Archival Report

Biological Psychiatry: CNNI

Indirect Effects of Racial Discrimination on Health Outcomes Through Prefrontal Cortical White Matter Integrity

Onyebuchi Okeke, Aziz Elbasheir, Sierra E. Carter, Abigail Powers, Yara Mekawi, Charles F. Gillespie, Ann C. Schwartz, Bekh Bradley, and Negar Fani

ABSTRACT

BACKGROUND: Racial discrimination is consistently associated with adverse health outcomes and has been linked to structural decrements in brain white matter. However, it is unclear whether discrimination-related neuroplastic changes could indirectly affect health outcomes. Our goal was to evaluate indirect associations of racial discrimination on health outcomes through white matter microstructure in a sample of trauma-exposed Black women.

METHODS: A trauma study in an urban hospital setting recruited 79 Black women who received a history and physical examination to assess medical disorders (compiled into a summed total of disorder types). Participants reported on experiences of racial discrimination and underwent diffusion tensor imaging; fractional anisotropy values were extracted from white matter pathways previously linked to racial discrimination (corpus callosum, including the body and genu; anterior cingulum bundle; and superior longitudinal fasciculus) and entered into mediational models.

RESULTS: Indirect effects of racial discrimination on medical disorders through left anterior cingulum bundle fractional anisotropy were significant ($\beta = 0.07$, SE = 0.04, 95% CI [0.003, 0.14]) after accounting for trauma and economic disadvantage. Indirect effects of racial discrimination on medical disorders through corpus callosum genu fractional anisotropy were also significant ($\beta = 0.08$, SE = 0.04, 95% CI [0.01, 0.16]).

CONCLUSIONS: Racial discrimination may increase risk for medical disorders via neuroplastic effects on microstructural integrity of stress-sensitive prefrontal white matter tracts. Racial discrimination–related changes in these tracts may affect health behaviors, which, in turn, influence vulnerability for medical disorders. These data highlight the connections between racial discrimination, prefrontal white matter connections, and incidence of medical disorders in Black Americans.

https://doi.org/10.1016/j.bpsc.2022.05.004

Racial discrimination is prevalent among marginalized groups in the United States, particularly Black Americans (1). This racism-related stressor emerges in various societal contexts, including interactions with housing officials and in occupational settings as well as within education, criminal justice, economic, and health care contexts (2). Experiences of racial discrimination have been consistently linked to adverse mental and physical health outcomes, including clinically significant depression, anxiety, and substance use as well as hypertension, obesity, and cardiovascular disease (3). Notably, Black women, who experience discrimination on the basis of both race and gender, are among the population groups at highest risk for these outcomes, particularly cardiovascular mortality, hypertension, obesity, and type 2 diabetes; for example, the prevalence rate of both hypertension and obesity in Black women is approximately 58% as compared with 40% in White women (4,5). Racial discrimination is often experienced as a chronic form of stress that contributes to allostatic load (6). Allostatic load describes the cumulative burden of stress/adversity on the body as a consequence of frequent or sustained activity of the physiological systems orchestrating the acute adaptation to stress or threat (7). As with other chronic stressors, racial discrimination–related increases in allostatic load can serve to increase risk for various adverse mental and physical health outcomes (8). Chronic racial discrimination wears down protective resources, heightening vulnerability to illness by increasing susceptibility to infection (6).

Racial discrimination contributes to allostatic dysregulation via effects on stress-response mechanisms, such as the hypothalamic-pituitary-adrenal axis. Chronic activation of the hypothalamic-pituitary-adrenal axis is a mechanism through which racial discrimination may alter neuroplasticity (8). In response to psychosocial stressors, activation of the hypothalamic-pituitary-adrenal axis leads to the increased synthesis and release of the glucocorticoid cortisol from the adrenal cortex into systemic circulation. This, in turn, regulates the duration and impact of the initial stress response (9). Chronic activation of glucocorticoid signaling negatively affects plasticity in stress-sensitive regions of the brain enriched

SEE COMMENTARY ON PAGE 685

ISSN: 2451-9022

in glucocorticoid receptors, such as the hippocampus and medial prefrontal cortex (9); these regions all are involved with the regulation of emotional response. Increased glucocorticoid activity has been shown in animal stress models to reduce apical dendrite length and neuronal density in frontolimbic regions, specifically within the medial prefrontal cortex and hippocampus (10).

Acute and chronic stress in the form of psychological trauma has also been consistently associated with reductions in white matter volume and degraded microstructural integrity of frontolimbic and frontoparietal white matter connections, such as the cingulum bundle (CB), uncinate fasciculus, and superior longitudinal fasciculus (SLF) (11,12). The majority of these studies demonstrate white matter microstructural differences via lower fractional anisotropy (FA), a metric of white matter integrity that reflects the strength of directionality of water diffusion within axons (13). Animal models indicate that chronic exposure to psychosocial stressors and concomitant chronically high levels of cortisol adversely affect neural architecture, particularly myelin (14). These effects are particularly potent in stress-sensitive white matter connections for prefrontal and limbic brain regions, which are enriched in glucocorticoid receptors.

Similar to other types of trauma exposure, racial discrimination may also contribute to changes in white matter microstructure. Meyer *et al.* (15) observed an inverse relationship between elevated experiences of racial discrimination and total white matter (as well as gray matter) volume in Black research participants. In our recent study of trauma-exposed Black women, we observed potent associations between racial discrimination experiences and diminished white matter integrity in anterior aspects of the corpus callosum (CC) and CB as well as the SLF (16). These findings support the notion that racial discrimination may be an independent contributor to brain microstructure alterations, especially in prefrontal regions.

