Priority Communication

Biological Psychiatry

Racial Discrimination and White Matter Microstructure in Trauma-Exposed Black Women

Negar Fani, Nathaniel G. Harnett, Bekh Bradley, Yara Mekawi, Abigail Powers, Jennifer S. Stevens, Kerry J. Ressler, and Sierra E. Carter

ABSTRACT

BACKGROUND: Experiences of racial discrimination are linked to a range of negative brain health outcomes, but little is known about how these experiences impact neural architecture, including white matter microstructure, which may partially mediate these outcomes. Our goal was to examine associations between racially discriminatory experiences and white matter structural integrity in a sample of Black American women.

METHODS: We recruited 116 Black American women as part of a long-standing study of trauma. Participants completed assessments of racial discrimination, trauma exposure, and posttraumatic stress disorder and underwent diffusion tensor imaging. Fractional anisotropy and mean diffusivity values were extracted from major white matter tracts throughout the brain.

RESULTS: Experiences of racial discrimination were associated with significantly lower fractional anisotropy in multiple white matter tracts, including the corpus callosum, cingulum, and superior longitudinal fasciculus ($ps < .004$), even after accounting for variance associated with trauma, posttraumatic stress disorder, and demographic- and scanner-related factors.

CONCLUSIONS: These findings suggest that experiences of racial discrimination are independently related to decrements in white matter microarchitecture throughout the brain. In individuals who have experienced other types of adversity, racial discrimination clearly has additive and distinctive deleterious effects on white matter structure. Our findings suggest a pathway through which racial discrimination can contribute to brain health disparities in Black Americans; the deleterious contributions of racial discrimination on the microstructure of major white matter pathways may increase vulnerability for the development of neurodegenerative disorders as well as the development of mental health problems.

https://doi.org/10.1016/j.biopsych.2021.08.011

The majority of Black Americans experience racism in some form during their lifetime; this includes structural racism, which comprises policies, practices, and laws that oppress minoritized racial groups, and individual racism or discrimination, which describes unjust treatment of individuals on the basis of race (1,2). With respect to racial discrimination, national estimates range from 60% (3) to 73% (4) of Black Americans experiencing at least one event. For many, however, racial discrimination is experienced multiple times, representing a chronic, often ongoing form of stress. Experiences of exclusion, disadvantage, and unfair treatment that occur across different day-to-day life settings (school, work, shopping, dining) and in interactions with law enforcement and governmental agencies (e.g., encounters with police and court systems) and the racialized aspects of these events characterize racial discrimination. Experiences of racial discrimination are linked to multiple negative health outcomes, particularly poorer mental, cardiovascular, and brain health (5). Given the severity of these health consequences, racial discrimination is increasingly recognized as a national public health crisis (6).

Although the relationship between racial discrimination and these adverse health outcomes is well established (1), little is known about neuropathophysiology underlying this relationship. Experiences of racism have a clear impact among many populations, including those who have experienced psychological trauma, increasing risk for the development of posttraumatic stress disorder (PTSD) (7,8). Contemporary theorists suggest that discriminatory experiences lead to a cascade of neurophysiological reactions related to stress/threat response that can be deleterious to health (1). For example, racial discrimination can lead to chronic activation of the hypothalamic-pituitary-adrenal axis (9), activation of social pain networks, increased perseverative cognitions, increased vigilance for future race-related threat, and related increases in activation in threat-monitoring systems (10,11). Surprisingly, the effects of racism on brain structure among minoritized populations have largely been ignored despite long-standing theoretical and empirical research denoting the necessity of this research to address health inequities (12). This is particularly true among populations who disproportionately experience

ISSN: 0006-3223

other sources of stress, such as focal psychological traumas such as physical or sexual assault. There is increasing recognition that racism-related stressors represent a unique type of psychological trauma with sequelae that may overlap, in part, with posttraumatic stress symptoms (13).

Racism-related stress and concurrent chronic hypothalamic-pituitary-adrenal activation may alter neural plasticity; increased experiences of racial discrimination may contribute to structural disruptions in neural pathways that support defensive behaviors to threat/stress. This could contribute to the observation of race-related differences in brain structure (14), particularly in regions associated with emotion regulation/fear inhibition. For example, greater frontotemporal (orbitofrontal) volume has been observed in Black compared with White Americans (15). Although not assessed in their study, the authors note the possibility that race-related factors including discrimination could account for this difference. In line with this notion, a large-scale study of young adults observed an interaction of racial discrimination with depressive symptoms on brain macrostructure, particularly white matter volumes, in Black participants; participants with depression and experiences of racial discrimination demonstrated lower total white matter volume compared with participants with only depression, participants with only racial discrimination, or participants with neither (16). Like other types of chronic stressors that adversely affect neural plasticity (17), race-related stress may have a deleterious impact on white matter pathways, which continue to develop even until middle adulthood (18,19). Reductions in the integrity of white matter microstructure, assessed by reductions in fractional anisotropy (FA) and increased mean diffusivity (MD), have significant functional consequences; reduced FA and increased MD have been empirically identified as biomarkers for neurodegenerative diseases, such as Alzheimer's disease (20–22).

This prior work suggests that racial discrimination may impact brain macrostructure in Black Americans, but limited studies to date have investigated the unique impact of racial discrimination on white matter microarchitecture in Black Americans, particularly in the context of other types of chronic stress, such as psychological trauma and poverty. In the present study, we examined associations between experiences of racial discrimination and indices of white matter microstructure (FA and MD) in a large sample of trauma-exposed Black American women who participated in a long-standing study of trauma and stress-related disorders, the Grady Trauma Project. Only women were included in this study given that several Grady Trauma Project studies specifically recruited women (e.g., MH101380, MH111682, HD071982). We examined FA and MD of major white matter tracts previously linked to poverty, trauma exposure, and PTSD: the uncinate fasciculus (UF), cingulum bundle (CB), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), fornix, and corpus callosum (CC) (23–29). Both FA and MD were included in our analyses given that they are sensitive, reliable, and complementary indices of white matter microstructure (30,31). Further, we examined the unique associations of racial discrimination with white matter microstructure after accounting for the effects of poverty, trauma exposure, and PTSD.

