**Comparing Association between Psychopathology-Related Outcomes and Stress-Sensitivity and Psychiatric Polygenic Risk Scores in the Adolescent Brain Cognitive Development (ABCD) Study**

Kate Scheuer and Jennifer Forsyth

Department of Psychology, University of Washington

**Comparing Association between Psychopathology-Related Outcomes and Stress-Sensitivity and Psychiatric Polygenic Risk Scores in the Adolescent Brain Cognitive Development (ABCD) Study**

Transient changes in cortisol levels following an acute stressor can be adaptive. Typically, a stressful event activates the hypothalamic-pituitary-adrenal (HPA) axis and causes the hypothalamus to release corticotropin-releasing hormone which stimulates release of adrenocorticotropic hormone and the subsequent stimulates release of the cortisol from adrenal cortex (Palamarchuk et al., 2023). Cortisol binds to glucocorticoid receptors (GRs), creating negative feedback and decreasing HPA axis activity to return to homeostasis (Jimeno & Rubalcaba, n.d.). However, chronic or sustained stress can provoke longer-term, maladaptive changes in cortisol responses with negative physical and psychological consequences (Hoffman et al., 2024; Palamarchuk et al., 2023; Zorn et al., 2017). Repetitive stress exposure is a risk factor for psychological disorders such as anxiety, major depressive disorder (MDD), and schizophrenia (Zorn et al., 2017), and maladaptive hyperactivity of the HPA axis has been linked to anxiety and depression (Palamarchuk et al., 2023). Abnormal HPA axis responsiveness is also associated with post-traumatic stress disorder (PTSD)-like behavior, including changes in fear extinction and relapse, hippocampal volume, and rapid eye movement sleep, in offspring of rats with unusually exaggerated or blunted responses to cortisol (Monari et al., 2024). Specific changes in HPA axis activity can differ based on sex, psychiatric disorder, and whether the disorder is active or in remission (Zorn et al., 2017). For example, women with a current MDD diagnosis had lower baseline cortisol and decreased cortisol response to stress compared to controls, while men with a current MDD diagnosis displayed increased baseline cortisol but no difference in cortisol response to stress. Compared to controls, baseline cortisol levels were lower in women, but not men, with MDD in remission, and neither men nor women with MDD in remission had significant alterations in cortisol responses to stress. Also, women, but not men, with anxiety have decreased cortisol responses to stress, while men, but not women, with social anxiety disorder have increased cortisol responses to stress compared to controls. Both men and women with schizophrenia have decreased baseline cortisol levels (Zorn et al., 2017).

Disrupted HPA axis function in individuals with psychiatric disorders has also been linked to changes in gene expression. Although there were no differences in baseline gene expression in human induced pluripotent stem cell-derived glutamatergic neurons from combat veterans with PTSD and without PTSD, exposure to the GR agonist hydrocortisone provoked differential expression in 402 genes between cells derived from patients with and without PTSD, and these genes were enriched in postmortem brain tissue (Seah et al., 2022). Additionally, a polygenic risk score (PRS) created based on hippocampal gene changes in female macaques following chronic betamethasone administration moderated the relationship between exposure to early life adversity and diagnoses of adult psychotic disorders (Arcego et al., 2024).

Penner-Goeke et al. (2022) leveraged HPA axis responses to create an experimentally-derived stress-sensitivity genetic score associated with physiological stress responses and differentially expressed genes in postmortem brain tissue of individuals with psychiatric disorders. Beginning with a set of 3,662 SNPs linked to dexamethasone (a GR agonist) responsiveness in a prior genome-wide expression quantitative trait locus analysis (Arloth et al., 2015), they identified a 547 of these dexamethasone-responsive SNPs which were in regulatory elements (SNP-DREs). Transcripts associated with these SNP-DREs were enriched in postmortem cortical brain tissue from individuals with schizophrenia, autism spectrum disorder, MDD, bipolar disorder, or alcohol and substance use disorders. Penner-Goeke et al. (2022) then used Mendelian randomization based on a meta-GWAS of psychiatric disorders to select 79 of these SNP-DREs causally linked to psychiatric illness and created a weighted functional gene score (FGS) based on the SNP-DREs. Baseline cortisol levels did not differ based on FGS, but subjects with higher FGS had higher cortisol levels 30 minutes after completing a social stress task. Higher FGS scores were also associated with increased eyeblink startle response magnitude and decreased startle habituation in a fear conditioning task. SNP-DREs have therefore been linked to psychiatric disorders via differential gene expression in postmortem tissue and physiological stress-sensitivity markers. A logic extension of this work is to examine whether PRS derived from the SNP-DREs used to create the FGS can be linked directly to psychiatric diagnoses and psychopathology.

*RQ1:*  What relationship, if any, is there between an experimentally-derived stress-sensitivity PRS and psychiatric diagnoses or symptoms of psychopathology?

