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White matter microstructure in the young adult brain varies with neighborhood disadvantage in adolescence

Kristina L. Bell[a,*], **Juliann B. Purcell**[a,*], **Nathaniel G. Harnett**[a,1,2], **Adam M. Goodman**[a,3], **Sylvie Mrug**[a,4], **Mark A. Schuster**[b], **Marc N. Elliott**[c], **Susan Tortolero Emery**[d], **David C. Knight**[a]

[a]Department of Psychology, University of Alabama at Birmingham, Birmingham, Alabama, USA

[b]Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

[c]RAND, Santa Monica, California, USA

[d]School of Public Health, University of Texas Health Science Center at Houston (UTHealth), Houston, Texas, USA

Abstract

Neighborhood disadvantage and community violence are common in poor, urban communities and are risk factors for emotional dysfunction. Emotional processes are supported by neural circuitry that includes the prefrontal cortex, hippocampus, amygdala, and hypothalamus. These brain regions are connected by white matter pathways that include the cingulum bundle, uncinate fasciculus, stria terminalis, and fornix. Emotional function varies with the microstructure of these white matter pathways. However, it is not clear whether the microstructure of these pathways varies with risk factors for emotional dysfunction (e.g., neighborhood disadvantage and violence exposure). Therefore, determining the relationships between neighborhood disadvantage, violence exposure, and white matter microstructure may offer insight into the neural mechanisms by which adverse life experiences alter developing neural systems. The current study investigated the association that exposure to neighborhood disadvantage and violence have with the quantitative anisotropy (QA), a measure of the amount of directional water diffusion, of the cingulum bundle, uncinate fasciculus, stria terminalis, and fornix. Neighborhood disadvantage (M_{age}=11.20) and

Address Correspondence to: David C. Knight, PhD, knightdc@uab.edu, 1720 2nd Avenue S., Civitan International Research Center, 235H, Birmingham, Alabama 35233.

*Indicates co-first authorship

[1]Present Address: McLean Hospital, Division of Depression and Anxiety Disorders

[2]Present Address: Harvard Medical School, Department of Psychiatry

[3]Present Address: University of Alabama at Birmingham, Department of Neurology

[4]Present Address: Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, California, USA

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Data Statement

Participants in this study did not consent to the release of their data to a third party for reuse. Therefore, we are unable to publicly archive data due to the conditions of our ethics approval. Readers seeking access to the data should contact the corresponding author (David C. Knight). Data can and will only be released to named individuals who agree to collaborate with the principal investigators (i.e., through a formal collaboration agreement).

violence exposure (M_{W1age}=11.20; M_{W2age}=13.05; M_{W3age}=16.20; M_{W4age}=19.25) were assessed during adolescence and participants returned for magnetic resonance imaging as young adults (N=303; M_{age}=20.25, SD=1.55), during which diffusion weighted brain images were collected. The QA of the cingulum bundle, uncinate fasciculus, and stria terminalis/fornix varied negatively with neighborhood disadvantage such that the QA of these white matter tracts decreased as neighborhood disadvantage increased. Violence exposure was not related to QA in any tract (i.e., cingulum bundle, uncinate fasciculus, and stria terminalis/fornix) after correction for multiple comparisons. These results suggest that an adolescent's neighborhood may play an important role in the microstructure (i.e., QA) of white matter pathways that connect brain regions that support emotional function.

Keywords

diffusion weighted imaging; violence exposure; family income; adolescence

Introduction

Approximately 40.6 million people live in poverty in the United States and of these, 7.3 million are children (Smega et al., 2017). Living in disadvantaged, poverty-stricken neighborhoods can have a profound impact on a child's development, including his or her neural development (McLaughlin et al., 2013; Sheridan & McLaughlin, 2014). Neighborhood disadvantage and community violence exposure are common experiences in poor, urban areas (Benson et al., 2003; Friedson & Sharkey, 2015), and appear to affect neural development (Perkins & Graham-Bermann, 2012; Sheridan & McLaughlin, 2014). Atypical development of brain regions that control emotion processes can ultimately have a negative impact on mental health (Hill et al., 2005; McEwen & Gianaros, 2010; Ross & Mirowsky, 2001). The prefrontal cortex (PFC), hippocampus, amygdala, and hypothalamus control emotional function and are connected by large white matter pathways (i.e., cingulum bundle, uncinate fasciculus, stria terminalis, and fornix) that carry signals between these brain regions. Changes in the microstructure of these white matter pathways alter emotional function (Fields, 2008). Therefore, the impact neighborhood disadvantage and violence exposure have on emotional function may be mediated, in part, by changes in the microstructure of these white matter pathways. Determining the relationship neighborhood disadvantage and violence exposure have with the white matter that connects these brain regions may provide novel insights into neural processes that may explain the relationships neighborhood disadvantage and violence exposure have with emotional function.

