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Major lifetime discrimination exposure accelerates brain microstructural aging: Diffusion MRI evidence from MIDUS

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Dr. Richard J. Davidson is the founder, president, and serves on the board of directors for the non-profit organization, Healthy Minds Innovations, Inc.

Dr. Andrew L. Alexander is part owner and scientific advisor for ImgGyd, LLC which is developing technologies for image guided surgeries.

All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abstract

Objective

Experiencing discrimination is associated with faster biological aging, as reflected in telomere shortening and DNA methylation. However, the impact of discrimination on brain aging processes remains unclear. Here, we tested whether individuals who reported at least one major lifetime discrimination event would exhibit steeper age-related associations in microstructural metrics within whole-brain white matter and the hippocampus, consistent with accelerated brain microstructural aging, compared to those with no such experiences.

Methods

We analyzed multi-shell diffusion-weighted MRI data from the Midlife in the United States (MIDUS) cohort (n = 147, mean age = 65 years, range 48–95) to assess brain microstructure using complementary statistical and biophysical diffusion models. Diffusion kurtosis imaging representation was used to derive diffusion tensor imaging (DTI) and white matter tract integrity (WMTI) measures. Additional microstructural health indices were derived using the neurite orientation dispersion and density imaging (NODDI) model. Permutation analyses of linear models were run within the whole-brain white matter and bilateral hippocampi, adjusting for sex, race, and education.

Results

Participants who reported at least one major discriminatory experience during their lifetime exhibited accelerated age-associated changes in white matter microstructural measures, including higher mean and radial diffusivities, extra-axonal radial diffusivity, and free water fraction compared to those with no such experiences.

Conclusions

These converging findings from complementary measures of brain microstructure suggest that major discrimination experiences may contribute to accelerated brain microstructural aging.

Keywords: major lifetime discrimination, aging, diffusion weighted imaging, brain microstructure, MIDUS.

Abbreviations:

BIPOC: Black, Indigenous, and People of Color, CSF: cerebrospinal fluid, DKI: diffusion kurtosis imaging, DTI: diffusion tensor imaging, DWI: diffusion weighted imaging, FA: fractional anisotropy, FOV: field of view, FWE: family-wise error, MD: mean diffusivity, MIDUS: Midlife in the United States, MK: mean kurtosis, MRI: magnetic resonance imaging, NODDI: neurite orientation dispersion and density imaging, PALM: permutation analyses of linear models, PET: positron emission tomography, RD: radial diffusivity, RK: radial kurtosis, TE: echo time, TR: repetition time, WMTI: white matter tract integrity

1 Introduction

Discrimination is a social determinant of health with profound negative impacts, including increased risk for cardiovascular disease, depression, psychological distress, suicidal ideation, and mortality [1]. Experiencing discrimination is stressful. The biological weathering hypothesis suggests that exposure to psychosocial stressors such as discrimination can accelerate the aging process, increasing vulnerability to disease and early mortality [2]. For example, experiencing discrimination is positively associated with both heightened threat appraisals and greater negative affective reactivity to stress that mediate worse physical and mental health outcomes 20 years later [3]. However, whether experiences of discrimination can prematurely age the brain remains to be studied.

Major discriminatory events—such as being fired from a job, hassled by the police, or denied a promotion due to an individual characteristic such as age, gender, race, ethnicity, disability—are widespread in the United States. At least one-third of the population reports experiencing major discrimination during their lifetime [4, 5]. Discrimination has detrimental consequences that are particularly relevant to aging. Age is one of the strongest risk factors for many neurodegenerative conditions, yet the pace of biological aging may differ from chronological age [6]. Major discrimination has been associated with greater biological aging, as indicated by shorter telomere length [7]. Individuals who reported more frequent or multiple forms of discrimination showed older biological ages and a faster pace of aging, based on blood DNA methylation markers [8]. Other adverse outcomes associated with discrimination, and relevant to aging, include smaller hippocampal volume [9] and poorer cognition, including worse episodic memory [10] and reduced executive function [11].

Age is also strongly associated with declining brain health among older individuals, with reductions in volumes of most brain structures, especially the hippocampus, accelerating from the fifties

onwards [12, 13]. Even before volumetric changes or neurodegenerative conditions become detectable in the hippocampus and other brain regions, subtle microstructural changes can be identified using diffusion weighted magnetic resonance imaging (DWI) [14, 15]. However, the association between major discrimination and brain microstructure in the context of aging has not yet been examined.

By leveraging the diffusion properties of water molecules, DWI can be used to derive measures that are sensitive to cellular microstructure such as changes caused by edema or necrosis [16]. Statistical models based on signal representations, such as diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI), can be applied to each voxel to obtain measures dependent on the normal distribution of water displacement, including: (1) fractional anisotropy (FA), reflecting the extent of diffusivity in a preferential direction such as along axonal fibers, (2), mean diffusivity (MD), the average diffusivity in all directions, and (3) radial diffusivity (RD), the diffusivity perpendicular to axonal fibers, or complementary measures such as (4) mean kurtosis (MK) and (5) radial kurtosis (RK) that indicate deviations from the normal displacement distribution.

Advanced biophysical models, such as neurite orientation dispersion and density imaging (NODDI) and white matter tract integrity (WMTI), represent the underlying tissue microstructure by separating each voxel into compartments with restricted and hindered diffusion of water molecules representing diffusion of water molecules within axons or in extra-cellular space [17, 18]. For example, the NODDI model estimates (1) neurite density index, representing density of axons and dendrites (collectively called neurites), (2) orientation dispersion index, which indicates if these neurites are tightly packed or spread out, and (3) proportion of cerebrospinal fluid (CSF) estimated as the free water fraction [18]. The WMTI model estimates measures such as: (1) axonal water fraction, related to axonal density, (2) intra-axonal diffusivity, capturing restricted diffusion within myelinated axons and (3) extra-axonal diffusivities, including hindered diffusion alongside the axon (typically higher than intra-axonal diffusivity) and perpendicular to the axon (typically lower than along the axon) [17].