The proposed stress-sensitivity PRS is unique in that it is experimentally derived, whereas PRS are typically created based on summary statistics from large GWAS. This approach is well-established, and prior work has identified significant relationships between psychopathology and PRS for a wide variety of disorders including panic disorder, schizophrenia, MDD, ADHD, and externalizing disorders (Lahey et al., 2024; Qiu & Liu, 2023; Teeuw et al., 2023; Wainberg et al., 2022). However, PRS created based on GWAS summary statistics relies on associations between genetic variants and the target trait which can make it difficult to identify causal variants and their associated underlying mechanisms. The stress-sensitivity PRS capitalizes on results of an experimental manipulation, thus illuminating a mechanistic pathway between the identified variants (SNP-DREs) and outcomes significantly associated with the PRS. To compare the experimentally-derived and standard, GWAS-derived PRS scores, we ask:

*RQ2:* How does the variance in psychiatric diagnoses or symptoms of psychopathology explained by an experimentally-derived stress-sensitivity PRS compare to that explained by PRS for psychiatric disorders calculated based on GWAS summary statistics?

In addition to genetic influences on stress-related psychiatric disorders, there is strong evidence for the role of exposure to social and environmental stressors in the development of psychopathology. Likelihood of developing a psychiatric disorder increases as exposure to adversity increases, and children exposed to adverse experiences are approximately twice as likely to develop a mental disorder compared to unexposed peers (McLaughlin et al., 2019). One common method of quantifying exposure to stress is through cumulative adverse event measures such as the Adverse Childhood Experiences Questionnaire (ACE-Q), the Life Events Scale (LES), or the Posttraumatic Stress Disorder (PTSD) module within the Kiddie Schedule for Affective Disorders and Schizophrenia. These cumulative measures sum the number of stressful experiences to which an individual has been exposed. While the specific type of adverse events identified in each measure vary, cumulative adverse event scores across measurement scales are associated with increased psychopathology. Higher scores on the ACE-Q have been linked to increased levels of depression, drug abuse and alcoholism, and suicide attempts (Felitti et al., 1998). Increased negative lifetime event exposure quantified by the LES is associated with increased emotion-driven impulsivity, psychotic-like experiences, and externalizing and internalizing symptoms (Barnhart et al., 2022; Karcher et al., 2022; Weiss et al., 2023). Finally, exposure to larger numbers of potentially traumatic events as measured with the KSADS-5 PTSD module tended to increase risk for depression, anxiety, PTSD, oppositional defiant disorder, conduct disorder, attention-deficit hyperactivity disorder, and suicidality (Thompson et al., 2022).

Broader family- and community-level factors can add to individual stress exposure and further increase risk for psychopathology. School environmental factors such as engagement were significantly related to symptoms of internalizing, externalizing, anxiety, and depression (Qiu & Liu, 2023; Thapaliya et al., 2021). Lower levels of household income and parental education and higher neighborhood poverty as measured with area deprivation index were associated with increased externalizing (Maxwell et al., 2021; Teeuw et al., 2023). The exposome theoretically captures all non-genetic influences, and exposome scores capturing a wide array of factors including cumulative adverse event exposure have been associated with increased psychopathology. For example, individuals with higher exposome scores based on 348 environmental variables including LES scores tended to have higher levels of self- and parent-reported psychopathology. When combined with basic demographic information, a model including these exposome scores was able to capture 38.2% of the variance in the psychopathology p-factor in a large cohort of American adolescents, the Adolescent Brain Cognitive Development (ABCD) Study (Hoffman et al., 2024; Moore et al., 2022).

In addition to additive genetic and environmental effects on psychopathology, numerous studies have demonstrated gene by environment interactions on psychiatric symptoms and diagnoses. For example, internalizing and externalizing scores for youth in the ABCD Study were best explained by models including genome-exposome interactions where the exposome measured cumulative negative life events and proximal contextual factors such as school risk and protective factors and parental monitoring (Choi et al., 2022). MDD-PRS and anxiety PRS also interacted with measures of stress such that there was a stronger relationship between PRS and depression or anxiety symptoms, respectively, for subjects with increased loneliness, long-term difficulties, greater numbers of stressful life events, and decreased social support (Wang et al., 2023). Interactions between a stress-sensitivity PRS based on four HPA axis genes (FKBP5, NR3C1, NR3C2, and GRHR1) and environmental factors were also associated with symptoms of depression and anxiety in a sample of Han Chinese adolescents. Higher levels of childhood maltreatment were linked with increased comorbid depression and anxiety symptoms in individuals with high levels of this stress-sensitivity PRS, but not those with low stress-sensitivity PRS (Cao et al., 2024). Similarly, subjects with high, but not those with low, stress-sensitivity PRS displayed stronger interactions between childhood maltreatment, exposure to recent interpersonal stress, and symptoms of depression (Sun & Cao, 2024).

* Could be gene x environment interaction or genetics could influence both outcome and environment: Relationship between psych-related PRS and ACE exposure could be due to child’s behavior (genetic) leading to ‘harsh parenting or stress responses in their parents’ ie gene by environment correlation or due to common genetics between parent with psychopathology and child with psychopathology (Baldwin et al., 2022)

