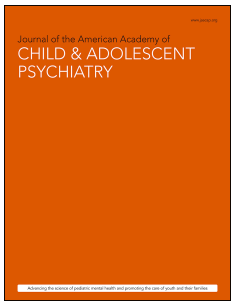
Journal Pre-proof



Smaller Hippocampal Volume Among Black and Latinx Youth Living in High-Stigma Contexts

Mark L. Hatzenbuehler, PhD, David G. Weissman, PhD, Sarah McKetta, ScM, PhD, Micah R. Lattanner, PhD, Jessie V. Ford, PhD, Deanna M. Barch, PhD, Katie A. McLaughlin, PhD

PII: S0890-8567(21)01361-7

DOI: https://doi.org/10.1016/j.jaac.2021.08.017

Reference: JAAC 3631

To appear in: *Journal of the American Academy of Child & Adolescent Psychiatry*

Received Date: 7 April 2021

Revised Date: 4 August 2021

Accepted Date: 20 August 2021

Please cite this article as: Hatzenbuehler ML, Weissman DG, McKetta S, Lattanner MR, Ford JV, Barch DM, McLaughlin KA, Smaller Hippocampal Volume Among Black and Latinx Youth Living in High-Stigma Contexts, *Journal of the American Academy of Child & Adolescent Psychiatry* (2021), doi: https://doi.org/10.1016/j.jaac.2021.08.017.

Smaller Hippocampal Volume Among Black and Latinx Youth Living in High-Stigma Contexts
RH = Stigma and Hippocampal Volume

Mark L. Hatzenbuehler, PhD, David G. Weissman, PhD, Sarah McKetta, ScM, PhD, Micah R. Lattanner, PhD, Jessie V. Ford, PhD, Deanna M. Barch, PhD, Katie A. McLaughlin, PhD

Editorial
Supplemental Materials

Accepted August 26, 2021

Drs. Hatzenbuehler, Weissman, Lattanner, McLaughlin are with Harvard University, Cambridge, Massachusetts. Drs. McKetta and Ford are with Mailman School of Public Health, Columbia University, New York. Dr. Barch is with Washington University in St. Louis, Missouri.

Support for this research came from R01-MH103291, R01-MH106482, R56-MH119194, R37-MH119194, and T32-MH013043 from the National Institute of Mental Health (NIMH). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

This article is part of a special series devoted to addressing bias, bigotry, racism, and mental health disparities through research, practice, and policy. The series is edited by Assistant Editor Eraka Bath, MD, Deputy Editor Wanjikũ F.M. Njoroge, Associate Editor Robert R. Althoff, MD, PhD, and Editor-in-Chief Douglas K. Novins, MD.

The research was performed with permission from Harvard University's Institutional Review Board.

This work has been previously posted on a preprint server: https://doi.org/10.1101/2020.10.09.333328.

This work has been prospectively registered: https://osf.io/9axqr.

Author Contributions
Conceptualization: Hatzenbuehler, McLaughlin
Data curation: Weissman, McKetta, Lattanner, Ford
Formal analysis: Weissman, McKetta
Funding acquisition: Barch, McLaughlin
Investigation: Barch
Methodology: Barch
Supervision: Hatzenbuehler, Barch, McLaughlin
Visualization: Weissman
Writing – original draft: Hatzenbuehler
Writing – review and editing: Weissman, McKetta, Lattanner, Ford, Barch, McLaughlin

ORCID

Mark L. Hatzenbuehler, PhD: https://orcid.org/0000-0002-7430-0853
David G. Weissman, PhD: https://orcid.org/0000-0001-9966-3338
Sarah McKetta, ScM, PhD: https://orcid.org/0000-0001-8953-1809
Micah R. Lattanner, PhD: https://orcid.org/0000-0002-5732-7464
Jessie V. Ford, PhD: https://orcid.org/0000-0001-9426-3351
Deanna M. Barch, PhD: https://orcid.org/0000-0003-1693-8506
Katie A. McLaughlin, PhD:

Disclosure: Dr. Hatzenbuehler has received grant or research support from NIMH, the Centers for Disease Control and Prevention, and the William T. Grant Foundation. He was on a consensus committee at the National Academy of Sciences, Engineering, and Medicine. Dr. Weissman has received a research grant from the Sackler Scholar Programme in Psychobiology. Dr. Barch has received grants from the National Institute on Drug Abuse and NIMH. Drs. McKetta, Lattanner, Ford, and McLaughlin have reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Mark Hatzenbuehler, PhD, 33 Kirkland Street, Cambridge, MA 02138; e-mail: markhatzenbuehler@fas.harvard.edu.

ABSTRACT

Objective: To determine whether structural and individual forms of stigma are associated with neurodevelopment in children.

Method: Stigma related to gender, race, and Latinx ethnicity was measured at the structural level using objective state-level indicators of social policies and prejudicial attitudes, and at the individual level using self-reports of perceived discrimination. We examined their respective associations with hippocampal volume and amygdala reactivity to threat using data from the Adolescent Brain and Cognitive Development study (N=11,534; *M*=9.9 years), the first multi-site neuroimaging study that provided substantial variability in sociopolitical contexts and that included individual-level measures of stigma among youth.

Results: In a pre-registered analysis, we found that Black (*B*=-57.27, *p*=0.025) and Latinx (*B*=-41.02, *p*=0.037) youths in higher (vs. lower) structural stigma contexts had smaller hippocampal volume, controlling for demographics and family socioeconomic status. This association was also observed at a trend-level among girls (*p*=0.082). The magnitude of the difference in hippocampal volume between high and low structural stigma states was equivalent to a $20,000 difference in annual family income. As hypothesized, structural stigma was not associated with hippocampal volume in non-stigmatized youth, providing evidence of specificity. Perceived discrimination was unrelated to hippocampal volume in stigmatized groups. No associations between perceived discrimination or structural stigma and amygdala reactivity to threat were observed.

Conclusion: We provide novel evidence that an objective measure of structural stigma may be more strongly related to hippocampal volume than subjective perceptions of stigma, suggesting

that contextual approaches to stigma could yield new insights into neurodevelopment among marginalized youth.

