**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**

Brief literature review

rationale

This part should be 5-10 pages total

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to MDD and SAD diagnoses based on the KSADS-COMP and the following CBCL subscales: internalizing, anxious/depressed, withdrawn/depressed, social problems, somatic problems (physiological symptoms which are often associated with anxiety).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.

**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 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 and MDD PRS 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) or Howard et al. (2019), respectively. 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. Summary statistics used to generate stress-sensitivity PRS were experimentally derived from a sample of European men. However, for MDD, summary statistics were acquired from a meta-analysis of multiple genome-wide association studies (GWAS) from Howard et al. (2019).

To better account for ancestry-related effects, final results will use a more sophisticated method to generate PRS such as PRS-Csx (Ruan et al., 2022), BridgePRS (Hoggart et al., 2024), or SBayesRC (Zheng et al., 2024). In addition to stress-sensitivity and MDD PRS, full results will include PRS for ADHD, PTSD, and anxiety disorders will be calculated based on summary statistics from ADHD Working Group of the Psychiatric Genomics Consortium (PGC) et al. (2019), Nievergelt et al. (2024), and Otowa et al. (2016) respectively.

**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.

**MDD PRS**

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

***Lifetime Psychiatric Diagnoses***

**Discussion**

Discussion of anticipated findings

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

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

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

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

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

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)*.

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

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.

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

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

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