Behavior Genetics
https://doi.org/10.1007/s10519-023-10134-1

ORIGINAL RESEARCH

Polygenic Risk for Schizophrenia, Major Depression, and Post-traumatic Stress Disorder and Hippocampal Subregion Volumes in Middle Childhood

Jacob G. Pine[1] · Sarah E. Paul[1] · Emma Johnson[2] · Ryan Bogdan[1] · Sridhar Kandala[2] · Deanna M. Barch[1,2,3]

Received: 2 November 2022 / Accepted: 17 January 2023

Abstract
Studies demonstrate that individuals with diagnoses for Major Depressive Disorder (MDD), Post-traumatic Stress Disorder (PTSD), and Schizophrenia (SCZ) may exhibit smaller hippocampal gray matter relative to otherwise healthy controls, although the effect sizes vary in each disorder. Existing work suggests that hippocampal abnormalities in each disorder may be attributable to genetic liability and/or environmental variables. The following study uses baseline data from the Adolescent Brain and Cognitive Development^{SM} Study (ABCD Study®) to address three open questions regarding the relationship between genetic risk for each disorder and hippocampal volume reductions: (a) whether polygenic risk scores (PGRS) for MDD, PTSD, and SCZ are related to hippocampal volume; (b) whether PGRS for MDD, PTSD, and SCZ are differentially related to specific hippocampal subregions along the longitudinal axis; and (c) whether the association between PGRS for MDD, PTSD, and SCZ and hippocampal volume is moderated by sex and/or environmental adversity. In short, we did not find associations between PGRS for MDD, PTSD, and SCZ to be significantly related to any hippocampal subregion volumes. Furthermore, neither sex nor enviornmental adversity significantly moderated these associations. Our study provides an important null finding on the relationship genetic risk for MDD, PTSD, and SCZ to measures of hippocampal volume.

Keywords Hippocampus · Schizophrenia · Depression · Postraumatic-stress disorder

Introduction

Hippocampal abnormalities are associated with a host of mental disorders (Heckers and Konradi 2015; Belleau et al. 2019). The hippocampus plays a critical role in learning, memory, and stress responsivity, and as a result hippocampal abnormalities in clinical populations are thought to convey etiological information about the ultimate causes and consequences of mental illness (Lisman et al. 2017; McEwen 2012). Studies demonstrate that individuals with diagnoses for Major Depressive Disorder (MDD), Post-traumatic Stress Disorder (PTSD), and Schizophrenia (SCZ) may exhibit smaller hippocampal gray matter relative to otherwise healthy controls (Schmaal et al. 2020; van Erp et al. 2016; Logue et al. 2018), although the effect sizes vary in each disorder (Cohen's d: SCZ = −0.46; PTSD = −0.17; MDD = −0.14). Existing work suggests that hippocampal abnormalities in each disorder may be attributable to genetic liability (Frodl et al. 2012; Gilbertson et al. 2002; Grotzinger et al. 2022) and/or environmental variables (Kronmüller et al. 2008; Mondelli et al. 2011).

Current knowledge regarding the relationship between MDD, PTSD, SCZ and hippocampal volume reductions is limited by several open questions. First, although hippocampal volume is highly heritable in populations of healthy adults (Elman et al. 2019; Patel et al. 2017: ~ 80%), it is not clear to what extent these findings translate to clinical populations. Environmental adversity can influence the heritability of a phenotype in a population (Harden 2021; Rimfeld et al. 2018), and those with MDD, PTSD, and SCZ

Edited by Chun Chieh Fan.

✉ Jacob G. Pine
j.pine@wustl.edu

[1] Department of Psychological & Brain Sciences, Washington University in St. Louis, St. Louis, MO 63130, USA

[2] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA

[3] Department of Radiology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110, USA

Published online: 31 January 2023

tend to have experienced more environmental adversity relative to healthy populations (Hammen 2005; Werner et al. 2007; Agerbo et al. 2015). Thus it is unclear whether individual differences in genetic loci may explain hippocampal volume reductions in MDD, PTSD, and SCZ in the same way that they do in healthy populations. Second, although hippocampal volume is reduced in MDD, PTSD, and SCZ, it is unclear to what extent hippocampal volume reductions in each of these disorders might reflect either a shared neurobiological mechanism that is common across disorders, or a set of unique neurobiological mechanisms that are specific to each respective disorder. Individual differences in genetic risk loci for MDD, PTSD, and SCZ may capture shared and unique elements of the neurobiological mechanisms that produce hippocampal volume reductions in these disorders. Thus, genetically-informative studies may provide some clarity regarding the source of hippocampal volume reductions across MDD, PTSD, and SCZ. Lastly, it is unclear to what extent the genetic relationship between MDD, PTSD, and SCZ and hippocampal volume may be moderated by variables such as sex or exposure to stress (Walker and Difiorio 1997; McKeever and Huff 2003; Colodro-Conde et al. 2018).

The following study addresses these three open questions by applying polygenic risk scores (PGRS) to understand genetic contributions to hippocampal volume measurements from the Adolescent Brain and Cognitive Development (ABCD) study. A polygenic risk score is a measure of genetic risk that can be computed for an individual based on the weighted sum of common variant, genetic-risk loci that individual possesses; the relative weighting of genetic loci is determined by available genome wide association study (GWAS) summary statistics. Thus, PGRS offer a way to capture genetic risk in an individual without the use of a GWAS or family-based study design. Consequently, this tool offers an opportunity to investigate open questions regarding the relationship between individual differences in genetic risk for MDD, PTSD, and SCZ and associations with hippocampal volume.

At present, it is not clear whether there is a link between the genetic contributions to MDD, PTSD, and SCZ and reductions in hippocampal volume. It is reasonable to hypothesize that such a link exists, though, given that each disorder is significantly heritable on the one hand, and hippocampal volume is also significantly heritable on the other (Elman et al. 2019; Patel et al. 2017: ~ 82%). Twin and family-based study designs find that SCZ is generally the most heritable condition of the three disorders (SCZ: Cardno et al. 1999: 80%; Hilker et al. 2018: 79%), while there are no clear differences in the magnitude of heritability estimates between PTSD (Sartor et al. 2012: 46%; Sartor et al. 2011: 72% [all-female sample]), and MDD (Bierut et al. 1999: 36–44%; Guffanti et al. 2016: 67%; Kendler et al. 1993: 70%). When considering GWAS, SNP-based heritability estimates are somewhat higher for SCZ (Baselmans et al. 2021: 26%) than PTSD (Duncan et al. 2018: 15%) and MDD (Duncan et al. 2018: ~22%; Baselmans et al. 2021: 11%). Existing work, however, suggests that SNP-based heritability estimates are much higher for PTSD in females than in males (Duncan et al. 2018, female: 29%; male: not-significant). In summary, the existing literature clearly demonstrates that genetic inheritance confers a significant amount of risk for each disorder. This suggests that phenotypes associated with each disorder (e.g., hippocampal volume) may share at least some common genetic correlates with risk for each respective disorder.

Some studies have investigated links between PGRS for MDD, PTSD, and SCZ and hippocampal volume, however, findings from these studies are mixed: some studies find associations between PGRS and hippocampal volume (Alnæs et al. 2019; Harrisberger et al. 2016; Jalbrzikowski et al. 2019; Liu et al. 2020), while others fail to demonstrate such relationships (Reus et al. 2017; null genetic correlations: Bahrami et al. 2022; Grotzinger et al. 2022). Several factors may be contributing to the lack of consistency regarding these findings. First, PGRS-based studies of hippocampal volume typically treat the hippocampus as a homogeneous structure. The hippocampus, however, is composed of various "subregions", which delineate discrete subsections of the hippocampus along its longitudinal axis, and "subfields," which delineate discrete subsections of the hippocampus along its transverse axis (Genon et al. 2021). Furthermore, certain hippocampal subregions are thought to be uniquely affected in certain disorders (McHugo et al. 2018, 2020), and some subregions may be uniquely associated with risk for developing a disorder (Sahakyan et al. 2021). Thus, PGRS-based studies of hippocampal volume may miss important subregion-specific associations by only investigating total hippocampal volume. In addition, PGRS-based studies of hippocampal volume may also miss important developmental influences. For instance, PGRS-based studies of hippocampal volume are often conducted in populations of varying ages, with some studies including participants with decades of age difference (Reus et al. 2017; also see Bahrami et al. 2022; Grotzinger et al. 2022). For some disorders, however, hippocampal volume reductions are thought to be caused by developmentally-specific neurobiological processes, which may not have yet occurred in all individuals of a given study's sample. For instance, hippocampal volume reductions in SCZ are thought to be influenced by NMDA receptor dysfunction, which causes excitotoxic dysregulation of pyramidal cell firing in the hippocampus (Lieberman et al. 2018), but this may only occur in post-pubertal adults (Olney et al. 1999). Hippocampal volume reductions in other disorders (e.g PTSD, MDD) are thought to be mediated by less developmentally specific neurobiological processes,

such as stress-induced HPA-axis dysregulation (Belleau et al. 2019; McEwen 2012; Dunsmoor et al. 2022). The following study investigates relationships between PGRS and specific hippocampal subregions, and does so in a sample of individuals that are all within 2 years old of one another. As our study is more homogeneous with respect to age, we may be better equipped to demonstrate relationships between PGRS for MDD, PTSD, and SCZ and hippocampal volume than previous PGRS-based studies.

