

**Concept Paper Form**

<b>Provisional Paper Title:</b> Midlife Structural Neural Correlates of Adverse Childhood Experiences
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<b>Today's Date:</b> 10/16/2019

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

**Objective of the study:**

Adverse childhood experiences (ACEs) are deleterious, as the stress associated with abuse, neglect, and trauma in childhood is understood to have lasting negative effects on physical and mental health (Felitti et al., 1998; Teicher et al., 2003; McCrory et al., 2011; McEwen, 2012; Moffitt & Klaus-Grawe 2012 Think Tank, 2013; Frodl & O'Keane, 2013; Hodel et al., 2015; Bick & Nelson, 2016; Nelson et al., 2019). Research on the effects of ACEs on long-term physical and mental health has resulted in a rise in policy initiatives focused on interventions targeting early life negative experiences and the widespread adoption of the Adverse Childhood Experience (ACE) model, developed by the Center for Disease Control (CDC). Reflecting this growing interest in early-life experiences, several studies have investigated whether neurodevelopmental effects of ACEs are reflected in the structural integrity of the adult brain (Rao et al, 2010; Edmiston et al., 2011; Sheridan et al., 2012; Hanson et al., 2015, Hodel et al., 2015; Bick & Nelson, 2016; Luby et al., 2019). However, there are several limitations among previous studies that we hope to address with our proposed project.

First, a subset of these studies examines extreme cases of childhood adversity, such as the severe deprivation experienced by institutionalized Romanian children in the Bucharest Early Intervention Project and the English and Romanian Adoptees Study (Zeanah et al., 2003; Mehta et al., 2009; Sheridan et al., 2012, Kumsta et al., 2015). 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 (thankfully) experience less extreme adversity. Additionally, there are few prospective studies investigating the

neural impact of adverse childhood experiences in adults; most do so in pre-adolescent or adolescent samples (e.g. Luby et al., 2019). As adolescent participants are only a few years removed from the ACEs being measured, these studies cannot examine long-term neural effects of ACE exposure. To address these limitations, I propose to utilize the longitudinal and richly phenotyped Dunedin Study dataset to examine associations between ACEs and multiple MRI-derived indices of structural brain integrity at age 45. The ACEs measured in the Dunedin study are relatively common forms of childhood adversity, and the distribution of ACEs in the Dunedin cohort resembles that of other large-scale studies (Reuben et al., 2016). Thus, any findings from the proposed study will be generalizable. Additionally, we will be able to capture the long-term effects of childhood experiences on structural brain integrity by utilizing MRI data collected at mid-life. Evidence that early life experiences are associated with indices of midlife brain health would not only demonstrate the far-reaching impact of childhood events, but would also raise the possibility that these neural correlates subsequently contribute to physical and mental health outcomes in late life as participants age.

Another common limitation among previous studies that the current study hopes to address is the use of retrospective ACE reports as a proxy for prospective reports (e.g. Rao et al, 2010; Edmiston et al., 2011; Sheridan et al., 2012; Hanson et al., 2015, Hodel et al., 2015; Bick & Nelson, 2016; Luby et al., 2019). There is increasing evidence that these measures differ in their ability to predict biological and psychological outcomes later in life (Reuben et al., 2016). Indeed, Baldwin et al. (2019) suggest that these measures identify largely different groups of individuals, which raises the concern that the mechanisms underlying the lasting negative effects on physical and mental health that are routinely observed in children exposed to ACEs may differ between individuals identified through prospective and retrospective reports. Therefore, a second objective of this study is to investigate the extent to which the neural effects of ACEs are captured by prospective versus retrospective ACE assessments. If either retrospective or prospective assessments were found to be more associated with structural brain integrity, studies utilizing the other would require cautious interpretation. It would be unwise to continue to treat prospective and retrospective assessments as proxies for the other, as one may underestimate the extent to which brain structure is affected by adverse childhood events.

### **Data analysis methods:**

A series of analyses will be conducted investigating associations between ACEs and brain structure in midlife:

1. Bivariate correlations of ACEs with each of the following global measures of brain structure: total brain volume, total cortical surface area, average cortical thickness, and total white matter hyperintensity volume. Each of these correlations will be conducted with prospective and retrospective reporting of ACEs, separately.
2. Modeling the contributions of prospectively and retrospectively measured ACEs to the above global measures using multivariate linear regression, in

order to investigate the relative contribution of each assessment type and to account for relevant covariates (see below for details).

3. As the global measures of average cortical thickness and cortical surface area can be driven by regionally-specific differences, we will conduct an exploratory parcel-wise analysis of the association between both prospective and retrospective ACEs and cortical thickness and surface area.
4. We will also follow up with an ROI analysis of subcortical volumes. Specifically, we will examine associations between prospective and retrospective ACEs and grey matter volume (GMV) of the hippocampus and amygdala, which may be especially sensitive to the effects of childhood maltreatment and adversity (Luby et al., 2019; Hanson et al., 2015).

