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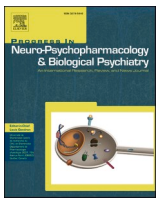

Polygenic predisposition to transdiagnostic symptom dimensions and treatment outcomes across psychiatric disorders

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ABSTRACT

Background: Mood and psychotic disorders, including major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ), show overlapping symptoms that challenge diagnostic boundaries and may inform personalised treatments. We examined the contribution of genetic liability to transdiagnostic symptom dimensions in treatment outcomes across disorders using polygenic scores (PGSs).
Methods: We analysed two MDD cohorts (total $N = 2548$), one BD cohort ($N = 755$), and one SCZ cohort ($N = 449$). Outcomes included treatment resistance, symptomatic remission, and change in functioning defined using cohort-specific data. PGSs for anhedonia, anxiety, sociability, resilience, cognitive and sleep-related traits were computed using SBayesRC. Regressions adjusted for potential confounders were run in each cohort and results

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meta-analysed with random-effects models; heterogeneity was assessed with leave-one-out and influence diagnostics, and meta-regressions. Multiple testing was controlled using a Bonferroni correction adjusted for the effective number of independent tests ($\alpha_{adj} = 0.0034$).

Results: In meta-analyses, no result survived multiple testing correction. The strongest signal was for the Trail Making Test Part B PGS, indexing worse executive function/processing speed, and non-remission (OR = 1.13, $p = 0.012$; $I^2 = 13$ %); modelling diagnosis (mood disorders vs SCZ) reduced heterogeneity to $I^2 = 0$ %, and leave-one-out excluding SCZ reached statistical significance (OR = 1.17, $p = 0.001$). Verbal-numerical reasoning PGS, indexing predisposition to higher fluid intelligence, was nominally associated with improved functioning ($\beta = -0.06$, $p = 0.016$), confirmed in leave-one-out excluding BD ($\beta = -0.07$, $p = 0.0095$).

Conclusion: PGSs for cognitive traits showed trait- and diagnosis-specific associations with treatment outcomes. Cross-diagnostic analyses may identify shared genetic influences, but variability in symptom expression across disorders may introduce heterogeneity and reduce the detectability of such effects.

1. Introduction

Mood and psychotic disorders, such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ), show overlapping symptom dimensions that challenge categorical diagnostic boundaries and may complicate treatment, leading to high subjective burden for patients and their families (Estradé et al., 2023; Fusar-Poli et al., 2023). Key transdiagnostic features, including anhedonia, cognitive impairment, social functioning, anxiety, and sleep disturbances, are linked to symptoms severity, functional impairment, and poorer treatment outcomes (Guineau et al., 2023; Millan et al., 2012; Kist et al., 2023; Dolsen et al., 2014). This recognition of symptom overlap has driven a shift towards dimensional approaches, which conceptualise psychopathology along continuous dimensions rather than discrete categories, aiming to improve prognosis and guide personalised interventions (Dalgleish et al., 2020).

Polygenic scores (PGSs), which aggregate small-effect genetic variants from genome-wide association studies (GWASs), capture an individual's genetic predisposition to complex traits, and may be potential biomarkers for treatment response (Wray et al., 2021; Fanelli et al., 2022a; Oliva et al., 2023). In this context, PGSs indexing transdiagnostic symptom dimensions may be of particular interest when studying treatment outcomes across various psychiatric disorders. Emerging evidence suggests that PGSs may assist in predicting treatment resistance (TR), which affects 30 % of patients with MDD (McIntyre et al., 2023) and 20–50 % of patients with SCZ (Nucifora et al., 2019). For instance, a higher SCZ-PGS in MDD has been linked to a poorer response to antidepressants (Fanelli et al., 2021; Fanelli et al., 2022a), while cognitive function and sleep patterns PGSs have been associated with treatment-resistant depression (TRD) (Xu et al., 2024). However, the association between PGSs for transdiagnostic symptom dimensions and treatment outcomes across psychiatric disorders remains largely unexamined.

Among these dimensions, anhedonia, defined as the diminished ability to experience pleasure, has been consistently linked to poor outcomes. In MDD, higher levels of anhedonia predict poorer response to pharmacotherapy (Luca et al., 2024); in BD, anhedonia is often unresponsive to mood stabilizers and antidepressants (Wilkowska et al., 2024); and in SCZ, it is considered a negative symptom associated with poorer functional outcomes and non-response to antipsychotic treatment (Liang et al., 2022). Similarly, anxiety symptoms have a detrimental effect on treatment outcomes, with higher baseline anxiety predicting symptom persistence and lower remission rates across various psychiatric disorders (Chai et al., 2024). Cognitive symptoms are other important transdiagnostic factors modulating treatment response. For instance, impaired cognitive flexibility, assessed by the Trail Making Test Part B (TMT—B), is associated with executive dysfunction and poorer clinical outcomes (Sánchez-Cubillo et al., 2009; Grant and Chamberlain, 2023). Sleep disturbances have also been extensively investigated as predictors of greater symptom severity, higher relapse rates, and poorer treatment response across psychiatric disorders (Dolsen et al., 2014). Finally, sociability and resilience have a more general importance, extending beyond psychiatric disorders and being linked to both psychological and physical wellbeing measures (Regan et al., 2022; McGowan et al., 2018).

Given the clinical relevance of these transdiagnostic dimensions, their corresponding PGSs may represent potential biomarkers for treatment outcomes across psychiatric disorders. Examining the PGSs for these traits across cohorts with different psychiatric diagnoses may represent an innovative strategy, which, to the best of our knowledge, has not been implemented in previous studies. This approach may contribute to move beyond traditional categorial diagnoses, towards a dimensional understanding of the genetic factors involved in treatment outcomes.

In the present study, we leveraged data from four large cohorts of patients with MDD, BD, and SCZ to examine the association between PGSs for symptom dimensions/traits with transdiagnostic clinical relevance and treatment outcomes, including functioning. Results were then meta-analysed to provide cross-diagnostic evidence.

2. Methods

2.1. Transdiagnostic symptom dimensions and related GWASs

We selected discovery phenotypes *a priori* based on transdiagnostic clinical relevance, construct validity with standardised administration, availability of large, high-quality GWASs, and single-nucleotide polymorphism (SNP)-based heritability (h^2_{SNP}) $\geq$0.05. The traits and corresponding GWASs used to calculate PGSs are presented in Table 1, including information on data availability. Cognitive domain mapping followed established taxonomies (processing speed, set-shifting/executive control, working memory, fluid intelligence) (Fanelli et al., 2022b; Sánchez-Cubillo et al., 2009). For Symbol Digit Substitution test (SDST) we used GWAS summary statistics referred to the UK Biobank (UKB) score "matches made correctly" (Data-Field 23324), which is widely used in genetic/neuroscience studies and captures accuracy-weighted processing speed better than "matches attempted" (Data-Field 23323); UKB cognitive tests have acceptable reliability and validity (Fanelli et al., 2022b; Fawns-Ritchie and Deary, 2020). For TMT we prioritised GWAS data referred to Part B ("alternating number–letter sequencing for trail #2", Data-Field 20157) over Part A because TMT-B incorporates set-shifting/executive control and shows higher h^2_{SNP} than Part A (~0.12 vs ~0.05), increasing expected PGS informativeness (Watanabe et al., 2019). Additional UKB-derived cognitive phenotypes with robust GWAS (e.g., verbal-numerical reasoning [VNR] for fluid intelligence; numeric memory for working memory) and affective/behavioural traits of transdiagnostic relevance were also included (Table 1). This strategy maximised construct relevance and power for downstream transdiagnostic association testing.

2.2. Target samples

Data for Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE), Sequenced Treatment Alternatives to Relieve Depression (STAR*D), and Systematic Treatment Enhancement Program for Bipolar

Disorder (STEP-BD) studies were accessed through the NIMH Repository & Genomics Resource (https://www.nimhgenetics.org). Data for the European Group for the Study of Resistant Depression (GSRD) were obtained under data-use agreements with the original investigators.

2.2.1. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

CATIE was a multicentre, double-blind trial that compared the effectiveness of perphenazine with several second-generation antipsychotics. In phase 1, participants were randomly assigned to one of these medications. In phase 2, patients who discontinued their initial treatment due to ineffectiveness were reassigned to clozapine or a different second-generation antipsychotic not previously prescribed, while those who discontinued due to side effects were randomly assigned to either ziprasidone or another second-generation antipsychotic. Phase 3 involved clinicians assisting patients in selecting an open-label treatment based on their experiences from the earlier phases. A total of 738 patients were genotyped using the Affymetrix 500K and Perlegen's custom 164K chip. Further details are available in Stroup et al. (2003).

2.2.2. European Group for the Study of Resistant Depression (GSRD)

The GSRD is a multicentre study involving 1410 patients with MDD (DSM-IV-TR criteria, assessed by the Mini International Neuropsychiatric Interview [MINI]). Individuals were excluded if they received a diagnosis of another primary psychiatric disorder within six months prior to enrolment. The severity of symptoms was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) at inclusion in the study, while the severity at the beginning of the current depressive episode was determined retrospectively by reviewing medical records and patients' histories. Inclusion required a MADRS score >22 at episode onset. Participants underwent genotyping using the Infinium PsychArray-24 BeadChip. Further details on the study were previously reported (Kautzky et al., 2019).

2.2.3. Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

STAR*D evaluated the effectiveness and tolerability of antidepressants across four sequential treatment phases in patients with MDD of at least moderate severity. Participants were excluded in case of other primary psychiatric diagnoses. Initially, all participants received citalopram for 12 weeks (Phase 1). In Phases 2-3-4, patients with insufficient improvement in each phase were eligible for randomisation to different switch or augment options (Rush et al., 2004). Symptom severity was monitored biweekly using the Quick Inventory of Depressive Symptomatology Clinician-rated scale (QIDS-C16). A total of 1948 participants were genotyped using the Affymetrix GeneChip Human Mapping 500 K Array Set or the Affymetrix Genome-Wide Human SNP Array 5.0. A comprehensive study description was previously published (Rush et al., 2004).