It is currently not clear whether hippocampal volume reductions in MDD, PTSD, and SCZ are the product of common or unique neurobiological mechanisms; although our study does not directly measure the components of these neurobiological processes in those with MDD, PTSD, or SCZ, our study may nevertheless be able to provide insight through the use of PGRS. Recent Genomic SEM (Grotzinger et al. 2019) analyses have demonstrated that the genetic factor that captures the most variance in genetic risk for PTSD and MDD is largely separable from the genetic factor that captures genetic risk for SCZ (Grotzinger et al. 2022. As a result, it is possible that PGRS for SCZ may be associated with hippocampal volume estimates, while PGRS for PTSD and MDD may not demonstrate such associations (or vice versa). This may be expected given that different neurobiological mechanisms may be accounting for hippocampal volume reductions in SCZ (Lieberman et al. 2018; Olney et al. 1999), relative to MDD and PTSD ((Belleau et al. 2019; McEwen 2012; Dunsmoor et al. 2022). On the other hand, other evidence suggests that dysregulation in glutamatergic and GABAergic systems may represent a common mechanism of hippocampal volume reductions in MDD, PTSD, and SCZ (Heckers and Konradi 2015; Belleau et al. 2019). If this is the case, we might expect PGRS from each disorder, to the extent that they relate to such common mechanisms, to be similarly related to hippocampal volume. Although our study will not be able to directly test whether different neurobiological mechanisms are accounting for hippocampal volume reductions in MDD, PTSD, and SCZ, our investigations of PGRS for each of these disorders and hippocampal subregion volumes may provide additional insight regarding this consideration.

It is also possible that the genetic link between MDD, PTSD, SCZ, and hippocampal volume may be moderated by other variables. For instance, as previously mentioned, sex may moderate the influence of genetic variables on disease risk. This hypothesis is supported by evidence that PTSD is more heritable in women than men (Duncan et al. 2018), as well as evidence that SCZ may be more prevalent in men than women (Abel et al. 2010). In addition, the genetic link between MDD, PTSD, SCZ, and hippocampal volume may be moderated by exposure to environmental adversity. This is the premise of the diathesis-stress model (Rosenthal 1963), which proposes that psychopathological outcomes are the result of multiplicative interactions between genetic risk factors and environmental stressors. There has been broad support for this theory in SCZ (Pruessner et al. 2017), PTSD (McKeever and Huff 2003), and MDD (Colodro-Conde et al. 2018). In addition, numerous studies have demonstrated the influence of chronic stress on hippocampal gray matter (e.g McEwen, 2012; Taylor et al. 2020). It is thus possible that genetic risk for MDD, PTSD, and SCZ may interact with exposure to environmental stressors in order to predict relative reductions in hippocampal volume. In this case, one might hypothesize that PGRS for several forms of psychopathology may be more predictive of hippocampal volume reductions in the context of adversity.

The following study provides a cross-sectional investigation of the above three questions through the analysis of 4,619 participants from the Adolescent Brain and Cognitive Development^{SM} Study (ABCD Study®). First, mixed-effects regression analyses were used to investigate the relationships between PGRS for MDD, PTSD, and SCZ, and subregions of the hippocampal longitudinal axis. This is the first study to investigate PGRS for these disorders in hippocampal longitudinal axis regions. Previous studies have investigated associations between PGRS and hippocampal transverse axis subregions (Alnæs et al. 2019), however recent work suggests that hippocampal transverse axis segmentations may be invalid when using conventional MRI imaging parameters (Wisse et al. 2014, 2021). Therefore, transverse axis subfields were not analyzed as part of this study. Second, differential relationships between PGRS for MDD, PTSD, and SCZ and hippocampal subregion volumes were investigated. These analyses cannot provide definitive conclusions regarding the mechanisms that give rise to hippocampal volume reductions in each disorder, however, these analyses may be able to contribute our understanding of these mechanisms. Lastly, this study investigated whether PGRS for MDD, PTSD, and SCZ interacted with either sex or environmental exposures to stress in order to predict hippocampal volume. These analyses examined whether hippocampal volume reductions commonly seen in MDD, PTSD, and SCZ may result from gene-environment interactions.

Materials and methods

Participants

A sample of 11,886 children who completed the baseline session of the ABCD Study provided data for this investigation (release 3.0 for genomic data; release 3.0 for phenotypic data). The ABCD Study is an ongoing longitudinal study of child development and health that recruited from 22 research sites across the United States (Volkow et al. 2018). Participants who did not have quality controlled T1 and T2

structural scans (N =2,249), those whose T1 or T2 structural scans failed quality control checks (N = 1,108), and those of non-European genomic ancestry (n=5,734) were excluded leaving a final primary analytic sample of 4,619 participants of European ancestry (EA). We also conducted analyses in those of genomically-confirmed African-American ancestry (AA: 1063). Discovery GWASs of European (Trubetskoy et al. 2022) and African American (Bigdeli et al. 2021) ancestries were used to form ancestry specific polygenic risk scores (PGRS; see below). No other ancestries were evaluated due to the lack of ancestry-specific discovery GWAS across all three phenotypes, the relatively small sample size of other ancestries in our ABCD target sample, and the poor predictive utility of PGRS applied across ancestries (Duncan et al. 2019; Martin et al. 2019).

MRI acquisition and processing

Structural T1- and T2-weighted MRI scans were acquired at the baseline session using harmonized pulse sequences (T1: TE = 2–2.9 ms, TR = 6.31–2500 ms, T1 = 1,060 ms, flip angle = 8 degrees, FOV = 256 x 256, resolution = 1 mm isotropic, slice thickness, slices = 176–225; T2: TE = 60–565 ms, FOV = 256 x 256, resolution = 1 mm isotropic, slices= 176–225) across seven 3T MRI scanner models (Siemens: Prisma, Prisma Fit; Phillips: Achieva dStream, Ingenia, Signa Creator, Discovry MR 750). Acquisition details are provided in Casey et al. (2018). The T1 and T2-weighted structural scans used for this study were processed by the Developmental Cognition and Neuroimaging (DCAN) labs as part of the ABCD-BIDS Community Collection (ABCC). These methods are described in detail at the following webpage: https://collection3165.readthedocs.io/en/stable/.

Hippocampal volume estimation

Segmentation of hippocampal subregions was conducted using both T1 and T2 images from the Freesurfer v7.0 automated hippocampal subfield segmentation tool (Iglesias et al. 2015). This tool yields numerous hippocampal subregions as well as an aggregated measure of total hippocampal volume. Only the longitudinal axis subregions and total hippocampal volume estimates were utilized; this study did not utilize hippocampal volume estimates from transverse axis subfields. Thus, this study involved the analysis of twelve hippocampal volume estimates: one estimate each for the hippocampal head, hippocampal body, hippocampal tail and whole hippocampus, with one set of these four estimates being obtained for both the left and right hemispheres, and an additional set of these four estimates being obtained by averaging across hemispheres.The Freesurfer hippocampal segmentation tool employs a probabilistic atlas built from a combination of 7T ultra-high field resolution, 0.13 mm^3 ex vivo, MRI scans, which were used to isolate hippocampal substructures, and a separate dataset of in vivo T1-weighted, 1 mm, MRI scans of the whole brain, which were used to isolate the total hippocampus from surrounding neural structures (e.g entorhinal cortex, amygdala). The main body of this paper utilizes hippocampal subregion measures that are averaged across hemispheres, although analyses for left and right hippocampal subregions are displayed in the supplementary materials.

