DIFFERENTIAL IMPACT OF ADVERSE CHILDHOOD EXPERIENCES AND AGING ON BRAIN HEALTH

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Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
July, 2022

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CHILDHOOD EXPERIENCES AND AGING ON

BRAIN HEALTH

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ACKNOWLEDGEMENTS

It is a genuine pleasure to thank to an amazing woman, advocate, and academic role model, Dr. Misty Hawkins. Her dedication to me, my academic success, and my well-being made this work possible. By supporting our team and always having a positive attitude, my lab mates and I owe much of our accomplishments to her continuous encouragement.

I would also like to thank my dissertation committee members and grants team, Dr. Jennifer Bryd-Craven, Dr. Eileen Crimmins, Dr. Jason Defreitas, and Dr. Cindy Reese-Melancon, for their thoughtful comments and suggestions throughout all stages of the dissertation process, as well as their continuous support in my success. Additionally, this study would not have been possible without the generous funding from the National Institute on Aging, who sponsored this research, as well as the study participants who inspire me to continue this work.

Furthermore, this degree was achievable with the help of my family, friends, cohort, lab mates, and faculty members who believed in me and motivated me. Your patience, guidance, and understanding were invaluable, and I thank you for cheering me on the whole way.

Name: CINDY E. TSOTSOROS

Date of Degree: JULY, 2022

Title of Study: DIFFERENTIAL IMPACT OF ADVERSE CHILDHOOD EXPERIENCES AND AGING ON BRAIN HEALTH

Major Field: PSYCHOLOGY

Abstract: Adverse childhood experiences (ACEs) are events composed of several forms of abuse that children under the age of 18 are subjected to. These events include forms of physical or emotional abuse, neglect, and household dysfunction. Experiencing trauma as a child has been linked to a variety of negative psychical, emotional, and psychological outcomes. This research aims to explore how ACEs influence brain health later in life. Additionally, the purpose of this research is to link these traumatic events to a biological marker of brain health (brain-derived neurotrophic factor; BDNF) and neurocognitive performance across two age cohorts. The data for this project was collected cross-sectionally through survey, cognitive testing, and blood samples on 106 women between the age of 18-25 and 65-85 in the state of Oklahoma. Veinous blood draws were completed to collect serum for analysis of BDNF levels. The Automated Neuropsychological Assessment Metrics (ANAM) and National Institute of Health Toolbox Cognition Battery (NIH-Toolbox) were used to assess neurocognitive function. Independent sample *t*-tests on age and cognition suggest that age is linked to poorer cognitive performance, with the older adult cohort showing significantly lower scores than the emerging adult cohort. An independent *t*-test observing age and BDNF suggests that age did not affect BDNF levels. When examining differences in cognitive scores using significance and effect size, the overall sample found individuals in the higher ACE group had higher cognitive scores. The cognitive batteries have subtests that capture different areas of cognition. When looking at the subtests separately, it is suggested that ACEs may be an underlying factor that contributes to increases in some cognitive functions as an adaptive trait and negatively to other cognitive domains, also as an adaptive trait. This suggests that ACEs may be associated with adaptive cognitive performance under some circumstances while harmful in others.

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CHAPTER I

INTRODUCTION

Overview

Adverse childhood experiences (ACEs) may be causing individuals to have different neurological aging patterns than others, both cognitively and biologically. These preventable, early-life factors are repeatedly shown to predict negative biopsychosocial and neurocognitive health outcomes in adulthood (Anda et al., 2006; Merz & Noble, 2017; Shonkoff et al., 2012). An ACE is a trauma or adversity that a child experiences before the age of 18. These traumatic events can lead to outcomes as serious as alterations in brain structure and increased risk for major neurocognitive diseases as well as more mild effects, such as subclinical and/or relative deficits in cognitive function (Lemche, 2018; Nichols et al., 2019; Disability and Life Lost, 2018).

Cognitive function is commonly associated with memory, but it encompasses many mental functions, such as attention, thinking, understanding, learning, problem-solving, and decision making (Blazer et al., 2015). Early-life experiences are found to affect long-term

cognitive performance and play a role in old-age cognitive trajectories (Alley et al., 2007; Langa, 2018). Notably, the ACEs-cognitive burden relationship may not be unique to older adults and may even be found in younger populations. For example, higher ACE scores have recently been associated with lower scores in fluid cognition, executive control, and episodic memory in middle-aged and younger samples (Alley et al., 2007; Danese et al., 2017; Hawkins et al., 2020; Langa, 2018).

Such findings may not be surprising given that ACEs are purported to damage children's neural and brain structures as well as their neural function early in development, effects that often persist through adulthood (Felitti et al., 1998; Wegman & Stetler, 2009). One way these impairments are studied is through physiological indicators or mechanisms of brain health, such as neurotrophins. Neurotrophins are families of proteins essential for neuronal and glial function, including development, survival, and plasticity (Huang & Reichardt, 2001; Massague, 1990). Brain-derived neurotrophic factor (BDNF) is a specific neurotrophic marker of brain health and plasticity. Individuals who experience significant ACEs have exhibited lower levels of BDNF compared with their counterparts without trauma history (Danese & McEwen, 2012; Pietras & Goodman, 2013; Slopen et al., 2013).

Past research has linked BDNF to memory function with findings that decreased levels of BDNF have been associated with cognitive decline in aging individuals, especially memory loss. However, how levels of BDNF are impacted by the process of aging and traumatic experiences or how they relate to performance-based cognitive measures is not well understood. Although prospective cohort studies show that exposure to early-life adversity confers up to 4x increased odds of developing Alzheimer's Disease and Related Dementias (ADRD), the pathways by which ACEs exert neurocognitive injury or ultimate ADRD risks are unclear. Thus, examining ACEs, BDNF, and cognitive performance levels across different age cohorts would be an essential step in understanding the relative contributions of age versus early-life factors like ACEs on indicators of brain health. Such

a study is also warranted, given the plausible theory and associated mechanisms that have been identified linking ACEs to cognition and BDNF (summarized below).

Potential Theories and Mechanisms of ACEs-Cognition and ACEs-BDNF Relationships

Why might ACEs and early-life trauma impact cognitive function and/or associated BDNF levels? Potential theoretical mechanisms include the role of ACEs in stress responses, which may ultimately signal reduced opportunity to accrue reproductive potential that, in turn, hastens reproductive maturation (i.e., life history theory). Specifically, research on child sexual abuse (i.e., a specific type of ACE) has found that individuals who experience child sexual abuse are at higher risk for physical, emotional, psychological, and social well-being later in life (Molnar et al., 2001; Steel et al., 2004; Vigil et al., 2005). These individuals show traits consistent with being "fast strategists" using life history theory, such as earlier age at menarche and earlier age of first intercourse (Vigil et al., 2005). Fast strategies seek to maximize earlier reproductive opportunities given that the unstable, stressful environment may mean such opportunities are limited and survival is at risk. Unfortunately, this early reproductive maturation could come at a cost to brain development and cognitive maturation. Indeed, recent work suggests that fast life history strategists tend to be less 'neurologically mature' in terms of frontal functioning when compared to slow strategists (Wenner et al., 2013). Such neurological maturity may be compromised by the overactivation of stress pathways (e.g., hypothalamic-pituitary-adrenal axis) (Fernando et al., 2012) that have can have a negative impact on brain regions (e.g., hippocampal damage) (Avital et al., 2003; Frank et al., 2012; Schneider et al., 1998; Vyas et al., 2002). These research models give insight into the many ways early-life factors may play a role throughout the lifespan on brain and cognitive health.

Current Study

This study is a critical first step in determining how patterns of ACE-related cognitive deficits differ across the lifespan, leading to long-term neurocircuitry changes critical for neural health and

cognition, such as executive function. As indicated in the previous sections and the literature reviewed in extended literature review (Appendix A), ACEs have been linked to cognition and brain health and may be linked to the aging brain's cognition as well as neuroplasticity (e.g., BDNF). This study's goals were to advance the science of cognitive function and BDNF levels; in addition, it examined associations between ACEs and BDNF that are currently under-explored.

In doing so, the study attempted to address two critical steps in advancing the science of ACEs, neurocognition, and aging. The study is novel in that it tested how ACEs are related to neurocognitive performance and/or markers of brain health (e.g., BDNF) in younger vs. older persons. Doing so advances the science of whether ACEs are differentially related to cognitive function and/or brain-related indices of neural health/plasticity across the life stage. Such studies are particularly important given previous work exhibiting that BDNF is malleable. In targeting this biomarker, it might be possible to reverse ACEs-related neural and cognitive deficits, therefore, increasing neuroplasticity. For example, studies have shown levels of BDNF fluctuating from: sunlight exposure (Molendijk et al., 2012), time of day (Piccinni et al., 2008), menstruation cycle (Pluchino et al., 2009), exercise (Ferris et al., 2007), aromatherapy massages (Wu et al., 2014), meditation (Tolahunase et al., 2018), and body mass index (Shugart et al., 2009).

Such studies point to pathways for potential interventions to mitigate the negative health effects of reduced BDNF levels and cognitive function by potentially increasing BDNF. Malleable markers of brain health should certainly be examined in attempts to maximize healthy aging, especially among those at potential risk for poor outcomes (e.g., those with ACE history). Such results could clarify the cognitive profiles or brain substrates that could ultimately be more amenable to prevention or intervention to promote healthy aging.

In sum, negative early-life factors can exacerbate neurocognitive degeneration, and early-life factors significantly influence later-life cognition. Furthermore, higher ACE scores are linked to

many negative health outcomes, including an increased risk of dementia in late life. BDNF is a potential mechanism of ACE-related cognitive deficits or decline. This study anticipates advancing the science of how ACEs are differentially related to cognitive function and/or BDNF and how the patterns differ across life stages. It does so by testing the following aims and associated *a priori* hypotheses in a sample comprised of two cohorts of adult women (emerging adults versus older adults) with low or high ACE history.

Aim 1: To characterize and define cognitive performance across the two age cohorts – stratified by ACE exposure.

Hypothesis 1. The older, high ACE group will have the lowest cognitive scores, and the young, no ACE group will have the highest cognitive scores. The young, high ACE group will have the next highest scores, followed by the older, no ACE group.

Aim 2: To characterize and define BDNF levels across the two age cohorts – stratified by ACE exposure.

Hypothesis 2. The older, high ACE group will have the lowest BDNF levels, and the young, no ACE group will have the highest BDNF. The young, high ACE group will have the next highest BDNF levels, followed by the older, no ACE group.

Lower cognitive scores are associated with relatively poorer cognitive performance and higher levels of BDNF and are expected to be an indicator of better brain health. Given that age is the leading risk factor for cognitive decline and neurodegeneration (Klimova et al., 2017), we did expect that – without or without ACE history – the young cohort would have superior cognitive scores and higher BDNF levels than the older adult cohort.

CHAPTER II

METHOD

Participants

Participants ($N = 106$) were adult women (76.4% white, $M_{age} = 47.0 \pm 27.2$ years, $M_{BMI} = 28.5 \pm 8.1$ kg/m^2), from two age cohorts: emerging adults (aged 18-25 years; $N = 52$) and older adults (65-85 years; $N = 54$), who were enrolled in the ACEs and Aging Study. This study was funded by the National Institute of Aging (NIA; R36 AG072342; PI Tsotsoros). ACEs and Aging was funded to investigate the interrelationships between ACEs, cognitive function, and neurotrophic factors (primary focus) as well as inflammatory markers (secondary focus) in relation to age. Participants were community-based, recruited from Oklahoma State University and the surrounding areas (Payne County, Tulsa County, OK). Participants recruited from Oklahoma State University were recruited primarily from email blast and the SONA system data management platform, which is the university's online research data collection system. Those collected from the larger community were done via study advertisements (i.e., flyers, civic organizations, referrals).

Individuals interested in participating in the study were invited to complete a brief online screening questionnaire to assess eligibility. Eligibility criteria included the following: a) the ability to read and understand English written materials, b) willingness and informed consent to participate, c) no evidence of dementia (participants with MMSE scores of 25 or less were excluded), d) no significant medical or psychiatric comorbidities, and e) not currently pregnant, breastfeeding, or taking hormonal birth control. To ensure equivocal groups of participants without ACEs and those with high ACEs, individuals chosen for this study had an ACE score of 0 or ACE score of ≥ 3, respectively.

Assessments and Measures

Primary Measures

Assessment of Adverse Childhood Experiences (ACEs). ACEs were measured in the online screening prior to study enrollment using the self-report Adverse Childhood Experiences Survey (ACEs Survey; Felitti et al., 1998) from the Kaiser Permanente ACE Study to test 10 traumatic events occurring before the participants' eighteenth birthday. The 10 traumatic childhood events include abuse, neglect, domestic violence, parental separation/divorce, familial mental illness, substance use, and/or incarceration. These experiences were coded as "No" (0) or "Yes" (1), resulting in total scores ranging from 0-10. Higher scores represent a greater ACE history. All enrolled participants had either no ACEs (ACEs = 0) or high ACEs (ACEs ≥ 3). The ACE questionnaire is a reliable and valid screen for retrospective assessment of adverse childhood experiences and demonstrated good internal consistency in the present study ($\alpha = .84$).

