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Research Articles

Polygenic scores of subcortical brain volumes as possible modulators of treatment response in depression

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ABSTRACT

A significant proportion of patients with major depressive disorder (MDD) do not experience remission after one or more pharmacological treatments. Research has explored brain structural measures, particularly hippocampal volume, as potential predictors of treatment response, as well as genetic factors.

This study investigated the association of polygenic scores (PGSs) for seven subcortical brain volumes (including the hippocampus, nucleus accumbens, amygdala, and caudate nucleus) with treatment non-response and non-remission in MDD.

Patients with MDD were recruited in the context of five clinical studies, including a total of 3637 individuals. PGSs were estimated using a Bayesian framework and continuous shrinkage priors (PRS-CS-auto) after standard

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genotype quality control and imputation. Logistic regressions were performed between PGSs and non-response or non-remission in each sample, adjusting for age, sex, baseline symptom severity, recruitment sites, and population stratification. Results were meta-analysed across samples, using a random-effect model.

No association was significant in the meta-analysis after Bonferroni correction. The top finding was found for the caudate volume PGS and non-remission (OR = 1.09, 95% CI = 1.01–1.19, p = 0.036), with no evidence of heterogeneity. Leave-one-out sensitivity analyses showed that this result was influenced by the two largest samples in the meta-analysis.

This result should be considered as preliminary as it did not reach the Bonferroni-adjusted significance threshold. Future studies with greater statistical power may enhance the predictive performance of PGSs and contribute to the identification of polygenic predictors of treatment outcomes in MDD, contributing to precision psychiatry.

1. Introduction

Major depressive disorder (MDD) is a prevalent psychiatric condition and one of the leading causes of disability worldwide, with a 61.1% increase in the number of disability-adjusted life years (DALYs) over the past two decades (Vos et al., 2020).

Depending on the severity of depression and individual preferences, patients may be prescribed psychotherapeutic or pharmacological treatments, or their combination (Kendrick et al., 2022). The first prescribed medication for depression may fail to produce symptom remission in up to 60% of patients, leading to therapy changes that follow a trial and error approach (e.g., switch to another drug, or augmentation with a different pharmacological agent) (De Carlo et al., 2016; van Westrhenen and Ingelman-Sundberg, 2021). Patients without adequate medication response have higher relapse rates (Rush et al., 2006). Identifying the most suitable treatment for each patient early on, in line with the principles of precision psychiatry (Fusar-Poli et al., 2022; Zanardi et al., 2021), may reduce the burden of the disease and the related costs to society (Serretti, 2022).

Several socio-demographic and clinical factors have been recognised as important predictors of response and remission to psychopharmacological treatment in MDD, such as longer duration of depressive episodes, greater baseline severity, older age, and the presence of anxiety symptoms (Kautzky et al., 2017; Olgiati et al., 2022; Domschke et al., 2010).

Common genetic variants were demonstrated to explain at least 13% of the variability in remission (Pain et al., 2022), therefore polygenic scores (PGSs) represent a promising opportunity for investigating the genetic factors involved in treatment efficacy in MDD (Choi and O'Reilly, 2019). PGSs, alternatively called polygenic risk scores (PRSs), are estimates of an individual's genetic predisposition to a trait or disease based on common genetic polymorphisms across the genome. These scores are calculated according to the individual's genotype profile and relevant data from genome-wide association studies (GWAS) (Craig et al., 2020). PGSs have been employed to understand disease pathogenesis (Fabbri et al., 2020), to identify the genetic overlap between different traits (Oliva et al., 2023; Fanelli et al., 2022a), and are promising potential predictors of treatment outcome (Natarajan et al., 2017). Higher PRSs for MDD, schizophrenia, and attention-deficit hyperactivity disorder were associated with a worse response to medications for depression (Fanelli et al., 2022b; Fabbri et al., 2021a). Interestingly, a low PRS for schizophrenia may decrease the benefits of augmentation with medications commonly employed as first-line treatments for schizophrenia (Fanelli et al., 2021). PGSs for conscientiousness and neuroticism were other factors associated with response, while the PGSs for openness was inversely associated with remission and response (Amare et al., 2018). PGSs for nonpsychiatric phenotypes, including PRSs for coronary artery disease, obesity, and cardioembolic stroke, were also inversely associated with response to treatment (Amare et al., 2019; Marshe et al., 2021).

