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## Interrogating Associations Between Polygenic Liabilities and Electroconvulsive Therapy Effectiveness

Jurjen J. Luykx, Dore Loef, Bochao Lin, Linda van Diermen, Jasper O. Nuninga, Eric van Exel, Mardien L. Oudega, Didi Rhebergen, Sigfried N.T.M. Schouws, Philip van Eijndhoven, Esmée Verwijk, Didier Schrijvers, Tom K. Birkenhager, Karen M. Ryan, Baer Arts, Suzanne C. van Bronswijk, Gunter Kenis, Geert Schurgers, Bernhard T. Baune, Martijn Arns, Edwin E. van Dellen, Metten Somers, Iris E.C. Sommer, Marco P. Boks, Sinan Gülöksüz, Declan M. McLoughlin, Annemiek Dols, and Bart P.F. Rutten

### ABSTRACT

**BACKGROUND:** Electroconvulsive therapy (ECT) is the most effective treatment for severe major depressive episodes (MDEs). Nonetheless, firmly established associations between ECT outcomes and biological variables are currently lacking. Polygenic risk scores (PRSs) carry clinical potential, but associations with treatment response in psychiatry are seldom reported. Here, we examined whether PRSs for major depressive disorder, schizophrenia (SCZ), cross-disorder, and pharmacological antidepressant response are associated with ECT effectiveness.

**METHODS:** A total of 288 patients with MDE from 3 countries were included. The main outcome was a change in the 17-item Hamilton Depression Rating Scale scores from before to after ECT treatment. Secondary outcomes were response and remission. Regression analyses with PRSs as independent variables and several covariates were performed. Explained variance ( $R^2$ ) at the optimal  $p$ -value threshold is reported.

**RESULTS:** In the 266 subjects passing quality control, the PRS-SCZ was positively associated with a larger Hamilton Depression Rating Scale decrease in linear regression (optimal  $p$ -value threshold = .05,  $R^2 = 6.94\%$ ,  $p < .0001$ ), which was consistent across countries: Ireland ( $R^2 = 8.18\%$ ,  $p = .0013$ ), Belgium ( $R^2 = 6.83\%$ ,  $p = .016$ ), and the Netherlands ( $R^2 = 7.92\%$ ,  $p = .0077$ ). The PRS-SCZ was also positively associated with remission ( $R^2 = 4.63\%$ ,  $p = .0018$ ). Sensitivity and subgroup analyses, including in MDE without psychotic features ( $R^2 = 4.42\%$ ,  $p = .0024$ ) and unipolar MDE only ( $R^2 = 9.08\%$ ,  $p < .0001$ ), confirmed the results. The other PRSs were not associated with a change in the Hamilton Depression Rating Scale score at the predefined Bonferroni-corrected significance threshold.

**CONCLUSIONS:** A linear association between PRS-SCZ and ECT outcome was uncovered. Although it is too early to adopt PRSs in ECT clinical decision making, these findings strengthen the positioning of PRS-SCZ as relevant to treatment response in psychiatry.

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Major depressive episodes (MDEs) in the context of bipolar disorder or major depressive disorder (MDD) pose a heavy burden on patients and their relatives, as well as on society as a whole, especially in the event of severe symptoms, recurrence, or chronicity. Despite several treatment options, one third of patients with MDEs do not respond to the most common pharmacological and psychotherapeutic treatment strategies, and chronic courses are associated with disease burden, increased risk of somatic comorbidities, and suicide (1). Electroconvulsive therapy (ECT) is an effective treatment with remission rates up to 50% to 80%, even in difficult-to-treat depression (2,3). However, ECT continues to be subject to stigmatization and is still frequently presented negatively in media (4). Moreover, ECT is often inappropriately considered a

treatment of last resort and is mostly applied to severe and/or difficult-to-treat MDEs (5). Recent findings substantiating that ECT may be positioned as a relatively early choice for some patients will hopefully ameliorate the course of illness in many patients (6).

ECT response is highly variable, and currently, no established algorithm can reliably determine how a person will respond to ECT. Nonetheless, 2 recent meta-analyses have revealed that various clinical measures, including the presence of psychotic features, older age, shorter episode duration, and absence of medication resistance, predict a more favorable ECT response (6,7). In general, interindividual variability in response to interventions may be based (partly) on the genetic background of the individual (8). Genetic data may therefore be

useful to guide treatment selection because even a resulting modest increase in the proportion of responding patients could help boost effectiveness and reduce time to recovery at a group level (8).