Assessment of Cognitive Function. Participants completed the NIH Toolbox Cognition Battery for Fluid Cognition tests (NIHTBCB) and Automated Neuropsychological Assessment Metrics (ANAM-IV) to assess fluid performance-based cognitive function indices. The fluid cognitive function tests that were given from NIH Toolbox are as follows: the Dimensional

Change Card Sorting Test, the Flanker Inhibitory Control Test, the List Sorting Working Memory Test, the Pattern Comparison Processing Speed Test, and the Picture Sequence Memory Test. The NIH created the NIHTB-CB for participants aged 3 to 85 years, offering testing in multiple domains typically found in a neuropsychological battery test. Administered in under 30 minutes, participants completed the testing with a trained RA who conducted the assessment on a tablet. This battery was chosen because it is time-efficient, it tests cognitive abilities that are sensitive to aging and neurological disease, and results can be used for comparison across existing studies. All tests in the battery have been validated against gold standard instruments (Weintraub et al., 2013). The subscales generate uncorrected standard scores for each domain and a cognition fluid composite score for each participant. This standardized score metric (M = 100, SD = 15) compares the subject's performance to the national NIH Toolbox sample regardless of age or education. By using this unstandardized score, researchers can assess an individual's overall performance without controlling for demographic factors. While T-scores corrected for age and education are commonly used in clinical studies, it was necessary for this study—examining the effects of age—not to use age-adjusted scores to detect age effects on the standard cognitive performance. Higher standard scores indicate better performance, indicating superior cognitive function.

The ANAM-IV is a library of computer-based tests of cognitive domains including attention, concentration, reaction time, memory, processing speed, and decision-making. The subtests used in this study are Go No Go Performance Test and Stroop. Combined, these two subtests can be administered in 10 minutes. The scores generated from each subtest were Stoop Color Score, Stroop Word Score, Stroop Color-Word Score, Stroop Interference Score, Go/No-Go Hits, Go/No-Go Commissions, and Go/No-Go Omissions. Commission is defined as responding to nontarget stimuli, and omission is defined as failing to respond to target stimuli. Subsequently, for the Go/No-Go commissions score and the Go/No-Go omissions score, lower

scores indicate greater cognitive efficiency. Go/No-Go omissions scores were reverse coded in the corresponding figure for easier interpretation. For all other ANAM subtests, higher scores indicate better cognitive performance.

Assessment of Neurotrophic Factors and Blood Biomarkers. Serum BDNF was assessed in picograms per milliliter (pg/mL) from peripheral venous blood sample (see Procedure for brief blood collection protocol and Appendix B for complete detailed protocol). Although attempts to examine both pro and mature BDNF were made, only mature BDNF was analyzed due to errors in assay analyses for pro BDNF. Importantly, circulating BDNF originates from peripheral (Fujimura et al., 2002; Kerschensteiner et al., 1999; Nakahashi et al., 2000) and cerebral sources, as the blood brain barrier is permeable in both directions (Pan et al., 1998). Collecting BDNF from the central nervous system is more invasive. Therefore, since previous studies were able to correlates BDNF from the central nervous system with measures of BDNF from the periphery, most human studies rely on inferences about BDNF levels in the central nervous system from peripheral levels. Additionally, links between peripheral BDNF with brain levels have also been suggested by animal studies (Erickson et al., 2010; Hwang et al., 2015; Karege et al., 2002; Klein et al., 2011; Lang et al., 2007; Pillai et al., 2010; Sartorius et al., 2009). The kits used in this study to assay for BDNF were Biosensis # BEK2214 and were read on a Bio-Rad iMark plate reader. Though not a primary aim, inflammatory markers were also measured and assayed using the Pro-inflammatory Panel (IL-1B, IL-6, IFNg, and TNFa # K15D2D-1) and CRP # K151STD-2 using the MESO QuickPlex SQ 120 system. All reagents and instruments are from Mesoscale Discovery. All samples were run in duplicate according to the manufacturer's instructions. Blood samples were collected on all participants, but those below detection level have missing data. Below detectible ranges were found on iL-6 and Pro BDNF. Pro BDNF was below detection range for more than 50% of the sample, subsequently, pro BDNF was excluded from the analysis.

Other Variables. In addition to the primary study variables of ACEs, cognitive function, and BDNF, numerous other variables were used in screening and collected as key covariates and confounders (e.g., demographic factors).

Key Screening Measures

Mini Mental State Exam (MMSE). The MMSE is the most widely used cognitive screening measure, and the 30-point exam is used to measure thinking ability or cognitive impairment. Participants from the older adult cohort were screened using the MMSE (Folstein et al., 1975) in person prior to beginning computerized testing. The standard for normal cognition and no signs of dementia is a sum score between 23-30. The experimental session would have been terminated if a participant performed poorly on the measure (≤ 25). All enrolled participants meet the criterion on the MMSE. The younger adult cohort was not administered the MMSE.

Mania and Psychosis. Individuals were screened for mania and psychosis using seven questions from the 22-question Modified Mini Screen (MMS; Brandau et al., 2005) and seven questions from the 14-item Mood Disorder Questionnaire (MDQ; Hirschfeld et al, 2000). The Modified Mini Screen is a short form of the Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998). Combined, these measures were given to identify individuals who endorse symptoms of psychotic and mood disorders experiencing psychotic features. No individuals enrolled in the study endorsed "yes" on any questions.

Depression. Depressive symptoms were measured via self-report using the eight-item Patient Health Questionnaire (PHQ-8; Kroenke et al., 2009). The PHQ-8 is a valid, reliable measure for assessing the frequency of depressive symptoms, including loss of interest, feeling down, sleep disturbance, loss of energy, appetite changes, feeling like a failure, difficulty concentrating, and psychomotor agitation or retardation, over the past two weeks. Response options range from 0 (*Not at all*) to 3 (*Nearly every day*). The sum of responses generates a total

score, where higher scores reflect more severe depressive symptoms. The PHQ-8 demonstrated excellent internal consistency in the present study (α = .92).

Anxiety. Anxiety symptoms were assessed via self-report using the Generalized Anxiety Disorder Questionnaire (GAD-7; Spitzer et al., 2006). The GAD-7 is a valid measure for assessing the frequency of anxiety symptoms over the past two weeks, including nervousness/feeling on edge, frequent and uncontrollable worry, difficulty relaxing, restlessness, irritability, and fear of something awful happening. Response options range from 0 (*Not at all*) to 3 (*Nearly every day*). The sum of responses generates a total score. Higher scores reflect greater symptoms of anxiety. The GAD-7 has shown excellent reliability (α=0.92) (Spitzer et al, 2006) and in the present sample (α = .92).

Covariates and Confounders

Demographic Factors. Participants' age, race/ethnicity, education, history of medical illness, current medications, and race-ethnic discrimination experiences (Lewis et al., 2012)/historical trauma (Whitbeck et al., 2004) were assessed via self-report. Height and weight were taken at the assessment to compute BMI. BMI (kg/m^2) was measured using a TANITA bioelectrical impedance device (Model TBF 310GS; Tanita Corporation: Arlington Heights, IL, USA).

Race/ethnicity was collected as: African American, Black; American Indian, Alaska Native; Asian; Asian Indian; Caucasian, White; Hispanic/Latino/Spanish' Middle Eastern; Multiracial; Other Race/Ethnicity; or Pacific Islander and then coded as: white (0) or marginalized group (1) for analyses. Education was collected as: Less than 7^{th} grade; Junior High School (9^{th} grade); Partial High School (11^{th} grade); High School graduate; Partial college (at least 1 year)/Vocational training; Bachelor's degree; Master's degree; or Ph.D. or MD degree and then coded as: Less than high school diploma (0); High School diploma/GED (1); Some

college/Vocational training; Bachelor's degree; or Graduate or Professional degree (2) for *t*-test analyses.

Procedure

All participants completed an initial online self-report questionnaire prior to the study visit to ensure they met initial screening eligibility criteria. Participants were asked to fast for at least 8 hours prior to the study onset and completed the informed consent before beginning the study session. After consent, older adult participants were administered the MMSE to ensure they could cognitively consent and had no signs of cognitive impairment. All participants from the older adult group met the criteria for the study. Following the MMSE, details of the procedure were consistent among groups. All participants partook in one assessment and one blood draw at the single in-lab study session. The study session ranged from 45 minutes to 1 hour and 15 minutes. All study procedures were IRB-approved by Oklahoma State University Institutional Review Board and adhered to APA ethical guidelines, including the blood collection and analysis of blood specimens. A brief description of the blood collection protocol is described below. See Appendix B for complete and detailed blood collection protocol.

After consent and final checks for eligibility, blood pressure readings were taken twice by a trained research assistant for consented and eligible participants. Then, a trained and certified phlebotomist inserted a 23-gauge butterfly needle into the non-dominant forearm or top of the hand of the participant to obtain the venous blood sample. Two 7.5 mL tiger top tubes of whole blood were drawn into appropriate (non-glass) vacutainers. Vacutainers were placed in an upright position and left to clot at room temperature for one hour, then centrifuged for 10 minutes at 3300 rpm. After sample separation, serum was aliquoted into microcentrifuge tubes and stored at -80° C until transported to an external lab for analysis. Quality control standards were followed to ensure samples were properly maintained during storage and shipment. For example, the samples

were transported on dry ice to the Integrative Immunology Center at OU-Tulsa, where they were again stored at -80° C until analyzed using sandwich enzyme-linked immunosorbent assays (ELISAs). For BDNF, the Human BDNF ELISA Kit (U-Plex Human BDNF, MSD; Rockville, MD, USA) was used, the V-Plex Human Proinflammatory Panel (4-plex: IFN-gamma, IL-1beta, IL-6, TNF-alpha) was used for inflammatory analysis, as well as the V-Plex Human CRP Kit (MSD; Rockville, MD, USA).

After completing blood draw, participants completed approximately 30 minutes of cognitive testing. The first cognitive test administered was the selected instruments from ANAM, and then the NIH Toolbox Cognition Battery. All subjects were given the cognitive batteries in the same order. After completing cognitive tests, investigator collected body measurements (i.e., height, weight, and body fat %). The experimenter was available to discuss concerns and answer any questions the participants had.

Furthermore, the consent form contained contact information for the PI. When participants left the lab if they later had questions, they had the ability to contact the experimenter to have those concerns addressed. At the end of the session, older adult participants were compensated $50 for completing the in-lab study visit. Younger adult participants were either compensated $50 or SONA credit for completion of the in-lab study visit.

Data Analysis

Power Analysis

The goal of this study was to assess the feasibility of the cohort study design and to collect preliminary data for a future larger-scale prospective cohort study across the lifespan to determine the role of ACEs and aging on neurotrophic mechanisms of cognitive health. Given that this study is the first of its kind, no preliminary estimates of the *f* effect size (i.e., comparing four groups of high vs. low ACEs by emerging vs./ older adults on cognitive function or BDNF)

were available. This study was the first to generate an estimate of an *f* effect size for the fixed effect ANCOVA comparing emerging adults with low or high ACEs to older adults with low or high ACEs on cognitive performance and BDNF. In the absence of the exact preliminary estimates, available preliminary data from a study of middle-aged adults were used to inform the sample size for Aim 1 of the current study. Specifically, the pilot data from our team suggest that adult women with high ACEs (4+) have relatively poorer cognitive scores (an average cognitive z-score of -0.35) than individuals with low ACEs (0) (an average cognitive z-score of 0.33), with a standardized mean difference (*d*) of .68, which is a moderately large effect. If a similarly sized effect is assumed when comparing across other age groups (emerging, older adults), then a sample of size of 96 would be needed, using power of .80, alpha of .05, an *f* of .35 (moderately large), for a 4-group fixed effect two-way ANCOVA omnibus test.

Data Cleaning

Data are reported across the four study groups: low ACEs/young, high ACEs/young, low ACEs/older, high ACEs/older. The sampling design of having extreme groups in age (emerging vs. older adults) and extreme groups in ACEs (high, 3+ or low, 0) was chosen to maximize potential observed effects. Prior to analyses, all data were summarized using mean (SD) and were checked for outliers (z-score $\geq \pm 3.3$) and normality (skewness < 3, kurtosis < 10). Data were log-transformed as necessary to correct for non-normality. Outliers that impacted the normality of the data were corrected with transformation, and outliers that did not impact normality were retained. There were no missing scores in the survey data, so no scores were imputed.

Data Analyses

Descriptive statistics and bivariate correlations were first run for all key study variables. Preliminary analyses then compared primary variables (i.e., cognitive scores, mature BDNF) via independent samples *t*-test across 2) age groups (young/older), and b) ACE groups (low/high).

For **Aim 1**, a two-way Analysis of Covariance (ANCOVA) tested differences in levels of cognitive function scores across two independent variables, age (young/old) and ACE group (low/high), while controlling four continuous variables: BMI, education, PHQ8 scores, and GAD7 scores. For NIH-toolbox, a composite score, as well as each of the five cognitive subtests, were examined in separate ANCOVAs as the dependent variables, with an adjusted p-value using Bonferroni-correction for testing of multiple inter-related variables. For ANAM, all seven cognitive subtests were examined, looked at separately, and were tested according to the same adjustment for multiple testing. There is no standard composite score for ANAM. **Aim 2** was analyzed with the model inputs, using the neurotrophic indicator as the outcome. Specifically, a two-way ANCOVA was used to analyze the same age by ACE groups across different levels of mature BDNF.

CHAPTER III

RESULTS

Participants

Based on the *a priori* power analysis, the planned enrollment was $N = 100$. Of the 850 individuals who took the pre-screener survey, the first 106 eligible individuals participated in the study. Thus, the enrollment goal was exceeded with a final sample of $N = 106$. Blood draws were completed for all participants; however, iL-6 was not detected in 10 participants (9.4%). No participants were excluded for MMSE score, and no participants withdrew from the study.