This part should be 5-10 pages total

**Methods**

**Sample description**

The Adolescent Brain Cognitive Development (ABCD) Study is an ongoing, longitudinal study which samples adolescents from across the United States. Subject composition is similar to national demographic composition in terms of race, ethnicity, urbanicity, and sex (Compton et al., 2019). Data are available for 11868 adolescents at baseline when participants were 9-10 years old, and sample attrition has been relatively low (participants at year one: 11220, year two: 10973, year three: 10336). While the full data set for the year four follow-up visit has not been released (data currently available for 3718 participants), based on prior attrition, information should be available for about 9826 adolescents. The proposed study will use outcome measures from year four follow-up visits, as preliminary data suggest that prevalence for psychopathology is much greater in year four compared to earlier timepoints. For example, current diagnoses of GAD in year four were 2.8 times larger than those in year two, and current diagnoses of MDD in year four were about four times larger than those in year two. In year four, youth participants were 52.82% male, 47.15% female, and 0.02% intersex. Youth parent-reported race was: 79.44% White, 16.10% Black/African American, 0.04% Alaska Native, 0.15% Native Hawaiian, 0.02% Guamanian, 0.09% Samoan, 0.26% other Pacific Islander, 0.92% Asian/Indian, 1.96% Chinese, 1.45% Filipino, 0.75% Japanese, 0.94% Korean, and 0.38% Vietnamese. Combined family household incomes pre-tax were as follows: 1.86% less than $5,000; 1.69% $5,000 through $11,999; 1.43% $12.000 through $15,999; 3.25% $16,000 through $24.999; 4.14% $25,000 through $34,999; 6.56% $35,000 through $49,999; 10.84% $50,000 through $74,999; 12.64% $75,000 through $99,999; 32.92% $100,000 through $199,999; and 16.03% $200,000 and greater.

**Genetics**

Genetic material was collected primarily through saliva, though some participants provided blood samples. Genotyping was performed with Affymetrix Axiom Smokescreen Arrays and reads were aligned with Human Genome hg19 build. The ABCD Data Analysis, Informatics, and Resource Center performed quality control which included removal of variants with more than 10% missingness and removal of subjects with more than 20% missing calls or excessive relatedness (Fan et al., 2023).

**Measures**

***Child Behavior Checklist (CBCL)***

The CBCL is part of the Achenbach System of Empirically Based Assessment and measures emotional and behavioral problems in youth (T. M. Achenbach, 2009). Score on 113 items are grouped into eight subscales (rule-breaking, aggression, withdrawn/depressed, anxious/depressed, somatic, attention problems, thought problems, and social problems) as well as composite scores for internalizing (withdrawn/depressed, anxious/depressed, and somatic subscales), externalizing (rule-breaking and aggression subscales), and total problems (all subscales). Scores are t-scored based on a mean of 50 points and a standard deviation of 10 points. Values between 65 and 69 are considered subclinical, while scores of 70 or more suggest clinically significant problems. Externalizing, internalizing, and total scores have high internal consistency (Cronbach’s α: .94) and high test-retest reliability (r = .92) (T. Achenbach, 2011). CBCL scores in the ABCD Study reflect caregiver assessments as it was not administered to youth.

***Kiddie Schedule for Affective Disorders and Schizophrenia Computerized Version for DSM-5 (KSADS-COMP)***

The KSADS-COMP is a standardized interview with items based on DSM-5 criteria for psychiatric disorders such as including MDD, ADHD, PTSD, and a variety of anxiety disorders (Kobak et al., 2013). It has good internal reliability (Cronbach’s α = .91) and convergent validity with clinician-administered scales such as the CBCL (Townsend et al., 2020). The KSADS has adequate test-retest reliability (κ = .63 to 1.00) (Kaufman et al., 1997). The present study will consider both past and present diagnoses and will include information from both youth and caregiver reports when available. ADHD and PTSD items were not administered to youth.

**Ancestry**

Principal component analysis was performed on unpruned ABCD data with the conservative Hardy-Weinberg flag using plink. Prior work identified the first eight principal components (PCs) as the optimal number to account for ancestry in this sample (J. Zhu and M. Hyat, personal communication, February 2024). Samples were separated into three ancestry groups (African, American admixed, and European) using a random forest model with a probability threshold of 0.7 (J. Zhu and M. Hyat, personal communication, February 2024). After applying this threshold, genetic data was currently available for 3307 participants (2299 European ancestry, 517 African ancestry, 491 American admixed ancestry) in year four.

**Genetic Relatedness**

To account for genetic relatedness between participants, genetic relatedness matrices (GRMs) were calculated for each ancestry using plink (Purcell et al., 2007) based on unpruned ABCD data (J. Zhu and M. Hyat, personal communication, February 2024).

**Polygenic Risk Scores (PRS)**

Stress-sensitivity used for the preliminary results included here were generated with plink (Purcell et al., 2007) based on summary statistics from Penner-Goeke et al. (2023). Briefly, for each PRS, a data frame containing risk alleles and their associated effect sizes for each SNP was provided to plink, and plink then calculated the sum of the risk alleles for each participant weighted by effect size.

Final results will compare stress-sensitivity PRS to PRS for MDD, ADHD, PTSD, and anxiety disorders calculated based on summary statistics from Howard et al. (2019), ADHD Working Group of the Psychiatric Genomics Consortium (PGC) et al. (2019), Nievergelt et al. (2024), and Otowa et al. (2016) respectively. To better account for ancestry-related effects, final results will use a more sophisticated method to generate PRS for anxiety, MDD, and ADHD such as PRS-Csx (Ruan et al., 2022), BridgePRS (Hoggart et al., 2024), or SBayesRC (Zheng et al., 2024). These techniques are not applicable to the stress-sensitivity PRS because it was generated experimentally based on results from individuals of unknown ancestry.