Polygenic risk scores

The Rutgers University Cell and DNA repository (now known as Sampled) genotyped saliva samples from study participants using the Smokescreen array (Baurley et al. 2016). We used the Rapid Imputation and Computational PIpeLIne for Genome-Wide Association Studies (RICOPILI; Lam et al. 2019) to perform quality control (QC) on the 11,099 individuals with available ABCD Study phase 3.0 genotypic data, using RICOPILI's default parameters. The 10,585 individuals who passed QC checks were matched to broad self-report racial groups using the ABCD Study parent survey. 6,787 parents/caregivers indicated that their child's race was only "white", and 5,561 of those individuals did not endorse any Hispanic ethnicity/origin. Further, we identified 1,675 parents/caregivers who indicated that their child's race was only "black", and 1,584 of those individuals did not endorse any Hispanic ethnicity/origin. After performing a second round of QC on these sub-samples, 5,556 non-Hispanic White and 1,584 non-Hispanic Black individuals were retained in the analyses. Principal component analysis (PCA) in RICOPILI was used to confirm the genetic ancestry of these individuals by mapping onto the 1000 Genomes reference panel, resulting in PCA-selected European- and African-ancestry subsets. Each ancestry subset was then imputed to the TOPMed imputation reference panel 38. Imputation dosages were converted to best-guess hard-called genotypes, and only SNPs with $R^2 > 0.8$ and MAF > 0.01 were kept for PGRS analyses.

PGRS were generated using the PRS-CS software package and the largest available GWASs for schizophrenia, depression, and PTSD in European and African American ancestries (Ge et al. 2019; see supplementary materials for characteristics of GWASs used). PRS-CS assumes a general distribution of effect sizes across the genome, and then reweights SNPs based on this assumption, their observed effect size in the discovery GWAS, and their linkage disequilibrium (LD) before averaging weights for every SNP to create a final score. To maximize prediction in the African ancestry subset of ABCD, we used PRS-CSx's (Ruan et al. 2022) "meta"option 23 to create polygenic risk scores that leveraged the larger sample size of the European ancestry version of the discovery GWAS by meta-analyzing those

weights along with weights from the smaller, ancestry-matched discovery GWAS. After deriving SNP weights using PRS-CS and PRS-CSx, we then used PLINK 1.9's (Chang et al. 2015) *–score* command to produce PGRS in the ABCD sample. We scaled the PGRS to a mean of zero and standard deviation of one before including them in regression models.

Environmental adversity

Parent self-reported income, trauma exposure, and area deprivation index were used as independent indices of environmental adversity. Parent self-reported income was the combined income of the primary caretaker and any additional household members, and was represented on a one-to-ten scale, with one representing incomes of less than $5,000 a year, and ten representing incomes greater than $200,000 a year (Barch et al. 2016). Parent-reported child trauma exposure was defined as the summation of traumatic events endorsed on the 16 yes/no list of traumatic experiences (e.g., natural disaster, car accident, sexual abuse, etc.) within the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al. 1997). The area deprivation index captures 17 factors associated with socioeconomic disadvantage given an individual's home address, including median income, educational attainment levels, and rates of employment for a given area, among other factors (Kind et al. 2014; Kind and Buckingham 2018). Area Deprivation scores in our sample ranged from 0 to 100 (Median = 32) with higher scores reflecting greater socioeconomic disadvantage (i.e worse socioeconomic status). These indices were selected due there use in previous studies that have investigated relationships between environmental adversity and hippocampal volume (Botdorf et al. 2022; Hanson et al. 2011; Taylor et al. 2020).

Statistical analyses

Linear mixed effects models were used to assess the relationship between PGRS and hippocampal subregion volumes. Thirty-six models were run; each model analyzed the association between one of three PGRS scores and one of twelve hippocampal volume measures (i.e the left, right, and hemisphere-aggregated hippocampal head, body, tail, and whole hippocampus). The influence of participant age, participant sex at birth, total brain volume, and each of ten ancestral genomic principal components were included as covariates in each model. Given that prior work (Kraus et al. 2019; Bossini et al. 2007; Vermetten et al. 2003, though see Vythilingam et al. 2004; Godlewska et al. 2014 for counter-examples) provides some indication that psychiatric treatment, most notably the use of selective serotonin reuptake inhibitors (SSRIs) may be related to hippocampal volume, both prenatal SSRI exposures and childhood use of SSRIs were included as covariates. These two variables were coded as discrete, binary, variables. Approximately 3% of the European American (N = 124) and 2% of the African American sample (N = 25) reported prenatal exposure to SSRIs. Approximately 3% of the European American (N = 102) and 2% of the African American sample (N = 16) reported childhood SSRI use. In these models, PGRS for MDD, PTSD, and SCZ were included as fixed effects, and the influence of data collection site was modeled as both a random intercept and random slope on the effect of PGRS on each hippocampal subregion volume. Participant family was not included as a random effect as the majority of our sample was composed of families with only one child, which precluded estimating the influence of family as a random variable. In each model, PGRS were standardized, while all other variables were untransformed. In secondary analyses, we tested whether PGRS-hippocampal associations (n=36) were moderated by environmental adversity (n=3: income, trauma exposure, area deprivation index) in 108 additional independent models estimating the associations between the PGRS-by-environmental adversity interaction terms and hippocampal volumes.Test of statistical significance for each effect were performed by using the Sattherwaite degrees of freedom method via lmerTest, with multiple comparisons being corrected using the Benjamini-Hochberg method, which accounts for the false-discovery rate across repeated statistical tests (Benjamini and Hochberg 1995).

Results

The associations between PGRS for SCZ, MDD, and PTSD and aggregated hippocampal volume measures in those of European Ancestry are displayed in Table 1. Associations between PGRS, covariates, and volume estimates from the left hippocampus, right hippocampus, and aggregated hippocampus are displayed in the supplementary materials (Table S2-S4), along with correlations among the predictors (e.g PTSD-PGRS), covariates (e.g sex, Total Brain Volume), and outcome measures (e.g left hippocampal head) (Table S5). There were no statistically significant associations between any of the PGRS and the aggregated hippocampal volume measures (displayed in Table 1), or between the PGRS and either the left or right hippocampi (displayed in Table S2-S4). These null relationships can be visualized in the supplementary materials (Figure S1). Furthermore, the effects of PGRS or the effects of PGRS and their interactions did not explain more than a tenth of a percent of variance in any of the statistical models ($R^2 < 0.001$). These effects contrast with those of the full models, which explained a sizeable amount of variance in hippocampal volume in many cases. The full model explained approximately 44% of variance in hippocampal head volume ($R^2 \approx 0.44$),

Table 1 PGRS Fixed Effects in sample from European Ancestry from Mixed Effects Models

	Schizophrenia			Major Depression			Post Traumatic Stress Disorder		
	Beta (Standard Error)	T Statistic	P Value	Beta (Standard Error)	T Statistic	P Value	Beta (Standard Error)	T Statistic	P Value
Effect of Polygenic Risk Score									
Head	2.31 (4.90)	0.47	0.64	−3.45 (5.04)	−0.68	0.50	8.88 (5.20)	1.71	0.09
Body	−1.87 (2.97)	−0.63	0.53	−0.49 (3.15)	−0.15	0.88	0.47 (3.13)	0.15	0.88
Tail	0.26 (2.02)	0.13	0.90	1.29 (2.10)	0.62	0.54	−0.73 (2.23)	−0.32	0.75
Whole	0.45 (8.20)	0.06	0.96	−2.93 (8.41)	−0.35	0.73	8.54 (8.72)	0.98	0.33
Interaction with Income									
Head	0.00 (0.01)	0.35	0.73	0.00 (0.01)	0.03	0.98	0.01 (0.01)	1.09	0.28
Body	0.00 (0.01)	0.12	0.90	0.00 (0.01)	−0.09	0.93	0.02 (0.01)	1.89	0.06
Tail	0.01 (0.01)	1.51	0.13	0.01 (0.01)	0.96	0.34	0.01 (0.01)	2.04	0.04
Whole	0.01 (0.02)	0.63	0.53	0.00 (0.02)	0.22	0.82	0.04 (0.02)	1.83	0.07
Interaction with Sex									
Head	1.97 (2.10)	0.94	0.35	0.02 (1.99)	0.01	0.99	−0.26 (2.42)	−0.11	0.92
Body	0.61 (1.27)	0.48	0.63	−0.87 (1.20)	−0.72	0.47	−2.20 (1.47)	−1.50	0.13
Tail	−0.60 (0.86)	−0.70	0.49	−0.61 (0.81)	−0.75	0.45	−1.78 (0.99)	−1.81	0.07
Whole	2.03 (3.52)	0.58	0.57	−1.42 (3.32)	−0.43	0.67	−4.21 (4.05)	−1.04	0.30
Interaction with Trauma Exposure									
Head	−0.31 (0.11)	−2.73	0.01	−0.08 (0.11)	−0.66	0.51	−0.24 (0.12)	−2.02	0.04
Body	−0.12 (0.07)	−1.71	0.09	−0.12 (0.07)	−1.67	0.10	−0.05 (0.07)	−0.74	0.46
Tail	−0.06 (0.05)	−1.21	0.23	−0.07 (0.05)	−1.41	0.16	−0.01 (0.05)	−0.12	0.91
Whole	−0.48 (0.19)	−2.53	0.01	−0.25 (0.19)	−1.32	0.19	−0.30 (0.20)	−1.53	0.13
Interaction with Area Deprivation Index									
Head	7.94 (4.77)	1.66	0.10	5.83 (4.72)	1.23	0.22	−4.34 (4.78)	−0.91	0.36
Body	4.48 (2.89)	1.55	0.12	5.18 (2.86)	1.81	0.07	−0.61 (2.89)	−0.21	0.83
Tail	1.57 (1.94)	0.81	0.42	1.17 (1.92)	0.61	0.54	0.40 (1.95)	0.20	0.84
Whole	14.07 (7.99)	1.76	0.08	12.08 (7.90)	1.53	0.13	−4.66 (8.00)	−0.58	0.56