On average, enrolled participants were white (76.4%), educated (71.7% Bachelor's degree or above), and spoke English as their first language (95.3%). Two age cohorts were represented, with the younger adult cohort in their late teens/early 20s (younger group $M_{age} = 19.8 \pm 2.0$ years) and the older adults in their early 70s (older group $M_{age} = 73.2 \pm 5.9$ years). Participants' average BMI was in the overweight range ($M_{BMI} = 28.51 \pm 8.1$ kg/m^2). The sample had almost half of the participants (47.20%) endorse no ACEs, and 52.80% endorsed high aces (3+). The older adult cohort had significantly higher education than the younger adults (older

adults 35.2% graduate or professional degree; younger adults 7.7%), but between ACE group, there were no significant differences among education due to attempts to match on education. Detailed characteristics of participants as well as participants within groups, descriptive statistics for variables, and bivariate correlations can be seen in Tables 1-3.

Preliminary Analyses

Preliminary analyses were conducted to observe group differences. Independent samples *t*-tests were run to observe differences in age cohorts and ACE groups for continuous variables of age, BMI, and primary outcome variables (i.e., mature BDNF and cognitive function scores). Chi-Square tests were run on categorical variables of race and education. Details of these analyses can be seen in Table 1, along with total combined sample means (SD) (young and old cohorts combined). Table 2 shows the characteristics of participants grouped by age cohort and ACE group. Independent samples *t*-tests were run to test for differences in ACEs across age groups. A correlation matrix of the combined total sample containing key study variables can be found in Table 3. Correlations for each age cohort separately are also available (see Appendix C).

Comparing Age Cohorts

Independent sample *t*-tests were conducted to compare cognitive scores and BDNF and biomarker data for the younger and older groups – without respect to ACEs. There were significant differences ($p < .001$) for all of the cognitive battery scores, such that individuals in the older age group performed lower overall on all the cognitive tests than the younger age group (see Table 1). These results suggest that older age is associated with lower cognitive test performance. There were also significant ($p < .001$) differences in three of the five biomarkers (i.e., IFN-γ, IL-6, and TNF-α) (see Table 1). However, mature BDNF was non-significant and did not achieve a small effect across the younger ($M = 31463.95$, $SD = 9915.25$) and older adults

Table 1

Characteristics of Participants

		Age Groups		ACE Groups	
	Total Sample (N = 106)	18-25 (n = 52)	65-85 (n = 54)	0 ACEs (n = 50)	3+ ACEs (n = 56)
Demographics					
Age	47.0 ± 27.2	19.8 ± 2.0	73.2 ± 5.9**	47.8 ± 28.4	46.3 ± 26.3
BMI	28.51 ± 8.1	26.2 ± 6.1	30.76±9.1**	26.92 ± 6.7	29.9 ± 8.9*
Race					
AA, Black	5 (4.7)	2 (3.8)	3 (5.6)	1 (2.0)	4 (7.1)
AI, AN	7 (6.6)	3 (5.8)	4 (7.4)	3 (6.0)	4 (7.1)
Asian	6 (5.7)	6 (11.5)	0	2 (4.0)	4 (7.1)
Asian Indian	1 (.9)	1 (1.9)	0	1 (2.0)	0
C, White	81 (76.4)	34 (65.4)	47 (87.0)	41 (82.0)	40 (71.4)
Hispanic, L. S	4 (3.8)	4 (7.7)	0	1 (2.0)	3 (5.4)
Middle Eastern	1 (0.9)	1 (1.9)	0	1 (2.0)	0
Multiracial	1 (0.9)	1 (1.9)	0	0	1 (1.8)
Highest Education Level					
High School Diploma/GED	30 (28.3)	23 (44.2)	7 (13.0)*	13 (26.0)	17 (30.4)
Some College	36 (34.0)	22 (42.3)	14 (25.9)	16 (32.0)	20 (35.7)
Bachelor's Degree	17 (16.0)	3 (5.8)	14 (25.9)*	11 (22.0)	6 (10.7)
Graduate/PD	23 (21.7)	4 (7.7)	19 (35.2)*	10 (20.0)	13 (23.2)
ACEs	2.59 ± 2.76	2.60 ± 2.79	2.59 ± 2.75	0	4.91 ± 1.71**
Cognitive Factors					
ANAM					
Stroop Color Score	50.29 ± 13.1	59.52 ± 8.8	41.41 ± 10.1**	49.24 ± 14.6	51.23 ± 11.7
Stroop Word Score	53.93 ± 13.2	63.31 ± 10.0	44.91±9.0**	53.56 ± 13.7	54.27 ± 12.9
Stroop Color-Word Score	38.09 ± 16.3	49.29 ± 12.7	27.30 ± 11.4**	36.64 ± 18.0	39.38 ± 14.6
Stroop Interference Score	12.15 ± 11.1	18.66 ± 9.3	5.88 ± 8.8**	11.11 ± 12.3	13.08 ± 9.8
Go/No-Go Hits	94.25 ± 2.9	95.13 ± 1.5	93.39±3.7**	94.28 ± 3.5	94.21 ± 2.5
Go/No-Go Commissions	5.01 ± 3.7	6.39 ± 3.9	3.69 ± 2.9**	4.68 ± 3.6	5.30 ± 3.7
Go/No-Go Omissions	1.61 ± 3.2	0.52 ± 0.9	2.67 ± 4.1**	1.74 ± 3.9	1.50 ± 2.2

NIH Toolbox					
Cognition Fluid Composite	100.16 ± 15.6	112.67 ± 8.5	87.89 ± 10.4**	100.67 ± 17.9	99.71 ± 13.6
Flanker	94.92 ± 7.9	100.29 ± 6.4	89.74±5.4**	95.76 ± 8.4	94.16 ± 7.5
List Sorting	99.79 ± 13.6	106.58 ± 8.7	92.96 ± 14.1**	97.00 ± 15.2	102.29 ± 1.6*
Card Sort	101.36 ± 9.9	107.73 ± 7.1	95.13±8.2**	101.26 ± 10.9	101.36 ± 9.1
Pattern Comparison	106.36 ± 21.6	123.92 ± 12.2	89.44 ± 13.6**	107.00 ± 22.7	105.79 ± 20.7
Picture Sequence	102.16 ± 15.6	111.37 ± 13.2	93.46 ± 11.2**	104.86 ± 16.4	99.91 ± 13.6*
Biomarkers					
Mature BDNF (pg/mL)	31994 ± 13489	31463 ± 9915	32505 ± 16289	31881 ± 12383	32095 ± 1939
IFN-g (pg/mL)	5.77 ± 4.72	4.51 ± 3.35	6.88±5.54**	5.62 ± 4.0	5.90 ± 5.28
IL-6 (pg/mL)	0.19 ± 4.25	0.63 ± 0.42	1.09 ±0.92**	0.89 ± 0.76	0.94 ± 0.77
TNF-a (pg/mL)	0.61 ± 5.04	2.25 ± 0.51	2.73 ±0.80**	2.39 ± 0.71	2.59 ± 0.70†
CRP (mg/L)	4.07 ± 2.79	2.87 ± 4.77	2.60 ± 3.30	2.70 ± 4.55	2.76 ± 3.62

Note. BMI = body mass index; AA = African American, AI = American Indian, AN = Alaska Native, C = White, L = Latino, S = Spanish; PD = Professional Degree; ACEs = Adverse childhood experiences; **p < .001, *$p < .05$, $^{\dagger}p \leq .10$.

Continuous variables represented with mean ± SD. Categorical variables represented with N (%).

Table 2

Characteristics of Participants Grouped by Age Cohort and ACEs Score

	Younger Females		d =	Older Females		d =
	0 ACE (n = 25)	3+ ACE (n = 27)		0 ACE (n = 25)	3+ ACE (n =29)	
Demographics						
Age	20.0 ± 2.1	19.6 ± 2.0	.20	75.6 ± 5.6	71.2 ± 5.3*	.80
BMI	24.3 ± 4.4	27.9 ± 6.9*	-.61	29.5 ± 7.6	31.8 ± 10.2	-.25
Race						
AA, Black	1 (4.0)	1 (3.7)		0	3 (10.3)	
AI, AN	1 (4.0)	2 (7.4)		2 (8.0)	2 (6.9)	
Asian	2 (8.0)	4 (14.8)		0	0	
Asian Indian	1 (4.0)	0		0	0	
C, White	18 (72.0)	16 (59.3)		23 (92.0)	24 (82.8)	
Hispanic, L, S	1 (4.0)	0		0	0	
ME	1 (4.0)	0		0	0	
Multiracial	0	1 (3.7)		0	0	
Highest Education						
HS Diploma /GED	8 (32.0)	15 (55.6)		5 (20.0)	2 (6.9)	
Some College	11 (44.0)	11 (40.7)		5 (20.0)	9 (31.0)	
Bachelor's	3 (12.0)	0		8 (32.0)	6 (20.7)	
Graduate/PD	3 (12.0)	1 (3.7)		7 (28.0)	12 (41.4)	
ACEs	0	5.00±1.66*		0	4.83 ± 1.77*	
Cognitive Factors						
ANAM						
Stroop Color Score	58.44 ± 9.3	60.52 ± 8.3	-.24	40.04 ± 13.1	42.59 ± 6.5	-.25
Stroop Word Score	61.76±11.1	64.74 ± 8.7	-.30	45.36 ± 10.9	44.52 ± 7.1	.09
Stroop Color-Word Score	48.36 ± 14.6	50.15 ± 10.7	-.14	24.92 ± 12.8	29.34 ± 9.7†	-.39
Stroop Interference Score	18.41 ± 10.6	18.89 ± 8.1	-.05	3.81 ± 9.37	7.66 ± 8.1*	-.44
Go/No-Go Hits	94.96 ± 2.0	95.29 ± 1.0	-.22	93.16 ± 5.4	93.21 ± 2.9	-.01
Go/No-Go Commissions	5.92 ± 4.1	6.81 ± 3.7	-.23	3.44 ± 2.6	3.90 ± 3.2	-.16
Go/No-Go Omissions	0.64 ± 1.15	0.41 ± 0.7	.24	2.84 ±5.4	.52 ± 2.6	.08

NIH Toolbox						
Cognition Fluid Composite	114.52 ± 9.4	110.96 ± 7.4†	.42	86.25 ± 12.2	89.24 ± 8.7	-.29
Flanker	101.08 ± 7.1	99.56 ± 5.8	.24	90.44 ± 5.8	89.14 ± 5.0	.24
List Sorting	106.60 ± 7.0	107.15 ± 10.2	-.06	87.40 ± 15.2	97.76 ± 11.3*	-.78
Card Sort	108.48 ± 7.6	107.04 ± 6.6	.20	94.04 ± 8.6	96.07 ± 8.0	-.25
Pattern Comparison	125.48 ±11.5	122.48 ± 10.9	.25	88.52 ± 12.6	90.24 ± 14.6	-.13
Picture Sequence	115.20 ±13.3	107.81 ±12.3*	.58	94.52 ± 12.2	92.55 ± 10.4	.18
Biomarkers						
Mature BDNF (pg/mL)	30120 ± 6655	30681 ± 8088	-.08	33384 ± 19290	32960 ± 17951	.02
IFN-γ (pg/mL)	5.31 ± 4.1	3.95 ± 2.3†	.41	5.92 ± 4.0	7.70 ± 6.5	-.32
IL-6 (pg/mL)	0.67 ± 0.4	0.71 ± 0.4	-.11	1.05 ± 0.9	1.13 ± 0.9	-.09
TNF-α (pg/mL)	2.22 ± 0.5	2.29 ± 0.5	-.14	2.56 ± 0.8	2.88 ± 0.7†	-.40
CRP (mg/L)	3.20 ± 5.5	2.56 ± 4.0	.13	2.19 ± 3.4	2.95 ± 3.3	-.23

Note. BMI = body mass index; AA = African American, AI = American Indian, AN = Alaska Native, C = White, L = Latino, S = Spanish; ME = Middle Eastern; HS = High School; PD = Professional Degree; ACEs = Adverse childhood experiences; **p < .001, *$p < .05$, †$p \leq .10$; Cohen's *d* .20-.49=small, .50-.79=medium, ≥.80=large

Continuous variables represented with mean ± SD. Categorical variables represented with N (%).

Table 3

Pearson Correlations Among Key Study Variables Including Demographic Indicators for Full Sample

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. ACEs	-														
2. Stroop Color Score	.13	-													
3. Stroop Word Score	.07	.92**	-												
4. Stroop Color-Word Score	.10	.85**	.86**	-											
5. Stroop Interference Score	.08	.67**	.69**	.96**	-										
6. Go/No-Go Hits	.03	.46**	.44**	.45**	.38**	-									
7. Go/No-Go Commission	.07	.31**	.36**	.28**	.21*	-.11	-								
8. Go/No-Go Omissions	-.05	-.51**	-.47**	-.45**	-.36**	.91**	.06	-							
9. Cog Fluid Composite	-.05	.63**	.63**	.55**	.43**	.41**	.21*	-.50**	-						
10. Flanker	-.12	.52**	.54**	.46**	.35**	.32**	.15	-.41**	.83**	-					
11. List Sorting	.20*	.43**	.38**	.34**	.25**	.35**	.21*	-.37**	.73**	.47**	-				
12. Card Sort	.00	.59**	.61**	.51**	.39**	.40**	.16†	-.48**	.86**	.83**	.52**	-			
13. Pattern Comparison	-.07	.60**	.62**	.55**	.45**	.32**	.24*	-.43**	.91**	.78**	.50**	.77**	-		
14. Picture Sequence	.18†	.43**	.43**	.40**	.32**	.28**	.03	-.35**	.78**	.49**	.50**	.55**	.58**	-	
15. Mature BDNF	.03	.08	.04	-.03	-.08	.05	-.12	-.07	-.01	.06	-.01	.02	.05	-.05	-

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age	-.02	-.70**	-.71**	-.69**	-.59**	-.32**	-.35**	.34**	-.82**	-.67**	-.56**	-.65**	-.82**	-.62**	.06
BMI	.19*	-.15	-.18†	-.15	-.12	-.17	-.09	.19*	-.27**	-.27**	-.20*	-.29**	-.21*	-.20*	-.0
Race	.07	.19*	.15	.22*	.22*	.07	.03	-.07	.14	.09	.06	.08	.18†	.10	.09
Years of Education	-.07	-.29**	-.23*	-.20*	-.14	-.03	-.26**	.09	-.32**	-.30**	-.31**	-.23**	-.33**	-.16†	-.1

Note. BMI = body mass index; $^{**}p < .001$, $^{*}p < .05$, $^{\dagger}p < .10$.