Key words: stigma, hippocampal volume, neurodevelopment, population neuroscience

Introduction

Stigma—defined as the co-occurrence of labeling, stereotyping, status loss, and discrimination in a context in which power is exercised[1]—contributes to adverse mental health outcomes for marginalized groups through its influence on processes across individual, interpersonal, and structural levels.[1–3] At the individual level, stigma manifests as psychological responses through which stigmatized individuals perceive and react to stigma, including identity concealment,[4] self-stigma,[5] and expectations of rejection.[6] Interpersonal forms of stigma refer to interactional processes that occur between the stigmatized and non-stigmatized, such as discriminatory treatment.[7] Although most research has focused on the mental health consequences of stigma at the individual and interpersonal levels,[7] growing evidence indicates that structural stigma—defined as "societal-level conditions, cultural norms and institutional policies and practices that constrain the opportunities, resources, and wellbeing of the stigmatized"[8(p2)]—represents an additional risk factor for psychopathology among the stigmatized.[3] For instance, observational studies have shown that individuals living in states with fewer legal protections for their stigmatized group (e.g., restrictive immigration policies) have higher levels of psychological distress[9,10] and psychiatric disorders[11] than those in states with greater protections. Further, quasi-experimental studies have demonstrated that rates of mental disorders[12] and psychological distress[13] increase among stigmatized populations following increases in structural stigma (e.g., passage of laws denying services to same-sex couples).

Despite consistent evidence for the adverse mental health consequences of stigma, the biological mechanisms through which stigma contributes to risk for psychopathology are only beginning to be understood.[3,14] Experimental and observational studies have documented a variety of physiological responses to stigma-related experiences, including changes in immune

functioning, inflammatory processes, and regulation of the hypothalamic-pituitary-adrenal (HPA) axis.[15,16] Surprisingly, although social factors like rejection, exclusion, and early-life adversity (e.g., childhood trauma) have been associated consistently with brain structure and function,[17–30] few studies have examined neurodevelopmental sequelae of stigma.

The current study begins to address this gap in the literature. Specifically, we examine whether individual and structural forms of stigma are associated with two neural outcomes: hippocampal volume and amygdala reactivity to threat. We chose these outcomes because they are associated with stress exposure,[19–22,24,29–31] consistent with social identity threat theories of stigma that conceptualize it as a chronic stressor.[7] Additionally, both neural outcomes are associated with multiple forms of psychopathology,[32–38] and thus may serve as mechanisms linking stigma with mental health problems.[7,8] To address our research question, we required a unique data structure that not only included measures of stigma at the individual level, but also sampled respondents from a range of social environments that differed in structural stigma. This presented a methodological challenge, because most neuroimaging studies are conducted in one (or a small number) of communities. In such designs, respondents are similarly exposed to the same macro-social context—known as a ubiquitous exposure[39]—precluding the possibility of linking contextual variation with neural outcomes. Fortunately, neuroimaging studies with meaningful variation in social context have recently become available. In this study, we use data from one of the first national, multi-site neuroimaging studies with substantial variability in sociopolitical contexts: the Adolescent Brain and Cognitive Development (ABCD) study. This dataset measured brain structure and function in 11,534 youth sampled from 17 states, affording significant geographic variability in exposure to stigmatizing contexts among youth.

We examined three stigmatized groups—girls, racial (Black), and ethnic (Latinx) minority youth (mean age=9.9 years)—informed by the developmental literature on identity awareness, formation, and responsivity to identity-based stressors, which indicates that gender,[40] racial,[41] and ethnic[42] identities emerge during early childhood. Girls, Black, and Latinx youth report identity awareness and constancy, as well as perceptions of group-based stereotypes, by 9-10 years, the age of the baseline ABCD sample. We tested two pre-registered hypotheses. First, we predicted that greater exposure to individual and structural stigma would be associated with smaller hippocampal volume and elevated amygdala reactivity to threat cues (i.e., fearful relative to neutral faces) among girls, Black, and Latinx youth, controlling for demographics and family socioeconomic status (SES). Second, we hypothesized that structural stigma would be unrelated to hippocampal volume or amygdala reactivity in the non-stigmatized comparison groups: boys, Whites, and non-Hispanic Whites. This analysis serves as a negative control approach,[43] in that we test whether there is an association among the groups where we would not theoretically expect it.

Method

Sample

Data come from the Adolescent Brain and Cognitive Development (ABCD) study, the largest study of brain development in the U.S. (https://abcdstudy.org). We drew data from the Year 1 assessment (ABCD 2.0) of 11,534 youth. Twenty-one study sites were included from across the U.S. From these sites, a stratified probability sample of schools within the catchment areas for each site were selected, and eligible youth were recruited from each school. The ABCD study approximates a multi-stage probability sample, but is not nationally-representative.[44] The

imaging procedures were harmonized across sites.[45] The study protocol received ethics approval from [redacted].

Measures

Structural stigma. Consistent with conceptualizations of structural stigma[8] and prior research on this topic,[3] we selected items that captured societal-level conditions, social/cultural norms, and/or institutional policies to create proxy measures of the social climate relevant to the three groups of interest (female, Black, and Latinx youth). We compiled items from publicly available data sources used in prior work to assess structural forms of stigma related to gender,[46–48] race,[49–52] and Latinx ethnicity.[10] We modeled these items as indicators in a factor analysis (described below), with the final factor score determining the structural stigma score for each state for each domain of stigma (Figure 1). We chose a factor analytic approach because it 1) recognizes that different dimensions of structural stigma (e.g., norms, policies) are highly correlated; 2) improves construct validity; and 3) captures shared variance, thereby reducing measurement error.

Because we used a data-driven technique, the final factor scores included different components across the three groups. For instance, while the index of structural stigma related to Latinx ethnicity included both state laws and aggregated social norms, the index of structural stigma related to race included only aggregated norms. We nevertheless refer to all of these indicators as "structural," in that they represent factors at the contextual rather than individual/interpersonal level. This approach is consistent with conceptualizations of individual attitudes shaping structural factors (e.g., laws and policies) in ways that subsequently influence the attitudes of individuals within a particular social context; as such, aggregated attitudes

represent more than individual bias because they not only reflect but also shape broader social structures.[53,54]

Below, we describe the items and sources of data for each group; further details are in Supplement 1 and Tables S1 and S2, available online.

