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

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ABSTRACT

Are macro-level features of the social context associated with neurodevelopment in children? Answering this question is challenging, because most neuroimaging studies are conducted in one location, making it impossible to link contextual variation with neural outcomes. Here, we use one of the first national, multi-site neuroimaging studies with substantial variability in sociopolitical contexts: the Adolescent Brain and Cognitive Development study (N=11,534; *M*=9.9 years). We measured stigma surrounding gender, race, and Latinx ethnicity using objective state-level indicators of social policies and prejudicial attitudes and two neural markers consistently linked with stress exposure: hippocampal volume and amygdala reactivity to threat. In a pre-registered analysis, we find that African-American and Latinx youth in higher stigma environments have smaller hippocampal volume, controlling for demographics and family socioeconomic status. Stigmatizing environments were unrelated to hippocampal volume in non-stigmatized youth, providing evidence of specificity. We demonstrate that contextual approaches may yield new insights into neurodevelopment.

Keywords: stigma, hippocampal volume, youth, context effects

Stigma—defined as the co-occurrence of labeling, stereotyping, status loss, and discrimination in a context in which power is exercised—is a central topic in numerous social science disciplines, including psychology,[1] sociology,[2] anthropology,[3] and history.[4] Of the many insights to emerge from the stigma literature, three are well-established across these disciplines. First, stigma exists at multiple levels[5]—ranging from individual responses (e.g., self-stigma, concealment) and interpersonal events (e.g., discriminatory treatment) to structural factors, which include societal-level conditions, cultural norms, and institutional policies and practices.[6] Second, robust evidence links stigma at individual,[7] interpersonal,[1] and structural[8] levels to adverse physical and mental health outcomes across the life course among a diverse range of stigmatized groups. Third, stigma exerts these negative consequences through numerous intervening mechanisms;[9] one of the most widely studied is stress.[1,10] Stress is experienced when the demands of a situation outweigh one's ability to cope, triggering a cascade of physiological, affective, and behavioral responses.[11,12] Stress arising from stigma can be measured at multiple levels, including environmental stressors (e.g., experiences of discrimination or other characteristics of the environment that contribute to stigma), stress perceptions, or cognitive, affective, or physiological aspects of the stress response. To date, existing work has measured stigma-related stressors almost exclusively at individual or interpersonal levels, either via self-perceptions[13] or through manipulating social interactions in a laboratory setting.[14] Consequently, the extent to which broader, macro-social forms of stigma—known as structural stigma—also contribute to stress responses among the stigmatized remains largely unknown. Here, we examine whether living in a context characterized by high structural stigma early in life is associated with aspects of brain structure and function known to be influenced by exposure to stress in a large population-based study of children.

Although we are unaware of prior work examining the influence of structural stigma on neurodevelopment, other social factors have been shown to play a meaningful role in shaping brain structure and function. For example, rejection and exclusion[15-17] are associated with altered neural responses to affectively salient stimuli, particularly in the amygdala and other regions of the salience network. Some forms of social adversity—particularly those that are chronic or occur early in life, such as childhood trauma and exposure to interpersonal violence—have been linked to changes in brain structure in regions with a high density of glucocorticoid receptors, such as the hippocampus—a region that exhibits morphological changes following stress exposure in animal models that are mediated by glucocorticoids.[18-20] Reductions in hippocampal volume following experiences of extreme or chronic stress are well-replicated in humans.[21-23] Exposure to trauma in childhood is also associated with changes in brain function in regions involved in salience processing, threat detection, and aversive learning, such as the amygdala.[23-28] Hippocampal volume and amygdala responses to threat cues are thus two well-established neural markers linked to experiences of stress, with reduced hippocampal volume associated with experiences of chronic stress as well as trauma and amygdala reactivity most consistently associated with exposure to trauma.

Although many have highlighted the importance of studying whether macro-social (i.e., structural and contextual) factors also influence brain structure and function,[29-31] the ability to do so has been hindered by the fact that 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[32]—precluding the possibility of linking contextual variation with neural outcomes. Given these methodological constraints, it has not previously been possible to evaluate the neurobiological consequences of exposure to

stigmatizing contexts. Fortuitously, neuroimaging studies with meaningful variation in social context have recently become available. In the current study, we leverage this opportunity by using 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, thereby affording significant geographic variability in exposure to stigmatizing contexts (i.e., structural stigma) among youth.