(*M* = 32505.26, *SD* = 16289.72), *t*(104) = -0.396, *p* = .347, Cohen's *d* = -.08. Likewise, CRP was also non-significant and did not achieve a small effect across the younger (*M* = 2.87, *SD* = 4.77) and older adults (*M* = 2.60, *SD* = 3.30), *t*(104) = 0.335, *p* = .369, Cohen's *d* = .07.

Comparing ACEs Group Within Each Age Cohort

Independent sample *t*-tests were run to compare differences in cognitive scores and biomarker data within younger females with and without ACEs and older females with and without ACEs.

Younger Adult Females. The younger female cohort showed no significant differences in the ANAM subtests when comparing the no ACE group to the High ACEs group – although five of the seven subtests showed a meaningful effect size magnitude, ranging from -.22 to -.30. Within the NIH Toolbox battery, the cognitive fluid composite score for individuals with no ACEs (*M* = 114.52, *SD* = 9.4) did not significantly differ from the individuals with high ACEs (*M* = 110.96, *SD* = 7.4), *t*(50) = 1.529, *p* = .066, Cohen's *d* = .42, but was trending and showed a small effect size. There was a significant difference found in the picture sequence memory test in individuals from the no ACE group (*M* = 115.20, *SD* = 13.29), and the high ACE group (*M* = 107.81, *SD* = 12.28), *t*(50) = 2.082, *p* = .022, Cohen's *d* = .58, with a medium effect size. All other NIH Toolbox subtests showed non-significant differences between the ACE groups. Still, the flanker inhibitory control and attention test, dimensional change card sort test, and the pattern comparison processing speed test did show small effects (.24, .20, .25, respectively). These results suggest that higher ACEs may be associated with lower scores on certain cognitive battery subtests. The younger adults did not show significant differences or small effects in BDNF, IL-6, TNF-α, or CRP across ACE group. IFN-γ showed a trending difference and a small effect in that the no ACE group (*M* = 5.31, *SD* = 4.12) had higher levels than the high ACE group (*M* = 3.95,

SD = 2.33), *t*(50) = 1.478, *p* = .073, Cohen's *d* = .41, suggesting that certain inflammatory markers may be associated with ACEs history.

Older Adult Females. Consistent with the younger adults, the older adult group had few significant differences in cognitive subtests but showed some potentially meaningful effect sizes. Four of the ANAM subtests were non-significant and did not show an effect. The Stroop interference test showed a small effect and significantly lower scores in the no ACE group (*M* = 3.81, *SD* = 9.37), when compared to the high ACE group (*M* = 7.66, *SD* = 8.11), *t*(52) = -1.615, *p* = .050, Cohen's *d* = -.44. A small effect was also seen in the Stroop color-word test with only trending significance between the no ACE group (*M* = 24.92, *SD* = 12.84), and the high ACE group (*M* = 29.35, *SD* = 9.71), *t*(52) = -1.440, *p* = .078, Cohen's *d* = -.39. The Stroop color score was non-significant but had a small effect (Cohen's *d* = -.25). The NIH Toolbox had one subtest, the List Sorting Working Memory Test, with significant differences and a medium effect with the no ACE group (*M* = 87.40, *SD* = 15.18) having lower scores than the high ACE (*M* = 97.76, *SD* = 11.27), *t*(52) = -2.871, *p* = .003, Cohen's *d* = -.78. The three other NIH Toolbox scores that showed small effects were the cognition fluid composite score, the Flanker Inhibitory Control and Attention Test, and the Dimensional Change Card Sort Test (-.29, .24, and -.25, respectfully). Similar to the younger adult group, the older adult group had no significant differences in biomarkers. The largest biomarker effect was seen in TNF-α, trending on significance with the no ACE group (*M* = 2.56, *SD* = 0.88), having lower scores than the high ACE group (*M* = 2.88, *SD* = 0.74), *t*(52) = -1.470, *p* = .074, Cohen's *d* = -.40. Of the other biomarkers, IFN-γ and CRP had small effects (-.32 and -.23, respectively). Although many of the *t*-tests were non-significant, effect sizes suggest that significant results may have been found with larger groups.

Primary Analyses

Aim 1: Cognitive Performance across Age Cohorts by ACEs Exposure

Thirteen two-way ANCOVA were conducted to test for differences in cognitive testing across two independent variables, age (young/old) and ACE group (low/high), while controlling four continuous variables: BMI, education, PHQ8 scores, and GAD7 scores. For the seven subtests in the ANAM battery, all interactions were non-significant (see Table 4). Figure 1 displays performance on ANAM fluid cognition subtests across age and ACE group for more illustration of the results. When controlling for BMI, education, PHQ8, and GAD7, there was no significant interaction between age and ACE group on the Stroop Color Score [$F(1, 98) = 0.030$, $p > .05$, partial $\eta^2 = .000$], the Stroop Word Score [$F(1, 98) = 1.595$, $p > .05$, partial $\eta^2 = .016$ (small effect)], the Stroop Color-Word Score [$F(1, 98) = 0.055$, $p > .05$, partial $\eta^2 = .001$], or the Stroop Interference Score [$F(1, 98) = 0.297$, $p > .05$, partial $\eta^2 = .003$]. There was no statistically significant interaction between age and ACE group on the Go/No-Go Hits [$F(1, 98) = 0.427$, $p > .05$, partial $\eta^2 = .004$], the Go/No-Go Commissions [$F(1, 98) = 0.005$, $p > .05$, partial $\eta^2 = .000$] or the Go/No-Go Omissions [$F(1, 98) = 0.006$, $p > .05$, partial $\eta^2 = .000$].

For four of the five NIH Toolbox subtests, interactions were non-significant (see Table 4). Figure 2 displays performance on NIH Toolbox subtests across age and ACE group to illustrate results. There was no statistically significant interaction between age and ACE group on the Flanker Inhibitory Control and Attention Test [$F(1, 98) = 0.000$, $p = .992$, partial $\eta^2 = .000$], the Dimensional Change Card Sort Test [$F(1, 98) = 0.742$, $p = .391$, partial $\eta^2 = .008$], the Pattern Comparison Processing Speed Test [$F(1, 98) = 0.527$, $p = .470$, partial $\eta^2 = .005$ (small effect)], or the Picture Sequence Memory Test [$F(1, 98) = 1.267$, $p = .263$, partial $\eta^2 = .013$ (small effect)]. There was also no statistically significant interaction between age and ACE group on the Cognition Fluid Composite score [$F(1, 97) = 2.853$, $p = .094$, partial $\eta^2 = .029$ (small effect)]. Due to the interaction being non-significant, pairwise comparisons are shown in Table 4, but not reported. The subtest with a significant interaction between age and ACE group was the List

Table 4

ANCOVA Results for Cognitive Tests by Age and ACE Group with Covariates

	Younger Adults	Older Adults	No ACEs	High ACEs	Young-No	Young-High	Old-No	Old-High	*F*	*p*	Partial η^2
ANAM											
Stroop Color											
Age	59.85± 1.56	41.01± 1.55	-	-	-	-	-	-	57.24	**	.37 (lg)
ACEs	-	-	49.79± 1.57	51.07± 1.48	-	-	-	-	.279	.599	.00
*Age*ACEs*	-	-	-	-	59.38± 2.06	60.32± 2.46	40.21± 2.27	41.82± 1.95	.030	.862	.00
BMI	-	-	-	-	-	-	-	-	.234	.630	.00
Education	-	-	-	-	-	-	-	-	.906	.343	.01 (sm)
PHQ8	-	-	-	-	-	-	-	-	1.43	.234	.01 (sm)
GAD7	-	-	-	-	-	-	-	-	.196	.659	.00
Stroop Word											
Age	64.65± 1.52	43.69± 1.51	-	-	-	-	-	-	73.60	**	.43 (lg)
ACEs	-	-	53.64± 1.53	54.61± 1.44	-	-	-	-	.170	.681	.00
*Age*ACEs*	-	-	-	-	62.88± 2.01	66.24± 2.40	44.41± 2.22	42.98± 1.91	1.595	.210	.02 (sm)
BMI	-	-	-	-	-	-	-	-	.114	.737	.00
Education	-	-	-	-	-	-	-	-	5.004	*	.05 (sm)
PHQ8	-	-	-	-	-	-	-	-	2.642	†	.03 (sm)
GAD7	-	-	-	-	-	-	-	-	1.527	.220	.02 (sm)
Stroop Color-Word											
Age	50.66± 1.96	25.83± 1.94	-	-	-	-	-	-	63.20	**	.39 (lg)

	Younger Adults	Older Adults	No ACEs	High ACEs	Young-No	Young-High	Old-No	Old-High	*F*	*p*	Partial η^2
ACEs	-	-	37.01± 1.97	39.48± 1.85	-	-	-	-	.667	.416	.01 (sm)
*Age*ACEs*	-	-	-	-	49.71± 2.58	51.61± 3.09	24.31± 2.85	27.35± 2.45	.055	.815	.00
BMI	-	-	-	-	-	-	-	-	.298	.586	.00
Education	-	-	-	-	-	-	-	-	4.355	*	.04 (sm)
PHQ8	-	-	-	-	-	-	-	-	.153	.697	.00
GAD7	-	-	-	-	-	-	-	-	.002	.960	.00
Stroop Interference											
Age	19.67± 1.48	4.79± 1.46	-	-	-	-	-	-	39.92	**	.30 (lg)
ACEs	-	-	11.31± 1.48	13.14± 1.39	-	-	-	-	.645	.424	.01 (sm)
*Age*ACEs*	-	-	-	-	19.25± 1.94	20.08± 2.33	3.37± 2.15	6.21± 1.85	.297	.587	.00
BMI	-	-	-	-	-	-	-	-	.254	.615	.00
Education	-	-	-	-	-	-	-	-	3.965	*	.04 (sm)
PHQ8	-	-	-	-	-	-	-	-	.047	.828	.00
GAD7	-	-	-	-	-	-	-	-	.132	.717	.00
Go/No-Go Hits											
Age	95.08± 0.47	93.48± 0.46	-	-	-	-	-	-	4.697	*	.05 (sm)
ACEs	-	-	94.54± 0.47	94.02± 0.44	-	-	-	-	.520	.473	.01 (sm)
*Age*ACEs*	-	-	-	-	95.15± 0.61	95.01± 0.73	93.92± 0.68	93.03± 0.58	.427	.515	.00
BMI	-	-	-	-	-	-	-	-	.823	.366	.01 (sm)
Education	-	-	-	-	-	-	-	-	2.476	.119	.03 (sm)
PHQ8	-	-	-	-	-	-	-	-	1.028	.313	.01
GAD7	-	-	-	-	-	-	-	-	.142	.707	.00

	Younger Adults	Older Adults	No ACEs	High ACEs	Young-No	Young-High	Old-No	Old-High	*F*	*p*	Partial η^2
Go/No-Go Comm											
Age	6.14± 0.57	3.89± 0.57	-	-	-	-	-	-	6.146	**	.06 (md)
ACEs	-	-	4.74± 0.57	5.30± 0.54	-	-	-	-	.406	.525	.00
*Age*ACEs*	-	-	-	-	5.84± 0.75	6.45± 0.90	3.63± 0.90	4.14± 0.71	.005	.943	.00
BMI	-	-	-	-	-	-	-	-	.038	.846	.00
Education	-	-	-	-	-	-	-	-	.752	.388	.01
PHQ8	-	-	-	-	-	-	-	-	.118	.732	.00
GAD7	-	-	-	-	-	-	-	-	.010	.921	.00
Go/No-Go Omiss											
Age	0.61± 0.49	2.58± 0.49	-	-	-	-	-	-	6.203	**	.06 (md)
ACEs	-	-	1.58± 0.50	1.61± 0.47	-	-	-	-	.001	.975	.00
*Age*ACEs*	-	-	-	-	0.58± 0.65	0.65± 0.78	2.59± 0.72	2.56± 0.62	.006	.938	.00
BMI	-	-	-	-	-	-	-	-	1.077	.302	.01 (sm)
Education	-	-	-	-	-	-	-	-	.875	.352	.01 (sm)
PHQ8	-	-	-	-	-	-	-	-	.631	.425	.01 (sm)
GAD7	-	-	-	-	-	-	-	-	.024	.876	.00
NIH Toolbox											
Fluid Composite											
Age	113.12± 1.53	87.34± 1.54	-	-	-	-	-	-	110.7	**	.53 (lg)
ACEs	-	-	100.12 ±1.56	100.35 ±1.44	-	-	-	-	.010	.919	.00