Taken together, the above measures provide complementary and overlapping information and are sensitive to brain microstructural changes in myelination and axonal density, across the lifespan, from early brain development [19] to aging and neurodegenerative conditions [20, 21]. A comprehensive assessment using multiple microstructural metrics can reveal distinct patterns of findings that, when considered together, can help infer specific biological processes that underlie associations with the predictor of interest (e.g., [22]), such as experiencing a major lifetime discriminatory event.

Using complementary parameters from statistical models (DTI and DKI), and biophysical models (WMTI and NODDI), we investigated brain microstructural features associated with age across a wide age range and examined how experiencing at least one major discriminatory event compared to no experiences of major discrimination moderated age associations with DWI measures. Brain regions showing converging findings across multiple DWI models and measures robustly reflects moderation of age-related changes with a discrimination experience. We specifically examined microstructural features in two regions of interest: 1. The whole brain white matter, and 2. The hippocampus, given its previous associations suggesting vulnerability to both age and discrimination experiences. We hypothesized that experiencing at least one major discrimination event would be associated with steeper age-related associations in microstructural metrics within whole-brain white matter and the hippocampus, consistent with accelerated brain microstructural aging.

2 Materials and Methods

2.1 Study Overview

We used data from the Midlife in the United States (MIDUS) longitudinal study, which recruited baseline participants aged 25-74 years in 1995/96 and followed them at multiple timepoints. An

oversample of Black/African American participants from Milwaukee, Wisconsin was added during the second follow-up (MIDUS2; 2004-2009). MIDUS seeks to understand the interplay of sociodemographic, psychosocial, and neurobiological determinants of health and disease among aging adults. MIDUS data are publicly available for use by scientists around the world (https://midus.wisc.edu/). During the third follow-up of the MIDUS Core sample, multi-shell DWI data were acquired for the first time by the MIDUS Neuroscience Project (MIDUS3; 2017-2022). All participants travelled to Madison, Wisconsin and were scanned on the same MRI scanner. Only MIDUS3 data were used for the cross-sectional analyses reported in the present work. Approval was obtained from relevant institutional review boards. Participants were briefed on study procedures, screened for MRI compatibility, and provided informed consent prior to data collection.

2.2 Participant characteristics

Participants (n = 147) were between the ages of 48-95 (mean = 65.03, median = 64, SD = 9.35) years. There were 87 females (59%) and 40 Black, Indigenous, and People of Color (BIPOC, 27.2%) in the sample. Among the BIPOC group, most participants were Black (80%) with very few reporting other racial minorities (2 Native American /Alaska Native, 2 Asian American, and 4 Other). There were 64 participants with a college degree (43.5%), 45 with some college education (30.6%), and 38 with a high school education or less (25.9%).

2.3 Major Experiences of Discrimination assessment

The Major Experiences of Discrimination Scale was administered at MIDUS3 [23, 24]. The scale assesses major discriminatory experiences across multiple settings, including academics (discouraged from continuing education), employment (denied promotion), financial services (prevented from renting or buying a home), health care (denied or provided inferior medical care), and social hostility (hassled by the police). Table S1, Supplemental Digital Content,

http://links.lww.com/PSYMED/B161, presents the full list of 11 questions included in the scale. Participants responded to each item by providing the frequency (number of times) they experienced this type of discrimination over their lifetime, and the item responses were summed to create a total score. The scale has been validated and used widely in prior research [25–27]. In the current sample, scores ranged from 0 to 9, with a median of 0 and a mean score of 1.177. Participants were categorized into two groups: those who reported no major experiences of discrimination (no discrimination group; score = 0), and those who reported experiencing at least one major discriminatory event (major discrimination group; score ≥ 1). Table S2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/B161, presents sample characteristics stratified by major discrimination group status. Individuals identifying as BIPOC were significantly more likely to report having experienced major discrimination compared to White participants. No other group differences reached statistical significance. Within the segment of the sample (n = 64; 43.5%) that reported experiencing at least one major discriminatory event, the median score was 2 and the mean was 2.7. Individual responses to the major lifetime discrimination questions spanned several categories (17 hassled by the police, 17 fired, 13 participants reported being discouraged from higher education, 12 denied or provided inferior service, 9 denied a bank loan, 8 prevented from rent/buying a home, 5 denied or provided inferior medical care, 3 denied a scholarship and 2 prevented from remaining in a neighborhood). Available attributions for overall discrimination experience, not specific to major discrimination, were diverse in both BIPOC and White participants with some overlap. Table S3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/B161, presents attributions of overall discrimination experience stratified by race.

2.4 DWI data acquisition

A multi-shell spin-echo, echo-planar imaging sequence was used to collect DWI data on a 3 Tesla GE MR750 scanner with a Nova 32 channel head coil. Three shells of different diffusion-weighting

strengths were acquired at b-values of 500, 800 and 2000 s/mm^2 with 9, 18, and 36 directions, respectively. There were six reference scans without any diffusion encoding (b=0 s/mm^2). Other parameters included: repetition time/echo time (TR/TE) = 7000/91 ms; field of view (FOV) = 256 mm; 75 slices; voxel resolution = 2x2x2 mm^3.

2.5 DWI analysis

Figure S1 (Supplementary Digital Content 1, http://links.lww.com/PSYMED/B161) provides an overview of the multi-model analysis approach used in the study.

