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Polygenic risk for depression is associated with neural stress responses and sex-specific stress adaptation

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Abstract

Psychosocial stress is a central risk factor for the development of major depressive disorder (MDD) and may represent a key pathway through which genetic liability manifests. While polygenic scores for depression (DEP-PGS) have been linked to neural phenotypes, their association with experimentally induced psychosocial stress responses and stress adaptation dynamics remains unclear.

We investigated associations between DEP-PGS and whole-brain neural responses to acute psychosocial stress in 190 healthy young adults (117 female) using the fMRI-compatible Scan*STRESS* paradigm. Whole-brain analyses examined associations between DEP-PGS and stress-related activation, including sex-specific effects. Exploratory analyses further examined associations with current depressive symptom severity. In addition to overall stress reactivity, we tested whether DEP-PGS predicted exposure-time effects, reflecting changes in neural activation across two consecutive stress runs.

Higher DEP-PGS was associated with reduced stress-related activation in striatal regions (ncl. caudatus/ncl. accumbens). A significant sex × DEP-PGS interaction revealed opposite associations in males (positive) and females (negative). Symptom severity was additionally associated with increased stress-related activation in the ncl. caudatus and thalamus. Beyond stress response magnitude, DEP-PGS was associated with altered exposure-time dynamics across a distributed fronto-cingulo-insular network. In the putamen, higher DEP-PGS predicted increasing activation across runs in females but decreasing activation in males.

The present findings suggest that genetic liability for depression is associated not only with altered neural stress reactivity but also with sex-dependent changes in stress adaptation dynamics under repeated psychosocial stress. Polygenic risk for depression may manifest in altered temporal regulation of stress-responsive circuits, potentially representing an early neural vulnerability marker.

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1. Introduction

Major depressive disorder (MDD) is characterized by persistent depressed mood, anhedonia, recurrent thoughts of worthlessness or death, and accompanying somatic and cognitive symptoms[1,2]. It is associated with substantial impairments in quality of life and functional capacity and frequently co-occurs with medical comorbidities[3]. Globally, approximately 5.7% of the adult population is affected by depression, corresponding to several hundred million individuals worldwide, with prevalence rates increasing over recent years[4–6]. Twin and family studies indicate a moderate heritability of MDD, estimated at approximately 30–40%, underscoring the contribution of genetic liability to its etiology[7,8]. Complementing this, genome-wide association studies (GWAS) in very large samples have identified an

increasing number of common genetic variants associated with depression, some of which implicate biological pathways such as inflammatory processes[9,10]. These findings provide the basis for calculating polygenic scores to investigate depression liability.

Beyond genetic influences, exposure to adverse life events and chronic psychosocial stress represents one of the most robust risk factors for the onset and persistence of depressive symptoms and MDD[11,12]. Based on this assumption, stress reactivity has been proposed as a central mechanism linking genetic vulnerability to the development and manifestation of depressive pathology, for instance by influencing stress-regulatory systems such as the hypothalamic-pituitary-adrenal axis. Consequently, neural stress processing might constitute a particularly informative intermediate phenotype: it is biologically well-characterized, experimentally inducible, and reliably engages fronto-limbic and striatal circuits previously implicated in depression[13,14].

At the neural level, acute psychosocial stress robustly recruits fronto-limbic and striatal brain regions, including the amygdala, anterior cingulate cortex (ACC), insula, ventral striatum, and medial prefrontal cortex (mPFC)[15–18]. Importantly, alterations within these stress-responsive circuits have also been consistently implicated in MDD: Compared to healthy controls, individuals with depression exhibit altered resting-state measures of intrinsic brain function (e.g., amplitude of low-frequency fluctuations) and exaggerated neural responses to negative or salient emotional stimuli, particularly in limbic and striatal regions[19–21]. Emerging evidence further suggests altered neural responses to acute psychosocial stress in patients with MDD, predominantly in ventromedial prefrontal, limbic, and striatal regions[22,23]. Together, these findings indicate substantial overlap between neural systems involved in stress processing and those implicated in depressive pathology.

Neural stress responses show distinct interindividual variability and they are significantly modulated by sex. Sex-specific activation patterns during stress have been reported particularly in striato-limbic and mPFC regions involved in affective salience, reward processing, and stress regulation[16,22,24]. These differences align with pronounced sex disparities in depression prevalence and stress-related vulnerability and suggest that sex may moderate the neural expression of genetic risk during stress processing[25–27].

While clinical studies are essential for understanding disorder-related alterations, research in non-clinical populations is necessary to identify vulnerability markers and disentangle stable risk factors from transient symptom-related effects. Polygenic scores (PGS) provide a powerful approach to quantify an individual's genetic liability for complex psychiatric disorders, including depression[28,29]. Polygenic scores for depression (DEP-PGS) aggregate the effects of thousands of common genetic variants identified in large GWAS studies and can be calculated in independent target cohorts; they have been linked to a broad range of behavioral, affective, and neural phenotypes[30–34]. Importantly, evidence from both family/twin studies and polygenic score studies suggest that genetic liability for depression is associated with stress-related phenotypes, including heightened stress sensitivity, altered

neuroendocrine stress responses, and increased susceptibility to stress-related psychopathology[35–38], suggesting that stress processing may represent a key pathway through which polygenic risk manifests.

Neuroimaging studies examining DEP-PGS have reported associations with altered cognitive functioning, reward and punishment processing, as well as resting-state functional connectivity[30,31,39]. However, despite the central role of stress in depression risk, neuroimaging investigations linking DEP-PGS to experimentally induced psychosocial stress remain scarce. Existing imaging genetics studies using stress induction paradigms have predominantly relied on region-of-interest and resting-state designs[40–44], or whole-brain approaches in the context of candidate genes[45–48]. To date, whole-brain analyses of neural responses to acute psychosocial stress as a function of polygenic risk for depression are lacking.

In parallel, only a few studies in non-clinical samples have examined whether dimensional measures of depressive symptoms are associated with altered neural stress processing[49,50]. Available evidence suggests that while global stress-related activation patterns may be largely preserved, higher levels of subclinical depressive symptoms are linked to subtle alterations in specific regions, such as differential deactivation of the subgenual ACC[49]. Whether current depressive symptom severity and genetic liability converge on similar neural stress-related activation patterns or instead reflect dissociable state- and trait-related mechanisms remain unclear. Investigating both – symptom severity and genetic risk – within the same experimental framework offers the opportunity to disentangle stable genetic vulnerability from transient symptom-related effects.

In addition to the overall magnitude of neural stress responses, psychosocial functional magnetic resonance imaging (fMRI) stress paradigms have revealed dynamic changes across repeated stress exposure. Specifically, a decrease in activation across successive runs – often referred to as an exposure-time effect – has been observed in stress-responsive regions and interpreted as neural habituation or an index of adaptive stress regulation[16,17]. In contrast, individuals with burnout symptomatology have shown a reversal of this pattern, characterized by increasing activation over time in regions such as the dorsal ACC (dACC), suggesting stress sensitization rather than habituation[51]. Similarly, altered exposure-related trajectories have been reported in patients with MDD, particularly in females, including increasing dACC activation during repeated psychosocial stress exposure[22]. Recent longitudinal evidence further underscores the clinical relevance of such stress-exposure dynamics[52]: increases in nucleus (ncl.) accumbens activation across repeated stress exposure have been shown to predict future relapse in MDD, whereas decreasing activation was observed in individuals who remained stable. Notably, these effects were particularly pronounced in females, suggesting that stress sensitization in reward- and salience-related circuits may represent a key neural mechanism underlying vulnerability to relapse. Together, these findings indicate that not only the magnitude but also the temporal dynamics of neural stress responses may index vulnerability versus resilience. If genetic liability for depression contributes to stress-related vulnerability, it may also be reflected in altered exposure-time trajectories during acute psychosocial stress. To date, however, it remains unknown

whether polygenic risk for depression is associated with individual differences in neural exposure-time effects and whether such associations differ by sex.

Building on this, the primary aim of the present study was to investigate the association between polygenic risk for depression and whole-brain neural responses to acute psychosocial stress. Additionally, and exploratively, we examined whether current depressive symptom severity was associated with overlapping or distinct stress-related activation patterns and whether these effects were moderated by sex. To this end, we employed the Scan*STRESS* paradigm[17,42] in a sample of young, healthy adults. Participants provided genetic material for the calculation of DEP-PGS and completed the Beck Depression Inventory (BDI-II)[53] to assess current depressive symptom severity. We hypothesized that higher DEP-PGS would be associated with altered activation in fronto-limbic and striatal regions during stress processing and that these associations would differ by sex. Beyond overall stress-related activation, we further tested whether polygenic risk for depression is associated with individual differences in the exposure-time effect, reflecting changes in neural activation across Scan*STRESS* runs. Given prior evidence for sex-specific alterations in stress dynamics, these analyses additionally examined potential sex differences.