The prediction of treatment response may be improved by considering PGSs for brain-related traits other than those expressing disease risk. Brain structural measures have been investigated as predictors of response to treatments in MDD. Alterations in the volumes of subcortical brain structures, particularly the hippocampus, have been among the most replicated findings (Perlman et al., 2019). Patients with MDD showed a volumetric reduction of the hippocampus compared to healthy controls (Dusi et al., 2015), and the hippocampal volume may distinguish treatment responders from non-responders (Chi et al., 2015). The integrity of white matter tracts in the cortico-striatal-limbic systems was also useful in predicting response to treatment (Perlman et al., 2019); these tracts connect the orbitofrontal cortex with subcortical structures, such as the nucleus accumbens, amygdala, caudate nucleus, globus pallidus, putamen, and thalamus (Fettes et al., 2017). The importance of subcortical structures in the modulation of response to medications for depression was also highlighted by functional studies showing that the activity of the amygdala may predict response to psychedelic drugs (Kuburi et al., 2022).

Genetic studies in family cohorts and twin studies have revealed varying levels of heritability for the volume of each subcortical structure, ranging from moderate to high. Heritability estimates based on single nucleotide polymorphisms (SNPs) were lower compared to those based on genetic studies in family cohorts and twin studies, as expected. These estimates range from 17% to 47% for the thalamus and from 9% to 33% for the amygdala and brainstem, depending on the specific estimation method used (Rentería et al., 2014; Satizabal et al., 2019; Hibar et al., 2017). However, the possible association between the polygenic component of brain subcortical structures and response to medications in MDD has not been investigated to the best of our knowledge. To contribute to fill this gap, we investigated the relationship between the PGSs for seven subcortical brain structure volumes (i.e., nucleus accumbens, amygdala, caudate nucleus, globus pallidus, putamen, thalamus, and hippocampus) and non-response and non-remission, across five clinical cohorts of patients with MDD. We hypothesised that the PGSs of these traits could be associated with treatment efficacy and could contribute to the future development of models able to aid the early identification of non-responders and non-remitters. This could have clinical implications, e.g., these individuals could benefit from early intensive pharmacological treatments or medications potentiated with non-pharmacological interventions for MDD, rather than following the traditional stepwise trial-and-error approach.

2. Material and methods

2.1. Target samples

2.1.1. Brescia

This sample included 501 subjects with MDD (DSM-IV criteria) who were referred to the "Villa Santa Chiara" Psychiatric Hospital in Verona, Italy. The diagnosis was confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Participants who had other primary neuropsychiatric disorders, including intellectual disabilities, substance/alcohol abuse or dependence, dementias, or comorbid eating disorders, were excluded. The severity of symptoms was evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS). Response was defined as ≥50% improvement in symptom severity during the

current pharmacological treatment. Non-responders were patients who did not respond to at least one pharmacological treatment and were categorised as Stage I-III according to the Thase and Rush staging method (Thase and Rush, 1997). Genome-wide genotyping was conducted using either the Infinium PsychArray-24 BeadChip or the Infinium Multi-Ethnic Genotyping Array (N = 215 and 286, respectively, denominated Brescia sample 1 and Brescia sample 2 in the supplementary materials). Further details are available elsewhere (Minelli et al., 2015).

2.1.2. European Group for the Study of Resistant Depression

A total of 1410 participants were recruited by the European Group for the Study of Resistant Depression (GSRD) as part of a multicentric cross-sectional study. Patients had a diagnosis of MDD (DSM-IV-TR criteria), according to the Mini International Neuropsychiatric Interview (MINI), and they were treated with a medication for depression for ≥4 weeks. The main exclusion criterion was another primary psychiatric disorder in the six months before enrolment. Depression severity was assessed using the MADRS at study entry and at the beginning of current episode (retrospectively, from anamnestic information and medical records). Treatment response was defined as a ≥50% reduction in the MADRS total score compared to the beginning of the current episode, after treatment with a medication for depression for ≥4 weeks. Non-responders were patients who did not respond to one or more pharmacological treatments during the current depressive episode. Remission was determined based on a current MADRS ≤10 after treatment with a medication for depression for ≥4 weeks. Genome-wide genotyping was performed with Infinium PsychArray-24 BeadChip. Additional information on this study is available elsewhere (Fanelli et al., 2021, 2022b; Dold et al., 2022).