Structural Stigma Related to Gender. The measure of structural stigma related to gender was comprised of 18 items. Twelve of these indicators assessed aggregated implicit and explicit attitudes, which were obtained from two sources: Project Implicit (pooled across years 2003-2018) and the General Social Survey (pooled across years 1974-2014). The explicit indicators directly queried gender role attitudes and sexist beliefs. The implicit indicators were obtained through the Implicit Association Test (IAT) and examined to what extent respondents associate gender with career and scientific domains. The other 6 items were taken from previous state-level composite indicators of women's social status,[46,47] including: economic (e.g., ratio of men's to women's earnings); political (e.g., women's representation in elected office); social and economic autonomy (e.g., women's business ownership); and reproductive factors (e.g., percentage of women who live in a county without an abortion provider). These items were obtained from several sources, including the Bureau of Labor Statistics, Current Population Survey, and Center for American Women in Politics.

Structural Stigma Related to Race. The measure of structural stigma related to race was comprised of 31 items, all of which assessed aggregated attitudes related to race and racial prejudice, which were obtained from three sources: Project Implicit (pooled across years 2002-2017), the General Social Survey (pooled across years 1973-2014), and the American National Election Survey (pooled across years 1992-2016). Collectively, these items assessed several different components of racial prejudice, including general attitudes towards Black individuals,

the impact of discrimination on the lives of Black people, the existence of racial prejudice, and endorsement of racial stereotypes. A similar aggregate measure of explicit racial bias has demonstrated strong retest reliability and convergent/discriminant validity.[53]

Structural Stigma Related to Latinx Ethnicity. For structural stigma related to Latinx ethnicity, we used 3 indicators: 1) a feelings thermometer of explicit attitudes of immigrants (obtained from the American National Election Survey); 2) a composite index of state-level policies related to immigration (e.g., whether immigrants were granted access to health services); and 3) a feelings thermometer of explicit attitudes of Hispanics (obtained from the American National Election Survey). We included attitudes and policies related to immigration, despite the obvious fact that not all Latinx individuals are immigrants, because of: 1) the conflation of immigration with Latinx ethnicity in the US; 2) the mixed status nature of many Latinx households; 3) the concealability of immigration status, which makes people targets regardless of citizenship; and 4) the salience of immigration policy to Latinx individuals in the U.S.[55]

Factor analysis. We created a factor score for each state for each structural stigma measure by using exploratory factor analysis with a factor loading cut off of 0.40; we reran the factor analysis iteratively and excluded variables until all retained items met the 0.40 threshold (Table S1, available online). For each measure, a 1-factor solution emerged, indicating that these items load onto a single construct of structural stigma, providing some evidence of construct validity. Cronbach's alpha was calculated to assess reliability.[56] The measures of structural stigma indicated high reliability for gender (α=0.94) and race (α=0.97) but lower reliability for Latinx ethnicity (α=0.57). Because Cronbach's alpha is influenced by the number of items that comprise a scale, the low alpha for Latinx structural stigma likely reflects the small number of items contributing to the factor (n=3) rather than poor reliability.

Perceived discrimination. Respondents were asked a series of questions about their perceptions of discrimination, unfair treatment, and perceived acceptance based on their identity (see Table S3, available online). After preregistering our analysis plan, we discovered that the perceived discrimination measure was first administered in the year after the baseline neuroimaging assessment (Wave 1). The measure was then re-administered during a follow-up assessment (Wave 2), in which neuroimaging data were collected a second time. Currently, ABCD has only released half of the data on the Wave 2 sample. Because there are strengths and limitations associated with each assessment (e.g., reduced power at Wave 2 but temporal concurrence, increased power at Wave 1 but lacking in temporal precedence), we present results for Wave 1 in the main text and Wave 2 in Supplement 2, available online; both produce similar conclusions.

Brain Structure and Function. Hippocampal volume was obtained from the structural data release. Quality control measures were applied to structural MRI data, including visual inspection of structural volumes, inspection of outliers of segmented volumes for potential segmentation problems, and exclusion of data that did not meet the quality control standards in the public data release. Volume measures of left and right hippocampus, obtained using automatic segmentation in FreeSurfer 5.3, were summed to produce a measure of total hippocampal volume.

Amygdala activation to threat was measured by contrasting amygdala response to fearful faces relative to neutral faces during an emotional n-back working memory task.[45] The task includes two runs of eight blocks each. On every trial, participants respond as to whether the picture was a “Match” or “No Match.” Within each block, stimuli were either all fearful faces, all neutral faces, all happy faces, or all places. Individual-level estimates of task-related BOLD

signal were computed using a general linear model implemented in AFNI's 3dDeconvolve. Hemodynamic response functions were modelled for cues (~3 s) and trial blocks (~24 s) as square waves convolved with a gamma variate basis function plus its temporal derivative using AFNI's 'SPMG' option within 3dDeconvolve. The contrast of interest was activation during the fearful face blocks vs. activation during the neutral face blocks within an amygdala region-of-interest defined using automatic segmentation by Freesurfer 5.3. The region-of-interest coefficients for this contrast from this task were obtained from the ABCD study's curated data release. Analyses were conducted separately for right and left amygdala, because the associations of social stressors (e.g., childhood trauma) with amygdala reactivity to threat often exhibit hemispheric specificity.[19,21,22]

For both outcomes, ABCD guidelines were followed with regard to exclusion of participants based on data quality, motion, or inattention (See Supplement 3, available online, for details).

Analytic Strategy

We pre-registered our hypotheses and analyses (https://osf.io/9axqr). We focused on three groups of stigmatized youth in the ABCD sample: girls, Black, and Latinx youth. (In our pre-registration, we hypothesized null effects among sexual minorities at baseline, because sexual identities emerge later in development;[57] see Supplement 2, available online, for those results.) Analyses were conducted using generalized mixed-effects models with the gamm4 function in R.[58] Random effects included site and family. Fixed-effects included age, sex (in analyses not focused on gender), family SES (family income), parental marital status, race and ethnicity (in analyses not focused on race and Latinx ethnicity, respectively). Analyses examining hippocampal volume additionally controlled for total intracranial volume.