2.5.1 Pre-processing and estimation of brain microstructure metrics

The DESIGNER guidelines were used for preprocessing the data [28]. The preprocessing steps included the removal or mitigation of artifacts such as noise, Gibb's ringing, distortion because of eddy currents, and B1 and "Rician" bias correction using tools in FSL v6.0 [29], ANTS [30], and MRtrix3 [31]. Following weighted least-squares optimization for voxel-wise estimation of the diffusion kurtosis tensor and the diffusion tensor [32] in a joint estimation based on the Taylor series decomposition of the signal, image maps of the DKI and DTI metrics were generated. The WMTI model parameters were computed from the estimates of the kurtosis tensor. Gaussian smoothing of 2 voxels (full width half maximum of 4.7096) was uniformly used for DTI and NODDI maps. To address spatial variation in kurtosis estimates, spatially adaptive smoothing was applied to the DKI and WMTI measures [22] as follows. A mask was created using a threshold MK < 0.3 and was smoothed to effectively obtain a "weighting" map. Then each of the DKI and WMTI metric maps was smoothed and divided by the smoothed weighting mask resulting in smoothed metrics that downweigh the influence of the low-MK/noisy DKI estimates (also known in the literature as "black holes") [33–35]. This approach was used as a refinement to the typical solution of isotropic smoothing of the DKI metrics inspired by the T-

SPOON method [36] which aims to reduce the influence of misregistration errors in voxel-based analysis.

Additionally, the multi-tissue NODDI model [37] was fit to the DWI data to derive voxel-wise estimates of corresponding measures. The multi-tissue response functions used in estimating the NODDI parameters help account for the different tissue types (white matter, gray matter, and CSF) in mitigating biases in the derived measures [37]. Quality control was performed visually to ensure proper orientations of the images, brain masking, and to ensure the quality of the estimated parameter maps looks typical and appropriate without artifacts such as black holes. All parameter maps were warped to a study specific population template that was estimated using individual subject FA and MD maps from all the participants [38]. Parameter maps from all participants were grouped measure-wise and merged for statistical analyses.

2.5.2 Statistical analyses and visualization

Permutation analyses of linear models (PALM) examined differences in DWI microstructure metrics by major lifetime discrimination experience [39]. For primary analyses, models examined the moderating influence of discrimination group status (major lifetime discrimination group vs. no major lifetime discrimination group) on age-associated changes in microstructure (i.e., included a discrimination group × age interaction term) adjusting for sociodemographic covariates: sex (male, female), race (White, BIPOC), educational attainment level (high school or less, some college, college degree). The analyses were restricted to voxels in two regions of interest (ROIs) using the following approach: (1) White matter skeleton in the whole brain mask provided with FSL [40] was warped to the study population template space and binarized. Note that the skeleton was not applied within the TBSS framework [41] but was instead used purely as a voxel mask for the analyses. (2)

Bilateral hippocampal regions from the Harvard-Oxford subcortical atlas [42] were warped to the study population template space. Analyses were run using analytical tail acceleration and 500 permutations. Joint inference was carried out for each set of models (DTI, DKI, WMTI and NODDI) using non-parametric combination, along with simultaneous inference for each individual metric. Threshold-free cluster enhancement and family-wise error (FWE) correction for multiple comparisons were used to control for false positives at an □ < .05, and corresponding statistical brain maps were generated. The XTRACT HCP Probabilistic Tract Atlas from FSL was used to identify regions with significant findings.

To visualize significant associations between microstructure metrics and variables of interest, the mean value of each outcome metric was computed from all significant voxels within each ROI for each participant. These participant-level averages were then used as summary outcome measures for visualization. Corresponding linear models were run, and partial residuals were plotted for significant associations. Model coefficients presented in the results section are for descriptive purposes as these models utilize data extracted from voxels found significant after statistical testing. Influential outliers were defined as those exceeding a threshold of 5% of the F-distribution of Cook's distance and were removed. All results were consistent with and without outlier removal. Visualizations were carried out using R statistical software v4.4.0 [43]. To illustrate spatial convergence across models, conjunction maps were generated to visualize the overlap of significant age × discrimination group interaction effects across DTI, WMTI, and NODDI metrics.

3 Results

Major lifetime discrimination group status significantly moderated the associations between age and microstructural measures derived from DTI, WMTI, and NODDI, in both the whole-brain white matter skeleton and the hippocampus, after adjusting for the sociodemographic covariates (sex, race,

and educational attainment). No significant associations were observed for the DKI parameters. Unless otherwise specified, findings reported were consistent with and without inclusion of sociodemographic covariates in the models. Table S4, Supplemental Digital Content 1, http://links.lww.com/PSYMED/B161, summarizes the significant findings across the tested models. All significant models exhibited a sign/directionality consistent with an age-moderation effect suggestive of accelerated microstructural aging. None of the models with inverse contrasts were statistically significant. Note that counts or frequency of major lifetime discrimination experience was not significantly associated with age in this sample ($r = -.07$, $p = .40$; see Figure S3, Supplemental digital Content 1, http://links.lww.com/PSYMED/B161, but age was significantly associated with all white matter metrics reported below (see Table S5, Supplemental digital Content 1, http://links.lww.com/PSYMED/B161). Considerable overlap was observed in white matter voxels showing significant age × discrimination group interactions, as shown in the conjunction map across DTI, WMTI, and NODDI models (Figure S2, Supplemental digital Content 1, http://links.lww.com/PSYMED/B161).

3.1 Age-Discrimination interactions in whole-brain white matter: statistical models

Two statistical models were used to examine age-discrimination interactions in the whole-brain white matter skeleton: Diffusion Tensor Imaging (DTI) and Diffusion Kurtosis Imaging (DKI). For DTI, fractional anisotropy, mean diffusivity, and radial diffusivity were tested, and for DKI, mean kurtosis and radial kurtosis were assessed.

Individuals who reported experiencing at least one major discriminatory experience showed higher mean diffusivity values with greater age ($\beta = .00362$, $p < .001$, one outlier removed), compared to those with no such experiences. These associations were observed across widespread regions,

including the anterior and superior thalamic radiations, forceps minor, corticospinal tract, inferior fronto-occipital fasciculus, and acoustic and optic radiations (Figure 1A-B).

A similar pattern was observed for radial diffusivity ($\beta = .00428$, $p < .001$), with higher values associated with greater age in the anterior and superior thalamic radiations, forceps minor, corticospinal tract, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, dorsal cingulum subsection, and the acoustic radiation (Figure 1C-D).

No significant age-discrimination interactions were observed for DKI metrics.