2.2.4. Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

STEP-BD was a comprehensive prospective clinical trial designed to enhance understanding of the management and long-term outcomes of BD (Sachs et al., 2003). Participants were required to meet DSM-IV criteria for BD type I, type II, cyclothymia, BD not otherwise specified, or schizoaffective disorder. Treatment was administered according to evidence-based medicine principles in a real-world clinical setting, with follow-up visits scheduled based on clinical needs. Participants were genotyped using the Affymetrix GeneChip Human 500 K Mapping Array Set. Further details are published elsewhere (Sachs et al., 2003).

2.3. Treatment outcomes and cross-cohort harmonisation

2.3.1. Remission

In CATIE, remission was determined by a Positive and Negative Syndrome Scale (PANSS) score <60 and ≤3 on items P1, P2, P3, G5, G9, N1, N4, and N6 (Opler et al., 2007; van Os et al., 2006) within 12 weeks. In STAR*D, remission was defined as a QIDS-C16 score ≤5 at Level 1 exit after 12 weeks of citalopram under measurement-based care (Trivedi et al., 2006). In GSRD and STEP-BD, remission was defined as MADRS ≤10 (Zimmerman et al., 2004). In STEP-BD, we considered only patients who were at least moderately depressed (MADRS ≥19) at baseline, month 6, or 9, and evaluated remission after 3 months of treatment. STAR*D and STEP-BD used prospective ascertainment at 12 weeks, whereas GSRD used retrospective ascertainment after ≥4 weeks at adequate antidepressant dose in a naturalistic setting enriched for difficult-to-treat depression (Kautzky et al., 2019). These thresholds were chosen according to existing standards in the field (Doraiswamy et al., 2010; Trivedi et al., 2006; Zimmerman et al., 2004; Opler et al., 2007; van Os et al., 2006).

2.3.2. Treatment resistance

In CATIE, TRS was determined by clozapine prescription, or alternatively, as lack of remission to ≥2 antipsychotics trials (considering phase 1A, 1B, and 2); indeed not all patients are eligible for clozapine and the drug is highly underutilised due to potential side effects (Remington et al., 2016). In GSRD, TRD was determined by non-response (MADRS score >22 and a score decrease <50 % compared to the episode onset) to ≥2 antidepressant treatments of adequate dose and duration (≥4 weeks), while response to the current treatment was considered as the comparator group, in line with previous studies (Kautzky et al., 2019). For comparability, in STAR*D, TRD was defined as lack of response (QIDS-C16 improvement <50 %) to ≥2

Table 1
GWAS summary statistics used to estimate the polygenic scores (PGSs) for the traits of interest.

Trait	First author	Year	PMID	Sample size	h^2_{SNP}	Access/Repository
Anhedonia	Ward	2019	31797917	375,275	0.056	Available from corresponding author upon request
Anxiety/tension	Hill	2019	30867560	270,059	0.057	NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/summary-statistics), Study accession: GCST007710
Chronotype - morningness	Jones	2019	30696823	449,734	0.137	Sleep Disorder Knowledge Portal (https://sleep.hugeamp.org/datasets.html), excluding 23andMe subset
Insomnia	Lane	2019	30804566	453,379	0.167	Sleep Disorder Knowledge Portal (https://sleep.hugeamp.org/datasets.html)
Numeric memory - max digits remembered correctly	Watanabe	2019	31427789	89,799	0.119	GWAS Atlas (https://atlas.ctglab.nl/traitDB)
Resilience	Stein	2019	31081985	11,492	0.162	Available from corresponding author upon request
Sleep duration - overall	Dashti	2019	30846698	446,118	0.098	GWAS Atlas (https://atlas.ctglab.nl/traitDB)
Sociability	Bralten	2021	34054130	342,461	0.060	DANS Data Station Life Sciences (https://lifesciences.datastations.nl)
Symbol digit substitution test (SDST) - correct matches	Watanabe	2019	31427789	95,669	0.111	GWAS Atlas (https://atlas.ctglab.nl/traitDB)
Trail making test part B (TMT—B) - duration to complete alphanumeric path	Watanabe	2019	31427789	84,259	0.122	GWAS Atlas (https://atlas.ctglab.nl/traitDB)
Verbal-numerical reasoning - correct answers	Davies	2018	29844566	168,033	0.207	GWAS Atlas (https://atlas.ctglab.nl/traitDB)

Abbreviations: PGS, polygenic score; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; h^2_{SNP}, SNP-based heritability; PMID, PubMed identifier; NHGRI–EBI, National Human Genome Research Institute–European Bioinformatics Institute.

antidepressants during the first two prospective treatments of the study, with responders considered as the comparator group. In STEP-BD, TR was defined using the Clinical Monitoring Form (CMF) as persistent depressive, (hypo)manic, or rapid cycling symptoms with a Clinical Global Impression (CGI) score >2 during ≥2 different therapeutic trials, including antipsychotics, mood stabilizers, antidepressants, and/or their combinations; patients with CGI ≤2 and classified as recovered or recovering during at least one treatment were considered as non-TR. Across diagnoses, comparability of the TR outcome was established by failure of ≥2 adequate therapeutic trials, consistent with the most used criteria, with also clozapine treatment for TRS, in line with the prescription indication of this drug and previous studies (Howes et al., 2022; Remington et al., 2016).

2.3.3. Change in functioning after treatment

The percentage change in functioning was calculated from baseline to follow-up using cohort-specific measures of functional impairment. In CATIE, functioning was assessed with the Quality-of-Life Scale (QOLS); scores were reversed so that higher values denoted worse functioning, and percentage change was computed between baseline and visit 6 (mean = 173 days, SD = 11), selected for its low variability in timing and higher data availability. In STEP-BD, functioning was measured using the Life-Range of Impaired Functioning Tool (LIFE-RIFT), with higher scores reflecting greater impairment; total scores included items on work, social functioning, and hobbies, excluding the "Satisfaction" item to focus on functional impairment rather than quality of life; the percentage change was calculated between baseline and the 3-month follow-up. Only patients with CGI >2 were included to ensure comparable symptom severity at baseline. In STAR*D, functioning was evaluated using the Work and Social Adjustment Scale (WSAS) and the Work Productivity and Activity Impairment scale (WPAI), both of which capture functional impairment across occupational and social domains, with higher scores indicating greater impairment; percentage change was computed between baseline and the Level 1 exit, using the mean of percentage change in WSAS and WPAI when both were available; if only one measure was available, that measure was used. Harmonisation across cohorts was achieved by (i) computing within-person percentage change (unitless), (ii) aligning directionality so higher values always reflected worse functioning, and (iii) using comparable follow-up windows. In GSRD, there was no measure of functioning at baseline and after treatment.

2.4. Statistical analysis

2.4.1. Polygenic scores computation

We estimated PGSs using SBayesRC, which incorporates functional annotations to distinguish between probably causal and non-causal SNPs in high linkage disequilibrium (LD), thus improving predictive accuracy (Zheng et al., 2024). Preliminary pre-processing of GWAS summary statistics was performed using the *sumstats.py* tool (https://github.com/precimed/python_convert). Quality control of summary statistics retained biallelic SNPs with valid rsIDs (dbSNP) and, where available, INFO >0.6 (Pain et al., 2021). Exclusion criteria included minor allele frequency (MAF) <0.01 (Lloyd-Jones et al., 2019; Márquez-Luna et al., 2021), ambiguous or palindromic SNPs (Vilhjálmsson et al., 2015; B. K. Bulik-Sullivan et al., 2015a), and SNPs in long-range LD regions defined in European populations (Anderson et al., 2010; Price et al., 2008).

After variants' weight estimation with SBayesRC, PGSs were calculated in each target sample using PLINK 2.0. Genotypes had previously undergone quality control and imputation. Variants were pruned for missingness ≥5 % and MAF <1 %, while participants were excluded in case of genotyping rate <97 %, sex discrepancies, abnormal heterozygosity, relatedness (identity by descent (IBD) >0.1875; Anderson et al. (2010)) or if they were population outliers according to Eigensoft analysis of LD-pruned genetic data (Patterson et al., 2006; Price et al., 2006). Imputation was performed using the Haplotype Reference Consortium (HRC) r1.1 as reference panel. Variants with poor imputation quality (R^2 <0.30) were excluded (Li et al., 2010).

2.4.2. Association modelling and meta-analysis

We employed linear and logistic regression models to evaluate the associations between each PGS, standardised within each cohort (z-scored), and the three outcomes of interest. Models were adjusted for age, sex, baseline symptom severity (for non-remission), relevant population principal components, recruitment sites, and genotyping array. Baseline severity was included as a covariate only for non-remission because remission thresholds are severity-dependent; for TR, severity is partly embedded in the operational definitions (risking over-adjustment), and for functioning change it is intrinsically captured by baseline scores. Variance explained was assessed using R^2 for the continuous outcome and Nagelkerke's R^2 for binary outcomes, comparing the full (including the PGS) against null (covariates only) model. For change in functioning, outlier values (0.22 % of observations) were excluded if exceeding Q1 − 4 × IQR or Q3 + 4 × IQR and laying ≥2 SD beyond the nearest retained observation in the same distribution tail.