After preregistering our analysis plan, we discovered substantial missing data on family income (~9%). Multiple imputation (100 imputations) was used to handle this missing data. Given difficulties in imputing in 3-level multi-level models and models with small (e.g., 2 siblings) cluster sizes,[59] we imputed based on 2-level structure with a random intercept of site, but not family. We also conducted supplementary analyses that controlled for an alternate measure of SES—family education—which had substantially lower missingness (0.7%) and was strongly correlated with family income (r=.64). The direction, magnitude, and significance of associations were unchanged with this alternative measure (see Supplement 4, available online).

A pre-registered power analysis indicated that within female participants and in all control analyses, we have adequate sample size to detect an effect size of r=0.1 with close to 100% power. Within Black and Latinx participants, we have sample size to detect an effect size of r=0.1 with 99% power.

Results

To test our predictions, we linked the three indicators of structural stigma to the ABCD dataset via the FIPS code of the state where each ABCD study site is located (n=21 sites) to determine their association with neural outcomes (See Table S4, available online). Because our independent variable (structural stigma) is a contextual factor coded at the site level, the degrees of freedom for the p-values presented below are based on the site (df=19), rather than on the total sample size of youth (e.g., n=5,489 girls) included in each analysis, which should be considered when interpreting the statistical and practical significance of the beta estimates.

Structural Stigma and Hippocampal Volume

Figure 2 shows the results for hippocampal volume. Higher structural stigma related to gender was associated with smaller hippocampal volume among girls (n=5,489, B=-29.50,

SE=16.96), although this was not statistically significant after controlling for covariates (*p*=0.082).

Higher structural stigma related to race was associated with smaller hippocampal volume among Black youth (n=2,421, *B*=-58.26, *SE*=25.70, *p*=0.023). A 1-unit increase in racial structural stigma was associated with a 58 mm^3 decrease in hippocampal volume among Black youth.

Higher structural stigma related to Latinx ethnicity was associated with smaller hippocampal volume among Latinx youth (n=2,346, *B*=-40.10, *SE*=19.90, *p*=0.044). A 1-unit increase in Latinx structural stigma was associated with a 40mm^3 decrease in hippocampal volume among Latinx youth.

A non-preregistered analysis indicated that the magnitude of associations between structural stigma and hippocampal volume was similar for the right and left hippocampus among all three stigmatized groups (see Supplement 5, Table S5, available online).

As hypothesized, structural stigma was unrelated to hippocampal volume in the non-stigmatized comparison groups: boys (n=6,037, *B*=-12.7, *p*=0.486), non-Latinx White (n=6,887, *B*=6.27, *p*=0.780), and White (n=8,594, *B*=-21.56, *p*=0.231) youth.

Structural Stigma and Amygdala Reactivity to Threat

There was no association between structural stigma and amygdala activation to fearful relative to neutral faces for any of the 3 stigmatized groups, or for the non-stigmatized comparison groups (see Supplement 2, available online).

Perceived Discrimination and Neural Outcomes

Perceived discrimination (measured continuously) was not associated with hippocampal volume among female (*B*=-13.1, *SE*=21.5, *p*=0.542), Black (*B*=16.1, *SE*=22.5, *p*=0.473), or

Latinx (*B*=-41.9, *SE*=25.5, *p*=0.101) youth. Similar results were obtained with the dichotomous indicators of perceived discrimination (see Supplement 2, available online). Further, no association between perceived discrimination and amygdala reactivity was observed (see Supplement 2, available online).

Discussion

Capitalizing on an innovative data structure, we were in the unique position to simultaneously measure stigma at both individual and structural levels and to determine their relative associations with neural outcomes in youth. We provide novel evidence that structural stigma is associated with brain structure in children, such that youth living in higher structural stigma contexts had smaller hippocampal volume when they had an identity that was a target of that structural stigma, as compared to youths living in lower stigma contexts. This association was observed consistently across three stigmatized groups (although it reached statistical significance only for Black and Latinx youth), suggesting that this relationship is generalizable across diverse types of stigmatized identities and statuses. In contrast, perceived discrimination was not associated with hippocampal volume among stigmatized youth. Thus, findings suggest that an objective measure of stigma at the structural level may be more strongly related to hippocampal volume than subjective perceptions of stigma measured at the individual level.

The associations of structural stigma with hippocampal volume build on a substantial literature documenting reduced hippocampal volume in children who have experienced trauma, who are raised in families with lower SES, and who have low levels of parental support and nurturance.[29,60–62] We extend this work beyond individual-level experiences by demonstrating that being raised in a social context characterized by higher levels of stigma towards members of one's group also influences hippocampal volume. The effect sizes for the association between

structural stigma and hippocampal volume, while relatively modest in magnitude, are similar to those observed for relatively extreme stressors—like childhood trauma—that are established correlates of reduced hippocampal volume. For instance, Black youth in the highest-structural stigma states had a hippocampus that was 177 mm^3 smaller than those in the lowest-structural stigma states, equivalent to about 2.3% of the average hippocampal volume among Black youth in the ABCD sample. A recent study, by comparison, found that the reduction in hippocampal volume attributable to childhood experiences of interpersonal violence was 364 mm^3,[63] about 3.8% of the average volume in that sample. To further contextualize this finding, the magnitude of the observed difference in hippocampal size between high and low structural stigma states was equivalent to the predicted impact of a $20,000 difference in annual family income in this sample. Statistically small effects can have societally important consequences if they apply to many people, or if they apply repeatedly to the same person.[64] These findings therefore suggest that structural stigma may be meaningfully associated with brain development in youth.

Our measure of state-level structural stigma related to gender, race, and ethnicity is a proxy for the social environment, which is hypothesized to influence a variety of intermediary variables that in turn may shape brain structure and function. Future research is needed to identify the specific environmental and neurobiological mechanisms linking structural stigma to reduced hippocampal volume. Animal and human studies have documented lasting reductions in hippocampal volume following exposure to chronic stress,[24,27–30,65,66] and resulting from low levels of support and nurturance in early life.[61,62] These effects are mediated by excessive production of corticotropin-releasing hormone in animal models,[24] although the precise neurobiological mechanisms contributing to these volume reductions in humans are unknown. The association of structural stigma with hippocampal volume may be due, in part, to exposure

to chronic stress or to a lack of social support associated with living in a stigmatizing context. Stressors resulting from structural stigma are conceptualized as chronic because they are related to fairly stable underlying social structures.[3] Support for a developmental pathway from structural stigma to hippocampal volume via experiences of chronic stress or low levels of support should be considered provisional, however, until it can be tested directly with longitudinal data that incorporates measures of stigma-related chronic stressors,[67] which will be possible in future waves of the ABCD study.