An estimate of an individual's genetic liability to a certain characteristic, trait, or disease can be calculated with a polygenic risk score (PRS) based on genome-wide data. PRSs have been shown to have predictive value for onset and course of some psychiatric disorders (8). For MDD, higher PRSs are associated with measures of increased severity, such as early age of onset, number of symptoms, and recurrence (9). To our knowledge, only one study to date has examined whether PRS-MDD is associated with antidepressant effects of ECT in patients with MDD. In a study of 51 subjects, no significant relationship between PRS-MDD and ECT response was observed, possibly as a result of limited statistical power (10). In addition, the number of genetic risk loci has increased substantially in more recent genome-wide association studies (GWASs) of psychiatric traits, including MDD (11). Furthermore, as shown in a recent GWAS of pharmacological antidepressant response (AR), possibly not only PRS-MDD but also other PRSs may be relevant to response to antidepressant interventions (12). Of particular interest in this context is the schizophrenia (SCZ) PRS, because 1) just as depression with psychotic features is characterized by greater severity, so may PRS-SCZ reflect a relatively more severe psychiatric predisposition with plausibly greater effects on mental health than other psychiatric genetic liabilities (13,14); 2) depression with psychotic features is known to be more responsive to ECT (6,15); 3) PRS-SCZ is based on relatively well-powered GWASs with substantial explained phenotypic variance (16); and 4) patients receiving ECT show a different genetic architecture than patients with general MDD, with higher single nucleotide polymorphism (SNP)-based heritability and stronger genetic correlations with severe psychiatric disorders (17). PRS-SCZ also has the advantage of being linear relative to the (often) binary documentation of the presence of psychotic features in clinical studies to date, thus allowing one to disentangle linear associations between SCZ liability and ECT outcomes.

Seeking to deepen the understanding of genetic associations with ECT effectiveness, we set out to collect a unique multicohort study population of patients undergoing ECT with extensive phenotyping available. We aimed to elucidate whether polygenic liabilities to MDD, SCZ, pharmacological AR, and cross-disorder (CD) are associated with the antidepressant effects of ECT. To that end, we generated whole-genome data using the most recent Illumina Genotyping Screening Array platform and performed a range of statistical analyses to examine PRS associations with ECT effectiveness.

## METHODS AND MATERIALS

### Study Population

Well-characterized clinical cohorts were selected on the basis of having rich phenotype data (including validated depression scales administered before and after ECT treatment) as well as DNA samples available from their participants. The resulting study population included European cohorts from 3 different countries consisting of 288 participants, of whom 6 participants were excluded because no depression measure was

assessed after ECT. All procedures involved in this study were performed in accordance with the ethical standards of the Declaration of Helsinki 2013 version. This study was approved by the local ethics committees of each recruiting center. All patients included provided written consent. Details about each cohort, including references to primary studies, are provided in the [Supplement](#). Briefly, all cohorts had recruited individuals with a diagnosis of MDD or a depressive episode in the context of bipolar disorder according to DSM-IV criteria and confirmed by a structured clinical interview (see the [Supplement](#)). Patients were assessed for depressive symptoms before and after treatment with brief-pulse ECT using validated depression severity scales.

### Choice of Primary and Secondary Outcome Measures

The primary outcome measure of this study was the change in the 17-item Hamilton Depression Rating Scale (HDRS-17) score ( $\Delta$ HDRS score), i.e., the pre-post ECT difference in depression severity (18).  $\Delta$ HDRS score was chosen as the primary outcome because it is a continuous measure that does not depend on predefined cutoffs and displays a larger amount of variance in depression severity than remission and response. Secondary outcomes were the HDRS-17 score after ECT as well as response and remission status. For participants for whom no HDRS-17 score was available, HDRS-24 scores were converted to the 17-item version using an established method (19). For patients without HDRS scores available, a validated equation was used to convert their Montgomery-Åsberg Depression Rating Scale scores to HDRS-17 (19,20). Conversion to HDRS-17 instead of using HDRS-24 was preferred to avoid double conversion of the Montgomery-Åsberg Depression Rating Scale. After conversion to HDRS-17, response to ECT was defined as a decrease of  $\geq 50\%$  in the HDRS-17 score and remission after ECT was defined as an HDRS-17 score of  $\leq 7$ .

Several demographic, clinical, and ECT variables were assessed. Demographic variables included age, sex, marital status, and level of education. Clinical variables were age at onset of first depression, number of previous depressive episodes, duration of the index depressive episode in weeks, HDRS-17 score before ECT, treatment-resistance measures [using the Antidepressant Treatment History Form (21) or the Maudsley staging method (22)], diagnosis, and presence of psychotic features based on DSM-IV criteria and confirmed by structured clinical interviews (for details, see the [Supplement](#)). ECT variables included total number of sessions in the ECT course and ECT application mode (unilateral vs. bilateral).

### Genotyping and Quality Control

Genotype data for 288 individuals were generated using the Illumina Infinium Global Screening array v.3 with 725,830 SNPs (Illumina) in November 2020. Rigorous SNP and individual-level preimputation quality control (QC) procedures were conducted as reported in the [Supplement](#). The preimputation QC SNPs were then used for imputation of additional SNPs on the Michigan server using the Haplotype Reference Consortium (version r1.1, 2016) reference panel with European samples after phasing with Eagle v.2.3 (23). A total of 47,109,523 SNPs

were downloaded from the Michigan server. Postimputation QC involved removing SNPs with a minor allele frequency (MAF)  $<0.01$  ( $n = 37,180,495$ ), SNPs with  $R^2$  info score  $<0.8$  ( $n = 1,309,996$ ), SNPs that had a discordant MAF (MAF differences  $>0.15$ ) compared with the reference panel ( $n = 1,019,713$  SNPs), strand ambiguous AT/CG SNPs ( $n = 1,219,422$ ), and multiallelic SNPs ( $n = 432,019$ ). The 22 imputed variant call format files per chromosome excluding the above-mentioned SNPs were converted into PLINK version 1.90 (24) best guess format data and then merged for all chromosomes, leaving 272 samples and 4,947,878 SNPs for PRS calculation.