35% of variance in hippocampal body volume ($R^2 \approx 0.35$), 19% of variance in hippocampal tail volume ($R^2 \approx 0.19$), and 45% of variance in whole hippocampal volume ($R^2 \approx 0.45$)

In addition, interactions between PGRS and several additional variables on aggregated hippocampal volume measures are displayed in Table 1. Interactions that involved left and right hippocampal measures are displayed in the supplementary materials (Table S2-S4). There were no statistically significant interactions between PGRS for any of the disorders and either sex, trauma exposure, income, or area deprivation index. This was the case for the left, right, and aggregated hippocampal volume measures. One of the strongest interactions was between the SCZ PGRS and trauma exposure; increases in rates of trauma exposure were non -significantly associated with decreases in the association between SCZ PGRS and the hippocampal head ($\beta = -0.31$ (0.11); $\tau = 2.73$; P value = 0.01). In addition, increases in trauma exposure were associated with decreases in the association between SCZ PGRS and whole hippocampal volume ($\beta = -0.42$ (0.19); $\tau = -2.53$; P value = 0.01). Although these statistical effects are intriguing, they are still considerably above our false discovery rate adjusted alpha value ($\alpha \approx 0.0005$).

Sample characteristics and sampling bias

Given the number of null findings, follow up analyses were conducted in order to investigate whether sample characteristics may be contributing to possible type II errors. For instances, our analyses were necessarily restricted to only those with usable MRI data, which may have inadvertently removed certain subjects from our sample in a way that introduced bias. Independent samples t-tests were conducted in order to investigate whether individuals with usable-quality T1 and T2 MRI images had lower polygenic risk for psychopathology than those whose data failed

quality control procedures. These analyses revealed that individuals whose MRI data failed quality control checks had significantly higher PGRS for MDD ($\tau = -3.74$, p < 0.02e−2, df = 496.53) relative to those whose MRI data that passed quality control checks. There were no differences between these samples with regard to SCZ-PGRS ($\tau = -0.54$, p-value = 0.59, df = 482.14) or PTSD-PGRS ($\tau = -1.78$, p-value = 0.07, df = 493.86).

Analysis of African American ancestral group

Although our primary analyses utilized data only from those of European Ancestry, secondary analyses were conducted in those of African-American ancestry with valid hippocampal volume segmentations (n = 1063). Results from these analyses are displayed in Table 2. Similar to analyses conducted in those of European ancestry, no PGRS score was predictive of hippocampal subregion volume. These null relationships can be visualized in Supplementary Figure 2, which shows scatter plots of raw scores from PGRS and hippocampal volume measures in those of African American Ancestry. Given that GWAS summary statistics for psychopathology in those of African-American Ancestry were computed using underpowered sample sizes, results from these analyses should be interpreted with extreme caution.

Discussion

The current study found no evidence that polygenic risk for SCZ, MDD, or PTSD and their interactions with adversity during early life (i.e., income, trauma, area deprivation) are associated with hippocampal volumes during middle childhood. Despite the large heritability of hippocampal volume (Elman et al. 2019; Patel et al. 2017: ~ 80%), and the association of hippocampal volume with MDD, PTSD, and SCZ, which are also largely heritable (Baselmans et al. 2021), genetic liability to SCZ, MDD, and PTSD, as captured through the use of contemporary polygenic risk scores, does not seem to be shared with hippocampal volume during early life. It remains possible that these null findings are developmentally constrained or are

Table 2 PGRS Fixed Effects in sample from African American Ancestry from Mixed Effects Models

	Schizophrenia			Major Depression			Post Traumatic Stress Disorder		
	Beta (Standard Error)	T Statistic	P Value	Beta (Standard Error)	T Statistic	P Value	Beta (Standard Error)	T Statistic	P Value
Effect of Polygenic Risk Score									
Head	−6.46 (13.45)	−0.48	0.63	−3.49 (14.16)	−0.25	0.81	6.78 (13.71)	0.49	0.62
Body	−11.96 (9.12)	−1.31	0.19	3.84 (9.58)	0.40	0.69	−4.70 (14.50)	−0.32	0.75
Tail	−5.38 (6.48)	−0.83	0.41	17.78 (6.66)	2.67	0.01	0.32 (6.57)	0.05	0.96
Whole	−23.58 (24.41)	−0.97	0.33	17.36 (25.67)	0.68	0.50	−0.31 (29.12)	−0.01	0.99
Interaction with Income									
Head	0.00 (0.01)	−0.16	0.87	−0.02 (0.02)	−1.53	0.13	−0.01 (0.02)	−0.49	0.63
Body	0.00 (0.01)	0.23	0.82	−0.01 (0.01)	−0.87	0.38	0.00 (0.01)	−0.31	0.76
Tail	0.00 (0.01)	−0.09	0.92	0.01 (0.01)	1.05	0.29	0.01 (0.01)	0.64	0.52
Whole	0.00 (0.03)	−0.02	0.99	−0.03 (0.03)	−0.89	0.37	−0.01 (0.03)	−0.27	0.79
Interaction with Sex									
Head	9.14 (4.75)	1.93	0.05	2.65 (4.29)	0.62	0.54	1.25 (4.64)	0.27	0.79
Body	4.99 (3.22)	1.55	0.12	−1.07 (2.91)	−0.37	0.71	2.84 (3.11)	0.91	0.36
Tail	2.65 (2.27)	1.17	0.24	0.56 (2.03)	0.28	0.78	3.33 (2.20)	1.52	0.13
Whole	16.89 (8.62)	1.96	0.05	1.97 (7.80)	0.25	0.80	7.28 (8.50)	0.86	0.39
Interaction with Trauma Exposure									
Head	0.11 (0.16)	0.67	0.50	−0.04 (0.17)	−0.23	0.82	−0.18 (0.17)	−1.05	0.29
Body	0.12 (0.11)	1.12	0.26	0.00 (0.11)	−0.04	0.97	0.12 (0.13)	0.91	0.36
Tail	0.04 (0.08)	0.47	0.64	−0.23 (0.08)	−2.84	0.00	−0.04 (0.08)	−0.46	0.65
Whole	0.27 (0.29)	0.93	0.35	−0.26 (0.30)	−0.86	0.39	−0.10 (0.35)	−0.29	0.77
Interaction with Area Deprivation Index									
Head	−8.06 (9.92)	−0.81	0.42	8.12 (9.89)	0.82	0.41	1.47 (9.66)	0.15	0.88
Body	−3.02 (6.75)	−0.45	0.66	−0.75 (6.71)	−0.11	0.91	2.48 (6.42)	0.39	0.70
Tail	−1.59 (4.75)	−0.33	0.74	−0.49 (4.68)	−0.10	0.92	−0.87 (4.58)	−0.19	0.85
Whole	−12.61 (18.05)	−0.70	0.48	6.72 (17.97)	0.37	0.71	2.01 (17.57)	0.11	0.91

attributable to an ascertained sample that was not recruited for psychopathology. Indeed, prior studies have observed reduced hippocampal volumes in those with high SCZ-PGRS within adult patient/control (Alnæs et al. 2019: patient n=1,151; control n=2,010, see also Alnæs et al. 2019) and child high risk studies (Harrisberger et al. 2016, n = 65). Reduced hippocampal volumes have also been linked to PGRS for psychopathology in typically developing children (Jalbrzikowski et al. 2019). Our findings diverge from these previously conducted studies. At the same time, our findings align with the null findings from genetic correlations in large adult samples (Bahrami et al. 2022; van der Meer et al. 2020; Grotzinger et al. 2022) as well as null associations with polygenic risk scores in large samples of adults (e.g. Reus et al. 2017). Notably, in our dataset, post-hoc tests revealed no evidence that child SSRI use or prenatal SSRI exposure are associated with hippocampal subfield volumes; its inclusion as a covariate did not meaningfully alter the observed null associations between PGRS and hippocampal subfields (see Supplement for additional details).