These changes may then contribute to adverse health outcomes via changes in behavior, given that the integrity of these pathways is essential to self-regulatory behaviors and emotion modulation. Compromised white matter integrity secondary to a variety of mechanisms (e.g., inflammation) has been linked to complex behaviors (e.g., consumption of food, substance use, engagement in physical activity) that affect physical health. White matter integrity has been identified as a likely mediator of the relationship between maladaptive self-regulatory behaviors and medical disorders, such as hypertension, diabetes, and obesity (17,18). Chronic stress, including racial trauma, is thought to be a causative factor for these medical disorders (2,19–21). Chronic stressors are also known to affect white matter integrity through inflammatory mechanisms, with particularly potent effects observed in frontal white matter pathways, including the genu of the CC (22). Given these findings, it is possible that diminished microstructure of select white matter pathways has an indirect effect on the relationship between racial discrimination and adverse health outcomes, but this hypothesis has not yet been tested.

As such, the objective of this study was to examine whether white matter microstructure in pathways of relevance to racial discrimination (CC, SLF, and anterior CB [ACB]) indirectly affects the relationship between racial discrimination and medical disorders. Our participants were trauma-exposed Black American women with varying medical comorbidities (e.g., hypertension, dyslipidemia, cardiovascular disease, diabetes) recruited from the Grady Trauma Project, a longstanding study of trauma and stress-related disorders. Given that the CC, left ACB, and bilateral SLF were identified in our prior study of racial discrimination (16), we examined the indirect effects of FA in these pathways on the number of medical disorders through racial discrimination. We conducted secondary exploratory analyses to examine whether any observed indirect effects are specific to greater disease burden and/or complexity.

METHODS AND MATERIALS

Participants

For this study, 79 Black American women ranging in age from 19 to 61 (mean [SD] age = 39.70 [11.29] years) were recruited from the Grady Trauma Project, a collection of studies investigating risk and resilience for posttraumatic stress disorder (PTSD) and related psychiatric and physical health comorbidities in a Black American population. Participants were approached in general medical clinics of a county hospital in Atlanta, Georgia. Eligibility for participation in the 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 disorders, bipolar disorder, current substance or alcohol dependence, or primary psychotic disorder as assessed with a structured clinical interview (23). Participants with magnetic resonance imaging contraindications (e.g., claustrophobia, metal implants) were also excluded. Participants received clinical assessments for trauma and PTSD (clinical and demographic characteristics are detailed in Table 1) and underwent a magnetic resonance imaging scan. Participants received a history and physical examination by a study physician to assess for medical disorders (Table 2). The Emory University Institutional Review Board and Grady Research Oversight Committee approved the conduct of this study.

More than half (58%) of the study participants demonstrated significant economic disadvantage, reporting household incomes of less than $1000 per month. As in our prior studies, income levels were self-reported, and monthly income was dichotomized into 2 groups ($\leq$ $1000 vs. $>$ $1000/month) and entered into statistical analyses to account for variance associated with economic disadvantage. Medical disorders listed as present in the history and physical examination were summed and entered into statistical analyses; the disorders summed included asthma, lung disease, diabetes (type 1 or type 2), cardiovascular disease, thyroid disease, hepatitis, hypertension, dyslipidemia, chronic pain, chronic headache, obesity, and gastroesophageal reflux. The average number of medical disorders was 2.37 (median = 2, mode = 1, SD = 1.75). See Table 2 for a complete list of medical disorders and their frequencies in this sample. Medical disorders were also separated into 2 different variables for secondary analyses to test whether observed indirect effects relate to disease burden/complexity: 1) systemic disorders (a proxy for greater disease burden/complexity) and 2) health conditions (a proxy for lesser disease burden/complexity). The systemic disorders

Table 1. Demographic and Clinical Characteristics

Characteristics	Mean (SD) (Range) or *n* (%)
Age, Years[a]	39.7 (11.3) (19–61)
TEI Total Types	3.34 (2.17) (0–10)
EOD Total Score	2.67 (2.46) (0–9)
Education[b]	
<12th grade	13.6 (11%)
High school graduate/GED	28.4 (22%)
Some college/technical school	30.9 (24%)
College/technical school graduate	20.9 (16%)
Graduate school	6.2 (4%)
Monthly Income[b]	
$0–$249	13.6 (11%)
$250–$499	11.1 (8%)
$500–$999	34.6 (27%)
$1000–$1999	24.7 (19%)
≥ $2000	16.0 (12%)

EOD, Experiences of Discrimination; TEI, Traumatic Events Inventory.
[a]Data missing for 1 participant.
[b]Data missing for 2 participants.

variable was a summed composite of the presence of systemic disorders, which included cardiovascular disease, diabetes, arthritis, hepatitis, lung disease, and thyroid disease. The health conditions variable was a summed composite of health conditions and symptoms that can occur in the context of systemic disorders, which included hypertension, dyslipidemia, obesity, gastroesophageal reflux, chronic headache, and chronic pain.

Clinical Assessments

Participants completed an assessment of trauma, the Traumatic Events Inventory (TEI) (24). The TEI was administered to measure trauma exposure across the life span, inclusive of trauma occurring during childhood and adulthood. A sum total of different types of trauma experienced (number of types of trauma to which the person was exposed; score range = 0–15, range = 0–10 for this sample) was entered as a covariate in statistical analyses. Participants also completed the Experiences of Discrimination (EOD) questionnaire (25). The EOD is a 9-item self-report measure that assesses exposure to discriminatory experiences associated with race or ethnicity across various situations, including school, work, medical care, or personal interactions. The number of types of racial discrimination experienced was summed (mean [SD] = 2.67 [2.46], range = 0–9) and entered into statistical analyses. The EOD total was significantly correlated with age ($r = 0.38$, $p < .001$). Correlations of EOD total with trauma exposure, income, number of medical disorders, and white matter indices are provided in Table 3.