2. Methods and Materials

2.1 Sample

The present manuscript draws on data from three previously published cohorts, all collected at the University of Regensburg (for cohort-specific descriptions see original publiactions[17,54,55]). Participants were recruited via flyers, social media advertisements, and brief presentations in university courses and related academic settings. In total, 219 individuals underwent MRI scanning; after quality control, 203 datasets were retained, while 16 were excluded due to excessive motion (mean framewise displacement > .5 mm), insufficient image quality, or technical issues. Of the remaining sample, 190 participants (117 female; mean age = 22.32 ± 2.46 years) additionally provided genetic data.

Females not using hormonal contraceptives were scheduled during the luteal phase of the menstrual cycle (n = 64), determined via chromatographic urinary ovulation testing (gabmed GmbH, Cologne, Germany), in line with established procedures[56]. Exclusion criteria included self-reported psychiatric, neurological, or endocrine disorders; medication affecting the central nervous or endocrine systems; regular night-shift work; and MRI contraindications (e.g., pregnancy, implanted metal). Additional cohort-specific exclusion criteria are detailed in the respective publications[17,54,55].

All procedures adhered to the Declaration of Helsinki and were approved by the Ethics Committee of the University of Regensburg. Written informed consent was obtained from all participants, who received monetary compensation for their participation.

2.2 General procedure

Participants attended the MRI laboratory and received standardized instructions before completing a 45-minute relaxation phase during which they viewed a neutral film. During this period, they consumed a sugary drink (75 g glucose in 200 ml herbal tea) to enhance cortisol reactivity[57–59].

Approximately 15 minutes prior to the onset of Scan*STRESS* (for a detailed description see[17,42]), participants completed a brief training session using the paradigm's control blocks. Scan*STRESS* is designed to elicit stress through uncontrollability and social-evaluative threat[60]. The paradigm consisted of two runs with alternating stress and control blocks (total duration ~ 23 minutes). During stress blocks, participants performed challenging arithmetic and mental rotation tasks under time pressure, with adaptive difficulty, repeated failure experiences, and standardized negative feedback from an observation panel shown via live video stream. Control blocks involved simple figure- and number-matching tasks without time pressure or evaluative feedback. In addition to Scan*STRESS*, the scanning session included a resting-state fMRI acquisition (results to be reported elsewhere) and high-resolution structural MRI scans[61].

After scanning, participants completed questionnaires including the 21-item BDI-II[53,62], assessing depressive symptom severity over the past two weeks and the Childhood Trauma Questionnaire (CTQ)[63] to characterize early-life adversity. All testing sessions were conducted between 1:00 p.m. and 5:00 p.m. A buccal swab for DNA analysis was collected during the laboratory session or an additional appointment.

The present analyses constitute a secondary analysis of previously published datasets. In all three cohorts, Scan*STRESS* has been shown to reliably elicit robust endocrine, affective, cardiovascular, and neural stress responses, as reported in the original publications[17,54,55]. Therefore, no additional manipulation checks are reported here.

2.3 DNA sampling, genotyping, quality control, genotype imputation, and polygenic scores

As previously described[64], genomic DNA was obtained using a non-invasive buccal swab procedure (Analytik Jena GmbH, Jena, Germany), followed by DNA extraction via a standard salting-out protocol[65]. Genotyping was performed at the Life & Brain facilities (Bonn, Germany) using the Illumina Infinium™ Global Screening Array v3.0 with Multi-Disease Drop-In content (Illumina, San Diego, CA, USA).

Quality control procedures were conducted in PLINK v1.9 (www.cog-genomics.org/plink/1.9/). Single nucleotide polymorphisms (SNPs) were excluded if they exhibited a minor allele frequency (MAF) <.01, Hardy–Weinberg equilibrium (HWE) *p*-values < 1×10^{-6}, or missingness > .02. Participants were removed if they showed genotype missingness > .02, sex discrepancies, or extreme heterozygosity ($|z|>.20$), capturing both elevated heterozygosity and unusually high homozygosity (e.g., potential inbreeding). Relatedness and population structure filtering were performed using a high-quality SNP subset (HWE *p* > .02, MAF > .20, missingness = 0) after linkage disequilibrium (LD) pruning using a sliding window

approach (200 SNP window, step size 50 SNPs, pairwise r^2 =.10). For pairs of related individuals (pi-hat > .20), one individual was removed at random. Population stratification was controlled by computing ancestry principal components (PCs) computed on an LD-pruned high-quality SNP set; participants with $|z| > 4.5$ on any of the first 20 PCs were excluded and PCA was recomputed on the filtered sample. The first five PCs from the final PCA were used as covariates. Duplicate SNPs were identified, and one instance per duplicate set was retained.

Genotype imputation was subsequently conducted using Eagle v2.4.1[66] for phasing and Minimac4[67] for imputation, with the 1000 Genomes Phase 3 v5 reference panel[68]. Post-imputation, we retained the most likely genotype calls without additional filtering on posterior probabilities and restricted analyses to SNPs with imputation info scores ≥ .90. Additional filtering removed SNPs with MAF < .01 and duplicate markers, retaining one per duplicate set, and added rsIDs where applicable. The final dataset used for PGS calculations included 5,302,446 SNPs.

DEP-PGS were derived using summary statistics from a large-scale genome-wide association meta-analysis combining data from the Psychiatric Genomics Consortium (PGC), 24 other independent cohorts of European ancestry, and 12 cohorts with participants of diverse and mixed ancestry comprising 608,808 cases and 4,364,225 controls[28]. To derive the SNP effect sizes used for score construction, we applied PRS-CS, a Bayesian polygenic scoring method that estimates posterior SNP effect sizes using continuous shrinkage priors while accounting for LD across the genome. This approach eliminates the need for *p*-value thresholding and LD clumping by yielding a genome-wide set of shrunk, LD-adjusted effect size estimates. For the present analysis, we used the precomputed European LD reference panel from the 1000 Genomes Project and default PRS-CS hyperparameters. Polygenic scores were subsequently calculated in PLINK using these posterior effect sizes and were finally z-standardized.

2.4 fMRI data acquisition and analysis

All MRI data were acquired on a Siemens MAGNETOM Prisma 3T scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 64-channel head coil. Functional images were obtained using a blood-oxygenation-level-dependent gradient echo planar imaging sequence (repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, matrix = 64×64, field of view (FoV) = 192 mm, 37axial slices, slice thickness = 3 mm with 1-mm interslice gap, voxel size = 3 mm isotropic, interleaved acquisition). High-resolution structural images were obtained using a T1-weighted sequence (TR = 2400 ms, TE = 2.18 ms, flip angle = 9°, voxel size = 0.8 mm isotropic, distance factor = 50%).

Anatomical images were skull-stripped using SynthSeg, a convolutional neural network providing contrast- and resolution-robust tissue segmentation[69]. Functional images were preprocessed using ENIGMA HALFpipe[70], incorporating motion correction, distortion correction, coregistration, and spatial normalization via fMRIPrep[71]. Subsequent preprocessing steps included spatial smoothing (6 mm

FWHM), grand-mean intensity scaling, motion regression, and high-pass temporal filtering (cutoff: 125 s).

Neural responses were modeled in HALFpipe (via FSL). At the first level, a general linear model (GLM) was estimated for each participant including regressors for stress, control, and announcement periods. Parameter estimates from the two Scan*STRESS* runs were combined using fixed-effects models at the second level. Group-level mixed-effects analyses (third level; FLAME) were used to quantify stress-related responses (stress > control and control > stress). Voxel-wise statistical inference was performed at the whole-brain level. All reported whole-brain analyses were corrected for multiple comparisons using false-discovery rate correction (FDR, p_{FDR}<.05), as implemented in the FSL *fdr* tool[72].