There are several possible interpretations of these null findings. First, it may be that the hippocampal volume reductions commonly seen in samples of individuals with MDD, PTSD, and SCZ diagnoses are accounted for by non-genetic mechanisms, and that genetic risk for these disorders plays a limited role in hippocampal volume reductions. This interpretation is supported by evidence showing that hippocampal volume reductions in some forms of psychopathology are contingent upon stressful life event exposure (Kronmüller et al. 2008), and that conventional analyses in some cases fail to find genetic overlap between hippocampal volume and risk for psychopathology (Bahrami et al. 2022; van der Meer et al. 2020; Grotzinger et al. 2022). Nevertheless. the existing literature offers some contrary evidence, which suggests that genetic risk for psychopathology may be related to hippocampal morphology. As mentioned previously, hippocampal volume is highly heritable (Elman et al. 2019; Patel et al. 2017: ~ 80%), which suggests that individual differences in genetic loci are important contributors to hippocampal volume. In addition, although population-based studies have failed to find significant genetic correlations between hippocampal volume and psychopathology (Bahrami et al. 2022; Grotzinger et al. 2022), these same studies have found a number of genetic loci that capture variation in both risk for psychopathology and hippocampal morphology. In other words, while conventional analyses of genetic overlap have at times failed to find genetic relationships between psychopathology and hippocampal structure, other metrics of genetic overlap provide some evidence that psychopathology and hippocampal structure may share some genetic components. In addition, we observed no evidence that adversity experienced early in life moderates associations between genetic risk for MDD, PTSD, and SCZ, although our interaction analyses were likely severely underpowered (Duncan and Keller 2011). It remains possible that the variability in hippocampal volumes associated with psychopathology risk is only through non-genetic mechanisms as has been reported in numerous studies linking stress exposure to hippocampal volume reductions (Botdorf et al. 2022; Hanson et al. 2011; Taylor et al. 2020).

Another interpretation of these findings is that polygenic risk markers for MDD, PTSD, and SCZ may be related to hippocampal gray matter volume, but that our study design was unable to detect this effect. It is possible that genetic associations between psychopathology risk and hippocampal volumes only emerge at extremely heightened genetic risk. Our sample was not ascertained for psychopathology risk, and so we may not have had enough participants of sufficiently high genetic risk to demonstrate associations between PGRS and hippocampal volume. In addition, the influence of polygenic risk for MDD, PTSD, and SCZ may be more readily observable in longitudinal designs. A limitation of our study was its cross-sectional nature, and so we were unable to investigate relationships between polygenic risk for MDD, PTSD, and SCZ and hippocampal volume over time. In addition, our sample consisted of the baseline visit for the ABCD study so our sample was comprised of pre-adolescent children between the ages of 9–11. Thus, another limitation of our study was that we were unable to investigate how PGRS for MDD, PTSD, and SCZ may relate to hippocampal volume in the context of adolescence or puberty, a question we can revisit in the ABCD study as children age. The nature of the our sample also prevented us from investigating additional potentially critical effects, such as dynamic relationships between polygenic risk and hippocampal volume including gene-by-environment correlations (Beam and Turkheimer 2013) and developmental changes in gene expression (Bouchard 2013). Lastly, our study investigated relationships between polygenic risk for psychopathology and hippocampal structure using only one hippocampal phenotype (gray matter volume). Relationships between PGRS for MDD, PTSD, and SCZ and hippocampal structure may emerge when considering other hippocampal phenotypes (e.g microstructure, functional connectivity). All of the above modifications to this study would likely increase our statistical power. Nevertheless, the minimum meaningful effect size is not clear when relating PGRS to hippocampal volume in the general population using cross-sectional designs. Our current study was adequately powered (β = 0.8) to detect an effect in which PGRS explains one percent of variance in hippocampal volume, as was demonstrated in Harrisberger et al. (2016) and Jalbrzikowski et al. (2019). Our results demonstrate, however, that in population-based, cross-sectional designs, PGRS for MDD, PTSD, and SCZ explain less than a tenth of a percent in hippocampal volume

variance, and it is unclear whether effects of such size are of any practical significance.

In summary, this study provides significant contributions to at least two research efforts: the investigation of links between common genetic variation for psychopathology and brain-based phenotypes, as well as the contribution of genetic variation to psychopathology-associated hippocampal volume deficits. Our study provides important null findings in both of these respects. This study's results can reasonably be interpreted as evidence against the contribution of common genetic variation to MDD, PTSD, and SCZ-associated hippocampal volume reductions. Nevertheless, this study's results cannot not be used as an argument against the utility of genetic investigations of psychopathology-associated hippocampal abnormalities. Other genetic variables (e.g copy number variants) may relate to hippocampal volume. Furthermore, genetic variables may dynamically relate to environmental experiences in ways too complex to be investigated in this study. It would therefore be premature to use this study's null findings as an argument against future genomic investigations of hippocampal abnormalities in psychopathology. Lastly, our study's results do not reflect the associative strengths between PGRS for MDD, PTSD, and SCZ and cognitive-behavioral phenotypes for these disorders. A number of studies have demonstrated significant associations between PGRS for each of these disorders and cognitive-behavioral phenotypes (Loughnan et al. 2022; Mistry et al. 2018a, b). Cognitive-behavioral phenotypes are in many cases diagnostic of MDD, PTSD, or SCZ (e.g self-reported depressed mood is a diagnostic feature of MDD), so it makes sense that the genetic correlates of cognitive-behavioral phenotypes would be related to the genetic correlates of diagnostic labels like MDD, PTSD, and SCZ. The relationship between individual differences in neural structure and psychopathology is likely more complex. Hippocampal volume, for instance, does not appear to strongly relate to behavior in the absence of a known disorder or developmental change (Clark et al. 2020), which suggests that individual differences in hippocampal volume do not directly influence behavior and symptoms, and likely interact with other variables when relating to psychopathology. Thus, the genetic correlates of hippocampal structure may nevertheless may be causally related to psychopathology, as has been suggested by other work (Grotzinger et al. 2022), but the mediating effects of these genetic variables likely have more complex and diffuse relationships with psychopathology than the genetic correlates of cognitive-behavioral phenotypes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10519-023-10134-1.

Acknowledgements This project was supported by the following funding sources: F31AA029934-01 (S.E.P.); K01DA051759 (E.J.).

Author Contributions J.P designed the study, ran the hippocampal segmentation software, conducted the analyses, and wrote the manuscript. S.P and E.J computed the polygenic risk scores. R.B and D.B provided supervision and reviewed and edited the manuscript. S.K also ran hippocampal segmentation software and provided programming support.

Funding This project was supported by the following funding sources: F31AA029934-01 (S.E.P.); K01DA051759 (E.J.)

Declarations

Competing interests Jacob G. Pine, Sarah E. Paul, Ryan Bogdan, Sridhar Kandala, and Deanna Barch have no conflicts of interest to declare.

Ethical Approval This study was approved by the local Institutional Review Board. Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children age 9–10 and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, U24DA041147, U01DA041093, and U01DA041025. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/Consortium_Members.pdf. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

Consent to Participate All participants in ABCD provided informed consent (or assent).

