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Concept Paper Form

Provisional Paper Title: Associations between Adverse Childhood Experiences (ACEs) and microstructural integrity of white matter in midlife
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Today's Date: 8/24/2020

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

Adverse childhood experiences (ACEs), including instances of abuse, neglect, and family disruption, have been consistently associated with lasting negative health outcomes, including an increased risk for psychopathology (Felitti et al., 1998; Green et al., 2010; Hughes et al., 2017; Schaefer et al., 2018). An interest in identifying mechanisms through which ACEs disrupt neurodevelopment and become "biologically embedded" has resulted in an extensive literature investigating associations between ACEs and measures of grey matter in the brain, including cortical thickness, cortical surface area, and grey matter volume (for reviews, see McLaughlin et al., 2019; Teicher et al., 2016). Fewer studies have investigated whether the neurodevelopmental effects of ACEs are reflected in the white matter of the brain. Results from these previous studies have been mixed and limited by heterogeneous designs, methods, and measures precluding characterization of the associations between childhood adversity and long-term differences in the structural integrity of white matter across the brain (for reviews, see Daniels et al., 2013; McCrory et al., 2011; Teicher & Samson, 2016). There are four key limitations of prior research, detailed next, which the current proposal seeks to address.

First, most studies have compared a group of individuals determined to have experienced some amount of childhood adversity against a group who have similarly been determined to be unexposed or exposed to a lesser degree. In many of these studies, the group of individuals exposed to ACEs is small, with many studies including consisting of less than 50 exposed individuals (e.g., Behen et al., 2009; Eluvathingal et al., 2006; Govindan et al., 2010; Govindan et al., 2010; Hanson et al., 2013; Huang et al., 2012; Jackowski et al., 2008; Korgaonkar et al., 2013, Kumar et al., 2014; Lim et al., 2019; Lu et al., 2013; Ugwu et al., 2014). With such small sample sizes, many studies are not adequately powered to conduct whole-brain analyses of white matter, and some therefore limit their analyses to a few regions of interest (ROIs) (e.g., Eluvathingal et al., 2006;

Jackowski et al., 2008; Korgaonkar et al., 2013; Kumar et al., 2014; Ugwu et al., 2014). A study by Gur et al. (2019) is a notable exception; over 1300 individuals were scanned (672 of which experienced at least one form of adversity), and associations between adversity exposure and white matter were investigated across the whole brain. However, the Gur et al. study only adds to the mixed results regarding the associations between child adversity and measures of white matter integrity; for example, the study found that greater exposure to childhood adversity is associated with higher fractional anisotropy (FA) values, which are generally interpreted as indicative of better white matter structural integrity, of the uncinate fasciculus, whereas several previous studies have reported lower FA in those with greater exposure (e.g., Eluvathingal et al., 2006; Govindan et al., 2010; Kumar et al., 2014), and still others have found no associations (e.g., Bick et al., 2015; Korgaonkar et al., 2013; Park et al., 2016).

Second, most studies of white matter and ACEs have focused on pre-adolescent or adolescent samples (McLaughlin et al., 2019; McCrory et al., 2011). There is evidence that white matter tracts develops in a curvilinear fashion across the lifespan; with FA increasing until adolescence, decreasing in adulthood, plateauing around midlife, and then further decreasing as aging continues. Therefore, the associations between ACEs and white matter in adolescence may not reflect long-term effects and be difficult to disentangle from normative development.

Third, a subset of published studies have examined only extreme or uncommon cases of childhood adversity, such as the severe deprivation experienced by institutionalized Romanian children in the Bucharest Early Intervention Project (e.g., Behen et al., 2009; Bick et al., 2015; Eluvathingal et al., 2006). Although such studies provide valuable insight into the extent to which environment can impact neurodevelopment, these findings are not generalizable to the vast majority of children who experience less extreme adversity. Additionally, several studies of the neural correlates of childhood adversity have examined single adverse events, such as witnessing domestic violence (Choi et al., 2012), or experiencing verbal abuse (Teicher et al., 2012). The findings from these studies, in which the effects of other forms of childhood adversity are statistically controlled, or in which the sample is comprised of individuals having only experienced the one form of adversity, are also not generalizable, as childhood adverse events are highly intercorrelated and seldom occur in isolation (Smith & Pollak, 2020).

Finally, a common limitation among previous studies is the reliance on retrospectively-reported measures of ACEs. There is increasing evidence that retrospective-reporting of ACEs differs from prospective-ascertainment of ACEs in mapping onto biological and psychological outcomes later in life (Danese et al., 2020; Reuben et al., 2016). Indeed, our recent work found that associations between ACEs and brain grey matter in midlife are largely driven by prospective measures of ACEs, and that retrospective measures likely underestimate these effects (Gehred et al., under review).