The primary estimand was the mean cross-diagnostic association between each PGS and outcome across cohorts. Random-effects meta-analyses with Paule–Mandel variance estimation were used to model heterogeneity arising from instruments, ascertainment windows, and clinical context (Paule and Mandel, 1982). Between-study heterogeneity was quantified with Cochran's Q and Higgins & Thompson's I^2. Pre-specified leave-one-out analyses (LOOs) were performed for each meta-analysis to assess result stability, and influence diagnostics flagged studies with disproportionate impact, defined as standardised residuals $|r_{student}| > 2$, or Cook's distance >4/k, where k is the number of studies. Meta-regressions tested potential moderators, including diagnosis (mood disorders vs SCZ) and cohort-level/outcome characteristics (remission rate, proportion TR, interquartile range [IQR] of functioning change scores, mean age, sex, follow-up duration); these were conducted only if any trigger was met: (i) I^2 ≥30 % or Q-test $p \leq 0.10$; (ii) nominal evidence of association in the main or any LOO meta-analysis ($p < 0.05$); or (iii) directionally discordant cohort effects suggesting confounding. Meta-regression findings were reported in the main text if they (i) reduced I^2 by ≥20 %, or (ii) resolved residual heterogeneity (I^2 =0 %), or (iii) yielded QM $p \leq 0.10$.

To account for correlation among the GWASs used to derive PGSs, we estimated pairwise genetic correlations (r_g) using LD Score Regression (LDSC v1.0.1) applied to munged summary statistics harmonised to HapMap3 SNPs and LD reference data from the 1000 Genomes European panel

(Bulik-Sullivan et al., 2015b). The eigenvalue-based method of Li and Ji (Li and Ji, 2005) was applied to the LDSC-derived genetic correlation matrix to estimate the effective number of independent PGS predictors ($M_{eff,PGS}$). Regarding the outcomes, published evidence supports moderate correlations between treatment response, symptomatic remission, and functional improvement in mood disorders and schizophrenia (Lam et al., 2014; Mosolov et al., 2012; Sheehan et al., 2011). Based on this, a 3 × 3 outcome correlation matrix with $r = 0.50$ was constructed, and the Li and Ji method was used to estimate the effective number of independent outcomes ($M_{eff,out}$). The total effective number of independent tests was $M_{eff,tot} = M_{eff,PGS} \times M_{eff,out}$, and the significance threshold was defined as a Bonferroni correction for $M_{eff,tot}$ ($\alpha_{adj} = 0.05/M_{eff,tot}$).

All analyses were conducted using R version 4.5.0 (2025-04-11) (R Foundation for Statistical Computing, Vienna, Austria, https://cran.r-project.org/) and the *metafor* package (v4.8–0) (https://cran.r-project.org/web/packages/metafor).

3. Results

3.1. Socio-demographic characteristics of the sample

After quality control, 3351, 2872, and 1821 patients were included in the PGS analyses for remission, TR and percentage change in functioning, respectively (non-remission: $N = 2348$ [70 %]; TR: $N = 1303$ [45 %]). Cohort-level descriptives, including treatments, illness-course indicators, and outcome assessment/prevalences are summarised side-by-side for cross-cohort comparability in **Supplementary Tables S1-S2**.

3.2. Correlations among base GWAS traits and outcomes

Pairwise LDSC genetic correlations between the 11 base GWAS traits are shown in **Supplementary Table S3**. Several traits were moderately to strongly correlated, notably SDST with TMT–B ($r_g = -0.80$, $p < 1 \times 10^{-4}$), VNR with numeric memory ($r_g = 0.64$, $p < 1 \times 10^{-4}$), sociability inversely with anhedonia ($r_g = -0.66$, $p < 1 \times 10^{-4}$), and sleep duration inversely with insomnia ($r_g = -0.51$, $p < 1 \times 10^{-4}$). Eigen-decomposition yielded $M_{eff,PGS} = 7.34$; with $M_{eff,out} = 2$, $M_{eff,tot} = 14.69$. The resulting Bonferroni-corrected two-sided statistical significance threshold was $\alpha_{adj} = 0.05/14.69 = 0.0034$.

3.3. Associations between PGSs and remission

At the cohort level, the SDST PGS was associated with higher remission odds in STAR*D (OR = 0.797, $p = 1.41 \times 10^{-4}$) and STEP-BD (OR = 0.642, $p = 0.0016$), but not in the other samples (**Supplementary Table S4**). No associations were statistically significant in the primary meta-analyses (**Supplementary Table S5**). The TMT-B PGS showed a nominal association with non-remission (OR = 1.13, 95 % CI = 1.03–1.25, $p = 0.012$, $I^2 = 13$ %; Fig. 1A, Table 2), with consistent direction in mood disorders cohorts but not in SCZ. A meta-regression of diagnosis eliminated residual heterogeneity ($I^2 = 0$ %; QM $p = 0.116$), and the pre-specified LOO excluding CATIE became statistically significant (OR = 1.17, 95 % CI = 1.06–1.29, $p = 0.001$, $I^2 = 0$ %; Fig. 1B), indicating a mood-disorder-specific signal (**Supplementary Tables S6-S7**). Across cohorts, the variance explained by the TMT-B PGS was ≤1.37 % (Nagelkerke's PGS-R^2), while for other PGSs cohort-level PGS-R^2 spanned 0–4.30 % (median 0.08 %; **Supplementary Table S4**). Influence diagnostics for TMT-B identified no outliers (all $|r_{student}| < 2$), and sub-threshold Cook's (Cook's ≤0.37; **Supplementary Table S8**). For other PGS within this outcome, isolated residual outliers (e.g., sociability in STAR*D; numeric memory in CATIE) did not alter the results (**Supplementary Table S8** and **Figs. S1-S3**). A nominal LOO association for sociability-PGS after excluding STAR*D ($p = 0.042$; $I^2 = 0$ %) is reported in **Supplementary Table S6**.

3.4. Associations between PGSs and treatment resistance

In single-cohort analyses (**Supplementary Table S9**), higher sociability PGS was associated with lower odds of TR in STEP-BD (OR = 0.82, 95 % CI = 0.71–0.95, $p = 0.007$), whereas anhedonia (OR = 1.18, 95 % CI = 1.02–1.37, $p = 0.027$) and chronotype PGSs (morningness; OR = 1.19, 95 % CI = 1.03–1.37, $p = 0.021$) were associated with higher odds. In CATIE, insomnia PGS was associated with greater odds of TR (OR = 1.46, 95 % CI = 1.11–1.92, $p = 0.006$). In the meta-analysis, no association reached statistical significance, although TMT-B PGS showed directionally consistent effects across cohorts (**Supplementary Tables S9-S10**). Heterogeneity was substantial for anhedonia, chronotype, insomnia, and sociability PGSs (I^2 ≥50 %), and moderate for SDST and VNR PGS (I^2 ~39–46 %). Meta-regressions indicated that diagnosis moderated insomnia and VNR, TR prevalence and age moderated anhedonia, and age also moderated SDST (all QM p ≤0.074, $I^2 = 0$ %); LOO analyses yielded nominal associations for SDST after excluding GSRD ($p = 0.013$, $I^2 = 0$ %), TMT-B after excluding STAR*D ($p = 0.046$, $I^2 = 0$ %), and anhedonia after excluding GSRD ($p = 0.041$, $I^2 = 0$ %) (meta-regressions/LOO in **Supplementary Tables S11-S12**). Influence diagnostics identified cohort-specific signals: sociability in STEP-BD ($|r_{student}| = 2.29$), anhedonia and SDST in GSRD ($|r_{student}| = 2.23$ and 2.11), insomnia in CATIE ($|r_{student}| = 2.10$); Cook's distance exceeded 4/k for numeric memory and resilience in STAR*D (1.21 and 1.19) (**Supplementary Table S13** and **Figs. S4-S8**). Apart from the LOO findings above, removing these cohorts did not change the results. Across cohorts, Nagelkerke's PGS-R^2 for TR ranged from 0 to 4.10 % (median 0.16 %; **Supplementary Table S9**).

3.5. Associations between PGSs and change in functioning

At cohort level (**Supplementary Table S14**), in STAR*D higher SDST PGS was associated with improved functioning ($\beta = -0.080$, $p = 0.013$) and higher anhedonia PGS with worse functioning ($\beta = 0.078$, $p = 0.013$); in STEP-BD, higher sociability PGS associated with worse functioning ($\beta = 0.121$, $p = 0.017$). In the meta-analysis, no association

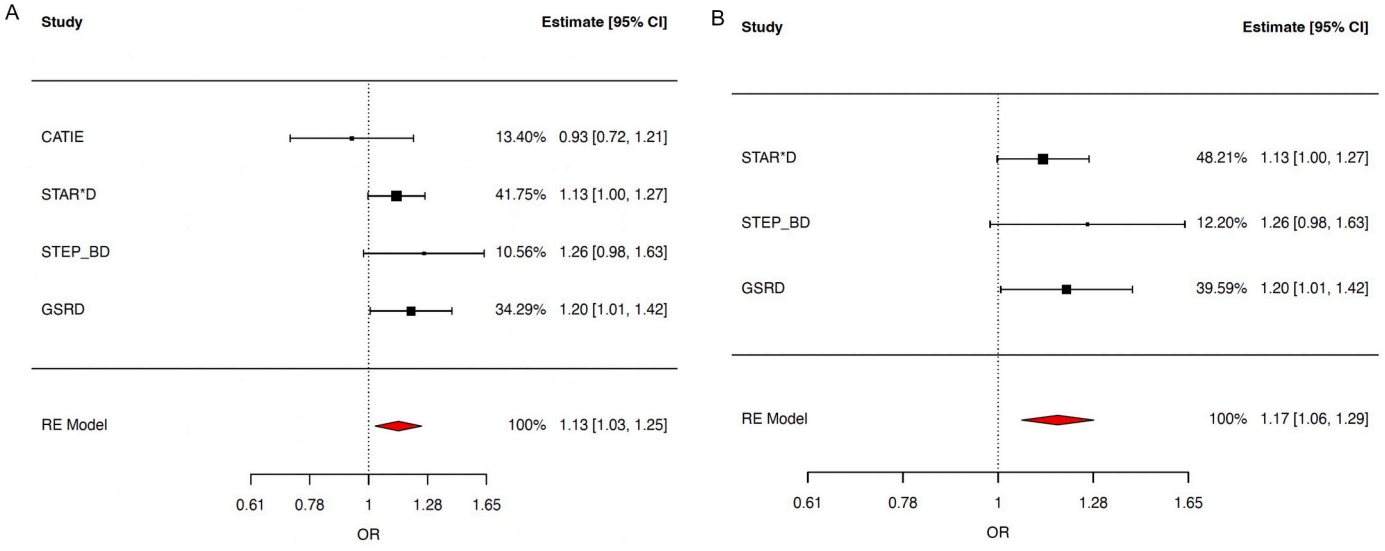

Fig. 1. Forest plots for the association between Trail Making Test Part B (TMT-B) polygenic score (PGS) and remission status, coded as 1 = non-remission and 0 = remission. (A) Main meta-analysis including all cohorts. (B) Leave-one-out sensitivity analysis excluding CATIE.