METHODS AND MATERIALS

Participants

A total of 116 Black American women 18 to 62 years of age were recruited from the Grady Trauma Project, which represents a collaboration of studies investigating risk and resilience for trauma-related disorders (MH101380, MH071537, MH094757). Individuals were approached in general medical clinics of a publicly funded hospital in inner-city Atlanta, Georgia. The eligibility criteria for participation in the current study included the ability to understand English (assessed by a study researcher) and willingness to provide informed consent. Participants were excluded if they had current neurological conditions, bipolar disorder, current substance or alcohol dependence, or primary psychotic disorder as assessed with the Mini-International Neuropsychiatric Interview (32). We also excluded participants who had any magnetic resonance imaging (MRI) contraindications (e.g., claustrophobia, metal implants). Participants received clinical assessments for trauma and PTSD and also underwent an MRI scan; clinical and demographic characteristics are detailed in Table 1. On average, participants were 39 years of age (SD = 11.84 years), and over half (54%) demonstrated significant economic disadvantage, reporting household incomes of less than $1000 per month. Incomes were self-reported, and monthly income was dichotomized into two groups ($\leq$\$1000/mo vs. $>$\$1000/mo) for statistical analyses; this classification described economic disadvantage in participants (low/minimal economic resources vs. moderate or greater economic resources). The institutional review board of Emory University and the Grady Hospital Research Oversight Committee approved all study procedures.

Clinical Assessments

We administered the following assessments, detailed further in the Supplement. The Traumatic Events Inventory was administered to measure lifetime trauma exposure, inclusive of childhood and adult trauma; trauma types (number of types of trauma to which the person was exposed; score range = 0–10) was the Traumatic Events Inventory index included as a covariate in statistical analyses. The PTSD Symptom Scale (score range = 0–51) (33) was administered on the day of the MRI scan and was also used as a covariate in analyses, given the presence of PTSD symptoms in some participants. Participants also completed the Experiences of Discrimination Questionnaire (EOD) (34). The EOD is a 9-item, self-report measure of experiences of racial discrimination with good reliability and validity (34). Items assess discriminatory experiences due to race or ethnicity that occurred in various situations over the lifetime, including experiences in accessing housing, medical care, interactions with the police or government, or general interpersonal experiences (items listed in Table S4). Participants were asked to endorse the number of different types of racially discriminatory experiences that they had experienced. The EOD total score (range = 0–9) reflects a count of the number of situations for which each participant reported having unfair treatment as a racial reason; this was used as an index of racial discrimination. For secondary analyses, we created groups reflecting

Table 1. Demographic and Clinical Characteristics (*N* = 116)

Characteristics	Mean ± SD (Range) or *n* (%)
Age, Years[a]	39.04 ± 11.84 (18–62)
TEI Types Total	3.58 ± 2.33 (0–10)
PSS Total Score[a]	13.99 ± 12.71 (0–45)
EOD Total Score	2.63 ± 2.42 (0–9)
Education[b]	
<12th grade	13 (11.4%)
High school graduate/GED	36 (31.6%)
Some college/tech school	35 (30.7%)
Technical school graduate	13 (11.4%)
College graduate	12 (10.5%)
Graduate school	5 (4.4%)
Monthly Income[c]	
$0–$249	13 (11.6%)
$250–$499	12 (10.7%)
$500–$999	35 (31.3%)
$1000–$1999	30 (26.8%)
$2000+	22 (19.6%)

EOD, Experiences of Discrimination Questionnaire; PSS, PTSD Symptom Scale; TEI, Traumatic Events Inventory.
[a]Data missing for 1 participant.
[b]Data missing for 2 participants.
[c]Data missing for 4 participants.

frequency of racial discrimination experiences: low (0–1 type; n = 47 [41%]), moderate (2–4 types; n = 42 [36%]), and high (5–9 types; n = 27 [23%]). Experiences of racial discrimination (EOD total) were significantly correlated with trauma exposure throughout the lifetime (r = 0.48, $p = 4.36 \times 10^{-8}$), current PTSD symptoms (r = 0.29, p = .002), and age (r = 0.40, p = .00001) but not with income level (Spearman's ρ = 0.05, p = .57).

Diffusion-Weighted MRI Acquisition, Image Processing, and Statistical Analyses

Scanning was conducted on either of two research-dedicated Siemens 3T TIM-Trio scanners (Siemens Healthcare) at Emory University Hospital. Diffusion-weighted images were acquired similarly across both sites, with maximum gradient strength of 40 mTm^{-1} with the following parameters: slice thickness: 39 × 2.5 mm, matrix = 128 × 128, field of view = 220 × 220 mm, voxel size = 1.72 × 1.72 × 2.5 mm. Diffusion weighting was isotropically distributed along 60 directions using a b value of 1000 s/mm^2. Four normalization images, with no diffusion encoding (b = 0), were acquired and averaged for each direction using linear rigid body registration (FLIRT) (35). All diffusion-weighted image processing and analysis was conducted using FSL version 4.1 (www.fmrib.ax.ac.uk/fsl) (36) and is detailed in the Supplement. Voxelwise associations were conducted with diffusion tensor imaging scalar indices, assessed using tract-based spatial statistics (version 1.2) (37) available in FSL. Tracts of interest included the CC and UF, CB, SLF, ILF, and fornix derived from the probabilistic Johns Hopkins University ICBM DTI-81 white matter atlas provided by FSL (38). FA and MD values were extracted from these regions using FSLmaths to examine potential associations with racial discrimination.