Structural Stigma

Stigma contributes to adverse outcomes for marginalized groups through its influence on numerous mechanisms across individual, interpersonal, and structural levels of analysis.[2] At the individual level, stigma manifests as psychological responses through which stigmatized individuals both perceive and react to stigma. Psychologists have identified numerous individual-level stigma processes that shape the health and wellbeing of the stigmatized, including identity concealment,[7] self-stigma,[33] and expectations of rejection.[34] Interpersonal forms of stigma, in contrast, are interactional in nature, and exist along a continuum ranging from relatively overt to covert actions targeting the stigmatized, such as discrimination and mistreatment. Similar to research on individual forms of stigma, there is a large body of evidence on the adverse consequences of stigma at the interpersonal level.[1]

At the structural level, stigma is enacted through institutional policies and practices, and it is promulgated through broad cultural and social norms that are held towards members of stigmatized groups. Collectively, these structural forms of stigma have been defined as "societal-level conditions, cultural norms and institutional policies and practices that constrain the opportunities, resources, and wellbeing of the stigmatized."[6,p.2] Although most psychological

research has focused on the adverse consequences of individual and interpersonal forms of stigma,[1] growing evidence indicates that structural stigma represents an additional risk factor for a variety of negative outcomes among the stigmatized.[8]

Typically, studies have operationalized structural stigma in two distinct ways. The first approach conducts legal content analyses that capture the presence of structural stigma in the policies of social institutions,[35] such as restrictive immigration policies and laws denying services to same-sex couples. Across a range of methods and stigmatized groups, more adverse outcomes among stigmatized individuals in communities with higher (vs. lower) levels of structural stigma, as proxied by social policies, have been observed consistently. For instance, observational studies have shown that sexual minorities living in states with fewer legal protections for lesbian, gay, and bisexual (LGB) individuals have higher levels of psychological distress[36] and psychiatric disorders[37] than those in states with more protective policies. Further, quasi-experimental studies have demonstrated that rates of mental disorders and psychological distress among stigmatized populations increase following constitutional amendments banning same-sex marriage[38] and laws denying services to same-sex couples.[39] In contrast, rates of adverse mental and physical health outcomes decrease following reductions in structural stigma—for example, after the implementation of civil union laws that are inclusive of same-sex couples[40] and the abolishment of Jim Crow laws in the southern United States.[41]

In a second methodological approach, structural stigma has been measured through social/cultural norms. Individuals' attitudes (both implicit and explicit) are aggregated to the community level—defined at various geographic scales (e.g., counties, states)—such that the level of structural stigma can be compared across communities. This measurement approach is viewed as structural because aggregated social/cultural norms not only reflect, but also shape,

structural factors, such as policy regimes. Aggregated social norms have been used in previous research to measure contextual features of stigma and prejudice across a range of groups, including Blacks,[42] immigrants,[43] sexual minorities,[44] and people with psychopathology,[45] and HIV/AIDS.[46,47] This work has shown that community-level prejudicial attitudes are associated with self-stigma,[45] disclosure concerns,[46] psychological distress,[48] poor self-rated health,[49] and even shortened lifespans,[42] among the stigmatized.

Accumulating evidence therefore demonstrates that structural stigma—as measured via social policies and aggregated community norms—is associated with numerous adverse psychological consequences, many of which are correlates of stress exposure.[8] Evidence for a stress pathway linking structural stigma to these adverse outcomes has largely been indirect, however. One exception is a lab-based study indicating that prior exposure to structural stigma is associated with changes in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis among sexual minority young adults,[50] providing preliminary support that structural stigma may be directly associated with neurobiological stress responses. However, the degree to which structural stigma influences neurodevelopmental processes has, to our knowledge, never been examined. We do so in the current study.