	Younger Adults	Older Adults	No ACEs	High ACEs	Young-No	Young-High	Old-No	Old-High	*F*	*p*	Partial η^2
*Age*ACEs*	-	-	-	-	110.61±2.02	111.63±2.41	85.60±2.26	89.01±1.92	2.853	†	.03 (sm)
BMI	-	-	-	-	-	-	-	-	.569	.452	.01 (sm)
Education	-	-	-	-	-	-	-	-	.610	.437	.01 (sm)
PHQ8	-	-	-	-	-	-	-	-	3.608	†	.04 (sm)
GAD7	-	-	-	-	-	-	-	-	2.752	†	.03 (sm)
Flanker											
Age	100.59±0.67	89.47±0.96	-	-	-	-	-	-	51.83	**	.35 (lg)
ACEs	-	-	95.16±0.93	94.90±0.92	-	-	-	-	.030	.684	.00
*Age*ACEs*	-	-	-	-	100.71±1.28	100.46±1.28	89.60±1.41	89.33±1.21	.000	.992	.00
BMI	-	-	-	-	-	-	-	-	.963	.329	.01 (sm)
Education	-	-	-	-	-	-	-	-	.017	.895	.00
PHQ8	-	-	-	-	-	-	-	-	1.554	.216	.02 (sm)
GAD7	-	-	-	-	-	-	-	-	3.468	†	.03 (sm)
List Sorting											
Age	106.01±1.80	93.33±1.79	-	-	-	-	-	-	19.49	**	.17 (lg)
ACEs	-	-	96.26±1.81	103.07±1.70	-	-	-	-	6.008	*	.06 (md)
*Age*ACEs*	-	-	-	-	105.45±2.37	106.57±2.84	87.07±2.62	99.58±2.25	6.488	*	.06 (md)
BMI	-	-	-	-	-	-	-	-	1.870	.175	.02 (sm)
Education	-	-	-	-	-	-	-	-	2.166	.144	.02 (sm)
PHQ8	-	-	-	-	-	-	-	-	3.799	*	.04 (sm)
GAD7	-	-	-	-	-	-	-	-	4.152	*	.04 (sm)
Card Sort											
Age	108.07±1.26	94.70±1.24	-	-	-	-	-	-	44.59	**	.31 (lg)

	Younger Adults	Older Adults	No ACEs	High ACEs	Young-No	Young-High	Old-No	Old-High	*F*	*p*	Partial η^2
ACEs	-	-	100.62 ±1.26	102.14 ±1.19	-	-	-	-	.614	.435	.01 (sm)
*Age*ACEs*	-	-	-	-	107.98± 1.65	108.15± 1.98	93.27± 1.82	96.12± 1.57	.742	.391	.01 (sm)
BMI	-	-	-	-	-	-	-	-	2.325	.131	.02 (sm)
Education	-	-	-	-	-	-	-	-	.659	.419	.01 (sm)
PHQ8	-	-	-	-	-	-	-	-	.526	.470	.01 (sm)
GAD7	-	-	-	-	-	-	-	-	1.203	.275	.01 (sm)
Pattern Comparison											
Age	125.03± 2.15	88.37± 2.13	-	-	-	-	-	-	114.7	**	.54 (lg)
ACEs	-	-	107.00 ±2.16	106.40 ±2.03	-	-	-	-	.033	.857	.00
*Age*ACEs*	-	-	-	-	126.30± 2.83	123.77± 3.38	87.70± 3.12	89.04± 2.69	.527	.470	.01 (sm)
BMI	-	-	-	-	-	-	-	-	.119	.731	.00
Education	-	-	-	-	-	-	-	-	1.273	.262	.01 (sm)
PHQ8	-	-	-	-	-	-	-	-	.360	.550	.00
GAD7	-	-	-	-	-	-	-	-	.278	.599	.00
Picture Sequence											
Age	112.19± 1.95	92.97± 1.93	-	-	-	-	-	-	38.37	**	.28 (lg)
ACEs	-	-	105.75 ±1.96	99.41 ±1.84	-	-	-	-	4.445	*	.04 (sm)
*Age*ACEs*	-	-	-	-	116.72± 2.56	107.67± 3.07	94.78± 2.83	91.16± 2.44	1.267	.263	.01 (sm)
BMI	-	-	-	-	-	-	-	-	.032	.859	.00
Education	-	-	-	-	-	-	-	-	2.916	†	.03 (sm)
PHQ8	-	-	-	-	-	-	-	-	3.384	†	.03 (sm)

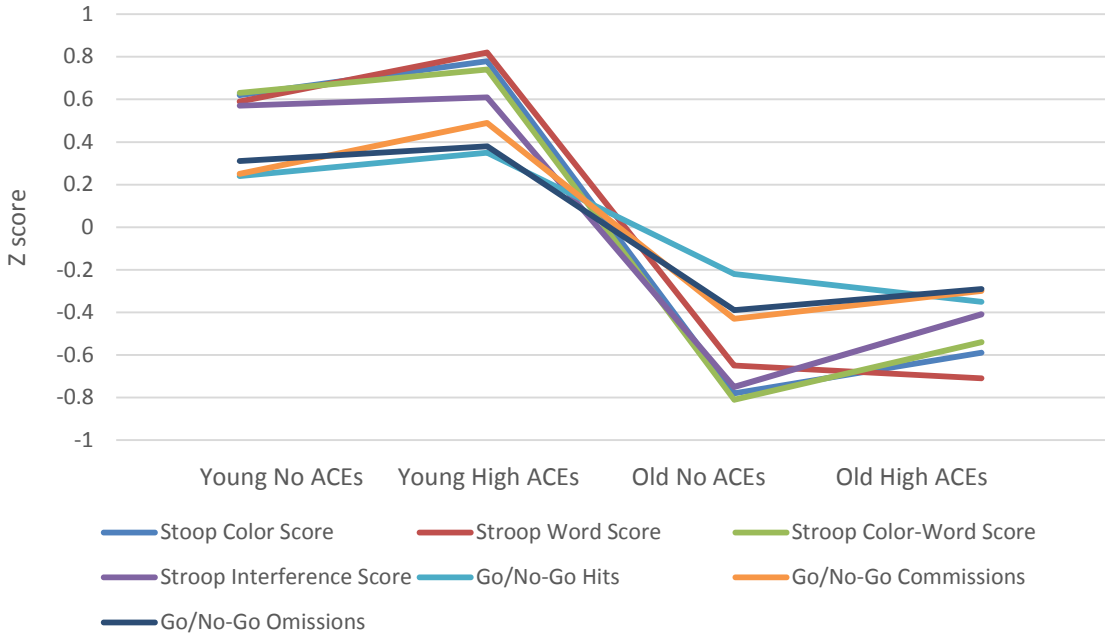
GAD7	-	-	-	-	-	-	-	-	.488	.486	.01 (sm)

Note: **p < .001, *p < .05, $^{\dagger}p \leq .10$; ACE = adverse childhood experience; BMI = body mass index; Younger Adults = 18-25, Older Adults = 65-85; High ACEs = 3+; Partial η^2 .01-.05 = small effect, 06-.13 = medium effect, ≥.14 = large effect.

Estimated marginal means are presented with standard error.

Figure 1

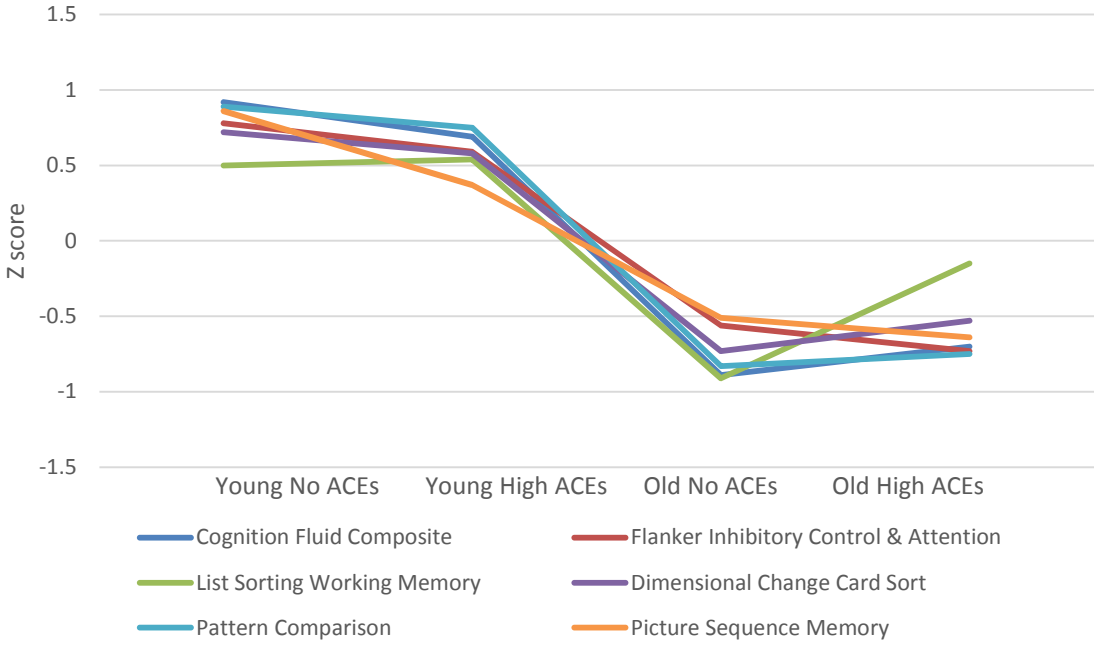
Performance on ANAM for Fluid Cognition Subtests Across Age and ACE Groups



Note. Go/No-Go Omissions was reverse coded for the purpose of this graph.

Figure 2

Performance on NIH Toolbox for Fluid Cognition Tests Across Age and ACE Groups



Sorting Working Memory Test, whilst adjusting for BMI, education, PHQ8, GAD7 [$F(1, 98) = 6.488$, $p = .012$, partial $\eta^2 = .062$].

Aim 2: BDNF Levels across Age Cohorts by ACEs Exposure

A two-way ANCOVA was conducted to examine a statistically significant difference of mature BDNF with two independent variables, age (young/old) and ACE group (low/high), while controlling four continuous variables: BMI, education, PHQ8 scores, and GAD7 scores. No interaction was observed between age group and ACE group whilst adjusting for BMI, education, PHQ8, GAD7 [$F(1, 98) = 0.343$, $p = .559$, partial $\eta^2 = .003$]. Results show that the mature BDNF is not associated with age and ACE group (see Table 5). There was a small effect for age $\eta^2 = .03$, education $\eta^2 = .02$, depressive symptoms (PHQ8) $\eta^2 = .01$, and anxiety symptoms $\eta^2 = .03$, indicating that mature BDNF may be associated with age, education level, depression, and anxiety in a sample with more power. ANCOVA results, along with estimated marginal means, are presented in Table 5. For mean scores prior to adjustment, refer to Table 2. Due to the interaction being non-significant, pairwise comparisons are not reported.

Table 5

ANCOVA Results for Mature BDNF by Age and ACE Group with Covariates

	Younger Adults	Older Adults	No ACEs	High ACEs	*F*	*p*	Partial η^2
BDNF							
Age	29172 ± 2213	34762 ± 2195	-	-	2.504	.117	.03 (small)
ACEs	-	-	32695 ± 2226	31240 ± 2091	.181	.672	.00
*Age*ACEs*	-	-	-	-	.073	.797	.00
BMI	-	-	-	-	.669	.415	.00
Education	-	-	-	-	2.270	.135	.02 (small)
PHQ8	-	-	-	-	1.391	.241	.01 (small)
GAD7	-	-	-	-	2.972	.088	.03 (small)

Note. ACE = adverse childhood experience; BMI = body mass index; Younger Adults = 18-25, Older Adults = 65-85; High ACEs = 3+; Partial η^2 .01-.05 = small, .06-.13 = medium, ≥.14 = large.

Estimated marginal means are presented.

CHAPTER IV

DISCUSSION

The present pilot study's overall objective was to examine ACEs' relationships between neurocognitive performance and BDNF, a marker of brain health, across two different age cohorts: emerging adults and older adults. Aim 1 was conducted to generate preliminary data to advance our understanding of how ACEs relate to cognition across the lifespan using this cohort design. It was hypothesized that more ACEs and older age would have a negative effect on cognitive scores. The second objective (Aim 2) was to advance the science of how ACEs are associated with neuroplasticity, specifically BDNF across the two different age cohorts. Similarly, it was hypothesized that more ACEs and older age would have a negative effect on BDNF levels (i.e., lower levels). Additionally, this study aimed to explore potential covariates (i.e., BMI, education, depressive scores, and anxiety scores) that may impact these relationships. Given that statistical significance testing is largely driven by sample size, effect sizes were additionally used to report our findings. By interpreting effect sizes, available data were maximized, and we were able to assess the preliminary estimates of the magnitude of relationships, even with a modest sample size. Such information will help inform larger scale

cohort studies examining ACEs, cognitive function, and BDNF across the lifespan.