Table 2
Description of top results in the primary meta-analyses (uncorrected $p < 0.05$) and corresponding findings in the leave-one-out sensitivity analyses (LOO). Odds ratio (OR) and 95 % confidence interval (CI) were reported for binary outcomes and β (SE) for continuous ones. Incremental PGS-Nagelkerke's R^2 (for binary outcomes) or -R^2 range (for the continuous outcome) indicates the smallest and highest value found in the analysed samples.

PGS	Phenotype, analysis	OR (95 % CI) or β (SE)	*p* value	Heterogeneity	PGS- Nagelkerke's R^2 or R^2 range
Trail Making Test Part B	Non-remission, meta-analysis	1.13 (1.03–1.25)	0.012	$I^2 = 13$ %; Q test $p = 0.35$	0.0006 (CATIE) - 0.014 (STEP-BD)
	Non-remission, LOO excluding CATIE	1.17 (1.06–1.29)	0.0012**	$I^2 = 0$ %; Q test $p = 0.67$	0.0032 (STAR*D) - 0.014 (STEP-BD)
	Non-remission, LOO excluding STEP-BD	1.12 (0.99–1.26)	0.06	$I^2 = 30$ %; Q test $p = 0.29$	0.0006 (CATIE) - 0.0056 (GSRD)
	Non-remission, LOO excluding STAR*D	1.14 (0.95–1.37)	0.15	$I^2 = 43$ %; Q test $p = 0.20$	0.0006 (CATIE) - 0.014 (STEP-BD)
	Non-remission, LOO excluding GSRD	1.10 (0.95–1.28)	0.19	$I^2 = 37$ %; Q test $p = 0.25$	0.0006 (CATIE) - 0.014 (STEP-BD)
Verbal-numerical reasoning	Change in functioning, meta-analysis	−0.057 (0.024)	0.016	$I^2 = 0$ %; Q test $p = 0.48$	1.90×10^{-05} (STEP-BD) - 0.01 (CATIE)
	Change in functioning, LOO excluding CATIE	−0.046 (0.027)	0.083	$I^2 = 0$ %; Q test $p = 0.42$	1.90E-05 (STEP-BD) - 0.0032 (STAR*D)
	Change in functioning, LOO excluding STEP-BD	−0.070 (0.027)	0.0095	$I^2 = 0$ %; Q test $p = 0.51$	0.0032 (STAR*D) - 0.01 (CATIE)
	Change in functioning, LOO excluding STAR*D	−0.054 (0.044)	0.220	$I^2 = 32$ %; Q test $p = 0.22$	1.90×10^{-05} (STEP-BD) - 0.01 (CATIE)

** Statistically significant at $\alpha_{adj} = 0{\cdot}0034$.

reached statistical significance (**Supplementary Table S15**). A nominal association was found between VNR PGS and improved functioning (β = −0.057, $p = 0.016$, $I^2 = 0$ %; Fig. 2A, Table 2); LOO excluding STEP-BD retained nominal significance (β = −0.07, $p = 0.0095$, $I^2 = 0$ %; Fig. 2B, Table 2). Additional nominal associations were observed when excluding STEP-BD: higher anhedonia PGS (β = 0.07, $p = 0.006$, $I^2 = 0$ %) and insomnia PGS (β = 0.05, $p = 0.045$; $I^2 = 0$ %) were associated with worse functioning, whereas higher sociability PGS (β = −0.06, $p = 0.032$, $I^2 = 0$ %) was associated with improved functioning (**Supplementary Table S16**). In the main meta-analyses, heterogeneity was moderate for SDST and TMT-B (I^2 ~30–35 %), and high for anhedonia and sociability (I^2 ~60–82 %); excluding STEP-BD reduced I^2 to 0 % for both traits (**Supplementary Table S14-S16**). For SDST, both mean age and the interquartile range (IQR) of the functioning-change distribution moderated effects (QM p ~0.09; $I^2 = 0$ %) (**Supplementary Table S17**). Influence diagnostics identified STEP-BD as influential for anhedonia and sociability ($|r_{student}| = 2.2$–3.14), with Cook's values <4/k; full influence results are provided in **Supplementary Tables S18** and **Figs. S9-S13**. Across cohorts, PGS-R^2 for functioning was ≤1.42 % (median 0.14 %; **Supplementary Table S14**); for VNR PGS specifically, PGS-R^2 was ≤0.97 %.

4. Discussion

This is, to our knowledge, the first meta-analysis investigating the association between PGSs for multiple transdiagnostic symptom dimensions and treatment outcomes across MDD, BD, and SCZ (N up to 3351). We used a cross-diagnostic design to assess whether genetic liability to these dimensions exerts measurable effects across disorders, while accommodating between-cohort variability with random-effects models. No association survived multiple testing correction in the primary meta-analyses, suggesting that, despite the hypothesised transdiagnostic relevance of the selected PGSs, their effects may vary across mood and psychotic disorders. We prespecified outcome harmonisation, and systematically evaluated heterogeneity with LOO, influence diagnostics, and meta-regressions on diagnosis and cohort features. Together, these steps quantified and adjusted for clinically between-study differences and support the interpretability of cross-cohort synthesis.

The most interesting finding concerned the TMT−B PGS, indexing genetic predisposition towards worse executive function (specifically, worse set-shifting/cognitive flexibility) and processing speed. This PGS was significantly associated with non-remission ($p = 0.001$) when considering only samples with mood disorders, as for prespecified LOO. A meta-regression evaluating the moderator mood disorders vs SCZ

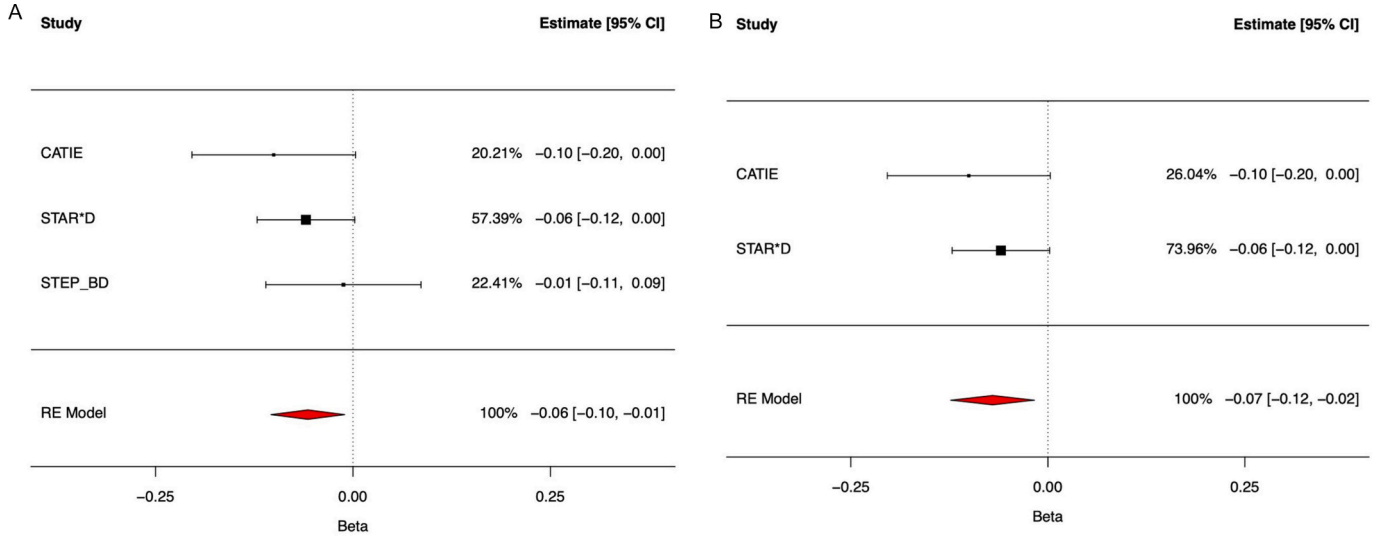

Fig. 2. Forest plots for the association between verbal-numerical reasoning (VNR) polygenic score (PGS) and change in functioning: (A) results of the main meta-analysis including all cohorts and (B) results of the leave-one-out sensitivity analysis excluding STEP-BD. Negative β's = improvement in functioning.

absorbed residual heterogeneity ($I^2 = 0$ %) but, as expected with k = 4, was likely underpowered to detect moderator significance (QM p = 0.116). Influence diagnostics identified no outlying residuals, and sub-threshold Cook's distances, indicating that the mood-disorder–specific signal reflects diagnosis-linked effect modification rather than study incompatibility or single-cohort distortion. This pattern aligns with evidence that deficits in executive functioning predict poor treatment response and functioning in MDD and BD (Dawson et al., 2017; Rybakowski et al., 2009; Drakopoulos et al., 2020; Knight and Baune, 2018). Interestingly, the TMT was demonstrated to be one of the four most sensitive tasks to cognitive impairment in BD in a meta-analysis of 126 studies (Cotrena et al., 2020). Although deficits in cognitive flexibility and executive function are also a core, early feature of SCZ (Freedman and Brown, 2011), different pathogenesis and trajectories of these cognitive deficits in SCZ vs mood disorders may explain our results.

