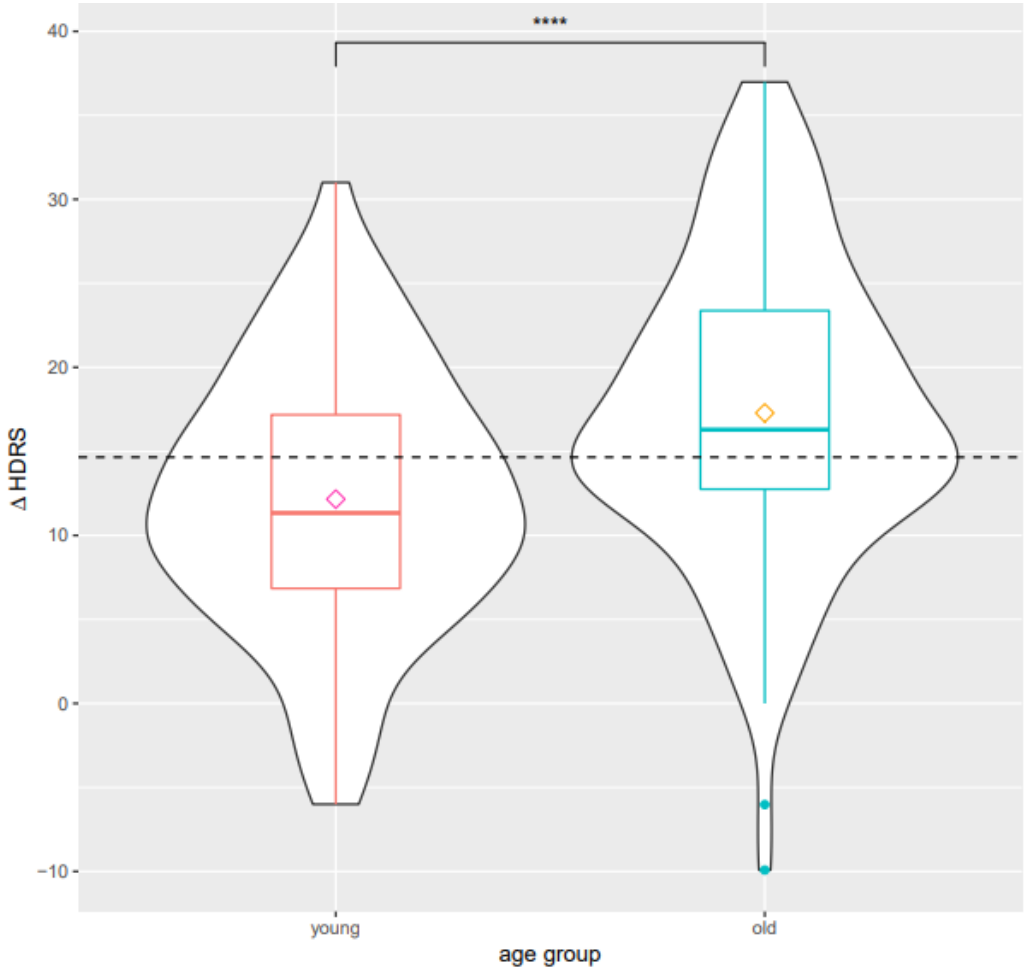
Supplementary Figure S6A. QQ plot of residual of outcomes for the 17-item Hamilton Depression Rating Scale (HDRS-17) score after electroconvulsive therapy of the base linear regression model.



Supplementary Figure S6B. QQ plot of residual of outcomes for change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score of the base linear regression model. This shows an expected residual distribution for our primary outcome.