2.1.3. Münster

This naturalistic study involved 621 individuals with MDD (DSM-IV criteria), confirmed using the SCID-I (Baune et al., 2010), recruited at the Department of Psychiatry, University of Münster, Germany. Patients with current alcohol/drug dependence or other primary neuropsychiatric disorders were excluded. Treatment response and remission were evaluated after six weeks of treatment, using the 21-item Hamilton Depression Rating Scale ($HAMD_{21}$) (≥50% improvement from baseline and $HAMD_{21} \leq 7$, respectively). Genome-wide genotyping was conducted using the Infinium PsychArray-24 BeadChip.

2.1.4. Sequenced treatment alternatives to relieve depression

The Sequenced treatment alternatives to relieve depression (STAR*D) study evaluated the effectiveness and tolerability of different medications in treating moderate-severe MDD (DSM-IV-TR) in primary care or psychiatric outpatient clinics. Patients with any other primary psychiatric diagnosis were excluded. The study initially involved treatment with citalopram for 12 weeks, and only this phase of the study was considered for the present analyses. Symptom severity was assessed using the Quick Inventory of Depressive Symptomatology Clinician-rated scale ($QIDS\text{-}C_{16}$). Response was defined as a ≥50% decrease in symptom severity after 12 weeks of treatment with citalopram, and remission as $QIDS\text{-}C_{16} \leq 5$ at week 12. A total of 1948 participants were genome-wide genotyped using the Affymetrix GeneChip Human Mapping 500 K Array Set or Affymetrix Genome-Wide Human SNP Array 5.0. Further details of the study are available elsewhere (Howland, 2008).

2.1.5. Tartu

This sample included 83 outpatients with MDD (DSM-IV criteria) recruited at the Psychiatric Clinic of the University Hospital of Tartu, Estonia. The diagnosis was verified using medical records and MINI 5.0.0. Patients with current suicide risk or another primary neuropsychiatric disorder were excluded. Treatment response was defined as a ≥50% decrease in MADRS scores from baseline, while remission as MADRS ≤ 10 at week six. The Illumina 370CNV array was used for genome-wide genotyping. Additional details are available elsewhere (Tammiste et al., 2013).

2.2. Quality control of genotypes in the target datasets

Each of the five target samples underwent quality control (QC) and population principal component analysis (PCA) through the Ricopili pipeline (Lam et al., 2020). SNPs were filtered retaining those with call rate ≥0.95, missing difference between cases-controls ≤0.02, minor allele frequency (MAF) ≥ 0.01, and Hardy-Weinberg equilibrium p-value ≥ $1e^{-6}$. Individuals were retained if they had an autosomal heterozygosity deviation not outside of ±0.2, call rate ≥0.98, and no genetic/phenotypic sex mismatch.

To assess between-subjects relatedness and population stratification, linkage disequilibrium-pruned data ($R2 < 0.2$) were used to identify all pairs of individuals with identity-by-descent proportion >0.2, and one individual from each pair was removed. Population stratification was determined using PCA (Eigenstrat); population outliers were removed according to the mean ± 6 standard deviations of the first 20 principal components (PCs). Only individuals of European ancestry were retained based on self-report/anamnestic information and inspection of PCA plots (Lam et al., 2020).

Genotype imputation was carried out on the Michigan Imputation Server (Das et al., 2016) using Minimac4 and the Haplotype Reference Consortium (HRC) r1.1 2016 (GRCh37/hg19).

Post-imputation QC was performed by filtering out variants having a poor imputation quality score ($R^2 < 0.3$) and MAF < 0.05.

2.3. Statistical analyses

Summary statistics of the largest available GWASs on subcortical brain structure volumes were used as base datasets (Satizabal et al., 2019; Hibar et al., 2017). We computed PGSs using PRS-CS-auto, a Bayesian method that places continuous shrinkage priors on SNP effect sizes and obviates the need to select any *a priori* GWAS P-threshold for SNP inclusion (Ge et al., 2019).