Following suggestions during the peer review process, we performed GWAS analyses as well as functional annotation and pathway analyses and report those in the Supplement (p. 7–19). However, we caution against interpreting these results as final and prefer to call them preliminary given the lack of statistical power for GWAS and post-GWAS analyses with the current sample size. We advocate collaborative efforts to ramp up sample sizes in GWASs of ECT responsiveness.

### PRS Calculation

The PRSs for 272 samples passing genetic QC were calculated using summary statistics of MDD excluding 23andMe cohorts (11), SCZ (25), CD (26), and quantitatively ascertained AR (namely improvement percentage) (12) as base datasets. These were chosen based on the disorder most represented in our cohort (PRS-MDD), previously reported strongest associations with treatment outcomes in psychiatry and ECT associations with psychotic features (PRS-SCZ), size of study cohort (PRS-CD), and resemblance of phenotype under investigation (PRS-AR). First, all overlapping SNPs between each GWAS summary statistics (base dataset, 1000 Genomes phase I reference dataset: <https://www.internationalgenome.org/data/>) and our target dataset were selected. Then the following SNPs were excluded: 1) insertion or deletion, ambiguous SNPs; 2) SNPs with MAF  $<0.01$  and SNPs with imputation quality ( $R^2$ )  $<0.8$  in both training dataset and target datasets; and 3) SNPs located in complex linkage disequilibrium regions (Table S2) (27), leaving 3,446,085 SNPs for SCZ, 4,155,073 for CD, 4,472,298 for MDD, and 3,894,664 for AR PRS calculations. These SNPs were clumped in 2 rounds using PLINK version 1.90 (24); round 1 with the default parameters (physical distance threshold 250 kb and linkage disequilibrium threshold [ $R^2$ ]  $<0.5$ ), and round 2 with a physical distance threshold of 5000 kb and linkage disequilibrium threshold ( $R^2$ )  $<0.2$ , resulting in 120,654 SNPs for PRS-SCZ, 181,434 SNPs for PRS-CD, 243,065 SNPs for PRS-MDD, and 149,077 SNPs for PRS-AR calculations. Odds ratios in the summary statistics were log-converted to beta values. PRSs were calculated using PRSice-2 for 13 GWAS  $p$ -value thresholds:  $5 \times 10^{-8}$ ,  $5 \times 10^{-7}$ ,  $5 \times 10^{-6}$ ,  $5 \times 10^{-5}$ ,  $5 \times 10^{-4}$ ,  $5 \times 10^{-3}$ , .05, .1, .2, .3, .4, .5, and 1 (28). Finally, we explored the role of the top associated PRS gene set derived from a previous study, *TCF4*, and overall found no evidence of consistent associations in our cohort for our phenotype of interest (29). Again, we caution against overinterpreting these findings given the lack of power to draw firm conclusions, and thus these analyses should also be regarded as highly preliminary.

### Data Analysis

Data were analyzed using R version 3.6.0 (R Foundation for Statistical Computing). Analyses were executed with PRS-MDD, PRS-SCZ, PRS-CD, and PRS-AR as independent variables and the above-mentioned primary outcome ( $\Delta$ HDRS) as a dependent variable, using linear regression in the entire study population. Covariates were age, sex, and the first 3 genetic ancestry principal components (PCs) because only 1 PC, i.e., PC2, correlated with  $\geq 1$  outcomes ( $\Delta$ HDRS). We applied 2 models: a base model including age, sex, and the first 3 PCs [which have been shown to be sufficient in a relatively homogeneous population (30)], and an extended model to which ECT application mode (solely unilateral or bilateral) was added as a covariate. ECT application mode was the only covariate independently (not correlated to another covariate) and nominally significantly ( $p < .05$ ) correlated with  $\Delta$ HDRS score. We tested such correlations between all available phenotypic and genetic variables using Pearson correlation statistic and show correlation matrices in Figure S5. For the secondary outcomes, no independent covariates were found (in addition to age, sex, and 3 PCs); therefore, only a base model for these three is reported. Before analysis, we checked the residual distribution of our base linear regression model and confirmed a normal distribution (Cramer–von Mises test  $p$  values  $<.001$  for all quantitative outcomes) (Figure S6). Two-sided  $p$  values are reported for statistical significance. Bonferroni correction for 4 outcomes and 4 PRSs at 13  $p$ -value thresholds ( $p_t$ s) ( $p = .05/[4 \times 4 \times 13] = .0002$ ) was used to account for multiple testing in a conservative manner. Any PRSs significantly associated with  $\Delta$ HDRS score were also tested for association with secondary outcomes (linear regression for the HDRS score after ECT; logistic for response and remission as defined above). To establish significance for associations with secondary outcomes, again Bonferroni correction for the number of  $p_t$ s and positively associated PRSs was applied. For positive associations with the primary outcome measure, we also divided in tertiles any significantly associated PRS at the optimal  $p_t$  ( $op_t$ ) for our primary outcome (base and extended models) and then tested differences in  $\Delta$ HDRS score between tertiles (alpha  $<0.05$ ) using analysis of variance.

Then, using all covariates and all PRSs significantly and nominally significantly ( $p < .05$ ) associated with  $\Delta$ HDRS score, we performed forward stepwise multiple linear regression to estimate the amount of variance explained by each of the variables in 1 model.