The Current Study

We examine whether living in a context characterized by high structural stigma early in life is associated with two aspects of brain structure and function known to be influenced by exposure to stress: hippocampal volume and amygdala reactivity to threat. We strategically selected these two particular neural outcomes because they have each been associated consistently with exposure to stressors. Both animal and human studies have documented lasting reductions in hippocampal volume following exposure to chronic stress in both children and

adults.[18,21-24,51,52] Heightened amygdala reactivity to threat has largely been observed following exposure to relatively acute and severe forms of early-life adversity, such as childhood trauma.[18-20,23,53] Stressors resulting from structural stigma are conceptualized as chronic because they are related to fairly stable underlying social structures.[10] At the same time, structural stigma may also increase the risk of exposure to acute stigma-related stressors, such as bias-based bullying or victimization.[54,55] Thus, it is reasonable to expect that structural stigma would be associated with neural markers associated with both chronic and acute forms of stress. On the other hand, if we observe divergent associations between structural stigma and these two neural markers, such a finding might point to different underlying mechanisms. For instance, an association with only reduced hippocampal volume might suggest that structural stigma increases risk for negative consequences via a chronic stress pathway, whereas an association with only heightened amygdala reactivity to threat might instead suggest that structural stigma increases risk for adverse outcomes via exposure to relatively acute interpersonal stressors, such as victimization experiences.

We also strategically selected three stigmatized groups—girls, racial (Black), and ethnic (Latinx) minority youth (mean age=9.9 years)—in which to test our research question. The selection of these groups was informed by the developmental literature on identity awareness, formation, and responsivity to identity-based stressors. This literature indicates that gender,[56] racial,[57] and ethnic[58] identities emerge during early childhood, with girls as well as Black and Latinx youth reporting identity awareness and constancy, as well as perceptions of group-based stereotypes, by approximately 9-10 years, the age of the baseline ABCD sample.

We tested two hypotheses. First, we predicted that greater exposure to structural stigma would be associated with smaller hippocampal volume and elevated amygdala reactivity to threat

cues (i.e., fearful faces 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 to threat among the non-stigmatized comparison groups: boys, Whites, and non-Hispanic Whites. This analysis serves as a negative control approach,[59] in that we test whether there is an association among the groups where we would not theoretically expect it. We pre-registered these predictions and analytic approach (see https://osf.io/9axqr). Because we were measuring a distal social factor (i.e., structural stigma), we expected that the effect sizes would be small in magnitude as compared to those of proximal social factors (e.g., childhood trauma, social rejection), which have been the focus of most neuroimaging research. Nonetheless, even small effect sizes can be substantively meaningful,[60] especially when they relate to factors whose potential influence is scaled over large populations.[61]

Results

We created objective indicators of structural stigma related to sex/gender, Black race, and Latinx ethnicity measured at the state level (Figure 1), drawing on existing measures of this construct.[49,62,63] To test our predictions, we linked these three indicators of structural stigma (described below) 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 the two neural measures. It is important to note that our independent variable (structural stigma) is a contextual factor and coded at the site level. Consequently, 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 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 sex/gender was associated with smaller hippocampal volume among girls (n=5,489, *B*=-29.56, *SE*=16.96), although this did not reach statistical significance (*p*=0.081) controlling for covariates. A 1-unit increase in sex/gender structural stigma was associated with a 30 mm^2 decrease in hippocampal volume among girls.

Higher structural stigma related to race was associated with significantly smaller hippocampal volume among Black youth (n=2,421, *B*=-57.27, *SE*=25.53, *p*=0.025). A 1-unit increase in racial structural stigma was associated with a 57 mm^2 decrease in hippocampal volume among Black youth.

Higher structural stigma related to Latinx ethnicity was associated with significantly smaller hippocampal volume among Latinx youth (n=2,346, *B*=-41.02, *SE*=19.70, *p*=0.037). A 1-unit increase in Latinx structural stigma was associated with a 41mm^2 decrease in hippocampal volume among Latinx youth.

As hypothesized, structural stigma was unrelated to hippocampal volume in the non-stigmatized comparison groups: boys (n=6,037, *B*=-12.76, *SE*=18.36, *p*=0.487), non-Latinx White (n=6,887, *B*=6.74, *SE*=22.40, *p*=0.760), and White (n=8,594, *B*=-21.76, *SE*=17.96, *p*=0.227) 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 (results shown in SI Appendix).

Discussion

We provide novel evidence that an objectively-coded macro-social contextual factor—structural stigma—is associated with brain structure in children as young as 9 years old, such that youth living in higher (vs. lower) structural stigma contexts had smaller hippocampal volume when they had an identity that was a target of that structural stigma. This association was observed consistently across three stigmatized groups (girls, Black, and Latinx youth), although the association 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 to the pattern of associations between structural stigma and hippocampal volume, we did not observe an association between structural stigma and amygdala reactivity to fearful faces.