Treatment outcomes were non-response and non-remission, defined in accordance with the standard definitions and scales used in each study (paragraph 2.1 and Table 1); outcomes were used as binary dependent variables in multiple logistic regression models. The independent variables were each PGS (standardised to have mean = 0, SD = 1), age, sex, baseline symptom severity (for non-remission), relevant population principal components, and recruitment sites, as performed in a previous study (Fanelli et al., 2022b). The analyses were conducted using R v4.0.2. The variance in the outcomes explained by each PGS was estimated as the difference between the Nagelkerke's pseudo R^2 of the full models and those including covariates only, in each cohort separately (Oliva et al., 2023).

The results obtained in each sample were meta-analysed using the R metafor package (Viechtbauer, 2010), within a random-effects model, using the restricted maximum-likelihood estimator (Harville, 1977). Analyses of heterogeneity were performed using the Cochran's Q test (Cochran, 1950), and I^2 statistic (0% indicates no heterogeneity, and 25%, 50%, and 75% define the thresholds for low, moderate, and high, respectively) (Higgins et al., 2019). Leave-one-out sensitivity analyses were conducted as a systematic approach to assess the impact of each individual study on the overall results. This was achieved by systematically excluding one study at a time from the analyses, allowing for a thorough exploration of how each study's inclusion or exclusion influences the robustness and stability of the findings (Viechtbauer and Cheung, 2010).

The Bonferroni correction was applied considering the seven base phenotypes analysed ($\alpha = 0.05/7 = 0.007$).

We estimated statistical power using the AVENGEME R package (Palla and Dudbridge, 2015). Assuming a covariance of 50% between the base and target phenotypes, all the analysed PGSs showed adequate

Table 1
Main clinical-demographic characteristics of the target samples included in the meta-analysis. For further information and descriptive statistics see a previously published work (Fanelli et al., 2022).

Target sample	N total	Definition of treatment outcomes	Distribution of the outcome	Time point of outcome evaluation	Age (mean ± SD)	Proportion of males
Brescia	453	Response: ≥50% reduction in symptom severity vs baseline (MADRS scale)	Response/non-response = 72/381	≥4 weeks	Responders: 53.92 ± 13.27 Non-responders: 56.74 ± 13.70	Responders: 0.26 Non-responders: 0.33
GSRD	1149	Response: ≥50% reduction in symptom severity vs baseline (MADRS scale)	Response/non-response = 279/870	≥4 weeks	Responders: 51.57 ± 15.70 Non-responders: 51.93 ± 13.51	Responders: 0.35 Non-responders: 0.33
		Remission: MADRS ≤ 10	Remission/non-remission = 189/960		Remitters: 52.238 ± 15.48 Non-remitters: 51.761 ± 13.79	Remitters: 0.32 Non-remitters: 0.34
Münster	557	Response: ≥50% reduction in symptom severity vs baseline ($HAMD_{21}$ scale)	Response/non-response = 351/206	6 weeks	Responders: 49.63 ± 15.11 Non-responders: 49.68 ± 16.07	Responders: 0.58 Non-responders: 0.57
		Remission: $HAMD_{21} \leq 7$	Remission/non-remission = 249/308		Remitters: 49.01 ± 15.02 Non-remitters: 50.16 ± 15.81	Remitters: 0.57 Non-remitters: 0.58
STAR*D	1400	Response: ≥50% reduction in symptom severity vs baseline ($QIDS\text{-}C_{16}$ scale)	Response/non-response = 795/605	12 weeks	Responders: 42.28 ± 13.48 Non-responders: 43.73 ± 13.46	Responders: 0.39 Non-responders: 0.42
		Remission: $QIDS\text{-}C_{16} \leq 5$	Remission/non-remission = 597/803		Remitters: 42.02 ± 13.85 Non-remitters: 43.56 ± 13.18	Remitters: 0.39 Non-remitters: 0.41
Tartu	78	Response: ≥50% reduction in symptom severity vs baseline (MADRS scale)	Response/non-response = 53/25	6 weeks	Responders: 30.45 ± 12.23 Non-responders: 31.92 ± 10.46	Responders: 0.42 Non-responders: 0.20
		Remission: MADRS ≤ 10	Remission/non-remission = 50/28		Remitters: 29.86 ± 11.99 Non-remitters: 32.82 ± 10.95	Remitters: 0.40 Non-remitters: 0.25