References

Abel KM, Drake R, Goldstein JM (2010) Sex differences in schizophrenia. Int Rev Psychiatry 22(5):417–428. https://doi.org/10.3109/09540261.2010.515205

Agerbo E, Sullivan PF, Vilhjálmsson BJ, Pedersen CB, Mors O, Børglum AD, Hougaard DM, Hollegaard MV, Meier S, Mattheisen M, Ripke S, Wray NR, Mortensen PB (2015) Polygenic risk score, parental socioeconomic status, family history of psychiatric disorders, and the risk for schizophrenia: a Danish population-based study and meta-analysis. JAMA Psychiatry 72(7):635–641. https://doi.org/10.1001/jamapsychiatry.2015.0346

Alnæs D, Kaufmann T, van der Meer D, Córdova-Palomera A, Rokicki J, Moberget T, Bettella F, Agartz I, Barch DM, Bertolino A, Brandt CL, Cervenka S, Djurovic S, Doan NT, Eisenacher S, Fatouros-Bergman H, Flyckt L, Di Giorgio A, Haatveit B (2019) Karolinska Schizophrenia Project Consortium, Brain heterogeneity in schizophrenia and its association with polygenic risk. JAMA Psychiatry 76(7):739–748. https://doi.org/10.1001/jamapsychiatry.2019.0257

Bahrami S, Nordengen K, Shadrin AA, Frei O, van der Meer D, Dale AM, Westlye LT, Andreassen OA, Kaufmann T (2022)

Distributed genetic architecture across the hippocampal formation implies common neuropathology across brain disorders. Nat Commun 13(1):3436. https://doi.org/10.1038/s41467-022-31086-w

Barch DM, Gotlib IH, Bilder RM, Pine DS, Smoller JW, Brown CH, Huggins W, Hamilton C, Haim A, Farber GK (2016) Common measures for national institute of mental health funded research. Biol Psychiatry 79(12):e91–e96. https://doi.org/10.1016/j.biopsych.2015.07.006

Baselmans BML, Yengo L, van Rheenen W, Wray NR (2021) Risk in relatives, heritability, SNP-based heritability, and genetic correlations in psychiatric disorders: a review. Biol Psychiatry 89(1):11–19. https://doi.org/10.1016/j.biopsych.2020.05.034

Baurley JW, Edlund CK, Pardamean CI, Conti DV, Bergen AW (2016) Smokescreen: a targeted genotyping array for addiction research. BMC Genom 17:145. https://doi.org/10.1186/s12864-016-2495-7

Beam CR, Turkheimer E (2013) Phenotype-environment correlations in longitudinal twin models. Dev Psychopathol 25(1):7–16. https://doi.org/10.1017/S0954579412000867

Belleau EL, Treadway MT, Pizzagalli DA (2019) The impact of stress and major depressive disorder on hippocampal and medial prefrontal cortex morphology. Biol Psychiatry 85(6):443–453. https://doi.org/10.1016/j.biopsych.2018.09.031

Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soci Ser B 57(1):289–300

Bierut LJ, Heath AC, Bucholz KK, Dinwiddie SH, Madden PAF, Statham DJ, Dunne MP, Martin NG (1999) Major depressive disorder in a community-based twin sample: are there different genetic and environmental contributions for men and women? Arch Gen Psychiatry 6(6):557–563

Bigdeli TB, Fanous AH, Li Y, Rajeevan N, Sayward F, Genovese G, Gupta R, Radhakrishnan K, Malhotra AK, Sun N, Lu Q, Hu Y, Li B, Chen Q, Mane S, Miller P, Cheung K-H, Gur RE, Greenwood TA, Harvey PD (2021) Genome-wide association studies of schizophrenia and bipolar disorder in a diverse cohort of US veterans. Schizophr Bull 47(2):517–529. https://doi.org/10.1093/schbul/sbaa133

Bossini L, Tavanti M, Lombardelli A, Calossi S, Polizzotto NR, Galli R, Vatti G, Pieraccini F, Castrogiovanni P (2007) Changes in hippocampal volume in patients with post-traumatic stress disorder after sertraline treatment. J Clin Psychopharmacol 27(2):233. https://doi.org/10.1097/01.jcp.0000264979.09862.a8

Botdorf M, Dunstan J, Sorcher L, Dougherty LR, Riggins T (2022) Socioeconomic disadvantage and episodic memory ability in the ABCD sample: contributions of hippocampal subregion and subfield volumes. Dev Cogn Neurosci 57:101138. https://doi.org/10.1016/j.dcn.2022.101138

Bouchard TJ (2013) The Wilson effect: the increase in heritability of IQ with age. Twin Res Hum Genet 16(5):923–930. https://doi.org/10.1017/thg.2013.54

Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, Venturi P, Jones LA, Lewis SW, Sham PC, Gottesman II, Farmer AE, McGuffin P, Reveley AM, Murray RM (1999) Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 56(2):162–168. https://doi.org/10.1001/archpsyc.56.2.162

Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, Soules ME, Teslovich T, Dellarco DV, Garavan H, Orr CA, Wager TD, Banich MT, Speer NK, Sutherland MT, Riedel MC, Dick AS, Bjork JM, Thomas KM, Dale AM (2018) The adolescent brain cognitive development (ABCD) study: imaging acquisition across 21 sites. Dev Cogn Neurosci 32:43–54. https://doi.org/10.1016/j.dcn.2018.03.001

Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ (2015) Second-generation PLINK: rising to the challenge of larger and richer datasets. GigaScience 4(1):s13742-015-0047-8. https://doi.org/10.1186/s13742-015-0047-8

Clark IA, Monk AM, Hotchin V, Pizzamiglio G, Liefgreen A, Callaghan MF, Maguire EA (2020) Does hippocampal volume explain performance differences on hippocampal-dependant tasks? NeuroImage 221:117211. https://doi.org/10.1016/j.neuroimage.2020.117211

Colodro-Conde L, Couvy-Duchesne B, Zhu G, Coventry WL, Byrne EM, Gordon S, Wright MJ, Montgomery GW, Madden P, aF, Ripke S, Eaves LJ, Heath AC, Wray NR, Medland SE, Martin NG, (2018) A direct test of the diathesis-stress model for depression. Mol Psychiatry 23(7):1590–1596. https://doi.org/10.1038/mp.2017.130

Duncan LE, Keller MC (2011) A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. Am J Psychiatry 168(10):1041–1049. https://doi.org/10.1176/appi.ajp.2011.11020191

Duncan LE, Ratanatharathorn A, Aiello AE, Almli LM, Amstadter AB, Ashley-Koch AE, Baker DG, Beckham JC, Bierut LJ, Bisson J, Bradley B, Chen C-Y, Dalvie S, Farrer LA, Galea S, Garrett ME, Gelernter JE, Guffanti G, Hauser MA, Koenen KC (2018) Largest GWAS of PTSD (n=20070) yields genetic overlap with schizophrenia and sex differences in heritability. Mol Psychiatry 23(3):666–673. https://doi.org/10.1038/mp.2017.77

Duncan L, Shen H, Gelaye B, Meijsen J, Ressler K, Feldman M, Peterson R, Domingue B (2019) Analysis of polygenic risk score usage and performance in diverse human populations. Nat Commun 10(1):3328. https://doi.org/10.1038/s41467-019-11112-0

Dunsmoor JE, Cisler JM, Fonzo GA, Creech SK, Nemeroff CB (2022) Laboratory models of post-traumatic stress disorder: the elusive bridge to translation. Neuron 110(11):1754–1776. https://doi.org/10.1016/j.neuron.2022.03.001

Elman JA, Panizzon MS, Gillespie NA, Hagler DJ Jr, Fennema-Notestine C, Eyler LT, McEvoy LK, Neale MC, Lyons MJ, Franz CE, Dale AM, Kremen WS (2019) Genetic architecture of hippocampal subfields on standard resolution MRI: how the parts relate to the whole. Hum Brain Map 40(5):1528–1540. https://doi.org/10.1002/hbm.24464

Frodl T, Carballedo A, Hughes M, Saleh K, Fagan A, Skokauskas N, McLoughlin D, Meaney J, O'Keane V, Connor T (2012) Reduced expression of glucocorticoid-inducible genes GILZ and SGK-1: high IL-6 levels are associated with reduced hippocampal volumes in major depressive disorder. Transl Psychiatry 2:1–8

Ge T, Chen C-Y, Ni Y, Feng Y-CA, Smoller JW (2019) Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun 10(1):1776. https://doi.org/10.1038/s41467-019-09718-5

Genon S, Bernhardt BC, La Joie R, Amunts K, Eickhoff SB (2021) The many dimensions of human hippocampal organization and (dys)function. Trends Neurosci 44(12):977–989. https://doi.org/10.1016/j.tins.2021.10.003

Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5(11):1242–1247. https://doi.org/10.1038/nn958

Godlewska BR, Hasselmann HWW, Igoumenou A, Norbury R, Cowen PJ (2014) Short-term escitalopram treatment and hippocampal volume. Psychopharmacology 231(23):4579–4581. https://doi.org/10.1007/s00213-014-3771-3

Grotzinger AD, Rhemtulla M, de Vlaming R, Ritchie SJ, Mallard TT, Hill WD, Ip HF, Marioni RE, McIntosh AM, Deary IJ, Koellinger PD, Harden KP, Nivard MG, Tucker-Drob EM (2019) Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. Nat Hum Behav 3(5):513–525. https://doi.org/10.1038/s41562-019-0566-x

Grotzinger AD, Mallard TT, Akingbuwa WA, Ip HF, Adams MJ, Lewis CM, McIntosh AM, Grove J, Dalsgaard S, Lesch K-P, Strom N, Meier SM, Mattheisen M, Børglum AD, Mors O, Breen G, Lee PH, Kendler KS, Smoller JW, Nivard MG (2022) Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic and molecular genetic levels of analysis. Nat Genet 54(5):548–559. https://doi.org/10.1038/s41588-022-01057-4