Finally, in the event of obtaining positive findings, we assessed robustness of our findings by performing several subgroup and sensitivity analyses for both the base model (with covariates age, sex, and 3 PCs) and the extended model (with covariates age, sex, 3 PCs, and ECT application mode). Subgroup analyses included 1) exclusion of individuals with psychotic features, 2) exclusion of people with bipolar disorders, and 3) age median split. Then the above-mentioned primary outcome analysis was repeated, at the Bonferroni-corrected significance level of  $.05/13 = .0038$  because 13  $p_t$ s were examined. Two sensitivity analyses were conducted. A first sensitivity analysis included adding 10 PCs instead of 3 PCs as covariates at the same Bonferroni-corrected significance level (.0038). Second, given differences in ECT



procedures across countries (e.g., dosing method and ECT device) and observed differences in remission rates across countries (Table 1), we repeated the association analysis at the  $op_t$  for our primary outcome per country (Ireland, Belgium, and the Netherlands) at a Bonferroni-corrected significance level of  $.05/3 = .017$  because we examined patients from 3 countries.

## RESULTS

### Descriptive Statistics

Of the 272 subjects passing genetic QC, 6 subjects with missing outcome variables were excluded, resulting in 266 individuals included in the analyses. For 1 subject, the primary outcome was unknown, but exclusion was not applied because secondary outcome measures were available. The age of these 266 participants ranged from 19 to 90 years (mean = 58.6, SD = 15.5) and 65.8% were female (Table 1). After splitting the entire sample by age median split, the older age group showed a significantly higher decrease in HDRS scores than the younger age group (Figure S7).

### Primary Outcomes

In the base model, PRS-SCZ was significantly associated with  $\Delta$ HDRS score in the entire study population ( $\beta = 0.54$ , SE = 0.11,  $p < .0001$ ), explaining up to 6.94% of the variance in  $\Delta$ HDRS score at  $op_t = .05$  (Figure 1A). This result was similar in the extended model ( $\beta = 0.53$ , SE = 0.11,  $p < .0001$ ), where it also explained up to 6.94% of the variance in  $\Delta$ HDRS score at  $op_t = .05$  (Figure S8).

Significant differences between PRS-SCZ tertiles were observed (analysis of variance  $F_{2,64} = 4.29$ ;  $p = .015$ ) (Figure 1B). The lowest tertile differed significantly from both the other tertiles ( $t$  test  $p$  value against middle = .0498;  $t$  test  $p$  value against upper = .0037).

The second most strongly associated PRS with  $\Delta$ HDRS score was PRS-CD, but this association did not meet our predefined Bonferroni-corrected significance level ( $\beta = 0.11$ , SE = 0.05,  $p = .017$ ), explaining a maximum of 1.85% of the variance in  $\Delta$ HDRS score (Figure S9). Although PRS-MDD was nominally significantly associated with a higher HDRS score before ECT ( $R^2 = 3.05\%$ ,  $\beta = 2.72$ , SE = 0.90,  $p = .0027$ ), PRS-MDD was not significantly associated with  $\Delta$ HDRS score ( $\beta = 1.67$ , SE = 1.19,  $p = .16$ ). Furthermore, PRS-AR was not significantly associated with  $\Delta$ HDRS score ( $\beta = -0.02$ , SE = 0.09,  $p = .78$ ).

In our forward multiple linear regression model including all positively associated covariates, PRS-SCZ, and PRS-CD, each variable added additional explained variance with  $\Delta$ HDRS score as the outcome. However, PRS-CD added little while PRS-SCZ added substantial explained variance to the model (Table S3). Similarly, fractional variance by age and PRS-SCZ were consistently high in the entire study population and across countries (with explained variances by PRS-SCZ ranging from 4.5% to 25.4%) (Table S4).

### Subgroup and Sensitivity Analyses

After exclusion of subjects with psychotic features ( $n = 82$ ), PRS-SCZ was still significantly associated with  $\Delta$ HDRS score

**Table 1. Baseline Demographic and Clinical Characteristics, ECT Characteristics, and Depression Measures Including a Significance Test for Differences Between Countries**