To examine associations between whole-brain neural stress responses and genetic liability for depression, group-level models included DEP-PGS (*z*-transformed) as a covariate of interest, adjusting for age, sex, and grand-mean-centered ancestry principal components (PC1–PC5). Sex-specific effects were examined using interaction models (two-group design with sex × DEP-PGS interaction term). In addition to these primary analyses focusing on genetic liability as a trait-like risk marker, we conducted complementary analyses examining current depressive symptom severity (BDI-II) as a state-related measure using the same whole-brain approach. These analyses were considered exploratory as the primary aim of the study was to investigate genetic risk, and no *a priori* hypotheses were formulated regarding BDI-II-related effects. Finally, exposure-time effects were investigated to assess whether genetic liability is reflected not only in stress reactivity but also in stress adaptation dynamics.

To investigate exposure-time effects, we modeled run-wise stress contrasts within a repeated-measures framework (run1 and run2 as within-subject factor) and tested run-related changes (run1 > run2 and run2 > run1) at the group level using the Sandwich Estimator (SwE), which provides robust variance estimates for repeated-measures neuroimaging data and accounts for within-subject dependence[73]. Associations between polygenic risk for depression and exposure-time effects were examined via run × DEP-PGS interaction terms, reflecting differences in DEP-PGS-related slopes between runs, adjusted for age, sex, and PC1-PC5. Sex-specific effects were tested using run × DEP-PGS × sex interaction models, adjusted for age and PC1–PC5. Voxel-wise exposure-time analyses were also corrected for multiple comparisons using FDR (p_{FDR}<.05). Based on prior findings using the same paradigm that did not show sex-specific exposure-time effects[24], we additionally tested for main effects of sex-by-exposure-time interactions in this larger and partially overlapping sample.

3. Results

Table 1 presents the demographic characteristics of the study participants. The sample was predominantly female (117 out of 190 participants) and ranged in age from 18 to 30 years. Regarding depressive symptom severity, the BDI-II scores ranged from 0 to 48 (‘none/minimal’: score ≤ 13 (*n* = 102), ‘mild’: score ≤ 19 (*n* = 22), ‘moderate’: score ≤ 28 (*n* = 34), ‘severe’: score ≥ 29 (*n* = 30)). CTQ total scores ranged from 25 to 63 (‘none/minimal’: score ≤ 36, ‘low to moderate’: score ≤ 51, ‘moderate to severe’:

score ≤ 68, 'severe to extreme': score ≥ 69). Information about the distribution of DEP-PGS and BDI-II scores can be found in the supplements (Supplementary Figures S1 – S3).

Table 1
Sociodemographic characteristics of the study sample.

	Total	**Males**	**Females**
n	**190**	**73**	**117**
Age (M ± SD)	22.32 ± 2.46	23.07 ± 2.62	21.85 ± 2.23
DEP-PGS (M ± SD)	0.00 ± 1.00	0.07 ± 0.93	-0.04 ± 1.05
BDI-II score (M ± SD)	15.19 ± 11.60	13.64 ± 10.34	16.17 ± 12.28
CTQ score (M ± SD)	31.09 ± 6.74	30.82 ± 5.95	31.26 ± 7.24
Note. BDI-II = Beck Depression Inventory, CTQ = Childhood Trauma Questionnaire, DEP-PGS = depression polygenic score.			

[Table 1]

Whole-brain analyses revealed a significant association between polygenic risk for depression and neural psychosocial stress reactivity: Higher DEP-PGS values were associated with reduced activation (stress > control) within a striatal cluster encompassing the ncl. caudatus and ncl. accumbens (z_{FDR}>3.70; Fig. 1A&B; peak voxels can be found in Supplementary Table S1). In addition, a whole-brain interaction analysis testing sex differences in the association between DEP-PGS and neural stress responses revealed a significant cluster in the precuneus. Parameter estimates indicated a positive association between DEP-PGS and stress-related precuneus activation in males, whereas females showed a negative association (z_{FDR}>4.26; Fig. 1C&D; for peak voxels see Supplementary Table S2). No cluster exhibited stronger positive DEP-PGS-related stress activation in females compared to males.

[Figure 1]

In an exploratory analysis, we examined whether current depressive symptom severity was associated with neural stress reactivity. Whole-brain analyses revealed that higher BDI-II scores were associated with increased stress-related activation (stress > control) in a cluster encompassing the ncl. caudatus (Fig. 2A&B) and the thalamus (Fig. 2C&D; z_{FDR}>3.89; peak voxels can be found in Supplementary Table S3).

[Figure 2]

Given that both genetic depression risk and current depressive symptom severity were associated with stress-related activation in the ncl. caudatus in separate whole-brain analyses, we conducted a follow-up analysis to examine whether these effects reflect shared or independent mechanisms. Specifically, we tested whether current depressive symptom severity moderates the association between DEP-PGS and

ncl. caudatus stress reactivity. A linear regression model including the DEP-PGS × BDI-II interaction term was fitted, adjusting for age, sex, and PC 1–5. The main effect of DEP-PGS remained statistically significant (b = -0.34, SE = 0.15, $t(177)$ = -2.24, p = .026). In contrast, neither the interaction term (b = -0.00, SE = 0.01, $t(177)$ = -0.07, p = .947) nor the main effect of BDI-II (b = 0.00, SE = 0.01, $t(177)$ = 0.14, p = .888) reached statistical significance. These findings provide no evidence that current depressive symptom severity moderates the association between polygenic depression risk and ncl. caudatus stress reactivity, suggesting that genetic liability and current symptoms contribute independently to neural stress processing in this region.

Whole-brain analyses examining the association between polygenic risk for depression and exposure-time effects revealed that higher DEP-PGS values were associated with altered run-related changes in stress activation across a distributed fronto-cingulo-insular network. Significant clusters were observed in the ACC and paracingulate cortex, medial and superior to inferior frontal regions, bilateral thalamus, insular cortex, parahippocampal cortex, and fusiform gyrus (all z_{FDR}>2.36; peak voxels are reported in Supplementary Table S4). Notably, one of the significant clusters was located in the dorsal ACC (Fig. 3A), overlapping with a region in which a reversed exposure-time effect has previously been observed in individuals suffering from burnout symptoms compared to healthy controls[51]. As illustrated in Fig. 3B, higher DEP-PGS scores were associated with a shift in the exposure-time trajectory within this ACC region.

Sex-specific analyses further revealed significant run × DEP-PGS × sex interaction effects, indicating differential associations between genetic depression risk and exposure-time dynamics in males and females. Importantly, no significant main effects of sex or sex-by-exposure-time interactions were observed. Significant clusters were observed in the putamen (Fig. 3C&D), insular cortex, cingulate cortex, orbitofrontal regions (superior to inferior), precuneus, thalamus, ncl. caudatus, para-hippocampus, fusiform gyrus, and additional fronto-temporo-limbic regions (all z_{FDR}>2.36; peak voxels are reported in Supplementary Table S5). As illustrated in Fig. 3D, the interaction effect in the putamen reflected opposing exposure-time trajectories as a function of DEP-PGS in males and females. Specifically, higher DEP-PGS values were associated with a relative increase in activation from run1 to run2 in females, whereas in males higher DEP-PGS values were associated with a relative decrease across runs.

[Figure 3]

4. Discussion

In the present study, we examined the association between genetic liability for depression and neural responses to acute psychosocial stress in young, healthy participants. Using the Scan*STRESS* paradigm, we found that higher genetic risk was associated with altered stress-related activation and temporal dynamics in neural systems involved in motivation, self-referential cognition, and adaptation, with several effects showing sex-specific patterns. Exploratory analyses further assessed whether current depressive symptom severity shows similar associations and whether it interacts with genetic risk in shaping neural

stress responses. Together, these findings suggest multiple, partly sex-dependent neurocognitive mechanisms through which genetic vulnerability may shape responses to psychosocial stress.

Higher genetic liability for depression was associated with altered neural responses to psychosocial stress in striatal regions, particularly the ncl. caudatus and ncl. accumbens. These regions are key components of the striatal reward system and are involved in reward processing, motivational drive, effort-outcome integration, and goal-directed behavior[74,75]. Reduced stress-related activation in these regions among individuals with higher DEP-PGS may therefore indicate diminished motivational engagement when facing uncontrollable stress. Such a pattern is broadly consistent with models of MDD that emphasize anhedonia and reduced reward sensitivity as core features[76,77]. Neuroimaging studies in patient samples have similarly reported reduced striatal activation during depressive episodes, whereas remitted individuals sometimes show increased activation, which has been interpreted as potential compensatory recruitment of motivational processes[78,79]. Within this framework, the present findings suggest that DEP-PGS may be associated with subtle alterations in stress-related motivational processing at the neural level, potentially reflecting a vulnerability that precedes the onset of clinically manifest depressive symptoms.

