THE EFFECTS OF CHILDHOOD MALTREATMENT AND GENOMIC VARIATION IN THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS ON NEUROPSYCHOLOGICAL FUNCTIONING IN OFFSPRING OF DEPRESSED PARENTS

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The Effects of Childhood Maltreatment and Genomic Variation in the Hypothalamic-Pituitary-Adrenal (HPA) Axis on Neuropsychological Functioning in Offspring of Depressed Parents

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Childhood maltreatment has been associated with an increased risk for psychiatric disorders and suicide. The primary role of the hypothalamic-adrenal-pituitary (HPA) axis is to maintain homeostasis when challenged with stress. Genomic variation in genes of the HPA axis may play a role in the effects of maltreatment on neuropsychological functioning. The aims of the dissertation study were: (1) to examine the effect of childhood maltreatment on neuropsychological functioning; (2) to examine the effects polymorphisms in genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) with neuropsychological functioning; and (3) to explore gene environment interactions between genes of the HPA axis and exposure to childhood maltreatment on neuropsychological function. This was a secondary data analysis of neuropsychological testing, psychiatric assessments, and genomic data from the Familial Pathways to Early Onset Suicide Attempt Study. A total of 369 subjects were included in Aim 1 and 145 subjects in Aims 2 and 3. Multiple linear regression was used to analyze the effects of maltreatment, genotype, and their interactions on neuropsychological functioning. Physical abuse was associated with poorer performance in the memory domain (p=.006). While no longer significant after controlling for multiple comparisons, results trended trend toward significance (q=.088). Emotional abuse was associated with better scores on measures of verbal fluency (p=.03), but the results were no longer significant after false discovery rate (FDR) correction. Before FDR testing, significant protective effects were detected for two SNPs in the CRHBP gene and one single nucleotide polymorphisms (SNPs) in the CRHR2 gene; and significant risk

effects were detected for two SNPs in the CRHR1 gene and one SNP in the NR3C2 gene. However, after FDR corrections, only one result remained significant, a protective effect for CRHBP rs7704995 on the Impulse Control Domain. No significant gene environment interactions were detected. These findings are consistent with the literature showing that exposure to physical abuse is associated with deficits in memory. Further studies are needed with larger sample sizes and all the relevant genes of the HPA axis to determine whether genomic variation in genes of the HPA axis have a direct effect on neuropsychological functioning.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

Jamie would like to thank her outstanding committee members for their direction, guidance, and expert advice in completing this dissertation. She would especially like to thank her family and peers for their support and encouragement along the way. Jamie would like to acknowledge dissertation support from the Jennifer Thurheimer-Cacciotti, PhD Student Award. While Jamie did not have grant support for this secondary data analysis, she would like to acknowledge support for the parent study "Familial Pathways to Early Onset Suicide Attempts", PI: David A Brent, MD (R01 MH56612).

1.0 PROPOSAL INTRODUCTION

The purpose of the student's dissertation study, *The Effects of Childhood Maltreatment and Genomic Variation in the Hypothalamic-Pituitary-Adrenal (HPA) Axis on Neuropsychological Functioning in Offspring of Depressed Parents*, is to examine the effect of childhood maltreatment, genomic variation, and their interactions on the neuropsychological functioning in offspring of depressed parents. This pilot study is a secondary data analysis of a longitudinal study of "high risk" offspring of depressed parents, ***"Familial Pathways to Early Onset Suicide Attempt"*** (R01 MH56612, PI: David A Brent, MD). The primary aim of the parent study was to compare the offspring of depressed suicide attempters with the offspring of depressed non-attempters at baseline and yearly follow-ups over a period of 15 years. Dr. Brent has granted the student access to the clinical, neuropsychological and genomic data for her dissertation project.

A thorough literature review has been conducted and preliminary analyses have examined the effect of childhood maltreatment on neuropsychological functioning in offspring (age 21 or less) of depressed parents. Although findings were not significant after controlling for multiple comparisons, results in the memory domain trended towards significance. The HPA pathway has been shown to affect neuropsychological functioning; and the interaction between HPA genomic variation and maltreatment has been implicated in the development of psychiatric disorders. Therefore, it is hypothesized that exposure to childhood maltreatment, genes of the

HPA axis and their interaction will be associated with deficits in neuropsychological functioning in offspring of depressed parents.

1.1 PURPOSE AND SPECIFIC AIMS

The specific aims of the dissertation study are:

- Specific Aim 1: To examine the effect of childhood maltreatment on neuropsychological functioning
- Specific Aim 2: To examine the effect of polymorphisms in genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) with neuropsychological functioning
- Specific Aim 3: To explore gene environment interactions between genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) and exposure to childhood maltreatment on neuropsychological functioning

1.2 CONCEPTUAL FRAMEWORK

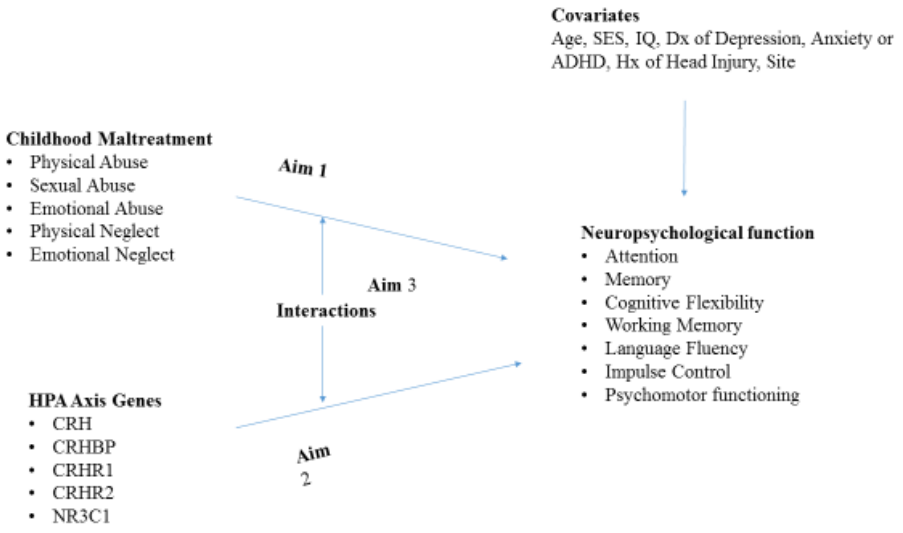

Figure 1. Conceptual framework

Preliminary analyses have been conducted for Aim 1 in offspring age 21 or less. These same analyses will be conducted in offspring age 21 and older. Aim 2 will examine the effect of HPA Axis genes on neuropsychological function. Finally, Aim 3 will explore if interaction between childhood maltreatment and genomic variation of HPA axis genes have an effect on neuropsychological functioning. The proposed study aims to provide a better understanding of the underlying mechanisms in which childhood maltreatment negatively impacts neuropsychological functioning, often with long term detrimental effects into adulthood.

1.3 SIGNIFICANCE/INNOVATION

1.3.1 Significance

According to the Department of Health and Human Services, there were approximately 702,000 victims of child abuse and neglect in the United States in 2014 (US DHHS, 2016). This equates to a rate of 9.4 victims per 1,000 children in the US population. The number is likely much higher since many cases of abuse are not reported. Exposure to childhood maltreatment can have detrimental and long lasting effects persisting into adulthood. There is evidence that individuals with a history childhood maltreatment are at increased risk for psychiatric disorders such as major depression, post-traumatic stress disorder (PTSD), alcohol and substance use disorders, and suicidal behavior as well as medical disorders such as obesity, cardiovascular disease, and diabetes and obesity (Anda et al, 2006; Nemeroff, 2016). Studies have also found that individuals who were exposed to early childhood trauma exhibit deficits in executive function and working memory and that these deficits often persist into adulthood (Barrera et al, 2013; Gould et al, 2012; Minzenberg et al, 2008; Narvaez et al, 2012; Pears and Fisher, 2005; Perna and Kiefner, 2013; Spann et al, 2012).

1.3.2 Innovation

There is a growing body of evidence suggesting that genes and their interactions with childhood maltreatment are areas for continued research. Further study of this sample, including gene-environment interactions, is warranted. This proposal aims to investigate the interactions between genes of the HPA axis and childhood maltreatment on executive function. Genetic

variability may explain some inconsistencies in neurobiological results. It is also possible that executive function may serve as a mediator between childhood maltreatment and psychiatric disorders. Long lasting impairments in executive function and working memory may affect the ability to learn and to problem solve during childhood and adolescence, which can lead to poorer functioning and increased risk for psychiatric disorders into adulthood. Executive function and memory deficits have been associated with suicide attempts (Keilp et al, 2013). Executive function may be an endophenotype of suicidal behavior through which genes of the HPA axis and childhood maltreatment increase the risk for suicidal behavior.

1.4 BACKGROUND

A literature search was conducted on published literature in Medline, PsychInfo, CINAHL, and Pub Med for articles published after the year 2000. The search terms were “Child Abuse”, “Child Maltreatment”, “Early Life Trauma” with “Executive Function”, “Mental Recall”, “Problem Solving” or Neuropsychological Tests”. Published articles that met the following criteria were included: Studies of childhood maltreatment including child abuse and/or neglect which included a validated neuropsychological testing battery that included measures of memory, attention, problem solving and/or executive function. Studies addressing autobiographical memory and repressed memories were excluded. Meta-analyses were also excluded. Assessment of maltreatment was not limited to validated measures. Five studies were included in which maltreatment was identified by Child Protective Services. Clear definitions of abuse and neglect were provided. One study was included in which maltreatment was identified via chart review.

1.4.1 Maltreatment and cognitive flexibility

Severe physical abuse and physical neglect were significantly associated with deficits in cognitive flexibility in adolescents aged 12-17 with no history of psychiatric disorder (Spann et al, 2012). Similar results were found in a small study of younger children with a documented history of physical or emotional abuse or neglect compared with controls (Perna and Kiefner, 2013). Children with a history of child sexual abuse who were involved in legal action against their abusers exhibited poorer performance on the Stroop test that controls (Barrera et al, 2013). The effects of neglect on executive function, including cognitive flexibility, were found even in children as young as 3-6 years of age in foster care (Pears and Fisher, 2005) A history of moderate to severe childhood trauma was associated with poorer cognitive flexibility in adult cocaine abusers (Narvaez et al, 2012), adults with borderline personality disorder (Minzenberg et al, 2008), as well adults with and without major depression (Gould et al, 2012), thus illustrating the long lasting detrimental effects.

1.4.2 Maltreatment and Memory

Moderate to severe childhood abuse and neglect were strongly associated with deficits in visual memory and spatial working memory in adults (Gould et al, 2012). Furthermore, childhood sexual abuse was associated with an additional visual working memory deficit than the physical or emotional forms of abuse in this sample (Gould et al, 2012). A small study (N=24) of 8-14 year old children with a documented history of sexual abuse did not find significant differences on performance on memory tests compared to healthy controls on performance on memory tests

after controlling for IQ and socioeconomic status (Porter et al, 2005) However, in a similar larger study (N=48), children with a documented history of physical or emotional abuse performed significantly poorer on measures of working memory (Perna and Kiefner, 2013). Neglected children also performed significantly lower on measures of language, learning and memory (DeBellis et al, 2009). Women with a history of early childhood penetrating sexual abuse and PTSD performed significantly worse on measures of declarative memory than women with a similar abuse history without PTSD or controls. There were also significant findings in this study between severity of abuse and declarative memory (Bremner et al, 2004). A strong, but not statistically significant association was found between duration of sexual abuse and poorer scores on memory tests, including short term, verbal, visual and global memory scores in college women with a history of repeated sexual abuse (Navalta et al, 2006). Adults with schizophrenia who had a history of moderate to severe childhood maltreatment exhibited significantly poorer working memory and episodic narrative memory than those who had exposure to low or no childhood maltreatment (Shannon et al, 2011). In a family study of adults with bipolar disorder, a history of emotional and sexual abuse was associated with poorer cognitive performance on verbal and visual recall memory tests (Savitz et al, 2008). Adults with borderline personality disorder and a history of abuse had a significantly lower percentage of recalled words on a memory test than those without a history of abuse and controls (Sala et al, 2009). In another study of adults with borderline personality disorder, the correlation between a history of childhood abuse and lower scores on recall and learning trended towards but did not reach statistical significance (Minzenberg et al, 2008).