The effect sizes, 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^2 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 direct experiences of interpersonal violence involving physical or sexual abuse or domestic violence was 364 mm,[2 64] 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.[61] These findings therefore suggest that structural stigma may be meaningfully associated with aspects of brain structure among youth.

Future research is needed to determine the environmental pathways and neurobiological mechanisms linking structural stigma to reduced hippocampal volume. The fact that structural stigma was related to a neural marker associated with a wide range of chronic stressors (i.e., hippocampal volume),[18,21-24,51,52] but not to a neural marker associated with more severe and acute forms of stress (i.e., amygdala reactivity to threat),[18-20,23,53] suggests that the established relationship between structural stigma and a variety of adverse outcomes[8] may be due, in part, to exposure to chronic stress. Support for a developmental pathway from structural stigma to hippocampal volume via experiences chronic stress should be considered provisional, however, until it can be tested directly with longitudinal data that incorporates measures of stigma-related chronic stressors,[65] which will be possible in future waves of the ABCD study. In addition, future research may wish to consider whether structural stigma is associated with neural outcomes other than the two examined in this study. For instance, social identity threat theories of stigma[1] have posited numerous non-voluntary responses resulting from stigma-induced identity threat, such as working memory load,[66] an additional outcome that could be explored in future research.

We note several limitations of the current study. First, this is a cross-sectional analysis. Although we used a cross-sectional design, issues of temporality are less of a concern for causal inference in our study, given that hippocampal volume cannot cause state-level structural stigma. Further, in studies of contextual factors, one concern is whether the results are due to social selection, whereby individuals with the observed outcome (in this case, lower hippocampal volume) sort into the exposure status (i.e., structural stigma). However, in studies of youth, such as in the ABCD sample, 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 parental SES and hippocampal volume among their children), we observed no meaningful association between structural stigma and parental SES for any group (structural stigma related to sex/gender: r=-0.162; structural stigma related to race: r=-0.155; and structural stigma related to Latinx ethnicity: r=0.104). Thus, there is minimal evidence for differential selection of low-income parents into high structural stigma states.

Second, although the ABCD study is one of the largest of its kind, the 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 that fell below the mean of structural stigma related to sex/gender, race, and Latinx ethnicity. This restricted range would have reduced our statistical power, which means that our estimates of the association between structural stigma and hippocampal volume are likely conservative. At the same time, the restricted range means that our findings are not generalizable to contexts not included in our sample, and consequently that different associations may be observed with a different set of contexts.

Third, our study measured structural stigma at the state level, as geographic units below the state level were not available. Our focus on distal environments at the state level offers a conservative test, given that more proximal environments are likely to exert stronger effects. 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) therefore represents an important area for future inquiry.

Fourth, while the concept of structural stigma has existed for decades,[5] its operationalization is a relatively recent occurrence.[6] Existing studies have used different approaches to operationalize this construct, depending on the focus of a particular study. These

approaches have ranged from single-item measures of an individual component of structural stigma (e.g., social attitudes[42,47,67,68]) to multi-item scales that capture several different dimensions.[49,62,63] Drawing on current conceptualizations of structural stigma,[6] 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, thereby minimizing unique 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,[63] did not load highly onto our factor. Thus, other measurement approaches may yield different relationships between structural stigma and neurodevelopment among youth, and further research is therefore needed to determine whether these results are generalizable across different operationalizations of this construct.

Finally, it is possible that other contextual factors influence both the level of structural stigma as well as smaller hippocampal volume among youth. However, our negative control analyses showing no association between structural stigma and hippocampal volume for any of the non-stigmatized comparison groups help to minimize this possibility, because if structural stigma were merely a proxy for other contextual factors (e.g., state-level socioeconomic status, conservatism), those other factors should operate similarly among both the stigmatized and non-stigmatized.

Our results have implications not only for the stigma literature but also for the field of social-cognitive neuroscience. With respect to the former, these findings expand our

understanding of the multi-level consequences of stigma, and suggest a potential neural mechanism underlying the established association between structural stigma and physical and mental health problems—including mood and anxiety disorders,[38] psychological distress,[39] post-traumatic stress disorder,[69] and cardiovascular disease[63]—among the stigmatized. With respect to the latter, our results suggest that macro-level features of the social context are associated with aspects of brain structure in children. 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.