Abbreviations: GSRD, European Group for the Study of Resistant Depression; $HAMD_{21}$, 21-item Hamilton Depression Rating Scale score; MADRS, Montgomery-Asberg Depression Rating Scale score; N, sample size; $QIDS\text{-}C_{16}$, Quick rated scale score; SD, standard deviations; STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

power (≥90%) for both target phenotypes. The power decreased to a range of 24%–48% when the covariance was set to 25%. Details on the power analysis are provided in the Supplementary materials.

3. Results

After QC, a total of 3637 patients with MDD were included in the analyses (Brescia n = 453; GSRD n = 1149; Munster n = 557; STAR*D n = 1400; Tartu n = 78), as reported in a previous publication (Fanelli et al., 2022b). The clinical-demographic characteristics of each sample

Table 2
Results of the meta-analyses.

PGS	Outcome	OR (95% CI)	Beta	SE	p	Qp	I^2	range pseudo-R^2 (%)
Nucleus accumbens	non-response	0.99 (0.92–1.07)	−0.004	0.039	0.911	0.44	0	0.004–2.3
	non-remission	1.03 (0.95–1.12)	0.029	0.042	0.493	0.55	0.01	0.01–2.1
Amygdala	non-response	1.06 (0.98–1.14)	0.055	0.039	0.162	0.51	0	0.001–1.6
	non-remission	1.05 (0.95–1.17)	0.052	0.054	0.34	0.26	26.26	0.001–1.4
Caudate nucleus	non-response	1.01 (0.93–1.11)	0.012	0.045	0.781	0.20	12.06	0.005–2.4
	non-remission	1.09 (1.01–1.19)	0.09	0.043	0.036	0.45	0	0.01–0.6
Hippocampus	non-response	1.02 (0.95–1.11)	0.022	0.04	0.578	0.63	0	0.005–2.2
	non-remission	1.01 (0.92–1.09)	0.005	0.043	0.901	0.85	0	0.009–0.6
Globus pallidus	non-response	1.06 (0.92–1.22)	0.057	0.071	0.427	0.05	55.33	0.01–5.7
	non-remission	1.03 (0.89–1.18)	0.027	0.071	0.705	0.07	52.09	0.1–3.7
Putamen	non-response	0.99 (0.92–1.08)	−0.001	0.042	0.989	0.56	0	0.1–1.6
	non-remission	1.01 (0.92–1.09)	0.003	0.046	0.955	0.46	0.01	9.64e-05 – 1.9
Thalamus	non-response	0.94 (0.86–1.02)	−0.064	0.043	0.138	0.21	9.36	0.005–3.6
	non-remission	0.91 (0.81–1.04)	−0.092	0.066	0.165	0.18	46.45	0.001–1.4

Abbreviations: Beta, regression coefficient; SE, standard error; CI, confidence interval; I^2, Higgin and Thompson's I^2 estimating how much of the total variability in the effect size estimates can be attributed to heterogeneity among the true effects; OR, odds ratio; Qp, p-value for the Cochran's Q-test of (residual) heterogeneity; PGS, polygenic score; range pseudo-R^2, Nagelkerke's R^2s (range of values, as pseudo-R^2 was calculated in each cohort, expressed as percentage).
Bonferroni corrected p-value was 0.007.

are reported in Table 1 and in a previous work (Fanelli et al., 2022b).

In the meta-analyses, no association survived after the Bonferroni correction (Table 2). The top result was found for the association between the caudate nucleus PGS and non-remission (OR = 1.09, 95% CI = 1.01–1.19, p = 0.036, range pseudo-R^2 = 0.01–0.6%), with no evidence of heterogeneity (Table 2); a forest plot is depicted in Fig. 1. Leave-one-out sensitivity analyses conducted for this association identified a significant influence of GSRD and STAR*D samples on the overall result; removing each one of these samples from the meta-analysis showed indeed an impact on the results (p = 0.230 and p = 0.351, respectively). The results of regression analyses in each sample and of the other leave-one-out sensitivity analyses are provided in the Supplementary materials. We briefly mention that all other leave-one-out sensitivity analyses showed p-values >0.05, except for the amygdala PGS when considering both non-response and non-remission after excluding the Münster sample (p = 0.048 and 0.041, respectively), and thalamus PGS and remission when excluding STAR*D (p = 0.009).