By investigating the associations between ACEs and white matter in a large, population-representative birth cohort followed for five decades, we hope to address these limitations in the current proposal. First, the Dunedin Study dataset consists of 854 Study members with high-quality diffusion MRI-based measures of white matter including FA. Thus, the proposed analyses are adequately powered to investigate associations between ACEs and whole-brain white matter and not just *a priori* ROIs. Examining these associations across 24 white matter tracts that provide whole-brain coverage allows us to determine whether ACE-related differences in FA are global or tract-specific. Second, by investigating these associations in midlife, the proposed study can help determine whether ACEs are associated with differences in white matter detectable decades after childhood when possible confounding by rapid developmental processes can be avoided. Third, the

ACEs measured in the Dunedin Study consist of relatively common forms of childhood adversity, and the distribution of ACEs resembles that of other large-scale studies (Reuben et al., 2016). Thus, findings from the proposed analyses will be more broadly generalizable. Finally, the proposed analyses will compare associations between midlife white matter and both prospectively-ascertained and retrospectively-reported ACEs to help further advance our understanding of how these different measurement strategies influence mapping of ACEs onto potential biological mechanisms.

Data analysis methods:

To better understand our data, we will first examine the bivariate associations between ACE scores, FA for 24 bilateral white matter tracts across the whole-brain, and covariates (perinatal health, age-3 brain health, and recent perceived stress; for more information about these variables, see "Variables needed at which ages" below).

Our primary analyses will consist of estimating OLS regression models to test associations between prospectively-ascertained ACEs and white matter microstructural integrity, in which FA measures for 24 bilateral white matter tracts will be mapped onto childhood adversity scores while controlling for sex. Each of these regression models will be re-estimated with the inclusion of perinatal complications, childhood neurocognitive health, and perceived adult stress as additional covariates.

While FA is sensitive to microstructural differences that impact tissue morphology, it lacks specificity regarding the source of these differences. Differences in FA could result from several processes, including dis- or de-myelination or axonal injury. Other DTI measures are required to distinguish between factors contributing to FA differences (Song et al., 2002). Therefore, in a secondary set of analyses, we will use axial diffusivity (AD) and radial diffusivity (RD) measures in an attempt to determine whether significant ACE-related differences in tract FA are driven by differences in axon or myelin morphology. Specifically, axial and radial diffusivity of each significantly-associated white matter tract will be mapped onto childhood adversity scores while controlling for sex.

Finally, although our primary analyses will be conducted using prospectively-ascertained ACE scores, retrospectively-reported ACE scores were also collected from Study members in adulthood. In a secondary analysis, reported in the supplement, we will investigate retrospectively-reported ACE associations with tract-specific measures of white matter microstructural integrity. We report these results for two reasons. First, providing the results of this analysis allows for consistency with our previous publication, in which we investigated the associations between both prospectively-ascertained and retrospectively-reported ACEs and grey matter measures of midlife structural brain integrity (Gehred et al., in review). Second, the results may help to characterize the differences between prospective and retrospective assessments, which has been of growing interest in the field.

We will correct for multiple comparisons across all tests performed using a false discovery rate (FDR) procedure (Benjamini & Hochberg, 1995).

Variables needed at which ages:

Primary Independent Variables

RetroACEs ACEs retrospective_1June2015

RetroACEs_trunc ACEs retrospective, 4 or more = 4, 1June 2015

ACEs, retrospective, as reported by Reuben et al. (2016). Score derived from the Family

Health History and Health Appraisal questionnaires, developed as part of the CDC-Kaiser ACE study (Felitti et al., 1998). These questionnaires were administered to the participants at age 38. ACE scores range from 1-10, with 1 point given for each type of adverse event experienced: physical abuse, emotional abuse, sexual abuse, physical neglect, emotional neglect, family member incarceration, household substance abuse, household mental illness, loss of parent, and household partner violence. Participants self-reported the adverse events remembered from their first 18 years of life.

RetroACEs_trunc is a truncated version of the scale, with ACE scores ranging from 1 to 4+. Those who experienced 4 or more ACEs were represented by the 4+ category to match the Center for Disease Control (CDC) categorizations of ACE exposure.

ProACEs Prospective ACEs scale

ProACEs_trunc Prospective ACES, 4 or more = 4, 20 April 2015

ACEs, prospective, as reported by Reuben et al. (2016). A composite score was created from data collected when the participants were children. These data include: social services visits, notes from structured interviews with the participants and their parents, observed interactions between participants and parents, self-reports collected from parents about parental criminality, notes from home visits, and notes from teachers asked about the children's performance. Data used to create the Prospective ACEs scores were collected during the study phases that occurred when participants were 3, 5, 7, 9, 11, 13 and 15 years old. The ProACEs Prospective ACEs scale runs from 1-10, with a point given for experience of each of the following: physical abuse, emotional abuse, sexual abuse, physical neglect, emotional neglect, family member incarceration, household substance abuse, household mental illness, loss of parent, and household partner violence.

ProACEs_trunc is a truncated version of the scale, with ACE scores ranging from 1 to 4+, with those who experienced more than 4 ACEs collected to form the 4+ group. This matches the way the CDC categorizes ACE exposure.