Methods

Sample

Data come from the Adolescent Brain and Cognitive Development (ABCD) study, the largest long-term study of brain development and child health in the United States (https://abcdstudy.org). Our study uses data from the Year 1 assessment (ABCD 2.0) of 11,534 youth in the cohort. Twenty-one study sites were selected from across the United States. From these sites, a stratified probability sample of schools within the 21 defined catchment areas for each site were selected, and eligible youth were recruited from each sample school. Thus, while the ABCD study approximates a multi-stage probability sample, it is not nationally representative of U.S. youth. A further description of the sample selection procedures is described by Garavan and colleagues;[70] the imaging procedures that were harmonized across the 21 study sites are described by Casey and colleagues.[71]

We focused on three groups of stigmatized youth: girls, Black, and Latinx youth. Sex, race, ethnicity, and nativity status (whether the respondent or his/her parent was born in the US) of the respondents were reported by parents in the ABCD Parent Demographics Survey

(https://nda.nih.gov/data_structure.html?short_name=pdem02). Family income and parent marital status were also obtained from this survey and used as covariates in all analyses.

Measures

Independent variables. Consistent with conceptualizations of structural stigma[6] and with prior empirical research on this topic,[8] we selected items that captured societal-level conditions, social/cultural norms, and institutional policies relevant to the three subgroup of interest in our analyses: girls, Black, and Latinx participants. The first step was to compile items from publicly available data sources that had been used in prior work to assess structural forms of stigma related to sex/gender,[62,69,72] race,[42,63,68,73] and Latinx ethnicity.[49] Next, 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. Although several studies have used single-item measures (e.g., aggregated IAT scores or aggregated feelings thermometers) to capture contextual features of prejudice,[42,47,67,68] 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) taps into shared variance (minimizing unique variance), thereby reducing measurement error. Below, we describe the items and sources of data for each group; further details about the structural stigma measures can be found in the SI Appendix.

Structural Stigma Related to Sex/Gender. The measure of structural stigma related to sex/gender was comprised of 18 items (selected from n=27 candidate indicators; see Factor Analysis section below for details on item selection). 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 (e.g., whether it is better for women to stay home and care for children) and sexist beliefs (e.g., whether men are more emotionally suited for politics than women, whether the gender disparity in STEM positions is due to differences in work ethic). The implicit indicators were obtained through the Implicit Association Test (IAT) examining 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,[62,69] including: economic (e.g., ratio of men's to women's labor force participation rates; 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, proportion of women with a college degree); and reproductive (e.g., percentage of women who live in a county without an abortion provider) factors. 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 (selected from n=54 candidate indicators), all of which assessed aggregated explicit 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 African Americans (e.g., whether the respondent would be in favor of having a close friend or family member marry a Black person), the impact of discrimination on the lives of African Americans (e.g., whether lower levels of income among Blacks compared to Whites is due to discrimination or to lack of "motivation or will power"), the existence of racial

prejudice (e.g., "the federal government should take decisive steps to override the injustices Black people suffer at the hands of local authorities"), and endorsement of racial stereotypes (e.g., "it is likely that Black people will bring violence to neighborhoods when they move in"). Recent research has provided evidence of the psychometric properties for aggregate, regional measures of explicit racial bias such as the ones used in the current study. These properties include strong retest reliability, convergent validity (i.e., associations with other, theoretically relevant outcomes, including racially charged internet searches), and discriminant validity (i.e., lack of associations with theoretically unrelated outcomes, such as birth rates).[74]

Structural Stigma Related to Latinx Ethnicity. For structural stigma related to Latinx ethnicity, we used 3 indicators (selected from n=15 candidate 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, rental housing, business licenses, higher education, and driver's licenses), based on a sum score for each state representing how supportive or restrictive the laws were, ranging from a score of -6 to +5; and 3) a feelings thermometer of explicit attitudes of Hispanics (obtained from the American National Election Survey). Our rationale for the inclusion of attitudes and policies related to immigration, despite the obvious fact that not all Latinx individuals are immigrants, was based on previous findings[49] that immigration policies and attitudes are associated with the mental health of Latinx respondents regardless of nativity status because of: a) the conflation of immigration with Latinx ethnicity in the US; b) the mixed status nature of many Latinx households; c) the concealability of immigration status, which makes people targets regardless of whether they are a citizen; and d) the salience of immigration policy and politics to Latinx individuals in the U.S.[75]