In contrast to the results for hippocampal volume, we did not observe an association between structural stigma and amygdala reactivity to fearful faces. Future research is needed to determine whether the divergent association of structural stigma with hippocampal volume and amygdala reactivity replicates and, if so, the reasons for this divergence. One possibility, supported by meta-analysis, is that task demands reduce amygdala response to salient cues.[68] Because amygdala activation was assessed during a working memory task in the ABCD study, it may have constrained variability in amygdala reactivity in our sample. The incorporation of additional tasks in future work may help to reveal whether this contributed to the divergent neural patterns observed herein.

We note several study limitations. First, these were cross-sectional analyses. However, issues of temporality are less of a concern for causal inference in our study, given that hippocampal volume cannot cause state-level structural stigma. Second, although the ABCD study is one of the largest of its kind, the 21 study sites are located in only 17 states. This resulted in a restricted range of structural stigma for each of our groups, with more than half of the sites located in states below the mean structural stigma scores (given the possible range from all 50 states). This restricted range reduced our statistical power, which means that our estimates

are likely conservative. At the same time, the restricted range limits generalizability to other social contexts.

Third, we measured structural stigma at the state level. Our focus on distal environments offers a conservative test, given that more proximal environments are likely to exert stronger effects.[69] However, this approach does not incorporate within-state heterogeneity, particularly with respect to local social environments that may differ from those at the state level. Exploring associations between structural stigma and hippocampal volume at more proximal levels of analysis (e.g., counties) represents an important area for future inquiry.

Fourth, we measured structural stigma using an empirically-derived approach (i.e., factor analysis) that combined multiple indicators of societal-level conditions, social attitudes, and public policies, in order to create a comprehensive index. This approach has several advantages, including providing evidence of construct validity (i.e., showing that multiple items related to structural stigma load onto a single factor) and reducing measurement error (i.e., tapping into shared variance). However, our approach likely missed other important dimensions of structural stigma. For instance, racial disparities in incarceration, which have been used in previous studies as indicators of structural racism,[49] did not load highly onto our factor. In addition, the internal consistency of the Latinx structural stigma measure was low. Although this likely reflected the small number of items comprising that scale, further research is needed to determine whether these results are generalizable across different operationalizations of this construct.

Fifth, although the indicators of structural stigma were obtained across a range of years, we aggregated all responses to the state level irrespective of year queried, which allowed for all states to have a sizable number of respondents, regardless of yearly sampling variation, thereby reducing measurement error. One potential limitation is that this approach does not capture

changes in temporal trends in structural stigma. However, while structural sexism and structural racism have declined nationally over time, the relative levels of structural stigma in individual states (i.e., rankings relative to other states) have remained highly stable,[48,70] suggesting that a time-invariant measure represents a valid approach to operationalizing this construct. Further, supplementary analyses showed that our structural stigma measures were highly correlated (*r*'s: .84 to .99) with an alternative measure that was restricted to the years following the birth of youth in the ABCD sample.

Sixth, there was low endorsement of perceived discrimination across stigmatized groups, which may have biased us towards the null. Additionally, while both Black and Latinx youth were significantly more likely to perceive discrimination than White and White non-Latinx youth, respectively, perceived discrimination was not higher among female than male youth, raising questions of construct validity for this group. Thus, future research is needed to confirm these results with measures of perceived discrimination that have demonstrated reliability and validity.

Seventh, because this is an observational study, we cannot definitively rule out alternative explanations. For instance, it is possible that other contextual factors influence both the level of structural stigma as well as smaller hippocampal volume among youth. In addition, structural stigma is confounded with site and scanner effects, and there are not enough degrees of freedom to control for scanner with interpretable results. However, there are two reasons why it is implausible that observed associations between structural stigma and hippocampal volume are due to scanner effects. First, if results were attributable to scanner effects, we would expect associations to be present among both the stigmatized and non-stigmatized. Yet, our negative control analyses showed no association between structural stigma and hippocampal volume for

any of the non-stigmatized comparison groups. Second, if certain scanners systematically under- or over-estimated hippocampal volume among members of a particular ethnic, racial, or gender group, we would expect to see an interaction between scanner type and that identity; however, a non-preregistered analysis revealed no significant interactions between scanner type and female sex, Black racial identity, or Latinx ethnicity in relation to hippocampal volume.

Finally, in observational studies of contextual factors, one concern is whether the results are due to social selection, whereby individuals with the observed outcome (i.e., lower hippocampal volume) sort into the exposure status (i.e., structural stigma). Yet, in studies of children, issues of social selection are less plausible, given that children are rarely responsible for moves into and out of certain environments. Although it is possible that the selection of parents into high structural stigma environments may contribute to the observed patterns (given strong associations between family SES and hippocampal volume in children), we observed no meaningful association between structural stigma and parental SES for any group (r's < 0.16). Thus, there is minimal evidence for differential selection of low-income parents into high structural stigma states.

Despite this study's limitations, the results not only expand our understanding of the multi-level consequences of stigma, but also suggest a potential neural mechanism underlying the established association between structural stigma and psychopathology.[3] Examining whether hippocampal volume mediates the structural stigma-mental health association will be possible in future waves of the ABCD dataset as the youth age into the developmental period of risk for depression and post-traumatic stress disorder, which have both been consistently linked with hippocampal volume.[32–35] Additionally, our results suggest that macro-level features of the social context are associated with brain structure in youth, which has implications for broadening the

range of potential explanatory variables in cognitive neuroscience to include contextual influences. Collectively, these findings set the stage for future studies to identify additional contextual correlates of neurodevelopment among youth, and to uncover the environmental and neurobiological mechanisms underlying these relationships.