Primary Dependent Variables

DTI measures:

1. Fractional Anisotropy (FA) is a summary statistic of the primary parameters obtained from DTI-three eigenvalues that characterize the magnitude of the diffusivities parallel and perpendicular to the axonal fibers. FA represents the variance of the diffusion magnitude in these directions and represents microstructural integrity.
2. Radial Diffusivity (RD) is the average of the second and third eigenvalues derived from the diffusion tensor matrix of diffusion-weighted images, $(\lambda_2 + \lambda_3)/2$. RD characterizes water diffusivity in a direction perpendicular to the axonal fibers.
3. Axial Diffusivity (AD) is the first eigenvalue derived from diffusion tensor matrices of diffusion weighted images, λ_1, and characterizes water diffusivity in a direction parallel to the axonal fibers (Song et al., 2002).

I will use the above three DTI measures to characterize white matter microstructure. The primary analyses, investigating differences in microstructural integrity associated with ACE exposure, will be conducted with FA. Follow-up analyses investigating the factors contributing to significant ACE-related FA differences, will be conducted with RD and AD.

For each individual, I will obtain an average value of FA or each of 24 bilateral white matter tracts

derived from the Johns Hopkins University (JHU) white matter parcellation atlas (Mori et al., 2005). In addition to FA values, average values of RD and AD for each tract will be used in follow-up analyses. As our analysis is exploratory and we have no prior hypotheses regarding differences in white matter tract structure across the right and left hemispheres, R and L hemisphere tracts will be averaged, resulting in the following ROIs:

1. Genu of corpus callosum
2. Body of corpus callosum
3. Splenium of corpus callosum
4. Fornix (column and body of fornix)
5. Corticospinal tract
6. Medial lemniscus
7. Inferior cerebellar peduncle
8. Superior cerebellar peduncle
9. Cerebral peduncle
10. Anterior limb of internal capsule
11. Posterior limb of internal capsule
12. Retrolenticular part of internal capsule
13. Anterior corona radiata
14. Superior corona radiata
15. Posterior corona radiata
16. Posterior thalamic radiation
17. Sagittal stratum
18. External capsule
19. Cingulum (cingulate gyrus)
20. Cingulum (hippocampus)
21. Fornix/Stria terminalis
22. Superior longitudinal fasciculus
23. Superior fronto-occipital fasciculus
24. Uncinate Fasciculus ROI (custom for accuracy)

Covariates

The following covariates will be added into our regression models to test whether ACEs are associated with microstructural integrity of white matter in midlife, after developmental risks in the prenatal or infancy periods may have exerted effects:

1. Perinatal Complications: assessed from hospital records and coded as the sum of the number of prenatal, intrapartum, and neonatal complications experienced (Shalev et al., 2014).

2. Age 3 Brain Health: a composite measure of childhood neurocognitive health derived from a 45-minute examination that included assessments by a pediatric neurologist, standardized tests of cognitive function, receptive language, motor skills, and examiners' ratings of emotional and behavioral regulation. Scores across these five domains were combined to create an Age 3 Brain Health score (Caspi et al., 2016).

In addition, the Perceived Stress Scale will be used as a covariate in order to isolate the effects of ACEs from current or recent stressors.
3. Perceived Adult Stress (Cohen et al., 1983): self-report measuring the extent to which Study members feel stressed, unable to cope, and as if events occurring to them are uncontrollable and unexpected.

Significance of the Study (for theory, research methods or clinical practice):
Past research examining the associations between childhood adversity and brain white matter has typically been conducted in small samples consisting of children or adolescents with severe or uncommon profiles of adversity, or for whom adversity exposure was determined through the use of retrospective reports. The methodological limitations of these studies have resulted in mixed findings (McLaughlin et al., 2019). The Dunedin Study, a longitudinal birth cohort followed for five decades, provides the opportunity to investigate the associations between prospectively-ascertained exposure to adversity and differences in measures of whole-brain white matter detectable in midlife. Evidence that early life experiences are associated with white matter would provide evidence for the long-term embedding of early adversity and would have implications for future research investigating the mechanisms through which environmental exposures become biologically embedded. Finding that ACEs are related to widely-distributed rather than localized differences in white matter would implicate broad, nonspecific biological mechanisms. Alternatively, finding specific and not widely-distributed associations would suggest the presence of more targeted biological mechanisms. Evidence that ACEs are associated with indices of midlife brain health would also have clinical implications, as this would not only demonstrate the far-reaching impact of childhood adversity but also the possibility that differences in white matter may subsequently contribute to physical and mental health outcomes in late life.

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Data Security Agreement

Provisional Paper Title: Associations between Adverse Childhood Experiences (ACEs) and microstructural integrity of white matter in midlife
Proposing Author: Maria Gehred
Today's Date: 8/24/2020

☒	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
☒	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
☒	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
☒	I will not "sync" the data to a mobile device.
☒	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
☒	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
☒	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. Study participants have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Temi or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
☒	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. This data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: Maria Gehred