Neighborhood disadvantage shows a robust association with the emotional development of children. Specifically, children raised in disadvantaged neighborhoods are more susceptible to internalizing (e.g., anxiety and depression) and externalizing (e.g., conduct problems) disorders (Goodnight et al., 2012; Hackman et al., 2012; Susman et al., 1997; Xue et al., 2005). Although little is known about the neural mechanisms through which neighborhood disadvantage affects the emotional development of children, prior work has linked the PFC, hippocampus, and amygdala to the internalizing symptoms that are associated with anxiety and depression (Burghy et al., 2012; MacMillan et al., 2003). Further, the hippocampus and

amygdala have been linked to externalizing behaviors that are often observed in conduct and other behavioral disorders (Davidson et al., 2000; Hanson et al., 2015; Hill et al., 2005). These findings suggest that the PFC, hippocampus, and amygdala play a fundamental role in emotion expression and regulation processes that are important for healthy emotional function.

Similar to neighborhood disadvantage, exposure to violence during adolescence affects emotional development. Violence exposure during childhood and adolescence increases stress levels, which, in turn, may alter brain development and lead to emotional dysfunction (Mead et al., 2010). Further, repeated exposure to violence increases stress, leading to the disproportionate use of neural pathways that underlie the stress response, which alters emotion expression and regulation processes (Perry & Pollard, 1998). Thus, elevated stress linked to violence exposure may lead to the disproportionate use of these white matter pathways, altering their microstructure and resulting in long term changes in emotional function. In fact, prior research has linked childhood experiences of parental verbal abuse to decreased white matter microstructure of the cingulum bundle and fornix, which connect brain regions that are associated with depression and anxiety (e.g., dorsomedial PFC, ventromedial PFC, hippocampus, and hypothalamus) (Choi et al., 2009).

The PFC, hippocampus, amygdala, and hypothalamus are connected by large white matter fibers (i.e., bundles of myelinated axons) that support communication between these brain regions. The anterior portion of the cingulum bundle connects medial regions of the PFC, including the dorsomedial PFC and ventromedial PFC (Bubb et al., 2018; Catani & Thiebaut de Schotten, 2008). In turn, the uncinate fasciculus extends from the ventromedial PFC to the anterior temporal lobe (Catani & Thiebaut de Schotten, 2008; Von Der Heide et al., 2013). Finally, the stria terminalis and fornix connect the amygdala and hippocampus to the hypothalamus (Catani & Thiebaut de Schotten, 2008; Kamali et al., 2015; Kwon et al., 2011; Mori et al., 2008). Reductions in the microstructure of the cingulum bundle, uncinate fasciculus, stria terminalis, and fornix have been linked to impaired emotional control (e.g., bipolar disorder, generalized anxiety disorder, major depressive disorder, and posttraumatic stress disorder) (Bae et al., 2006; Barysheva et al., 2013; Benedetti et al., 2011; Harnett et al., 2018; Harris et al., 2008; Korgaonkar et al., 2011; Lin et al., 2011; Phan et al., 2009). Further, reductions of stria terminalis and fornix microstructure have also been found among adolescents who engage in high risk behaviors (McQueeny et al., 2009). This prior work suggests that the microstructure of the white matter tracts that connect the PFC and limbic system plays an important role in emotional health.

Prior research has demonstrated that the brain matures in stages, with the most growth between 7 and 11 years of age (Epstein, 1986). However, white matter pathways continue to develop throughout childhood, adolescence, and young adulthood (Paus et al., 2001; Schmithorst et al., 2005). While the maturation of some white matter pathways (e.g., superior longitudinal fasciculus, inferior longitudinal fasciculus) is largely completed by adolescence, the white matter pathways that support emotion processes (e.g., cingulum bundle, uncinate fasciculus, stria terminalis, fornix) continue to develop into young adulthood (Asato et al., 2010; Steinberg, 2005). This longer developmental timeline may leave these white matter pathways and the brain regions they connect vulnerable to the

disruptive effects of neighborhood disadvantage and violence exposure during adolescence. Disadvantaged neighborhoods and exposure to violence may alter the development of the white matter that connects the PFC, hippocampus, amygdala, and hypothalamus during adolescence, thereby increasing the risk of emotional dysfunction.

The current study investigated the relationship between neighborhood disadvantage and violence exposure during adolescence and QA of the cingulum bundle, uncinate fasciculus, stria terminalis/fornix in young adulthood. We hypothesized that the QA of these white matter pathways would vary negatively with neighborhood disadvantage and violence exposure. Determining the relationship that neighborhood disadvantage and violence exposure have with the QA of the cingulum bundle, uncinate fasciculus, stria terminalis, and fornix will provide new insights into the impact adolescent experiences have on brain development.