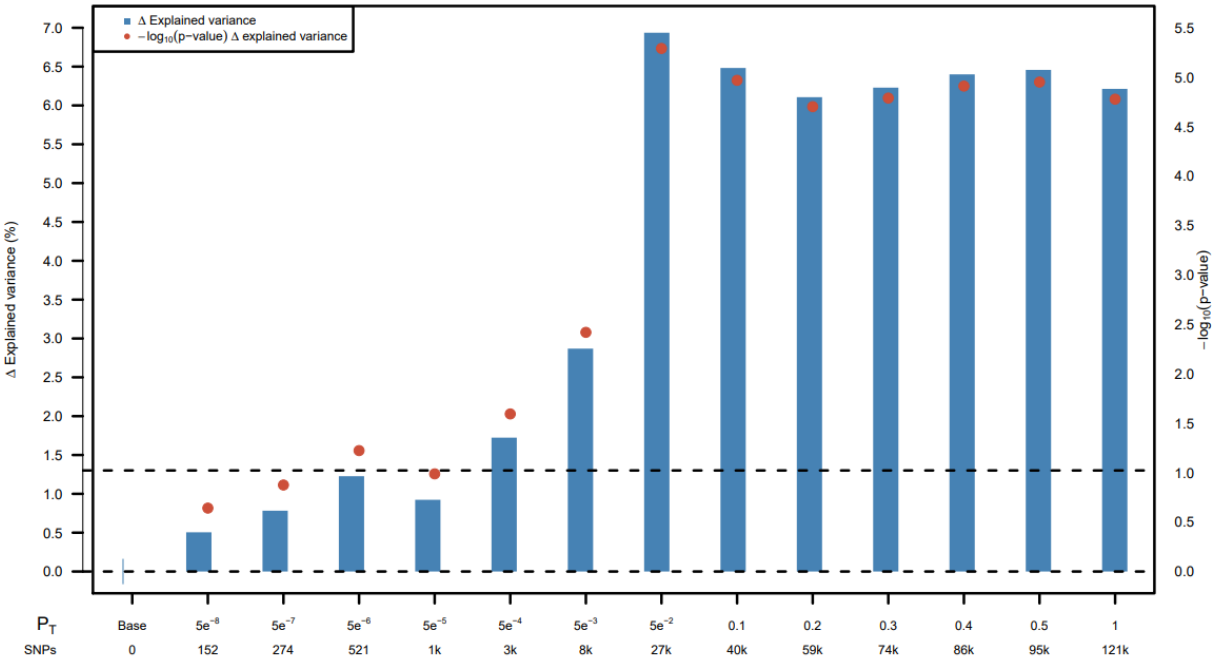


Supplementary Figure S7. Difference between age groups in the primary outcome measure: change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score. The older age group had a significantly higher decrease in HDRS score than the younger age group.



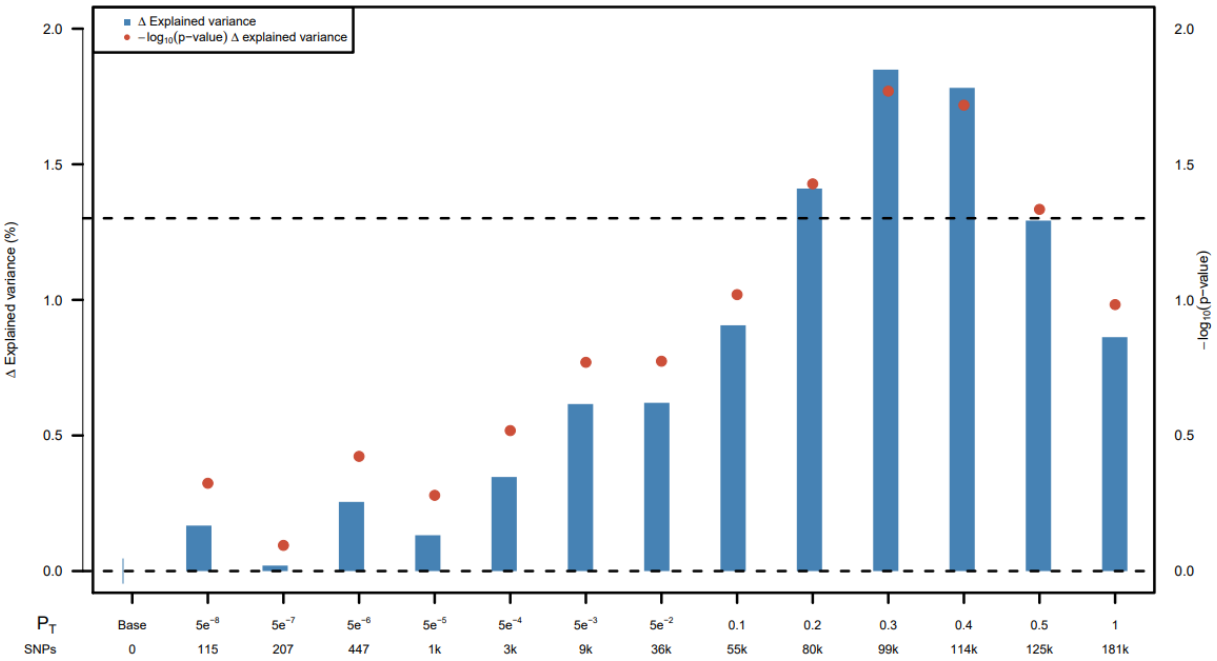
The dashed line denotes the mean of subscales over all participants, respectively. The diamonds denote ΔHDRS in each group, respectively. Mean comparisons between pairs were examined using T-tests: ****=$p<5.0x10^{-5}$. Abbreviations: ΔHDRS=change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score.