1.4.3 Hypothalamic-Pituitary-Adrenal (HPA) Axis

Animal and human studies have shown that exposure to trauma early in life can lead to long-term dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. The role of the HPA axis when challenged with stress is to maintain homeostasis. Stress triggers the release of corticotropin releasing hormone (CRH) by the hypothalamus. In the initial stress response CRH acts at the CRH receptor 1 (CRHR1) in the pituitary gland to stimulate the release of adrenocorticotropic hormone (ACTH) from the adrenal cortex. A delayed, residual/adaptation occurs approximately 1-2 hours later and involves negative feedback regulation of cortisol on CRH receptor site 2 (CRHR2) (Gold et al, 1988). Figure 2 illustrates the cascade of activity occurring within the HPA axis with the onset of stress.

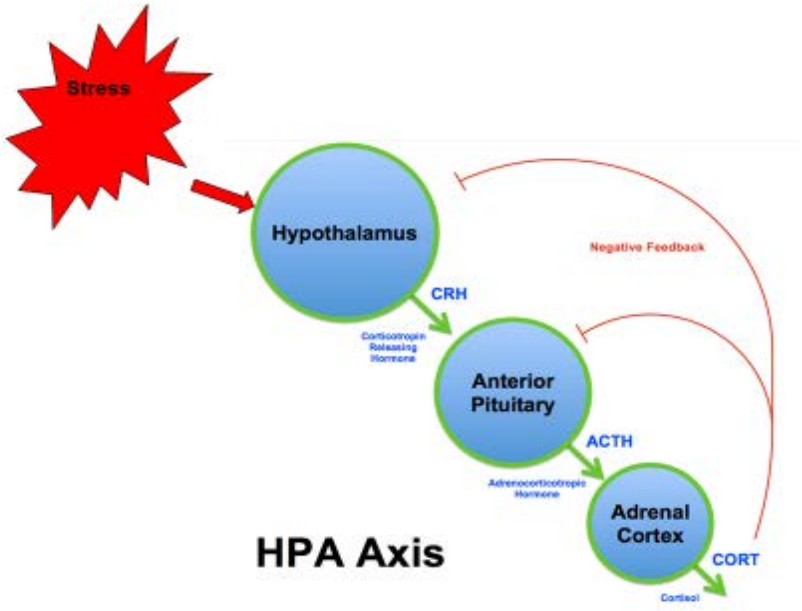

Figure 2. Hypothalamic-pituitary-adrenal (HPA) axis stress response (Boundless, 2016)

While the neurobiological effects of childhood maltreatment have been widely studied, there are conflicting results regarding the direction of the response of the HPA axis from hyperactivity to a blunted response (Nemeroff, 2016). Several factors may impact the effect of childhood maltreatment on HPA axis activity, including the type, severity, chronicity and number of episodes of maltreatment, age of first maltreatment, psychosocial support, additional traumatic events in adulthood, family history of psychiatric disorders, and genetic and epigenetic factors (Nemeroff, 2016). Longitudinal studies have found that over time, individuals move from HPA hyperactivity to a blunted response. According to McEwen' allostatic load theory, the body's stress response is protective in the short term, when glucocorticoids are elevated in response to stress and then return to normal after the stressor has ended . However, when faced with chronic stress, allostatic overload can have damaging effects over time, such as chronically dysregulated levels of glucocorticoids (McEwen and Wingfield, 2003). This dysregulation may explain conflicting results in the literature.

1.4.4 HPA Axis Genes of Interest

Figure 3 shows the genes of interest in the HPA Axis (Bogdan et al, 2013) were selected for study. These include: the Corticotropin Releasing Hormone (CRH) gene, the CRH Binding Protein (CRHBP) gene, the CRH Receptor 1 (CRHR1) gene, the CRH Receptor 2 CRHR2) gene, and the glucocorticoid receptor (GR) gene (NR3C1). CRH stimulates HPA axis to release cortisol and mediates the stress response in amygdala. CRHBP binds to CRH and inactivates it. CRHR1 initiates the stress response by stimulating the HPA axis. CRHR1 binds primarily to CRH and plays a role in mediating the stress response. CRHR2 binds to both CRH and urocortin and is involved in appetitive behaviors and stress. FKBP5 mediates the negative feedback loop

to terminate the stress response after exposure to the threat by activating the glucocorticoid receptor which induces FKBP5 transcription. Increased transcription impairs glucocorticoid receptor activity. The glucocorticoid receptor gene NR3C1 is involved in feedback inhibition of the HPA axis which impacts the duration of the stress response. NR3C1 has been implicated in studies of cognition and immune response. The mineralocorticoid receptor gene (NR3C2) affects glucocorticoid binding at the hippocampus and has been found to interact with childhood trauma on negative memory bias (Vrijsen et al, 2015). Stimulation of MR in healthy adults improved performance on a spatial memory task.

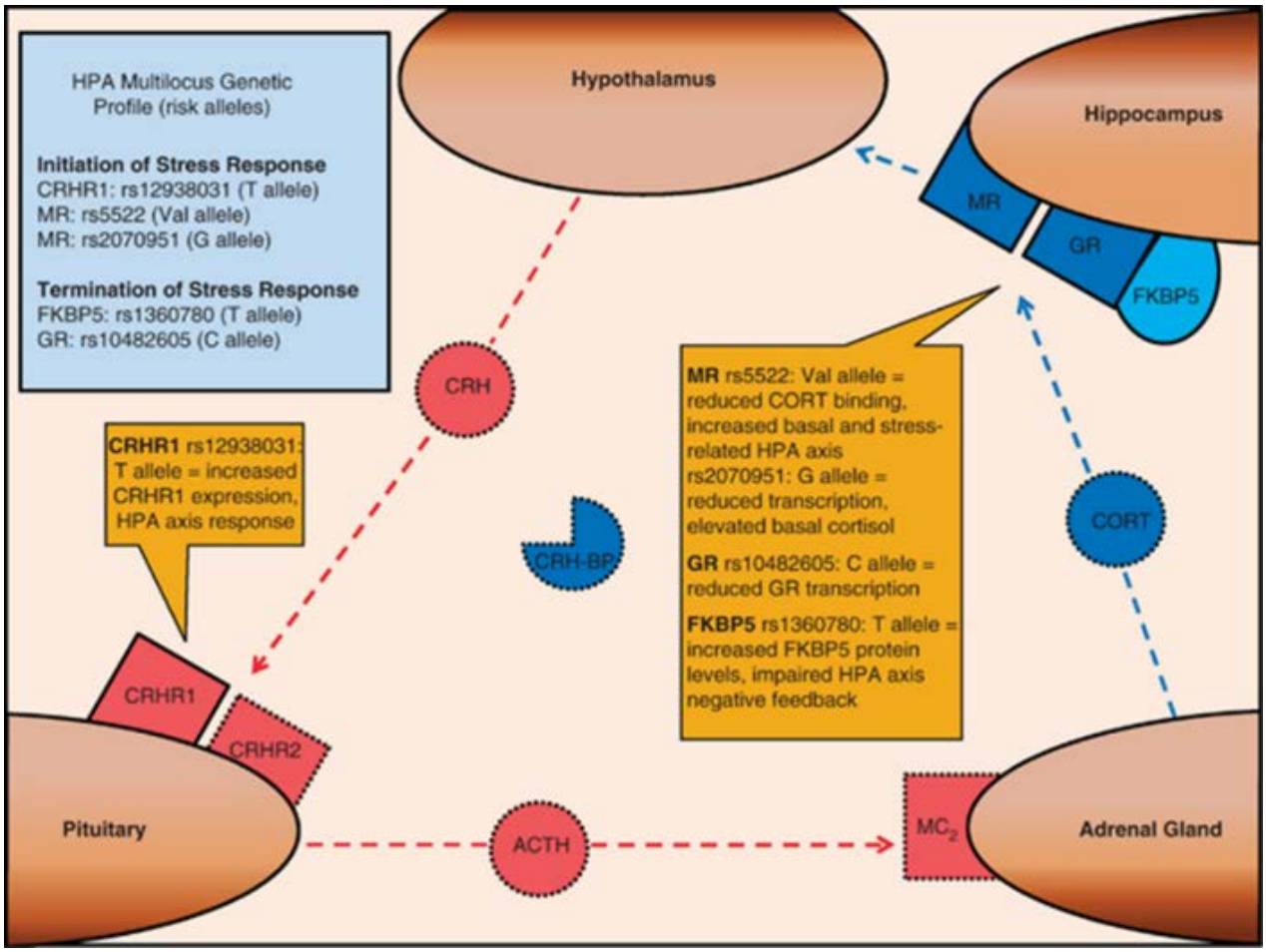

Figure 3. Genes of the HPA Axis (Bogdan et al, 2013)

1.4.5 GENE ENVIRONMENT INTERACTION

The interaction of childhood maltreatment and genes of the HPA axis have been associated with the development of psychiatric disorders. Polymorphisms in genes coding for CRHR1 appear to modulate the risk of early life trauma on the development of adult psychiatric disorders and suicide attempts (Ben-Efraim, et al, 2011). Functional polymorphisms in the serotonin transporter gene were found to moderate the effects of stressful life events on the development of depression and suicide attempts (Caspi et al, 2003). Further studies have also found that functional polymorphisms in the serotonin transporter gene moderate the relationship between childhood maltreatment and chronic depression (Brown et al, 2013) and recurrent depression (Fisher et al, 2013) but not with single episode depression (Uher et al, 2011), illustrating the long lasting impact of early childhood trauma. Additionally, in a bipolar family study, interactions between the low acting allele of the BDNF gene and the 4 allele of apolipoprotein-E (APO-E) gene with sexual abuse which resulted in poorer performance on memory tests (Savitz et al, 2007). Polymorphisms within CRHR1 and CRHR2 genes were found to interact with childhood sexual abuse and neglect on decision making in a sample of suicide attempters (Guillaume et al, 2013). In post-partum mothers, the direct path from childhood maltreatment to spatial working memory was not significant, but was indirectly related through hypothalamic-pituitary-adrenal cortex (HPA) function (Gonzalez, 2012). A meta-analysis found marginally significant interaction between life events and the serotonin transporter gene, but a highly significant effect for maltreatment (Karg et al, 2011). While many of these gene by environment studies focused on negative outcomes, it's likely that genes influence an individual's reaction to stress in both

positive and negative ways (Rutter, 2012). Hence, these genes may have protective effects making individuals more resilient to stress or risk effects leading to more negative outcomes.

1.5 PRELIMINARY WORK ON DISSERTATION STUDY

In order to address Aim 1, a secondary data analysis has been conducted examining the relationship between exposure to childhood trauma and neuropsychological outcomes in a subset of the sample that will be used for this proposal. Initial analyses were conducted for subjects age 10-21, and these same analyses will be performed for offspring older than 21.

A total of 299 subjects between the ages of 10-21 were included in the analyses. History of childhood maltreatment was assessed using the Childhood Trauma Questionnaire (CTQ). Subjects underwent an extensive neuropsychological testing battery. Standard research interviews were conducted for demographic information and psychiatric diagnoses. Multiple linear regression was used to test the hypotheses. After controlling for age, history of head injury, site, household income and lifetime history of major depression, anxiety disorders and ADHD, exposure to moderate to severe physical abuse significantly predicated poorer scores on tests of memory ($p=.006$). However, after False Discovery Rate (FDR) correction, physical abuse was no longer significant ($q=0.081$) and none of the covariates approached significance. There is a growing body of evidence suggesting that genes and their interactions with childhood maltreatment are areas for continued research. Further study of this sample, including gene-environment interactions, will be conducted.