**Analysis**

Using the *R* package GENESIS (Gogarten et al., 2019), linear regression will be performed with scores from each of the eight subscales, externalizing, internalizing, and total problems on the CBCL as outcomes. Logistic regression will also be performed with lifetime diagnosis of MDD, ADHD, PTSD, and any anxiety disorder other than specific phobia as outcomes. Study site and genetic relatedness (quantified with GRMs) will be random effects. Subject sex, age, and the first eight ancestry PCs will be fixed effect covariates. Analysis code will be available in a Github repository.

**Preliminary Results**

**Stress-sensitivity PRS**

***Psychopathology-related Symptoms and Behavior***

For individuals of European ancestry, stress-sensitivity PRS was nominally significantly associated with somatic-related symptoms on the CBCL somatic subscale (uncorrected p-value = 0.022, FDR corrected p-value = 0.92), with an increase of 0.281 points for each standard deviation increase in stress-sensitivity PRS. Neither any other CBCL subscales nor total problems were significantly or nominally associated with stress-sensitivity PRS. Compared to average, girls’ scores were 1.00 point higher on the internalizing (FDR corrected p-value = 0.000045), 0.49 points higher on the anxious-depressed (FDR corrected p-value = 0.00055), and 0.40 points higher on the somatic (FDR corrected p-value = 0.0037) subscales and scores 0.26 points lower on the aggression subscale (FDR corrected p-value = 0.010).

For subjects of African ancestry, CBCL scores did not significantly differ based on stress-sensitivity PRS, sex, or age.

Finally, for individuals of American admixed ancestry, stress-sensitivity PRS was nominally associated with changes in withdrawn-depressed and total problem CBCL scores with a a one standard deviation increase in stress-sensitivity PRS linked to a decrease of 0.67 points on the withdrawn-depressed subscale (uncorrected p-value = 0.026, FDR corrected p-value = 0.20) and a decrease of 1.31 points on total problems (uncorrected p-value = 0.023, FDR corrected p-value = 0.20). Stress-sensitivity PRS did not significantly affect any other CBCL scores. Sex nominally significantly affected some CBCL scores. Compared to average, girls’ internalizing, anxious-depressed, and somatic scores were 1.12 points (uncorrected p-value = 0.024, FDR corrected p-value = 0.091), 0.54 points (uncorrected p-value = 0.032, FDR corrected p-value = 0.095), and 0.63 points (uncorrected p-value = 0.018, FDR corrected p-value = 0.091) higher, respectively. Age was not significantly related to any CBCL scores.

***Lifetime Psychiatric Diagnoses***

For individuals of European ancestry, compared to average, girls had an increase of 1.48 in odds of receiving a lifetime diagnosis of any anxiety disorder other than panic disorder (FDR corrected p-value = 0.00000000016), an increase of 1.63 in odds of receiving a lifetime MDD diagnosis (FDR corrected p-value = 0.00000000016, and a decrease of 0.72 in odds of receiving a lifetime ADHD diagnosis (FDR corrected p-value = 0.0089) compared to average. Sex did not significantly affect any other CBCL subscale scores and did not significant influence odds of receiving a lifetime PTSD diagnosis. There were no significant relationships between age and any CBCL score or diagnosis.

For subjects of African ancestry, stress-sensitivity PRS, sex, and age were not significantly associated with likelihood of receiving a lifetime anxiety, ADHD, MDD, or PTSD diagnosis, with the exception that girls had a nominally significant (uncorrected p-value = 0.025, FDR corrected p-value = 0.38) increase of 1.44 in odds of receiving a lifetime MDD diagnosis compared to average.

Finally, for subjects of American admixed ancestry, sex and age, but not stress-sensitivity, affected the likelihood of receiving a lifetime diagnosis of ADHD, anxiety, and MDD. For girls, odds of receiving a diagnosis of anxiety or MDD were 1.66 points (FDR corrected p-value = 0.011) or 1.75 points (FDR corrected p-value = 0.011) higher on average, respectively. Odds of receiving a lifetime diagnosis of ADHD were also 0.44 points lower on average for girls, but this difference did not survive FDR correction (uncorrected p-value = 0.046). Sex did not significantly affect likelihood of receiving a lifetime PTSD diagnosis. A one standard deviation increase in age was nominally associated (uncorrected p-value = 0.0063, FDR corrected p-value = 0.094) with an increase of 2.69 points in odds of receiving a lifetime MDD diagnosis. Age did not affect likelihood of receiving a lifetime diagnosis of anxiety, MDD, or PTSD.

**Discussion**

Discussion of anticipated findings

*H1:* Given the strong links between stress, HPA axis activity, and psychiatric disorders, higher stress-sensitivity PRS will be associated with higher levels of psychiatric diagnoses and symptoms of psychopathology.

*H2:* Because the stress-sensitivity PRS was created based on results of an experimental manipulation rather than large-scale associations, the stress-sensitivity PRS will explain more variance in psychiatric disorders and symptoms associated with differences in stress sensitivity as compared to more traditional GWAS-derived PRS.

Increased stress sensitivity has been linked to conditions such as major depressive disorder (MDD) and social anxiety disorder (SAD) (Farmer & Kashdan, 2015; Hasler et al., 2004). This suggests that the stress sensitivity PRS may be related to MDD and SAD diagnoses based on the KSADS-COMP and the following CBCL subscales: internalizing, anxious/depressed, withdrawn/depressed, social problems, somatic problems (physiological symptoms which are often associated with anxiety).