Statistical Analyses

We focused on the left and right UF, CB, SLF, and ILF, as well as the fornix and CC, as in prior studies of poverty, discrimination, trauma, and PTSD; we examined anterior (body) and hippocampal segments of the CB separately given earlier study findings indicating trauma-specific effects for anterior versus posterior segments (39–42). Hierarchical regression analyses were conducted to examine the unique contributions of racial discrimination on FA and MD for these tracts after accounting for effects of other potentially contributing factors, including PTSD, trauma exposure, monthly income, and scanner location; monthly income was dichotomized into two groups (≤$1000/mo vs. >$1000/mo) before being entered into analyses. Statistical significance was set at a Bonferroni-corrected p value of .004, accounting for the number of selected tracts, separating by hemisphere for associational tracts (12), for our a priori tests of the association between racial discrimination and white matter metrics; FA and MD were considered separate families of statistical tests. In the case of significant findings with the CC, given the span of this tract, separate segments of the CC (genu, body, splenium) were examined in separate follow-up models to determine whether associations were specific to any of CC subdivisions. Given that age has an established relationship with white matter microstructure and macrostructure (43,44), and given the strength of the relationship between racial discrimination and age in this sample, we excluded age from initial analyses to limit multicollinearity. However, tracts that emerged as being significantly associated with racial discrimination were subject to follow-up factorial analyses of covariance with age group (younger [18–50 years of age] vs. older [51–62 years of age]) and racial discrimination frequency (low/moderate/high frequency) to examine main effects and potential interactions with microstructure of these pathways, covarying scanner location (Table S1). Statistical significance was set at $p < .05$ for these follow-up analyses.

RESULTS

Fractional Anisotropy

Hierarchical regression models that included racial discrimination, income, trauma exposure, PTSD, and scanner location as predictors of FA values were significant for the CC, right and left SLF, and left anterior CB, detailed in Table 2. In each of these models, racial discrimination emerged as the only significant predictor at the a priori statistical threshold, with the exception of scanner site for some models. For the CC, the model accounted for 18% of the variance in FA (R = 0.42, p = .002); racial discrimination accounted for 10% of this variance (ΔR^2 = 0.10). Given these findings with the CC, we examined associations of racial discrimination for CC segments (genu, body, splenium) and found significant associations for the genu (ΔR^2 = 0.14) and body (ΔR^2 = 0.10) only. For the right SLF, the model accounted for 15% of the variance in FA (R = 0.39), and for the left SLF, the model accounted for 19% of the variance in FA (R = 0.42); racial discrimination accounted for 9.5% of this variance for the right SLF (ΔR^2 = 0.095) and for 8% of this variance for the left SLF (ΔR^2 = 0.078). The strongest association of racial discrimination with FA was for the left

Table 2. Multiple Regression Models of White Matter Fractional Anisotropy

Tract	Hemisphere	Full-Model *F* Statistic (*p* Value)	*R* Value	β (*p* Value)				
				Income	PSS	Trauma	Scanner	Discrimination
Corpus Callosum	Both	4.240 (.002)	0.422	0.031 (.741)	0.068 (.515)	−0.051 (.633)	0.199 (.040)	−0.357 (.001)[a]
Genu	–	6.143 (.000)	0.488	0.055 (.534)	0.164 (.107)	−0.086 (.402)	0.178 (.056)	−0.423 (.000)[a]
Body	–	2.958 (.016)	0.362	0.077 (.421)	−0.005 (.963)	0.073 (.502)	0.106 (.284)	−0.362 (.001)[a]
Splenium	–	3.427 (.007)	0.386	−0.035 (.712)	0.084 (.433)	−0.278 (.012)	0.200 (.043)	−0.121 (.252)
Fornix	Both	2.311 (.05)	0.325	0.00 (.996)	−0.048 (.659)	0.022 (.840)	0.220 (.030)	−0.246 (.024)
ILF	Left	4.962 (.000)	0.449	−0.016 (.857)	−0.026 (.801)	−0.036 (.729)	0.332 (.001)[a]	−0.293 (.005)
	Right	3.236 (.010)	0.376	0.033 (.729)	−0.030 (.779)	−0.104 (.340)	0.228 (.022)	−0.236 (.027)
SLF	Left	4.499 (.001)	0.432	−0.020 (.830)	−0.037 (.725)	0.015 (.886)	0.309 (.002)[a]	−0.313 (.003)[a]
	Right	3.454 (.006)	0.387	0.023 (.810)	0.067 (.533)	−0.020 (.850)	0.174 (.077)	−0.345 (.001)[a]
UF	Left	5.360 (.000)	0.463	0.028 (.755)	0.061 (.552)	−0.136 (.192)	0.341 (.000)[a]	−0.238 (.020)
	Right	2.885 (.018)	0.358	0.038 (.691)	0.171 (.116)	−0.142 (.193)	0.191 (.055)	−0.201 (.060)
Cingulum (Anterior)	Left	4.964 (<.001)	0.45	0.004 (.965)	0.085 (.409)	−0.034 (.748)	0.244 (.011)	−0.371 (<.001)[a]
	Right	2.72 (.024)	0.349	0.026 (.788)	0.054 (.619)	−0.033 (.762)	0.176 (.079)	−0.293 (.007)
Cingulum (Posterior)	Left	1.215 (.308)	0.242	−0.111 (.263)	0.036 (.752)	−0.080 (.481)	0.178 (.085)	−0.075 (.498)
	Right	1.253 (.209)	0.245	−0.032 (.746)	0.028 (.803)	−0.148 (.196)	0.149 (.149)	−0.089 (.418)

ILF, inferior longitudinal fasciculus; PSS, PTSD Symptom Scale; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus.
[a]$p < .004$.

anterior CB; the model accounted for 20% of the variance in FA ($R = 0.45$, $p = .0004$); discrimination accounted for 11% of this variance ($\Delta R^2 = 0.11$, $p = .0004$). Figure 1 illustrates these white matter pathways and correlations of tract FA with racial discrimination.

Given these findings, we conducted three follow-up analyses of covariance (Table S1) to examine main effects and potential interactive effects of age with racial discrimination experiences and FA of the CC, right and left SLF, and left anterior CB, after accounting for scanner location. In each of these models, both age and racial discrimination significantly contributed to variance in FA of these pathways; the inclusion of age did not diminish the significance of racial discrimination in these models. No significant interactions of racial discrimination and age were observed (*p*s $> .05$).