1.6 RESEARCH DESIGN AND METHODS

This is a secondary data analysis of baseline neuropsychological, clinical psychiatric and genetics data from the Familial Pathways to Early Onset Suicide Attempt Study. The parent study is a "high risk" longitudinal study of the offspring of depressed parents. The primary goal of the parent study was to compare the offspring of depressed suicide attempters with the offspring of depressed non-attempters at baseline and at yearly follow-ups over a period of 15 years.

1.6.1 Setting and Sample

Recruitment methods for the Familial Pathways to Early Onset Suicide Attempt study have been described previously (Brent et al, 2002). Probands (parents) were eligible for the parent study if they met DSM-IV criteria for an Axis I Mood Disorder (Major Depressive Disorder or Bipolar Disorder) and had at least one offspring age 10 years or older who was willing to participate in the study. Complete psychiatric assessments including diagnostic interviews were conducted on all subjects at baseline and follow-up. All subjects underwent baseline neuropsychiatric testing. Offspring who were under 18 years at the time of baseline assessment also underwent an additional neuropsychiatric assessment battery at least 2 years later. Blood or buccal samples were collected from all subjects age 10 and older for genetic analyses.

The dataset for Aim 1 of the secondary analysis included 299 offspring age 10-21 and included baseline data only. However, only 54 of 299 offspring included in those analyses had genetic data available. By including offspring of all ages who have both neuropsychological and genetic data, the number of subjects will increase to 145. The analyses already conducted in Aim 1 will be repeated for offspring older than 21.

1.6.2 Neuropsychological battery

Estimated verbal IQ was obtained using the Peabody Picture Vocabulary Test, 3rd Revision (PPVT-III), a brief receptive vocabulary test that is very highly correlated with IQ (Dunn, 1977). Neuropsychological testing assessed the following domains: (1) attention (computerized Continuous Performance Test (CPT) and Stroop Color Word test); (2) memory (Buschke Selective Reminding Task (SRT) and Benton Visual Retention Test (VRT); (3) executive function (Wisconsin Card Sorting Test); (4) working memory (N-back and A, Not B) ; (5) language fluency (Letter and Category Fluency); (6) impulse control (Time production and Go-No Go), and (7) Psychomotor functioning (WAIS-III Digit Symbol and Trail Making). Neuropsychological testers for both sites were trained at Columbia University and weekly meetings were held between the two sites with in-person re-training occurring yearly. Test scores were adjusted for age, education, and gender based on available norms. Aggregate domain scores were computed according to the algorithm described by Keilp et al 2013 in which the principal measure from each task was averaged with others within each domain.

Attention was assessed using the Continuous Performance Test (CPT) (Cornblatt et al, 1988). The CPT used in this study was adapted from the Identical Pairs version of the test, which is a standard research measure of sustained attention. This task requires subjects to monitor a series of 4-digit numbers flashed for 50 msec at a rate of 1 per second, and to respond when the same 4-digit number appears twice in a row. Hit and false alarm rates were recorded and the signal detection indices d' (sensitivity) and Beta (response bias) are computed as outcome measures. Computerized Stroop Color/Word Task is an adaptation of the standard color-word paradigm (MacLeod, 1991). Subjects are required to identify, by keypress, the name or color of a stimulus presented on a computer screen. Stimuli remain on the screen until a response is generated and there is 50 msec before the next stimulus. Presented in 3 blocks are: 1) printed names of the colors red, blue and green; 2) strings of X's printed in red, blue and green; and 3) words red, blue and green printed in incongruous colors. Verbal memory was assessed with the Buschke Selective Reminding Test, a 10-minute task that uses a multiple trial list-learning test to assess verbal memory (Buschke & Fuld, 1974). Working memory was assessed using The Wisconsin Card Sorting Test which measures abstract concept formation and the ability to maintain and shift mental sets (Kongs et al, 2000). Behavioral inhibition was measured using the Go no-go test, in which stimuli are presented in a continuous stream and subjects are required to decide whether to make a motor response or to withhold the response based on an instruction given at the beginning of the test (Nosek & Banaji, 2001). The N-back is a working memory test in which stimuli are presented in a continuous stream and subjects are asked to make a motor response when a picture appearing a specified number of flashes before reappears (Jaeggi et al, 2010). Neuropsychological testers were trained at Columbia University and weekly meetings were held between the two sites with in-person re-training occurring yearly.

1.6.3 Assessment of maltreatment

The Child Trauma Questionnaire (CTQ) is a 28-item self-report, which provides a brief, reliable and valid screening for a history of child abuse and neglect (Bernstein et al, 1994). It gathers information about five types of maltreatment: emotional, physical, and sexual abuse, and emotional and physical neglect.

1.6.4 Justification for Gene Selection

Neurobiological studies support a relationship between of childhood maltreatment and the HPA axis. Genotypic data are available for the following HPA axis related genes: CRH, CRHBP, CRHR1, CRHR2, and NR3C1. Other HPA axis related genes that have been implicated to interact with maltreatment or have been associated with psychiatric outcomes are FKBP5 and NR3C2. Neither of these genes were included in the addiction array chip and were not available for the dissertation project. For the five available genes, a total of 49 SNPs were included on the chip. All 49 SNPs will be considered for inclusion in the analyses with priority first given to known functional SNPs. Then, SNPs implicated in the literature as associated with mental health outcomes will be added.

1.6.5 Confounders/Covariates

The covariates were selected based on the published literature and on study specific factors, including site differences. Because the original study was a family study, this sample of offspring included siblings. To control for family relationships, a cluster effect for family membership will be included in all models. Site, socioeconomic status, history of head injury, and presence of lifetime mood, anxiety, or attention deficit hyperactivity disorder will be entered as covariates in each model. A general demographic form was used to collect age, gender, race, ethnicity, and socioeconomic status. The same form also included general medical questions, including past history of head injury. Offspring age 18 years and older were assessed for the presence of lifetime and current Axis I disorders using the Structured Clinical Interview for DSM-IV Diagnoses (SCID-I) (Spitzer et al., 1990). The SCID-I is a semi-structured interview designed for assessment and differential diagnosis of Axis I psychiatric disorders, using DSM-IV criteria. At baseline, subjects were assessed for the presence of lifetime and current disorders. Offspring age 10-17 years were assessed at baseline with regards to Axis I psychopathology using the School Aged Schedule for Affective Disorders and Schizophrenia: Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The K-SADS-PL is a widely used diagnostic instrument designed to obtain both lifetime and current DSM-IV Axis I diagnoses administered as a semi-structured interview. Interviews were conducted by masters or doctorally prepared psychologists, social workers or nurses across two sites. Inter-rater reliability was routinely assessed, both within each site and across sites, for the variables under study in this secondary data analysis. Site, socioeconomic status, history of head injury, and presence of lifetime mood, anxiety, or attention deficit hyperactivity disorder will be entered as covariates in each model.

1.6.6 Genomic Data Collection

DNA was collected from all subjects by either blood or buccal samples. For blood samples, 20 ml of whole blood in EDTA tubes were shipped to the New York State Psychiatric Institute in New York, NY for DNA extraction. DNA samples were isolated as previously described from buffy coat fraction and from buccal mucosal cheek swabs (Higuchi, 1992; Huang et al, 2003). (BuccalAmp DNA Extraction Kit; Epicentre, Madison, Wisconsin, USA). Samples were genotyped using a beadchip (Illumina, San Diego, California (USA) which contained 1350 SNPs of 130 candidate genes implicated in addiction and alcoholism (Hodgkinson et al, 2008; Deo et al, 2013).

1.6.7 Sample Size Justification

The sample size is fixed because this is a secondary data analysis. The dataset for Aim 1 of the proposed secondary analysis included 299 offspring age 10-21 with baseline neuropsychological data. However, only 54 of those subjects also have genotypic data available. By including offspring of all ages who have both neuropsychological and genetic data, the number of subjects will increase to 145. The analyses already conducted in Aim 1 will be repeated for offspring older than 21. Because of the small sample size, the study will be insufficiently powered for generalizable results. However, pilot data from this study will be used to design a larger study in the future.

1.6.8 Data Analysis

1.6.8.1 Data Screening Procedures

Data will be screened for anomalies prior to analyses. Data screening procedures will include screening for accuracy of data, amount and patterns of missing data, potential outliers or influential points and potential violation of assumptions required for the analyses. Data will be thoroughly checked for accuracy by checking descriptive statistics, including means, standard deviations, ranges, and graphical representations of the data.

For the continuous variables (neuropsychological test results, PPVT scores, and income), central tendency will be examined by assessing mean and medians; dispersion will be assessed by standard deviation and range; and, skewness and kurtosis will be examined graphically. Categorical variables such as presence of Axis I diagnoses, abuse status, and history of head injury will be described in terms of frequency, percentages, modes and ranges. Data will be grouped by abuse status and by genotype status group and descriptive statistics will be assessed. Data will be assessed for missing data, including assessment of the amount of missingness and patterns of missingness. Independent t-tests will be run to compare the characteristics of those with missing data compared to those without. Little's test will be used to check patterns to determine if missing completely at random (MCAR). MVA imputation will be used for MCAR data. All variables will be checked for outliers. Categorical variables will be assessed for univariate outliers by listing frequencies and looking for variables with very uneven splits. For continuous variables, graphical methods,

including histograms, box plots, normal probability plots, will be used to assess for univariate outliers.These will be visually inspected to look for data points that are far removed from the majority of the distribution of the data. Additionally, for continuous variables, cases with very large z-scores ($|Z| > 3.29$) will be identified as univariate outliers.

Data will also be assessed for multivariate outliers to look for unusual combinations of values on two or more variables. Because data will be analyzed in groups, each group will be screened separately for outliers. Bivariate scatter plots, Mahalanobis distance, and regression will be used to assess for multivariate outliers. When outliers are identified, they will be further assessed to determine on which variables the outlier is discrepant. A decision will be made as to how to handle the outlier: whether it is accurately part of the sample or should be deleted, whether it should be modified, or whether the outliers are providing insight as to types of cases to which the results are not generalizable. In order to make this decision, dummy grouping variables will be created in order to attempt to identify the outlier. The dummy grouping variable will be used as the dependent variable in either discriminant functional analysis or logistic regression. The means for the outlying cases compared to the non-outlying cases will be assessed.

1.6.8.2 Underlying Assumptions

The data will be assessed to ensure that the four assumptions for regression are met: normality, independence, homoscedascity and linearity. The data will be assessed for univariate and multivariate normality. All dependent variables will be checked for normality looking at means, medians, mode and standard deviations. Histograms will be visually

inspected for skewness and kurtosis as well as Shapiro-Wilks and Kolmogorov Smirnoff tests. The data will be screened for independence by graphing bivariate scatterplots. Because family members are enrolled in this study, there are expected to be issues of dependence, which will be addressed. Linearity of the data will be assessed by generating bivariate graphs and scatterplots. For continuous variables, bivariate scatter plots will be used to assess for homoscedascity and Levene tests will be used to test whether variances are similar among groups. Data transformation will be used as a remedy for outliers and for failures of normality, linearity, and homoscedascity. Data will also be screened for multicollinearity by performing a simple linear regression and checking tolerance and variance inflation factors (VIF). If multicollinearity is present, a decision will be made as to whether to drop the variable or whether to create a new composite variable that is a function of the collinear variables. Residual analyses will be performed to see how well the data fits in the model using DFFITS, DFBetas and Cook's D. Studentized deleted residuals and leverage statistics will be used together to identify cases that might be very influential.

1.6.8.3 Data Analysis Procedures

Because the parent study was a family study, this sample of offspring will include siblings. To control for family relationships, a cluster effect for family membership will be included in all models. To correct for multiple comparisons, Yekutieli's False Discovery Rate (FDR) will be used (Yekutieli & Benjamini, 1999).