References

1. Link BG, Phelan JC. Conceptualizing stigma. *Annu Rev Sociol*. 2001;27(1):363-385. doi:https://doi.org/10.1146/annurev.soc.27.1.363
2. Pescosolido BA, Martin JK. The stigma complex. *Annu Rev Sociol*. 2015;41:87-116. doi:https://doi.org/10.1146/annurev-soc-071312-145702
3. Hatzenbuehler ML. Structural stigma: Research evidence and implications for psychological science. *Am Psychol*. 2016;71(8):742-751. doi:10.1037/amp0000068
4. Pachankis JE. The psychological implications of concealing a stigma: a cognitive-affective-behavioral model. *Psychol Bull*. 2007;133(2):328-345. doi:10.1037/0033-2909.133.2.328
5. Corrigan PW, Sokol KA, Rüsch N. The impact of self-stigma and mutual help programs on the quality of life of people with serious mental illnesses. *Community Ment Health J*. 2013;49(1):1-6. doi:10.1007/s10597-011-9445-2
6. Mendoza-Denton R, Downey G, Purdie VJ, Davis A, Pietrzak J. Sensitivity to status-based rejection: Implications for African American students' college experience. *J Pers Soc Psychol*. 2002;83(4):896. doi:10.1037/0022-3514.83.4.896
7. Major B, O'Brien LT. The social psychology of stigma. *Annu Rev Psychol*. 2005;56:393-421. doi:10.1146/annurev.psych.56.091103.070137
8. Hatzenbuehler ML, Link BG. Introduction to the special issue on structural stigma and health. *Soc Sci Med*. 2014;103:1-6. doi:10.1016/j.socscimed.2013.12.017
9. Rostosky SS, Riggle EDB, Horne SG, Denton FN, Huellemeier JD. Lesbian, gay, and bisexual individuals' psychological reactions to amendments denying access to civil marriage. *Am J Orthopsychiatry*. 2010;80(3):302-310. doi:10.1111/j.1939-0025.2010.01033.x
10. Hatzenbuehler ML, Prins SJ, Flake M, et al. Immigration policies and mental health morbidity among Latinos: a state-level analysis. *Soc Sci Med*. 2017;174:169-178. doi:10.1016/j.socscimed.2016.11.040
11. Hatzenbuehler ML, Keyes KM, Hasin DS. State-level policies and psychiatric morbidity in lesbian, gay, and bisexual populations. *Am J Public Health*. 2009;99(12):2275-2281. doi:10.2105/AJPH.2008.153510
12. Hatzenbuehler ML, McLaughlin KA, Keyes KM, Hasin DS. The impact of institutional discrimination on psychiatric disorders in lesbian, gay, and bisexual populations: a prospective study. *Am J Public Health*. 2010;100(3):452-459. doi:10.2105/AJPH.2009.168815
13. Raifman J, Moscoe E, Austin SB, Hatzenbuehler ML, Galea S. Association of state laws permitting denial of services to same-sex couples with mental distress in sexual minority adults: a difference-in-difference-in-differences analysis. *JAMA Psychiatry*. 2018;75(7):671-677. doi:10.1001/jamapsychiatry.2018.0757
14. Hatzenbuehler ML. How does sexual minority stigma "get under the skin"? A

psychological mediation framework. *Psychol Bull*. 2009;135(5):707-730. doi:10.1037/a0016441

15. Flentje A, Heck NC, Brennan JM, Meyer IH. The relationship between minority stress and biological outcomes: A systematic review. *J Behav Med*. Published online 2019:1-22. doi:10.1007/s10865-019-00120-6

16. Busse D, Yim IS, Campos B, Marshburn CK. Discrimination and the HPA axis: current evidence and future directions. *J Behav Med*. 2017;40(4):539-552. doi:10.1007/s10865-017-9830-6

17. Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An fMRI study of social exclusion. *Science (80-)*. 2003;302(5643):290-292. doi:10.1126/science.1089134

18. Somerville LH, Heatherton TF, Kelley WM. Anterior cingulate cortex responds differentially to expectancy violation and social rejection. *Nat Neurosci*. 2006;9(8):1007-1008. doi:10.1038/nn1728

19. McLaughlin KA, Peverill M, Gold AL, Alves S, Sheridan MA. Child maltreatment and neural systems underlying emotion regulation. *J Am Acad Child Adolesc Psychiatry*. 2015;54(9):753-762.

20. McCrory EJ, De Brito SA, Sebastian CL, et al. Heightened neural reactivity to threat in child victims of family violence. *Curr Biol*. 2011;21(23):R947-R948.

21. Jenness JL, Peverill M, Miller AB, et al. Alterations in neural circuits underlying emotion regulation following child maltreatment: a mechanism underlying trauma-related psychopathology. *Psychol Med*. Published online 2020:1-10.

22. McCrory EJ, De Brito SA, Kelly PA, et al. Amygdala activation in maltreated children during pre-attentive emotional processing. *Br J Psychiatry*. 2013;202(4):269-276.

23. Cacioppo S, Frum C, Asp E, Weiss RM, Lewis JW, Cacioppo JT. A quantitative meta-analysis of functional imaging studies of social rejection. *Sci Rep*. 2013;3(1):1-3. doi:10.1038/srep02027

24. Ivy AS, Rex CS, Chen Y, et al. Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *J Neurosci*. 2010;30(39):13005-13015. doi:10.1523/JNEUROSCI.1784-10.2010

25. Lee T, Jarome T, Li S-J, Kim JJ, Helmstetter FJ. Chronic stress selectively reduces hippocampal volume in rats: a longitudinal MRI study. *Neuroreport*. 2009;20(17):1554. doi:10.1097/WNR.0b013e328332bb09

26. Schoenfeld TJ, McCausland HC, Morris HD, Padmanaban V, Cameron HA. Stress and loss of adult neurogenesis differentially reduce hippocampal volume. *Biol Psychiatry*. 2017;82(12):914-923. doi:10.1016/j.biopsych.2017.05.013

27. Hanson JL, Nacewicz BM, Sutterer MJ, et al. Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biol Psychiatry*. 2015;77(4):314-323. doi:10.1016/j.biopsych.2014.04.020