Summary of Findings

Preliminary analyses included independent samples *t*-test to observe group differences in age cohorts and ACE groups. Furthermore, independent *t*-tests suggest that age is negatively related to neurocognitive performance. The older adult group had significantly lower scores on all the ANAM and NIH Toolbox subtests and the cognition fluid composite score generated from NIH Toolbox cognitive battery. This result supported our hypothesis that older age would be linked to poorer cognitive performance and was expected given the vast literature on age-related declines on numerous cognitive testing measures. The independent samples *t*-test observing group differences in age and BDNF levels suggests that age group had no effect on BDNF levels. This result did not support our hypothesis and was unexpected given the literature suggesting that age is often the most significantly associated variable when looking at BDNF levels (Elfving et. al., 2012).

Independent *t*-tests suggest that when both age groups are combined, individual's ACE exposure was not significantly related to any of the ANAM subtests. Given the significant differences in age groups, combining the groups into a no ACE and high ACE group was further examined. Younger adult females were split into a no ACE and a high ACE group. Of the cognitive subtests, there was only one significant difference (lower picture sequence memory scores test, a measure of episodic memory) between groups and one difference that was trending (cognition fluid composite) within the emerging adult cohort. The relationship with the composite score was driven primarily by the strong association between greater ACEs and lower episodic memory scores, which showed a medium effect. Although most of the other associations were not significant, these results do not indicate that there were no effects for the other tests. Indeed, the pattern of effect sizes suggests that with a larger sample, there may be significant differences

between ACEs groups in young women for the other tests as well – given the consistent and meaningful effect sizes of .20 or larger (small effect) across all of the NIH Toolbox executive function tests, except for working memory. Thus, our hypothesis that higher ACEs would be linked to lower cognitive performance was partially supported – predominantly in the emerging adult cohort and the NIH Toolbox test of episodic memory. Interestingly, although the high ACEs group scored lower on five of the six NIH Toolbox scores than the no ACEs group, they scored higher on many ANAM subtests, opposing the hypotheses. Additionally, there was no difference seen in BDNF level among the young no ACE group and the young high ACE group, failing to support the study hypotheses.

Correspondingly, the older adult females were split into a no ACE and high ACE group. Of the cognitive subtests, two showed significant differences (i.e., Stroop interference score and list sorting) between groups and one trending difference (Stroop color-word score). Similar to the younger group, many small effects were shown. Specifically, seven of the 13 cognitive scores showed meaningful effects. Surprisingly, and similar to the young group, in the two cognitive batteries, the high ACEs group scored higher than the no ACEs group on some of the ANAM subtests and higher on four of the six NIH Toolbox scores. There was no difference or effect seen in BDNF level among the older no ACE group and the older high ACE group.

Expanding the analyses to compare all four age/ACE groups simultaneously while adjusting for key covariates, the primary analyses for Aim 1 included two-way ANCOVAs with BMI, education, depression scores, and anxiety scores to observe potential differences in cognitive scores between age and ACE groups. The only test that identified a significant interaction was the List Sorting Working Memory Test, and the effect was found within age group and within ACEs group. As hypothesized, younger individuals scored higher on this test, but surprisingly, the high ACE group had higher scores than the no ACE group. Primary analyses for Aim 2 included a two-way ANCOVA controlling for BMI, education, depression scores, and

anxiety scores to observe differences in mature BDNF levels within two variables, age group and ACE group. There was no interaction found between groups. This data opposed the theory that BDNF levels are affected by age and the hypothesis that individuals with ACEs would have lower BDNF levels.

Interpretation of Results

Across all the cognitive tests, older adults had lower scores compared to their younger counterparts. This is no surprise considering age has been identified as the greatest risk factor for cognitive decline (Klimova et al., 2017). It should be noted that, of the individuals in the younger adult group, 44% of the sample self-reported their highest level of education as "high school graduate." This may be misleading, as they were first-year college students. Age was significantly correlated to 9 of the 13 cognitive scores in the complete sample. After separating the sample into younger and older groups, education was not significantly correlated to any of the younger group cognitive scores and only one of the thirteen older group cognitive scores. This may be the age effect on cognitive scores resulting in education level as the older group had significantly higher education levels. The effect of education is consistent with the literature (Heaton et al., 1996; Leckliter et al., 1989; Reynolds et al., 1987) as shown in the ANCOVAs, with individuals who have higher education levels performing better statistically (or trending) higher on 4 of the 13 cognitive scores than same-aged individuals who have lower education. A small effect was shown for 11 of the 13 cognitive scores. Thus, it is promising that expected patterns were observed for lower cognitive test performance with greater age and lower education levels. To expand on these established findings, the study's goal was to identify whether ACEs are an identifying early-life risk factor to indices of potential cognitive decline: cognitive performance and BDNF levels.

To meet this goal, effect sizes, as well as significance levels, were examined. This suggestion is made in psychological research (Funder & Ozer, 2019). Still, it is noteworthy that

effect sizes in small samples may be unstable (Cumming, 2013), and interpretations should be considered with caution. Previous cognition studies looking at ACEs suggest that ACEs may be an early-life factor that impacts cognition (Anda et al., 2008; Brown et al., 2010; Danese et al., 2017; Dube et al., 2009; Hart & Rubia, 2012; Pechtel & Pizzagalli, 2011; Wegman & Stetler, 2009). Literature suggests that among a middle-aged sample, higher ACE scores were significantly correlated with lower fluid cognition scores (Hawkins et al., 2020; Ji & Wang, 2018), again with episodic memory showing the strongest associations with ACE history (Hawkins et al., 2020).

Given that this pattern between ACEs and episodic memory has replicated across multiple studies, it is warranted to provide more information on this cognitive function domain. Specifically, episodic memory may be defined as the declarative memory ability that helps an individual remember specific events or situations in a temporal order and is often associated with emotional context surrounding a situation (Eichenbaum, 2004; Ahmed-Leitao et al., 2016; Lambert et al., 2017). The hippocampus is largely implicated in episodic memory formation, so this pattern aligns with previous work linking maltreatment in childhood to lower volume of the hippocampus as well as brain activation patterns linked to worse memory ability when threats are present in the surrounding environment or context. One potential explanation for poor memory for environment/context when in a threatening situation is that a person focuses their attention on the threat at the cost of remembering the larger context. Indeed, previous studies do suggest that – under threatening circumstances, individuals with ACEs may have superior cognitive performance in some domains. Such findings may also help understand our findings that higher ACEs were not always linked to lower cognitive scores.

Specifically, when examining differences in cognitive scores across ACEs group for the whole sample, it was found that some of the cognitive scores were higher in the higher ACEs group, even while other cognitive scores decreased. This is important because the fluid cognitive

testing batteries used in this study captured different areas of cognition including attention, concentration, reaction time, memory, processing speed, and decision-making. This suggests that ACEs may be associated with adaptive cognitive performance under some circumstances while harmful in others. Other studies have found that flexibility is a protective factor associated with well-being in adulthood in contrast to early life adversities. Flexibility allows individuals to respond to stressful events in numerous ways, which in turn, increases their ability to adapt to adversities (Bonanno & Burton, 2013). Levels of cognitive flexibility can affect executive function processes differently (Diamond, 2013). The ACEs questionnaire used in this study categorizes ACEs by abuse, deprivation or neglect, and household dysfunction. It may be of importance to look further into the ACEs category when looking at how ACEs affect executive functioning. For example, higher working memory may be adaptive for individuals who experienced environments with a lot of dysfunction. In summary, ACEs may be an underlying factor that contributes to increases some cognitive functions as an adaptive trait and negatively to other cognitive domains, also as an adaptive trait.

With regards to our findings on markers of brain health that may underlie cognitive performance, our hypotheses were not supported. Reasons for these null findings may be attributable to methodology issues in the BDNF assessment. First, it is noteworthy to remind readers that pro BDNF, originally a key variable, was below minimum detectable concentration in more than 50% of the sample. For this reason, pro BDNF was not analyzed. Furthermore, mature BDNF showed a larger range of scores than similar past research. In a meta-analysis by Brunoni et al. (2008), 23 studies were examined to observe the association between depression and BDNF values. Brunoni et al. reported mean serum BDNF values of 27750 pg/ml in healthy subjects.

Similarly, two measurement studies, Gejl et al. (2019) and Polacchini et al. (2015) reviewed six BDNF ELISA kits. They reported that Biosenses, the kit used in this study, had a

median pg/ml of 25400 with a range between 21500-32000. Although we found a similar sample mean (31994 pg/ml), the range observed in the current sample (14616-81564 mg/ml) was inconsistent with previous findings, even after assuring normality of data and excluding outliers within age groups. The cause of this increased variability is unknown, though it may be driven by unique features of this sample, such as the extreme age groups and/or high ACE history.

Regardless of the cause, we believe the extreme variability in mature BDNF data may be related to why the well-established associations between older and lower serum BDNF levels, as seen in previous research, were not observed. The lack of literature on older adult samples in BDNF levels did not allow for comparison across means of this group. However, previous research did indicate that increasing age was associated with lower serum BDNF levels in healthy adults aged between 50 and 76 (Erickson et al., 2010; Collins et al., 2021). Due to the literature suggesting that hormone levels have an influence on BDNF, with post-menopausal women showing lower levels (Konishi et al., 2020), the age sample for this study was selected to minimize the effects of sex-specific hormones by looking only at women and by reducing the age range of the older cohort to post-menopausal women.

The explanatory results of the current study were to examine the effects of ACEs on different age cohorts. Still, differences in BDNF among age groups were unexpected as it was expected the variables would be correlated. Although we predicted that cognitive reserve would increase cognitive scores, there is a lack of literature correlating cognitive reserve as a functional compensation for the accumulation of pathology (Stern, 2002). Moreover, given that BDNF is released following cognitive stimulation (Novkovic et al., 2015), it is a possibility that people with more cognitive reserve find mundane tasks less cognitively demanding than those who have lower cognitive reserve, resulting in less release of BDNF into the serum. One study observed higher levels of education in young adulthood and significantly associated with an increase in BDNF serum (Collins et al., 2021).

One possible explanation for the older adult group having non-significant differences in BDNF levels compared to the younger group may also be linked to the survivor effect. The survivor effect is a term coined by McMichael (1976), describing the consistent tendency of actively employed individuals having a more favorable mortality rate than the general population. Early life adversity has been linked to premature mortality (Duszynski et al., 1981; Peled et al., 2008; Stein et al., 2010); thus, studies of ACEs in older adulthood may be impacted by a "survivor effect" in which the older individuals with an ACE history who are willing and able to participate are those with various protective factors, perhaps including better brain health (e.g., higher BDNF). Therefore, the survivor effect could confound studies of ACEs and aging as the available sample with higher ACE exposure may have certain features that protected them from early mortality. In the current study, this phenomenon may have led to higher-than-anticipated serum BDNF levels in the older adult/high ACE group, impairing the ability to detect age differences in BDNF. However, no significant correlations were observed between ACEs, BDNF, and/or age. In sum, while the survivor effect presents one hypothesis for why no significant associations between age and BDNF were observed, the exact reason is unknown. Larger scale studies are needed to disentangle and better understand relationships between ACEs, aging, and brain health.

In a longitudinal study (Kelly-Irving et al., 2013), the relationship between early life adversity and early life mortality (≤50 years) was examined for men and women separately. This study found that higher ACE scores had a graded relationship to mortality, specifically in women. The authors suggested that biological embedding during early development is a plausible explanatory mechanism for premature mortality. The specific role that BDNF may play in this pathway from ACE to premature mortality has yet to be established directly. Still, lower BDNF levels in women have been linked to greater all-cause mortality, pointing to the need to further explore these associations in larger scale, prospective investigations (Krabbe et al., 2009).

Limitations and Future Directions

As suggested from the details above, several limitations should be considered in the current study. First, this study was cross-sectional, suggesting that the temporal link between the dependent variables (BDNF and cognitive testing) and the exposure to ACEs cannot be determined. Causal inferences should be considered with caution. Baseline blood samples and cognitive testing would eliminate the third variable of time, but a longitudinal study of this extreme ACE group would require a much larger funding mechanism. A third variable not identified in our study is socio-economic status (SES). Collecting information on childhood SES may be a variable worth considering in future studies, given its clear connections with ACEs and cognitive development.

Another limitation is the study sample. The younger adult group consisted of primarily white, college-enrolled females with an above-average BMI. Older adults were primarily white, highly educated, living in an urban college city, and above-average BMI. Both groups were currently living in the mid-west portion of the United States. There were no men in this sample. This homogenous sample is limited and cannot be generalized to men, middle-aged women, or other more diverse samples. Future studies should aim to collect a larger sample size on a more diverse sample.

Furthermore, selection bias may have contributed to the sample collected in this study. Selection bias is a concern in older adult research because participants survive long enough to reach old age and are healthy enough to participate in a research study. Individuals who age well may also be more inclined to participate in research. In addition to the older adult selection bias, is it noteworthy that the data from this study was collected during the COVID-19 pandemic, specifically between two large surges of COVID cases. These individuals were willing to come to the testing site despite the pandemic, which may not be a generalizable sample.

ACEs score was coded as either no ACEs or high ACEs, implying that having three or more ACEs was a high number of adverse childhood events. Some literature suggests that four or more ACEs are to be considered high. Future studies should recruit individuals with higher ACE scores to see a possible effect.