Diffusion-Weighted Magnetic Resonance Imaging Acquisition, Image Processing, and Statistical Analyses

Participants were scanned at Emory University using either of 2 research-dedicated Siemens TIM Trio 3T (Siemens Corp.) scanners. Diffusion-weighted images were acquired similarly across both sites, with maximum gradient strength of 40 mTm^{-1} with the following parameters: 39 × 2.5-mm-thick axial slices, matrix = 128 × 128, field of view = 220 × 220 mm^2, voxel size = 1.72 × 1.72 × 2.5 mm^3. 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) (26).

All diffusion-weighted image processing and analyses were conducted using FMRIB Software Library (FSL version 4.1; www.fmrib.ox.ac.uk/fsl). Correction for head motion and eddy current distortion was performed using an automated affine registration algorithm. Images were skull stripped using the FSL brain extraction tool (27). DTIfit in the FMRIB Diffusion Toolbox was used to fit a tensor model at each voxel and produce FA maps. Voxelwise associations were conducted with diffusion tensor imaging scalar indices, assessed using tract-based spatial statistics (TBSS Version 1.2) available in FSL (28). The FA maps of all participants were coregistered using the nonlinear registration to the most typical participant's FA, then affine transformed into 1 × 1 × 1 mm^3 Montreal Neurological Institute space. Transformed FA images were averaged to create a mean FA image, then skeletonized and thresholded by an FA value of 0.2 to reduce the likelihood of

Table 2. Frequency of Medical Disorders

Medical Disorder	*n* (%)
Asthma	10 (12.7%)
Lung Disease of Unknown Etiology	1 (1.3%)
Cardiovascular Disease	5 (6.3%)
History of myocardial infarction	1 (1.3%)
Heart disorder of unknown etiology	4 (5.1%)
Hypertension	32 (40.5%)
Diabetes	20 (25.3%)
Type 1	3 (3.8%)
Type 2	13 (16.5%)
Type unknown	1 (1.3%)
Gastroesophageal Reflux Disorder	12 (15.2%)
Chronic Pain	20 (25.3%)
Osteoarthritis	9 (11.4%)
Chronic Headache	4 (5.1%)
Migraine headache	1 (1.3%)
Tension headache	2 (2.5%)
Hepatitis	4 (5.1%)
Hepatitis B	2 (2.5%)
Hepatitis C	2 (2.5%)
Dyslipidemia	14 (17.7%)
Hypercholesterolemia	5 (6.3%)
High triglycerides	1 (1.3%)
Hyperlipidemia	7 (8.9%)
Type unknown	1 (1.3%)
Obesity, >30 kg/m^2	11 (13.9%)
Thyroid Disease	5 (6.3%)
Hyperthyroidism	4 (5.1%)
Thyroid disorder of unknown etiology	1 (1.3%)

Table 3. Correlations Between Racial Discrimination, Trauma Exposure, Income, Total Medical Disorders, and FA in White Matter Pathways

	EOD	TEI	Income	Medical Disorders Sum
TEI	0.45[b]	–		
Income	−0.05 ρ	−0.07 ρ	–	
Medical Disorders	0.32[b]	0.06	−0.28[a] ρ	–
ACB FA				
Left	−0.24[a]	−0.06	0.14 ρ	−0.40[b]
SLF FA				
Left	−0.20	−0.05	0.12 ρ	−0.40[b]
Right	−0.02	−0.08	0.13 ρ	−0.41[b]
CC FA				
Genu	−0.30[b]	−0.09	0.15 ρ	−0.46[b]
Whole tract	−0.24[a]	−0.08	0.15 ρ	−0.43[b]
Body	−0.27[a]	−0.19	0.12 ρ	−0.36[b]

ρ is Spearman's rho value.

ACB, anterior cingulum bundle; CC, corpus callosum; EOD, Experiences of Discrimination; FA, fractional anisotropy; SLF, superior longitudinal fasciculus; TEI, Traumatic Events Inventory.

[a]$p < .05$ level (two tailed).

[b]$p < .01$ level (two tailed).

gray matter inclusion in analyses. Voxel values of FA maps of each participant were projected onto the skeleton by searching the local maxima along the perpendicular direction from the skeleton. Tracts of interest included the CC (body and genu), left ACB, and bilateral SLF, which emerged as significantly related to racial discrimination in our prior study (29); the white matter data presented here were also included in this prior study. Skeletonized FA maps were overlaid with atlas masks of these regions, derived from the probabilistic Johns Hopkins University ICBM-DTI-81 white matter atlas provided by FSL4. FA was extracted from these regions using the fslmaths program and entered into mediational models.