4. Discussion

In the present meta-analysis, we investigated whether the PGSs for seven brain subcortical volumes were associated with non-response or non-remission in a total sample of 3637 patients with MDD. No association survived after Bonferroni correction, but our top finding suggests possible genetic sharing between the PGS for caudate volume and non-remission, after adjusting for possible confounders. Previous evidence of associations between hippocampal volume, MDD and response to pharmacological treatment were not corroborated by our study (Dusi et al., 2015; Chi et al., 2015).

The caudate nucleus is important for executive function, which includes the regulation of affective states, hence the interest in this structure in the study of MDD (Gotlib and Joormann, 2010). A previous meta-analysis of neuroimaging studies reported significant volume reductions in the caudate nucleus in patients with depression compared to healthy controls (Bora et al., 2012), which were attributed to decreases in both grey matter volume (Kim et al., 2008) and neuronal density (Khundakar et al., 2011). Greater caudate reduction was associated with more severe depression (Butters et al., 2009). Preliminary evidence from small samples indicated that caudate nuclei do not differ between non-responders and responders to pharmacological treatment, although possible sex effects were suggested (Pillay et al., 1998). However, fronto-striatal atrophy, characterized by a reduction in caudate volume, was observed in patients with treatment-resistant depression when compared to patients with depression in remission (Willner et al., 2013). Additionally, reduced bilateral caudate volume was observed in patients with MDD and elevated anhedonic symptoms (Pizzagalli et al., 2009), which are also associated with treatment non-response (Perlman et al., 2019). The caudate nucleus has a key role in the reward system (Doi et al., 2020), and anhedonia is believed to result from the dysfunction of reward and motivational dopaminergic neural circuits (Satterthwaite et al., 2015). A PET study investigated dopaminergic receptor availability in the striatum, including the caudate nucleus, in individuals with MDD. Patients, particularly non-remitters, demonstrated higher dopaminergic receptor availability compared to healthy controls, suggesting a significant role of dopaminergic dysfunction in response to first-line treatments for depression (Peciña et al., 2017). Although our findings are apparently not in line with some previous evidence from brain imaging studies, a recent work showed a positive genetic correlation between MDD and caudate volume (Werme et al., 2023), therefore genetic factors associated with higher volume of this structure may overlap with both MDD and lack of remission to treatment. Environmental factors interact with genetic variables in determining brain volumes, therefore future studies should also consider the modulating effects of the environment on genetic factors. Taken collectively, these findings suggest the potential relevance of augmentation therapy employing drugs that target the dopaminergic system for MDD (Corponi et al., 2019). However, we underline that our result did not survive multiple-testing correction, and it was influenced by the two largest samples in the meta-analysis (i.e., GSRD and STAR*D), suggesting inadequate statistical power for a robust and stable finding. The contribution of the GSRD sample to this result can also be influenced by the higher prevalence of non-remission than all the other samples included in the analysis.

Despite these findings did not emerge in the main analysis and did not reach the Bonferroni corrected significance threshold, we briefly mention that leave-one-out analyses suggested a possible influence of