In hierarchical regression models for other tracts, variance associated with racial discrimination did not reach our corrected statistical threshold for FA of the right anterior CB ($R = 0.35$, $p = .02$) or left posterior CB ($R = 0.24$, $p = .31$), right posterior CB ($R = 0.24$, $p = .29$), right ILF ($R = 0.38$, $p = .01$), right UF ($R = 0.36$, $p = .018$), or fornix ($R = 0.33$, $p = .05$). The overall model for the left ILF ($R = 0.45$, $p = .0004$) and left UF ($R = 0.46$, $p = .0002$) was significant, but variance associated with racial discrimination did not reach our a priori statistical threshold (for the left ILF, $\beta = -2.89$, $p = .005$; for the left UF, $\beta = -2.36$, $p = .02$; for the right UF, $\beta = -1.9$, $p = .06$).

Mean Diffusivity

The model for the left anterior CB ($R = 0.26$, $p = .22$) and right anterior CB ($R = 0.34$, $p = .04$) was not significant at our a priori threshold (Table S2). Correlations between racial discrimination, MD, and other predictors in the model are provided in Table S3.

DISCUSSION

In the present study, we examined the association between racial discrimination and white matter microstructure in a large sample of trauma-exposed Black Americans. We observed that exposure to racial discrimination independently contributed ∼10% of the variance in FA within the brain's largest white matter pathway, the CC (particularly anterior segments), as well as within associational fibers including the right and left SLF and left anterior CB. Among these pathways, no interactions of age and racial discrimination were observed, but racial discrimination continued to demonstrate strong, significant associations with FA in the CC, SLF, and left anterior CB when age was included in these models. Overall, our findings indicate a potent relationship between experiences of racial discrimination and white matter microstructure across various pathways. These data suggest a pathway through which individual racism experiences may enhance vulnerability for brain health problems in trauma-exposed Black Americans.

Throughout the brain, the most robust associations of racial discrimination and white matter microstructure were observed for the largest brain commissural tract, the CC, as well as for frontolimbic and frontoparietal associational tracts, the anterior cingulum, and the SLF. The CC is the major set of interhemispheric projections of the brain; the morphology of this tract is affected by early-life adversity and PTSD more generally (45,46); CC decrements were observed in a mega-analysis of PTSD studies (25). Further, the SLF is a major frontoparietal connection that supports a range of cognitive and emotional functions including attention and executive functioning, language, and social cognition (47) and is implicated in trauma-related responses/PTSD (24,48,49). Finally, the CB is a major association tract connecting parahippocampal regions with the parietal cortex and prefrontal cortex. This pathway has been linked to attentional control and fear extinction processes (both of which are frequently impaired in PTSD) and is consistently implicated as a marker of trauma exposure and PTSD-related

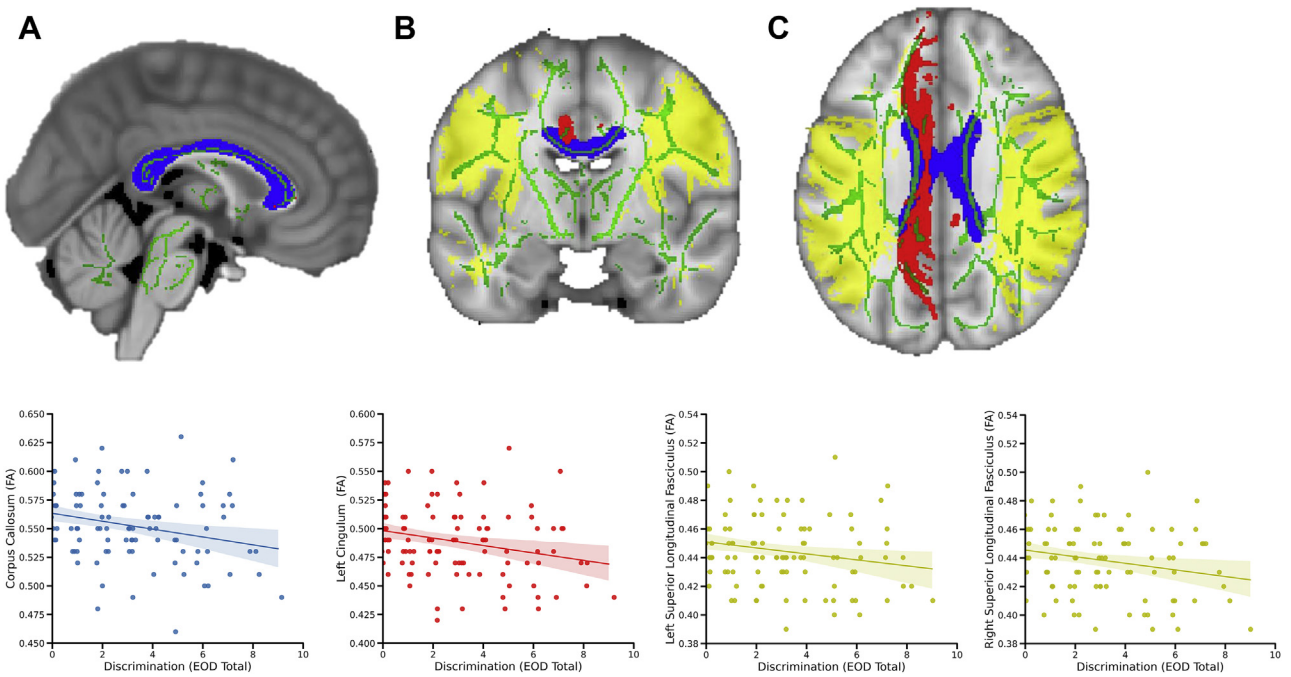

Figure 1. Associations of racial discrimination with fractional anisotropy (FA) in select tracts. Shown are masks of tracts that demonstrated significant relationships with racial discrimination, including the left anterior cingulum (red), corpus callosum (blue), and bilateral superior longitudinal fasciculus (yellow) overlaid on skeletonized FA (green). Scatterplots reflect zero-order correlations. **(A)** Experiences of racial discrimination correlate negatively with corpus callosum FA ($r = -0.27$, $p = .004$). **(B)** Experiences of racial discrimination correlate negatively with left anterior cingulum bundle FA ($r = -0.27$, $p = .004$). **(C)** Experiences of racial discrimination correlate negatively with right superior longitudinal fasciculus FA ($r = -0.27$, $p = .004$) and left superior longitudinal fasciculus FA ($r = -0.21$, $p = .02$). EOD, Experiences of Discrimination Questionnaire.