Factor analysis. We created a factor score for each state for each 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 items in the factor analysis met the 0.40 threshold. The variables selected for the final analysis are shown in Table S1. We performed this analysis using PROC FACTOR in SAS 9.4, with the prior communality estimate fixed at squared multiple correlations with all other variables and oblimin rotation. For each measure, a 1-factor solution emerged, indicating that these items load onto a single construct of structural stigma, thereby providing evidence of construct validity. To evaluate reliability (internal consistency) for each measure, Cronbach's alpha was calculated for all items included in the final models.[76] Using this metric, structural stigma related to sex/gender (standardized alpha=0.94) and race (standardized alpha=0.97) indicated high reliability; structural stigma related to Latinx ethnicity indicated fair reliability (standardized alpha=0.57), but was likely lower than the other measures due to the small number of items contributing to the factor (n=3).

Dependent variables. Hippocampal volume was obtained from the structural data release (https://nda.nih.gov/data_structure.html?short_name=abcd_smrip201). Quality control measures were applied to structural MRI data in ABCD including visual inspection of all structural volumes, inspection of outliers based on the mean and standard deviation of segmented volumes for potential segmentation problems, and exclusion of data that did not meet the quality control standards in 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. Total intracranial volume was also extracted to be used as a covariate in all analysis of hippocampal volume.

Amygdala activation to negative emotional faces was measured by contrasting amygdala response to fearful faces to amygdala response to neutral faces during an emotional n-back working memory task.[71] The task includes two runs of eight blocks each. On every trial, participants respond as to whether the picture is a "Match" or "No Match." Half the blocks are the 2-back conditions, during which participants respond "match" when the current stimulus is the same as the one shown two trials back. Half the trials are a 0-back condition, in which there is one target stimulus for each block presented at the beginning of the block. Within each block, stimuli are either all fearful faces, all neutral faces, all happy faces, or all faces. Estimates of task-related activation strength were computed at the individual subject level 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 for this study was activation during the fearful face blocks (both 2-back and 0-back) 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 (https://nda.nih.gov/data_structure.html?short_name=nback_bwroi02). Analyses were conducted separately for right and left amygdala (tfmri_nback_all_224, tfmri_nback_all_238), given that the associations of childhood adversity (e.g., abuse) with amygdala reactivity to threat often are observed in only one hemisphere, on either the left[25,27] or the right.[28] Due to incorrect post-processing, all fMRI data obtained on Phillips scanners were excluded from all analyses. These data were removed using a script available at https://github.com/ABCD-STUDY/fMRI-cleanup.

For both outcomes, ABCD guidelines were followed with regard to exclusion of participants based on data quality, or, for functional scans, based on motion or inattention.

Analytic Strategy

We pre-registered our predictions and analyses (see https://osf.io/9axqr). With two exceptions, our analysis proceeded according to this preregistered plan. First, we also intended to examine associations between perceived discrimination (an individual-level measure of stigma) and neural outcomes to evaluate the relative strength of this measure as compared to structural stigma. We subsequently discovered that the perceived discrimination items were only administered to a subset of the ABCD 2.0 sample, reflecting less than half of the total sample included in our analysis (n=4950). This discovery led us to discard this aim, given the significantly reduced power to compare associations of perceived discrimination and structural stigma with neural outcomes and the differential power to detect associations of structural stigma versus discrimination with these outcomes. Second, in our pre-registration, we hypothesized a null association between structural stigma related to sexual orientation and both neural outcomes among sexual minority youth at baseline. Because minority sexual identities emerge later in development than gender, racial, and ethnic identities,[77] we hypothesized that these associations would emerge in subsequent waves of the ABCD dataset. However, a power analysis indicated that within sexual minority participants, we only had the sample size to detect an effect size of r=0.3 between structural stigma and amygdala reactivity with 65% power, and between structural stigma and hippocampal volume with 77% power. Since we were underpowered, it was not possible to determine whether our pre-registered hypothesis was, in fact, a true null effect or was instead due to low power. We report the results of these analyses—which are consistent with our pre-registered hypothesis—in the SI for transparency. However, given the lack of power to detect

these associations in ABCD due to the small number of children identifying as sexual minorities, we do not interpret these results.

Analyses were conducted using generalized mixed-effects models with the gamm4 function in R. Random effects included site and family. Fixed-effects included standard covariates in analyses of hippocampal volume and of amygdala activation: age, sex at birth (in analyses not focused on sex/gender), family SES (marital status of household and family income), race, and ethnicity (in analyses not focused on race and Latinx ethnicity, respectively). Analyses examining hippocampal volume additionally controlled for total intracranial volume.