Experimental Procedures

Participants

Three hundred and three right-handed young adults drawn from the Birmingham Metropolitan area (149 males, 154 females; 96 White American, 207 Black American; M_{age} = 20.25, SD ± 1.55) participated in this study. Prior to this study, all volunteers had participated as part of a larger local area cohort (N = 1,594), in the Healthy Passages study, a multi-site longitudinal study of adolescent health (Schuster et al., 2012; Windle et al., 2004). The original Healthy Passages study was approved by the Centers for disease Control and Prevention and the Institutional Review Boards at the original study sites. The current study was approved by the University of Alabama at Birmingham Institutional Review Board (IRB). Participants were initially recruited from 5th grade classrooms in local public schools and interviewed, along with their primary caregivers, at three time points (T1 Age: 11.20 ± 0.50, T2 Age: 13.04 ± 0.50, T3 Age: 16.20 ± 0.52, Mean ± SD). An additional T4 interview was conducted with the youth at the Birmingham site only (T4 Age: 19.25 ± 1.19 years) as part of the present study. Neuroimaging was completed shortly after T4 with approximately 22% of the initial Birmingham Healthy Passages cohort. Informed consent for the present study was obtained prior to both the T4 interview and neuroimaging session.

Given that only a fraction of the initial cohort completed neuroimaging (approximately 22% of the initial Healthy Passages cohort from the University of Alabama at Birmingham site), we assessed differences in key variables between participants who did versus did not complete the neuroimaging session. These two groups did not differ in sex [$\chi^2(1) = 0.04$, $p = 0.84$], exposure to violence [$t(1590) = 1.57$, $p = 0.12$], neighborhood disadvantage [$t(1586) = -1.68$, $p = 0.09$], or primary caregiver [$\chi^2(14) = 19.683$, $p = 0.140$]. However, a greater proportion of Black American participants completed neuroimaging [$\chi^2(1) = 12.20$, $p < 0.001$]. The biological parent was the primary caregiver for approximately 96% of the present sample. A grandparent, aunt, or uncle was the primary caregiver for an additional 3% of participants in the current sample. A further 1% identified the primary caregiver as either a stepmother (N=1), brother or sister (N=1), or friend (N=1). Two participants were missing data for this variable. None of the participants in the present analysis identified an adoptive or foster parent as a primary caregiver. Exclusionary criteria for this study included

left handedness, contraindications for magnetic resonance imaging (MRI), blood disorders (e.g., anemia), pregnancy, and a history of psychosis, seizures, or head injury.

Diffusion Weighted Imaging

Diffusion weighted images (DWI) were collected in sixty directions on 3 Tesla Siemens Allegra and Prisma scanners ($N_{Allegra}$=239, N_{Prisma}=64; TE=79 ms, TR=4600 ms, FOV=24 cm, b-value=1000s/mm^2, voxel dimensions= 2.5mm × 2.5 mm × 2.5mm). DSI Studio (November, 2016 build) (Yeh et al., 2013) was used to analyze diffusion data. DWI were eddy current and motion corrected prior to reconstruction into Montreal Neurologic Institute (MNI) standard space using Q-space diffeomorphic reconstruction (QSDR) (Yeh & Tseng, 2011). QSDR constructed spin distribution functions (SDF's) and quantitative anisotropy (QA) values were obtained for each major peak SDF (Yeh et al., 2013). QA is an index of the density of water diffusion in a fiber of a particular orientation (Yeh et al., 2010, 2013; Yeh & Tseng, 2011). QA was chosen to index white matter microstructure due to the reduced partial volume effects and the enhanced capability to resolve crossing fibers it provides (Yeh et al., 2013).

QA is similar to other common diffusion metrics (e.g., fractional anisotropy; FA) which provide information about the directional diffusion of water (i.e., anisotropy). The primary difference between QA and FA is the way the two metrics are computed. Specifically, isotropic diffusion is subtracted from the computation of QA by identifying two voxels as cerebrospinal fluid (CSF) and extracting the orientation distribution functions (ODFs) from these voxels (Yeh et al., 2010; DSI Studio documentation: http://dsi-studio.labsolver.org/Manual/Reconstruction#TOC-Step-T2b-1-:-Select-a-Reconstruction-Method). The ODFs from the two CSF voxels are then used in the calibration of QA (Yeh et al., 2010). This CSF calibration is automatically performed in DSI studio. Thus, QA is a measure of anisotropic diffusion only, rather than a combination of isotropic and anisotropic diffusion as indexed by other diffusion measures like FA. Relatedly, QA is scaled to spin density, rather than normalized from 0–1 in the way other diffusion metrics are normalized (Yeh et al., 2010, 2013; Yeh & Tseng, 2011). Therefore, values for QA can be larger than 1, with larger values indicating greater anisotropic diffusion. Because of these differences in computation (i.e., subtraction of isotropic diffusion and scaling to spin density), QA is more sensitive to individual differences in diffusion than other metrics (Yeh et al., 2016). Therefore, QA will often have more inter-subject variability than other metrics.