In addition to these striatal findings, we observed a sex-specific association between DEP-PGS and stress-related activation in the precuneus. The precuneus represents a central hub of the default mode network (DMN) and is implicated in self-referential processing, internally directed cognition, and rumination[80,81]. During psychosocial stress, large-scale neuroimaging mega-analyses have typically reported deactivation of DMN regions, including the precuneus[16,82]. This finding might reflect suppression of internally oriented cognition in favor of externally directed coping with the stressor. The present sex-dependent pattern suggests that genetic liability for depression may differentially modulate this suppression mechanism. Specifically, males with higher DEP-PGS exhibited stronger precuneus activation during stress, potentially indicating increased self-referential processing or rumination under acute stress. In contrast, females showed the opposite association, possibly reflecting stronger regulatory suppression of DMN activity at comparable levels of genetic risk. These sex-specific neural patterns may be related to well-established sex differences in depression prevalence, symptom expression, and coping styles[83–86]. For instance, rumination tendencies are generally reported to be higher in females[87,88]., raising the possibility that females with elevated genetic risk engage stronger regulatory mechanisms to suppress internally focused processing during stress exposure More broadly, such sex-dependent neural signatures of polygenic risk may point toward partially distinct neural pathways through which genetic vulnerability contributes to the development and expression of depressive symptoms.

Current depressive symptom severity was associated with increased stress-related activation in the ncl. caudatus and thalamus. The ncl. caudatus has been implicated in cognitive control and motivational aspects of behavior, whereas the thalamus functions as a central relay structure integrating salient sensory and affective information[89–91]. In contrast to the reduced activation associated with genetic

liability in striatal reward-related regions (particularly the ncl. accumbens and caudatus), higher current depressive symptom severity were linked to increased activation in different peak locations within the same subcortical structures (i.e., ncl. caudatus), as well as in the thalamus, during stress exposure. These findings suggest that trait-related and state-dependent effects may engage in partially overlapping but functionally divergent neural circuits. Although trait-like vulnerability and current symptom severity are conceptually related rather than fully independent, they may nevertheless capture separable dimensions of depression risk and neural processes associated with current symptom expression[92]. Notably, previous work using the same stress paradigm did not observe associations between neural stress responses and depressive symptoms assessed with the depression scale of the Hospital Anxiety and Depression Scale (HADS)[50,93]. Differences in symptom assessment, statistical power, and sample size may contribute to these divergent findings, as the present study employed the more comprehensive BDI-II in a substantially larger sample. Consistent with this interpretation, we did not observe a significant DEP-PGS × BDI-II interaction, suggesting that genetic risk and current symptom severity contributed largely additive rather than synergistic effects on neural stress processing.

Beyond overall activation magnitude, genetic risk for depression was also associated with altered exposure-time dynamics across repeated stress runs. Scan*STRESS* involves ongoing negative social feedback and thus models, in a sense, sustained, uncontrollable stress rather than simple task repetition[17]. In healthy individuals, stress-related neural activation typically decreases from the first to the second run, reflecting increasing deactivation that has been interpreted as habituation or adaptive regulation of stress responses over time[16,17,22,51]. In the present study, higher DEP-PGS was associated with altered exposure-time trajectories in the ACC and related regions. The ACC plays a central role in conflict monitoring, salience detection, and the allocation of cognitive and motivational resources under stress[94,95]. Deviations from the typical exposure-time effect pattern may therefore indicate reduced neural habituation or stress sensitization in individuals with elevated genetic risk[96]. Similar alterations in exposure-time dynamics have been reported in individuals with burnout and MDD, where reversed or attenuated habituation effects have been observed[22,51]. Recent longitudinal evidence further demonstrates the clinical relevance of such altered stress-exposure dynamics. Increases in ncl. accumbens activation across repeated stress exposure have been shown to predict future relapse in MDD, whereas decreasing activation was observed in individuals who remained stable. Notably, these effects were particularly pronounced in females, suggesting that stress sensitization in reward-related circuits may represent a mechanism contributing to the well-established higher prevalence of depression in females, and potentially to vulnerability to recurrent depressive episodes[6,97]. Together, these findings suggest that genetic vulnerability to depression may be reflected not only in altered overall stress-related activation patterns, but also in differences in how neural stress responses adapt over time during repeated stress exposure.

Moreover, we observed sex-dependent associations between genetic liability and exposure-time dynamics in the putamen. The putamen, as part of the dorsal striatum, contributes to goal-directed behavior, habit learning, motivational processes, and effort-based decision-making[98,99]. Importantly, we

did not observe a main effect of sex on exposure-time dynamics, consistent with prior work using the same paradigm[24] and extending this finding to a substantially larger sample. Instead, sex differences emerged specifically in the association with genetic liability: females with higher DEP-PGS showed increasing putamen activation from the first to the second run, which may reflect sensitization of motivational or effort-related neural processes under repeated stress exposure. In contrast, males with higher DEP-PGS exhibited decreasing activation across runs, suggesting enhanced habituation or motivational disengagement during sustained stress. These opposing trajectories indicate that genetic risk modulates neural stress adaptation in a sex-dependent manner, rather than reflecting general sex differences in average activation patterns. Notably, this pattern suggests that sex does not robustly influence exposure-time dynamics at the group level, but may become relevant under conditions of increased vulnerability, such as elevated genetic liability. More broadly, such striatal dynamics may reflect differences in motivational strategies or regulatory processes between males and females when confronted with repeated uncontrollable stress[100]. Sex-dependent modulation of exposure-time effects in motivational circuitry may therefore represent distinct neurobiological pathways through which genetic liability contributes to individual differences in stress vulnerability and the development of depressive symptoms.

Several limitations should be considered when interpreting the present findings: First, although PGS capture a substantial portion of common genetic risk for depression, they represent only one component of the complex genetic architecture of the disorder and do not account for rare variants or gene-environment interactions[34]. In addition, current GWAS and PGS do not yet fully capture common genetic variation, as there remains uncertainty in the estimations of SNP associations; but predictive performance is likely to improve with larger sample sizes and more refined phenotyping. Future studies integrating neural mechanisms and polygenic risk with environmental stress exposure and longitudinal symptom trajectories may provide a more comprehensive understanding of vulnerability mechanisms. Second, the sample consisted of generally healthy individuals with relatively low depressive symptom severity, which may limit the generalizability to clinical populations. On the other hand, a substantial proportion of participants showed mild to severe BDI-II scores. Since information on current mental diagnoses was based on self-report we cannot rule out that some participants may have met criteria for MDD or another mental disorder. Importantly, participants also reported low levels of childhood adversity, with CTQ scores largely falling within the none-to-minimal range, indicating that the present findings reflect neural correlates of genetic risk in a largely unexposed sample. While this strengthens the interpretation of DEP-PGS effects as relatively independent of early-life stress exposure, it also limits conclusions about potential interactions between genetic liability and environmental adversity. However, this design also allowed examination of neural correlates of genetic risk largely independent of manifest disorder. Finally, although the present paradigm models sustained psychosocial stress through repeated negative social feedback, additional work is needed to determine how these neural stress-response patterns generalize to other forms of stress and real-world stress exposure. Future research combining neuroimaging, ambulatory stress assessments, and genetic risk profiling may further clarify the pathways linking genetic vulnerability to stress-related disorders.

In summary, the present study provides evidence that polygenic risk for depression is associated with subtle but systematic differences in neural responses to psychosocial stress, particularly in brain systems involved in motivation, self-referential processing, and stress adaptation. These findings suggest that polygenic risk may be associated not only with altered stress-response magnitude but also with differences in how individuals regulate and adapt to sustained stress exposure, with additional sex-dependent effects in key neural circuits. Together, this work contributes to a more nuanced understanding of the neurobiological pathways linking genetic vulnerability, stress processing, and depressive symptom severity. Identifying such neural signatures of genetic vulnerability during stress may help refine neurobiological models of depression risk and inform future efforts to detect individuals at increased risk before the onset of clinical disorder.

Declarations

Contributors

CRediT: conceptualization: MG, G-IH, methodology: MG, G-IH, formal analysis: MG, G-IH, FS, investigation: MG, G-IH, CB, HLP, JK, data curation: MG, G-IH, writing - original draft: MG, G-IH, writing - review & editing: MG, G-IH, CB, HLP, JK, SZ, PK, JF, BMK, HW, FS, SW, visualization: MG, G-IH, funding acquisition: G-IH, BMK, SW.