1.6.8.4 Aim 1 Data Analysis Procedures: To examine the effect of childhood maltreatment on neuropsychological functioning

Multiple linear regression will be used to test the first aim. Dependent variables will be the domain scores for neuropsychological testing. Each domain will be examined separately as the dependent variable. The independent variable will be exposure to maltreatment before the age of 18. Site, socioeconomic status, history of head injury, and presence of lifetime mood, anxiety, or attention deficit hyperactivity disorder will be entered as covariates.

1.6.8.5 Aim 2 Data Analysis Procedures: To explore the relationship of polymorphisms in genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) with neuropsychological functioning

This aim will also be assessed using multiple linear regression. The same dependent variables will be studied, but now the independent variables of interest will be genotype. Each domain will be examined separately as the dependent variable. The genotypes of CRH, CRHBP, CRHR1, CRHR2, and NR3C1 will be assessed together for the effect of genes of the HPA axis as well as individually. The polymorphisms to be assessed for each gene are displayed in the Table 1. Site, socioeconomic status, history of head injury, and presence of lifetime mood, anxiety, or attention deficit hyperactivity disorder will be entered as covariates.

1.6.8.6 Aim 3 Data Analysis Procedures: To explore the gene by environment interactions between genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) and exposure to childhood maltreatment on neuropsychological functioning

The gene environment interactions will be obtained by entering the independent variables from aims 1 and 2: exposure to maltreatment before the age of 18 and genotype. The dependent variables will be domain scores for neuropsychological testing. Separate regression models will be estimated for each domain. Site, socioeconomic status, history of head injury, and presence of lifetime mood, anxiety, or attention deficit hyperactivity disorder will all be entered as covariates. Interactions between the independent variables will be tested.

For aims 1-3, regression coefficients and confidence intervals will be reported. Hypothesis testing will be conducted using the F-test statistic. R^2 values for the model will be reported as well as R^2 change and part and partial correlations to assess the additive effect of independent variables and interactions.

1.7 LIMITATIONS

There are several limitations to this pilot study. This study is a secondary data analysis with a small sample size. Because procedures were completed at different phases of this longitudinal study, the number of offspring with complete data (both genomic data and neuropsychological data) is small. Due to the small sample size and the larger number

of variables are being examined, the study is likely to be underpowered. Additionally, the genomic analyses performed for this study were completed several years ago and do not include all of the genes of interest associated with the HPA axis. Unfortunately, genomic data was not available for FKBP5 or NR3C2, which have been implicated in several studies of childhood maltreatment. While the CTQ is considered to be the "gold standard" in the study of childhood maltreatment, there are limitations in the use of self-report due to the tendency to under report and the use of retrospective recall of maltreatment. However, while the questionnaire assesses the presence or absence of abuse and maltreatment before the age of 18, there is no assessment of the age that the various types of maltreatment occurred. There is some evidence that age of exposure to childhood trauma may be associated with the severity of deficits in executive function and this may be related to disruption of neural development during critical periods of development. There is also data to suggest that the severity of trauma and the number of traumas experienced may be associated with more severe deficits in executive function and working memory. The data generated from this pilot study may be used to support a future larger studies. These limitations will be considered in the design of future studies.

1.8 RISKS TO HUMAN SUBJECTS

1.8.1 IRB Approval Status

The research proposal was approved by the University of Pittsburgh IRB as an exempt study under 45 CFR 46.101 b 4 for the analysis of data currently in existence. The exemption was justified because the proposal involves the secondary analysis of data from a previously

approved research study. The consent forms from the original study were reviewed by the IRB, and they contained no restrictive language that would prohibit the sharing of deidentified data for future research. All data are available for study, and no identifiers or sensitive information were provided to the student.

1.8.2 Source of Materials

All data provided to the student for this secondary analysis is provided in a de-identified manner and coded only by subject number and a family identification number. Samples have already been genotyped using a beadchip microarray. Only data related to HPA axis genes will be analyzed by the student.

Genetic samples (blood or buccal samples) were collected from most subjects in the Familial Pathways to Early Onset Suicide Attempt study at the time of the baseline assessment. However, during the first 5 years of the study, the University of Pittsburgh IRB did not permit the collection of genetic samples from children under the age of 18. At that time, all genetic research was considered to be “greater than minimal risk”. In this study, it was also considered to present no direct benefit to subjects. Therefore, it was not permitted under Subpart D without special permission from DHHS. Over the course of the study, the IRB deemed the study activities to be minimal risk and permitted collection of genetic samples from children in this study. Attempts were made to obtain genetic material from all subjects without samples at their next time point.

2.0 SUMMARY OF STUDY

The purpose of this dissertation research was: (1) to examine the effect of childhood maltreatment on neuropsychological functioning, (2) to examine the effect of polymorphisms in genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) on neuropsychological functioning, and (3) to explore gene environment interactions between genes of the HPA axis and exposure to childhood maltreatment on neuropsychological function. Unpublished manuscripts related to this dissertation project can be found in the appendices. A review of the literature entitled "*The effects of childhood abuse and neglect on executive function and memory- a review of the literature*" can be found in Appendix D. This paper described the body of literature illustrating the long-lasting and detrimental effects of childhood maltreatment on executive function and memory. The literature review also provided support for further examination of genes of the HPA axis and gene-environment interactions. A preliminary analysis that provided the basis for Aim 1 can be found in Appendix E, entitled "*The effects of childhood maltreatment on neuropsychological functioning*".

2.1 PROPOSAL CHANGES

After the dissertation proposal was approved, the following changes were made to the proposal in order to maximize the sample size.

1. Subjects less than or equal to 21 years of age were compared with subjects greater than 21years of age. There were no significant differences between the groups other than lifetime history of depression and anxiety. Offspring of all ages were included in the analyses for Aims 1-3.

2. Covariates were assessed for missing data. History of head injury was included as a covariate in the preliminary analyses. Further evaluation of the data found that history of head injury was ascertained by asking a single "yes/no" question on the adult version of the demographic form, and was not available for offspring less that age 18 at baseline. Head injury was not significant as a covariate in any of the models ran for the preliminary analyses. Removing head injury as a covariate added 83 additional subjects to the data analyses.

3. Dependent variables were assessed for missing data. It was noted that the psychomotor domain had large amounts of missing data. Additionally, the data were skewed and not normally distributed, with Shapiro Wilkes test p=.000. The psychomotor domain was not included in the data analyses.

4. The conceptual framework was revised to reflect the removal of head injury as a covariate and the psychomotor domain as a dependent variable.

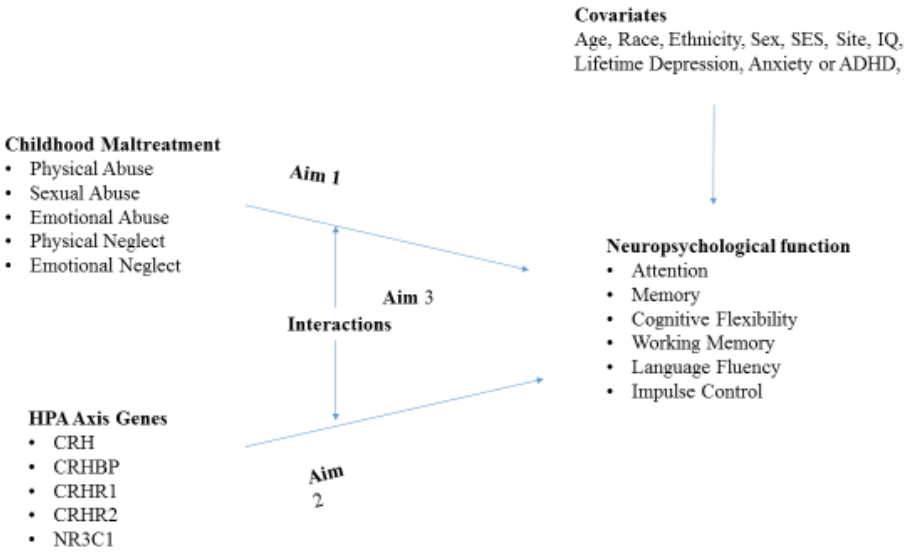

Figure 4. Revised Conceptual Framework

3.0 DATABASED MANUSCRIPT: THE EFFECTS OF CHILDHOOD MALTREATMENT AND GENOMIC VARIATION IN THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS ON NEUROPSYCHOLOGICAL FUNCTIONING IN OFFSPRING OF DEPRESSED PARENTS

3.1 ABSTRACT

Background: Childhood maltreatment has negative and potentially long-lasting effects, including increased risk for psychiatric and medical disorders and poor academic functioning. The primary role of the hypothalamic-adrenal-pituitary (HPA) axis is to maintain homeostasis when challenged with stress. Genomic variation in genes of the HPA axis may play a role in the effects of maltreatment on neuropsychological functioning.

Objectives: The aims of the dissertation study were (1) to examine the effect of childhood maltreatment on neuropsychological functioning; (2) to examine the effects of polymorphisms in genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) with neuropsychological functioning; and (3) to explore gene environment interactions between genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) and exposure to childhood maltreatment on neuropsychological function.

Methods: This was a secondary data analysis of baseline neuropsychological testing, clinical psychiatric assessments, and genomic data from the Familial Pathways to Early Onset Suicide Attempt Study (PI: David A Brent, MD). The analysis included a total of 369 subjects in Aim 1 and 145 subjects in Aims 2 and 3. Multiple linear regression was used to analyze the effects of the independent variables (maltreatment, genotype, and their interactions) on neuropsychological functioning.

Results: Moderate to severe physical abuse was associated with poorer performance in the memory domain (p=.006). After controlling for multiple comparisons, results were no longer significant, but continued to trend toward significance (q=.088). Moderate to severe emotional abuse was associated with better scores on measures of verbal fluency (p=.03), but the results were no longer significant after FDR correction for multiple comparisons. Before FDR testing, significant protective effects were detected for two SNPs in the CRHBP gene and one SNP in the CRHR2 gene; and significant risk effects were detected for two SNPs in the CRHR1 gene and one SNP in the NR3C2 gene. However, after FDR corrections, only one result remained significant, a protective effect for CRHBP SNP rs7704995 on the Impulse Control Domain. There were no significant gene environment interactions detected.

Conclusions: Our findings are consistent with the literature showing that moderate to severe physical abuse is associated with deficits in memory. Our genomic findings suggest that genes in the HPA axis may have some effect on neuropsychological functioning, but our sample sizes were small and results were not significant after controlling for multiple comparisons. Further work in this area is needed with larger sample sizes including all the relevant genes of the HPA axis to determine whether genomic variation in genes of the HPA axis have a direct effect on neuropsychological functioning.

3.2 BACKGROUND

Childhood maltreatment continues to be a major public health problem in the United States, with approximately 702,000 reported victims of child abuse and neglect in 2014 (US DHHS, 2016). The number is likely to be much higher since many cases of maltreatment are not reported. Exposure to childhood maltreatment can have detrimental and long lasting effects persisting into adulthood. Adults with a history of childhood maltreatment are at increased risk for psychiatric disorders such as major depression, post-traumatic stress disorder (PTSD), alcohol and substance use disorders, and suicidal behavior as well as medical disorders such as obesity, cardiovascular disease, and diabetes and obesity (Anda et al, 2006, Nemeroff, 2016).

Deficits in cognitive flexibility were found in adolescents exposed to severe physical abuse and physical neglect (Spann et al, 2012), in younger children with a history of physical or emotional abuse or neglect (Pears and Fisher, 2005; Perna and Kiefner, 2013) and victims of childhood sexual abuse (Barrera et al, 2013). Deficits in the memory domains have also been found in children with a history of physical or emotional abuse (Perna and Kiefner, 2013), and poorer scores on language, learning and memory tests were found in children with a history of neglect (DeBellis et al, 2009).