dysfunction (24,27,40,50,51). Racial discrimination appears to potentiate responses in ventral prefrontal and middle occipital regions linked to attention vigilance and modulation (11,52), for which the CB serves as a major white matter connection; it is possible that prolonged exposure to racism-related stressors erodes CB integrity over time. In this way, racial discrimination can promote dysfunctional threat inhibition and attentional control processes via effects on CB microstructure. As such, for those who have experienced additional psychological trauma, this likely enhances risk for the development of PTSD; it can likewise contribute to PTSD symptom maintenance. It is clear that racial discrimination merits consideration as a contributing factor in current models of PTSD in non-White populations.

Notably, the CB, CC, and SLF have also been implicated in earlier studies of chronic stressors such as poverty/low socioeconomic status (SES), including a longitudinal study on the effects of income on white matter developmental trajectories (53). As such, these pathways, including frontolimbic tracts that have the most protracted developmental trajectories (54), may be particularly susceptible to the effects of stress related to racial discrimination. Given that the effects of traumatic stress have been previously highlighted in the CC, SLF, and CB tracts, the present findings suggest that the often chronic stress of racial discrimination has its own unique associations with microstructure of these pathways, serving as an independent, potent contributor to damage in these large white matter connections.

Experiences of racial discrimination tend to start early in childhood and continue throughout life compared with other types of discrimination (e.g., sexism and ageism) (55). Racial discrimination may thus be a chronic and early-onset stressor similar to poverty and childhood maltreatment. Chronic adversity that starts early in development has demonstrable effects on brain structure (17,56), inducing plasticity in neural networks to accommodate and maintain functioning; these neuroplastic changes have wide-ranging outcomes. Early-life adversity in general appears to accelerate onset of maturation, including puberty (57–59), and similarly appears to increase the rate of myelination of white matter pathways, particularly frontolimbic tracts (60,61). This trajectory of myelination may similarly lead to earlier degradation of white matter pathways, which can enhance risk for a host of emotional and cognitive disruptions. Even after age was accounted for in our analyses, racial discrimination remained a significant predictor of FA, which suggests that this form of racism has its own unique links to white matter degradation. Given that reductions in FA in the CC, CB, and SLF have marked early onset of neurodegenerative diseases (22), it is possible that racial discrimination–related reductions in microstructure of these pathways creates greater vulnerability for later development of brain health disorders.

As with these other chronic stressors, racial discrimination is linked to dysregulation in multiple biological systems (62), with the hypothalamic-pituitary-adrenal axis and immune system being frequently implicated (63). Although the mechanism was not under investigation in this study, chronic immune activation caused by racism-related stressors has been shown to increase inflammation on a central and peripheral level, and over time, compromises brain health (64). In the present study

sample, experiences of racial discrimination were found to be a unique and unwavering stressor in the lives of Black Americans, above and beyond other forms of chronic adversity. As such, our findings may suggest that the impact of racial discrimination is a type of chronic adversity that takes its toll on white matter microstructure, similar to the effects of trauma (particularly childhood maltreatment) (24,25,27) and high allostatic load (65,66).

Experiences of racial discrimination are known contributors to allostatic load (62), and the accumulation of experiences encumber stress-regulation mechanisms, creating significant vulnerability for an array of health problems. Racial discrimination has been positively correlated with indicators of white matter pathology, including white matter lesion volume (67) and white matter hyperintensities (16) throughout the brain. The burden of racial discrimination experiences is clearly reflected in race-related disparities in brain health outcomes, with Black Americans showing disproportionately greater risk for poor brain health outcomes as compared with White Americans, including stroke risk, cognitive decline (68), and neurodegenerative disorders—older Black Americans are twice as likely to have Alzheimer's disease as White Americans (69). Thus, racial discrimination may be a pathway for increasing risk for white matter pathology, and, in turn, for neurodegenerative diseases; however, the cross-sectional nature of this study precludes our ability to establish this relationship. Future longitudinal research, combined with granular physiological assessments, is needed to fully test this hypothesis.

Our findings on the unique associations of racial discrimination with white matter, above and beyond factors such as income level, trauma exposure, and PTSD, are particularly notable given their established links with white matter microstructure. Racial discrimination can interact with structural inequities between racial groups. Poverty is a major structural inequity between racial groups that is directly related to the function and structure of brain regions that support emotion regulation (17,70). A recent report indicated that White Americans with higher SES demonstrated greater global gray and white matter volume than low-SES White Americans as well as low- and high-SES Black Americans (71). Lower SES has also been related to poorer white matter integrity throughout the brain; the authors of a recent study found that effects were not moderated by age, race, and gender (29). These study findings denote the importance of contextualizing multiple forms of oppression to understand health inequity. In the present study, it is notable that associations of racial discrimination and tract FA remained significant even after accounting for variance associated with income; this may suggest that the effects of racism on brain health remain potent, even in the context of higher socioeconomic status. Altogether, the current study supports future research examining intersecting forms of structural oppression to further understanding the cumulative burden of racism on brain health among Black Americans.