Supplementary Figure S8. In the extended model in which ECT application mode is included as covariate, polygenic liability for schizophrenia (PRS-SCZ) was also Bonferroni-corrected significantly associated with change in the 17-item Hamilton Depression Rating Scale (ΔHDRS) during electroconvulsive therapy (ECT) treatment in the entire study population.



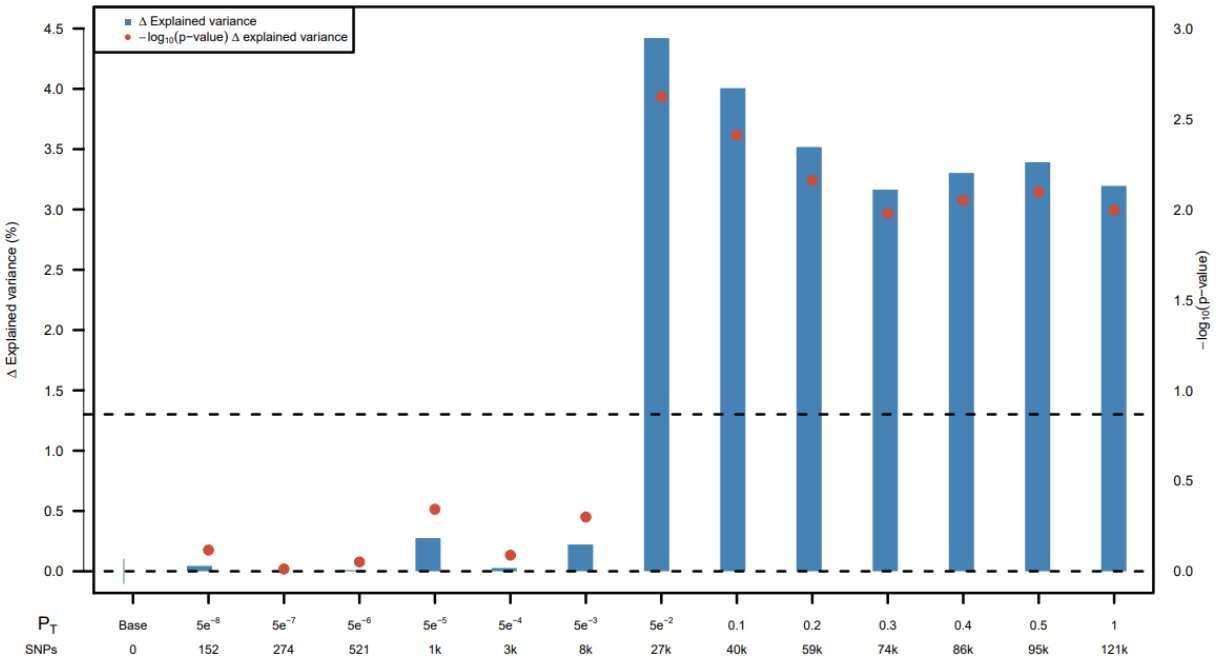
The dashed line represents the nominal significance threshold (p=0.05) for the association test of PRS-SCZ with ΔHDRS (covariates: age, gender, three principal components and ECT application mode). SNPs=single nucleotide polymorphisms, the number of which included in the regression analyses is shown. PRS-SCZ explained up to 6.94% of the variance in ΔHDRS at oPt=0.05 (β=0.53, SE=0.11, p<0.0001), which was highly similar to the base model.

Supplementary Figure S9. Polygenic risk score for cross-disorder (PRS-CD) with change in the 17-item Hamilton Depression Rating Scale (ΔHDRS) score (n=265).