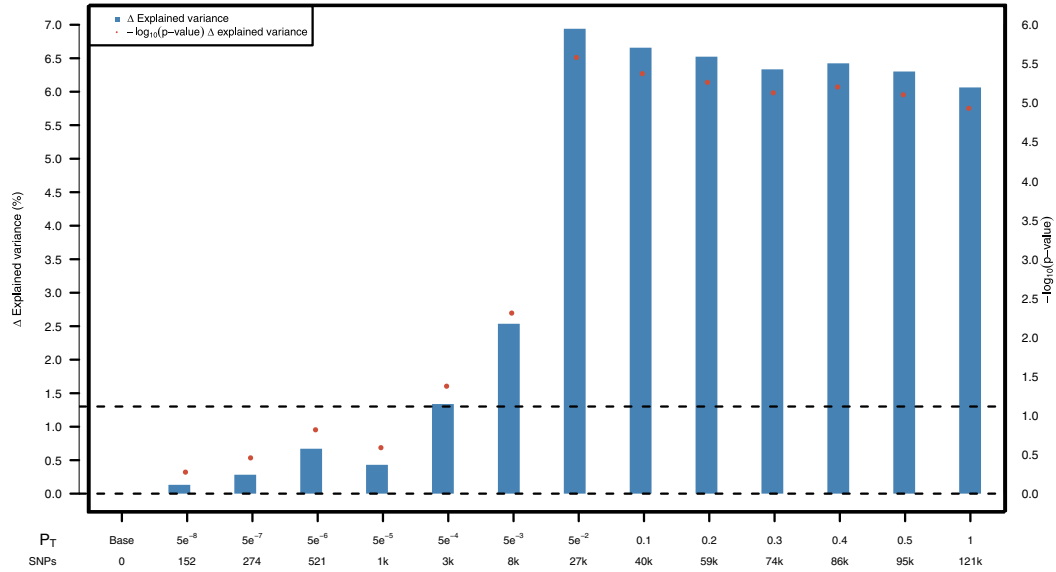
Characteristics	All Participants, <i>N</i> = 266	Ireland, <i>n</i> = 122	Belgium, <i>n</i> = 63	The Netherlands, <i>n</i> = 81	Difference Between Countries ANOVA
<b>Demographic Characteristics</b>					
Age, years, mean (SD)	58.6 (15.5)	57.2 (14.9)	58.1 (15.5)	60.9 (16.4)	$F_{2,263} = 1.41, p = .25$
Gender, female, <i>n</i> (%)	175 (65.8%)	77 (63.1%)	47 (74.6%)	51 (63.0%)	$F_{2,263} = 1.42, p = .24$
<b>Clinical Characteristics</b>					
Previous depressive episodes, median (IQR)	3.0 (4)	4.0 (5)	N/A	2.0 (4)	$F_{1,167} = 2.85, p = .093$
Duration of current episode, weeks, median (IQR)	24.0 (40)	20.0 (23)	26.0 (64)	30.0 (52)	$F_{2,224} = 4.07, p = .018^a$
Age at onset of first depression, late (>55 years), <i>n</i> (%)	46 (24.9%)	24 (20.7%)	N/A	22 (31.9%)	$F_{1,183} = 2.92, p = .089$
Diagnosis, unipolar, <i>n</i> (%)	223 (83.8%)	94 (77.0%)	51 (81.0%)	78 (96.3%)	$F_{2,263} = 7.70, p = .0006^a$
With psychotic features, <i>n</i> (%)	82 (30.8%)	26 (21.3%)	30 (47.6%)	26 (32.1%)	$F_{2,263} = 7.07, p = .0010^a$
<b>ECT Characteristics</b>					
Number of ECT treatments, mean (SD)	10.4 (5.9)	8.0 (2.5)	11.4 (5.8)	13.3 (8.1)	$F_{2,259} = 23.79, p < .0001^a$
Patients treated bilateral or switched to bilateral, <i>n</i> (%)	119 (50.0%)	60 (49.2%)	28 (44.4%)	59 (72.8%)	$F_{2,263} = 7.82, p = .0005^a$
<b>Depression Measures</b>					
HDRS-17 before, mean (SD)	23.3 (6.5)	21.3 (4.5)	24.9 (6.2)	25.0 (8.3)	$F_{2,262} = 11.15, p < .0001^a$
HDRS-17 after, mean (SD)	8.6 (6.1)	8.6 (6.0)	7.9 (4.8)	9.2 (6.9)	$F_{2,263} = 0.77, p = .46$
HDRS-17 change score, mean (SD)	-14.7 (8.7)	-12.7 (7.4)	-16.9 (8.0)	-15.9 (10.3)	$F_{2,262} = 6.41, p = .0019^a$
Response to ECT, <i>n</i> (%)	181 (68.0%)	79 (64.8%)	48 (76.2%)	54 (66.7%)	$F_{2,263} = 1.49, p = .23$
Remission after ECT, <i>n</i> (%)	128 (48.1%)	52 (42.6%)	39 (61.9%)	37 (45.7%)	$F_{2,263} = 3.28, p = .039^a$

Categorical variables document valid percentages, i.e., excluding missing data.