A history of moderate to severe childhood maltreatment was associated with poor cognitive flexibility in adult cocaine abusers, adults with borderline personality disorder, and adults with and without major depression (Gould et al, 2012; Minzenberg et al, 2008; Narvaez et

al, 2012). Exposure to childhood maltreatment has also been found to negatively impact performance on tests of executive function and memory and those deficits may persist into adulthood (Barrera et al, 2013; Gould et al, 2012; Minzenberg et al, 2008; Narvaez et al, 2012; Pears and Fisher, 2005; Perna and Kiefner, 2013; Spann et al, 2012). Adults with a history of moderate to severe childhood abuse and neglect exhibited memory deficits, including visual memory and spatial working memory, and victims of childhood sexual abuse were found to have additional visual working memory deficits than those with other forms of maltreatment (Gould et al, 2012). Memory deficits were found in adults with mood disorders, substance use disorders and personality disorders who were exposed to childhood maltreatment (Sala et al, 2009; Savitz et al, 2008).

Animal and human studies have shown that exposure to trauma early in life can lead to long-term dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. The role of the HPA axis when challenged with stress is to maintain homeostasis. Stress triggers the release of corticotropin releasing hormone (CRH) by the hypothalamus. In the initial stress response CRH acts at the CRH receptor 1 (CRHR1) in the pituitary gland to stimulate the release of adrenocorticotropic hormone (ACTH) from the adrenal cortex. A delayed, residual/adaptation occurs approximately 1-2 hours later and involves negative feedback regulation of cortisol on CRH receptor site 2 (CRHR2) (Gold et al, 1988). While the neurobiological effects of childhood maltreatment have been widely studied, there are conflicting results regarding the direction of the response of the HPA axis from hyperactivity to a blunted response (Nemeroff, 2016). Several factors may be involved in the effect of childhood maltreatment on HPA axis activity, including the type, severity, chronicity, and number of episodes of maltreatment, age of first maltreatment,

psychosocial support, additional traumatic events in adulthood, family history of psychiatric disorders, and genetic and epigenetic factors (Nemeroff, 2016). Longitudinal studies have found that over time, maltreated individuals move from HPA hyperactivity to a blunted response (Tyrka et al, 2009). According to McEwen' allostatic load theory, the body's stress response is protective in the short term, when glucocorticoids are elevated in response to stress and then return to normal after the stressor has ended. However, when faced with chronic stress, allostatic overload can have damaging effects over time, such as chronically dysregulated levels of glucocorticoids (McEwen & Wingfield, 2003).

In one of the first groundbreaking studies of interactions between stressful life events and genes on psychiatric outcomes, functional polymorphisms in the serotonin transporter gene were found to moderate the effects of stressful life events on the development of depression and suicide attempts (Caspi et al, 2003). Further studies also found that functional polymorphisms in the serotonin transporter gene moderate the relationship between childhood maltreatment and chronic depression (Brown et al, 2013) and recurrent depression (Fisher et al, 2013) but not with single episode depression (Uher et al, 2011), illustrating the long lasting impact of early childhood maltreatment. The interaction of childhood maltreatment and genes of the HPA axis have also been associated with the development of psychiatric disorders. Polymorphisms in genes coding for CRHR1 appear to modulate the risk of early life trauma on the development of adult psychiatric disorders and suicide attempts (Ben-Efraim, et al, 2011; Boscarino et al, 2012; Bradley et al, 2007; DeYoung et al, 2011; Grabe et al, 2010; Ishitobi et al, 2012; Laucht et al, 2013; Papiol et al, 2007; Polanczyk et al, 2009; Ray et al, 2013; Ressler et al, 2010; Roy et al, 2012; Starr et al, 2014; Wasserman et al, 2008; Wasserman et al, 2009; Weber et al, 2015).

While gene environment interactions have been studied with respect to psychiatric disorders, few studies have looked at whether interactions between genes and childhood maltreatment play a role in neuropsychological outcomes. In a bipolar family study, interactions between the low acting allele of the BDNF gene and the 4 allele of apolipoprotein-E (APO-E) gene with sexual abuse which resulted in poorer performance on memory tests (Savitz et al, 2007). Polymorphisms within CRHR1 and CRHR2 genes were found to interact with childhood sexual abuse and neglect on decision making in a sample of suicide attempters (Guillaume et al, 2013). In post-partum mothers, the direct path from childhood maltreatment to spatial working memory was not significant, but was indirectly related through hypothalamic-pituitary-adrenal cortex (HPA) function (Gonzalez, 2012). This study included direct measures of cortisol and did not include a genomic component. Variation in the CRHR1 gene has been found to modulate the effect of age on working memory (Grimm et al, 2015) in a study of aging. Interaction between the CRHR1 gene was found to interact with childhood maltreatment on measures of working memory and task accuracy decreased as the severity of maltreatment increased (Fuge et al, 2014)

Based on this information, it was hypothesized that exposure to childhood maltreatment, genes of the HPA axis and their interaction would be associated with deficits in neuropsychological functioning in offspring of depressed parents. The specific aims of the dissertation study were:

- Specific Aim 1: To examine the effect of childhood maltreatment on neuropsychological functioning
- Specific Aim 2: To examine the effect of polymorphisms in genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) on neuropsychological functioning
- Specific Aim 3: To explore gene environment interactions between genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) and exposure to childhood maltreatment on neuropsychological function.

3.3 MATERIALS AND METHODS

3.3.1 DESIGN

This was a secondary data analysis of baseline neuropsychological, clinical psychiatric and genomic data from the Familial Pathways to Early Onset Suicide Attempt Study, referred to as the FamPath study (Brent et al, 2002). The parent study was a "high-risk" longitudinal study of the offspring of depressed parents. The primary goal of the parent study was to compare the offspring of depressed suicide attempters with the offspring of depressed non-attempters at baseline and at yearly follow-ups for up to 15 years. Parents with mood disorders were recruited from inpatient units, partial hospitalization programs, and outpatient clinics. Although only cross sectional baseline neuropsychological data were used for this secondary analysis, the parent study had a recruitment period lasting from 1997-2000 and follow-ups continued until 2013. There were several changes to the assessment battery over the 15 years of the study, resulting in missing data for several variables, which will be addressed below.

3.3.2 SETTING/SAMPLE

The settings for the parent study have been described previously (Brent et al, 2002). The parent study was conducted at two sites: New York State Psychiatric Institute (PI: J. John Mann, MD) and Western Psychiatric Institute and Clinic (PI: David A. Brent, MD). Probands (parents) were eligible for the parent study if they met DSM-IV criteria for an Axis I Mood Disorder (Major Depressive Disorder or Bipolar Disorder) and had at least one offspring age 10 years or older who was willing to participate in the study. A total of 701 offspring of 334 probands were enrolled into the study across both sites. Complete psychiatric assessments including diagnostic interviews were conducted at baseline and follow-up. Probands and offpsring underwent baseline neuropsychological testing. Offspring who were under 18 years at the time of baseline assessment also underwent an additional neuropsychological assessment battery at least 2 years later. Blood or buccal samples were collected from subjects age 10 and older for genomic analyses.

3.3.3 NEUROPSYCHOLOGICAL BATTERY

Neuropsychological testing assessed the following domains: (1) attention (computerized Continuous Performance Test (CPT) and Stroop Color Word test); (2) memory (Buschke Selective Reminding Task (SRT) and Benton Visual Retention Test (VRT); (3) abstract/contingent learning (Wisconsin Card Sorting Test); (4) working memory (N-back and A, Not B) ; (5) language fluency (Letter and Category Fluency); and (6) impulse control (Time production and Go- No Go). Neuropsychological testers for both sites were trained at

Columbia University and weekly meetings were held between the two sites with in-person re-training occurring yearly. Test scores for offspring less than 18 years old were adjusted for age, education, and gender based on available norms. Domain scores were calculated by adjusting for age, education and/or gender effects based on available norms. The principal measure from each task was averaged with others within each domain to calculate domain scores, according to Keilp's algorithm which was previously described (Keilp et al. 2013).

Estimated verbal IQ was obtained using the Peabody Picture Vocabulary Test, 3rd Revision (PPVT-III), a brief receptive vocabulary test that is very highly correlated with IQ (Dunn, 1977). Attention was assessed using the Continuous Performance Test (CPT) (Cornblatt et al, 1988). The CPT used in this study was adapted from the Identical Pairs version of the test, which is a standard research measure of sustained attention. This task requires subjects to monitor a series of 4-digit numbers flashed for 50 msec at a rate of 1 per second, and to respond when the same 4-digit number appears twice in a row. Hit and false alarm rates were recorded and the signal detection indices d' (sensitivity) and Beta (response bias) are computed as outcome measures. Computerized Stroop Color/Word Task is an adaptation of the standard color-word paradigm (MacLeod, 1991). Subjects are required to identify, by keypress, the name or color of a stimulus presented on a computer screen. Stimuli remain on the screen until a response is generated and there is 50 msec before the next stimulus. Presented in 3 blocks are: 1) printed names of the colors red, blue and green; 2) strings of X's printed in red, blue and green; and 3) words red, blue and green printed in incongruous colors. Verbal memory was assessed with the Buschke Selective Reminding Test, a 10-minute task that uses a multiple trial list-learning test to assess verbal memory (Buschke & Fuld, 1974).

The Wisconsin Card Sorting Test was used to measure abstract concept formation and the ability to maintain and shift mental sets (Kongs et al, 2000). Behavioral inhibition was measured using the Go No-Go test, in which stimuli are presented in a continuous stream and subjects are required to decide whether to make a motor response or to withhold the response based on an instruction given at the beginning of the test (Nosek & Banaji, 2001). The N-back is a working memory test in which stimuli are presented in a continuous stream and subjects are asked to make a motor response when a picture appearing a specified number of flashes before reappears (Jaeggi et al, 2010). Neuropsychological assessments were not added to the study until year 6, and there were changes to the testing battery over the course of the longitudinal study, resulting in missing neuropsychological data. Patterns of missing data were assessed for the dependent variables (Table 2).

3.3.4 MALTREATMENT

The Childhood Trauma Questionnaire (CTQ) is a 28-item self-report, which provides a brief, reliable and valid screening for a history of child abuse and neglect (Bernstein et al, 1994). It gathers information about five types of maltreatment: emotional, physical, and sexual abuse, and emotional and physical neglect. The CTQ was added at Year 6, so not all subjects have complete data for this measure. Because the CTQ is widely used and considered to be the gold standard for assessment of childhood maltreatment, the CTQ was used for these data analyses even though a smaller number of subjects were available for the analyses.

3.3.5 GENE SELECTION

As indicated in the background, neurobiological studies support a relationship between childhood maltreatment and the HPA axis. Genotypic data were available in this dataset for five HPA axis related genes: The corticotropin releasing hormone (CRH) gene stimulates HPA axis to release cortisol and mediates the stress response in amygdala. The CRH Binding Protein (CRHBP) binds to CRH and inactivates it. The CRH Receptor 1 (CRHR1) gene initiates the stress response by stimulating the HPA axis. CRHR1 binds primarily to CRH and also plays a role in mediating the stress response. CRH Receptor 2 (CRHR2) binds to both CRH and urocortin and is involved in appetitive behaviors and stress. The glucocorticoid receptor gene NR3C1 is involved in feedback inhibition of the HPA axis which impacts the duration of the stress response. A total of 49 SNPs across these 5 genes were included on the addiction array chip. All 5 genes play important roles in the HPA axis.