Deterministic fiber tracking was used to complete tractography of white matter bundles (Yeh et al., 2013). Fiber tracts were generated using seeds from the Johns Hopkins University (JHU) (Mori et al., 2008) and the Harvard-Oxford Cortical/Subcortical (HOCS) (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006) atlases, included in the DSI studio package. Custom regions of avoidance (e.g., partitions through the sagittal midline to separate the hemispheres) were created to further limit streamlines. Tracts of interest (i.e., the cingulum bundle, uncinate fasciculus, and stria terminalis/fornix), that connect brain regions that support emotion expression and regulation processes, were identified *a priori*. The stria terminalis and fornix were combined into one tract for the current analyses because the limited spatial resolution of the images acquired for this study

prevented accurate separation of these tracts. Each white matter tract was reconstructed (1500 streamlines/tract, turning angle 40 degrees, minimum length 30 mm, maximum length 300 mm, QA threshold=0.2, step size=1) resulting in 6 bilateral tracts. Due to variance in individual white matter structure, some participants' tracts did not reconstruct, thereby reducing the total number of subjects available for some analyses. The cingulum bundle could not be reconstructed for 3 participants, the uncinate fasciculus could not be reconstructed for 25 participants, and the stria terminalis/fornix could not be reconstructed for 60 participants.

Neighborhood Disadvantage

Neighborhood disadvantage was determined using residential addresses, which were acquired from participants' primary caregivers at the initial assessment in 2004 – 2006 (participants' mean age at the time of address collection=11.20, *SD*=0.50; Harnett et al., 2019; Windle et al., 2004). The addresses were geocoded and matched with information from block-level (~600–3000 residents) data from the 2000 United States census. A factor score was derived from a principal component analysis of the following block-level census variables, which loaded on a single dimension: percentage of households below the federal poverty level, percentage of single-parent families, percentage of adult residents without a high-school diploma, percentage of unemployed adults, percentage of non-Hispanic Black American residents, median household income, and percentage of owner-occupied housing units. The absolute value of loadings ranged from 0.71 to 0.93, with negative loadings for median household income and percentage of owner-occupied housing units and positive loadings for all other disadvantage indicators. The neighborhood disadvantage scores were standardized and higher scores indicated greater socioeconomic disadvantage.

Violence Exposure

Violence exposure was assessed longitudinally at four time points (ages 11.2 ± 0.5, 13.1 ± 0.5, 16.2 ± .5, and 19.3 ± 1.2; Harnett et al., 2019; Windle et al., 2004). At each time point, participants were asked how frequently they had witnessed violence within the past twelve months, including 1) threat of violence, 2) physical violence), and 3) threat of or physical violence involving a weapon. Participants were also asked how frequently they had been victimized by violence within the past twelve months, including 1) threat of violence, 2) physical violence), 3) threat of or violence involving a weapon, and 4) violent injury requiring medical treatment. Participants rated items for both victimization and witnessing on a four-point frequency scale ranging from 0 to 3 (0 = Never, 1 = 1 time, 2 = A few times, 3 = Many times). The responses were averaged separately for witnessing and victimization questions. Witnessing and victimization scales were then summed to obtain a combined (witnessing + victimization) violence exposure score at each time point. Finally, violence exposure scores were averaged across the four time points to obtain the measure of adolescent violence exposure used in the present study.

Family Income

Family income was reported by the primary caregivers at T1 and was transformed into a percentage of the federal poverty line (FPL) taking into account household size. Family

income for one participant was unavailable, who was excluded from analyses involving family income.

Data Analysis

Statistical analyses were completed using IBM SPSS Statistics 27 (IBM Corp., 2020). Bivariate correlations were examined to understand relationships among predictor variables and to assess multicollinearity. T-tests were completed to evaluate whether participants scanned on the Siemens Allegra vs Prisma systems differed on key study variables (i.e., neighborhood disadvantage, violence exposure, and family income). Additional t-tests were completed to explore whether male and female participants differed on key demographic variables or DWI measures. Repeated measures analyses of covariance (RM-ANCOVAs) were run to evaluate whether the relationship between neighborhood disadvantage and QA differed by hemisphere. RM-ANCOVAs were run for each tract with hemisphere as a within-subjects factor and neighborhood disadvantage as a covariate. There was not a significant interaction between hemisphere and neighborhood disadvantage [cingulum bundle: $F(1,298) = 0.007$, $p > 0.05$; uncinate fasciculus: $F(1,276) = 0.411$, $p > 0.05$; stria terminalis/fornix: $F(1,241) = 1.59$, $p > 0.05$]. Therefore, QA was averaged across each hemisphere (i.e., across the left and right tract) to produce three QA values, one for each tract of interest. These values were used in subsequent analyses. Analyses examining each tract separately can be found in Supplementary Tables S1–S3.