Guffanti G, Gameroff MJ, Warner V, Talati A, Glatt CE, Wickramaratne P, Weissman MM (2016) Heritability of major depressive and comorbid anxiety disorders in multi-generational families at high risk for depression. Am J Med Genet Part B 171(8):1072–1079. https://doi.org/10.1002/ajmg.b.32477

Hammen C (2005) Stress and depression. Ann Rev Clin Psychol 1(1):293–319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938

Hanson JL, Chandra A, Wolfe BL, Pollak SD (2011) Association between income and the hippocampus. PLOS ONE 6(5):e18712. https://doi.org/10.1371/journal.pone.0018712

Harden KP (2021) Reports of my death were greatly exaggerated: behavior genetics in the postgenomic era. Ann Rev Psychol 72(1):37–60. https://doi.org/10.1146/annurev-psych-052220-103822

Harrisberger F, Smieskova R, Vogler C, Egli T, Schmidt A, Lenz C, Simon AE, Riecher-Rössler A, Papassotiropoulos A, Borgwardt S (2016) Impact of polygenic schizophrenia-related risk and hippocampal volumes on the onset of psychosis. Transl Psychiatry 6(8):e868–e868. https://doi.org/10.1038/tp.2016.143

Heckers S, Konradi C (2015) GABAergic mechanisms of hippocampal hyperactivity in schizophrenia. Schizophr Res 167(1):4–11. https://doi.org/10.1016/j.schres.2014.09.041

Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, Werge TM, Nordentoft M, Glenthøj B (2018) Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. Biol Psychiatry 83(6):492–498. https://doi.org/10.1016/j.biopsych.2017.08.017

Howard DM, Adams MJ, Clarke T-K, Hafferty JD, Gibson J, Shirali M, Coleman JRI, Hagenaars SP, Ward J, Wigmore EM, Alloza C, Shen X, Barbu MC, Xu EY, Whalley HC, Marioni RE, Porteous DJ, Davies G, Deary IJ, McIntosh AM (2019) Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci 22(3):343–352. https://doi.org/10.1038/s41593-018-0326-7

Iglesias JE, Augustinack JC, Nguyen K, Player CM, Player A, Wright M, Roy N, Frosch MP, McKee AC, Wald LL, Fischl B, Van Leemput K (2015) A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: application to adaptive segmentation of in vivo MRI. NeuroImage 115:117–137. https://doi.org/10.1016/j.neuroimage.2015.04.042

Jalbrzikowski M, Klei L, Devlin B (2019) T20. Polygenic risk for schizophrenia is associated with hippocampal volume in typically developing youth. Schizophr Bull 45:S211. https://doi.org/10.1093/schbul/sbz019.300

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. J Am Acad Child Adoles Psychiatry 36(7):980–988. https://doi.org/10.1097/00004583-199707000-00021

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ (1993) The lifetime history of major depression in women: reliability of diagnosis and heritability. Arch Gen Psychiatry 50(11):863–870. https://doi.org/10.1001/archpsyc.1993.01820230054003

Kind AJ, Buckingham WR (2018) Making neighborhood-disadvantage metrics accessible - the neighborhood atlas. N Engl J Med 378(26):2456–2458. https://doi.org/10.1056/NEJMp1802313

Kind AJ, Jencks S, Brock J, Yu M, Bartels C, Ehlenbach W, Greenberg C, Smith M (2014) Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. Ann Internal Med 161(11):765. https://doi.org/10.7326/M13-2946

Kraus C, Seiger R, Pfabigan DM, Sladky R, Tik M, Paul K, Woletz M, Gryglewski G, Vanicek T, Komorowski A, Kasper S, Lamm C, Windischberger C, Lanzenberger R (2019) Hippocampal subfields in acute and remitted depression-an ultra-high field magnetic resonance imaging study. Int J Neuropsychopharmacol 22(8):513–522. https://doi.org/10.1093/ijnp/pyz030

Kronmüller K-T, Pantel J, Götz B, Köhler S, Victor D, Mundt C, Magnotta VA, Giesel F, Essig M, Schröder J (2008) Life events and hippocampal volume in first-episode major depression. J Affect Disord 110(3):241–247. https://doi.org/10.1016/j.jad.2008.01.022

Lam M, Awasthi S, Watson HJ, Goldstein J, Panagiotaropoulou G, Trubetskoy V, Karlsson R, Frei O, Fan C-C, De Witte W, Mota NR, Mullins N, Brügger K, Lee SH, Wray NR, Skarabis N, Huang H, Neale B, Daly MJ, Ripke S (2019) RICOPILI: Rapid imputation for COnsortias PIpeLIne. Bioinformatics 36(3):930–933. https://doi.org/10.1093/bioinformatics/btz633

Levey DF, Stein MB, Wendt FR, Pathak GA, Zhou H, Aslan M, Quaden R, Harrington KM, Nuñez YZ, Overstreet C, Radhakrishnan K, Sanacora G, McIntosh AM, Shi J, Shringarpure SS, Concato J, Polimanti R, Gelernter J (2021) Bi-ancestral depression GWAS in the million veteran program and meta-analysis in> 1.2 million individuals highlight new therapeutic directions. Nat Neurosci 24(7):954–963. https://doi.org/10.1038/s41593-021-00860-2

Lieberman JA, Girgis RR, Brucato G, Moore H, Provenzano F, Kegeles L, Javitt D, Kantrowitz J, Wall MM, Corcoran CM, Schobel SA, Small SA (2018) Hippocampal dysfunction in the pathophysiology of schizophrenia: a selective review and hypothesis for early detection and intervention. Mol Psychiatry 23(8):1764–1772. https://doi.org/10.1038/mp.2017.249

Lisman J, Buzsáki G, Eichenbaum H, Nadel L, Ranganath C, Redish AD (2017) Viewpoints: how the hippocampus contributes to memory, navigation and cognition. Nat Neurosci 20(11):1434–1447. https://doi.org/10.1038/nn.4661

Liu S, Li A, Liu Y, Yan H, Wang M, Sun Y, Fan L, Song M, Xu K, Chen J, Chen Y, Wang H, Guo H, Wan P, Lv L, Yang Y, Li P, Lu L, Yan J, Liu B (2020) Polygenic effects of schizophrenia on hippocampal grey matter volume and hippocampus-medial prefrontal cortex functional connectivity. Br J Psychiatry 216(5):267–274. https://doi.org/10.1192/bjp.2019.127

Logue MW, van Rooij SJH, Dennis EL, Davis SL, Hayes JP, Stevens JS, Densmore M, Haswell CC, Ipser J, Koch SBJ, Korgaonkar M, Lebois LAM, Peverill M, Baker JT, Boedhoe PSW, Frijling JL, Gruber SA, Harpaz-Rotem I, Jahanshad N, Morey RA (2018) Smaller hippocampal volume in posttraumatic stress disorder: a multisite ENIGMA-PGC study: subcortical volumetry results from posttraumatic stress disorder consortia. Biol Psychiatry 83(3):244–253. https://doi.org/10.1016/j.biopsych.2017.09.006

Loughnan RJ, Palmer CE, Makowski C, Thompson WK, Barch DM, Jernigan TL, Dale AM, Fan CC (2022) Unique prediction of developmental psychopathology from genetic and familial risk. J Child Psychol Psychiatry 63(12):1631–1643. https://doi.org/10.1111/jcpp.13649

Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ (2019) Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet 51(4):584–591. https://doi.org/10.1038/s41588-019-0379-x

McEwen BS (2012) Brain on stress: how the social environment gets under the skin. Proc Natl Acad Sci 109:17180–17185. https://doi.org/10.1073/pnas.1121254109