Penner-Goeke et al. (2023) found that the stress sensitivity SNPs were associated with individuals with MDD who had previously experienced trauma. While they did not find a relationship between these SNPs and PTSD, they suggested that may be due to methodological constraints, as they were using data from a potentially underpowered GWAS. The stress sensitivity PRS in the proposed study may therefore be associated with PTSD diagnoses based on the KSADS-COMP.

SNPs in genetic regions linked to the HPA axis were able to predict ADHD symptom severity (van der Meer et al., 2017). This suggests that the stress sensitivity PRS in the proposed study might be associated with ADHD diagnoses based on the KSADS-COMP and increased scores on the CBCL attention subscale.

Because stress sensitivity has also been liked to increased risk of psychosis (Reininghaus et al., 2016), the stress sensitivity PRS may be associated with increased scores on the CBCL thought problems subscale.

Finally, increased stress sensitivity was recently linked to more externalizing problems (Borchers et al., 2024), suggesting that the stress sensitivity PRS could be associated with higher scores on the CBCL externalizing, rule-breaking, and aggression subscales.

*H1:* Higher stress-sensitivity PRS will be significantly associated with increased CBCL scores on internalizing, externalizing, total problems, and all eight subscales.

*H2:* Higher stress-sensitivity PRS will be significant associated with meeting criteria for MDD, ADHD, SAD, and PTSD based on the KSADS-COMP.

Limitations

Potential implications

**References**

Achenbach, T. (2011). *Encyclopedia of Clinical Neuropsychology*.

Achenbach, T. M. (2009). *The Achenbach system of empirically based assessment (ASEBA): Development, findings, theory, and applications*. University of Vermont, Research Center for Children, Youth, & Families.

ADHD Working Group of the Psychiatric Genomics Consortium (PGC), Early Lifecourse & Genetic Epidemiology (EAGLE) Consortium, 23andMe Research Team, Demontis, D., Walters, R. K., Martin, J., Mattheisen, M., Als, T. D., Agerbo, E., Baldursson, G., Belliveau, R., Bybjerg-Grauholm, J., Bækvad-Hansen, M., Cerrato, F., Chambert, K., Churchhouse, C., Dumont, A., Eriksson, N., Gandal, M., … Neale, B. M. (2019). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics*, *51*(1), 63–75. https://doi.org/10.1038/s41588-018-0269-7

Arcego, D. M., Buschdorf, J.-P., O’Toole, N., Wang, Z., Barth, B., Pokhvisneva, I., Rayan, N. A., Patel, S., De Mendonça Filho, E. J., Lee, P., Tan, J., Koh, M. X., Sim, C. M., Parent, C., De Lima, R. M. S., Clappison, A., O’Donnell, K. J., Dalmaz, C., Arloth, J., … Meaney, M. J. (2024). A Glucocorticoid-Sensitive Hippocampal Gene Network Moderates the Impact of Early-Life Adversity on Mental Health Outcomes. *Biological Psychiatry*, *95*(1), 48–61. https://doi.org/10.1016/j.biopsych.2023.06.028

Arloth, J., Bogdan, R., Weber, P., Frishman, G., Menke, A., Wagner, K. V., Balsevich, G., Schmidt, M. V., Karbalai, N., Czamara, D., Altmann, A., Trümbach, D., Wurst, W., Mehta, D., Uhr, M., Klengel, T., Erhardt, A., Carey, C. E., Conley, E. D., … Sullivan, P. F. (2015). Genetic Differences in the Immediate Transcriptome Response to Stress Predict Risk-Related Brain Function and Psychiatric Disorders. *Neuron*, *86*(5), 1189–1202. https://doi.org/10.1016/j.neuron.2015.05.034

Baldwin, J. R., Sallis, H. M., Schoeler, T., Taylor, M. J., Kwong, A. S. F., Tielbeek, J. J., Barkhuizen, W., Warrier, V., Howe, L. D., Danese, A., McCrory, E., Rijsdijk, F., Larsson, H., Lundström, S., Karlsson, R., Lichtenstein, P., Munafò, M., & Pingault, J.-B. (2022). A genetically informed Registered Report on adverse childhood experiences and mental health. *Nature Human Behaviour*, *7*(2), 269–290. https://doi.org/10.1038/s41562-022-01482-9

Barnhart, S., Garcia, A. R., & Karcher, N. R. (2022). Adolescent Mental Health and Family Economic Hardships: The Roles of Adverse Childhood Experiences and Family Conflict. *Journal of Youth and Adolescence*, *51*(12), 2294–2311. https://doi.org/10.1007/s10964-022-01671-9

Borchers, L. R., Yuan, J. P., Leong, J. K., Jo, B., Chahal, R., Ryu, J., Nam, A., Coury, S. M., & Gotlib, I. H. (2024). Sex-Specific Vulnerability to Externalizing Problems: Sensitivity to Early Stress and Nucleus Accumbens Activation Over Adolescence. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2024.01.011

Cao, C., Chen, M., Yang, S., Xu, Y., & Gu, J. (2024). Childhood maltreatment, multilocus HPA-axis genetic variation and adolescent comorbidity profiles of depressive and anxiety symptoms. *Child Abuse & Neglect*, *149*, 106683. https://doi.org/10.1016/j.chiabu.2024.106683