3.2 Age-Discrimination interactions in whole-brain white matter: biophysical models

Two biophysical models were used to examine age-discrimination interactions in the whole-brain white matter skeleton: Neurite Orientation Dispersion and Density Imaging (NODDI) and White Matter Tract Integrity (WMTI). For NODDI, neurite density index, orientation dispersion index, and CSF fraction were tested. For WMTI, axonal water fraction, intra-axonal diffusivity, extra-axonal radial diffusivity, and extra-axonal tortuosity were assessed.

Individuals who reported at least one major discriminatory experience showed steeper associations between age and the NODDI metric CSF fraction ($\beta = .00215$, $p < .001$) compared to those with no experiences of discrimination. These associations were observed in widespread regions including the anterior and superior thalamic radiations, forceps major, corticospinal tract, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, arcuate fasciculus, optic radiation, and the vertical occipital fasciculus (Figure 2A-B).

A similar pattern was observed for the WMTI metric extra-axonal radial diffusivity ($\beta = .00348$, $p <$

.001, one outlier removed), with higher values associated with greater age in the anterior and superior thalamic radiations, forceps minor, corticospinal tract, dorsal cingulum subsection, and the acoustic and optic radiations (Figure 2C-D).

While the association with CSF fraction remained consistent, the association with extra-axonal radial diffusivity was not significant when sociodemographic covariates were dropped.

No significant age-discrimination interactions were observed for WMTI metrics related to axonal water fraction, intra-axonal diffusivity, or extra-axonal tortuosity. Similarly, no significant interactions were found for NODDI metrics related to neurite density or orientation dispersion. However, a trend-level effect was observed for neurite density (p = .089), which is further discussed below.

3.3 Age-Discrimination interactions in hippocampal microstructure

Analyses within the hippocampal region of interest (ROI), which included both left and right hippocampi, examined age-discrimination interactions using diffusion metrics derived from the statistical models (DTI, DKI) and biophysical models (NODDI, WMTI). For DTI, mean diffusivity, radial diffusivity, and fractional anisotropy were tested. For DKI, mean kurtosis and radial kurtosis were assessed. For NODDI, neurite density index, orientation dispersion index, and CSF fraction were tested. For WMTI, axonal water fraction, intra-axonal diffusivity, extra-axonal radial diffusivity, and extra-axonal tortuosity were assessed.

Older participants who had experienced major discrimination showed higher extra-axonal radial diffusivity in the right hippocampus (β = .00694, p < .001; Figure 3A-B), whereas no significant

association with age was found in participants without major discrimination experience.

No significant age-discrimination interactions were observed for other metrics in the hippocampal ROI.

4 Discussion

The present study tested the hypothesis that experiences of major lifetime discrimination moderate age-related differences in brain health, as indicated by DWI measures of whole brain white matter and hippocampal microstructure. Supporting this hypothesis, we found that individuals who reported major lifetime discrimination (having experienced at least one severe discriminatory event such as being denied a job, a promotion, or a loan due to discrimination) showed steeper relationships between age and microstructural health consistent with accelerated brain aging. These effects were observed across widespread regions of whole brain white matter as well as in the hippocampus. Older age is a powerful predictor of adverse brain microstructural changes. However, major lifetime discrimination experience amplified (exacerbated) relationships between age and complementary diffusion parameters from both statistical and biophysical diffusion models in white matter and the hippocampus.

A growing literature describes the adverse effects of discrimination, including accelerated biological aging and increased risk for dementia [7, 8, 44–46]. These studies suggest multiple mechanisms, such as higher cardiometabolic risk, increased inflammation and overall allostatic load, and epigenetic dysregulation, by which discrimination may accelerate biological aging. The present study adds to this literature by identifying microstructural differences, suggesting that discrimination experience may accelerate brain aging. We found that participants who experienced at least one major

discriminatory experience in their lifetime had greater values of mean and radial diffusivities with age across widespread white matter regions. These regions also showed greater values of CSF fraction and extra-axonal radial diffusivity. As shown by the conjunction analysis in the supplementary material, Supplemental digital Content 1, http://links.lww.com/PSYMED/B161, most findings across the DWI metrics were in consistent, overlapping regions, suggesting that with greater age, participants who reported experiencing one or more major discriminatory events had higher free water content in these white matter regions than was evident for participants of the same age who had not experienced any such events. Increased brain interstitial water can occur via multiple pathways, including higher cerebrovascular pathology [47], edema [48], neuroinflammation [49], or white matter fiber shrinkage [14, 50]. Future research should assess which of these pathways mediate the relationship between discrimination and accelerated brain aging.

In a few white matter tracts, such as portions of the forceps minor, significant voxels were overlapping for radial diffusivity and extra-axonal radial diffusivity, but not for the CSF fraction. Higher values of these radial diffusivity measures, one from DTI and the other a more biophysically informed measure from WMTI, indicates greater movement of water perpendicular to the axonal fibers, and is suggestive of demyelination [51, 52]. Additionally, participants who experienced major lifetime discrimination had higher values of extra-axonal radial diffusivity in the hippocampus, although no other measures were sensitive to this effect. Interpreting this finding as demyelination is challenging because WMTI measures are less reliable in regions like the hippocampus, which contains white matter bundles but is predominantly gray matter. This is due to water exchange between neurites and extracellular space as well as signal contributions from neuronal somas [53]. The hippocampus is also located adjacent to the temporal horn of the lateral ventricles, making it prone to CSF contamination, especially with age related atrophy. Nevertheless, biophysical models have shown promise in characterizing hippocampal microstructure [54–56]. Despite these caveats, this result

is noteworthy given the important role of the hippocampus in brain health in the context of aging and discrimination due to its role in learning and memory, sensitivity to stress and inflammation, and vulnerability to volume loss with age and neurodegenerative conditions such as Alzheimer's disease [57, 58].