Statistical Analyses

Separate mediational analyses using bootstrapped confidence intervals were conducted using the PROCESS macro Version 4 (https://www.processmacro.org/index.html), implemented in IBM SPSS Version 27 (IBM Corp.); we examined the indirect effects of FA for select white matter pathways on the relationship between experiences of racial discrimination (EOD total) and number of medical disorders. The right and left SLF, left ACB, and CC (entire tract as well as the body and genu segments) were selected as regions of interest given our prior findings demonstrating associations with racial discrimination. As with our prior studies (16,30), we covaried trauma exposure (TEI total), scanner site, and economic disadvantage. Confidence intervals were derived from 5000 bootstrap resamples; coefficients of mediation analyses were considered statistically significant if the 95% upper and lower confidence intervals did not contain zero. Bonferroni correction was applied to adjust for error owing to multiple comparisons; statistical significance was set at a threshold of $p < .008$ for these primary analyses. For tracts that emerged as significant mediators of the relationship between racial discrimination and total number of medical disorders, we conducted follow-up mediational analyses to determine whether these effects were specific to systemic disorders (cardiovascular disease, diabetes, arthritis, hepatitis, lung disease, thyroid disease) or health conditions associated with systemic disorders (hypertension, dyslipidemia, obesity, gastroesophageal reflux, chronic headache, chronic pain). Given that age has an established relationship with white matter microstructure (31,32) and the strength of the relationship between racial discrimination and age in this sample, age was excluded from initial analyses to limit multicollinearity. As in our prior study (16), tracts that emerged as significant mediators of the relationship between racial discrimination and medical disorders were subject to follow-up regression analyses with age group (younger [18–50 years old] vs. older [51–62 years old]) and racial discrimination to examine potential interactions with microstructure of these pathways (Table S1). Statistical significance was set at $p < .05$ for these follow-up analyses.

RESULTS

We examined the indirect effect of ACB FA on number of medical disorders through racial discrimination. A regression that included racial discrimination as a predictor of medical disorders with income, trauma exposure, and scanner site as covariates was significant ($F_{4,74} = 4.51$, $p = .003$, $R^2 = 0.20$; racial discrimination, path c, $\beta = 0.28$, SE = 0.08, $p = .001$).

Anterior Cingulum Bundle

Racial discrimination significantly predicted left ACB FA (path a, $\beta = -0.28$, B = −0.003, SE B = 0.001, $p = .02$), and left ACB FA was a significant predictor of medical disorders (path b, $\beta = -.33$, B = −20.65, SE B = 6.62, $p = .003$). The addition of left ACB FA to the overall model was statistically significant, as shown in Figure 1 ($F_{5,73} = 5.98$, $p = .0001$, $R^2 = 0.29$); left ACB FA significantly mediated the relationship between racial discrimination and medical disorders ($\beta = 0.07$, SE = 0.04, 95% CI [0.003, 0.14]), reducing the strength of the direct effect of racial discrimination on health outcomes (path c′, $\beta = 0.22$, SE = 0.08, 95% CI [0.05, 0.38]).

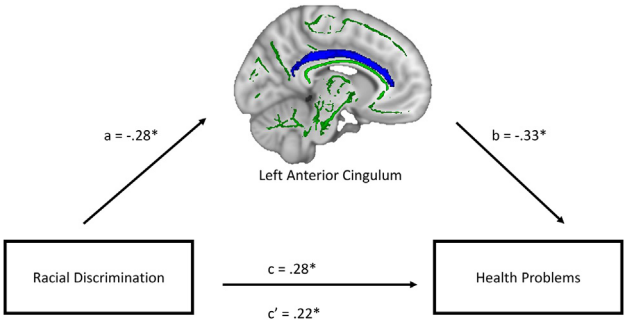

Figure 1. Significant indirect effects of racial discrimination on medical disorders through left anterior cingulum bundle (highlighted in blue) fractional anisotropy (β = 0.07, SE = 0.04, 95% CI [0.003, 0.14]). *indicates statistical significance.

Corpus Callosum

We examined the indirect effects of CC FA (entire tract) and CC body and genu FA separately on number of medical disorders through racial discrimination. Racial discrimination significantly predicted CC FA (path a, β = −0.27, B = −0.003, SE B = 0.002, p = .03), and CC FA was a significant predictor of medical disorders (path b, β = −0.32, B = −19.01, SE B = 6.32, p = .004). The addition of CC FA (entire tract) improved the overall model ($F_{5,73}$ = 5.81, p = .001, R^2 = 0.28), but CC FA (entire tract) did not significantly mediate the relationship between racial discrimination and medical disorders (β = 0.06, SE = 0.03, 95% CI [−0.001, 0.14]) and did not significantly reduce the strength of the direct effect of racial discrimination on medical disorders (path c′, β = 0.22, SE = 0.08, 95% CI [0.06, 0.39]). The addition of CC body FA to the overall model was also not statistically significant ($F_{5,73}$ = 2.07, p = .09, R^2 = 0.10) and thus did not mediate the relationship between racial discrimination and medical disorders.

Racial discrimination significantly predicted CC genu FA (path a, β = −0.34, B = −0.006, SE = 0.002, p = .005), and CC genu FA was a significant predictor of medical disorders (path b, β = −0.32, B = −14.54, SE B = 4.85, p = .004). The addition of CC genu FA to the overall model was statistically significant, as shown in Figure 2 ($F_{5,73}$ = 5.79, p = .0001, R^2 = 0.28). CC genu FA significantly mediated the relationship between racial discrimination and medical disorders (β = 0.08, SE = 0.04, 95% CI [0.01, 0.16]), reducing the strength of the direct effect of racial discrimination on health outcomes (path c′, β = 0.20, SE = 0.08, 95% CI [0.04, 0.37]).

Superior Longitudinal Fasciculus

Racial discrimination did not significantly predict left SLF FA (path a, β = −0.23, B = −0.002, SE B = 0.001, p = .06), but left SLF FA was a significant predictor of medical disorders (path b, β = −0.31, B = −24.42, SE B = 8.32, p = .006). The addition of left SLF FA improved the overall model ($F_{5,73}$ = 5.70, p = .0002, R^2 = 0.28), but left SLF FA did not significantly mediate the relationship between racial discrimination and medical disorders (β = 0.05, SE = 0.03, 95% CI [−0.01, 0.12]); it did not significantly reduce the strength of the direct effect of racial discrimination on medical disorders (path c′, β = 0.23, SE = 0.08, 95% CI [0.07, 0.40]). Likewise, the addition of right SLF FA to the overall model was not significant ($F_{5,73}$ = 1.66, p = .17, R^2 = 0.08).