3.3.6 COVARIATES

The covariates were selected based on the published literature as well as study specific factors. There were significant site differences in the sample with lower household income at the Pittsburgh site ($p=.001$) and higher numbers of Hispanic subjects at the NY site ($p<.001$), which were included as covariates. Age, sex, race, ethnicity, IQ, site, socioeconomic status, and presence of lifetime mood, anxiety, or attention deficit hyperactivity disorder (ADHD) were entered as covariates into each model. Age, race, ethnicity, sex and socioeconomic status

were collected using a general demographic form, which also included general medical questions, including past history of head injury. Offspring age 18 years and older were assessed for the presence of lifetime and current Axis I disorders using the Structured Clinical Interview for DSM-IV Diagnoses (SCID-I) (Spitzer et al., 1990). The SCID-I is a semi-structured interview designed for assessment and differential diagnosis of Axis I psychiatric disorders, using DSM-IV criteria. At baseline, subjects were assessed for the presence of lifetime and current disorders. Offspring age 10-17 years were assessed at baseline with regards to Axis I psychopathology using the School Aged Schedule for Affective Disorders and Schizophrenia: Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The K-SADS-PL is a widely used diagnostic instrument designed to obtain both lifetime and current DSM-IV Axis I diagnoses administered as a semi-structured interview. Interviews were conducted by masters' or doctorate prepared psychologists, social workers or nurses across two sites. Inter-rater reliability was routinely assessed, both within each site and across sites, for the variables under study in this secondary data analysis.

3.3.7 COLLECTION OF GENOMIC SAMPLES AND GENOTYPING PROCEDURES

During the first five years of the study, the University of Pittsburgh's IRB did not permit collection and assessment of genomic material from subjects under 18 years of age. Therefore, blood or buccal samples for genomic analyses were obtained throughout the study as subjects turned 18. In 2002, the IRB's policies changed allowing for collection of genomic material from children. The New York site did not have restrictions for the collection of genomic material, therefore samples were collected at baseline for subjects enrolled into the study.

DNA was collected by either blood or buccal samples. For blood samples, 20 ml of whole blood in EDTA tubes were shipped to the New York State Psychiatric Institute in New York, NY for DNA extraction. DNA samples were isolated as previously described from buffy coat fraction and from buccal mucosal cheek swabs (Higuchi, 1992; Huang et al, 2003). (BuccalAmp DNA Extraction Kit; Epicentre, Madison, Wisconsin, USA). Samples were genotyped using a beadchip (Illumina, San Diego, California (USA) which contained 1350 SNPs of 130 candidate genes implicated in addiction and alcoholism (Hodgkinson et al, 2008; Deo et al, 2013). Genotyping procedures used for the Familial Pathways study were described by Deo et al, 2013 (p. 49):

> *"Genotyping was performed using the Illumina GoldenGate genotyping protocols on 96-well format Sentrix arrays. Five hundred nanograms of sample DNA was used per assay. All pre-PCR processing was performed using a TECAN liquid handling robot running Illumina protocols. Arrays were imaged using an Illumina Beadstation GX500 and the data were analyzed using GenCall v6.2.0.4 and GTS Reports software v5.1.2.0 (Illumina). Genotype data quality control and filtering was performed as described previously (Hodgkinson et al., 2008). Briefly, genotypes with low GenCall scores (<0.25) were considered as undetermined. The GenCall score is a value between 0 and 1, yielding a confidence score for that genotype call (the higher the score, the higher the confidence in the call), and is derived from the tightness of the clusters for a given locus and the position of the sample relative to its cluster. The cluster plots for all SNPs were examined individually and where there was insufficient separation of the three genotype clusters, the SNP was not included in the analyses. Loci with a call rate more than 90%*

were included. In addition, SNPs were excluded from analysis if the minor allele was detected in fewer than 5% of the samples. Of the total 1350 loci genotyped, 1045 (77%) passed these quality control criteria and were subsequently used in downstream analyses. Furthermore, the genotyping call rates did not vary by the source and method of DNA preparation. Finally, all genotypes from the family data were examined for Mendelian errors using the PEDCHECK software (O'Connell and Weeks, 1998), and no errors were detected."

A total of 49 SNPs across 5 genes in the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) were included on the chip as shown in Table 15. Ten SNPs were identified as functional SNPs. However, 8 functional SNPs were dropped due for quality control purposes, and there was no allelic variation found in the dataset for 1 functional SNP. The remaining functional SNP (CRHR2 rs8192498) was included in the analyses (Table 16). CRHR2 is located on chromosome 7p14.3 and is a protein coding gene. CRHR2 rs8192498 is a missense polymorphism in which the nucleotide guanine is changed to adenine (GTC to ATC), resulting in a change in the amino acid from V[Val] to I[Ile]. This is considered to be a benign variant with unknown clinical significance.

Based on the literature review, a total of 17 SNPs available on the chip were implicated as SNPs associated with psychiatric disorders, suicidal behavior, or gene-environment interactions (Table 17). One of those SNPs was found to have no allelic variation in the dataset, and was dropped from the analyses. In summary, one functional SNP and 16 SNPs implicated in the literature were available for the analyses, for a total of 17 SNPs: CRHBP (rs3792738,

rs6453267, rs1875999, rs10474485; rs7704995, and rs1500), CRHR1 (rs4792887, rs110402, rs242924; rs81189, rs242939, rs173365, and rs17689918), CRHR2 (rs2190242 and rs8192498), and NR3C1 (rs10482672 and rs2918419).

Allele frequencies were compared between 1000 Genomes, the full Fam Path study dataset, and the dataset analyzed for this manuscript. The results were similar across these samples (Table 20). All SNPs were in Hardy Weinberg Equilibrium (HWE) except for rs6453267 in the CRHBP gene and rs242939 in the CRHR1 gene.

Linkage disequilibrium (LD) was assessed to determine whether any of the functional SNPs without data were in LD with SNPs available in the dataset. However, none were in LD. SNPs within the same gene were also assessed for LD (Table 18). Two SNPs in the CRHBP gene (rs7704995 and rs1500) were found to be in complete LD (R^2=1.00). Therefore, only one of the SNPs (rs7704995) was used in the analyses. Additionally, in the CRHR1 gene, 3 SNPs were in high LD with each other, rs110402, rs242924, and rs81189 (R^2=0.93 to 0.97).

3.4 STATISTICAL ANALYSES

Statistical analyses were run using STATA version 14.1 (StataCorp, 2015). Post-hoc power calculations were run using GPower 3.1.

3.4.1 PRELIMINARY ANALYSES

The sample size is fixed because this is a secondary data analysis. The dataset used for the preliminary analyses included 299 offspring age 10-21 with baseline neuropsychological data and CTQ data. The sample was limited to younger offspring to assess the effects of childhood maltreatment on neuropsychological functioning closer in time to the occurrence of maltreatment. However, only 54 of those subjects also had genomic data available. By including offspring of all ages who have both neuropsychological and genomic data, the number of subjects increased to 145 for the genomic data analyses (Aims 2 and 3).

After reviewing the data and assessing patterns of missingness, offspring of all ages were included in the analyses to maximize the number of subjects with complete data on CTQ, neuropsychological testing and genomic testing. To ensure there were no differences between age groups, the offspring in the 21 and younger age group (n=260) were compared with the offspring in the greater than 21 age group (n=109) (Tables 3-5). The age groups did not differ significantly on demographic variables except for race, with a higher percentage of Caucasians in the older group. The groups were also similar in terms of clinical variables except for a higher percentage of lifetime depression and anxiety in the older group, which would be expected, since the older group has lived longer. Therefore, all offspring were included in the analyses, for a total of 369 subjects in Aim 1 and 145 available subjects in Aims 2 and 3.

3.4.2 MULTIVARIATE ANALYSES

The sample was characterized with regards to demographic and clinical variables using standard univariate descriptive statistics. T-tests were used to examine site differences in the variables of interest and in the covariates (age, race, ethnicity, income, IQ, depression, anxiety, and head injury). There were significant site differences in the sample with lower household income at the Pittsburgh site ($p=.001$) and a higher numbers of Hispanic subjects at the NY site ($p<.001$). These variables were included as covariates. Bivariate correlations were evaluated between the covariates, the CTQ subscales and the neuropsychological domains (Tables 6-8). Multiple linear regression was used to test each hypothesis in Aims 1-3. Each domain was examined separately as the dependent variable. The domain scores were normally distributed. For Aim 1, the independent variables of interest were exposure to moderate to severe maltreatment before the age of 18 per the CTQ. Moderate to severe maltreatment was entered into the regression model as a dichotomous variable using the scoring procedure described by Bernstein et al 1994. For Aim 2, genotype was the independent variable of interest. For Aim 3, exposure to moderate to severe maltreatment, genotype and their interactions were the independent variables of interest. Age, gender, race, ethnicity, site, socioeconomic status, IQ, and presence of lifetime mood, anxiety, or ADHD were entered as covariates in each model for Aims 1-3. Because the parent study was a family study and included siblings, a cluster effect for family membership was included in all regression models. To control for multiple comparisons for correlated test statistics, Yekutieli's False Discovery Rate (FDR) analyses were used (Yekutieli & Benjamini, 1999). Post-hoc power calculations were run for results that reached significance in the

regression models as well as for those with non-significant results.

3.5 RESULTS

Demographic and clinical characteristics of the sample are presented in Table 1. A total of 369 subjects underwent baseline neuropsychological assessments. The number of subjects evaluated for each domain varied depending on the time point at which the test was added to the study procedures and whether the subject completed the tests. The average age at the time of neuropsychiatric assessment was 18.1 years and the sample included nearly equal numbers of males and females (52% and 48%, respectively). Childhood maltreatment was reported by 44% of offspring.

Aim 1: To examine the effect of childhood maltreatment on neuropsychological functioning

The full regression models are shown in tables 9-14). Significant results were found in two domains, described below.

Memory domain

Multiple regression was run with memory domain as the dependent variable and moderate to severe physical abuse as the independent variable, controlling for age, race, ethnicity, gender, site, IQ, household income and lifetime history of major depression, anxiety disorders and ADHD. In the full regression model, a history of moderate to severe physical abuse predicted poorer scores in the memory domain (β = -.53; 95% CI= -.90, -.15; p=.006) (Table 9). After FDR correction, moderate to severe physical abuse was no longer significant but continued to trend towards significance (q=.088) and none of the covariates approached

significance (q's>.30). A large effect size was detected (d=-.55). Post hoc power analyses were conducted and found that we were well powered [power (1-β) = 1.0] to detect a change in R^2.

Language Fluency Domain

Interestingly, significant results in a positive direction were found in the language fluency domain (Table 11). After controlling for age, race, ethnicity, gender, site, IQ, household income and lifetime history of major depression, anxiety disorders and ADHD, exposure to moderate to severe emotional abuse predicted better scores on measures of language fluency (β = .32; 95% CI= .04, .60; p=.03). A moderate effect size was found (d=.35). The results were no longer significant after FDR correction (q=.397). Post hoc power analyses were conducted and found that we were adequately powered [power (1-β) = .99].

There were no significant results or trends in any of the other domains.

Aim 2: To explore the relationship of polymorphisms in genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) with neuropsychological functioning

Separate multiple regressions were conducted with genotype as the independent variable and each neuropsychological domain as the dependent variable. The same covariates used in Aim 1 were entered into each regression equation. Covariates that were not statistically significant were removed from the final model except for age, sex, race, ethnicity, and IQ. We used an additive model for genotypes where each genotype was coded as 0= homozygote for

major allele, 1=heterozygote, 2= homozygote for minor allele. This is approach is commonly used in genome wide association studies (GWAS).

Before FDR testing, significant protective effects were detected for two SNPs in the CRHBP gene and one SNP in the CRHR2 gene; and significant risk effects were detected for two SNPs in the CRHR1 gene and one SNP in the NR3C2 gene (Table 21).

CRHBP. In the CRHPB gene, rs3792738 minor allele (A) was associated with better performance on tests of Abstract/Contingent Learning Domain (β = .31; 95% CI= .08, .54; p=.008), after controlling for age, race, ethnicity, sex and IQ. However, the effect size was small (std. beta =.18). After FDR correction, the result was no longer significant (q=.118). The sample size for this regression model was 102. Post hoc power analyses found power (1-β) = .70.

Also in the CRHBP gene, rs7704995 minor allele (T) was significantly associated with higher scores in the Impulse Control Domain (β = .52; 95% CI= .19, .85; p=.003) after controlling for age, race, ethnicity, sex, IQ, a lifetime history of depression, and lifetime history of ADHD. The effect size was modest (std. β= .47). After FDR correction, the result remained significant (q=.044). The sample size was small (n=62). Post hoc power analyses found power (1-β) = .77.