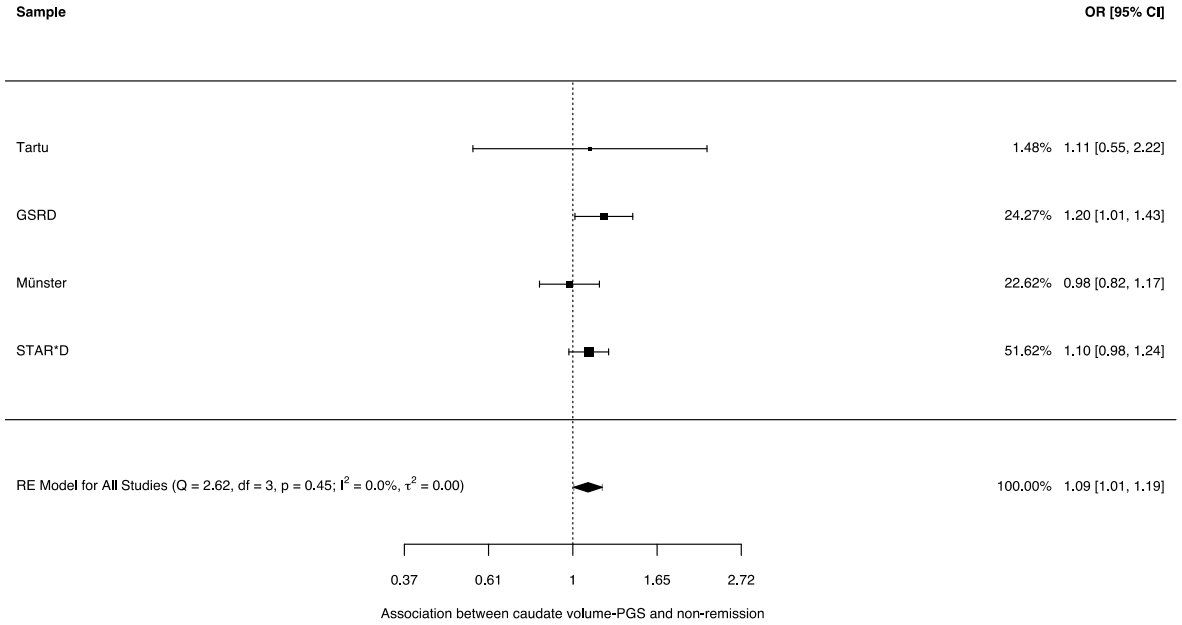

Fig. 1. Forest plot showing the association between the polygenic score for caudate volume and non-remission. *Abbreviations:* GSRD, European Group for the Study of Resistant Depression; CI, confidence interval; df, degree of freedom; I^2, Higgin and Thompson's I^2 estimating how much of the total variability in the effect size estimates can be attributed to heterogeneity among the true effects; OR, odds ratio; p, p-value for the Cochran's Q-test of (residual) heterogeneity; PGS, polygenic score; Q, Cochran's Q-test statistic; RE, random effect model; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; τ^2, between-study variance.

the amygdala PGS on both non-response and non-remission, as well as an association between the thalamus PGS and remission.

The results referred to the amygdala PGS and both non-remission/non-response were found after the exclusion of the Münster sample, which was the only one that used the $HAMD_{21}$ for the assessment of response and remission, a scale that was reported to show low sensibility to change (Jakobsen et al., 2020), with possible implications in terms of comparability with the other cohorts. The amygdala has long been an interesting region in neurobiological studies of depressive-anxious disorders, owing to its relevant role in emotional processing and regulation (Šimić et al., 2021; Kirstein et al., 2023). A previous neuroimaging meta-analysis found no difference in the amygdala volume between people with depression and healthy controls, despite including only patients taking medications may have influenced the result (Hamilton et al., 2008). Neuroimaging functional studies showed instead associations suggesting a link between non-remission and lower connectivity in white matter pathways to the amygdala (Chi et al., 2015) and decreased amygdala function (Rajeev and Jonathan, 2012; Kemp et al., 2008).

The result referred to the thalamus PGS and remission was found after excluding STAR*D, which was the largest sample in this meta-analysis. We therefore suggest that this could have affected substantially the result, in addition to heterogeneity factors linked to STAR*D's characteristics (e.g., participants were largely recruited in primary care settings, had long duration of illness, and significant medical and psychiatric comorbidities (Laje et al., 2009)). Despite the role of the thalamus in the regulation of emotion, memory, and arousal (Taber et al., 2004), there is no consistent evidence supporting structural changes of the thalamus in MDD. A meta-analysis of structural studies, including both treated and untreated patients with MDD, showed smaller grey matter volume in patients vs healthy controls (Du et al., 2012), while a later meta-analysis that focused only on untreated MDD patients revealed a result in the opposite direction (Peng et al., 2016). Therefore, medication use and potentially other variables may have an impact on the grey matter structure of the thalamus and explain these inconsistent findings. Our result suggests that common genetic variation could be one of these variables, even if it is discussed only for completeness and to provide elements for future hypotheses, being found only in the leave-one out sensitivity analyses and not significant after Bonferroni correction.