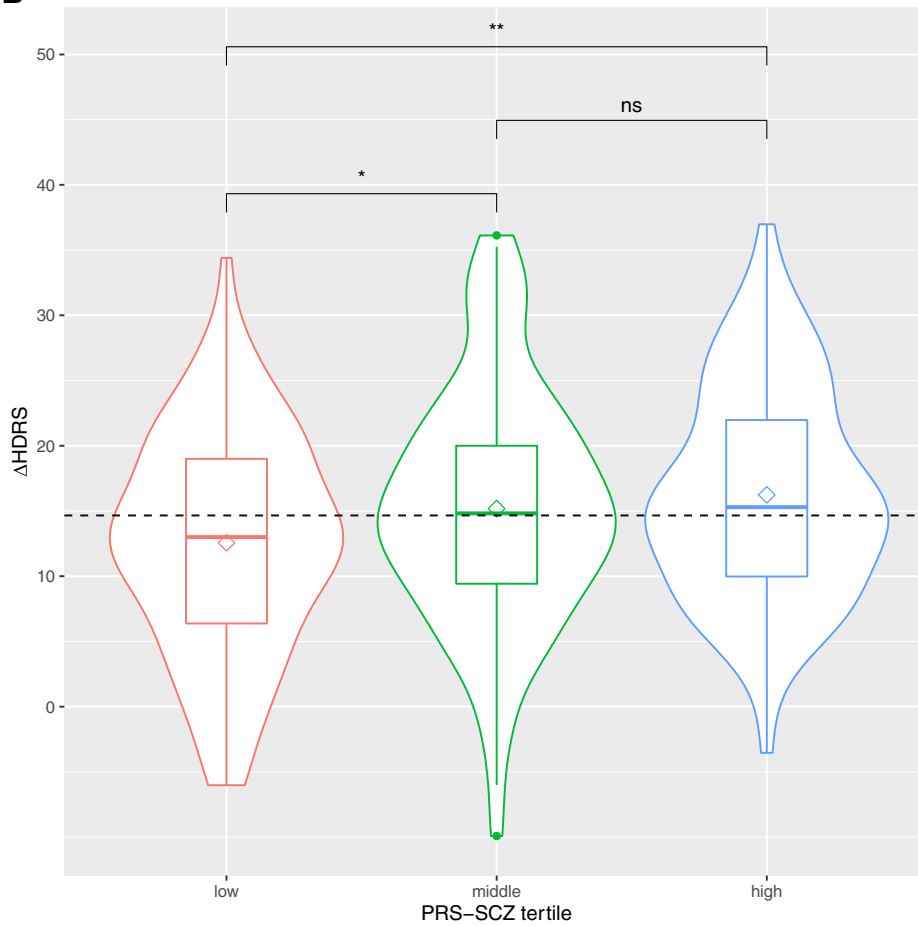
ANOVA, analysis of variance; ECT, electroconvulsive therapy; HDRS-17, 17-item Hamilton Depression Rating Scale; IQR, interquartile range; N/A, not applicable because this was not assessed.

<sup>a</sup>Significant differences between countries.

**A**



**B**



**Table 2. Consistency of the PRS-SCZ Association Results for  $\Delta$ HDRS Score at  $p_t = .05$  Across Countries Corrected for Age, Sex, and Three Genetic Ancestry Principal Components**

Country	$\beta$	SE	$R^2$	$p$ Value
Ireland, $n = 122$	0.50	0.15	8.18	.0013
Belgium, $n = 63$	0.45	0.18	6.83	.016
The Netherlands, $n = 80$	0.78	0.29	7.92	.0077

$R^2$  is explained variance;  $\beta$  is the regression coefficient of the regression model.

$\Delta$ HDRS, change in 17-item Hamilton Depression Rating Scale; PRS-SCZ, polygenic risk score for schizophrenia;  $p_t$ ,  $p$ -value threshold.

( $n = 184$ ;  $R^2 = 4.42\%$ ,  $\beta = 0.39$ ,  $SE = 0.13$ ,  $p = .0024$ ) (Figure S10). After exclusion of patients with bipolar disorders, an even stronger association between PRS-SCZ and  $\Delta$ HDRS score was observed ( $n = 222$ ;  $\beta = 0.56$ ,  $SE = 0.11$ ,  $p < .0001$ ), explaining up to 9.08% of the variance in  $\Delta$ HDRS score (Figure S11). Finally, when splitting the entire sample by age median split, similar results were found in both age groups (Table S5), and no difference was found in PRS-SCZ loading between age groups (Figure S12).

Next, 2 sensitivity analyses were run. A total of 10 PCs were added to our primary model, showing slightly more significant results and increased explained variance relative to our base model ( $R^2 = 7.02\%$ ,  $\beta = 0.56$ ,  $SE = 0.12$ ,  $p < .0001$ ) (Figure S13). Subsequently, the PRS-SCZ results were found to be highly consistent across countries at  $p_t = .05$  with equal directions of effect and similar  $\beta$  values,  $p$  values, and explained variances (Table 2; Figure S14). The range of 1.4% in  $R^2$  between countries could be explained by the smaller sample sizes for the separate countries relative to the entire study population. Of note, however, the effect sizes ( $\beta$ ) across countries were consistently positive and close to the effect size in the total sample, further highlighting the similarity in findings across countries. We provide graphical displays of the similarities in findings across countries in Figure S14, including regression slopes with confidence intervals in the entire cohort and per country. Moreover, the results for the subgroup and sensitivity analyses were similar for the extended model (Table S5).

### Secondary Outcomes

PRS-SCZ was also associated with the binary outcome of remission of MDEs after ECT (HDRS-17 score  $\leq 7$ ) at a Bonferroni-corrected  $p_t$  of  $.05/13 = .0038$  from  $p_t = .05$  at an  $op_t$  of  $.2$  ( $p = .0018$ ), explaining 4.62% of its variance (Figure 2). The binary outcome of response to ECT ( $\geq 50\%$  decrease in the HDRS-17 score) was nominally significantly associated with PRS-SCZ at  $op_t = .05$  ( $p = .029$ ), explaining 2.32% of its variance. In addition, PRS-SCZ was negatively associated with the HDRS score after ECT ( $\beta = -0.35$ ,  $SE = 0.08$ ,  $p < .0001$ ), explaining 6.09% of its variance at an  $op_t$  of  $.05$ .