The VNR PGS, reflecting genetic predisposition to higher fluid intelligence, showed a nominal association with improved functioning, strengthened after excluding the BD cohort (STEP-BD). Within-cohort dispersion in percentage change in functioning, quantified by IQRs (**Supplementary Table S1**), was largest in STAR*D. For anhedonia and sociability PGSs, influence diagnostics identified STEP-BD as the influential study, and modelling cohort IQR as a moderator removed residual heterogeneity for SDST ($I^2 = 0$ %; **Supplementary Table S17**). Together, these findings indicate that dispersion contributes to the LOO results. One possible interpretation is that variability in functional outcomes (Reinares et al., 2013), cognitive trajectories, state-dependent fluctuations, and affective instability in BD may modulate the relationship between PGSs and functioning, limiting detection of consistent genetic effects across diagnoses (Millett and Burdick, 2021).

No Bonferroni-significant or nominally significant findings were identified in the meta-analysis of TR. However, heterogeneity across samples was identified for some PGSs. For instance, the PGS for sociability was associated with lower odds of TR in STEP-BD (OR = 0.82, 95 % CI 0.71–0.95), whereas estimates in other cohorts overlapped with the null, consistent with diagnosis-specific effects on treatment outcomes. Prior work links social withdrawal to lower remission across disorders (Oliva et al., 2022). However, the latter study was focused on measures of social functioning, while the phenotype used to create the PGS we analysed was calculated as a composite score including both social isolation and feelings of loneliness (Bralten et al., 2021), making it difficult to discriminate between these two components. In any case, we underline that deficits in social functioning are considered a key and quite stable component of SCZ, typically linked to deficits in social cognition and mentalisation (Green et al., 2015; Fusar-Poli et al., 2022a), with a pathogenesis that has been suggested to be different compared to mood disorders (Kupferberg et al., 2016). Patients with mood disorders have clearly higher social impairment during the acute disease phases, particularly during mania, and impairments are related to mood-congruent bias in processing emotions, anhedonia during depression, and sensitivity to social rejection (Kupferberg et al., 2016). Interestingly, the latter may be more typical of BD compared to MDD (Ehnvall et al., 2014), and social dysfunction may be more prominent in BD vs MDD (Chang et al., 2024). These findings highlight that genetic predisposition to behavioural traits may not exert uniform effects across psychiatric diagnoses. In this regard, anhedonia is a particularly relevant trait. Despite its well-established association with poor treatment response in MDD, BD, and SCZ (Luca et al., 2024; Whitton and Pizzagalli, 2022), the PGS for anhedonia showed no consistent association with outcomes in our analyses. This may be partly explained by the relatively low h^2_{SNP} of the discovery GWAS ($h^2_{SNP} \sim 0.056$), which limits the predictive utility of the resulting score. Moreover, we observed substantial heterogeneity across cohorts ($I^2 > 50$ %) for remission/TR outcomes, likely depending on different sampling characteristics (i.e., TR prevalence across cohorts; QM p = 0.03) or differences in clinical presentation, which may have attenuated the detection of a consistent signal.

While the inclusion of different diagnoses represents an innovative approach, heterogeneity across cohorts, including study design and outcome definitions/distributions may have limited their comparability and the power of the study. For example, the proportion of remission was different between the two MDD samples, as GSRD was enriched in severe and difficult-to-treat cases recruited in tertiary health care centres. We also acknowledge that we selected PGSs of traits with evidence of transdiagnostic relevance on treatment outcomes. Despite their relevance, their effect may not be homogeneous across diagnoses, and PGSs for other phenotypes may be relevant and worth of investigation in future studies. In addition, our analyses were limited to the effect of common genetic variants, and we did not consider other sources of variability, such as non-genetic factors (e.g., environment, epigenetics) (Fusar-Poli et al., 2022b). Several GWASs used to compute PGSs in this study, particularly for affective/social constructs (e.g., anhedonia, anxiety/tension, sociability), report h^2_{SNP} in the order of ~5–10 % (Table 1). For such traits, out-of-sample R^2 of the corresponding PGS is modest even for the same phenotype in independent cohorts (e.g., anxiety/tension explained ~0.4–0.45 % of variance; (Hill et al., 2020). This reflects an inherent limitation of current GWAS architectures, rather than a lack of biological relevance, and likely constrains the detectability of associations with treatment outcomes. By contrast, cognitive traits show higher h^2_{SNP} in discovery GWASs (VNR = 20.7 %, TMT−B = 12.2 %, numeric memory = 11.9 %; Table 1) and higher predictive performance, with PGS explaining up to 4.3 % of general cognitive variance in large independent cohorts (Davies et al., 2018), setting a more favourable empirical ceiling for downstream analyses. The incremental R^2 values we observed align with these constraints and mirror the broader PGS literature, with PGS predictive utility linked to current GWAS sample sizes and PGS methodology, despite clear statistical associations (Lewis and Vassos, 2020). We therefore prioritised association testing as the primary inferential aim rather than prediction. Our incremental PGS-R^2 estimates were small as expected: for non-remission the median was 0.08 % (range 0–4.30 %), for TR 0.16 % (range 0–4.10 %), and for functioning 0.14 % (range 0–1.42 %) (**Supplementary Tables S4, S9, S14**). In our data, the LDSC matrix showed coherent genetic correlations within cognitive traits, consistent with prior evidence for a genetic "g" (De La Fuente et al., 2020), and across social/affective domains, supporting construct validity of the selected base traits. Importantly, we accounted for correlation among discovery GWASs and among outcomes when setting the multiple testing threshold, preserving rigorous type I error control while increasing statistical power relative to assuming full independence (Li and Ji, 2005).

In conclusion, this meta-analysis across major psychiatric disorders did not identify statistically significant associations between PGSs for symptom dimensions and treatment outcomes. A statistically significant association between the PGS for TMT—B, indexing worse executive function/processing speed, and non-remission was found only in mood disorders. This may indicate that symptom dimensions considered transdiagnostic may still have disorder-specific clinical presentations, trajectories, and underlying pathogenetic mechanisms. While dimensional approaches offer a useful framework for investigating psychiatric pathophysiology beyond categorical diagnostic boundaries, their clinical implementation remains challenging. Future studies may benefit from prioritising symptom dimensions with more uniform clinical expression and longitudinal trajectory across diagnoses, to improve the consistency and interpretive value of cross-diagnostic genetic findings.

Declaration of Generative AI and AI- assisted technologies in the writing process

None.

CRediT authorship contribution statement

Paolo Abondio: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Giuseppe Fanelli:** Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Valentina Baldini:** Writing – original draft. **Maria Giulia Bacalini:** Writing – review & editing, Funding acquisition. **Siegfried Kasper:** Writing – review & editing. **Joseph Zohar:** Writing – review & editing. **Daniel Souery:** Writing – review & editing. **Stuart Montgomery:** Writing – review & editing. **Diego Albani:** Writing – review & editing. **Gianluigi Forloni:** Writing – review & editing. **Panagiotis Ferentinos:** Writing – review & editing. **Dan Rujescu:** Writing – review & editing. **Julien Mendlewicz:** Writing – review & editing. **Alessandro Serretti:** Writing – review & editing, Resources, Funding acquisition. **Alessio Maria Monteleone:** Writing – review & editing, Funding acquisition. **Luigi Grassi:** Writing – review & editing, Funding acquisition. **Anna Rita Atti:** Writing – review & editing. **Marco Menchetti:** Writing – review & editing. **Chiara Fabbri:** Writing – review & editing, Visualization, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Diana De Ronchi:** Writing – review & editing, Funding acquisition.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2025.111512.

Data availability

Access to the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), Sequenced Treatment Alternatives to Relieve Depression (STAR*D), Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) data is granted to Principal Investigators after submission of a research proposal to the National Institute of Mental Health (NIMH) via the NIMH Repository & Genomics Resource (NRGR) (https://www.nimhgenetics.org).

References

Anderson, C.A., Pettersson, F.H., Clarke, G.M., Cardon, L.R., Morris, A.P., Zondervan, K. T., 2010. Data quality control in genetic case-control association studies. Nat. Protoc. 5, 1564–1573. https://doi.org/10.1038/nprot.2010.116.

Bralten, J., Mota, N.R., Klemann, C.J.H.M., De Witte, W., Laing, E., Collier, D.A., de Kluiver, H., Bauduin, S.E.E.C., Arango, C., Ayuso-Mateos, J.L., Fabbri, C., Kas, M.J., van der Wee, N., Penninx, B.W.J.H., Serretti, A., Franke, B., Poelmans, G., 2021. Genetic underpinnings of sociability in the general population. Neuropsychopharmacology 46, 1627–1634. https://doi.org/10.1038/s41386-021-01044-z.

Bulik-Sullivan, B., Anttila, V., Gusev, A., Day, F.R., Loh, P.-R., Duncan, L., Perry, J.R.B., Patterson, N., Robinson, E.B., Daly, M.J., Price, A.L., Neale, B.M., 2015a. An atlas of genetic correlations across human diseases and traits. Nat. Genet. 47, 1236–1241. https://doi.org/10.1038/ng.3406.

Bulik-Sullivan, B.K., Loh, P.-R., Finucane, H.K., Ripke, S., Yang, J., Patterson, N., Daly, M.J., Price, A.L., Neale, B.M., 2015b. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat. Genet. 47, 291–295. https://doi.org/10.1038/ng.3211.

Chai, K.E.K., Graham-Schmidt, K., Lee, C.M.Y., Rock, D., Coleman, M., Betts, K.S., Robinson, S., McEvoy, P.M., 2024. Predicting anxiety treatment outcome in community mental health services using linked health administrative data. Sci. Rep. 14, 20559. https://doi.org/10.1038/s41598-024-71557-2.