CRHR1. Two SNPs in the CRHR1 gene were associated with lower scores in the Attention Domain. After controlling for age, race, ethnicity, sex, IQ, and lifetime history of anxiety, the rs4792887 minor allele (T) was significantly associated with poorer functioning in the Attention Domain (β = -.21; 95% CI= -.42, -.01; p=.04), but the effect size was small (std. β= - .15). After FDR correction, the results were no longer significant (q=.588). Post hoc power analyses were conducted and power was found to be (1-β) = .70.

CRHR1 SNP rs242939 minor allele (G) was also significantly associated with lower scores in the Attention Domain after controlling for age, race, ethnicity, sex, IQ, lifetime history of depression and lifetime history of ADHD (β = -.46; 95% CI= -.68, .23; p=.00), with a moderate effect size (std. β = -.31). After FDR correction, the results remained close to significance (q=.059). Post hoc power analyses were conducted and power was found to be adequate, (1-β) = .91.

CRHR2. After controlling for age, race, ethnicity, sex, and IQ, functional allele rs8192498 minor allele (A) had a significant protective effect with higher scores in the language fluency domain (β = .65; 95% CI= (.08, 1.21; p=.03). The effect size was small (std. β = .13). The results were no longer significant after FDR correction (q=.441). The sample size was very small in this model (n=68). Post hoc power analyses were conducted and power was found to be inadequate, (1-β) = .38.

NR3C1. Minor allele (G) of rs2918419 significantly predicted lower scores in the memory domain after controlling for age, race, ethnicity, sex, IQ and site (β = -.67; 95% CI= -1.24, -.10; p=.02), with a small effect size (std. β = .13). After FDR correction, results were no longer significant (q = .294). Post hoc power analyses showed inadequate power ((1-β) = .34).

Aim 3: To explore the gene by environment interactions between genes of the HPA axis (CRH, CRHBP, CRHR1, CRHR2, and NR3C1) and exposure to childhood maltreatment on neuropsychological functioning

Significant genotypes in Aim 2 were analyzed for interactions. Multiple regression was performed separately for each neuropsychological domain. In each regression model, genotype and maltreatment variables (moderate to severe physical, sexual and emotional abuse and physical and emotional neglect) were entered into each model and assessed for independent effects and interactions, with the same covariates used in Aim 2. Due to small sample sizes, regression models analyzing interactions between moderate to severe sexual abuse and genotype would run only for CRHR1 rs4792887, with no significant findings. CRHR2 rs8192498 had no allelic variation in the subset of cases for this aim. Thus, interaction models for this SNP were not analyzed.

CRHBP. In the CRHPB gene, rs3792738 minor allele (A) continued to have a significant independent protective effect on the Abstract/Contingent Learning Domain in each model where maltreatment was also included as an independent variable, controlling for age, race, ethnicity, sex, and IQ (Table 22). In the model including both moderate to severe

emotional abuse and genotype, both had independent protective effects (p=.04 and .01, respectively), but no significant interaction was found between maltreatment and genotype.

Also in the CRHBP gene, rs7704995 minor allele (T) continued to have a significant protective effect on the Impulse Control Domain in each model where maltreatment type was also included as an independent variable, controlling for age, race/ethnicity, sex, IQ, lifetime history of depression and anxiety (Table 23). Exposure to childhood maltreatment had no significant effect on the Impulse Control Domain when included in the models with genotype and there were no significant interactions found between maltreatment and genotype.

CRHR1. The rs4792887 minor allele (T) continued to have a significant negative effect on the Attention Domain in models containing moderate to severe physical or sexual abuse and emotional neglect (Table 24). There were no significant independent effects of childhood maltreatment on the Attention Domain when included in the model with genotype. There were no significant interactions found between childhood maltreatment and genotype on the Attention Domain.

CRHR1 SNP rs242939 minor allele (G) continued to have a significant negative effect on the Attention Domain when entered into regression models with each type of childhood maltreatment while controlling for age, race, ethnicity, sex, IQ, lifetime history of anxiety and lifetime history of ADHD (Table 25). There were no independent effects of exposure to childhood maltreatment detected and no interactions between genotype and childhood maltreatment.

NR3C1. Minor allele (G) of rs2918419 continued to have a significant independent negative effect on the Memory Domain when entered into models containing physical abuse, physical neglect or emotional neglect (Table 26). Models including emotional abuse or sexual abuse with genotype would not run. Moderate to severe physical abuse and genotype were found to have significant independent negative effects on the Memory Domain ($p = .02$ and .03, respectively). However, no significant interaction was found between physical abuse and genotype.

3.6 DISCUSSION

Aim 1. Our study found that moderate to severe physical abuse predicted poorer scores in the memory domain, which is consistent with the literature suggesting that individuals with a history of childhood physical abuse exhibit deficits in measures of memory. The literature also suggests that the severity of trauma and the number of traumas experienced may be associated with more severe deficits (Spann et al, 2012; Nolan and Ethier, 2007). Our study included exposure to moderate to severe childhood maltreatment in each model, but we did not have data regarding the number of traumas experienced nor their duration. Per McEwen's allostatic load theory, exposure to chronic maltreatment would result in allostatic overload and unstable levels of glucocorticoids over long periods of time. In the initial stress response, glucorticoids play an important role in the formation of memories in the hippocampus, so that dangerous situations or events can be avoided in the future (Roozendaal, 2000). However, prolonged dysregulation of glucocorticoids can lead to atrophy in the

hippocampus, an area of the brain where neurogenesis occurs (McEwen and Wingfield 2003), which may lead to potentially long term negative consequences in cases of chronic dysregulation. There is evidence in the literature that the age of exposure to childhood trauma may affect the severity of deficits (Pears and Fisher, 2005; Bucker et al, 2012), which may be related to disruption of neural development during critical periods of development (Hensch, 2005). Anderson and Teicher (2008) describe the structural vulnerabilities to stress in the brain during critical periods of development. In our study, we know that exposure to trauma occurred prior to age 18, but the exact age was not ascertained and are difficult to assess retrospectively in any case. The profound effects of childhood trauma on the developing brain can cause long lasting impairments in executive function and working memory and can impact the ability to learn and to problem solve during childhood and adolescence, which can lead to poor performance and further increased stress and allostatic overload, placing these children at even higher risk for psychiatric disorders into adulthood.

There is vast literature showing that a history of maltreatment increases the risk of psychiatric disorders and suicide attempts (Nemeroff, 2016). It is possible that deficits in memory may potentially mediate the relationship between maltreatment and suicide attempt.

Our study found that individuals with a history of emotional abuse performed better on measures of language fluency. There is a dearth of literature supporting this finding. Emotional abuse has not been as widely studied as other forms of maltreatment and is not consistently defined across the literature. There is also considerable overlap between emotional abuse and other forms of maltreatment, both in our study and in other studies of

maltreatment. The CTQ items included in the emotional abuse domain included: (1) Called names by family. (2) Parents wished never born. (3) Felt hated by family. (4) Family said hurtful things. (5) Was emotionally abused. Since both groups (those with a history of maltreatment and those without) were offspring of depressed parents who had varying levels of severity and chronicity of depressive symptoms, this would not explain the difference between groups. Nor would it explain any positive effects of emotional abuse on verbal fluency. Choi et al, 2010 found that parental verbal abuse was associated with alterations in neural pathways responsible for language development, but there were no significant differences on verbal IQ or verbal comprehension between subjects exposed to parental verbal abuse and controls. Similarly, a review by Teicher & Samson (2015) suggested that maltreatment appeared to specifically target brain regions and pathways through which the maltreatment is experienced. While the predominant view of researchers is that maltreatment is harmful for the developing brain, the brain may be modified by early stress in a potentially adaptive way (McEwen, 2016; Teicher & Samson, 2016). Although our results were no longer significant after FDR correction, a moderate effect size was found. This is an interesting area worthy of further study.

Aims 2 and 3. While there is ample literature describing the relationship between HPA axis genes with cortisol expression and psychiatric outcomes, this is one of the first studies to our knowledge to examine the direct effects of HPA axis genotypes and interactions with maltreatment on neuropsychological domains.

Our study found that CRHBP rs3792738 minor allele (A) was associated with better performance on tests of Abstract/Contingent Learning Domain and rs7704995 minor allele (T)

was associated with higher scores in the Impulse Control Domain. There have been no other similar protective findings reported in the literature. CRHBP binds to CRH and inactivates it decreasing the cortisol response. Hyperactivity and impulsivity have been associated with blunted cortisol response in children with ADHD (van West et al, 2009).

CRHBP rs3792738 minor allele has been found to be correlated with stress induced cigarette cravings (Erblich et al, 2012). CRHBP rs7704995 was significantly associated with alcohol use disorders in Caucasians (OR for 11 vs 22 was 1.6 (1.0–2.5, 95% CI). No CRHBP genes were found to be associated with suicidal behavior (Roy et al, 2013). The implications of this finding are unclear at this time.

CRHR1. In our study, two SNPs in the CRHR1 gene, rs4792887 minor allele (T) and rs242939 minor allele (G), were significantly associated with lower scores in the Attention Domain**.** The CRHR1 gene has been implicated in depression and anxiety. Concentration and attention difficulties are key symptoms of both depression and anxiety. Homozygotes for the rs4792887minor allele (TT) have been found to produce the most basal cortisol throughout the day, while homozygotes for the major allele (CC) produce the least (Obasi et al, 2015). Higher levels of cortisol have been found to disrupt attention (Corominas-Roso et al, 2015).

CRHR1 rs242939 minor allele (G) is associated with peri- and postnatal depression (Engineer et al, 2013; Tan et al, 2015) and recurrent MDD (Liu et al, 2013; Xiao et al, 2011) and interacted with negative life events to predict MDD (Liu et al, 2006). CRHR1 rs242939 has also been studied for effects on antidepressant drug response (Liu et al, 2007; Ventura-Junca et al, 2014), but no similar findings associated with attention were found in the literature.

CRHR2. In our study, functional allele rs8192498 minor allele (A) had a significant protective effect with higher scores in the language fluency domain (p=.03). As described earlier, this missense polymorphism changes the nucleotide guanine to adenine (GTC to ATC), which results in a change in the amino acid from V[Val] to I[Ile]. This is considered to be a benign variant with unknown clinical significance.

NR3C1. In our study, minor allele (G) of rs2918419 significantly predicted lower scores in the memory domain. Lower cortisol levels have been associated with better performance on a short term memory task (Vedhara et al, 2000). It is possible that rs2918419 impacts memory through cortisol levels.

3.7 LIMITATIONS AND FUTURE CONSIDERATIONS

There were several limitations to this pilot study. The parent study, by design, enrolled offspring who specifically selected for the study because they were at high risk of negative outcomes due to parental psychopathology. Hence, these results may not be generalizable because the sample did not represent the full spectrum of risk and was already skewed in terms of negative outcomes. There was no healthy control group. Our small sample sizes in the genomic analyses were also a limitation. Because procedures were completed at different phases of a 15-year longitudinal study, the number of offspring with complete data (maltreatment data, genomic data and neuropsychological data) is small. Additionally, the genomic analyses performed for this study were completed several years ago and did not include all

genes of interest across the HPA axis. Unfortunately, genotypic data was not collected for two important genes in the HPA pathway. FKBP5 has been implicated in several studies of childhood maltreatment, suicide and treatment response. The MR receptor gene, NR3C2, affects glucocorticoid binding at the hippocampus and has been found to interact with childhood trauma on negative memory bias (Vrijsen et al, 2015). Stimulation of MR in healthy adults improved performance on a spatial memory task. Additionally, the genomic analyses did not capture all of variability across the genes available for the analyses as they were limited to the known SNPs of interest at the time of the analyses. Large GWAS studies have implicated other genes, not in the HPA axis, to be associated with cognitive function (Athanasiu et al, 2016) and major psychiatric disorders (Stein et al, 2016). In our study, race and ethnicity were included as covariates, but we were unable to stratify by race due to small sample size.