Follow-up Analyses

Follow-up analyses with age as well as follow-up mediational analyses with systemic disorders and health conditions are provided in the Supplement.

DISCUSSION

We examined whether racial discrimination was indirectly associated with adverse health outcomes via compromised white matter integrity in select frontolimbic and frontoparietal (ACB and SLF) and commissural (CC, body, and genu) pathways in a sample of trauma-exposed Black women. Integrity of the ACB and CC genu emerged as a significant mediator of this relationship. When we examined systemic disorders (e.g., cardiovascular disease, diabetes) and health conditions (e.g., hypertension, obesity) separately in follow-up analyses, FA of the CC genu demonstrated significant indirect effects on the relationship between racial discrimination and systemic disorders, indicating associations of this pathway with greater disease burden/complexity. These findings extend our prior findings on racial discrimination and white matter integrity, revealing ways in which degraded microstructure of these frontal pathways could contribute to the incidence of adverse health outcomes. Allostatic load owing to racial discrimination may potentiate neuroplastic changes, particularly within stress-sensitive prefrontal and limbic regions (9,16,33); these changes may serve to increase vulnerability to the development of medical disorders via different mechanisms.

Notably, our findings indicated that only prefrontal white matter pathways, namely, the anterior aspects of the CC and CB, were significant mediators of the relationship between racial discrimination and health outcomes. The CC is the main commissural fiber for inter- and intrahemispheric communication (34). This pathway has been consistently implicated in early life stress and PTSD (11,35). The genu of the CC connects prefrontal brain hemispheres, and disruptions in this aspect of the CC have been linked to dysregulation in cognitive and emotional processes, such as impulse control (36–40). The CB is an extensive associational white matter tract dorsal to the CC (41). Among white matter pathways, the CB has one of

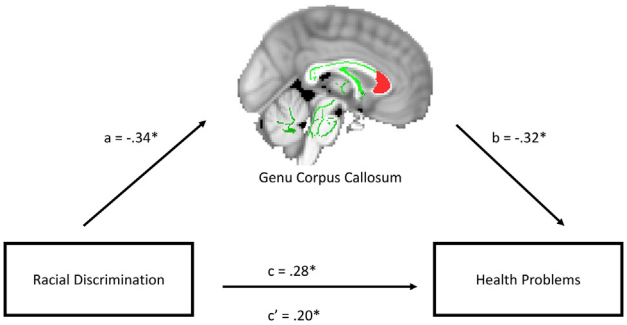

Figure 2. Significant indirect effects of racial discrimination on medical disorders through genu of the corpus callosum (highlighted in red) fractional anisotropy (β = 0.08, SE = 0.04, 95% CI [0.01, 0.16]). *indicates statistical significance.

the longest trajectories of growth, extending into middle adulthood (approximately age 35) (42). The protracted growth trajectory of the CB implies prolonged opportunities for neuroplastic changes, which affect cognitive processes, such as attention and working memory, as well as emotion regulation (42). The CB is particularly sensitive to the neurotoxic effects of stress, as reduced microstructural integrity of this pathway has been consistently implicated in trauma and PTSD (43,44). We recently observed that increased experiences of racial discrimination were linked to decrements in ACB and CC integrity; the present findings extend our earlier research, implicating that the diminished microstructure of these paths plays a role in adverse health outcomes in people who have experienced racism-related stress (16). The ACB is a frontoparietal connection (42,45) that supports cognitive-affective processes related to attentional control and emotion regulation (43). We previously observed that racial discrimination experiences were associated with proportionally increased function in the ventromedial prefrontal cortex during attention to threat-relevant stimuli (30). It is possible that, over time, chronically increased function in this modulatory brain region may serve to weather ventromedial prefrontal white matter connections, which include the ACB. Given the critical role of this region in emotion regulation, it is likely that these racism-related neuroplastic changes have consequent effects on regulatory behaviors and, in turn, health outcomes.

Racial discrimination can increase distress and impact emotion regulation (46), which is likely to affect self-regulatory behaviors that play a role in the development of mental and physical health disorders. Given the role of the CB and CC in emotion regulation (47,48) and reward-seeking behaviors (48), it is possible that alterations in the integrity of these pathways secondary to racism-related stress could affect the expression of appetitive and self-regulatory behaviors. Increased consumption of high-calorie comfort foods and/or increased use of nicotine or other substances increase risk for the development of cardiac and metabolic health problems (47,49–51). This pattern of eating can increase risk for obesity, hyperlipidemia, diabetes, cardiovascular disease, and gastroesophageal reflux (1,2,49,50,52–54), comorbidities that are prevalent in our sample [and are prevalent in our patient population as a whole (24,55,56)]. Microstructural integrity of these pathways has also been linked to markers of overall health; an inverse association has been observed between FA of the CC and cingulum and body mass index (48), and poorer cardiorespiratory fitness (a marker of cardiovascular and respiratory health) has been associated with lower FA in these regions (57). Our data suggest that white matter may be an important contributing factor for these health outcomes in the context of racial discrimination, even after accounting for other socioenvironmental factors, such as trauma exposure and economic disadvantage. Alternatively, it is possible that the white matter alterations observed here are secondary to the negative effects of self-regulatory behaviors themselves, such as high consumption of calorie-dense food or substances. For example, chronic smoking has been associated with lower CC FA, and acute nicotine administration also adversely affects CC FA (58,59). As such, we cannot rule out the possibility that these coping strategies, which clearly play a role in the development of physical and mental health conditions, have negative effects on these white matter pathways as well.