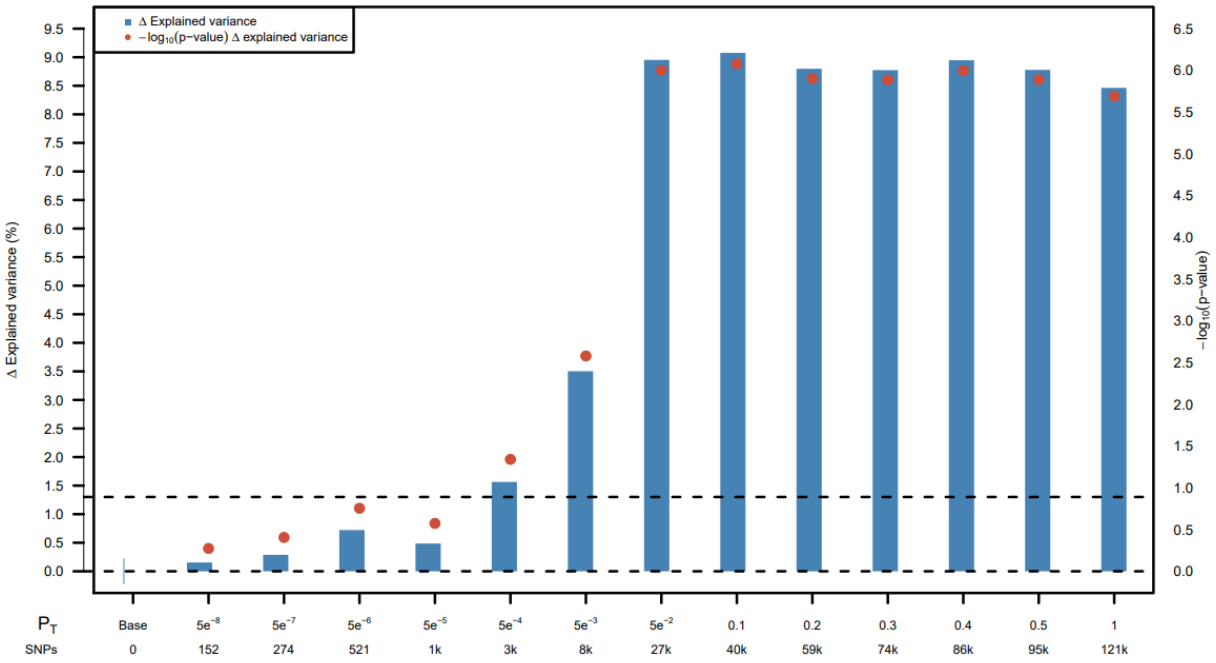
The dashed line represents the nominal significance threshold (p=0.05) for the association test of PRS-CD with ΔHDRS (covariates: age, gender, three principal components). SNPs=single nucleotide polymorphisms, the number of which included in the regression analyses is shown. PRS-SCZ explained up to 1.85% of the variance in ΔHDRS at optimal P_t (oP_t)=0.3 (β=0.11, SE=0.05, p=0.017), which was not Bonferroni-corrected significant.

Supplementary Figure S10. Polygenic risk score for schizophrenia (PRS-SCZ) with change in the 17-item Hamilton Depression Rating Scale (ΔHDRS) score in subjects without psychotic features (n=184).