McHugo M, Talati P, Woodward ND, Armstrong K, Blackford JU, Heckers S (2018) Regionally specific volume deficits along the

hippocampal long axis in early and chronic psychosis. NeuroImage 20:1106–1114. https://doi.org/10.1016/j.nicl.2018.10.021
McHugo M, Armstrong K, Roeske MJ, Woodward ND, Blackford JU, Heckers S (2020) Hippocampal volume in early psychosis: a 2- year longitudinal study. Transl Psychiatry 10(1):1–10. https://doi.org/10.1038/s41398-020-00985-1
McKeever VM, Huff ME (2003) A diathesis-stress model of posttraumatic stress disorder: ecological, biological, and residual stress pathways. Rev Gen Psychol 7(3):237–250. https://doi.org/10.1037/1089-2680.7.3.237
Mistry S, Harrison JR, Smith DJ, Escott-Price V, Zammit S (2018) The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: a systematic review. J Affect Disord 234:148–155. https://doi.org/10.1016/j.jad.2018.02.005
Mistry S, Harrison JR, Smith DJ, Escott-Price V, Zammit S (2018) The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: systematic review. Schizophr Res 197:2–8. https://doi.org/10.1016/j.schres.2017.10.037
Mondelli V, Cattaneo A, Murri MB, Forti MD, Handley R, Hepgul N, Miorelli A, Navari S, Papadopoulos AS, Aitchison KJ, Morgan C, Murray RM, Dazzan P, Pariante CM (2011) Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume. J Clin Psychiatry 72(12):20080. https://doi.org/10.4088/JCP.10m06745
Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen C-Y, Choi KW, Coleman JRI, Dalvie S, Duncan LE, Gelernter J, Levey DF, Logue MW, Polimanti R, Provost AC, Ratanatharathorn A, Stein MB, Torres K, Aiello AE, Almli LM, Koenen KC (2019) International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nat Commun 10(1):4558. https://doi.org/10.1038/s41467-019-12576-w
Olney JW, Newcomer JW, Farber NB (1999) NMDA receptor hypofunction model of schizophrenia. J Psychiatric Res 33(6):523–533. https://doi.org/10.1016/s0022-3956(99)00029-1
Patel S, Park MTM, Devenyi GA, Patel R, Masellis M, Knight J, Chakravarty MM (2017) Heritability of hippocampal subfield volumes using a twin and non-twin siblings design. Hum Brain Map 38(9):4337–4352. https://doi.org/10.1002/hbm.23654
Pruessner M, Cullen AE, Aas M, Walker EF (2017) The neural diathesis-stress model of schizophrenia revisited: an update on recent findings considering illness stage and neurobiological and methodological complexities. Neurosci Biobehav Rev 73:191–218. https://doi.org/10.1016/j.neubiorev.2016.12.013
Reus LM, Shen X, Gibson J, Wigmore E, Ligthart L, Adams MJ, Davies G, Cox SR, Hagenaars SP, Bastin ME, Deary IJ, Whalley HC, McIntosh AM (2017) Association of polygenic risk for major psychiatric illness with subcortical volumes and white matter integrity in UK biobank. Sci Rep 7(1):42140. https://doi.org/10.1038/srep42140
Rimfeld K, Krapohl E, Trzaskowski M, Coleman JR, Selzam S, Dale PS, Esko T, Metspalu A, Plomin R (2018) Genetic influence on social outcomes during and after the soviet era in estonia. Nat Hum Behav 2(4):269–275. https://doi.org/10.1038/s41562-018-0332-5
Rosenthal D (1963) A suggested conceptual framework. In: The Genain quadruplets: a case study and theoretical analysis of heredity and environment in schizophrenia, pp 505–511. Basic Books. https://doi.org/10.1037/11420-031
Ruan Y, Lin Y-F, Feng Y-CA, Chen C-Y, Lam M, Guo Z, He L, Sawa A, Martin AR, Qin S, Huang H, Ge T (2022) Improving polygenic prediction in ancestrally diverse populations. Nat Genet 54(5):573–580. https://doi.org/10.1038/s41588-022-01054-7
Sahakyan L, Meller T, Evermann U, Schmitt S, Pfarr J-K, Sommer J, Kwapil TR, Nenadić I (2021) Anterior vs posterior hippocampal subfields in an extended psychosis phenotype of multidimensional schizotypy in a nonclinical sample. Schizophr Bull 47(1):207–218. https://doi.org/10.1093/schbul/sbaa099
Sartor CE, McCutcheon VV, Pommer NE, Nelson EC, Grant JD, Duncan AE, Waldron M, Bucholz KK, Madden PAF, Heath AC (2011) Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. Psychol Med 41(7):1497–1505. https://doi.org/10.1017/S0033291710002072
Sartor CE, Grant JD, Lynskey MT, McCutcheon VV, Waldron M, Statham DJ, Bucholz KK, Madden PAF, Heath AC, Martin NG, Nelson EC (2012) Common heritable contributions to lowrisk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. Arch Gen Psychiatry 69(3):293–299. https://doi.org/10.1001/archgenpsychiatry.2011.1385
Schmaal L, Pozzi E, Ho C, T, van Velzen LS, Veer IM, Opel N, Van Someren EJW, Han L KM, Aftanas L, Aleman A, Baune BT, Berger K, Blanken TF, Capitão L, Couvy-Duchesne B, R Cullen K, Dannlowski U, Davey C, Erwin-Grabner T, Veltman DJ, (2020) ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing. Transl Psychiatry 10(1):1–19. https://doi.org/10.1038/s41398-020-0842-6
Stein MB, Levey DF, Cheng Z, Wendt FR, Harrington K, Pathak GA, Cho K, Quaden R, Radhakrishnan K, Girgenti MJ, Ho Y-LA, Posner D, Aslan M, Duman RS, Zhao H, Polimanti R, Concato J, Gelernter J (2021) Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the million veteran program. Nat Genet 53(2):174–184. https://doi.org/10.1038/s41588-020-00767-x
Taylor RL, Cooper SR, Jackson JJ, Barch DM (2020) Assessment of neighborhood poverty, cognitive function, and prefrontal and hippocampal volumes in children. JAMA Netw Open 3(11):e2023774. https://doi.org/10.1001/jamanetworkopen.2020.23774
Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, Bryois J, Chen C-Y, Dennison CA, Hall LS, Lam M, Watanabe K, Frei O, Ge T, Harwood JC, Koopmans F, Magnusson S, Richards AL, Sidorenko J, O'Donovan MC (2022) Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604(7906):502–508. https://doi.org/10.1038/s41586-022-04434-5
van der Meer D, Rokicki J, Kaufmann T, Córdova-Palomera A, Moberget T, Alnæs D, Bettella F, Frei O, Doan NT, Sønderby IE, Smeland OB, Agartz I, Bertolino A, Bralten J, Brandt CL, Buitelaar JK, Djurovic S, van Donkelaar M, Dørum ES (2020) Pediatric imaging, neurocognition and genetics study, brain scans from 21,297 individuals reveal the genetic architecture of hippocampal subfield volumes. Mol Psychiatry 25(11):3053–3065. https://doi.org/10.1038/s41380-018-0262-7
van Erp TGM, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, Agartz I, Westlye LT, Haukvik UK, Dale AM, Melle I, Hartberg CB, Gruber O, Kraemer B, Zilles D, Donohoe G, Kelly S, McDonald C, Morris DW, Turner JA (2016) Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry 21(4):547–553. https://doi.org/10.1038/mp.2015.63
Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD (2003) Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol Psychiatry 54(7):693–702. https://doi.org/10.1016/S0006-3223(03)00634-6
Volkow ND, Koob GF, Croyle RT, Bianchi DW, Gordon JA, Koroshetz WJ, Pérez-Stable EJ, Riley WT, Bloch MH, Conway K, Deeds BG, Dowling GJ, Grant S, Howlett KD, Matochik JA, Morgan GD, Murray MM, Noronha A, Spong CY, Weiss SRB (2018) The conception of the ABCD study: from substance use to a broad NIH

collaboration. Dev Cogn Neurosci 32:4–7. https://doi.org/10.1016/j.dcn.2017.10.002

Vythilingam M, Vermetten E, Anderson GM, Luckenbaugh D, Anderson ER, Snow J, Staib LH, Charney DS, Bremner JD (2004) Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. Biol Psychiatry 56(2):101–112. https://doi.org/10.1016/j.biopsych.2004.04.002

Walker EF, Diforio D (1997) Schizophrenia: a neural diathesis-stress model. Psychol Rev 104(4):667–685. https://doi.org/10.1037/0033-295x.104.4.667

Werner S, Malaspina D, Rabinowitz J (2007) Socioeconomic status at birth is associated with risk of schizophrenia: population-based multilevel study. Schizophr Bull 33(6):1373–1378. https://doi.org/10.1093/schbul/sbm032

Wisse LEM, Biessels GJ, Geerlings MI (2014) A critical appraisal of the hippocampal subfield segmentation package in FreeSurfer. Front Aging Neurosci 6:261. https://doi.org/10.3389/fnagi.2014.00261

Wisse LEM, Chételat G, Daugherty AM, de Flores R, la Joie R, Mueller SG, Stark CEL, Wang L, Yushkevich PA, Berron D, Raz N, Bakker A, Olsen RK, Carr VA (2021) Hippocampal subfield volumetry from structural isotropic 1 mm3 MRI scans: a note of caution. Hum Brain Map 42(2):539–550. https://doi.org/10.1002/hbm.25234