We discovered a high level of 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,[78] 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 was unchanged with this alternative measure (SI Appendix).

A pre-registered power analyses based on a sample size of 21 study sites indicated that within female participants as well as in all control analyses, we have the 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.

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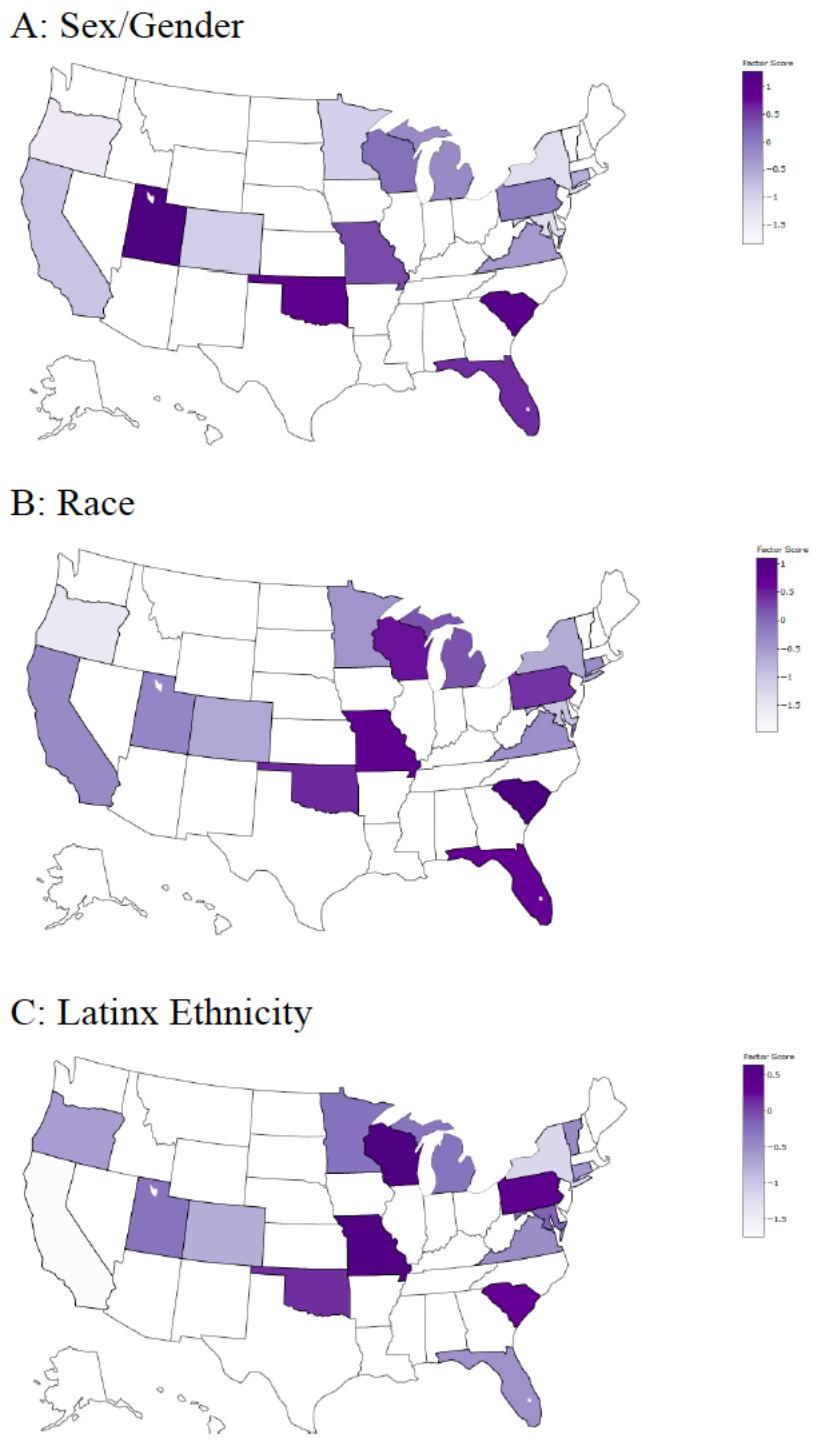

Figure 1. State-level structural stigma across four stigmatized groups. The figure shows the distribution of the four measures of structural stigma related to sex/gender (A), race (B), and Latinx ethnicity (C), across the 17 states in the ABCD sample.