28. Woon FL, Sood S, Hedges DW. Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. *Prog*

Neuro-Psychopharmacology Biol Psychiatry. 2010;34(7):1181-1188. doi:10.1016/j.pnpbp.2010.06.016

29. McLaughlin KA, Weissman D, Bitrán D. Childhood adversity and neural development: a systematic review. *Annu Rev Dev Psychol*. 2019;1. doi:10.1146/annurev-devpsych-121318-084950

30. Luby JL, Belden A, Harms MP, Tillman R, Barch DM. Preschool is a sensitive period for the influence of maternal support on the trajectory of hippocampal development. *Proc Natl Acad Sci USA*. 2016;113(20):5742-5747. doi:10.1073/pnas.1601443113

31. Thoon KC, Soh SBL, Liew WK, et al. Active surveillance of adverse events following childhood immunization in Singapore. *Vaccine*. 2014;32(39):5000-5005. doi:10.1016/j.vaccine.2014.07.020

32. Logue MW, van Rooij SJH, Dennis EL, et al. Smaller hippocampal volume in posttraumatic stress disorder: a multisite ENIGMA-PGC study: subcortical volumetry results from posttraumatic stress disorder consortia. *Biol Psychiatry*. 2018;83(3):244-253. doi:10.1016/j.biopsych.2017.09.006

33. Gilbertson MW, Shenton ME, Ciszewski A, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci*. 2002;5(11):1242-1247. doi:10.1038/nn958

34. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry*. 2004;161(11):1957-1966. doi:10.1176/appi.ajp.161.11.1957

35. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry*. 2004;161(4):598-607. doi:10.1176/appi.ajp.161.4.598

36. Swartz JR, Knodt AR, Radtke SR, Hariri AR. A neural biomarker of psychological vulnerability to future life stress. *Neuron*. 2015;85(3):505-511. doi:10.1016/j.neuron.2014.12.055

37. McLaughlin KA, Busso DS, Duys A, et al. Amygdala response to negative stimuli predicts PTSD symptom onset following a terrorist attack. *Depress Anxiety*. 2014;31(10):834-842. doi:10.1002/da.22284

38. Stein MB, Simmons AN, Feinstein JS, Paulus MP. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *Am J Psychiatry*. 2007;164(2):318-327. doi:10.1176/ajp.2007.164.2.318

39. Pearce N. Epidemiology in a changing world: Variation, causation and ubiquitous risk factors. *Int J Epidemiol*. 2011;40(2):503-512. doi:10.1093/ije/dyq257

40. Steensma TD, Kreukels BPC, de Vries ALC, Cohen-Kettenis PT. Gender identity development in adolescence. *Horm Behav*. 2013;64(2):288-297. doi:10.1016/j.yhbeh.2013.02.020

41. Alejandro-Wright MN. *The Child's Conception of Racial Classification: A Socio-Cognitive Developmental Model*. (W. R. Allen & M. B. Spencer GKB, ed.). Lawrence Erlbaum; 1985.

42. Bernal ME, Knight GP, Garza CA, Ocampo KA, Cota MK. The development of ethnic identity in Mexican-American children. *Hisp J Behav Sci*. 1990;12(1):3-24. doi:10.1177/07399863900121001

43. Lipsitch M, Tchetgen ET, Cohen T. Negative controls: A tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21(3):383-388. doi:10.1097/EDE.0b013e3181d61eeb

44. Garavan H, Bartsch H, Conway K, et al. Recruiting the ABCD sample: design considerations and procedures. *Dev Cogn Neurosci*. 2018;32:16-22. doi:10.1016/j.dcn.2018.04.004

45. Casey BJ, Cannonier T, Conley MI, et al. The adolescent brain cognitive development (ABCD) study: imaging acquisition across 21 sites. *Dev Cogn Neurosci*. 2018;32:43-54. doi:10.1016/j.dcn.2018.03.001

46. Homan P. Structural Sexism and Health in the United States: A New Perspective on Health Inequality and the Gender System. *Am Sociol Rev*. 2019;84(3):486-516. doi:https://doi.org/10.1177/0003122419848723

47. McLaughlin KA, Xuan Z, Subramanian S V, Koenen KC. State-level women's status and psychiatric disorders among US women. *Soc Psychiatry Psychiatr Epidemiol*. 2011;46(11):1161-1171. doi:10.1007/s00127-010-0286-z

48. Charles KK, Guryan J, Pan J. The Effects of Sexism on American Women: The Role of Norms vs. Discrimination. *SSRN Electron J*. Published online August 2018. doi:10.2139/ssrn.3233788

49. Lukachko A, Hatzenbuehler ML, Keyes KM. Structural racism and myocardial infarction in the United States. *Soc Sci Med*. 2014;103:42-50. doi:10.1016/j.socscimed.2013.07.021

50. Leitner JB, Hehman E, Ayduk O, Mendoza-Denton R. Blacks' death rate due to circulatory diseases is positively related to Whites' explicit racial bias: A nationwide investigation using Project Implicit. *Psychol Sci*. 2016;27(10):1299-1311. doi:10.1177/0956797616658450

51. Lee Y, Muennig P, Kawachi I, Hatzenbuehler ML. Effects of racial prejudice on the health of communities: A multilevel survival analysis. *Am J Public Health*. 2015;105(11):2349-2355. doi:10.2105/AJPH.2015.302776

52. Reid AE, Dovidio JF, Ballester E, Johnson BT. HIV prevention interventions to reduce sexual risk for African Americans: The influence of community-level stigma and psychological processes. *Soc Sci Med*. 2014;103:118-125. doi:10.1016/j.socscimed.2013.06.028

53. Hehman E, Calanchini J, Flake JK, Leitner JB. Establishing construct validity evidence for regional measures of explicit and implicit racial bias. *J Exp Psychol Gen*. 2019;148(6):1022-1040. doi:10.1037/xge0000623

54. Oishi S, Graham J. Social ecology: Lost and found in psychological science. *Perspect Psychol Sci*. 2010;5(4):356-377. doi:https://doi.org/10.1007/BF02310555

55. López M, González-Barrera A, Krogstad J. Views of immigration Policy. Pew Research Center. Published online 2018.

56. Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrika*. 1951;16(3):297-334. doi:https://doi.org/10.1007/BF02310555

57. Taylor P, Parker K, Kiley J, Lopez MH, Keeter S. *A Survey of LGBT Americans: Attitudes, Experiences and Values in Changing Times*. Pew Research Center; 2013.