Primary analyses used linear regression models to predict QA of each white matter tract based on neighborhood disadvantage and violence exposure. Multiple comparison correction was accomplished using a Bonferroni correction for the three regressions performed in the primary analyses, resulting in a critical p-value of 0.017 (0.05/3 = 0.017). In light of a moderately strong correlation between T1 family income and neighborhood disadvantage ($r = -0.60$, $p < 0.001$), secondary analyses were conducted to better understand the relationship of QA with family income and neighborhood disadvantage. Secondary analyses consisted of two additional sets of linear regression models: one set included T1 family income, neighborhood disadvantage, and violence exposure, while the other set included T1 family income and violence exposure. Data were collected on two different MRI scanners. Therefore, a covariate for scanner type was included in all regression analyses. Secondary analyses were Bonferroni corrected for the number of regressions in each set (i.e., 3) resulting in a critical p-value of 0.017 (0.05/3 = 0.017). As described above (Neighborhood Disadvantage), higher values of neighborhood disadvantage indicate greater socioeconomic disadvantage. Sensitivity analyses were conducted to explore the impact of high neighborhood disadvantage. Participants with neighborhood disadvantage scores of 1.5 and higher (N=20) were excluded and primary analyses were run again. Additionally, Shapiro-Wilk tests revealed that QA values were not normally distributed across participants for any of the tracts of interest (range of Ws: 0.92 – 0.96, all ps < 0.05). Finally, primary analyses were also run with generalized fractional anisotropy (GFA) to explore differences between QA and GFA (Supplementary Table S4). These results and a brief discussion are provided in the supplementary materials.

Results

Descriptive Information

Neighborhood disadvantage was positively correlated with violence exposure ($r = 0.30$, $p < 0.001$) and negatively correlated with T1 family income ($r = -0.60$, $p < 0.001$). Violence exposure was also negatively correlated with T1 family income ($r = -0.33$, $p < 0.001$). Table 1 provides additional descriptive information about the neighborhood disadvantage, family income, and violence exposure of the present sample.

Participants scanned on the Allegra did not differ from those scanned on the Prisma in terms of neighborhood disadvantage [$t(301)=-1.04$; $p=0.30$] and family income [$t(288)=0.65$; $p=0.52$]. Differences were observed in violence exposure [$t(172.86)=2.73$; $p=0.01$], with participants scanned on the Allegra reporting greater exposure to violence ($M=0.92$; $SD=0.73$) than those scanned on the Prisma ($M=0.72$; $SD=0.42$). Male and female participants did not differ in neighborhood disadvantage [$t(301)=0.69$; $p=0.49$] or T1 family income [$t(288)=-0.53$; $p=0.60$]. However, male and female participants differed in violence exposure [$t(280.27)=-3.10$; $p=0.002$], with male participants reporting greater exposure to violence (M=0.999; SD=0.75) than female participants (M=0.760; SD=0.58). Additionally, male participants had greater QA than female participants in all white matter tracts examined (i.e., cingulum bundle, uncinate fasciculus, and stria terminalis/fornix), all ps<0.05.

Primary Analyses

Linear regressions predicting QA of the cingulum bundle ($F(4,295) = 25.71$, $p < 0.001$); uncinate fasciculus ($F(4,273) = 6.97$, $p < 0.001$); and stria terminalis/fornix ($F(4,238) = 8.42$, $p < 0.001$) were significant. Adolescent neighborhood disadvantage was a significant predictor of young adult QA in the cingulum bundle ($\beta = -0.14$, $p = 0.011$; Figure 1A), uncinate fasciculus ($\beta = -0.18$, $p = 0.006$; Figure 1B), and stria terminalis/fornix ($\beta = -0.16$, $p = 0.013$; Figure 1C). In all cases, greater neighborhood disadvantage was associated with lower QA. Violence exposure predicted QA of the cingulum bundle ($\beta = -0.11$, $p = 0.040$), however, this result was not significant after multiple comparison correction (critical p-value of 0.017). Violence exposure did not predict QA for the uncinate fasciculus or stria terminalis/fornix (both ps > 0.05; see Table 2). After excluding participants with higher levels of neighborhood disadvantage (i.e., participants with values 1.5 and greater, N=20), neighborhood disadvantage was no longer a significant predictor of QA in any tract after multiple comparison correction (all ps > 0.017).

Secondary Analyses

Regressions predicting QA of the cingulum bundle ($F(4,282) = 24.47$, $p < 0.001$), uncinate fasciculus ($F(4,261) = 6.44$, $p < 0.001$), and stria terminalis/fornix ($F(4,227) = 7.76$, $p < 0.001$) from T1 family income were significant (additional results are presented in Table 3). Family income in adolescence predicted young adult QA in the cingulum bundle ($\beta = 0.14$, $p = 0.010$) and stria terminalis/fornix ($\beta = 0.20$, $p = 0.003$). In each case, QA increased as family income increased. In contrast, T1 family income did not predict the QA of the uncinate fasciculus after correcting for multiple comparisons ($\beta = 0.14$, $p = 0.032$). The

relationship between violence exposure and QA did not meet multiple comparisons correction for any of the white matter tracts (all *p*s > 0.05).

In models where both neighborhood disadvantage and T1 family income were included, regressions significantly predicted QA of the cingulum bundle ($F(5,281) = 20.11$, $p < 0.001$), uncinate fasciculus ($F(5,260) = 5.45$, $p < 0.001$), and stria terminalis/fornix ($F(5,226) = 6.92$, $p < 0.001$). Although all models were significant, neither adolescent family income nor neighborhood disadvantage remained unique predictors of young adult QA within the cingulum bundle (neighborhood disadvantage: $\beta = -0.10$; family income: $\beta = 0.09$); uncinate fasciculus (neighborhood disadvantage: $\beta = -0.09$; family income: $\beta = 0.09$); or stria terminalis/fornix (neighborhood disadvantage: $\beta = -0.14$; family income: $\beta = 0.12$), all *p*s > 0.05 (Table 4).