The present study has limitations that should be considered when interpreting our findings. We only included a single assessment of racial discrimination, and the inclusion of another measure that assesses not only frequency of discriminatory experiences but the perceived impact/severity of each experience would provide a richer examination of these effects on brain structure. Further, we also used a unimodal approach with respect to brain structure and only considered FA and MD metrics of white matter. Future work should consider leveraging multimodal approaches that incorporate other aspects of brain structure (e.g., gray matter assessments) and brain function, which may provide a more comprehensive approach. Further, aside from including income in our analyses, we did not assess the effects of structural racism, which are quite likely to have a significant impact on neural architecture; as such, substantially more research is needed to examine the unique effects of structural racism in addition to individual racism. We also did not assess the effects of other types of discrimination as well as discrimination occurring at the intersection of different systems of oppression (i.e., gendered racism), which is of value in understanding cumulative burden of psychosocial stressors, particularly for this sample of Black women. We do not have a reason to believe that the effects observed here are not generalizable to men, given that potential mechanisms for these effects are not gender specific. However, it is clear that much more research is needed to explore the intersectionality of sexism and racism on neural microarchitecture in Black women; the interaction of these stressors is likely to have potent effects on white matter microstructure. Further, we did not assess differences in perceptions of racial discrimination and related ruminations, which are likely to play a role in brain health outcomes. Finally, we also did not assess associations of white matter integrity with health outcomes such as cardiovascular or metabolic disease; as such, it is impossible to determine whether these associations are markers of risk for adverse health outcomes.

The effects of racism-related stressors on brain structure and function have been infrequently studied in people of color, and specifically, in Black populations; this gap in the scientific literature has been recently highlighted (15). Our findings from this large-scale study of Black Americans shed light on the unique associations between racial discrimination and white matter structure, indicating robust associations of racial discrimination on several major tracts. Of note, the effects of racial discrimination that we observed in the present study were present above and beyond other chronic stressors (e.g., trauma and poverty), and even after accounting for variance associated with age, racial discrimination remained a significant predictor of FA in the anterior CB, SLF, and CC. These results may suggest that Black Americans' experiences of racial discrimination indexed potentially chronic racism-related stress that uniquely impacted—or exacerbated—disruption of white matter integrity. Future research in brain health must take into account multiple forms of oppression as well as the historical legacies in the United States that uniquely embed racism within health inequity. These cross-sectional data indicate that racial discrimination's potential effects on white matter structure merit consideration as a pathway through which race-related brain health disparities emerge. The findings also highlight the potential role of racial discrimination in updated models of PTSD in non-White populations.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institute of Mental Health (Grant Nos. MH101380 [to NF], MH119603 [to NGH], MH-071537 [to KJR], MH094757 [to KJR], and HD071982 [to BB]), the National Center for

Complementary and Integrative Health (Grant No. AT011267 [to NF]), the Emory Medical Care Foundation, the Emory University Research Council, the American Psychological Association, the Society for Clinical Neuropsychology and the Frazier Foundation Grant for Mood and Anxiety Research at McLean Hospital, and the National Cancer Institute (Grant No. CA220254-02S1 [to SEC]).

We thank Allen Graham, Rebecca Hinrichs, Angelo Brown, and other members of the Grady Trauma Project, as well as members of the Fani Affective Neuroscience Lab, for their assistance with data collection. We thank Timothy Ely for his technical assistance. We thank participants of the Grady Trauma Project for their time and involvement in this study.

KJR has received unrelated consulting income or sponsored research from Alkermes, Brainsway, and Genomind, and is on scientific advisory boards for Janssen, Takeda, and Verily. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry and Behavioral Sciences (NF, BB, YM, AP, JSS, KJR), Emory University School of Medicine; and the Department of Psychology (SEC), Georgia State University, Atlanta; and Atlanta VA Medical Center (BB), Decatur, Georgia; and the Division of Depression and Anxiety (NGH, KJR), McLean Hospital, Belmont; and the Department of Psychiatry (NGH, KJR), Harvard Medical School, Boston, Massachusetts.

Address correspondence to Negar Fani, Ph.D., at nfani@emory.edu.

Received May 28, 2021; revised Jul 26, 2021; accepted Aug 16, 2021.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2021.08.011.