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Data availability statement

Derived fMRI contrast maps, polygenic scores, and questionnaire data (BDI, CTQ) are available from the corresponding author upon reasonable request and subject to a data sharing agreement. Raw genetic data and raw fMRI data cannot be shared due to restrictions in participant informed consent. A repository of studies that have already used and published these data is available here: https://osf.io/echja/.

Conflict of interest

The authors declare no conflict of interest.

References

1. Kennedy SH. Core symptoms of major depressive disorder: relevance to diagnosis and treatment. *Dialogues Clin Neurosci* 2008; 10: 271–277.
2. Marx W, Penninx BWJH, Solmi M, Furukawa TA, Firth J, Carvalho AF *et al.* Major depressive disorder. *Nat Rev Dis Primers* 2023; 9: 44.
3. IsHak WW, Steiner AJ, Klimowicz A, Kauzor K, Dang J, Vanle B *et al.* Major depression comorbid with medical conditions: analysis of quality of life, functioning, and depressive symptom severity. *Psychopharmacol Bull* 2025; 48: 8–25.
4. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiat* 2022; 9: 137–150.
5. Moreno-Agostino D, Wu Y-T, Daskalopoulou C, Hasan MT, Huisman M, Prina M. Global trends in the prevalence and incidence of depression:a systematic review and meta-analysis. *J Affect Disord* 2021; 281: 235–243.

6. Steffen A, Thom J, Jacobi F, Holstiege J, Bätzing J. Trends in prevalence of depression in Germany between 2009 and 2017 based on nationwide ambulatory claims data. *J Affect Disord* 2020; 271: 239–247.
7. Flint J, Kendler KS. The genetics of major depression. *Neuron* 2014; 81: 484–503.
8. Pettersson E, Lichtenstein P, Larsson H, Song J, Agrawal A, Bulik CM *et al.* Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls. *Psychol Med* 2019; 49: 1166–1173.
9. McIntosh AM, Sullivan PF, Lewis CM. Uncovering the genetic architecture of major depression. *Neuron* 2019; 102: 91–103.
10. Kendall KM, Van Assche E, Andlauer TFM, Choi KW, Luykx JJ, Schulte EC *et al.* The genetic basis of major depression. *Psychol Med* 2021; 51: 2217–2230.
11. Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinology* 2009; 5: 374–381.
12. Monroe SM, Anderson SF, Harkness KL. Life stress and major depression: the mysteries of recurrences. *Psychol Rev* 2019; 126: 791.
13. Bogdan R, Nikolova YS, Pizzagalli DA. Neurogenetics of depression: a focus on reward processing and stress sensitivity. *Neurobiol Dis* 2013; 52: 12–23.
14. De Kloet ER, Joëls M, Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci* 2005; 6: 463–475.
15. Berretz G, Packheiser J, Kumsta R, Wolf OT, Ocklenburg S. The brain under stress—a systematic review and activation likelihood estimation meta-analysis of changes in BOLD signal associated with acute stress exposure. *Neurosci Biobehav Rev* 2021; 124: 89–99.
16. Henze G-I, Giglberger M, Bärtl C, Konzok J, Neidhart M, Krause T *et al.* The ups and downs of brain stress: extending the triple network hypothesis. *Biol Psychiatry CNNI* 2025;: S2451902225002526.
17. Henze G-I, Konzok J, Kreuzpointner L, Bärtl C, Peter H, Giglberger M *et al.* Increasing deactivation of limbic structures over psychosocial stress exposure time. *Biol Psychiatry CNNI* 2020; 5: 697–704.
18. Noack H, Nolte L, Nieratschker V, Habel U, Derntl B. Imaging stress: an overview of stress induction methods in the MR scanner. *J Neural Transm* 2019; 126: 1187–1202.
19. Gong J, Wang J, Qiu S, Chen P, Luo Z, Wang J *et al.* Common and distinct patterns of intrinsic brain activity alterations in major depression and bipolar disorder: voxel-based meta-analysis. *Transl Psychiatry* 2020; 10: 353.
20. Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. *Am J Psychiatry* 2012; 169: 693–703.
21. Palmer SM, Crewther SG, Carey LM, START Project Team. A meta-analysis of changes in brain activity in clinical depression. *Front Hum Neurosci* 2015; 8: 1045.
22. Dong D, Ironside M, Belleau EL, Sun X, Cheng C, Xiong G *et al.* Sex-specific neural responses to acute psychosocial stress in depression. *Transl Psychiatry* 2022; 12: 2.

23. Ming Q, Zhong X, Zhang X, Pu W, Dong D, Jiang Y *et al.* State-independent and dependent neural responses to psychosocial stress in current and remitted depression. *Am J Psychiatry* 2017; 174: 971–979.
24. Henze G-I, Konzok J, Kreuzpointner L, Bärtl C, Giglberger M, Peter H *et al.* Sex-specific interaction between cortisol and striato-limbic responses to psychosocial stress. *Soc Cogn Affect Neurosci* 2021; 16: 972–984.
25. Kang H-J, Park Y, Yoo K-H, Kim K-T, Kim E-S, Kim J-W *et al.* Sex differences in the genetic architecture of depression. *Sci Rep* 2020; 10: 9927.
26. Labaka A, Goñi-Balentziaga O, Lebeña A, Pérez-Tejada J. Biological sex differences in depression: a systematic review. *Biol Res Nurs* 2018; 20: 383–392.
27. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of depression in the community from 30 countries between 1994 and 2014. *Sci Rep* 2018; 8: 2861.
28. Adams MJ, Streit F, Meng X, Awasthi S, Adey BN, Choi KW *et al.* Trans-ancestry genome-wide study of depression identifies 697 associations implicating cell types and pharmacotherapies. *Cell* 2025; 188: 640–652.
29. Lewis CM, Vassos E. Polygenic scores in psychiatry: on the road from discovery to implementation. *AJP* 2022; 179: 800–806.
30. Chen Y, Li H-T, Luo X, Li G, Ide JS, Li C-SR. Polygenic risks for depression and neural responses to reward and punishment in young adults. *Biol Psychiatry CNNI* 2025; 10: 1155–1165.
31. Chen Y, Li H-T, Luo X, Li G, Ide JS, Li C-SR. Polygenic risk for depression and resting-state functional connectivity of subgenual anterior cingulate cortex in young adults. *J Psychiatry Neurosci* 2025; 50: E31–E44.
32. Gard AM, Ware EB, Hyde LW, Schmitz LL, Faul J, Mitchell C. Phenotypic and genetic markers of psychopathology in a population-based sample of older adults. *Transl Psychiatry* 2021; 11: 239.
33. Kwong ASF, Morris TT, Pearson RM, Timpson NJ, Rice F, Stergiakouli E *et al.* Polygenic risk for depression, anxiety and neuroticism are associated with the severity and rate of change in depressive symptoms across adolescence. *J Child Psychol Psychiatry* 2021; 62: 1462–1474.
34. Wray NR, Lin T, Austin J, McGrath JJ, Hickie IB, Murray GK *et al.* From basic science to clinical application of polygenic risk scores: a primer. *JAMA Psychiatry* 2021; 78: 101.
35. Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. *Sci STKE* 2004; 2004. doi:10.1126/stke.2252004re5.
36. Cleary JL, Fang Y, Zahodne LB, Bohnert ASB, Burmeister M, Sen S. Polygenic risk and social support in predicting depression under stress. *AJP* 2023; 180: 139–145.
37. Harrison TJ, Docherty AR, Finsaas MC, Kotov R, Shabalin AA, Waszczuk MA *et al.* Examining the relationship between genetic risk for depression and youth episodic stress exposure. *J Affect Disord* 2023; 340: 649–657.