Chang, Y.-H., Yu, C.-L., Huang, C.-C., Wang, T.-Y., Dziobek, I., Lane, H.-Y., 2024. Discrepancy of social cognition between bipolar disorders and major depressive disorders. Brain Behav. 14, e3365. https://doi.org/10.1002/brb3.3365.

Cotrena, C., Damiani Branco, L., Ponsoni, A., Samamé, C., Milman Shansis, F., Paz Fonseca, R., 2020. Executive functions and memory in bipolar disorders I and II: new insights from meta-analytic results. Acta Psychiatr. Scand. 141, 110–130. https://doi.org/10.1111/acps.13121.

Dalgleish, T., Black, M., Johnston, D., Bevan, A., 2020. Transdiagnostic approaches to mental health problems: current status and future directions. J. Consult. Clin. Psychol. 88, 179–195. https://doi.org/10.1037/ccp0000482.

Davies, G., Lam, M., Harris, S.E., Trampush, J.W., Luciano, M., Hill, W.D., Hagenaars, S. P., Ritchie, S.J., Marioni, R.E., Fawns-Ritchie, C., Liewald, D.C.M., Okely, J.A., Ahola-Olli, A.V., Barnes, C.L.K., Bertram, L., Bis, J.C., Burdick, K.E., Christoforou, A., DeRosse, P., Djurovic, S., Espeseth, T., Giakoumaki, S., Giddaluru, S., Gustavson, D. E., Hayward, C., Hofer, E., Ikram, M.A., Karlsson, R., Knowles, E., Lahti, J., Leber, M., Li, S., Mather, K.A., Melle, I., Morris, D., Oldmeadow, C., Palviainen, T., Payton, A., Pazoki, R., Petrovic, K., Reynolds, C.A., Sargurupremraj, M., Scholz, M., Smith, J.A., Smith, A.V., Terzikhan, N., Thalamuthu, A., Trompet, S., van der Lee, S. J., Ware, E.B., Windham, B.G., Wright, M.J., Yang, J., Yu, J., Ames, D., Amin, N., Amouyel, P., Andreassen, O.A., Armstrong, N.J., Assareh, A.A., Attia, J.R., Attix, D., Avramopoulos, D., Bennett, D.A., Böhmer, A.C., Boyle, P.A., Brodaty, H., Campbell, H., Cannon, T.D., Cirulli, E.T., Congdon, E., Conley, E.D., Corley, J., Cox, S.R., Dale, A.M., Dehghan, A., Dick, D., Dickinson, D., Eriksson, J.G., Evangelou, E., Faul, J.D., Ford, I., Freimer, N.A., Gao, H., Giegling, I., Gillespie, N.A., Gordon, S.D., Gottesman, R.F., Griswold, M.E., Gudnason, V., Harris, T.B., Hartmann, A.M., Hatzimanolis, A., Heiss, G., Holliday, E.G., Joshi, P.K., Kähönen, M., Kardia, S.L.R., Karlsson, I., Kleineidam, L., Knopman, D.S., Kochan, N. A., Konte, B., Kwok, J.B., Le Hellard, S., Lee, T., Lehtimäki, T., Li, S.-C., Lill, C.M., Liu, T., Koini, M., London, E., Longstreth, W.T., Lopez, O.L., Loukola, A., Luck, T., Lundervold, A.J., Lundquist, A., Lyytikäinen, L.-P., Martin, N.G., Montgomery, G.W., Murray, A.D., Need, A.C., Noordam, R., Nyberg, L., Ollier, W., Papenberg, G., Pattie, A., Polasek, O., Poldrack, R.A., Psaty, B.M., Reppermund, S., Riedel-Heller, S. G., Rose, R.J., Rotter, J.I., Roussos, P., Rovio, S.P., Saba, Y., Sabb, F.W., Sachdev, P. S., Satizabal, C.L., Schmid, M., Scott, R.J., Scult, M.A., Simino, J., Slagboom, P.E., Smyrnis, N., Soumaré, A., Stefanis, N.C., Stott, D.J., Straub, R.E., Sundet, K., Taylor, A.M., Taylor, K.D., Tzoulaki, I., Tzourio, C., Uitterlinden, A., Vitart, V., Voineskos, A.N., Kaprio, J., Wagner, M., Wagner, H., Weinhold, L., Wen, K.H., Widen, E., Yang, Q., Zhao, W., Adams, H.H.H., Arking, D.E., Bilder, R.M., Bitsios, P.,

Boerwinkle, E., Chiba-Falek, O., Corvin, A., De Jager, P.L., Debette, S., Donohoe, G., Elliott, P., Fitzpatrick, A.L., Gill, M., Glahn, D.C., Hägg, S., Hansell, N.K., Hariri, A.R., Ikram, M.K., Jukema, J.W., Vuoksimaa, E., Keller, M.C., Kremen, W.S., Launer, L., Lindenberger, U., Palotie, A., Pedersen, N.L., Pendleton, N., Porteous, D.J., Räikkönen, K., Raitakari, O.T., Ramirez, A., Reinvang, I., Rudan, I., Rujescu, Dan, Schmidt, R., Schmidt, H., Schofield, P.W., Schofield, P.R., Starr, J.M., Steen, V.M., Trollor, J.N., Turner, S.T., Van Duijn, C.M., Villringer, A., Weinberger, D.R., Weir, D. R., Wilson, J.F., Malhotra, A., McIntosh, A.M., Gale, C.R., Seshadri, S., Mosley, T.H., Bressler, J., Lencz, T., Deary, I.J., 2018. Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. Nat. Commun. 9, 2098. https://doi.org/10.1038/s41467-018-04362-x.

Dawson, E.L., Caveney, A.F., Meyers, K.K., Weisenbach, S.L., Giordani, B., Avery, E.T., Schallmo, M.-P., Bahadori, A., Bieliauskas, L.A., Mordhorst, M., Marcus, S.M., Kerber, K., Zubieta, J.-K., Langenecker, S.A., 2017. Executive functioning at baseline prospectively predicts depression treatment response. Prim. Care Companion CNS Disord. 19. https://doi.org/10.4088/PCC.16m01949.

De La Fuente, J., Davies, G., Grotzinger, A.D., Tucker-Drob, E.M., Deary, I.J., 2020. A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data. Nat. Hum. Behav. 5, 49–58. https://doi.org/10.1038/s41562-020-00936-2.

Dolsen, E.A., Asarnow, L.D., Harvey, A.G., 2014. Insomnia as a transdiagnostic process in psychiatric disorders. Curr. Psychiatry Rep. 16, 471. https://doi.org/10.1007/s11920-014-0471-y.

Doraiswamy, P.M., Bernstein, I.H., Rush, A.J., Kyutoku, Y., Carmody, T.J., Macleod, L., Venkatraman, S., Burks, M., Stegman, D., Witte, B., Trivedi, M.H., 2010. Diagnostic utility of the quick inventory of depressive symptomatology (QIDS-C16 and QIDS-SR16) in the elderly. Acta Psychiatr. Scand. 122, 226–234. https://doi.org/10.1111/j.1600-0447.2009.01531.x.

Drakopoulos, J., Sparding, T., Clements, C., Pålsson, E., Landén, M., 2020. Executive functioning but not IQ or illness severity predicts occupational status in bipolar disorder. Int. J. Bipolar Disord. 8, 7. https://doi.org/10.1186/s40345-019-0168-6.

Ehnvall, A., Mitchell, P.B., Hadzi-Pavlovic, D., Parker, G., Frankland, A., Loo, C., Breakspear, M., Wright, A., Roberts, G., Lau, P., Perich, T., 2014. Rejection sensitivity and pain in bipolar versus unipolar depression. Bipolar Disord. 16, 190–198. https://doi.org/10.1111/bdi.12147.

Estradé, A., Onwumere, J., Venables, J., Gilardi, L., Cabrera, A., Rico, J., Hoque, A., Otaiku, J., Hunter, N., Kéri, P., Kpodo, L., Sunkel, C., Bao, J., Shiers, D., Bonoldi, I., Kuipers, E., Fusar-Poli, P., 2023. The lived experiences of family members and Carers of people with psychosis: a bottom-up review co-written by experts by experience and academics. Psychopathology 56, 371–382. https://doi.org/10.1159/000528513.

Fanelli, G., Domschke, K., Minelli, A., Gennarelli, M., Martini, P., Bortolomasi, M., Maron, E., Squassina, A., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., De Ronchi, D., Baune, B.T., European College of Neuropsychopharmacology (ECNP) Pharmacogenomics & Transcriptomics Thematic Working Group, Serretti, A., Fabbri, C., 2021. A meta-analysis of polygenic risk scores for mood disorders, neuroticism, and schizophrenia in antidepressant response. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 55, 86–95. https://doi.org/10.1016/j.euroneuro.2021.11.005.

Fanelli, G., Domschke, K., Minelli, A., Gennarelli, M., Martini, P., Bortolomasi, M., Maron, E., Squassina, A., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., De Ronchi, D., Baune, B.T., Serretti, A., Fabbri, C., 2022a. A meta-analysis of polygenic risk scores for mood disorders, neuroticism, and schizophrenia in antidepressant response. Eur. Neuropsychopharmacol. 55, 86–95. https://doi.org/10.1016/j.euroneuro.2021.11.005.

Fanelli, G., Mota, N.R., Salas-Salvadó, J., Bulló, M., Fernandez-Aranda, F., Camacho-Barcia, L., Testa, G., Jiménez-Murcia, S., Bertaina-Anglade, V., Franke, B., Poelmans, G., Van Gils, V., Jansen, W.J., Vos, S.J.B., Wimberley, T., Dalsgaard, S., Barta, C., Serretti, A., Fabbri, C., Bralten, J., 2022b. The link between cognition and somatic conditions related to insulin resistance in the UK biobank study cohort: a systematic review. Neurosci. Biobehav. Rev. 143, 104927. https://doi.org/10.1016/j.neubiorev.2022.104927.