REFERENCES

1. Williams DR, Lawrence JA, Davis BA (2019): Racism and health: Evidence and needed research. Annu Rev Public Health 40:105–125.
2. Jones CP (2000): Levels of racism: A theoretic framework and a gardener's tale. Am J Public Health 90:1212–1215.
3. Kessler RC, Mickelson KD, Williams DR (1999): The prevalence, distribution, and mental health correlates of perceived discrimination in the United States. J Health Soc Behav 40:208–230.
4. Lee RT, Perez AD, Boykin CM, Mendoza-Denton R (2019): On the prevalence of racial discrimination in the United States. PLoS One 14: e0210698.
5. Paradies Y, Ben J, Denson N, Elias A, Priest N, Pieterse A, *et al.* (2015): Racism as a determinant of health: A systematic review and meta-analysis. PLoS One 10:e0138511.
6. Causadias JM, Korous KM (2019): Racial discrimination in the United States: A national health crisis that demands a national health solution. J Adolesc Health 64:147–148.
7. Bird CM, Webb EK, Schramm AT, Torres L, Larson C, deRoon-Cassini TA (2021): Racial discrimination is associated with acute posttraumatic stress symptoms and predicts future posttraumatic stress disorder symptom severity in trauma-exposed Black adults in the United States [published online ahead of print Mar 14]. J Trauma Stress.
8. Mekawi Y, Watson-Singleton NN, Kuzyk E, Dixon HD, Carter S, Bradley-Davino B, *et al.* (2020): Racial discrimination and posttraumatic stress: Examining emotion dysregulation as a mediator in an African American community sample. Eur J Psychotraumatol 11:1824398.
9. Harrell CJ, Burford TI, Cage BN, Nelson TM, Shearon S, Thompson A, *et al.* (2011): Multiple pathways linking racism to health outcomes. Du Bois Rev 8:143–157.
10. Berger M, Sarnyai Z (2015): "More than skin deep": Stress neurobiology and mental health consequences of racial discrimination. Stress 18:1–10.
11. Fani N, Carter SE, Harnett NG, Ressler KJ, Bradley B (2021): Association of racial discrimination with neural response to threat in Black women in the US exposed to trauma. JAMA Psychiatry 78:1005–1012.
12. Mays VM, Cochran SD, Barnes NW (2007): Race, race-based discrimination, and health outcomes among African Americans. Annu Rev Psychol 58:201–225.
13. Kirkinis K, Pieterse AL, Martin C, Agiliga A, Brownell A (2021): Racism, racial discrimination, and trauma: A systematic review of the social science literature. Ethn Health 26:392–412.
14. LeWinn KZ, Sheridan MA, Keyes KM, Hamilton A, McLaughlin KA (2017): Sample composition alters associations between age and brain structure. Nat Commun 8:874.
15. Isamah N, Faison W, Payne ME, MacFall J, Steffens DC, Beyer JL, *et al.* (2010): Variability in frontotemporal brain structure: The importance of recruitment of African Americans in neuroscience research. PLoS One 5:e13642.
16. Meyer CS, Schreiner PJ, Lim K, Battapady H, Launer LJ (2019): Depressive symptomatology, racial discrimination experience, and brain tissue volumes observed on magnetic resonance imaging. Am J Epidemiol 188:656–663.
17. Gur RE, Moore TM, Rosen AFG, Barzilay R, Roalf DR, Calkins ME, *et al.* (2019): Burden of environmental adversity associated with psychopathology, maturation, and brain behavior parameters in youths. JAMA Psychiatry 76:966–975.
18. Koolschijn PC, Crone EA (2013): Sex differences and structural brain maturation from childhood to early adulthood. Dev Cogn Neurosci 5:106–118.
19. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW (2003): Mapping cortical change across the human life span. Nat Neurosci 6:309–315.
20. Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP (2011): A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 32:2322.e5–2322.e18.
21. Cochrane CJ, Ebmeier KP (2013): Diffusion tensor imaging in parkinsonian syndromes: A systematic review and meta-analysis. Neurology 80:857–864.
22. Lo Buono V, Palmeri R, Corallo F, Allone C, Pria D, Bramanti P, *et al.* (2020): Diffusion tensor imaging of white matter degeneration in early stage of Alzheimer's disease: A review. Int J Neurosci 130:243–250.
23. Dufford AJ, Kim P, Evans GW (2020): The impact of childhood poverty on brain health: Emerging evidence from neuroimaging across the lifespan. Int Rev Neurobiol 150:77–105.
24. Daniels JK, Lamke JP, Gaebler M, Walter H, Scheel M (2013): White matter integrity and its relationship to PTSD and childhood trauma–A systematic review and meta-analysis. Depress Anxiety 30:207–216.
25. Dennis EL, Disner SG, Fani N, Salminen LE, Logue M, Clarke EK, *et al.* (2019): Altered white matter microstructural organization in posttraumatic stress disorder across 3047 adults: Results from the PGC-ENIGMA PTSD consortium [published online ahead of print Dec 19]. Mol Psychiatry.
26. Fani N, King TZ, Jovanovic T, Glover EM, Bradley B, Choi K, *et al.* (2012): White matter integrity in highly traumatized adults with and without post-traumatic stress disorder. Neuropsychopharmacology 37:2740–2746.
27. Fani N, King TZ, Shin J, Srivastava A, Brewster RC, Jovanovic T, *et al.* (2016): Structural and functional connectivity in posttraumatic stress disorder: Associations with Fkbp5. Depress Anxiety 33:300–307.
28. Harnett NG, Stevens JS, van Rooij SJH, Ely TD, Michopoulos V, Hudak L, *et al.* (2021): Multimodal structural neuroimaging markers of risk and recovery from posttrauma anhedonia: A prospective investigation. Depress Anxiety 38:79–88.
29. Shaked D, Leibel DK, Katzel LI, Davatzikos C, Gullapalli RP, Seliger SL, *et al.* (2019): Disparities in diffuse cortical white matter integrity between socioeconomic groups. Front Hum Neurosci 13:198.
30. Jones DK (2008): Studying connections in the living human brain with diffusion MRI. Cortex 44:936–952.
31. Alexander AL, Lee JE, Lazar M, Field AS (2007): Diffusion tensor imaging of the brain. Neurotherapeutics 4:316–329.
32. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, *et al.* (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59:22–33; quiz 4–57.
33. Foa EB, Riggs DS, Dancu CV, Rothbaum BO (1993): Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. J Trauma Stress 6:459–473.