Conclusions

The present study aimed to examine ACEs and age as mechanisms affecting BDNF and cognitive function. At a population level and group level, these findings suggest that BDNF does not differ as women age and does not differ among individuals who have a high number of ACEs. Findings from this study suggest that older age is associated with lower cognitive scores. Still, ACEs generally were not, with the exception of an observed link between higher ACEs and lower episodic memory among the younger cohort. Potential covariates (i.e., BMI, education, depressive symptoms, and anxiety scores) were explored, and results revealed that these factors are significant predictors for some of the cognitive subtests. However, there was no consistency in which factors affected which tests. These factors were also explored in their relation to BDNF. Although potentially meaningful small effects were found, there were no significant results. This study advances the literature by expanding upon cognition in individuals who have ACEs. Future research is needed to determine if three or more ACEs are a sufficient level of adversity to yield impaired cognition and altered levels of BDNF. Identification of this ACEs score would allow for better understanding of the ACEs relationship to brain health as individuals age.

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APPENDICES

APPENDIX A

Literature Review

Adverse Childhood Experiences: An Early-Life Factor Linked to Brain Health

ACEs are defined as traumatic or challenging childhood events (e.g., abuse, deprivation or neglect, and household challenges). ACEs are commonly measured using the self-reported Adverse Childhood Experiences Survey (Felitti et al., 1998) from the Kaiser Permanente ACE Study. This survey examines ten traumatic events that occur before age 18, including abuse, neglect, domestic violence, parental separation/divorce, familial mental illness, substance use, and/or incarceration. The more trauma, maltreatment, or household disruption an individual is exposed to, the higher their ACE score. Findings indicate that these negative experiences predict harmful health outcomes across multiple biological, psychological, physiological, social, and neurocognitive domains (Hawkins et al., 2020; Kim et al., 2019; Vigil et al., 2005). Such toxic stressors may result in neurocognitive injury via dysregulation of the body's stress systems (e.g., hypothalamic-pituitary-adrenal axis) or via cognitive deprivation (Wegman & Stetler, 2009). Indeed, more recent evidence has now linked ACEs to reduced cortical volume and

differences in neural activation of brain regions associated with language, memory, and executive function (Kim et al., 2019).

As a person's ACE score increases, so do their negative health outcomes, suggesting a dose-response type relationship between higher ACES and poorer health. Combined, individuals aging with ACEs may be an at-risk group with high health concerns. Given the substantial evidence that links ACEs to negative health conditions, the high prevalence rate of ACEs is concerning (Centers for Disease Control and Prevention, Kaiser Permanente, 2017). On average, 22% of people report having at least 3 ACEs before they turn 18, and 64% of adults reported having at least 1 ACE before turning 18 (Hawkins et al., 2020).

Important Considerations for ACEs Assessment

There are two general ways ACEs are assessed, retrospectively and prospectively. The self-reported Adverse Childhood Experience Survey assesses ACEs retrospectively. The individuals answering the questionnaire are over the age of 18, and they are reporting events that happened to them before their 18th birthday. The second form of assessing ACEs is prospectively; this is when a child reports adverse events that are currently occurring. These two measures of childhood maltreatment may identify different groups of individuals. Furthermore, researchers should be aware of these critical measurement differences when conducting research on individuals who experience adverse events and when they are developing interventions. The timing in which an individual reports the event is important because children who identified ACEs prospectively may have different risk pathways to mental illness than those adults reporting the events retrospectively (Danese et al., 2017).

Sex Differences

It is critical not only to note sex differences in ACE exposure but also to acknowledge how the stress of ACEs affects men and women differently. Women are more likely to experience ACEs than men. Women may show greater susceptibility to the effects of early-life stress due to their neural and

inflammatory response to stressors being significantly greater than their male counterparts (Baldwin et al., 2019; Ganguly & Brenhouse, 2015; Kim et al., 2019). For example, in physically abused children, it was found that girls who had a history of physical abuse had higher levels of urinary oxytocin and lower levels of salivary cortisol after an experimental stressor compared to girls who were not abused (Seltzer et al., 2014). These differences were not found among boys. The neuroinflammatory network hypothesis (Nusslock & Miller, 2016) states that ACEs affect both the brain and immune system, promoting multiple disease processes. It is important to note that there are studies that do not find sex differences with physical health outcomes across ACE groups (Baumeister et al., 2016; Campbell et al., 2018). Despite the conflicting evidence on sex-based ACEs-health effects, the higher rates of ACEs in girls and women support females as a population with greater risk of ACEs-related negative outcomes. Considering females are more likely to experience ACEs and show higher physiological stress responses to ACES, the neuroinflammatory network hypothesis would suggest that ACEs' influence on neural and inflammatory systems could promote later-life problems. Thus, further investigation into sex differences in response to ACEs is an important next step. Such work may aid in implementing more effective methods to treat ACEs-related maladaptive neuroinflammatory pathways across sexes.

Cognition: One Approach to Estimating Brain Health

Cognition is multidimensional, encompassing a number of abilities that are determined by brain anatomy and physiology. These various mental abilities are a fundamental aspect of an individual's ability to engage in activities, accomplish goals, and successfully navigate the world. Distinguishing the different components of cognitive abilities is essential because these domains play different roles in the processing of information and are differentially impacted by the aging brain. See Appendix D for descriptions of common cognitive domains and their functions.

Across all cognitive domains, aging is the greatest risk factor for cognitive deceleration and decline. Bringing light to this is important because as the global population ages, the prevalence of

cognitive impairment and disease will continue to rise substantially. In 2016, almost 44 million people were living with dementia, an increase of 117% from 1990 (Nichols et al., 2019), and the estimated years of life lost due to ADRD doubled from 4.2 to 8.3 million between 2000 and 2012, costing the global economy over $800 billion ("Disability and life lost," 2018; "Human and financial impact"). The circumstance that drives these costs are driven by cognitive function, and its multiple domains play a critical role in activities of daily living and functional capacity (Reese & Cherry, 2002).

Aging is a non-modifiable risk factor for cognition; however, modifiable risk factors for cognitive health have been identified (Klimova et al., 2017). Some of the most well-known include biobehavioral factors such as head injury and lifestyle (e.g., physical activity, healthy diet, and cognitive training). Identifying modifiable risk factors is essential in combatting this global epidemic as these factors represent malleable targets for protecting and extending cognitive health. Critically, identifying early-life modifiable risk factors (e.g., ACEs, education) may be necessary to effectively maximize our prevention and intervention efforts for future optimal cognition.

Early-Life Factors

ACEs may be a critical early-life factor that impacts cognition (Anda et al., 2008; Brown et al., 2010; Danese et al., 2017; Dube et al., 2009; Hart & Rubia, 2012; Pechtel & Pizzagalli, 2011; Wegman & Stetler, 2009). To highlight this point: in a longitudinal study that prospectively collected ACEs, individuals who were exposed to adverse experiences showed impairments in cognition, including general intelligence, executive function, processing speed, memory, perceptual reasoning, and verbal comprehension during adolescence and these impairments persisted throughout adulthood (Danese et al., 2017). This study also speculated that cognitive deficits in the victimized individuals could be explained by existing deficits predating the individual's victimization and that genetic and environmental risks were confounding variables when looking at cognitive deficits and ACEs. Such patterns could point to potential intergenerational transmission of ACEs-related cognitive burdens (e.g., epigenetics) (Jones et

al., 2012; Van Wert et al., 2019) or socioeconomic risk factors that predict both cognitive deficits and ACEs (e.g., third variable confounding).

There are early-life factors that have a positive impact on cognition as well. Although aging is the greatest risk factor for cognitive decline, childhood education has been linked to higher performance on cognitive testing as well as slower decline in mental status in aged individuals (Lièvre et al., 2008). Research has found that early-life experiences, like higher education levels, show strong protective effects on long-term cognitive performance and ADRD cognitive trajectories (Meng & D'arcy, 2012). The term for this phenomenon has been called cognitive reserve.

The cognitive reserve hypothesis suggests that individuals have differences in resistance to cognitive decline, with some having a greater reserve of cognitive resources than others. Early-life factors like education "increase" the reserve and are protective against cognitive decline and ADRD risk. To illustrate, one study found that by age 90, older adults with four years of education remembered half as many words on a delayed recall test compared to their peers with 16 years of education (Alley et al., 2007). Individuals who had higher education levels scored higher on cognitive testing at all ages in later life. Such findings support education as a proxy for "cognitive reserve" (Alley et al., 2007; Lièvre et al., 2008; Stern, 2012) and highlight the evidence that certain early-life factors may buffer against cognitive deficits.

Unfortunately, ACEs are early-life risk factors that may deplete the cognitive reserve. As mentioned above, data suggests that having a high number of ACEs overall may adversely impact cognition via neglect or threat in separate middle-aged and young adult samples. What is unknown is how these deficits compare across age groups or how they map onto potential physiological mechanisms of cognitive injury or decline. A candidate biological mechanism of interest to the current proposal is a marker of brain plasticity, cognitive health, and ADRD progression (Balietti et al., 2018): brain-derived neurotrophic factor or BDNF.

Neurotrophin BDNF- A Potential Physiological Mechanism of Brain Health

As stated above, ACEs are related to cognitive deficits at various levels of severity, but the physiological mechanisms of how ACEs impact cognition are unclear. Brain health and cognitive functioning have been linked to a potential candidate mechanism of the ACEs-cognition relationship, a biological signaling molecule known as brain-derived neurotrophic factor—BDNF.

Definition & Description

BDNF levels are a critical component in the neuroplasticity involved with learning and memory (Lu & Gottschalk, 2000). The BDNF gene is responsible for providing instruction on making the brain-derived neurotrophic factor, a protein found in the brain and spinal cord. This protein plays a role in the growth, maturation, and maintenance of nerve cells. Similar to other neurotrophins, BDNF is synthesized as a precursor first, known as proBDNF, which then splits to generate the mature BDNF. The BDNF protein plays an essential role in the synapses where cell-to-cell communication occurs by regulating the synaptic plasticity. BDNF has been implicated in the hippocampus and in parahippocampal areas that control both normal and pathological aging as well as psychiatric disease. In particular, these areas are important for memory processing. Furthermore, BDNF is critical during brain development as it is an essential part of the nervous system involved in promoting the growth of new neurons (Binder & Scharfman, 2004).

BDNF, Cognitive Health, and ACEs

Given its roles in neuronal health, disruptions in BDNF signaling cause deadly effects on neurons, including cell deterioration, impaired cellular metabolism, and apoptosis (Miller & Kaplan, 1998). Such disruptions may be why low levels of BDNF have been correlated to cognitive impairments in non-dementia aging women (Komulainen et al., 2008), neurocognitive screener scores (i.e., mini-mental status examination; MMSE) in individuals with dementia (Laske et al., 2006), ADRD (Yasutake et al., 2006), depression (Karege et al., 2002a), and other neuropsychiatric disorders (Notaras et al., 2015).

Thus, BDNF may be a biomarker of interest in looking at aging individuals and their trajectory for cognitive impairments and ADRD. Importantly for this study, BDNF has also been linked to childhood trauma.

Literature suggesting that BDNF is a neurobiological mechanism significantly affected by childhood abuse (de Castro-Catala et al., 2016; Hemmings et al., 2013; Nöthling et al., 2019) is becoming increasingly prevalent. Variations in BDNF levels have been observed in those who were mistreated during childhood (Aas et al., 2016; Bortoluzzi et al., 2014; Gutierrez et al., 2015; van Velzen et al., 2016), suggesting that BDNF is a valid biomarker when assessing the effects childhood trauma have on brain plasticity (Theleritis et al., 2014) and hippocampal development (Hall et al., 2000). Furthermore, in animals, it has been found that exposure to early life stressors induced a decrease in BDNF, succeeding neuronal atrophy and degeneration in the hippocampus, which can persist into adulthood (Murakami et al., 2005; Roceri et al., 2004; Song et al., 2006). Subsequently, a study with females found that depressed women with a history of childhood neglect had lower BDNF compared to non-abused depressed women and controls (Grassi-Oliveira et al., 2008). Due to the prominent role BDNF has in brain health and development, including the regulation of neuronal survival, structure, and function, it follows, that having lower levels of BDNF may impact brain structure and function.

APPENDIX B

Blood Collection and Processing Protocol

Blood Specimen Collection & Materials:

A 23-gauge butterfly needle will be inserted into a vein of the participant's forearm. Following blood collection, participants will participate in cognitive testing session.

The needle will draw up to 15 mL of whole blood into a series of appropriate vacutainers (BD, Franklin Lakes, NJ, USA). All blood will be refrigerated and stored until time of analysis.

> **Blood neurotrophic factor analysis methods.** Serum BDNF levels will be measured using sandwich enzyme-linked immunosorbent assays (ELISAs). For BDNF, we used the Human BDNF ELISA Kit (U-Plex Human BDNF, MSD; Rockville, MD, USA. Other kits will be the V-Plex Human Proinflammatory Panel (4-plex: IFN-gamma, IL-1beta, IL-6, TNF-alpha), the V-Plex Human CRP, and the Human Leptin/Insulin Kit (MSD; Rockville, MD, USA).

Blood Specimen Storage & Analysis: Blood samples will be collected, processed, and stored at Oklahoma State University (OSU) through collaboration with Dr. Kent Teague (CIRCA Biomarker Core). Samples will first be collected at the study visit in the Department of Psychology, then left to clot at room temperature. Blood serum separation will be performed by centrifugation at 3000 rpm for 10 min. Serum will be kept at −80°C until serum neurotrophic factors (BDNF) and other biomarkers are analyzed.

WARNING: DO NOT USE GLASS FOR PROCESSING BLOOD. IT BINDS TO BDNF!!!

Before Starting

1) Put on protective equipment: Gloves, Lab Coat

Step 1. Drawing Blood and Labeling Vacutainer [Use Sharpie]

ASSESSOR: 1. **Put on gloves.** Assessor will draw blood into two 7.5 ml vacutainers and one 3ml syringe (if necessary). Vacutainers should be labeled with participants number, and should be a 4-digit code starting with 50XX.