Findings from a recent review suggest that white matter integrity mediates the relationship between health behaviors and adverse health outcomes such as obesity (60), potentially via inflammatory mechanisms. Although outside the scope of this study, it is possible that experiences of racial discrimination can promote chronic systemic inflammation, which, in turn, impacts white matter and subsequent health outcomes. Race-related differences in inflammatory markers have been previously observed (61), and recent reports suggest that the experience of racial discrimination leads to higher inflammatory tone in Black Americans (61–63). Diseases that are in part related to systemic inflammation, such as hypertension, disproportionately affect Black people (64), and diminished connectivity between cortical and cingulate regions is commonly observed in inflammation-related diseases (i.e., depression, obesity, arthritis, cardiovascular disease) (42,64–68). Increases in inflammatory markers have also been associated with decreased FA in the genu of the CC (22) and relative increases in body mass index, systolic blood pressure, and low-density lipoproteins (22). Increased inflammation may also lead to damage of myelin (69–71). It is possible that racism-related stress is an instigating factor in this cycle, increasing inflammation. This can lead to white matter changes that affect behaviors, which, in turn, increase vulnerability for adverse health outcomes in Black individuals.

Several study limitations must be noted. The cross-sectional nature of our investigation limits understanding of causal relationships between experiences of racial discrimination, white matter integrity, and health outcomes in our sample; as such, we cannot make claims about the temporal relationships between these factors; for example, poorer cardiovascular health has been linked to greater white matter lesion burden and poorer microstructural integrity (72). Further, the observed indirect effects may differ based on disorder type, which merits examination in future studies. However, these findings can guide hypotheses for long-term longitudinal studies designed to investigate the associations between racist experiences, white matter changes, and development of health problems in people from marginalized racial groups. Additionally, only women were included in this study, and the addition of men would greatly enhance generalizability of findings; notably, even in this restricted sample, a range of medical problems were reported that occur with similar frequency in men (e.g., diabetes, heart disease). As such, we do not believe that the findings are applicable only to women. Further, we did not assess discrimination owing to gender (gendered racism), which precluded our ability to include the intersection of other types of discrimination in our data analyses. Additionally, we aggregated health conditions in our statistical analyses to preserve statistical power, but future large-scale studies are warranted to examine specific medication effects on different types of health disorders. Lastly, we did not have data on mechanisms that could account for associations between racial discrimination and white matter indices, including inflammation. Future studies that include these mechanistic data can shed further light on relationships observed in this study, namely, the pathways through which racism can exert its effects on brain structure and, in turn,

adverse health outcomes that disproportionately affect Black Americans.

In summary, to our knowledge our study is the first to report associations between racial discrimination, white matter integrity, and incidence of medical disorders in Black American women. These findings support a model that highlights the indirect contributions of prefrontal white matter, specifically, ACB and CC genu FA, in the relationship between racial discrimination and adverse health outcomes, extending our earlier functional and structural findings on racism-related stress in Black Americans (16,30,73). The results of this study highlight the associations between racial discrimination, white matter, and medical disorders, suggesting a neurobiological pathway for the emergence of health disparities in Black American women.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institute of Mental Health (Grant Nos. MH101380 [to NF], MH099211 [to CFG], and HD071982 [to BB]), National Center for Complementary and Integrative Health (Grant No. AT011267 [to NF]), Emory Medical Care Foundation, Emory University Research Council, American Psychological Association, Society for Clinical Neuropsychology, and National Cancer Institute (Grant No. CA220254-02S1 [to SEC]).

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

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry and Behavioral Sciences (OO, AE, AP, CFG, ACS, BB, NF), Emory University; Department of Psychology (SEC), Georgia State University, Atlanta; Atlanta VA Medical Center (BB), Decatur, Georgia; and Department of Psychological and Brain Sciences (YM), University of Louisville, Louisville, Kentucky.

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

Received Mar 8, 2022; revised Apr 18, 2022; accepted May 5, 2022.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2022.05.004.