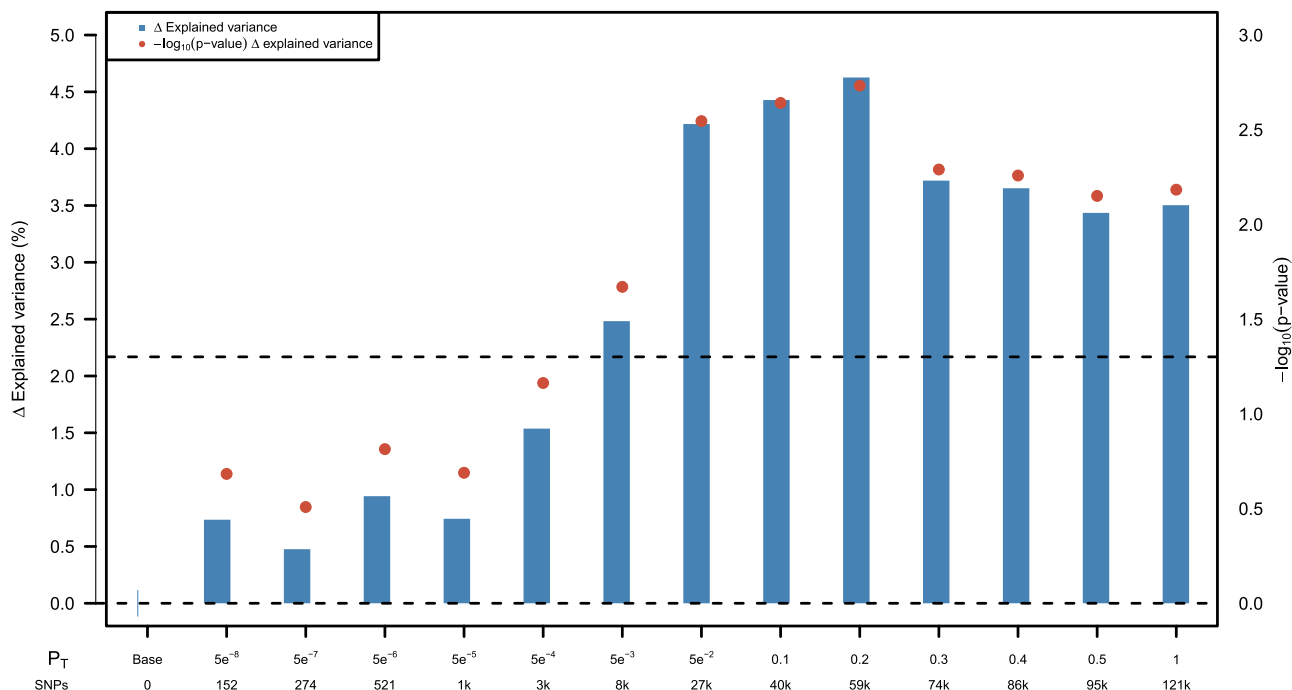
### DISCUSSION

Using a unique, multicohort study population of patients undergoing ECT for MDEs, we established for the first time that polygenic liability for SCZ is associated with the antidepressant effects of ECT. The robustness of our findings is supported by analyses across countries, across outcome measures, and in a range of subgroup and sensitivity analyses.

The main finding that people with a higher PRS-SCZ had more favorable ECT outcomes is in accordance with meta-analyses showing that psychotic features predict a favorable response to ECT (6,7). Here, the positive association between PRS-SCZ and decrease of depression severity was also observed in the subset of patients without psychotic features. This may indicate that psychosis vulnerability also plays a role in those without manifest psychotic symptoms, which would be consistent with psychosis as a continuous trait, possibly indexing depression severity. Furthermore, in line with Foo *et al.* (10), no significant association between PRS-MDD and decrease in depression severity was observed in our study. PRS-CD was only nominally significantly associated with decrease in depression severity and contributed little to multiple regression models. Similarly, we found no associations with PRS-AR.

Several explanations for our findings exist. First, PRS-SCZ is reported to be the best-performing PRS with more explained phenotypic variance than GWASs of other mental disorders (16). Second, SCZ could be considered the extreme end of the psychiatric disorder severity spectrum; hence, the polygenic liability for SCZ may have a greater impact on mental health at a group level than other mental disorders (14). Third, psychosis as a continuum is possibly associated with ECT effectiveness. In this respect, cellular mechanisms implicated in SCZ (e.g., neurogenesis, dendritic spines, cell-cell adhesion, and white matter neuron density) may also affect the remission rate in ECT. Although in a study of 34 patients with MDEs, one psychosis scale did not show added value over binary assessment of psychotic symptoms in terms of predicting ECT response (31), our findings warrant further research into associations between other continuous measures of psychosis symptoms and ECT response in larger cohorts of MDEs and psychotic disorders.