- 7.5 ml Tiger Top Vacutainer Tube: BDNF/GDNF Analyses
- 7.5 ml Tiger Top Vacutainer Tube: All inflammatory markers
- 3ml syringe: For Whatman Blood Spot Card

3 cc/ml syringe

Large 7.5 ml Red/Gray (Tiger Top SST) Tube – **Invert 5 times**
For centrifuge- go to step 4.A

BLOOD PROCESSOR RA 2. **Put on gloves.** Blood processor will receive the vacutainers with blood from the assessor. Vacutainers should be labeled with the participant number and time blood was taken. If the blood spot card does not have blood already on it, take blood from small syringe and put a drop of blood on each paper dot. Label the blood spot card to match (i.e., the same number). Use the following format:

ACEs & Aging 50XX

After blood spot card has been made, you can dispose of syringe in a biohazard container. Allow 5 minutes for the blood on the blood spot card to dry before closing the card and placing it in a plastic bag inside of the fridge. Bags will be labeled in the fridge for appropriate participant number.

Step 3. Set Timer for Tiger Top Clotting

Set the appropriate timer for your assessment room and time-point (e.g., 011 blood 1 hr).

Step 4.

4.A – For centrifuge

1. **Allow blood in Tiger Top tubes to clot in tubes for 1 hour at room temperature***
2. Confirm coagulation by inverting tube gently
3. Go to Step 5 after 1 hour has passed.

Step 5. Centrifuge the Tiger Top Tubes

Spin (centrifuge) samples in Tiger Top tubes

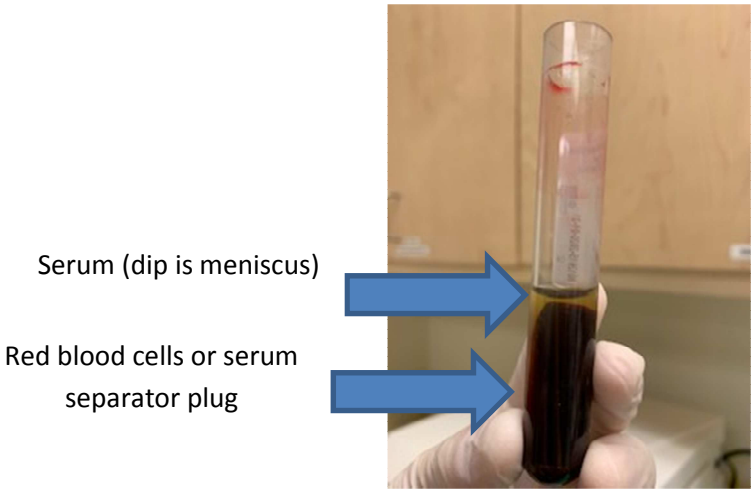
- Locate small centrifuge and turn on (switch on back right)
- Set centrifuge to: 3300 rpm speed and timer for 10 minutes
- Open centrifuge by turning knob on right and place tubes in the bucket
    - Make sure the bucket is balanced (match a pair of tubes across from one another with equivalent volumes of liquid).
- Close lid until it clicks and **press "RUN"**

Make sure to stay near centrifuge and ensure that it does not move off the counter. It can move once it starts vibrating. ****IF THIS IS HAPPENING, IT IS OFF BALANCE****

Step 6. Label Conical Tubes

Remove serum from tubes and place in.

Specifically, use a sterile transfer pipette to suck golden serum from above the pellet/plug. You want a deep golden hue with no pink/red containments. Do not get too close to the pellet or plug on bottom of tube or you will have to re-spin.
*Stop pipetting while the meniscus of the serum is just above the plug (see picture)



Step 7. Label Microcentrifuge Tubes
Label your microcentrifuge tube with participant number, date, and study name (see below). Participant number should be a 4-digit code starting with 50XX. Study name is "CTaging".

Step 8. Aliquot

Aliquot the serum from each colored-top centrifuge tube into 8 tubes labeled microcentrifuge tubes containers using 1000 microliter pipette. We only need to have 5 tubes, but the extra 3 will be taken if possible.

1000 µL Pipette	Pipette Tip	Microcentrifuge Tube
 Set volume to = **600 µL** in each tube	 Add **Fresh Tip** for Each Person, and Each Tube DO NOT CONTANIMATE TIP	 Put **600 µL (or at least ≥ 250 µL)** in each tube

Microcentrifuge Tube		Storage Box
 Put **600 µL** (or ≥ **250 µL**) in each tube		 Put mircocentrifuge tubes in box.

Step 9. Freeze Microcentrifuge Tubes

Freeze box at -80°C in the freezer as soon as filling all tubes.

Step 10. Congratulations & Clean Up

You made it! Make sure to run through protocol as needed for each sample. Use fresh gloves for each participant.

When all samples are frozen, clean up your space. All materials that contacted blood or serum need to go in Biohazard. The rest of the waste can go to regular trash.

Blood Specimen Assay Materials

Blood neurotrophic factor analysis methods. Serum BDNF and GDNF levels will be measured using sandwich enzyme-linked immunosorbent assays (ELISAs). For BDNF, we used the Human BDNF ELISA Kit (U-Plex Human BDNF, MSD; Rockville, MD, USA). Other kits will be the V-Plex Human Proinflammatory Panel (4-plex: IFN-gamma, IL-1beta, IL-6, TNF-alpha).

Blood Specimen Storage & Analysis: Blood samples will be collected, processed, and stored at Oklahoma State University (OSU) through collaboration with Dr. Dolores Vasquez Sanroman (Consultant) and Dr. Kent Teague (CIRCA Biomarker Core). Samples will first be collected at the study visit in the Department of Psychology, left to clot at room temperature, then blood serum separation will be performed by centrifugation at 3000 rpm for 15 min. Serum will be kept at −80°C until the analysis of serum neurotrophic factors (BDNF) and other biomarkers.

APPENDIX C

Pearson Correlations Among Key Study Variables Including Demographic Indicators for Younger Sample

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. ACEs	-														
2. Stroop Color Score	.15	-													
3. Stroop Word Score	.19	.86**	-												
4. Stroop Color-Word Score	.05	.80**	.80**	-											
5. Stroop Interference Score	-.03	.62**	.62**	.96**	-										
6. Go/No-Go Hits	.13	.41**	.29*	.51**	-.52**	-									
7. Go/No-Go Commissions	.08	.29*	.31*	.21	.14	.02	-								
8. Go/No-Go Omissions	-.10	-.34*	-.23†	-.42**	-.43**	-.86**	-.03	-							
9. Cog Fluid Composite	-.27*	-.32*	-.20	-.19	-.13	-.16	-.23†	.00	-						
10. Flanker	-.19	-.22	-.19	-.15	-.10	-.17	-.15	.04	.66**	-					
11. List Sorting	.04	-.11	-.10	-.19	-.20	.16	-.05	-.22†	.44**	.09	-				
12. Card Sort	-.09	-.16	-.03	.01	.06	-.12	-.05	-.01	.70**	.69**	.07	-			
13. Pattern Comparison	-.19	-.19	-.07	-.11	-.08	-.21	-.13	.06	.80**	.58**	.17	.59**	-		
14. Picture Sequence	-.32**	-.32*	-.24†	-.16	-.08	-.13	-.29*	.10	.62**	.09	.14	.19	.23†	-	
15. Mature BDNF	-.10	.00	-.04	-.04	-.04	-.01	-.30*	.00	.05	.22†	-.10	.01	.08	-.03	-
Age	-.03	.27*	.19	.28*	.26*	.21	.02	-.23†	.00	.17	-.20	.14	-.01	-.03	.19
BMI	.26†	.12	.15	.14	.12	.04	.01	-.06	-.12	-.11	-.22†	-.06	-.01	-.03	.00
Race	.08	-.04	-.08	-.06	-.05	.04	-.05	.07	-.18	-.11	-.30*	-.20	-.03	-.05	.26†
Years of Education	-.22†	.19	.20	.22†	.20	.10	-.03	-.16	-.02	.02	-.18	.03	-.01	.04	.16

Note. BMI = body mass index; $^{**}p < .001$, $^{*}p < .05$, $^{\dagger}p < .10$.

(continued)

Pearson Correlations Among Key Study Variables Including Demographic Indicators for Older Sample

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. ACEs	-														
2. Stroop Color Score	.20	-													
3. Stroop Word Score	-.00	.84**	-												
4. Stroop Color-Word Score	.23†	.65**	.66**	-											
5. Stroop Interference Score	.23†	.31*	.34*	.92**	-										
6. Go/No-Go Hits	.00	.38**	.43**	.33*	.20	-									
7. Go/No-Go Commissions	.06	-.17	-.09	-.21	-.19	-.45**	-								
8. Go/No-Go Omissions	-.06	.49**	-.46**	-.37**	-.21	-.92**	.38*	-							
9. Cognition Fluid Composite	.09	.51**	.50**	.23†	.01	.46**	-.13	-.51**	-						
10. Flanker	-.12	.44**	.57**	.21	-.01	.37**	-.14	-.42**	.68**	-					
11. List Sorting	.37**	.25†	.14	.09	.01	.27*	.08	-.27*	.70**	.29*	-				
12. Card Sort	.09	.55**	.59**	.26†	.01	.45**	-.19	-.48**	.79**	.74**	.40**	-			
13. Pattern Comparison	-.04	.32*	.34*	.14	.02	.29*	-.01	-.39**	.70**	.52**	.18	.53**	-		
14. Picture Sequence	-.11	.37**	.37**	.17	.02	.29*	-.20	-.32*	.66**	.24†	.40**	.37**	.21	-	
15. Mature BDNF	.11	.22†	.18	.02	-.09	.08	.02	-.11	.04	.06	-.09	.08	.17	-.03	-
Age	-.20	-.33**	-.35**	-.38**	-.29*	-.27*	.13	.31*	-.51**	-.26†	-.42**	-.31*	-.35**	-.37**	.14
BMI	.17	.03	-.06	-.00	.00	-.14	.02	.13	-.08	-.14	-.02	-.21	.02	-.05	-.08
Race	.06	.08	.00	.24†	.28*	-.03	-.11	.02	-.04	-.12	.08	-.01	-.07	-.09	-.02
Years of Education	.02	.01	.18	.19	.20	.16	-.17	-.10	.20	.05	-.04	.18	.21	.30*	-.26*

Note. BMI = body mass index; $^{**}p < .001$, $^{*}p < .05$, $^{\dagger}p < .10$.

APPENDIX D

Major Cognitive Domains with Descriptions and Tests

Cognitive Domain	Description	Tests Used
Attention	Ability to focus awareness on a given stimulus or task, to concentrate on that stimulus or task long enough to accomplish a goal	-Flanker Inhibitory Control
Memory	Cognitive processes involved in the acquisition, storage, and retrieval of new or retained information; can be auditory or visual	-Mini-Mental State Exam -Picture Sequence Memory Test
Processing Speed	Assesses the amount of information that can be processed within a certain unit of time	-Pattern Comparison Processing Speed Test
Executive Function	Higher cognitive processes that enable forethought and goal-directed action	
Inhibition	Ability to choose a more complex and effortful solution to be correct	-Stroop Task -Go/No-Go Task
Cognitive Flexibility	Ability to shift between two concepts, tasks, or response rules	-Dimensional Change Card Sorting Test
Working Memory	Ability to hold information for a brief period and to manipulate it	-List Sorting Memory

APPENDIX E

Institutional Review Board Approval Letter

Oklahoma State University Institutional Review Board

Application Number: AS-19-65

Proposal Title: Neurotrophic Indicators of Cognition, Executive Skills, Plasticity, and Adverse Childhood Experiences Study "NICE SPACES"

Principal Investigator: MISTY HAWKINS

Co-Investigator(s):

Faculty Adviser:

Project Coordinator:

Research Assistant(s): Cindy Tsotsoros, Harley Layman, Madison Stout, M.S., Natalie Keirns

Status Recommended by Reviewer(s):

Approved Study Review Level: Expedited

Modification Approval Date: 06/10/2021

The modification of the IRB application referenced above has been approved. It is the judgment of the reviewers that the rights and welfare of individuals who may be asked to participate in this study will be respected, and that the research will be conducted in a manner consistent with the IRB requirements as outlined in section 45 CFR 46. The original expiration date of the protocol has not changed.

Modifications Approved:
Modifications Approved: Add OSU CHS as a data collection site, make changes to flyer and email to include the OSU CHS site, removed questions from the PARQ measure, added a question to the HPLPII measure and added the physical activity questionnaire back into the study. Participants will be directed to the survey online instead of to the link on the labs site.

The final versions of any recruitment, consent and assent documents bearing the IRB approval stamp are available for download from IRBManager. These are the versions that must be used during the study.

As Principal Investigator, it is your responsibility to do the following:

1. Conduct this study exactly as it has been approved.
2. Submit a status report to the IRB when requested
3. Promptly report to the IRB any harm experienced by a participant that is both unanticipated and related per IRB policy.
4. Maintain accurate and complete study records for evaluation by the OSU IRB and, if applicable, inspection by regulatory agencies and/or the study sponsor.
5. Notify the IRB office when your research project is complete or when you are no longer affiliated with Oklahoma State University.

Sincerely,

Oklahoma State University IRB
223 Scott Hall, Stillwater,
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Ph: 405-744-3377 | Fax: 405-744-4335| irb@okstate.edu

VITA

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