Fawns-Ritchie, C., Deary, I.J., 2020. Reliability and validity of the UK biobank cognitive tests. PLoS One 15, e0231627. https://doi.org/10.1371/journal.pone.0231627.

Freedman, D., Brown, A.S., 2011. The developmental course of executive functioning in schizophrenia. Int. J. Dev. Neurosci. Off. J. Int. Soc. Dev. Neurosci. 29, 237–243. https://doi.org/10.1016/j.ijdevneu.2010.11.003.

Fusar-Poli, L., Pries, L.-K., Van Os, J., Erzin, G., Delespaul, P., Kenis, G., Luykx, J.J., Lin, B.D., Richards, A.L., Akdede, B., Binbay, T., Altınyazar, V., Yalınçetin, B., Gümüş-Akay, G., Cihan, B., Soygür, H., Ulaş, H., Cankurtaran, E.Ş., Kaymak, S.U., Mihaljevic, M.M., Andric-Petrovic, S., Mirjanic, T., Bernardo, M., Mezquida, G., Amoretti, S., Bobes, J., Saiz, P.A., García-Portilla, M.P., Sanjuan, J., Aguilar, E.J., Santos, J.L., Jiménez-López, E., Arrojo, M., Carracedo, A., López, G., González-Peñas, J., Parellada, M., Maric, N.P., Atbaşoğlu, C., Üçok, A., Alptekin, K., Saka, M. C., Aguglia, E., Arango, C., O'Donovan, M., Rutten, B.P.F., Guloksuz, S., 2022a. Examining facial emotion recognition as an intermediate phenotype for psychosis: findings from the EUGEI study. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 113, 110440. https://doi.org/10.1016/j.pnpbp.2021.110440.

Fusar-Poli, L., Rutten, B.P.F., Van Os, J., Aguglia, E., Guloksuz, S., 2022b. Polygenic risk scores for predicting outcomes and treatment response in psychiatry: hope or hype? Int. Rev. Psychiatry 34, 663–675. https://doi.org/10.1080/09540261.2022.2101352.

Fusar-Poli, P., Estradé, A., Stanghellini, G., Esposito, C.M., Rosfort, R., Mancini, M., Norman, P., Cullen, J., Adesina, M., Jimenez, G.B., Da Cunha Lewin, C., Drah, E.A., Julien, M., Lamba, M., Mutura, E.M., Prawira, B., Sugianto, A., Teressa, J., White, L. A., Damiani, S., Vasconcelos, C., Bonoldi, I., Politi, P., Vieta, E., Radden, J., Fuchs, T., Ratcliffe, M., Maj, M., 2023. The lived experience of depression: a bottom-up review co-written by experts by experience and academics. World Psychiatry 22, 352–365. https://doi.org/10.1002/wps.21111.

Grant, J.E., Chamberlain, S.R., 2023. Impaired cognitive flexibility across psychiatric disorders. CNS Spectr. 28, 688–692. https://doi.org/10.1017/S1092852923002237.

Green, M.F., Horan, W.P., Lee, J., 2015. Social cognition in schizophrenia. Nat. Rev. Neurosci. 16, 620–631. https://doi.org/10.1038/nrn4005.

Guineau, M.G., Ikani, N., Rinck, M., Collard, R.M., van Eijndhoven, P., Tendolkar, I., Schene, A.H., Becker, E.S., Vrijsen, J.N., 2023. Anhedonia as a transdiagnostic symptom across psychological disorders: a network approach. Psychol. Med. 53, 3908–3919. https://doi.org/10.1017/S0033291722000575.

Hill, W.D., Weiss, A., Liewald, D.C., Davies, G., Porteous, D.J., Hayward, C., McIntosh, A. M., Gale, C.R., Deary, I.J., 2020. Genetic contributions to two special factors of neuroticism are associated with affluence, higher intelligence, better health, and longer life. Mol. Psychiatry 25, 3034–3052. https://doi.org/10.1038/s41380-019-0387-3.

Howes, O.D., Thase, M.E., Pillinger, T., 2022. Treatment resistance in psychiatry: state of the art and new directions. Mol. Psychiatry 27, 58–72. https://doi.org/10.1038/s41380-021-01200-3.

Kautzky, A., Dold, M., Bartova, L., Spies, M., Kranz, G.S., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., Fabbri, C., Serretti, A., Lanzenberger, R., Dikeos, D., Rujescu, D., Kasper, S., 2019. Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. Acta Psychiatr. Scand. 139, 78–88. https://doi.org/10.1111/acps.12959.

Kist, J.D., Vrijsen, J.N., Mulders, P.C.R., van Eijndhoven, P.F.P., Tendolkar, I., Collard, R. M., 2023. Transdiagnostic psychiatry: symptom profiles and their direct and indirect relationship with well-being. J. Psychiatr. Res. 161, 218–227. https://doi.org/10.1016/j.jpsychires.2023.03.003.

Knight, M.J., Baune, B.T., 2018. Executive function and spatial cognition mediate psychosocial dysfunction in major depressive disorder. Front. Psychol. 9, 539. https://doi.org/10.3389/fpsyt.2018.00539.

Kupferberg, A., Bicks, L., Hasler, G., 2016. Social functioning in major depressive disorder. Neurosci. Biobehav. Rev. 69, 313–332. https://doi.org/10.1016/j.neubiorev.2016.07.002.

Lam, R.W., Endicott, J., Hsu, M.-A., Fayyad, R., Guico-Pabia, C., Boucher, M., 2014. Predictors of functional improvement in employed adults with major depressive disorder treated with desvenlafaxine: Int. Clin. Psychopharmacol. 29, 239–251. https://doi.org/10.1097/YIC.0000000000000031.

Lewis, C.M., Vassos, E., 2020. Polygenic risk scores: from research tools to clinical instruments. Genome Med. 12, 44. https://doi.org/10.1186/s13073-020-00742-5.

Li, J., Ji, L., 2005. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. Heredity 95, 221–227. https://doi.org/10.1038/sj.hdy.6800717.

Li, Y., Willer, C.J., Ding, J., Scheet, P., Abecasis, G.R., 2010. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. Genet. Epidemiol. 34, 816–834. https://doi.org/10.1002/gepi.20533.

Liang, S., Wu, Y., Hanxiaoran, L., Greenshaw, A.J., Li, T., 2022. Anhedonia in depression and schizophrenia: brain reward and aversion circuits. Neuropsychiatr. Dis. Treat. 18, 1385–1396. https://doi.org/10.2147/NDT.S367839.

Lloyd-Jones, L.R., Zeng, J., Sidorenko, J., Yengo, L., Moser, G., Kemper, K.E., Wang, H., Zheng, Z., Magi, R., Esko, T., Metspalu, A., Wray, N.R., Goddard, M.E., Yang, J., Visscher, P.M., 2019. Improved polygenic prediction by Bayesian multiple regression on summary statistics. Nat. Commun. 10, 5086. https://doi.org/10.1038/s41467-019-12653-0.

Luca, A., Luca, M., Kasper, S., Pecorino, B., Zohar, J., Souery, D., Montgomery, S., Ferentinos, P., Rujescu, D., Messina, A., Zanardi, R., Ferri, R., Tripodi, M., Baune, B. T., Fanelli, G., Fabbri, C., Mendlewicz, J., Serretti, A., 2024. Anhedonia is associated with a specific depression profile and poor antidepressant response. Int. J. Neuropsychopharmacol. 27, pyae055. https://doi.org/10.1093/ijnp/pyae055.

Márquez-Luna, C., Gazal, S., Loh, P.-R., Kim, S.S., Furlotte, N., Auton, A., 23andMe Research Team, Price, A.L., 2021. Incorporating functional priors improves polygenic prediction accuracy in UK biobank and 23andMe data sets. Nat. Commun. 12, 6052. https://doi.org/10.1038/s41467-021-25171-9.

McGowan, J.A., Brown, J., Lampe, F.C., Lipman, M., Smith, C., Rodger, A., 2018. Resilience and physical and mental well-being in adults with and without HIV. AIDS Behav. 22, 1688–1698. https://doi.org/10.1007/s10461-017-1980-6.

McIntyre, R.S., Alsuwaidan, M., Baune, B.T., Berk, M., Demyttenaere, K., Goldberg, J.F., Gorwood, P., Ho, R., Kasper, S., Kennedy, S.H., Ly-Uson, J., Mansur, R.B., McAllister-Williams, R.H., Murrough, J.W., Nemeroff, C.B., Nierenberg, A.A., Rosenblat, J.D., Sanacora, G., Schatzberg, A.F., Shelton, R., Stahl, S.M., Trivedi, M.H., Vieta, E., Vinberg, M., Williams, N., Young, A.H., Maj, M., 2023. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry Off. J. World Psychiatr. Assoc. WPA 22, 394–412. https://doi.org/10.1002/wps.21120.

Millan, M.J., Agid, Y., Brüne, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., DeRubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Gorwood, P., Jay, T.M., Joëls, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat. Rev. Drug Discov. 11, 141–168. https://doi.org/10.1038/nrd3628.

Millett, C.E., Burdick, K.E., 2021. Defining heterogeneous cognitive trajectories in bipolar disorder: a perspective. Harv. Rev. Psychiatry 29, 298–302. https://doi.org/10.1097/HRP.0000000000000297.

Mosolov, S.N., Potapov, A.V., Ushakov, U.V., 2012. Remission in schizophrenia: results of cross-sectional with 6-month follow-up period and 1-year observational therapeutic studies in an outpatient population. Ann. General Psychiatry 11, 1. https://doi.org/10.1186/1744-859X-11-1.

Nucifora, F.C., Woznica, E., Lee, B.J., Cascella, N., Sawa, A., 2019. Treatment resistant schizophrenia: clinical, biological, and therapeutic perspectives. Neurobiol. Dis. 131, 104257. https://doi.org/10.1016/j.nbd.2018.08.016.