Choi, K. W., Wilson, M., Ge, T., Kandola, A., Patel, C. J., Lee, S. H., & Smoller, J. W. (2022). Integrative analysis of genomic and exposomic influences on youth mental health. *Journal of Child Psychology and Psychiatry*, *63*(10), 1196–1205. https://doi.org/10.1111/jcpp.13664

Compton, W. M., Dowling, G. J., & Garavan, H. (2019). Ensuring the Best Use of Data: The Adolescent Brain Cognitive Development Study. *JAMA Pediatrics*, *173*(9), 809. https://doi.org/10.1001/jamapediatrics.2019.2081

Fan, C. C., Loughnan, R., Wilson, S., Hewitt, J. K., ABCD Genetic Working Group, Agrawal, A., Dowling, G., Garavan, H., LeBlanc, K., Neale, M., Friedman, N., Madden, P., Little, R., Brown, S. A., Jernigan, T., & Thompson, W. K. (2023). Genotype Data and Derived Genetic Instruments of Adolescent Brain Cognitive Development Study® for Better Understanding of Human Brain Development. *Behavior Genetics*, *53*(3), 159–168. https://doi.org/10.1007/s10519-023-10143-0

Farmer, A. S., & Kashdan, T. B. (2015). Stress Sensitivity and Stress Generation in Social Anxiety Disorder: A Temporal Process Approach. *Journal of Abnormal Psychology*, *124*(1), 102–114. https://doi.org/10.1037/abn0000036

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., Koss, M. P., & Marks, J. S. (1998). Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults. *American Journal of Preventive Medicine*, *14*(4), 245–258. https://doi.org/10.1016/S0749-3797(98)00017-8

Gogarten, S. M., Sofer, T., Chen, H., Yu, C., Brody, J. A., Thornton, T. A., Rice, K. M., & Conomos, M. P. (2019). Genetic association testing using the GENESIS R/Bioconductor package. *Bioinformatics*, *35*(24), 5346–5348. https://doi.org/10.1093/bioinformatics/btz567

Hasler, G., Drevets, W. C., Manji, H. K., & Charney, D. S. (2004). Discovering Endophenotypes for Major Depression. *Neuropsychopharmacology*, *29*(10), 1765–1781. https://doi.org/10.1038/sj.npp.1300506

Hoffman, K. W., Tran, K. T., Moore, T. M., Gataviņš, M. M., Visoki, E., Kwon, O., DiDomenico, G. E., Chaiyachati, B. H., Schultz, L. M., Almasy, L., Hayes, M. R., Daskalakis, N. P., & Barzilay, R. (2024). Exposomic and polygenic contributions to allostatic load in early adolescence. *Nature Mental Health*, 1–12. https://doi.org/10.1038/s44220-024-00255-9

Hoggart, C. J., Choi, S. W., García-González, J., Souaiaia, T., Preuss, M., & O’Reilly, P. F. (2024). BridgePRS leverages shared genetic effects across ancestries to increase polygenic risk score portability. *Nature Genetics*, *56*(1), 180–186. https://doi.org/10.1038/s41588-023-01583-9

Howard, D. M., Adams, M. J., Clarke, T.-K., Hafferty, J. D., Gibson, J., Shirali, M., Coleman, J. R. I., Hagenaars, S. P., Ward, J., Wigmore, E. M., Alloza, C., Shen, X., Barbu, M. C., Xu, E. Y., Whalley, H. C., Marioni, R. E., Porteous, D. J., Davies, G., Deary, I. J., … McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience*, *22*(3), 343–352. https://doi.org/10.1038/s41593-018-0326-7

Jimeno, B., & Rubalcaba, J. G. (n.d.). *Modelling the role of glucocorticoid receptor as mediator of endocrine responses to environmental challenge*.

Karcher, N. R., Klaunig, M. J., Elsayed, N. M., Taylor, R. L., Jay, S. Y., & Schiffman, J. (2022). Understanding Associations Between Race/Ethnicity, Experiences of Discrimination, and Psychotic-like Experiences in Middle Childhood. *Journal of the American Academy of Child & Adolescent Psychiatry*, *61*(10), 1262–1272. https://doi.org/10.1016/j.jaac.2022.03.025

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kobak, K. A., Kratochvil, C. J., Stanger, C., & Kaufman, J. (2013). Computerized screening of comorbidity in adolescents with substance or psychiatric disorders. *Anxiety Disorders and Depression.(La Jolaa, CA)*.

Lahey, B. B., Durham, E. L., Brislin, S. J., Barr, P. B., Dick, D. M., Moore, T. M., Pierce, B. L., Tong, L., Reimann, G. E., Jeong, H. J., Dupont, R. M., & Kaczkurkin, A. N. (2024). Mapping potential pathways from polygenic liability through brain structure to psychological problems across the transition to adolescence. *Journal of Child Psychology and Psychiatry*, jcpp.13944. https://doi.org/10.1111/jcpp.13944

Maxwell, M. Y., Taylor, R. L., & Barch, D. M. (2021, May 1). *Evidence That Neighborhood Threat and Brain Volume Mediate the Relationship Between Neighborhood Poverty and Children’s Psychopathology* [Poster].