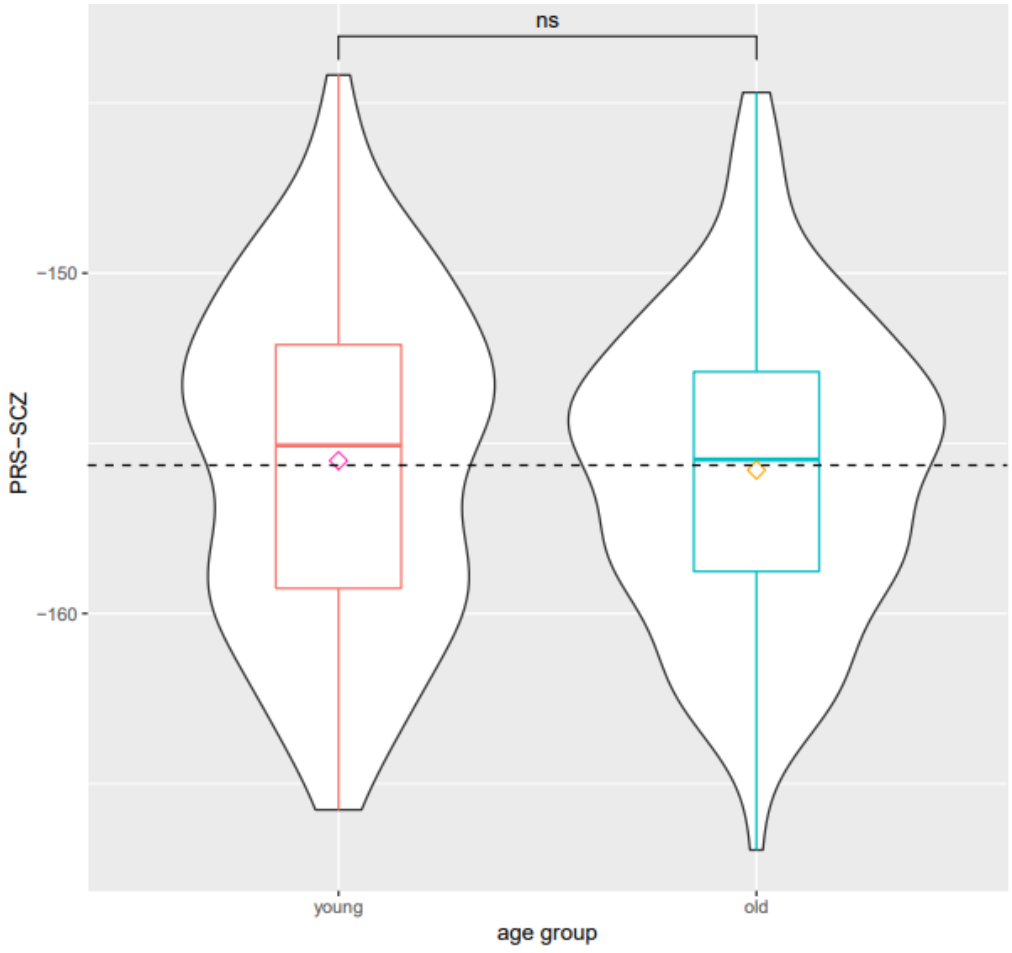
The dashed line represents the nominal significance threshold (p=0.05) for the association test of PRS-SCZ with ΔHDRS (covariates: age, gender, three principal components and electroconvulsive therapy application mode). SNPs=single nucleotide polymorphisms, the number of which included in the regression analyses is shown. PRS-SCZ explained up to 4.42% of the variance in ΔHDRS at optimal P_t (oP_t)=0.05 (β=0.39, SE=0.13, p=0.0024), which was similar to the main analysis including all patients.

Supplementary Figure S11. Polygenic risk score for schizophrenia (PRS-SCZ) with change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score in subjects with unipolar MDE (n=222).



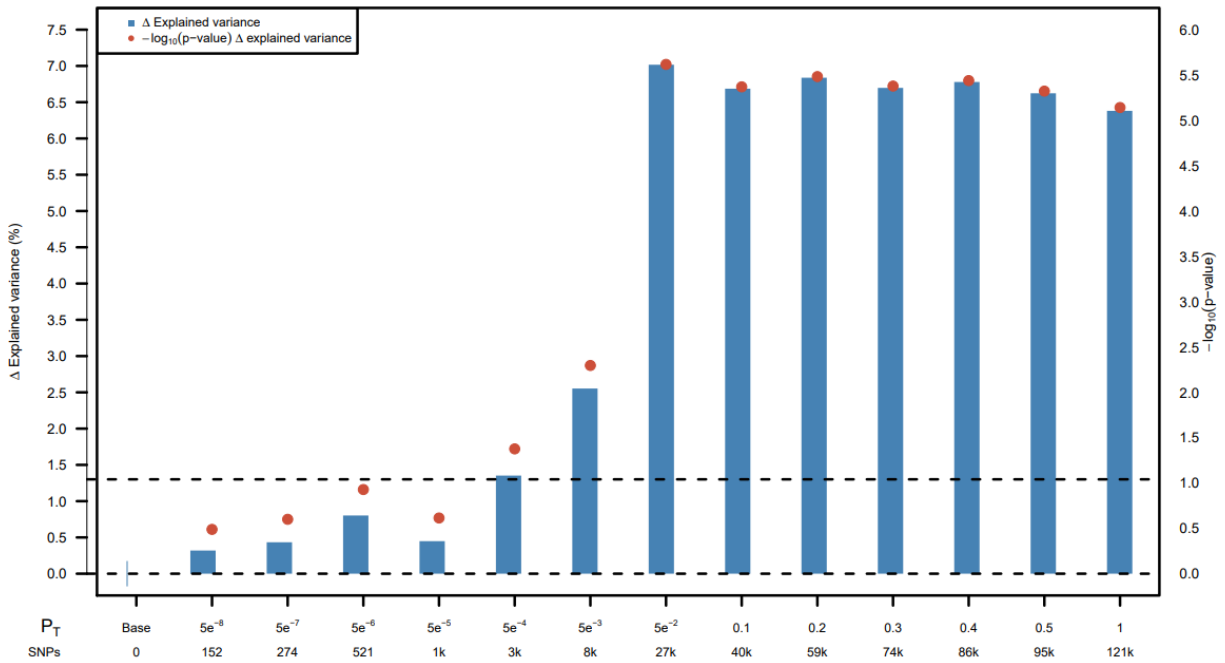
The dashed line represents the nominal significance threshold (p=0.05) for the association test of PRS-SCZ with ΔHDRS (covariates: age, gender, 3 principal components) in unipolar patients. SNPs=single nucleotide polymorphisms, the number of which included in the regression analyses is shown. PRS-SCZ explained up to 9.08% of the variance in ΔHDRS at optimal P_t (oP_t)=0.05 (β=0.56, SE=0.11, p<0.0001), which showed an even stronger association than the main analysis including all patients.