REFERENCES

1. Boutwell BB, Nedelec JL, Winegard B, Shackelford T, Beaver KM, Vaughn M, *et al.* (2017): The prevalence of discrimination across racial groups in contemporary America: Results from a nationally representative sample of adults. PLoS One 12:e0183356.
2. Williams DR, Lawrence JA, Davis BA (2019): Racism and health: Evidence and needed research. Annu Rev Public Health 40:105–125.
3. Pascoe EA, Smart Richman L (2009): Perceived discrimination and health: A meta-analytic review. Psychol Bull 135:531–554.
4. Chinn JJ, Martin IK, Redmond N (2021): Health equity among Black women in the United States. J Womens Health (Larchmt) 30:212–219.
5. National Center for Health Statistics. Available at: https://stacks.cdc.gov/view/cdc/106273. Accessed March 11, 2022.
6. Gee GC, Spencer MS, Chen J, Takeuchi D (2007): A nationwide study of discrimination and chronic health conditions among Asian Americans. Am J Public Health 97:1275–1282.
7. McEwen BS (2012): Brain on stress: How the social environment gets under the skin. Proc Natl Acad Sci U S Am 109(Suppl 2):17180–17185.
8. Berger M, Sarnyai Z (2015): "More than skin deep": Stress neurobiology and mental health consequences of racial discrimination. Stress 18:1–10.
9. Radley JJ, Kabbaj M, Jacobson L, Heydendael W, Yehuda R, Herman JP (2011): Stress risk factors and stress-related pathology: Neuroplasticity, epigenetics and endophenotypes. Stress 14:481–497.
10. Lupien SJ, Juster RP, Raymond C, Marin MF (2018): The effects of chronic stress on the human brain: From neurotoxicity, to vulnerability, to opportunity. Front Neuroendocrinol 49:91–105.
11. 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.
12. 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.
13. Jones DK (2008): Studying connections in the living human brain with diffusion MRI. Cortex 44:936–952.
14. Antontseva E, Bondar N, Reshetnikov V, Merkulova T (2020): The effects of chronic stress on brain myelination in humans and in various rodent models. Neuroscience 441:226–238.
15. 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.
16. Fani N, Harnett NG, Bradley B, Mekawi Y, Powers A, Stevens JS, *et al.* (2022): Racial discrimination and white matter microstructure in trauma-exposed Black women. Biol Psychiatry 91:254–261.
17. Verstynen TD, Weinstein AM, Schneider WW, Jakicic JM, Rofey DL, Erickson KI (2012): Increased body mass index is associated with a global and distributed decrease in white matter microstructural integrity. Psychosom Med 74:682–690.
18. Porter A, Leckie R, Verstynen T (2018): White matter pathways as both a target and mediator of health behaviors. Ann N Y Acad Sci 1428:71–88.
19. Kelly MM, Forsyth JP (2007): Sex differences in response to an observational fear conditioning procedure. Behav Ther 38:340–349.
20. Bjorntorp P (2001): Do stress reactions cause abdominal obesity and comorbidities? Obes Rev 2:73–86.
21. Sparrenberger F, Cichelero FT, Ascoli AM, Fonseca FP, Weiss G, Berwanger O, *et al.* (2009): Does psychosocial stress cause hypertension? A systematic review of observational studies. J Hum Hypertens 23:12–19.
22. Wersching H, Duning T, Lohmann H, Mohammadi S, Stehling C, Fobker M, *et al.* (2010): Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. Neurology 74:1022–1029.
23. 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(Suppl 20):22–33; quiz 34–57.
24. Lin C, Michopoulos V, Powers A, Wingo AP, Schwartz A, Bradley B, *et al.* (2018): Affect, inflammation, and health in urban at-risk civilians. J Psychiatr Res 104:24–31.
25. 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.
26. Jenkinson M, Smith S (2001): A global optimisation method for robust affine registration of brain images. Med Image Anal 5:143–156.
27. Smith SM (2002): Fast robust automated brain extraction. Hum Brain Mapp 17:143–155.
28. 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.
29. Fani N, Gutman D, Tone EB, Almli L, Mercer KB, Davis J, *et al.* (2013): FKBP5 and attention bias for threat: Associations with hippocampal function and shape. JAMA Psychiatry 70:392–400.
30. 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.
31. 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.
32. 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.
33. McEwen BS, Morrison JH (2013): The brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. Neuron 79:16–29.
34. Georgy BA, Hesselink JR, Jernigan TL (1993): MR imaging of the corpus callosum. AJR Am J Roentgenol 160:949–155.
35. Jackowski AP, de Araújo CM, de Lacerda AL, Mari JeJ, Kaufman J (2009): Neurostructural imaging findings in children with post-traumatic stress disorder: Brief review. Psychiatry Clin Neurosci 63:1–8.
36. Fineberg NA, Chamberlain SR, Goudriaan AE, Stein DJ, Vanderschuren LJ, Gillan CM, *et al.* (2014): New developments in human neurocognition: Clinical, genetic, and brain imaging correlates of impulsivity and compulsivity. CNS Spectr 19:69–89.
37. Matsuo K, Nielsen N, Nicoletti MA, Hatch JP, Monkul ES, Watanabe Y, *et al.* (2010): Anterior genu corpus callosum and impulsivity in suicidal patients with bipolar disorder. Neurosci Lett 469:75–80.
38. Moeller FG, Hasan KM, Steinberg JL, Kramer LA, Dougherty DM, Santos RM, *et al.* (2005): Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: Diffusion tensor imaging. Neuropsychopharmacology 30:610–617.
39. Rüsch N, Weber M, Il'yasov KA, Lieb K, Ebert D, Hennig J, *et al.* (2007): Inferior frontal white matter microstructure and patterns of psychopathology in women with borderline personality disorder and comorbid attention-deficit hyperactivity disorder. Neuroimage 35:738–747.
40. Whalley HC, Nickson T, Pope M, Nicol K, Romaniuk L, Bastin ME, *et al.* (2015): White matter integrity and its association with affective and interpersonal symptoms in borderline personality disorder. Neuroimage Clin 7:476–481.
41. Jones DK, Christiansen KF, Chapman RJ, Aggleton JP (2013): Distinct subdivisions of the cingulum bundle revealed by diffusion MRI fibre tracking: Implications for neuropsychological investigations. Neuropsychologia 51:67–78.