The examination of multiple microstructural imaging models and measures of brain health offers unique opportunities to identify which biological processes may or may not be involved. For example, increased radial diffusivity from DTI is classically suggestive of demyelination. However, DTI is non-specific and sensitive to any change that increases perpendicular water motion, including increased extra-axonal space. Biophysical models allow us to test the demyelination/axonal loss hypothesis more directly. A primary mechanism of demyelination or axonal loss would be expected to alter the neurite density index from NODDI. However, we did not find strong evidence that major discrimination experience amplified age-related decline in neurite density (the association showed a trend, $p < .1$). Conversely, we found strong, significant effects in measures of the extra-axonal space, specifically the CSF fraction from NODDI and extra-axonal radial diffusivity from WMTI. This suggests that processes such as demyelination or axonal loss [59] could be relevant, but are unlikely to be the primary mechanism linking discrimination to brain health. Instead, our findings suggest that the radial diffusivity finding is driven by changes in the extra-axonal space, such as increased interstitial water, which could be related to neuroinflammation, edema, or impaired glymphatic clearance. Larger and/or longitudinal studies will be important to determine whether subtle neurite alterations contribute to discrimination-related brain changes, as would the collection of more direct imaging modalities such as myelin water imaging[60]. Similarly, major discrimination was not significantly associated with the DKI metrics, despite the significant age-linked associations with NODDI and WMTI metrics. One possible explanation is that NODDI and WMTI derive biologically relevant parameters such as neurite density, orientation dispersion and free water, by

compartmentalizing tissue environments within each voxel into intra- (restricted diffusion) and extra- (hindered diffusion) axonal spaces. Here, restricted diffusion spaces model thermal motion of water that is physically blocked by impermeable or semi-permeable barriers (e.g., axonal membranes), while hindered diffusion spaces model free water motion that is not confined but is slowed down due to obstacles in the environment (e.g., glial cells, convoluted geometry of extracellular spaces) [61]. DKI, in contrast, estimates signal deviations from Gaussian diffusion without explicitly modeling tissue compartments and provides markers of overall microstructural complexity [62]. The absence of DKI effects in our analysis suggests that discrimination-related differences are not generalized alterations in tissue complexity but may reflect more specific microstructural alterations (e.g., axonal or myelin alterations) that are more sensitively captured by biophysical models such as NODDI and WMTI.

The white matter tracts where we observed convergent findings also suggest potential impacts of major lifetime discrimination on cognition. The inferior fronto-occipital fasciculus has been linked to various cognitive functions, including perception, context-dependent cognitive control, embodied cognition, and social cognition[63, 64]. The forceps minor has also been associated with social cognition[65]. The anterior thalamic radiation is implicated in embodied cognition, processing speed, and set shifting[64, 66]. Taken together, these findings suggest that major discrimination may be associated with accelerated age-related cognitive decline. The MIDUS study is currently following this sample up for the 4th timepoint, and their longitudinal cognitive and imaging data will provide an opportunity to examine the import of these discrimination and age-related microstructural findings for cognitive decline.

Because the timing, context, and frequency of discriminatory experiences can vary greatly, adverse associations of discrimination with health outcomes may also vary by participant background [67]. For

example, although in a multi-ethnic sample discrimination was associated with higher risk for dementia [44], a study among only Black Americans did not find any associations with dementia risk [68], potentially because in that sample, those with higher discrimination experience had higher education and income, factors that are protective against cognitive impairment and dementia [69]. Alternatively, a study including only non-Hispanic Black people found that racial discrimination in major life domains was associated with smaller hippocampal volumes, and everyday racial discrimination was associated with faster accumulation of white matter hyperintensities, although discrimination by all causes taken together did not show these associations [9].

Sources and attributions of discrimination in the United States may vary by sociodemographic group and may differ for daily vs. major lifetime discrimination experiences. Prior studies suggest that White individuals often attribute daily discrimination to gender and age, whereas BIPOC individuals more commonly attribute it to race, along with age, gender, and sexuality[70, 71]. As noted earlier, some evidence suggests that both daily and lifetime racial discrimination may be particularly detrimental to brain health, but discrimination regardless of attribution might not show the same effect[9]. As described in the supplemental material, Supplemental digital Content 1, http://links.lww.com/PSYMED/B161, discrimination attributions (self-reported broadly for both daily and lifetime discrimination) were highly variable for both White and BIPOC groups in this sample.

Another consideration is that major lifetime experiences of being discouraged from higher education and/or denied a scholarship may directly impact educational attainment, and educational attainment was included as a covariate in our models. Indeed, a subset of our participants (~11%) reported being discouraged from pursuing higher education or denied scholarships. However, most of our findings were consistent with and without adjusting for covariates, and educational attainment was not a

significant predictor in any of the white matter models, suggesting that this overlap does not bias our findings. Education remains important for brain health (and overall health and longevity), and needs to be accounted for, especially given the heterogeneity in the sample. Finally, our focus on the presence of any major discriminatory experience, regardless of attribution, is intentional, given the limited number of participants with both imaging and discrimination data which precludes examining specific types or sources of discriminatory experience. Given the potential links between discrimination, educational attainment, and other covariates, we interpret adjusted estimates to be robust to potential confounding, but conditional on sociodemographic profile (i.e., holding covariates constant). Future work with larger samples should explore how sociodemographic factors may moderate the effects of discrimination on brain health and how intersectionality may be especially important.

Experiences of discrimination contribute significantly to generalized stress, and are associated with more chronic conditions, greater functional limitations, and faster epigenetic aging [8, 46, 72]. One plausible pathway linking these effects is inflammation. Discrimination is associated with higher systemic inflammation and, in turn, with faster memory decline among older adults [73]. Markers of systemic inflammation can activate proinflammatory signaling pathways in the brain and lead to accelerated brain aging [8, 74]. Additionally, discrimination experiences of any kind may lead to heightened vigilance and threat perception, as suggested by higher resting amygdala activity and higher amygdala connectivity with regions within the salience network [75]. Prior experiences of discrimination can also prime individuals to anticipate discriminatory behavior even when none exists [76]. Additionally, the presence of concurrent mental health challenges can exacerbate outcomes—for example, individuals who experienced both racial discrimination and depressive symptoms had lower total brain matter and white matter volumes than those who experienced neither [77].