38. Wichers M, Geschwind N, Jacobs N, Kenis G, Peeters F, Derom C *et al.* Transition from stress sensitivity to a depressive state: longitudinal twin study. *Br J Psychiatry* 2009; 195: 498–503.
39. Yüksel D, Dietsche B, Forstner AJ, Witt SH, Maier R, Rietschel M *et al.* Polygenic risk for depression and the neural correlates of working memory in healthy subjects. *Prog Neuropsychopharmacol Biol Psychiatry* 2017; 79: 67–76.
40. Richter A, Al-Bayati M, Paraskevopoulou F, Krämer B, Pruessner JC, Binder EB *et al.* Interaction of *FKBP5* variant rs3800373 and city living alters the neural stress response in the anterior cingulate cortex. *Stress* 2021; 24: 421–429.
41. Van Der Meer D, Hartman CA, Pruim RHR, Mennes M, Heslenfeld D, Oosterlaan J *et al.* The interaction between 5-HTTLPR and stress exposure influences connectivity of the executive control and default mode brain networks. *Brain Imaging Behav* 2017; 11: 1486–1496.
42. Streit F, Haddad L, Paul T, Frank J, Schäfer A, Nikitopoulos J *et al.* A functional variant in the neuropeptide S receptor 1 gene moderates the influence of urban upbringing on stress processing in the amygdala. *Stress* 2014; 17: 352–361.
43. Streit F, Akdeniz C, Haddad L, Kumsta R, Entringer S, Frank J *et al.* Sex-specific association between functional neuropeptide S receptor gene (NPSR1) variants and cortisol and central stress responses. *Psychoneuroendocrinology* 2017; 76: 49–56.
44. Nair N, Hegarty JP, Ferguson BJ, Hooshmand SJ, Hecht PM, Tilley M *et al.* Effects of stress on functional connectivity during verbal processing. *Brain Imaging Behav* 2020; 14: 2708–2723.
45. Sun X, Li C, Zhong X, Dong D, Ming Q, Gao Y *et al.* Influence of psychosocial stress on activation in human brain regions: Moderation by the 5-HTTLPR genetic locus. *Physiol Behav* 2020; 220: 112876.
46. Sun X, Ming Q, Zhong X, Dong D, Li C, Xiong G *et al.* The MAOA gene influences the neural response to psychosocial stress in the human brain. *Front Behav Neurosci* 2020; 14: 65.
47. Kuhn L, Noack H, Skoluda N, Wagels L, Röhr A-K, Schulte C *et al.* The association of the 5-HTTLPR polymorphism and the response to different stressors in healthy males. *J Neural Transm (Vienna)* 2021; 128: 1347–1359.
48. Li C, Sun X, Dong D, Zhong X, Wang X, Yao S. Effect of corticotropin-releasing hormone receptor1 gene variation on psychosocial stress reaction via the dorsal anterior cingulate cortex in healthy adults. *Brain Res* 2019; 1707: 1–7.
49. Dedovic K, Duchesne A, Engert V, Lue SD, Andrews J, Efanov SI *et al.* Psychological, endocrine and neural responses to social evaluation in subclinical depression. *Soc Cogn Affect Neurosci* 2014; 9: 1632–1644.
50. Giglberger M, Peter HL, Henze G, Bärtl C, Konzok J, Kirsch P *et al.* Associations between the neural stress response and symptoms of anxiety and depression. *J of Neuroscience Research* 2025; 103: e70019.
51. Bärtl C, Henze G-I, Peter HL, Giglberger M, Bohmann P, Speicher N *et al.* Neural and cortisol responses to acute psychosocial stress in work-related burnout: The Regensburg Burnout Project. *Psychoneuroendocrinology* 2024; 161: 106926.

52. Dong D, Li C, Cheng C, Sun X, Xiong G, Yao S *et al.* Association of neural responses to acute psychosocial stress with relapse in depression. *Brain Imaging Behav* 2026; 20: 47.
53. Beck AT, Steer, Robert A., Brown, Gregory K. *Beck Depression Inventory*. Harcourt Brace Jovanovich: New York, 1987.
54. Giglberger M, Peter HL, Henze G-I, Kraus E, Bärtl C, Konzok J *et al.* Neural responses to acute stress predict chronic stress perception in daily life over 13 months. *Sci Rep* 2023; 13: 19990.
55. Konzok J, Henze G, Peter H, Giglberger M, Bärtl C, Massau C *et al.* Externalizing behavior in healthy young adults is associated with lower cortisol responses to acute stress and altered neural activation in the dorsal striatum. *Psychophysiology* 2021; 58: e13936.
56. Wolfram M, Bellingrath S, Kudielka BM. The cortisol awakening response (CAR) across the female menstrual cycle. *Psychoneuroendocrinology* 2011; 36: 905–912.
57. Gonzalez-Bono E, Rohleder N, Hellhammer DH, Salvador A, Kirschbaum C. Glucose but not protein or fat load amplifies the cortisol response to psychosocial stress. *Horm Behav* 2002; 41: 328–333.
58. Kirschbaum C, Bono EG, Rohleder N, Gessner C, Pirke KM, Salvador A *et al.* Effects of fasting and glucose load on free cortisol responses to stress and nicotine. *J Clin Endocrinol Metab* 1997; 82: 1101–1105.
59. Zänkert S, Kudielka BM, Wüst S. Effect of sugar administration on cortisol responses to acute psychosocial stress. *Psychoneuroendocrinology* 2020; 115: 104607.
60. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull* 2004; 130: 355–391.
61. Serin E, Schill LS, Bärtl C, Giglberger M, Konzok J, Peter HL *et al.* Linking brain structure to stress reactivity: Cingulate surface area predicts acute cortisol responses. *bioRxiv* 2025. doi:10.1101/2025.09.12.675570.
62. Hautzinger M, Keller F, Kühner C. *Beck-Depressions-Inventar - Revision (BDII-II)*. 2. Pearson Verlag: Frankfurt, 2009.
63. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T *et al.* Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *CAN* 2003; 27: 169–190.
64. Peter HL, Giglberger M, Streit F, Frank J, Kreuzpointner L, Rietschel M *et al.* Association of polygenic scores for depression and neuroticism with perceived stress in daily life during a long-lasting stress period. *Genes Brain Behav* 2023; 22: e12872.
65. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucl Acids Res* 1988; 16: 1215–1215.
66. Loh P-R, Danecek P, Palamara PF, Fuchsberger C, A Reshef Y, K Finucane H *et al.* Reference-based phasing using the haplotype reference consortium panel. *Nat Genet* 2016; 48: 1443–1448.
67. Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A *et al.* Next-generation genotype imputation service and methods. *Nat Genet* 2016; 48: 1284–1287.

68. The 1000 Genomes Project Consortium, Corresponding authors, Auton A, Abecasis GR, Steering committee, Altshuler DM *et al.* A global reference for human genetic variation. *Nature* 2015; 526: 68–74.
69. Billot B, Greve DN, Puonti O, Thielscher A, Van Leemput K, Fischl B *et al.* SynthSeg: segmentation of brain MRI scans of any contrast and resolution without retraining. *Med Image Anal* 2023; 86: 102789.
70. Waller L, Erk S, Pozzi E, Toenders YJ, Haswell CC, Büttner M *et al.* ENIGMA HALFpipe: interactive, reproducible, and efficient analysis for resting-state and task-based fMRI data. *Hum Brain Mapp* 2022; 43: 2727–2742.
71. Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A *et al.* fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nat Methods* 2019; 16: 111–116.
72. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage* 2002; 15: 870–878.
73. Guillaume B, Hua X, Thompson PM, Waldorp L, Nichols TE. Fast and accurate modelling of longitudinal and repeated measures neuroimaging data. *NeuroImage* 2014; 94: 287–302.
74. Pauli WM, O'Reilly RC, Yarkoni T, Wager TD. Regional specialization within the human striatum for diverse psychological functions. *Proc Natl Acad Sci USA* 2016; 113: 1907–1912.
75. Schultz W. Dopamine reward prediction-error signalling: a two-component response. *Nat Rev Neurosci* 2016; 17: 183–195.
76. Borsini A, Wallis ASJ, Zunszain P, Pariante CM, Kempton MJ. Characterizing anhedonia: a systematic review of neuroimaging across the subtypes of reward processing deficits in depression. *Cogn Affect Behav Neurosci* 2020; 20: 816–841.
77. Takamura M, Okamoto Y, Okada G, Toki S, Yamamoto T, Ichikawa N *et al.* Patients with major depressive disorder exhibit reduced reward size coding in the striatum. *Prog Neuropsychopharmacol Biol Psychiatry* 2017; 79: 317–323.
78. Admon R, Holsen LM, Aizley H, Remington A, Whitfield-Gabrieli S, Goldstein JM *et al.* Striatal Hypersensitivity During Stress in Remitted Individuals with Recurrent Depression. *Biological Psychiatry* 2015; 78: 67–76.
79. Ming Q, Zhong X, Zhang X, Pu W, Dong D, Jiang Y *et al.* State-independent and dependent neural responses to psychosocial stress in current and remitted depression. *AJP* 2017; 174: 971–979.
80. Dadario NB, Sughrue ME. The functional role of the precuneus. *Brain* 2023; 146: 3598–3607.
81. Utevsky AV, Smith DV, Huettel SA. Precuneus is a functional core of the default-mode network. *J Neurosci* 2014; 34: 932–940.
82. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci USA* 2001; 98: 676–682.
83. Marcus SM, Young EA, Kerber KB, Kornstein S, Farabaugh AH, Mitchell J *et al.* Gender differences in depression: findings from the STAR*D study. *J Affect Disord* 2005; 87: 141–150.

84. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms. *Psychol Bull* 2017; 143: 783–822.
85. Shi P, Yang A, Zhao Q, Chen Z, Ren X, Dai Q. A hypothesis of gender differences in self-reporting symptom of depression: implications to solve under-diagnosis and under-treatment of depression in males. *Front Psychiatry* 2021; 12: 589687.
86. Vetter JS, Spiller TR, Cathomas F, Robinaugh D, Brühl A, Boeker H *et al.* Sex differences in depressive symptoms and their networks in a treatment-seeking population – a cross-sectional study. *J Affect Disord* 2021; 278: 357–364.
87. Cavanagh A, Wilson CJ, Kavanagh DJ, Caputi P. Differences in the expression of symptoms in men versus women with depression: a systematic review and meta-analysis. *Harv Rev Psychiatry* 2017; 25: 29–38.
88. Nolen-Hoeksema S, Jackson B. Mediators of the gender difference in rumination. *Psychol Women Q* 2001; 25: 37–47.
89. Biesbroek JM, Verhagen MG, Van Der Stigchel S, Biessels GJ. When the central integrator disintegrates: a review of the role of the thalamus in cognition and dementia. *Alzheimers Dement* 2024; 20: 2209–2222.
90. Driscoll ME, Bollu PC, Tadi P. Neuroanatomy, nucleus caudate. In: *StatPearls*. StatPearls Publishing: Treasure Island (FL), 2026http://www.ncbi.nlm.nih.gov/books/NBK557407/ (accessed 15 Mar2026).
91. Hwang K, Bertolero MA, Liu WB, D'Esposito M. The human thalamus is an integrative hub for functional brain networks. *J Neurosci* 2017; 37: 5594–5607.
92. Kendler KS, Aggen SH. Symptoms of major depression: their stability, familiality, and prediction by genetic, temperamental, and childhood environmental risk factors. *Depress Anxiety* 2017; 34: 171–177.
93. Herrmann-Lingen C, Buss U, Snaith RP. *Hospital anxiety and depression scale: HADS-D; deutsche Version; manual*. Hans Huber: Bern, 2011.
94. Van Veen V, Cohen JD, Botvinick MM, Stenger VA, Carter CS. Anterior cingulate cortex, conflict monitoring, and levels of processing. *NeuroImage* 2001; 14: 1302–1308.
95. Seeley WW. The salience network: a neural system for perceiving and responding to homeostatic demands. *J Neurosci* 2019; 39: 9878–9882.
96. Sinha R, Lacadie CM, Constable RT, Seo D. Dynamic neural activity during stress signals resilient coping. *Proc Natl Acad Sci USA* 2016; 113: 8837–8842.
97. Dong D, Li C, Cheng C, Sun X, Xiong G, Yao S *et al.* Association of neural responses to acute psychosocial stress with relapse in depression. *Brain Imaging Behav* 2026; 20: 47.
98. Haber SN. Corticostriatal circuitry. *Dialogues Clin Neurosci* 2016; 18: 7–21.
99. Salamone JD, Correa M. The neurobiology of activational aspects of motivation: exertion of effort, effort-based decision making, and the role of dopamine. *Annu Rev Psychol* 2024; 75: 1–32.

100. Goldfarb EV, Seo D, Sinha R. Sex differences in neural stress responses and correlation with subjective stress and stress regulation. *Neurobiol Stress* 2019; 11: 100177.

Figures

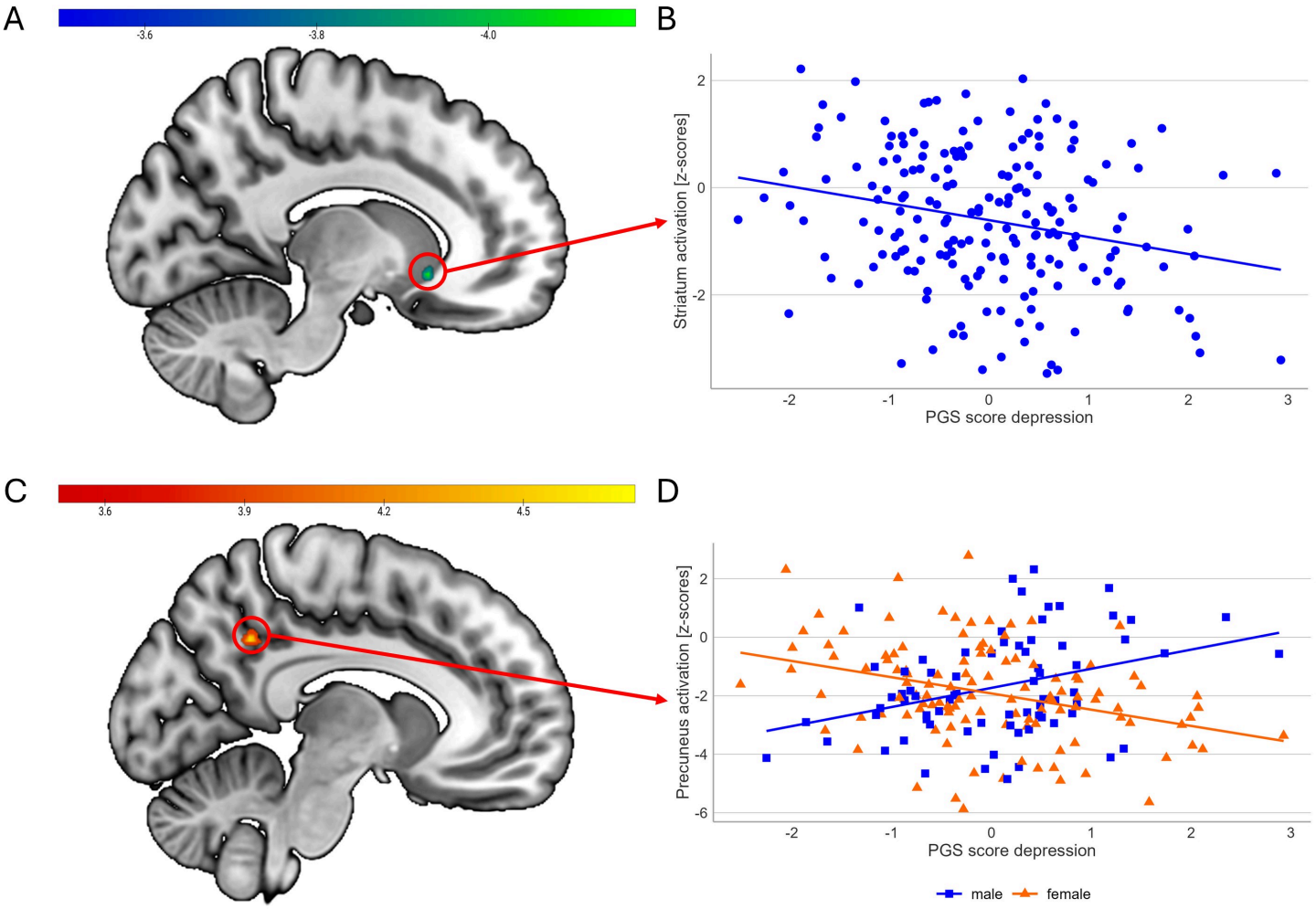


Figure 1

(A) Striatal cluster showing a significant association between depression polygenic scores (DEP-PGS; grand-mean centered) and stress-related activation (stress > control), adjusted for age, sex, and principal components 1–5 (PC1–PC5). (B) Scatterplot illustrating the association between DEP-PGS and extracted *z*-scores from the striatal cluster displayed in (A). (C) Precuneus cluster showing a significant sex × DEP-PGS interaction on stress-related activation (stress > control), derived from a whole-brain two-group analysis with DEP-PGS (grand-mean centered) as a continuous covariate. (D) Scatterplot illustrating the sex-specific associations between DEP-PGS and extracted *z*-scores from the precuneus cluster displayed in (C).