58. Wood S, Scheipl F. gamm4: Generalized additive mixed models using mgcv and lme4. Published online 2020:9. doi:10.1214/18-STS646

59. Audigier V, White IR, Jolani S, et al. Multiple imputation for multilevel data with continuous and binary variables. *Stat Sci*. 2018;33(2):160-183. doi:10.1214/18-STS646

60. Noble KG, Houston SM, Brito NH, et al. Family income, parental education and brain structure in children and adolescents. *Nat Neurosci*. 2015;18(5):773. doi:10.1038/nn.3983

61. Luby JL, Barch DM, Belden A, et al. Maternal support in early childhood predicts larger hippocampal volumes at school age. *Proc Natl Acad Sci*. 2012;109(8):2854-2859. doi:10.1073/pnas.1118003109

62. Rao H, Betancourt L, Giannetta JM, et al. Early parental care is important for hippocampal maturation: evidence from brain morphology in humans. *Neuroimage*. 2010;49(1):1144-1150. doi:10.1016/j.neuroimage.2009.07.003

63. Weissman DG, Lambert HK, Rodman AM, Peverill M, Sheridan MA, McLaughlin KA. Reduced hippocampal and amygdala volumes as mechanisms of stress sensitization to depression following childhood violence exposure. *bioRxiv*. Published online 2019:798033. doi:10.1002/da.23062

64. Greenwald AG, Banaji MR, Nosek BA. Statistically small effects of the Implicit Association Test can have societally large effects. *J Pers Soc Psychol*. 2015;108(4):553-561. doi:10.1037/pspa0000016

65. Gianaros PJ, Jennings JR, Sheu LK, Greer PJ, Kuller LH, Matthews KA. Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. *Neuroimage*. 2007;35(2):795-803. doi:10.1016/j.neuroimage.2006.10.045

66. Conrad CD. Chronic stress-induced hippocampal vulnerability: the glucocorticoid vulnerability hypothesis. *Rev Neurosci*. 2008;19(6):395. doi:10.1515/revneuro.2008.19.6.395

67. MacKinnon D. *Introduction to Statistical Mediation Analysis*. Erlbaum; 2008.

68. Costafreda SG, Brammer MJ, David AS, Fu CHY. Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Res Rev*. 2008;58(1):57-70. doi:10.1016/j.brainresrev.2007.10.012

69. Lattaner M, Ford J, Bo N, et al. A contextual approach to the psychological study of identity concealment: Examining direct, interactive, and indirect effects of structural stigma on concealment motivation across proximal and distal levels. *Psychol Sci*.:In press.

70. McKetta S, Hatzenbuehler ML, Pratt C, Bates L, Link BG, Keyes KM. Does social selection explain the association between state-level racial animus and racial disparities in self-rated health in the United States? *Ann Epidemiol*. 2017;27(8). doi:10.1016/j.annepidem.2017.07.002

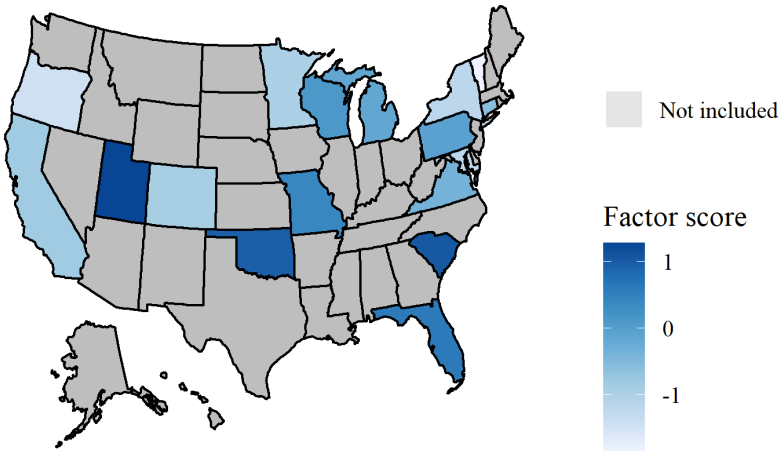
Figure 1. State-level Structural Stigma Across Three Stigmatized Groups

Note: The figure shows the distribution of the three measures of structural stigma related to sex/gender (A), race (B), and Latinx ethnicity (C), across the 17 states in the ABCD sample.

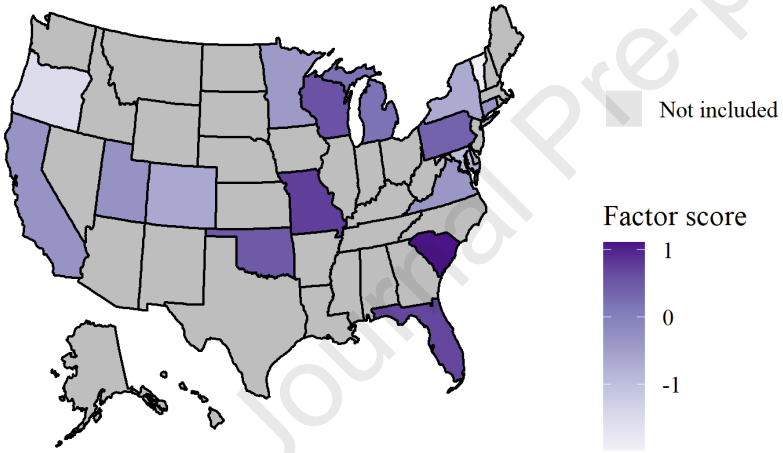
Figure 2. Plot of Hippocampal Volume Among Female, Non-Immigrant Latinx, and Black Youth by State

Note: States are ordered from left to right in each plot based on their structural stigma factor scores. Violin plots depict the density distribution of hippocampal volume in that state. Black points represent the hippocampal volume predicted based on each states' structural stigma score when all other covariates in the multilevel models of the relation between structural stigma and hippocampal volume are at their mean.

A. Sex/Gender



B. Race



C. Latinx ethnicity