**Figure 1.** (A) PRS-SCZ is positively associated with a decrease in the HDRS score ( $\Delta$ HDRS) during electroconvulsive therapy treatment in the entire study population at  $P_T$  ranging from  $5 \times 10^{-4}$  to 1. From  $P_T = .005$  with 8000 SNPs to  $P_T = .005$  with 27,000 SNPs, a substantial increase in explained variance is observed, possibly indicating polygenicity. The maximum explained variance in change score by PRS-SCZ was 6.94% at  $P_T = .05$  ( $p < .0001$ ). The dashed line represents the nominal significance threshold ( $p = .05$ ) for the association test of PRS-SCZ with  $\Delta$ HDRS score (covariates: age, sex, and 3 genetic ancestry principal components). The numbers of SNPs included in the regression analyses are shown. (B)  $\Delta$ HDRS score during electroconvulsive therapy was plotted for each tertile of the PRS-SCZ. Significant differences between the tertiles were observed (analysis of variance:  $F_{2,64} = 4.29$ ;  $p = .015$ ). Low, middle, and high PRS-SCZ tertiles in the entire study population are plotted. \* $p < .05$ ; \*\* $p < .005$ .  $\Delta$ HDRS, change in the Hamilton Depression Rating Scale; ns, nonsignificant; PRS-SCZ, polygenic risk score for schizophrenia;  $P_T$ ,  $p$ -value thresholds; SNP, single nucleotide polymorphism.



**Figure 2.** The PRS-SCZ is significantly associated with remission (defined as a 17-item HDRS score  $\leq 7$  after electroconvulsive therapy treatment) in the entire study population at  $P_T$  ranging from .005 to 1. The maximum explained variance in remission by PRS for SCZ was 4.62% at  $P_T = .2$  ( $p = .0018$ ). The dashed line represents the nominal significance threshold ( $p = .05$ ) for the association test of PRS-SCZ with remission (covariates: age, sex, and 3 principal components). HDRS, Hamilton Depression Rating Scale; PRS-SCZ, polygenic risk score for schizophrenia;  $P_T$ ,  $p$ -value thresholds; SNP, single nucleotide polymorphism.

Although directly comparing the results of different studies is challenging, our findings hint that the direction of the relationship between PRS-SCZ and response to ECT is opposite to the direction of the relationship between PRS-SCZ and pharmacological treatment for MDEs (12,32). This could suggest that the mechanism of action of ECT is (partly) different from that of currently used antidepressant medications. Alternatively, ECT may be applied relatively more often to severely ill people in whom associations between outcomes of treatment and PRS-SCZ are different from those observed in less severely ill people or those earlier in their course treated with antidepressant medication. Similar observations have been made for associations between PRSs and antipsychotic treatment response in psychotic disorders (33).

Strengths of this study include the sample of patients treated with ECT drawn from cohorts in 3 different European countries for which results were highly consistent. We also believe we applied a range of statistical analyses to reduce the possibility of a type I error. Nonetheless, some limitations should be borne in mind. First, our study population was derived from multiple cohorts with subtle differences in study sample and methodology. For example, some cohorts excluded patients with bipolar disorder. Arguably, this could be considered a strength, because in clinical practice patients undergoing ECT are not homogeneous. Second, although our sample is fairly large for an ECT study, our findings await replication in larger cohorts. Third, in light of the lack of diverse ancestries in our study, inclusion of larger cohorts with diverse

ancestries is paramount. Fourth, because we here only focused on PRS as a biological feature, future studies may integrate PRS with body fluid constituents, electroencephalography, and magnetic resonance imaging to help disentangle the degree to which each of these biological variables is associated with ECT effectiveness.

Given the consistent explained variance across models and validation across countries, we speculate that PRS-SCZ may one day become a variable to help optimize treatment in MDEs. For example, if future studies confirm that low PRS-SCZ scores predict better response to repetitive transcranial magnetic stimulation, this would open the possibility of using PRS-SCZ to stratify patients between repetitive transcranial magnetic stimulation and ECT and thus optimize clinical response in difficult-to-treat MDEs. Yet, before clinical implementation of PRS-SCZ in clinical decision making in MDE may be considered, predictive modeling studies are needed to establish such a role for PRS-SCZ in ECT effectiveness. In addition, clinical trials may investigate whether PRS-SCZ could help optimize personalized treatment in psychiatry, e.g., by offering ECT as a relatively early treatment choice to patients with high polygenic liability for SCZ, which in turn may help mitigate a chronic trajectory of MDEs and curtail disease burden in some patients. Finally, future induced pluripotent stem cell studies may investigate potential overlap in mechanisms underlying SCZ and ECT response, which in turn may help us better understand what makes ECT so effective.

In conclusion, we have unraveled a linear association between PRS-SCZ and ECT effectiveness, hinting at increased



SCZ genetic liability increasing chances of ECT response. Although it is too early to adopt PRSs in ECT clinical decision making, the results also illustrate the power of cross-cohort genetic association analysis in ECT research and strengthen the positioning of PRS-SCZ as relevant to treatment response in psychiatry.

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JLL, AD, and BPFRR were responsible for study conception. BL and DL were responsible for data analysis. DMM, Lvd, AD, EvE, MLO, DR, SNTMS, MPB, JON, IECS, BA, and BPFRR contributed samples. JLL, GK, BPFRR, and MPB contributed genotyping. DL, AD, JLL, BL, and BPFRR were responsible for the first draft of the manuscript. JLL, DL, BL, Lvd, JON, EvE, MLO, DR, SNTMS, PVE, EV, DS, TKB, KMR, BA, GS, GK, SCvB, BTB, MA, EevD, IECS, MS, MPB, SG, DMM, AD, and BPFRR were responsible for critical revision of the final draft.

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