Supplementary Figure S12. No difference between age groups was found in the polygenic risk score for schizophrenia (PRS-SCZ).



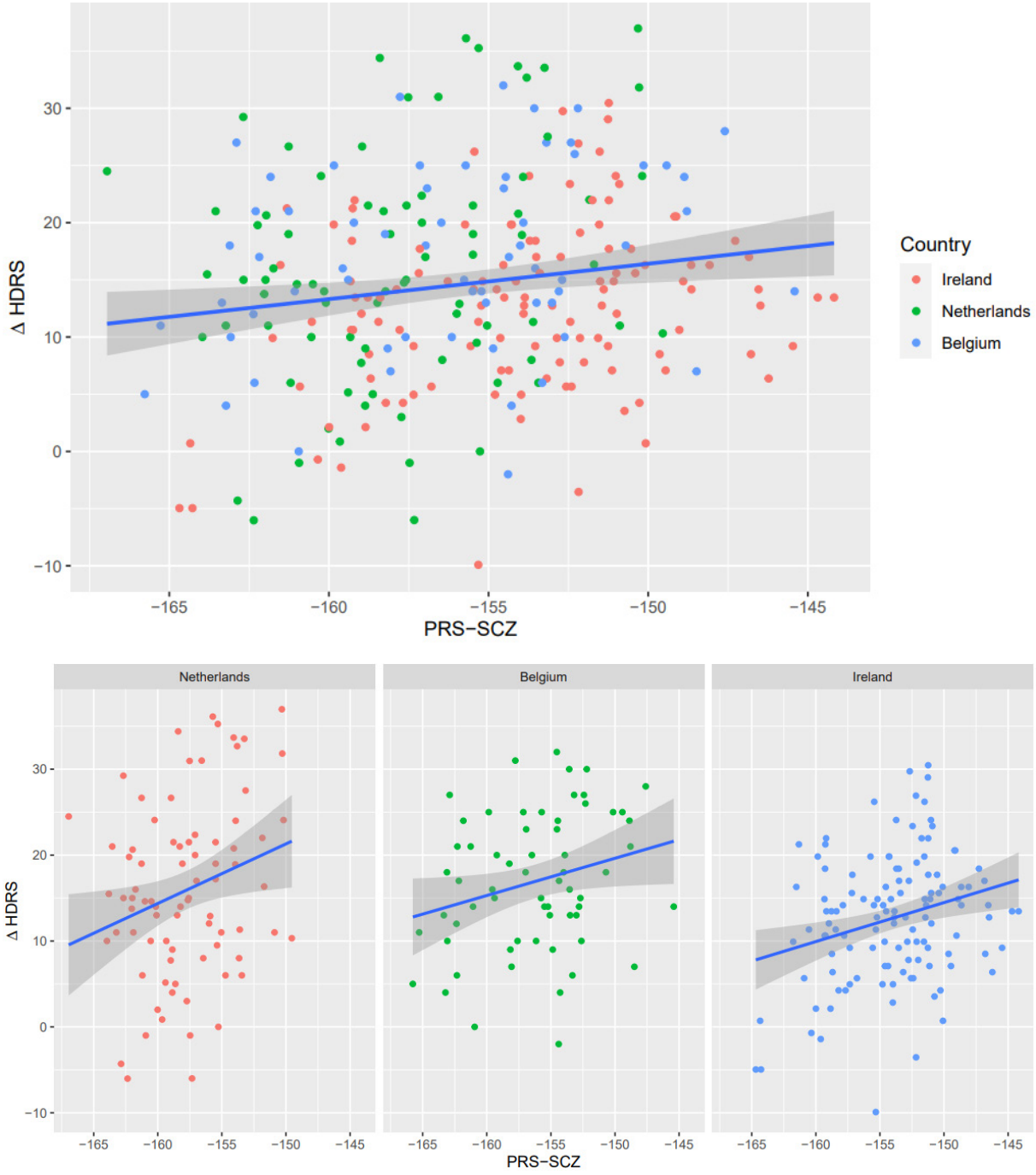
The dashed line denotes the mean of subscales over all participants, respectively. The diamonds denote PRS-SCZ (optimal P_t=0.05) in each group, respectively. Mean comparisons between pairs were examined using T-tests: ns=non-significant. PRS-SCZ=polygenetic risk score of schizophrenia (P_t=0.05).