Oliva, V., Fanelli, G., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., Kas, M.J., de Ronchi, D., Fabbri, C., Serretti, A., 2022. Social withdrawal as a trans-diagnostic predictor of short-term remission: a meta-analysis of five clinical cohorts. Int. Clin. Psychopharmacol. 37, 38–45. https://doi.org/10.1097/YIC.0000000000000384.

Oliva, V., Fanelli, G., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., De Ronchi, D., Fabbri, C., Serretti, A., 2023. Melancholic features and typical neurovegetative symptoms of major depressive disorder show specific polygenic patterns. J. Affect. Disord. 320, 534–543. https://doi.org/10.1016/j.jad.2022.10.003.

Opler, M.G.A., Yang, L.H., Caleo, S., Alberti, P., 2007. Statistical validation of the criteria for symptom remission in schizophrenia: preliminary findings. BMC Psychiatry 7, 35. https://doi.org/10.1186/1471-244X-7-35.

Pain, O., Glanville, K.P., Hagenaars, S.P., Selzam, S., Fürtjes, A.E., Gaspar, H.A., Coleman, J.R.I., Rimfeld, K., Breen, G., Plomin, R., Folkersen, L., Lewis, C.M., 2021. Evaluation of polygenic prediction methodology within a reference-standardized framework. PLoS Genet. 17, e1009021. https://doi.org/10.1371/journal.pgen.1009021.

Patterson, N., Price, A.L., Reich, D., 2006. Population structure and eigenanalysis. PLoS Genet. 2, e190. https://doi.org/10.1371/journal.pgen.0020190.

Paule, R.C., Mandel, J., 1982. Consensus values and weighting factors. J. Res. Natl. Bur. Stand. 1977 (87), 377–385. https://doi.org/10.6028/jres.087.022.

Price, A.L., Patterson, N.J., Plenge, R.M., Weinblatt, M.E., Shadick, N.A., Reich, D., 2006. Principal components analysis corrects for stratification in genome-wide association studies. Nat. Genet. 38, 904–909. https://doi.org/10.1038/ng1847.

Price, A.L., Weale, M.E., Patterson, N., Myers, S.R., Need, A.C., Shianna, K.V., Ge, D., Rotter, J.I., Torres, E., Taylor, K.D., Goldstein, D.B., Reich, D., 2008. Long-range LD can confound genome scans in admixed populations. Am. J. Hum. Genet. 83, 132–135. https://doi.org/10.1016/j.ajhg.2008.06.005 author reply 135-139.

Regan, A., Radošić, N., Lyubomirsky, S., 2022. Experimental effects of social behavior on well-being. Trends Cogn. Sci. 26, 987–998. https://doi.org/10.1016/j.tics.2022.08.006.

Reinares, M., Papachristou, E., Harvey, P., Mar Bonnín, C., Sánchez-Moreno, J., Torrent, C., Ayuso-Mateos, J.L., Ploubidis, G.B., Vieta, E., Frangou, S., 2013. Towards a clinical staging for bipolar disorder: defining patient subtypes based on functional outcome. J. Affect. Disord. 144, 65–71. https://doi.org/10.1016/j.jad.2012.06.005.

Remington, G., Lee, J., Agid, O., Takeuchi, H., Foussias, G., Hahn, M., Fervaha, G., Burton, L., Powell, V., 2016. Clozapine's critical role in treatment resistant schizophrenia: ensuring both safety and use. Expert Opin. Drug Saf. 15, 1193–1203. https://doi.org/10.1080/14740338.2016.1191468.

Rush, A.J., Fava, M., Wisniewski, S.R., Lavori, P.W., Trivedi, M.H., Sackeim, H.A., Thase, M.E., Nierenberg, A.A., Quitkin, F.M., Kashner, T.M., Kupfer, D.J., Rosenbaum, J.F., Alpert, J., Stewart, J.W., McGrath, P.J., Biggs, M.M., Shores-Wilson, K., Lebowitz, B.D., Ritz, L., Niederehe, G., STAR*D Investigators Group, 2004. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control. Clin. Trials 25, 119–142.

Rybakowski, J.K., Permoda-Osip, A., Borkowska, A., 2009. Response to prophylactic lithium in bipolar disorder may be associated with a preservation of executive cognitive functions. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 19, 791–795. https://doi.org/10.1016/j.euroneuro.2009.06.002.

Sachs, G.S., Thase, M.E., Otto, M.W., Bauer, M., Miklowitz, D., Wisniewski, S.R., Lavori, P., Lebowitz, B., Rudorfer, M., Frank, E., Nierenberg, A.A., Fava, M., Bowden, C., Ketter, T., Marangell, L., Calabrese, J., Kupfer, D., Rosenbaum, J.F., 2003. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol. Psychiatry 53, 1028–1042.

Sánchez-Cubillo, I., Periáñez, J.A., Adrover-Roig, D., Rodríguez-Sánchez, J.M., Ríos-Lago, M., Tirapu, J., Barceló, F., 2009. Construct validity of the trail making test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J. Int. Neuropsychol. Soc. JINS 15, 438–450. https://doi.org/10.1017/S1355617709090626.

Sheehan, D.V., Chokka, P.R., Granger, R.E., Walton, R.J., Raskin, J., Sagman, D., 2011. Clinical and functional outcomes in patients with major depressive disorder and painful physical symptoms switched to treatment with duloxetine. Hum. Psychopharmacol. Clin. Exp. 26, 242–251. https://doi.org/10.1002/hup.1199.

Stroup, T.S., McEvoy, J.P., Swartz, M.S., Byerly, M.J., Glick, I.D., Canive, J.M., McGee, M.F., Simpson, G.M., Stevens, M.C., Lieberman, J.A., 2003. The National Institute of Mental Health clinical antipsychotic trials of intervention effectiveness (CATIE) project: schizophrenia trial design and protocol development. Schizophr. Bull. 29, 15–31.

Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., STAR*D Study Team, 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am. J. Psychiatry 163, 28–40. https://doi.org/10.1176/appi.ajp.163.1.28.

van Os, J., Burns, T., Cavallaro, R., Leucht, S., Peuskens, J., Helldin, L., Bernardo, M., Arango, C., Fleischhacker, W., Lachaux, B., Kane, J.M., 2006. Standardized remission criteria in schizophrenia. Acta Psychiatr. Scand. 113, 91–95. https://doi.org/10.1111/j.1600-0447.2005.00659.x.

Vilhjálmsson, B.J., Yang, J., Finucane, H.K., Gusev, A., Lindström, S., Ripke, S., Genovese, G., Loh, P.-R., Bhatia, G., Do, R., Hayeck, T., Won, H.-H., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Discovery, Biology, and Risk of Inherited Variants in Breast Cancer (DRIVE) study, Kathiresan, S., Pato, M., Pato, C., Tamimi, R., Stahl, E., Zaitlen, N., Pasaniuc, B., Belbin, G., Kenny, E.E., Schierup, M.H., De Jager, P., Patsopoulos, N.A., McCarroll, S., Daly, M., Purcell, S., Chasman, D., Neale, B., Goddard, M., Visscher, P.M., Kraft, P., Patterson, N., Price, A.L., 2015. Modeling linkage disequilibrium increases accuracy of polygenic risk scores. Am. J. Hum. Genet. 97, 576–592. https://doi.org/10.1016/j.ajhg.2015.09.001.

Watanabe, K., Stringer, S., Frei, O., Umićević Mirkov, M., de Leeuw, C., Polderman, T.J.C., van der Sluis, S., Andreassen, O.A., Neale, B.M., Posthuma, D., 2019. A global overview of pleiotropy and genetic architecture in complex traits. Nat. Genet. 51, 1339–1348. https://doi.org/10.1038/s41588-019-0481-0.

Whitton, A.E., Pizzagalli, D.A., 2022. Anhedonia in depression and bipolar disorder. Curr. Top. Behav. Neurosci. 58, 111–127. https://doi.org/10.1007/7854_2022_323.

Wilkowska, A., Wiglusz, M.S., Arciszewska-Leszczuk, A., Gałuszko-Węgielnik, M., Cubała, W.J., 2024. Anhedonia in bipolar depression treated with ketamine. Bipolar Disord. 26, 356–363. https://doi.org/10.1111/bdi.13409.

Wray, N.R., Lin, T., Austin, J., McGrath, J.J., Hickie, I.B., Murray, G.K., Visscher, P.M., 2021. From basic science to clinical application of polygenic risk scores: a primer. JAMA Psychiatry 78, 101–109. https://doi.org/10.1001/jamapsychiatry.2020.3049.

Xu, B., Forthman, K.L., Kuplicki, R., Ahern, J., Loughnan, R., Naber, F., Thompson, W.K., Nemeroff, C.B., Paulus, M.P., Fan, C.C., 2024. Genetic correlates of treatment-resistant depression: insights from polygenic scores across cognitive, temperamental, and sleep traits in the all of US cohort. MedRxiv Prepr. Serv. Health Sci. https://doi.org/10.1101/2024.07.03.24309914, 2024.07.03.24309914.

Zheng, Z., Liu, S., Sidorenko, J., Wang, Y., Lin, T., Yengo, L., Turley, P., Ani, A., Wang, R., Nolte, I.M., Snieder, H., LifeLines Cohort Study, Yang, J., Wray, N.R., Goddard, M.E., Visscher, P.M., Zeng, J., 2024. Leveraging functional genomic annotations and genome coverage to improve polygenic prediction of complex traits within and between ancestries. Nat. Genet. 56, 767–777. https://doi.org/10.1038/s41588-024-01704-y.

Zimmerman, M., Posternak, M.A., Chelminski, I., 2004. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. J. Psychiatr. Res. 38, 577–582. https://doi.org/10.1016/j.jpsychires.2004.03.007.