McLaughlin, K. A., Weissman, D., & Bitrán, D. (2019). Childhood Adversity and Neural Development: A Systematic Review. *Annual Review of Developmental Psychology*, *1*(1), 277–312. https://doi.org/10.1146/annurev-devpsych-121318-084950

Monari, S., Guillot De Suduiraut, I., Grosse, J., Zanoletti, O., Walker, S. E., Mesquita, M., Wood, T. C., Cash, D., Astori, S., & Sandi, C. (2024). Blunted Glucocorticoid Responsiveness to Stress Causes Behavioral and Biological Alterations That Lead to Posttraumatic Stress Disorder Vulnerability. *Biological Psychiatry*, *95*(8), 762–773. https://doi.org/10.1016/j.biopsych.2023.09.015

Moore, T. M., Visoki, E., Argabright, S. T., Didomenico, G. E., Sotelo, I., Wortzel, J. D., Naeem, A., Gur, R. C., Gur, R. E., Warrier, V., Guloksuz, S., & Barzilay, R. (2022). Modeling environment through a general exposome factor in two independent adolescent cohorts. *Exposome*, *2*(1), osac010. https://doi.org/10.1093/exposome/osac010

Nievergelt, C. M., Maihofer, A. X., Atkinson, E. G., Chen, C.-Y., Choi, K. W., Coleman, J. R. I., Daskalakis, N. P., Duncan, L. E., Polimanti, R., Aaronson, C., Amstadter, A. B., Andersen, S. B., Andreassen, O. A., Arbisi, P. A., Ashley-Koch, A. E., Austin, S. B., Avdibegoviç, E., Babić, D., Bacanu, S.-A., … Koenen, K. C. (2024). Genome-wide association analyses identify 95 risk loci and provide insights into the neurobiology of post-traumatic stress disorder. *Nature Genetics*, *56*(5), 792–808. https://doi.org/10.1038/s41588-024-01707-9

Otowa, T., Hek, K., Lee, M., Byrne, E. M., Mirza, S. S., Nivard, M. G., Bigdeli, T., Aggen, S. H., Adkins, D., Wolen, A., Fanous, A., Keller, M. C., Castelao, E., Kutalik, Z., Der Auwera, S. V., Homuth, G., Nauck, M., Teumer, A., Milaneschi, Y., … Hettema, J. M. (2016). Meta-analysis of genome-wide association studies of anxiety disorders. *Molecular Psychiatry*, *21*(10), 1391–1399. https://doi.org/10.1038/mp.2015.197

Palamarchuk, I. S., Slavich, G. M., Vaillancourt, T., & Rajji, T. K. (2023). Stress-related cellular pathophysiology as a crosstalk risk factor for neurocognitive and psychiatric disorders. *BMC Neuroscience*, *24*(1), 65. https://doi.org/10.1186/s12868-023-00831-2

Penner-Goeke, S., Bothe, M., Kappelmann, N., Kreitmaier, P., Kaya, E., Pöhlchen, D., Kühnel, A., Czamara, D., BeCOME working group, Glaser, L. V., Roeh, S., Ködel, M., Monteserin-Garcia, J., Rummel, C., Arloth-Knauer, J., Diener-Hölzl, L., Woelfel, B., Sauer, S., Riesenberg, S., … Binder, E. B. (2022). *Assessment of glucocorticoid-induced enhancer activity of eSNP regions using STARR-seq reveals novel molecular mechanisms in psychiatric disorders* [Preprint]. Genetic and Genomic Medicine. https://doi.org/10.1101/2022.05.18.22275090

Penner-Goeke, S., Bothe, M., Rek, N., Kreitmaier, P., Pöhlchen, D., Kühnel, A., Glaser, L. V., Kaya, E., Krontira, A. C., Röh, S., Czamara, D., Ködel, M., Monteserin-Garcia, J., Diener, L., Wölfel, B., Sauer, S., Rummel, C., Riesenberg, S., Arloth-Knauer, J., … Binder, E. B. (2023). High-throughput screening of glucocorticoid-induced enhancer activity reveals mechanisms of stress-related psychiatric disorders. *Proceedings of the National Academy of Sciences*, *120*(49), e2305773120. https://doi.org/10.1073/pnas.2305773120

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A. R., Bender, D., Maller, J., Sklar, P., de Bakker, P. I. W., Daly, M. J., & Sham, P. C. (2007). PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *American Journal of Human Genetics*, *81*(3), 559–575.

Qiu, A., & Liu, C. (2023). Pathways link environmental and genetic factors with structural brain networks and psychopathology in youth. *Neuropsychopharmacology*, *48*(7), 1042–1051. https://doi.org/10.1038/s41386-023-01559-7

Reininghaus, U., Kempton, M. J., Valmaggia, L., Craig, T. K. J., Garety, P., Onyejiaka, A., Gayer-Anderson, C., So, S. H., Hubbard, K., Beards, S., Dazzan, P., Pariante, C., Mondelli, V., Fisher, H. L., Mills, J. G., Viechtbauer, W., McGuire, P., van Os, J., Murray, R. M., … Morgan, C. (2016). Stress Sensitivity, Aberrant Salience, and Threat Anticipation in Early Psychosis: An Experience Sampling Study. *Schizophrenia Bulletin*, *42*(3), 712–722. https://doi.org/10.1093/schbul/sbv190