Future research needs to better understand how discrimination combines with other stressful life experiences to affect accelerated brain aging. Discrimination is only one type of stressor that can adversely affect health, and prior research reveals that experiences of discrimination, like other stressors, are not randomly distributed: socially disadvantaged populations have higher levels of exposure. For example, a study of a probability sample of over 3,000 adults in Chicago found that Black/African Americans and US-born Hispanics had higher levels of three indicators of discrimination compared to White individuals, and also had higher levels of multiple other stressors (major life events [e,g., death of a loved one], financial stress, relationship stress, work stress and neighborhood stress); each additional domain of stress was associated with worse physical and mental health [78]. Another priority for future research is to identify how discrimination and other stressors combine, starting early in life, and accumulate over time to affect brain functioning and aging across the life course. The stress acceleration hypothesis indicates that, in response to threatening environments, the brain adapts by expediting neurodevelopment [79, 80]. For example, youth in socioeconomically deprived neighborhoods show reductions in cortical thickness and grey matter volume [81, 82]. Our current understanding is limited regarding how these processes evolve over the life course, and how and when we might optimally intervene to reverse or mitigate them.

A critical challenge for those experiencing major discrimination is that they often face inequities in resources, rest, and access to preventive care. Individuals from minoritized communities or with low socioeconomic status often have significant non-paid caregiving roles that lead to inadequate sleep and poorer sleep quality [83, 84]. Similarly, minoritized communities often experience differences in neighborhood quality due to historical segregation, and resulting neighborhood disadvantage has been shown to partially account for race differences in sleep [85]. Poorer sleep is, in turn, associated with a higher overall inflammatory profile [86, 87], and mediation analyses suggest that poorer global

sleep quality underlies the link between major discrimination experience and inflammation burden [66]. Inadequate sleep also leads to detrimental late life cognitive outcomes due to poorer clearance of brain metabolites caused by altered functioning of the glymphatic system, a sleep-dependent pathway for interstitial fluid drainage [88]. In this context, our finding of greater age-related increases in interstitial water content among individuals exposed to major discrimination is noteworthy. Elevated interstitial water, as indexed by higher free water or isotropic volume fraction metrics from diffusion imaging, has been interpreted as a marker of altered interstitial fluid dynamics and is increasingly linked to neuroinflammation, cellular atrophy, impaired glymphatic clearance, and neurodegeneration [47, 50, 89]. While we did not directly examine sleep or glymphatic function in this project, these pathways offer a compelling hypothesis for how psychosocial adversity may contribute to brain aging and warrant further longitudinal and multimodal investigation.

Despite the considerable burden on those facing discrimination, it is important to note that individuals may have some agency in ameliorating its impact, and some individuals may *grow* after encountering discriminatory events and become more resilient to life's adversities [90–92]. Building strong sources of social support [93], being part of religious or spiritual communities [94], engaging in active coping strategies such as values affirmation [95], and practicing meditation [96], may buffer against, at least some harmful effects of discrimination. These factors warrant future research in the context of brain microstructural changes in aging and potential resilience even in the face of adversity and discriminatory experiences.

Our study has several limitations that need to be considered. Firstly, our analyses are cross-sectional and do not permit causal inference. Secondly, consistent with existing literature such as in the Health and Retirement Study, there were few individuals with high levels of multiple major discriminatory experiences in our sample [74]. We therefore dichotomized discrimination experience into groups who

reported experiencing at least one major discriminatory event compared to those who had no major experiences of discrimination, and thus we cannot infer dose-dependent effects of discrimination on brain-health. Nevertheless, it is likely that the accelerated aging we observe in our sample may be considerably worse in a sample with higher levels of major discrimination across their lifetime. Thirdly, although diffusion measures from DTI, DKI, WMTI, and NODDI models have all been reported to be sensitive to age-related microstructural changes [20, 62, 97, 98], they differ in their interpretability [19]. Metrics derived from the statistical models (DTI and DKI) have been widely reported to be sensitive to changes due to normal aging and pathological changes, but as they can be influenced by multiple processes, they do not permit precise interpretation of the underlying biological changes [16, 99], whereas biophysical models of diffusion such as NODDI and WMTI using multiple compartments provide more interpretable information about neuronal tissue microstructure [100]. Therefore, the biophysical models do not supersede the statistical ones, rather they refine and validate the interpretation. Each of these approaches make assumptions that need to be considered, none of them offer a comprehensive picture or are unequivocally better than the others, and newer improved models continue to be developed [53, 101, 102]. Finally, we tested these diffusion models only in the whole-brain white matter skeleton and the left and right hippocampal regions, but not within the whole-brain grey matter. Future investigations of the association between discrimination and grey matter microstructure are warranted. Despite these limitations, the robust converging evidence we see from the DTI, NODDI, and WMTI diffusion MRI models, and lack of findings with DKI models, offers insights into the likely neurobiological pathways through which discrimination may be exerting adverse effects.

The next wave of MIDUS data collection in the same participants includes follow-up assessments of the measures included in this study as well as new measures of vascular imaging and both blood-based and positron emission tomography (PET) biomarkers for Alzheimer's disease pathology.

Similar data have been collected in the MIDUS Refresher cohort, which will further expand the study sample. The combined dataset will provide sufficient power to examine interactions between discrimination, sex, education, and race. In addition to investigating longitudinal changes in DWI metrics [103, 104], future investigations using these additional measures will clarify and help determine the mediating processes through which discrimination impacts brain health.

In summary, our findings suggest that experiencing at least one major discriminatory event is associated with accelerated brain microstructural aging. These data add to the accumulating evidence of the detrimental and widespread impacts of experiencing discrimination, ranging from the personal to the societal level. It is crucial to develop and disseminate effective tools and supportive interventions to reduce the impact of experiencing discrimination at the individual level. However, the burden of change should not solely rest on the individuals already coping with discrimination. Rather, given the high prevalence of discriminatory experiences, our findings underscore the need for policy interventions [95] to address and reduce discriminatory experiences that contribute to disparities in healthy and active aging, including brain health.