Discussion

Adolescence is a pivotal period of neural development during which the white matter tracts that connect the PFC, hippocampus, amygdala, and hypothalamus continue to mature (Asato et al., 2010; Bava et al., 2010). These white matter tracts support important emotional processes (Zheng et al., 2018). In fact, prior research has demonstrated that the development of healthy emotional function parallels the maturation of these white matter pathways (Bolhuis et al., 2019; Nagy et al., 2004). Therefore, adverse environmental conditions during adolescence may disrupt the typical neurodevelopment of white matter in these areas, which may ultimately alter emotional function. The present study investigated the relationship that adolescent neighborhood disadvantage and violence exposure have with the QA of white matter pathways that are important for healthy emotional function (i.e., cingulum bundle, uncinate fasciculus, stria terminalis, and fornix). The present results demonstrate that greater neighborhood disadvantage during adolescence (i.e., assessed at age 11) is associated with reduced QA of the cingulum bundle, uncinate fasciculus, and stria terminalis/fornix in young adulthood (i.e., assessed at age 20). These findings suggest that the neighborhood environment in which children live may play an important role in the development of white matter pathways that are linked to emotion expression and regulation. However, neighborhood disadvantage was closely related to family income. Both neighborhood disadvantage and family income demonstrated similar relationships with QA, suggesting that these relationships apply to the broader socioeconomic context during development and adolescence – as experienced within the family and neighborhood.

The PFC, hippocampus, amygdala, and hypothalamus are important components of a neural circuit that supports emotion expression and regulation. These brain regions are connected by white matter pathways that include the cingulum bundle, uncinate fasciculus, stria terminalis, and fornix. Reduced microstructure within these white matter pathways has been previously linked to emotion dysregulation. Specifically, reduced microstructure of the cingulum bundle has been implicated in depression, anxiety, and posttraumatic stress disorder (Bubb et al., 2018; Davis et al., 1997; Harnett et al., 2018; Tröstl et al., 2011). Furthermore, decreased microstructure of the uncinate fasciculus has been implicated in social anxiety disorder and childhood major depressive disorder (Adluru et al., 2017; LeWinn et al., 2014; Tröstl et al., 2011). Similarly, reduced microstructure of the stria

terminalis/fornix appears to play an important role in depression (Korgaonkar et al., 2011). Therefore, disruption of the microstructure of these white matter pathways may impair neural communication between the PFC, hippocampus, amygdala, and hypothalamus, resulting in maladaptive emotion expression and regulation and ultimately long-term emotional dysfunction. The disruption of these pathways may help to explain the higher prevalence of psychiatric disorders in individuals growing up in economically disadvantaged contexts (Johnson et al., 2011; McLaughlin et al., 2011) Thus, the current findings have important implications regarding the neural impact of the larger socioeconomic environment in which a child is raised. Our findings suggest that growing up in disadvantaged families and neighborhoods may alter the development of white matter pathways that are important for the neural communication that supports emotional processes.

Prior work that has investigated the relationship between family income and white matter structure support the present findings. This prior research examined family income as an income-to-needs ratio and found that as family income decreased, microstructure of the cingulum bundle and uncinate fasciculus decreased (Dufford & Kim, 2017). However, family income is only one of many variables that factor into neighborhood disadvantage (Finch et al., 2010; Santiago et al., 2011). Therefore, the current study focused on a broader range of integrated environmental factors that comprise neighborhood disadvantage, rather than on family income alone. Our findings suggest that both family income and the neighborhood in which a child is raised (or factors associated with these socioeconomic indicators) may have a significant impact on white matter development. In fact, low family income and high neighborhood disadvantage constitute environmental deprivation, as conceptualized in McLaughlin and Sheridan's model of childhood adversity (McLaughlin et al., 2014; McLaughlin & Sheridan, 2016). According to this framework, childhood adversity that is characterized by significant deprivation (e.g., lack of caregiver support and impoverished environment) may negatively affect neurodevelopmental processes, such as synaptic pruning and myelination (McLaughlin et al., 2017). The present findings are consistent with the expected outcomes of deprivation. Specifically, we observed that as neighborhood disadvantage increased and family income decreased, the QA of the cingulum bundle, uncinate fasciculus, and stria terminalis/fornix decreased. The decreased QA of these white matter pathways may affect emotional function and may ultimately influence susceptibility to psychopathology.

In contrast to the findings with neighborhood disadvantage and family income, QA did not vary with violence exposure in any tract (i.e., cingulum bundle, uncinate fasciculus, and stria terminalis/fornix). Although previous research suggests that violence exposure may have deleterious effects on white matter tracts that include the cingulum bundle and fornix (Choi et al., 2009; Lu et al., 2013), we were not able to replicate these prior findings in the present study. Differences between the findings of the present study and prior work (Choi et al., 2009; Lu et al., 2013) may be due to differences in the conceptualization of violence exposure. Prior work examined the impact of childhood trauma (i.e., emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect; Choi et al., 2009; Lu et al., 2013), while the current study examined the impact of community-based violence exposure (i.e., threatened with or without a weapon, physical attacks, or witnessing others being threatened or physically attacked). Thus, these differences in the conceptualization of

violence exposure may account for inconsistencies between the present study and prior research.