34. Krieger N, Smith K, Naishadham D, Hartman C, Barbeau EM (2005): Experiences of discrimination: Validity and reliability of a self-report measure for population health research on racism and health. Soc Sci Med 61:1576–1596.
35. Jenkinson M, Smith S (2001): A global optimisation method for robust affine registration of brain images. Med Image Anal 5:143–156.
36. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, *et al.* (2004): Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23:S208–S219.
37. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, *et al.* (2006): Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. NeuroImage 31:1487–1505.
38. Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, *et al.* (2008): Tract probability maps in stereotaxic spaces: Analyses of white matter anatomy and tract-specific quantification. NeuroImage 39:336–347.
39. De Bellis MD, Keshavan M, Shifflett H, Iyengar S, Beers SR, Hall J, *et al.* (2002): Brain structures in pediatric maltreatment-related PTSD: A sociodemographically matched study. Biol Psychiatry 52:1066–1078.
40. Choi J, Jeong B, Rohan ML, Polcari AM, Teicher MH (2009): Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. Biol Psychiatry 65:227–234.
41. McCarthy-Jones S, Oestreich LKL, Lyall AE, Kikinis Z, Newell DT, Savadjiev P, *et al.* (2018): Childhood adversity associated with white matter alteration in the corpus callosum, corona radiata, and uncinate fasciculus of psychiatrically healthy adults. Brain Imaging Behav 12:449–458.
42. Rinne-Albers MA, van der Wee NJ, Lamers-Winkelman F, Vermeiren RR (2013): Neuroimaging in children, adolescents and young adults with psychological trauma. Eur Child Adolesc Psychiatry 22:745–755.
43. Gunning-Dixon FM, Brickman AM, Cheng JC, Alexopoulos GS (2009): Aging of cerebral white matter: A review of MRI findings. Int J Geriatr Psychiatry 24:109–117.
44. Lebel C, Treit S, Beaulieu C (2019): A review of diffusion MRI of typical white matter development from early childhood to young adulthood. NMR Biomed 32:e3778.
45. Jackowski AP, Douglas-Palumberi H, Jackowski M, Win L, Schultz RT, Staib LW, *et al.* (2008): Corpus callosum in maltreated children with posttraumatic stress disorder: A diffusion tensor imaging study. Psychiatry Res 162:256–261.
46. Kitayama N, Brummer M, Hertz L, Quinn S, Kim Y, Bremner JD (2007): Morphologic alterations in the corpus callosum in abuse-related posttraumatic stress disorder: A preliminary study. J Nerv Ment Dis 195:1027–1029.
47. Nakajima R, Kinoshita M, Shinohara H, Nakada M (2020): The superior longitudinal fascicle: reconsidering the fronto-parietal neural network based on anatomy and function. Brain Imaging Behav 14:2817–2830.
48. Hu H, Zhou Y, Wang Q, Su S, Qiu Y, Ge J, *et al.* (2016): Association of abnormal white matter integrity in the acute phase of motor vehicle accidents with post-traumatic stress disorder. J Affect Disord 190:714–722.
49. Siehl S, King JA, Burgess N, Flor H, Nees F (2018): Structural white matter changes in adults and children with posttraumatic stress disorder: A systematic review and meta-analysis. NeuroImage Clin 19:581–598.
50. Fani N, King TZ, Clendinen C, Hardy RA, Surapaneni S, Blair JR, *et al.* (2019): Attentional control abnormalities in posttraumatic stress disorder: Functional, behavioral, and structural correlates. J Affect Disord 253:343–351.
51. Fani N, King TZ, Brewster R, Srivastava A, Stevens JS, Glover EM, *et al.* (2015): Fear-potentiated startle during extinction is associated with white matter microstructure and functional connectivity. Cortex 64:249–259.
52. Masten CL, Telzer EH, Eisenberger NI (2011): An fMRI investigation of attributing negative social treatment to racial discrimination. J Cogn Neurosci 23:1042–1051.
53. Dufford AJ, Evans GW, Dmitrieva J, Swain JE, Liberzon I, Kim P (2020): Prospective associations, longitudinal patterns of childhood socioeconomic status, and white matter organization in adulthood. Hum Brain Mapp 41:3580–3593.
54. Asato MR, Terwilliger R, Woo J, Luna B (2010): White matter development in adolescence: A DTI study. Cereb Cortex 20:2122–2131.
55. Gee GC, Hing A, Mohammed S, Tabor DC, Williams DR (2019): Racism and the life course: Taking time seriously. Am J Public Health 109:S43–S47.
56. Gehred MZ, Knodt AR, Ambler A, Bourassa KJ, Danese A, Elliott ML, *et al.* (2021): Long-term neural embedding of childhood adversity in a population-representative birth cohort followed for five decades. Biol Psychiatry 90:182–193.
57. Sumner JA, Colich NL, Uddin M, Armstrong D, McLaughlin KA (2019): Early experiences of threat, but not deprivation, are associated with accelerated biological aging in children and adolescents. Biol Psychiatry 85:268–278.
58. Chisholm JS, Quinlivan JA, Petersen RW, Coall DA (2005): Early stress predicts age at menarche and first birth, adult attachment, and expected lifespan. Hum Nat 16:233–265.
59. Mendle J, Ryan RM, McKone KM (2016): Early childhood maltreatment and pubertal development: Replication in a population-based sample. J Res Adolesc 26:595–602.
60. Fani N, Stenson AF, van Rooij SJH, Jovanovic T (in press): White matter microstructure in trauma-exposed children: Associations with pubertal stage. Dev Sci.
61. Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C (2012): Diffusion tensor imaging of white matter tract evolution over the lifespan. NeuroImage 60:340–352.
62. Ong AD, Williams DR, Nwizu U, Gruenewald TL (2017): Everyday unfair treatment and multisystem biological dysregulation in African American adults. Cultur Divers Ethnic Minor Psychol 23:27–35.
63. Cuevas AG, Ong AD, Carvalho K, Ho T, Chan SWC, Allen JD, *et al.* (2020): Discrimination and systemic inflammation: A critical review and synthesis. Brain Behav Immun 89:465–479.
64. O'Donovan A, Bahorik A, Sidney S, Launer LJ, Yaffe K (2021): Relationships of inflammation trajectories with white matter volume and integrity in midlife. Brain Behav Immun 91:81–88.
65. Dufford AJ, Kim P (2017): Family income, cumulative risk exposure, and white matter structure in middle childhood. Front Hum Neurosci 11:547.
66. Zsoldos E, Filippini N, Mahmood A, Mackay CE, Singh-Manoux A, Kivimaki M, *et al.* (2018): Allostatic load as a predictor of grey matter volume and white matter integrity in old age: The Whitehall II MRI study. Sci Rep 8:6411.
67. Beatty Moody DL, Taylor AD, Leibel DK, Al-Najjar E, Katzel LI, Davatzikos C, *et al.* (2019): Lifetime discrimination burden, racial discrimination, and subclinical cerebrovascular disease among African Americans. Health Psychol 38:63–74.
68. Writing Group M, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, *et al.* (2016): Executive summary: Heart Disease and Stroke Statistics–2016 Update: A report from the American Heart Association. Circulation 133:447–454.
69. Alzheimer's Association: Alzheimer's Disease Facts and Figures Report 2020. Available at: https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed June 10, 2021.
70. Kim P, Evans GW, Angstadt M, Ho SS, Sripada CS, Swain JE, *et al.* (2013): Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. Proc Natl Acad Sci U S A 110:18442–18447.
71. Waldstein SR, Dore GA, Davatzikos C, Katzel LI, Gullapalli R, Seliger SL, *et al.* (2017): Differential associations of socioeconomic status with global brain volumes and white matter lesions in African American and White adults: The HANDLS SCAN study. Psychosom Med 79:327–335.