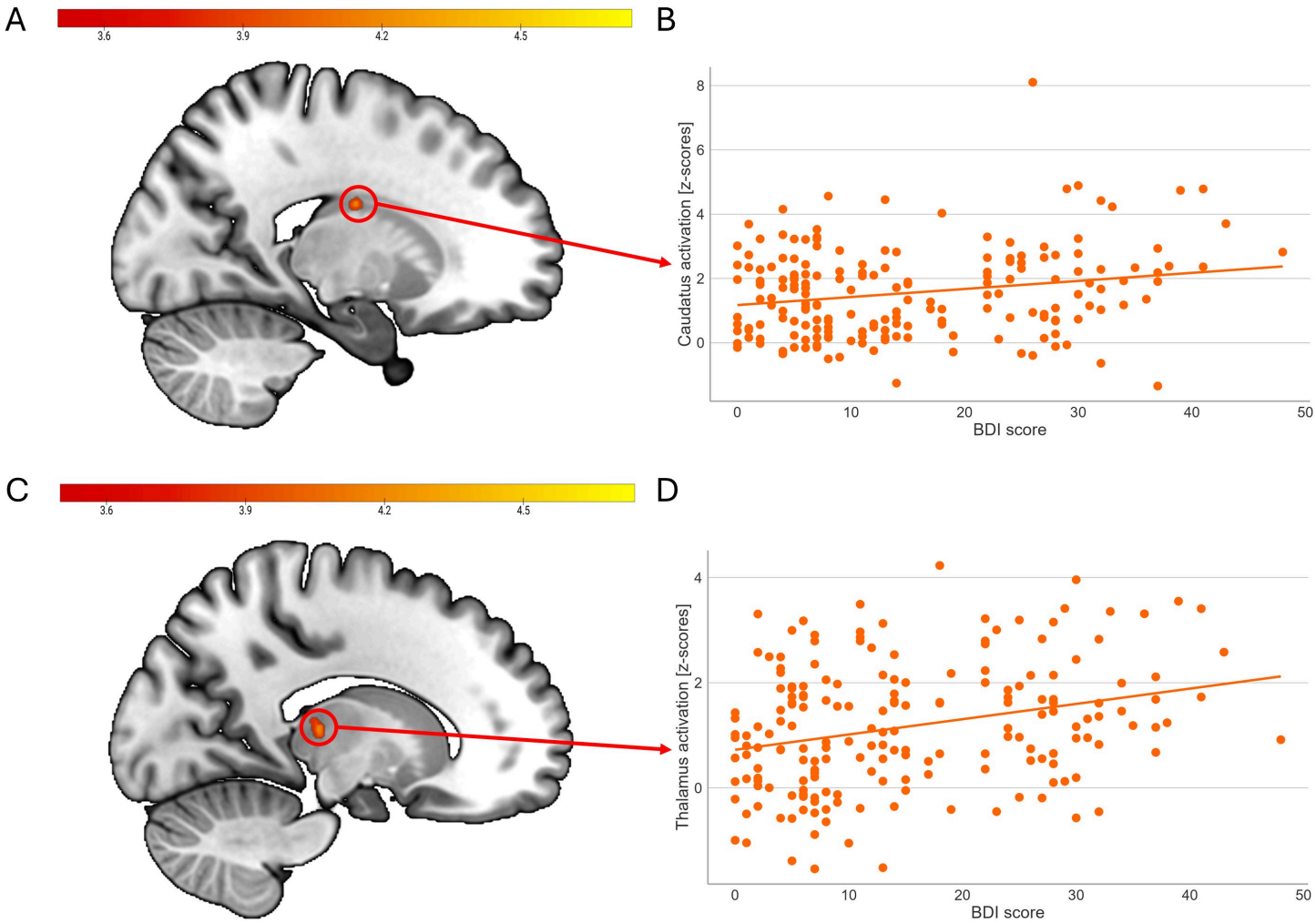


Figure 2

(A) and (C) Significant clusters from the whole-brain main task effect analysis (stress > control) with depressive symptom severity (BDI-II scores; grand-mean centered) entered as a continuous covariate, adjusted for age and sex. (B) and (D) Scatterplots illustrating the associations between BDI-II scores and extracted *z*-scores of the stress > control contrast from the ncl. caudatus (B) and thalamus (D).

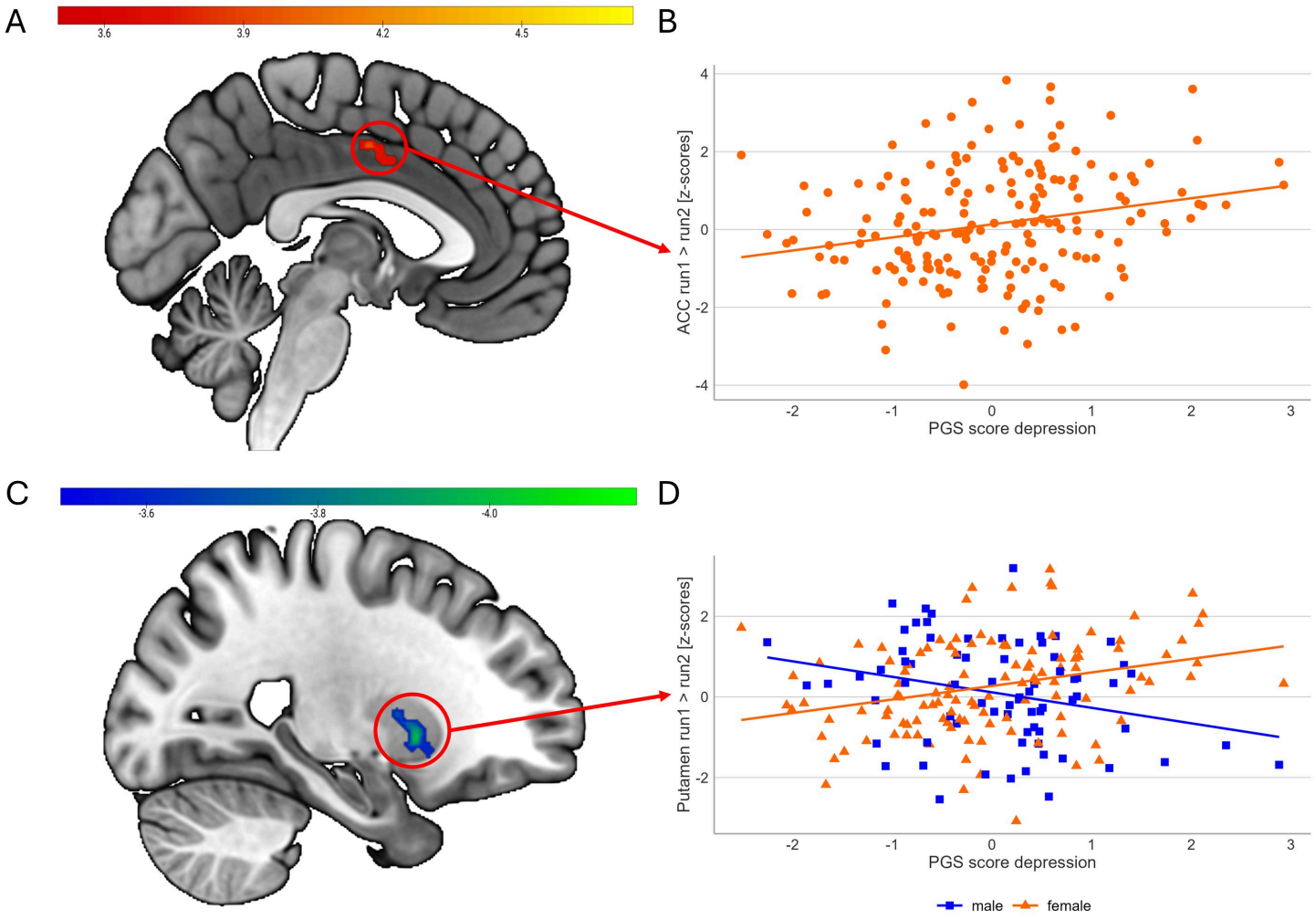


Figure 3

(A) Significant cluster from the whole-brain exposure-time analysis (run1>run2) showing an association between depression polygenic risk (DEP-PGS; grand-mean centered) and run-related changes in stress activation across the entire sample, adjusted for age, sex, and PC1–PC5 (dorsal ACC cluster). (B) Scatterplot illustrating the association between DEP-PGS and extracted *z*-scores (run1>run2) from the ACC-cluster. (C) Significant cluster from the sex-specific run × DEP-PGS interaction analysis, adjusted for age and PC1–PC5, demonstrating differential exposure-time effects in males and females (putamen). (D) Scatterplot depicting the sex-specific associations between DEP-PGS and putamen *z*-scores (run1>run2), illustrating opposing exposure-time trajectories in males and females.

Supplementary Files

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