Results of the present investigation should be interpreted with several considerations. First, the assessment of neighborhood disadvantage took place when participants were approximately 11 years of age, while neuroimaging was completed when participants were around 20 years of age. Thus, there was a relatively long period of time between the collection of neighborhood disadvantage and neuroimaging data. The larger study from which these data were drawn did not have resources to geocode addresses after T1 of data collection. Therefore, addresses were updated so participants could be contacted, but were not systematically maintained. Thus, we were unable to determine whether participants' exposure to neighborhood disadvantage changed across adolescence. Tracking the impact of neighborhood disadvantage across adolescence is an important area for future exploration. Longitudinal evaluation of neighborhood disadvantage would provide further information regarding how changing levels of neighborhood disadvantage might impact the development of white matter across time. Additionally, participants did not complete any cognitive assessments as part of the present investigation. Thus, we were unable to evaluate the relationship our findings have with cognitive ability. Further, the present study used an average QA value for each participant across each tract of interest, consistent the with procedures used in prior work (Acheson, Wijtenburg, Rowland, Bray, et al., 2014; Acheson, Wijtenburg, Rowland, Winkler, et al., 2014; Harnett et al., 2018; Squeglia et al., 2015). Thus, the full microstructural complexity of each tract was not examined. Although this does not directly limit the findings of the current work, a more complete characterization of the tracts examined in the present study may be a fruitful avenue for future investigation. Finally, results pertaining to the stria terminalis/fornix should be interpreted with caution. The parameters of the diffusion weighted imaging may not have had adequate resolution to accurately reconstruct very small tracts, such as the stria terminalis and fornix, due to crossing fibers and partial volume effects. Although prior work suggests that QA is better able to resolve crossing fibers and manage partial volume effects than other diffusion metrics, (Yeh et al., 2013), results for the stria terminalis/fornix should be interpreted with caution.

The present study found that neighborhood disadvantage and low family income in adolescence (i.e., assessed at age 11) varied with the QA of the cingulum bundle, uncinate fasciculus, and stria terminalis/fornix in young adulthood (i.e., assessed at age 20). These findings suggest that a developing child's socioeconomic context can have a meaningful impact on the QA of white matter tracts that are important for emotional function. Reductions in the QA of these white matter tracts could interfere with normal, healthy emotion processes. The disruption of healthy neural function may, in turn, interfere with neural maturation during key development stages, and ultimately lead to the dysfunction of important emotional processes during adulthood (e.g., mood and anxiety disorders).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Youth neighborhood impacts adult brain white matter quantitative anisotropy (QA)
- Neighborhood disadvantage linked with decreased QA of the cingulum bundle
- Neighborhood disadvantage linked with decreased QA of the uncinate fasciculus
- Neighborhood disadvantage linked with decreased QA of the stria terminalis/fornix
- Adolescent neighborhood impacts white matter linked to emotion expression/regulation

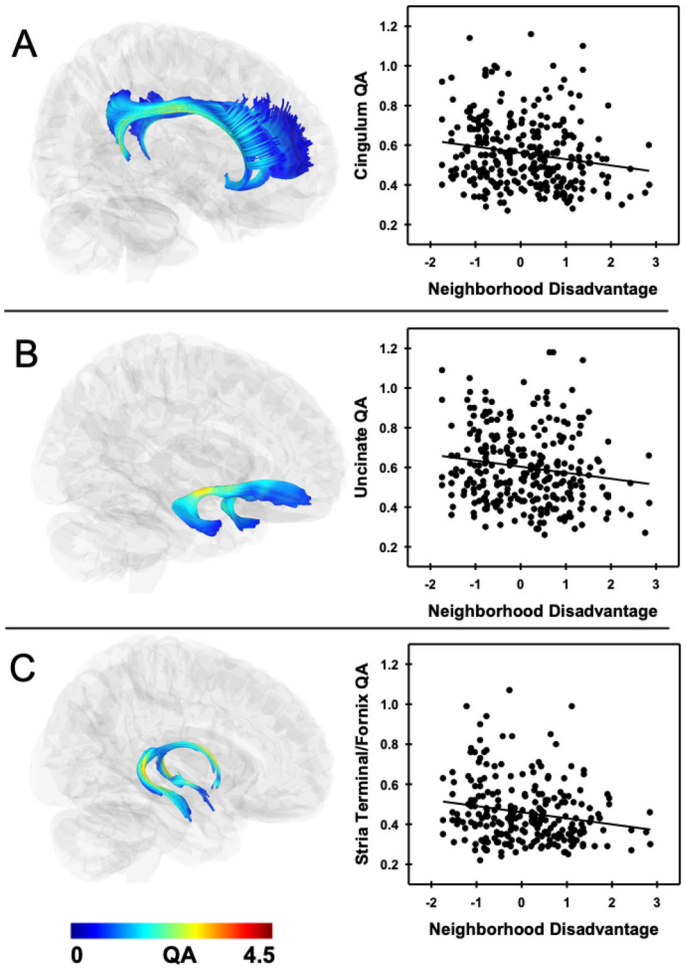

Figure 1.