5 Author Contributions

AKN: writing – original draft, software, data curation, methodology, investigation, formal analysis, visualization. NA: writing – review and editing, software, data curation, methodology, investigation, visualization. AJF: writing – review and editing, investigation. LKG: writing – review and editing, data collection, data curation, project administration. SES: writing – review and editing, data collection, data curation. SRK: writing – review and editing, methodology. ALA: writing – review and editing, investigation. RJD: writing – review and editing, funding acquisition. DRW: writing – review and editing. CDR: writing – review and editing, funding acquisition. SMS: writing – review

and editing, investigation, funding acquisition, conceptualization, resources, supervision. All authors read and approved the final manuscript.

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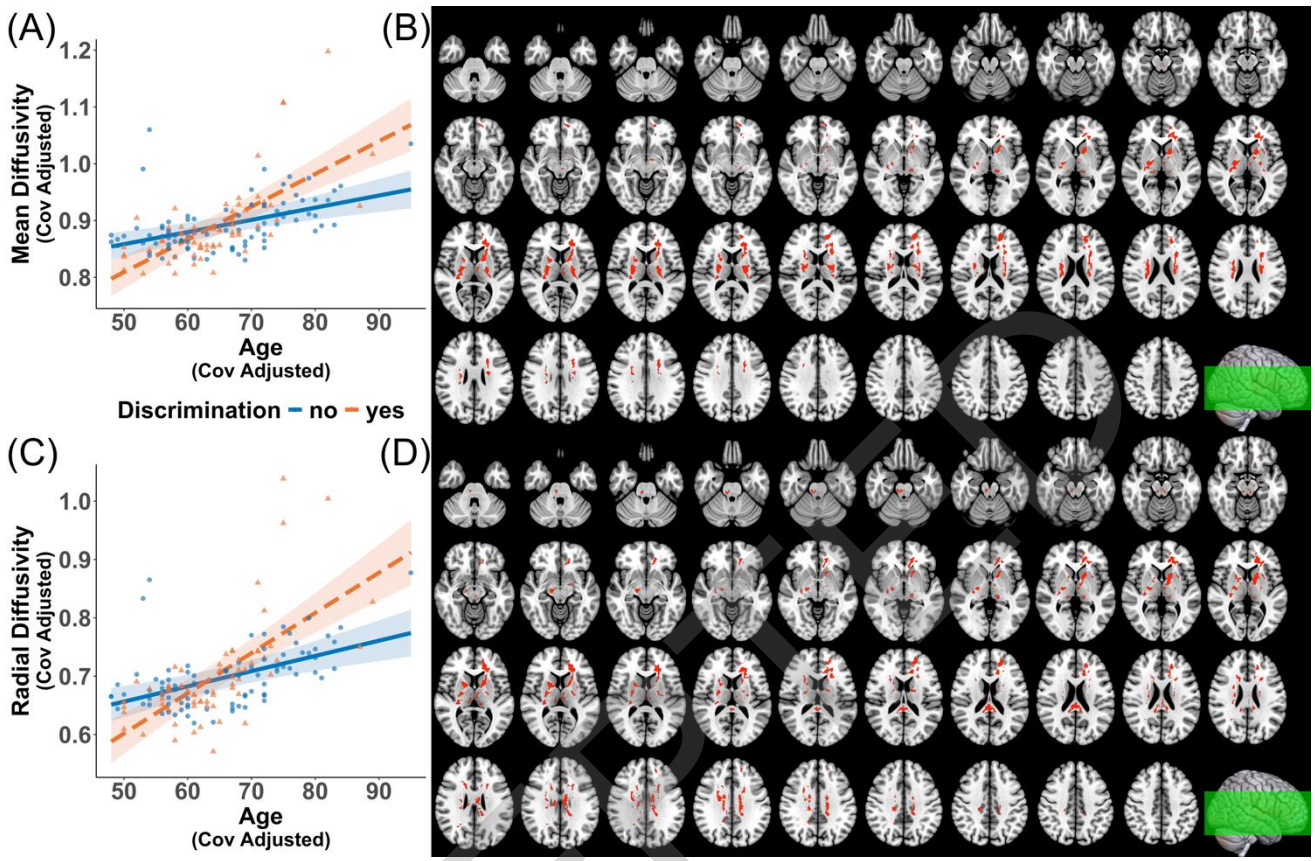

Figure 1: Associations between white matter diffusion tensor metrics and age by major lifetime discrimination group status. Scatter plots visualizing the moderating influence of major lifetime discrimination group status on the voxel-wise relationships between age and (A) mean diffusivity, and (C) radial diffusivity within the whole brain white matter mask. Data points are color coded and represented as triangles for those who experienced major discrimination, and circles for those who did not. Each data point represents the mean of all significant voxels for one individual, adjusted for sex, race, and educational attainment. Representative brain slices show voxels with significant relationships (at □ < .05, family-wise error corrected) for (B) mean diffusivity and (D) radial diffusivity. Brain images are in radiological convention (left hemisphere is shown on the right side).