The strengths and limitations of this study should be considered. We used a standardised genetic QC procedure on the target datasets in line with current standards, we applied a strict correction for multiple testing, we performed a random-effect meta-analysis of our results across the five target samples, and we included socio-demographic and clinical variables as potential confounders in the regression models. Potential limitations included the heterogeneity in the time points used for the assessment of efficacy outcomes (i.e., six weeks, at least four weeks, or 12 weeks, depending on the cohort), which could not be assessed in a sensitivity analysis as each cohort used a different time point. However, it is important to note that all studies considered treatment efficacy in the short term and after a period of treatment of at least four weeks, which is considered adequate to measure medication therapeutic effects (Fabbri et al., 2021b). Other heterogeneity factors across studies were the scales used to measure depressive symptoms and treatment, as all studies had a naturalistic design (i.e., pharmacological treatment was prescribed according to the principles of best medical practice), except STAR*D (all patients were treated with citalopram). Future studies should aim to obtain a better harmonization of efficacy outcomes (Sforzini et al., 2022). Additionally, the disparity in statistical power across different genetic covariance estimates suggests a probable lack of sufficient power, emphasising the necessity of conducting studies with larger sample sizes. This might explain the fact that no association survived after multiple testing correction and the proportion of phenotypic variance explained by PGSs was limited. Finally, environmental factors should be considered in conjunction with genetic variation by studies evaluating brain imaging measures. For example, childhood trauma could act as a mediator between alterations in grey matter volumes (Kang et al., 2023) and treatment outcomes (Oliva et al., 2022; Fares-Otero et al., 2023).

In conclusion, our study found a potential association between the PGS for caudate nucleus volume and non-remission, suggesting shared underlying genetic factors. However, the examined PGSs were not able to predict treatment response or remission after multiple-testing correction. In the future, it will be crucial to include larger sample sizes, as our power analysis suggested a probable insufficient power despite our meta-analytical approach. Collaborative efforts through consortia and networks could enhance the availability of further samples and ideally of harmonised phenotypic definitions, enabling the discovery of genetic associations.

Statement of ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants were included after obtaining their written informed consent. Brescia study protocol was approved by the Ethics Committee of the province of Verona, Italy; the European Group for the Study of Resistant Depression (GSRD) study protocol was approved by the Ethics Committee of the coordinating center at Hôpital Erasme, Cliniques universitaires de Bruxelles (Université Libre de Bruxelles), Belgium, and the local ethical committees of all the other nine participating centres; the Münster study protocol was approved by the ethical board of the University of Münster, Germany; the Tartu study protocol was approved by the Human Studies Ethics Committee of the University of Tartu and State Agency of Medicines; the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study protocol received ethics approval from 14 participating institutional review boards, a National Coordinating Center, a Data Coordinating Center, and the Data Safety and Monitoring Board at the National Institute of Mental Health (NIMH), Bethesda, Maryland, US.

Authors statement contributors

Vincenzo Oliva contributed to the conceptualisation of the study, performed the analyses, interpreted the results, and wrote the first draft of the manuscript. Alfonso Martone contributed to data analyses. Giuseppe Fanelli conceptualised the study, performed quality control and imputation of individual genotype data in each target sample, and reviewed the first draft of the manuscript. Alessandro Serretti and Chiara Fabbri conceptualised the study, helped with the interpretation of the results, reviewed the first draft of the manuscript. Chiara Fabbri created the polygenic scores and supervised the process leading to the final version of the work. The other authors contributed to data collection, data preparation and/or provided comments, suggestions, and revisions, leading to the final version of the paper. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Declaration of interest

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Data availability

Access to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) data is granted to Principal Investigators after approval of a research proposal to the National Institute of Mental Health (NIMH) via the NIMH Repository & Genomics Resource (NRGR) (https://www.nimhgenetics.org).

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nsa.2024.103937.

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