Neighborhood disadvantage and quantitative anisotropy (QA) of the cingulum bundle (A), uncinate fasciculus (B), and stria terminalis/fornix (C). The graphs depict the relationship between the QA, averaged across each tract, and neighborhood disadvantage. QA decreased within each tract as neighborhood disadvantage increased.

Table 1.

Descriptive Information

	Mean	Std. Dev.	Range
Neighborhood disadvantage	0.08	0.96	−1.74 – 2.85
Violence exposure	0.88	0.68	0 – 3.81
T1 family income	259.93	273.50	0 – 1416.10

Note: Mean, standard deviation, and range for the present sample (N=303).

Values for neighborhood disadvantage represent a principal component score. The violence exposure scale had a total possible range of zero to six, where zero reflects no violence exposure over the four assessment time points and six reflects frequently experiencing all types of violence at all four time points. T1 family income was calculated as a percentage of the federal poverty line (FPL), thus 0 reflects income that was at or below the FPL, while 259.93 (sample mean) reflects an income that was approximately 260% above the federal poverty line.

Table 2.

Results of primary analysis regression models predicting QA

	F-statistic	*p*-value	β	t-value	*p*-value
Cingulum Bundle (QA)					
Overall Model	25.71	< 0.001*			
Neighborhood disadvantage			−0.135	−2.55	0.011*
Violence exposure			−0.111	−2.06	0.040
Uncinate Fasciculus (QA)					
Overall Model	8.42	< 0.001*			
Neighborhood disadvantage			−0.175	−2.77	0.006*
Violence exposure			−0.063	−0.972	0.332
Stria Terminalis/Fornix (QA)					
Overall Model	7.60	< 0.001*			
Neighborhood disadvantage			−0.160	−2.51	0.013*
Violence exposure			−0.061	−0.948	0.344

Note: Primary analysis results: linear regressions predicting quantitative anisotropy (QA) from neighborhood disadvantage and violence exposure. F-statistics indicate the significance of each overall model. Standardized beta values are presented. Cingulum bundle n = 300, Uncinate fasciculus n = 278, Stria terminalis/fornix n = 243. Statistically significant tests are indicated with an asterisk beside the significant *p*-value (critical *p*-value = 0.017).

Table 3.

Results of secondary analysis predicting QA from family income and violence exposure

	F-statistic	*p*-value	β	t-value	*p*-value
Cingulum Bundle (QA)					
Overall Model	24.47	< 0.001*			
Family income			0.142	2.59	0.010*
Violence exposure			−0.112	−2.00	0.046
Uncinate Fasciculus (QA)					
Overall Model	6.44	< 0.001*			
Family income			0.136	2.16	0.032
Violence exposure			−0.044	−0.686	0.493
Stria Terminalis/Fornix (QA)					
Overall Model	7.76	< 0.001*			
Family income			0.200	3.03	0.003*
Violence exposure			−0.046	−0.679	0.498

Note: Linear regressions predicting quantitative anisotropy (QA) from T1 family income and violence exposure. F-statistics indicating the significance of each overall model are reported. Standardized beta values are presented. Cingulum bundle n = 287, Uncinate fasciculus n = 266, Stria terminalis/fornix n = 232. Statistically significant tests are indicated with an asterisk beside the significant *p*-value (critical *p*-value = 0.017).

Table 4.

Results of secondary analysis predicting QA from family income, neighborhood disadvantage, and violence exposure

	F-statistic	*p*-value	β	t-value	*p*-value
Cingulum Bundle (QA)					
Overall Model	20.11	< 0.001*			
Family income			0.089	1.37	0.172
Neighborhood disadvantage			−0.097	−1.50	0.135
Violence exposure			−0.099	−1.75	0.081
Uncinate Fasciculus (QA)					
Overall Model	5.45	< 0.001*			
Family income			0.087	1.16	0.246
Neighborhood disadvantage			−0.089	−1.19	0.234
Violence exposure			−0.032	−0.492	0.623
Stria Terminalis/Fornix (QA)					
Overall Model	6.92	< 0.001*			
Family income			0.122	1.55	0.122
Neighborhood disadvantage			−0.139	−1.80	0.073
Violence exposure			−0.034	−0.495	0.621

Note: Linear regressions predicting quantitative anisotropy (QA) from T1 family income, neighborhood disadvantage, and violence exposure. F-statistics indicating the significance of each overall model are reported. Standardized beta values are presented. Cingulum bundle n = 281, Uncinate fasciculus n = 266, Stria terminalis/fornix n = 232. Statistically significant tests are indicated by an asterisk beside the significant *p*-value (critical *p*-value = 0.017).