Ruan, Y., Lin, Y.-F., Feng, Y.-C. A., Chen, C.-Y., Lam, M., Guo, Z., Stanley Global Asia Initiatives, Ahn, Y. M., Akiyama, K., Arai, M., Baek, J. H., Chen, W. J., Chung, Y.-C., Feng, G., Fujii, K., Glatt, S. J., Ha, K., Hattori, K., Higuchi, T., … Ge, T. (2022). Improving polygenic prediction in ancestrally diverse populations. *Nature Genetics*, *54*(5), 573–580. https://doi.org/10.1038/s41588-022-01054-7

Seah, C., Breen, M. S., Rusielewicz, T., Bader, H. N., Xu, C., Hunter, C. J., McCarthy, B., Deans, P. J. M., Chattopadhyay, M., Goldberg, J., Desarnaud, F., Makotkine, I., Flory, J. D., Bierer, L. M., Staniskyte, M., NYSCF Global Stem Cell Array® Team, Bauer, L., Brenner, K., Buckley-Herd, G., … Yehuda, R. (2022). Modeling gene × environment interactions in PTSD using human neurons reveals diagnosis-specific glucocorticoid-induced gene expression. *Nature Neuroscience*, *25*(11), 1434–1445. https://doi.org/10.1038/s41593-022-01161-y

Sun, K., & Cao, C. (2024). The effects of childhood maltreatment, recent interpersonal and noninterpersonal stress, and HPA-axis multilocus genetic variation on prospective changes in adolescent depressive symptoms: A multiwave longitudinal study. *Development and Psychopathology*, 1–12. https://doi.org/10.1017/S0954579424000269

Teeuw, J., Mota, N. R., Klein, M., Blankenstein, N. E., Tielbeek, J. J., Jansen, L. M. C., Franke, B., & Hulshoff Pol, H. E. (2023). Polygenic risk scores and brain structures both contribute to externalizing behavior in childhood—A study in the Adolescent Brain and Cognitive Development (ABCD) cohort. *Neuroscience Applied*, *2*, 101128. https://doi.org/10.1016/j.nsa.2023.101128

Thapaliya, B., Calhoun, V. D., & Liu, J. (2021). Environmental and genome-wide association study on children anxiety and depression. *2021 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, 2330–2337. https://doi.org/10.1109/BIBM52615.2021.9669291

Thompson, E. L., Lever, N. A., Connors, K. M., Cloak, C. C., Reeves, G., & Chang, L. (2022). Associations between potentially traumatic events and psychopathology among preadolescents in the Adolescent Brain and Cognitive Development Study ®. *Journal of Traumatic Stress*, *35*(3), 852–867. https://doi.org/10.1002/jts.22793

Townsend, L., Kobak, K., Kearney, C., Milham, M., Andreotti, C., Escalera, J., Alexander, L., Gill, M. K., Birmaher, B., Sylvester, R., Rice, D., Deep, A., & Kaufman, J. (2020). Development of Three Web-Based Computerized Versions of the Kiddie Schedule for Affective Disorders and Schizophrenia Child Psychiatric Diagnostic Interview: Preliminary Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *59*(2), 309–325. https://doi.org/10.1016/j.jaac.2019.05.009

van der Meer, D., Hoekstra, P. J., van Donkelaar, M., Bralten, J., Oosterlaan, J., Heslenfeld, D., Faraone, S. V., Franke, B., Buitelaar, J. K., & Hartman, C. A. (2017). Predicting attention-deficit/hyperactivity disorder severity from psychosocial stress and stress-response genes: A random forest regression approach. *Translational Psychiatry*, *7*(6), e1145–e1145. https://doi.org/10.1038/tp.2017.114

Wainberg, M., Jacobs, G. R., Voineskos, A. N., & Tripathy, S. J. (2022). Neurobiological, familial and genetic risk factors for dimensional psychopathology in the Adolescent Brain Cognitive Development study. *Molecular Psychiatry*, *27*(6), 2731–2741. https://doi.org/10.1038/s41380-022-01522-w

Wang, R., Lifelines Cohort Study, Hartman, C. A., & Snieder, H. (2023). Stress-related exposures amplify the effects of genetic susceptibility on depression and anxiety. *Translational Psychiatry*, *13*(1), 27. https://doi.org/10.1038/s41398-023-02327-3

Weiss, N. H., Goncharenko, S., Forkus, S. R., Ferguson, J. J., & Yang, M. (2023). Longitudinal Investigation of Bidirectional Relations Between Childhood Trauma and Emotion-Driven Impulsivity in the Adolescent Brain Cognitive Development Study. *Journal of Adolescent Health*, *73*(4), 731–738. https://doi.org/10.1016/j.jadohealth.2023.05.027

Zheng, Z., Liu, S., Sidorenko, J., Wang, Y., Lin, T., Yengo, L., Turley, P., Ani, A., Wang, R., Nolte, I. M., Snieder, H., LifeLines Cohort Study, Aguirre-Gamboa, R., Deelen, P., Franke, L., Kuivenhoven, J. A., Lopera Maya, E. A., Sanna, S., Swertz, M. A., … Zeng, J. (2024). Leveraging functional genomic annotations and genome coverage to improve polygenic prediction of complex traits within and between ancestries. *Nature Genetics*, *56*(5), 767–777. https://doi.org/10.1038/s41588-024-01704-y

Zorn, J. V., Schür, R. R., Boks, M. P., Kahn, R. S., Joëls, M., & Vinkers, C. H. (2017). Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *77*, 25–36. https://doi.org/10.1016/j.psyneuen.2016.11.036