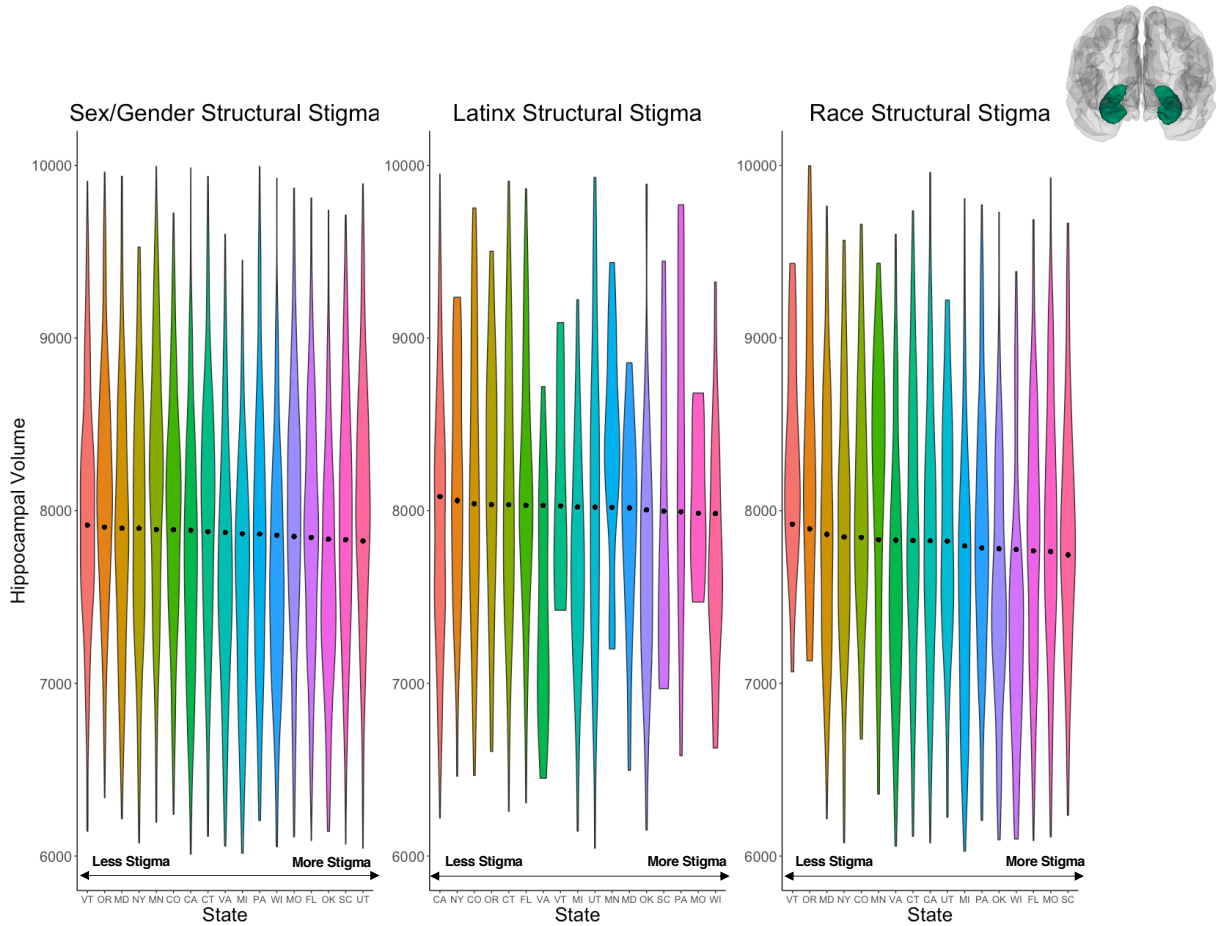

Figure 2. Plot of hippocampal volume among female, non-immigrant Latinx, and Black youth by state. States are ordered from left to right in each plot based on their structural stigma factor scores. Violin plots depict the density distribution of hippocampal volume in that state. Black points represent the hippocampal volume predicted based on each states' structural stigma when all other covariates in the multilevel models of the relation between structural stigma and hippocampal volume are at their mean.