### **Variables needed at which ages:**

#### *Primary Independent Variables*

RetroACEs ACEs retrospective

RetroACEs\_trunc ACEs retrospective, 4+ = 4

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

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*

img\_BV\_TOT45 total wholebrain intracranial volume

Total brain volume, as measured by grey and white matter and cerebrospinal fluid, in mm<sup>3</sup>. Collected at age 45 during the first imaging wave.

img\_SA\_TOT45 total cortical surface area

Total area of the cortical sheet, in mm<sup>2</sup>. Collected at age 45 during the first imaging wave.

img\_CT\_AVG45 average wholebrain cortical thickness

Average cortical thickness, across the whole brain, in mm. Collected at age 45 during the first imaging wave.

img\_WMHvol\_wholeBrain45 and img\_WMHvol\_whlBrain\_lg45

Total volume of white matter hyperintensities, in mm<sup>3</sup>. White matter hyperintensities are brain lesions, usually caused by issues resulting from changes in vasculature in the brain. It has been argued that these white matter hyperintensities could be considered a neural marker of brain frailty (Wardlaw, 2015). Collected at age 45 during the first imaging wave.

img\_WMHvol\_whlBrain\_lg45 is a natural log-transformed total volume of white matter hyperintensities.

CT, SA, and GMV values of cortical and subcortical parcels.

For parcel-wise analyses.

### *Covariates*

#### *Perinatal Complications*

Sum of the number of prenatal, intrapartum, and neonatal complications as assessed from hospital records. As there is evidence that perinatal complications result in increased biomarkers of aging at mid-life (Shalev et al., 2014), and complications related to pre-term births (included in the perinatal complication measure) are also related to grey matter alterations (Bauml et al., 2015; Meng et al., 2016), we will account for the impact of this factor by including it as a covariate.

#### *Age 3 Brain Health*

Global measure of childhood neurocognitive health and brain integrity. Assessed at 3 years with examiner ratings of child intelligence, language and motor skills, and neurological soft signs. As age 3 brain health has also been demonstrated to be a predictor of poor adult outcomes (Caspi et al., 2016, and is significantly positively correlated with average cortical thickness, total surface area, and total brain volume at age 45, this measure will be used as a covariate.

#### *Adult Stress*

Variable measuring stress experienced in adulthood, currently under development by Line Jee Hartmann Rasmussen and Kyle Bourassa. To be

used as a covariate in order to isolate the effects of ACEs from current or recent stressors.

**Significance of the Study (for theory, research methods or clinical practice):**

Past research examining the neural correlates of ACEs has typically been conducted in cross-sectional studies and with retrospective reports. The few longitudinal imaging studies with prospectively measured ACEs have been in samples of adolescents or young adults (Luby et al., 2019), as longitudinal studies with cohorts at midlife began before MRI was routinely available. The Dunedin study, a longitudinal study with both prospective and retrospective measurement of ACEs as well as imaging data in midlife, is poised to test both (a) potentially differential brain associations of prospective and retrospective assessments, and (b) whether previously reported associations in adolescents and young adults extend to the brain in midlife. Understanding associations between ACEs and midlife brain health is important because midlife brain health may be a major determinant of later life physical and mental health and, as such, represent a link between early adversity and later life well-being.

Comparing the midlife brain correlates of ACEs from prospective and retrospective measures has methodological and clinical implications. Many prior studies have used retrospective measurement of ACEs, assuming that retrospective reports provided similar information as prospective assessments. However, there is growing evidence that these measures differ in their ability to predict biological and psychological outcomes later in life, and that discrepancies between prospective and retrospective reports do not impact all outcome measures in the same way (Reuben et al., 2016). Therefore, it is important to test how brain outcomes are impacted by different assessment methods. This can inform interpretations of previous studies, as well as help in the design of future studies.

Finally, the brain health of individuals having experienced childhood adversity may be important in clinical practice, and clinicians will need to understand the extent to which the measure that they administer may reflect underlying brain health. For example, if prospective measures are more predictive of brain health in midlife, and clinicians have patients reporting adverse events through retrospective self-report, they may need take into account that such reporting may underestimate the extent to which the brain may be affected. For example, if prospective measures are more predictive of brain health in midlife, and clinicians have patients reporting adverse events through retrospective self-report, they may need take into account that such reporting may underestimate the extent to which the brain may be affected.

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## Data Security Agreement

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<b>Proposing Author:</b> Maria Gehred
<b>Today's Date:</b> 10/16/2019

<input checked="" type="checkbox"/>	I am current on Human Subjects Training (CITI ( <a href="http://www.citiprogram.org">www.citiprogram.org</a> ) or equivalent)
<input checked="" type="checkbox"/>	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
<input checked="" type="checkbox"/>	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.
<input checked="" type="checkbox"/>	I will not "sync" the data to a mobile device.
<input checked="" type="checkbox"/>	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
<input checked="" type="checkbox"/>	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
<input checked="" type="checkbox"/>	I will not post data online or submit the data file to a journal for them to post.  <i>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>
<input checked="" type="checkbox"/>	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**