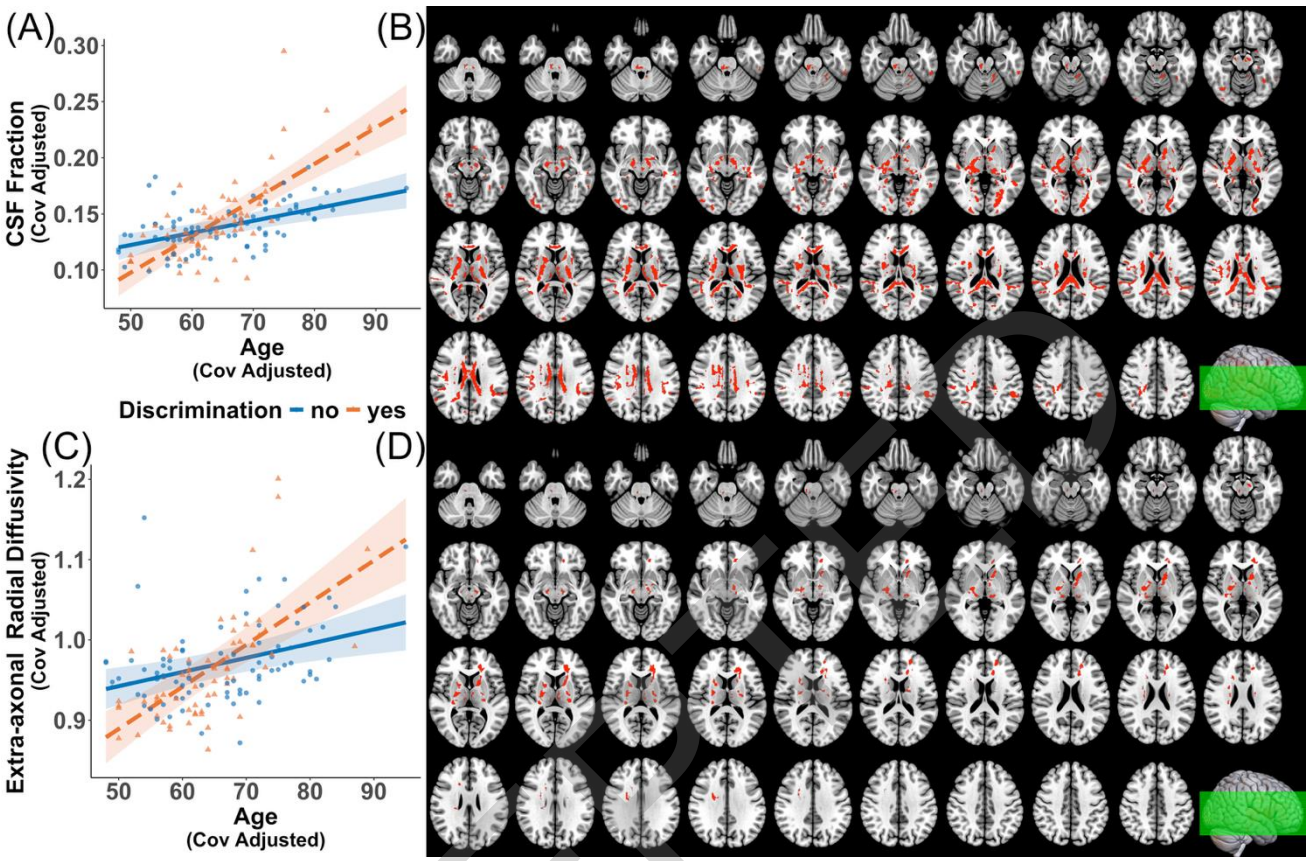

Figure 2: Associations of white matter microstructural metrics from biophysical models and age by major lifetime discrimination group status. Scatter plots visualizing the moderating influence of major lifetime discrimination group status on the voxel-wise relationships between age and (A) CSF fraction, and (C) extra-axonal radial diffusivity in the whole brain white matter mask. Data points are color coded and represented as triangles for those who experienced discrimination, and circles for those who did not. Each data point represents the mean of all significant voxels for one individual, adjusted for sex, race, and educational attainment after removing influential outliers, if any. There was one influential outlier for the model with extra-axonal radial diffusivity. Results were consistent with (β = .0046) and without the outlier (β = .0034). Representative brain slices show voxels with significant relationships (at □ < .05, family-wise error corrected) for (B) CSF fraction and (D) extra-axonal radial diffusivity. Brain images are shown in radiological convention (left hemisphere is shown on the right side).

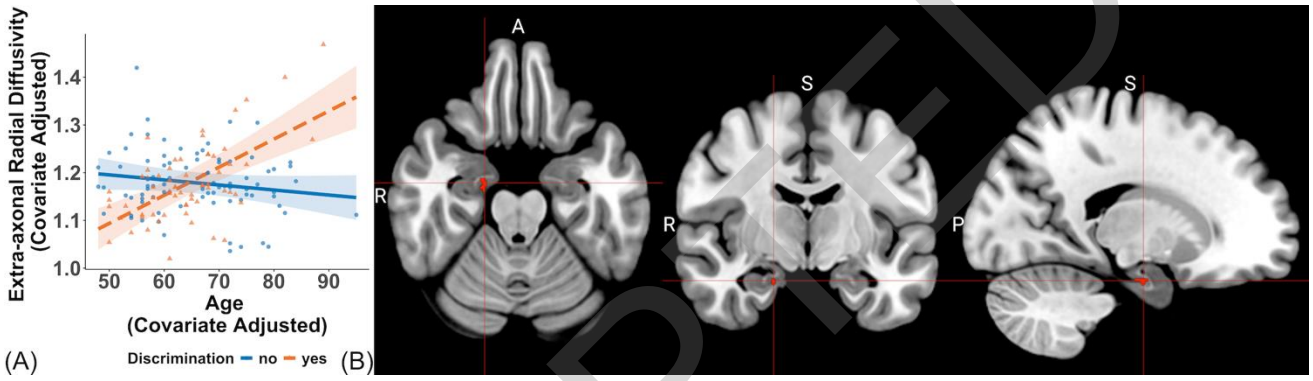

Figure 3: Associations of hippocampal microstructure metrics and age by major lifetime discrimination group status. (A) Scatter plot visualizing the moderating influence of major lifetime discrimination group status on the voxel-wise relationships between age and extra-axonal radial diffusivity in the bilateral hippocampal mask, adjusting for sex, race, and educational attainment. Data points are color coded and represented as triangles for those who experienced discrimination, and circles for those who did not. Each data point represents the mean of all significant voxels for one individual. (B) Representative brain slices show voxels with significant relationships (at □ < .05, family-wise error corrected).