Supplementary Figure S13. Polygenic risk score for schizophrenia (PRS-SCZ) with change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score in the sensitivity analysis with ten principal components (PCs).



The dashed line represents the nominal significance threshold (p=0.05) for the association test of PRS-SCZ with ΔHDRS (covariates: age, gender, and ten principal components). SNPs=single nucleotide polymorphisms, the number of which included in the regression analyses is shown. PRS-SCZ explained up to 7.02% of the variance in ΔHDRS at optimal P_t (oP_t)=0.05 (β=0.56, SE=0.11, p<0.0001).

Supplementary Figure S14. Similarity across countries in the association findings between the polygenic risk score for schizophrenia (PRS-SCZ) and change in 17-item Hamilton Depression Rating Scale (ΔHDRS) score. The blue lines show the best fitting lines with the grey areas representing the 95% confidence interval for that regression.



Supplementary Table S1. Summary of the quality control (QC) steps of genotypic data.

	SNP start	SNP end	Subjects start	Subjects end
Pre-imputation steps				
Conversion to plink format file	725830	725830	288	288
Remove SNPs with missingness >0·05	725830	722172	288	288
Remove samples >2% missing genotypes	722172	722172	288	285
Strict SNP QC for removal of bad samples -- remove SNPs with MAF < 10 %, Hardy-Weinberg p 0.00001	**722172**	**247714**	**285**	**285**
Strict SNP QC -- Prune SNPs on 0.2 max. LD	**247714**	**73213**	**285**	**285**
Strict SNP QC -- Check gender	**73213**	**73213**	**285**	**278**
Strict SNP QC -- Check heterozygosity	**73213**	**73213**	**278**	**277**
Strict SNP QC -- Check relatedness (identical – pi_hat >0·8)	**73213**	**73213**	**277**	**277**
Strict SNP QC -- Check relatedness (family structures with FID)	**73213**	**73213**	**277**	**277**
Strict QCed SNPs were merge wirh HAMAPS 3 and perform PCA	**70218**	**70218**	**277**	**277**
±3SD ethnicity outliers based on PCA plot with HapMap 3	**70218**	**70218**	**277**	**276**
±3SD ethnicity outliers based on PCA plot with own	**70218**	**70218**	**276**	**272**
Remove all bad samples strict QC	722172	722172	285	272
SNP QC – missing SNPs 2%,	722172	713099	272	272
SNP QC – hardy-weinberg 1e-6	713099	712907	272	272
SNP QC – MAF 1%	712907	502388	272	272
Include only autosomal SNPs	502388	478588	272	272
Remove insertions and deletions	478588	478406	272	272
Remove SNPs that are strand ambiguous	478406	475869	272	272
Remove duplicate SNPs	478406	475865	272	272
Miss haplotypes (+ repeat check missingness >2% & missing genotype >2%)	475865	473763	272	272
Imputation using Michigan server	473763	47109523	272	272
Post-imputation steps				
MAF<0·01	47109523	9929028	272	272
INFO<0·8	9929028	8619032	272	272
Remove discordant MAF compared to the reference panel >0·15	8619032	7599319	272	272
Remove strand-ambiguous AT/CG SNPs	6599319	5379897	272	272
Remove multi-allelic SNPs	5379897	4947878	272	272

Note: The QC steps in boldface were to generate a strict quality control Single Nucleotide Polymorphisms (SNPs) list, which were only used to assess bad samples and to calculate principal components (PCs). Abbreviations: MAF=minor allele frequency, PCA=principal components analysis

Supplementary Table S2. 20 Complex-LD regions and long-range LD regions which were excluded from PRS analysis.