42. Kelly AM, Di Martino A, Uddin LQ, Shehzad Z, Gee DG, Reiss PT, *et al.* (2009): Development of anterior cingulate functional connectivity from late childhood to early adulthood. Cereb Cortex 19:640–657.
43. Harnett NG, Ference EW, Knight AJ, Knight DC (2020): White matter microstructure varies with post-traumatic stress severity following medical trauma. Brain Imaging Behav 14:1012–1024.
44. Bubb EJ, Metzler-Baddeley C, Aggleton JP (2018): The cingulum bundle: Anatomy, function, and dysfunction. Neurosci Biobehav Rev 92:104–127.
45. Margulies DS, Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP (2007): Mapping the functional connectivity of anterior cingulate cortex. Neuroimage 37:579–588.
46. Mekawi Y, Carter S, Brown B, Martinez de Andino A, Fani N, Michopoulos V, *et al.* (2021): Interpersonal trauma and posttraumatic stress disorder among Black women: Does racial discrimination matter? J Trauma Dissociation 22:154–169.
47. Mekawi Y, Watson-Singleton NN, Kuzyk E, Dixon HD, Carter S, Bradley-Davino B, *et al.* (2020): Racial discrimination and post-traumatic stress: Examining emotion dysregulation as a mediator in an African American community sample. Eur J Psychotraumatol 11: 1824398.
48. Papageorgiou I, Astrakas LG, Xydis V, Alexiou GA, Bargiotas P, Tzarouchi L, *et al.* (2017): Abnormalities of brain neural circuits related to obesity: A diffusion tensor imaging study. Magn Reson Imaging 37:116–121.
49. Dallman MF, Pecoraro N, Akana SF, La Fleur SE, Gomez F, Houshyar H, *et al.* (2003): Chronic stress and obesity: A new view of "comfort food. Proc Natl Acad Sci U S A 100:11696–11701.
50. Tomiyama AJ, Dallman MF, Epel ES (2011): Comfort food is comforting to those most stressed: Evidence of the chronic stress response network in high stress women. Psychoneuroendocrinology 36:1513–1519.
51. Williams DR, Mohammed SA (2009): Discrimination and racial disparities in health: Evidence and needed research. J Behav Med 32:20–47.
52. 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.
53. Zhang R, Beyer F, Lampe L, Luck T, Riedel-Heller SG, Loeffler M, *et al.* (2018): White matter microstructural variability mediates the relation between obesity and cognition in healthy adults. Neuroimage 172:239–249.
54. MacFarlane B (2018): Management of gastroesophageal reflux disease in adults: A pharmacist's perspective. Integr Pharm Res Pract 7:41–52.
55. Dixon HD, Michopoulos V, Gluck RL, Mendoza H, Munoz AP, Wilson JG, *et al.* (2020): Trauma exposure and stress-related disorders in African-American women with diabetes mellitus. Endocrinol Diabetes Metab 3:e00111.
56. Weiss T, Skelton K, Phifer J, Jovanovic T, Gillespie CF, Smith A, *et al.* (2011): Posttraumatic stress disorder is a risk factor for metabolic syndrome in an impoverished urban population. Gen Hosp Psychiatry 33:135–142.
57. Oberlin LE, Verstynen TD, Burzynska AZ, Voss MW, Prakash RS, Chaddock-Heyman L, *et al.* (2016): White matter microstructure mediates the relationship between cardiorespiratory fitness and spatial working memory in older adults. Neuroimage 131:91–101.
58. Umene-Nakano W, Yoshimura R, Kakeda S, Watanabe K, Hayashi K, Nishimura J, *et al.* (2014): Abnormal white matter integrity in the corpus callosum among smokers: Tract-based spatial statistics. PLoS One 9: e87890.
59. Kochunov P, Du X, Moran LV, Sampath H, Wijtenburg SA, Yang Y, *et al.* (2013): Acute nicotine administration effects on fractional anisotropy of cerebral white matter and associated attention performance. Front Pharmacol 4:117.
60. Steffen PR, McNeilly M, Anderson N, Sherwood A (2003): Effects of perceived racism and anger inhibition on ambulatory blood pressure in African Americans. Psychosom Med 65:746–750.
61. Surachman A, Jenkins AIC, Santos AR, Almeida DM (2021): Socioeconomic status trajectories across the life course, daily discrimination, and inflammation among Black and white adults. Psychoneuroendocrinology 127:105193.
62. Gillespie SL, Bose-Brill S, Giurgescu C, Gondwe KW, Nolan TS, Spurlock EJ, *et al.* (2021): Racial discrimination and stress across the life course: Associations with prenatal inflammation, perceived stress, and depressive symptoms. Nurs Res 70(5S Suppl 1):S21–S30.
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. Hicken MT, Lee H, Morenoff J, House JS, Williams DR (2014): Racial/ethnic disparities in hypertension prevalence: Reconsidering the role of chronic stress. Am J Public Health 104:117–123.
65. Powers KE, Somerville LH, Kelley WM, Heatherton TF (2013): Rejection sensitivity polarizes striatal-medial prefrontal activity when anticipating social feedback. J Cogn Neurosci 25:1887–1895.
66. Mensah GA, Mokdad AH, Ford ES, Greenlund KJ, Croft JB (2005): State of disparities in cardiovascular health in the United States. Circulation 111:1233–1241.
67. Sharma S, Malarcher AM, Giles WH, Myers G (2004): Racial, ethnic and socioeconomic disparities in the clustering of cardiovascular disease risk factors. Ethn Dis 14:43–48.

68. Clark R, Anderson NB, Clark VR, Williams DR (1999): Racism as a stressor for African Americans. A biopsychosocial model. Am Psychol 54:805–816.
69. Stadelmann C, Wegner C, Brück W (2011): Inflammation, demyelination, and degeneration—recent insights from MS pathology. Biochim Biophys Acta 1812:275–282.
70. Taib T, Leconte C, Van Steenwinckel J, Cho AH, Palmier B, Torsello E, *et al.* (2017): Neuroinflammation, myelin and behavior: Temporal patterns following mild traumatic brain injury in mice. PLoS One 12: e0184811.
71. Aktas O, Ullrich O, Infante-Duarte C, Nitsch R, Zipp F (2007): Neuronal damage in brain inflammation. Arch Neurol 64:185–189.
72. Fuhrmann D, Nesbitt D, Shafto M, Rowe JB, Price D, Gadie A, *et al.* (2019): Strong and specific associations between cardiovascular risk factors and white matter micro- and macrostructure in healthy aging. Neurobiol Aging 74:46–55.
73. 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.