	Base pair position (start point to end point)
Chromosome	
1	48000000-52000000
2	86000000-100500000
2	183000000-190000000
3	47500000-50000000
3	83500000-87000000
5	44500000-50500000
5	129000000-132000000
6	25500000-33500000
6	57000000-64000000
6	140000000-142500000
7	55000000-66000000
8	8000000-12000000
8	43000000-50000000
8	112000000-115000000
8	8135000-12000000
10	37000000-43000000
11	87500000-90500000
12	33000000-40000000
20	32000000-34500000
17	40900000-45000000

Supplementary Table S3. Adding significantly associated variables to a linear regression model with change in the 17-item Hamilton Depression Rating Scale (ΔHDRS) score as outcome using forward stepwise linear regression. Although each variable added additional explained variance, the polygenic risk score for schizophrenia (PRS-SCZ) added substantial explained variance and the polygenic risk score for cross-disorder (PRS-CD) added little variance to the model.

	R^2(%) total	R^2(%) Dublin	R^2(%) Belgium	R^2(%) The Netherlands
ΔHDRS~ Age	11.63	4.25	26.26	13.87
ΔHDRS~ Age + ECT application mode	14.84	6.45	29.21	22.34
ΔHDRS~ Age + ECT application mode + PC 2	18.54	6.83	30.46	22.88
ΔHDRS~ Age + ECT application mode + PC 2 + PRS-SCZ	24.22	14.18	38.12	29.07
ΔHDRS~ Age + ECT application mode + PC 2 + PRS-SCZ + PC 1	25.62	14.94	41.08	29.09
ΔHDRS~ Age + ECT application mode + PC 2 + PRS-SCZ + PC 1 + PRS-CD	26.26	16.91	43.38	30.1

Note: ECT=electroconvulsive therapy, PC=principal component, R^2=explained variance.

Supplementary Table S4. Fractional variance in change in the 17-item Hamilton Depression Rating Scale (ΔHDRS) score explained by variables significantly associated with ΔHDRS score.

	R^2(%) all	R^2(%) Dublin	R^2(%) Belgium	R^2(%) The Netherlands
Age	11.63	4.25	26.26	13.87
PRS-SCZ	5.68	7.35	7.66	6.19

Note: Model X=ECT application mode + PC2, model Y=ECT application mode + PC1 + PC2. ECT=electroconvulsive therapy, PRS=polygenic risk score, SCZ=schizophrenia, CD=cross-disorder, R^2=explained variance.

Supplementary Table S5. Polygenic risk score for schizophrenia (PRS-SCZ) including several subgroup and sensitivity analyses for both the base and extended model with change in the 17-item Hamilton Depression Rating Scale (ΔHDRS) as outcome. Results for the optimal p-value thresholds (oP_ts) were described if not otherwise specified.

	Base model (age, sex, three PCs)				**Extended model** (age, sex, three PCs, ECT application mode)			
	B	SE	R^2	*p*	β	SE	R^2	*p*
PRS-SCZ (n=265)	0.54	0.11	6.94	<0.0001	0.53	0.11	6.94	<0.0001
Subgroup analyses								
- Subjects without psychotic features (n=184)	0.39	0.13	4.42	0.0024	0.38	0.13	4.09	0.0031
- Subjects with unipolar depression (n=222)	0.56	0.11	9.08	<0.0001	0.52	0.12	6.26	<0.0001
- Median split by age for the younger group (n=136)	0.42	0.11	9.77	<0.0001	0.32	0.10	7.99	0.0018
- Median split by age for the older group (n=130)	0.58	0.19	6.60	0.0021	0.66	0.19	8.20	0.0005
Sensitivity analyses								
- With ten PCs (n=265)	0.56	0.12	7.02	<0.0001	0.55	0.12	6.69	<0.0001
- Across countries at P_t=0.05								
● Ireland (n=122)	0.50	0.15	8.18	0.0013	0.50	0.15	7.96	0.0014
● Belgium (n=63)	0.45	0.18	6.83	0.016	0.47	0.18	7.49	0.010
● The Netherlands (n=80)	0.78	0.29	7.92	0.0077	1.00	0.25	12.23	0.0058

Note: PCs=principal components, ECT=electroconvulsive therapy. From the 266 individuals included in the analyses the primary outcome was unknown for one subject, but exclusion was not applied as secondary outcome measures were available.

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