While the CTQ is considered to be the "gold standard" in the study of childhood maltreatment, there are limitations to the use of self-report, including the tendency to under report and the use of retrospective recall of maltreatment. Age of exposure to maltreatment was not collected. There is evidence that age of exposure to childhood trauma may be associated with the severity of deficits in executive function. These limitations will be considered in the design of future studies.

Our findings are consistent with the literature showing that moderate to severe physical abuse is associated with deficits in memory. Our genomic findings suggest that genes in the HPA axis may have some effect on neuropsychological functioning, but our

sample sizes were small and results were not significant after controlling for multiple comparisons. Further work in this area is needed with larger sample sizes including all the relevant genes of the HPA axis to determine whether genomic variation in genes of the HPA axis have a direct effect on neuropsychological functioning.

3.8 IMPLICATIONS FOR NURSING PRACTICE

Childhood maltreatment has detrimental short term and long term effects on victims. Nurses have many opportunities to make an impact. (1) Nurses can be integral in preventing maltreatment through programs such as the Nurse Family Partership (Olds, 2008), which consisted of nurse home visits prenatally until 2 years of age. These programs have shown that nurses are very effective in this role. (2) Nurses are instrumental in detecting childhood maltreatment in hospitals and clinical settings. Early detection and intervention is vital to protect the child and mitigate the long term consequences. (3) Advanced practice nurses must be mindful that exposure to maltreatment can lead to cognitive difficulties which may affect treatment. A history of childhood maltreatment was found to be a significant moderator of both short-term and long-term response to cognitive behavioral therapy (CBT) combined with antidepressant therapy (Asarnow et al, 2009; Vitiello et al, 2011). Individuals with a history of maltreatment may have difficulty completing the tasks involved in CBT due to the effects of childhood maltreatment on executive function and memory. (4) As further research is conducted, there may be interventions that can affect or ameliorate the long term

biological effects of maltreatment. McEwen (2016) proposed several interventions shown to increase hippocampal and/or amygdala volume and to increase blood flow to the prefontal cortex, including regular physical activity, mindfulness based stress reduction and improving social support and integration. According to McEwen, these activities may actually promote reversal of the negative effects caused by prolonged stress and allostatic overload, although further research is needed to support this hypothesis. Advanced practice nurses may be instrumental in the design, implementation and delivery of interventions that may reverse negative changes in the brain caused by childhood maltreatment. Further research is warranted in this area.

APPENDIX A

DATA BASED MANUSCRIPT TABLES

Table 1. Descriptive Statistics for Total Sample (n=369)

Variable	Statistics
Age (years); M, SD (range)	18.11, 6.64 (10-38)
Household income (Hollingshead scale); M, SD (range)	4.56, 2.83 (1-9)
Site (Pittsburgh); N,%	253, 72%
Sex (Female); N,%	181, 52%
Race (Caucasian); N,%	216, 63%
Ethnicity (Non-Hispanic); N,%	314, 90%
Head Injury; N,%	71, 26.5%
Lifetime depression; N,%	149, 43%
Lifetime bipolar; N,%	18, 5%
Lifetime anxiety; N,%	131, 38%
Lifetime ADHD; N,%	61, 18%
Physical abuse (score >=10); N,%	49, 14%
Sexual abuse (score >= 8); N,%	33, 9.43%
Emotional abuse (score >=15); N,%	68, 19.43%
Physical neglect (score >=10); N,%	91, 25.93%
Emotional neglect (score >=15); N,%	59, 16.86%

Table 2. Assessment of missing data - dependent variable by domain

	Test included Domain Score	Age ≤21 n=260	Age >21 n=109	Comments
Attention	Continuous Performance Test Stroop	245	102	
Abstract/ Contingent Learning	Wisconsin Card Sorting	242	104	
Working Memory	N-Back A not B	249	88	
Language Fluency	Controlled Oral Word Association: word and category fluency	178	39	Controlled Oral Word Association not done in Fam Path 3
Memory	Buschke Benton Visual Retention Test	178	39	Benton not done in Fam Path 3
Impulse Control	Time Production Go-No-Go	168	38	Time production not done in FamPath 3

Table 3. Assessment of missing data-covariates

	Age ≤ 21 n=260	**Age >21 n=109**
Hispanic	258	109
Caucasian	254	109
Site	260	109
Head Injury	**190**	**96**
Income	256	109
IQ (PPVT)	254	107
Lifetime Depression	258	109
Lifetime Anxiety	258	109
Lifetime ADHD	253	106

Table 4. Differences by age groups- continuous variables

	Age ≤21		Age >21		t-	p-value
	mean	n	mean	n	statistic	
Household income	4.59	298	4.29	109	0.9448	0.35
Emotional Abuse Score	9.19	260	9.22	90	-0.065	0.95
Physical Abuse Score	7.03	260	7.03	90	.0120	0.99
Sexual Abuse Score	6.01	260	5.96	90	0.124	0.90
Emotional Neglect Score	10.35	260	11.18	90	-1.585	0.11
Physical Neglect Score	8.07	260	8.04	90	.057	0.95

Table 5. Differences by age groups – categorical variables

	Age ≤21		Age >21		χ^2	p-value
	Count	%	Count	%		
Site (Pittsburgh)	184/260	72%	82/109	75%	0.759	0.38
Sex (Female)	123/260	47%	57/109	52%	0.764	0.38
Caucasian	**123/254**	**60%**	**78/109**	**72%**	**4.23**	**0.04**
Hispanic	29/229	11%	7/109	6%	2.01	0.16
Head Injury	48/190	25%	31/96	32%	1.58	0.21
Lifetime Depression	**89/258**	**35%**	**66/109**	**61%**	**20.32**	**0.00***
Lifetime Anxiety	**80/258**	**31%**	**58/109**	**53%**	**16.10**	**0.00***
Lifetime ADHD	47/253	19%	15/106	14%	1.02	0.31
Moderate to Severe Emotional Abuse (score ≥13)	53/260	20%	15/90	17%	0.590	0.442
Moderate to Severe Physical Abuse (score≥10)	39/260	15%	10/90	11%	0.840	0.359
Moderate to Severe Sexual Abuse (score≥8)	24/260	9%	9/90	10%	0.046	0.830
Moderate to Severe Emotional Neglect (score≥15)	41/260	16%	18/90	20%	0.854	0.355
Moderate to Severe Physical Neglect (score≥10)	68/260	26%	23/91	25%	0.027	0.869
Any Abuse	77/260	30%	24/90	27%	0.2832	0.595
Any Neglect	81/260	31%	32/91	35%	0.4968	0.481

Table 6. Correlations between types of maltreatment

	Emotional abuse	Physical abuse	Sexual abuse	Emotional neglect	Physical neglect
Emotional abuse	1.00				
Physical abuse	**0.38***	1.00			
Sexual abuse	**0.29***	**0.24***	1.00		
Emotional neglect	**0.34***	**0.24***	**0.17***	1.00	
Physical neglect	**0.37***	**0.27***	**0.24***	**0.38***	1.00

^=p<.05 *p<.01

Table 7. Correlations between moderate to severe maltreatment and covariates

	Site	Head injury	Sex	Household Income	Age	PPVT	Lifetime Depression	Lifetime Anxiety	Lifetime ADHD
Emotional abuse	0.03	0.07	0.09	**-0.15***	0.02	**-0.14***	**0.15***	0.07	0.07
Physical abuse	-0.01	-0.01	-0.05	**-0.16***	-0.03	-0.09	0.09	0.08	0.08
Sexual abuse	-0.02	-0.01	**0.16***	**-0.13**^	0.02	**-0.11**^	**0.13**^	**0.12**^	0.02
Emotional neglect	-0.06	-0.001	-0.03	**-0.21***	0.10	**-0.16***	**0.17***	0.09	0.01
Physical neglect	-0.02	0.05	-0.09	**-0.20***	0.03	**-0.16***	**0.14***	0.07	0.03

^=p<.05
*p<.01

Table 8. Correlations between covariates

	Site	Head injury	Sex	Household Income	Age	PPVT	Lifetime Depression	Lifetime Anxiety	Lifetime ADHD
Site	1.00								
Head injury	-0.02	1.00							
Sex	0.006	-0.16	1.00						
Income	**-0.17***	0.07	0.02	1.00					
Age	0.01	0.09	0.03	-0.02	1.00				
PPVT	0.02	0.06	**-0.15***	**0.45***	**-0.20***	1.00			
Lifetime Depression	0.005	0.06	-0.002	-0.07	**0.38***	-0.10	1.00		
Lifetime Anxiety	-0.06	-0.03	0.03	-0.03	**0.28***	**-0.13^**	**0.41***	1.00	
Lifetime ADHD	0.07	0.06	**-0.20***	-0.04	-0.08	0.03	**0.14^**	0.04	1.00

^=p<.05 *p<.01

Table 9. Aim 1 regression analysis memory domain

(n=189)	β 95% CI	p- value	Effect size 95% CI	FDR
Physical Abuse	**-.53** **(-.90, -.15)**	**0.006**	**-0.55** **(-0.93, -0.17)**	**.088**
Sexual Abuse	-.091 (-.49, .31)	0.650	-0.09 (-0.57, 0.38)	
Emotional Abuse	-.03 (-.37, .30)	0.849	-0.03 (-0.39, 0.33)	
Physical Neglect	-.18 (-.47, .11)	0.219	-0.19 (-0.50, 0.13)	
Emotional Neglect	-.27 (-.69, .15)	0.201	-0.28 (-0.67, 0.11)	

Table 10. Aim 1 regression analysis working memory domain

(n=295)	β 95% CI	p- value	Effect size 95% CI
Physical Abuse	.05 (-.20, .30)	0.686	0.06 (-0.27, 0.39)
Sexual Abuse	-.17 (-.54, .21)	0.390	-0.19 (-0.58, 0.20)
Emotional Abuse	.06 (-.15, .28)	0.556	0.07 (-0.21, 0.36)
Physical Neglect	-.06 (-.27, .15)	0.581	-0.0681 (-0.33, 0.19)
Emotional Neglect	.14 (-.05, .34)	0.156	0.16 (-0.15, 0.48)

Table 11. Aim 1 regression analysis language fluency domain

(n=189)	β 95% CI	p- value	Effect size 95% CI	FDR
Physical Abuse	-.11 (-.40, .20)	0.510	-0.11 (-0.49, 0.27)	
Sexual Abuse	.10 (-.32, .53)	0.634	0.11 (-0.36, 0.59)	
Emotional Abuse	**.32** **(.04, .60)**	**0.027**	**0.35** **(-0.01, 0.71)**	**.397**
Physical Neglect	.16 (-.08, .40)	0.199	0.17 (-0.15, 0.49)	
Emotional Neglect	.08 (-.22, 398)	0.587	0.09 (-0.29, 0.47)	

Table 12. Aim 1 regression analysis impulse control domain

(n=180)	β 95% CI	p- value	Effect size 95% CI
Physical Abuse	-.08 (-.40, .25)	0.641	-0.10 (0.49, 0.29)
Sexual Abuse	-.15 (-.52, .21)	0.405	-0.20 (-0.67, 0.28)
Emotional Abuse	-.05 (-.34, .23)	0.708	-0.07 (-0.43, 0.30)
Physical Neglect	.06 (-.20, .31)	0.666	0.07 (-0.25, 0.40)
Emotional Neglect	-.14 (-.49, .21)	0.424	-0.18 (-0.58, 0.22)

Table 13. Aim 1 regression analysis abstract/contingent learning

(n=310)	β 95% CI	p- value	Effect size 95% CI
Physical Abuse	-.01 (-.23, .22)	0.950	-0.01 (-0.33, 0.31)
Sexual Abuse	.003 -(.26, .27)	0.984	0.004 (-0.38, 0.39)
Emotional Abuse	-.04 (-.21, .13)	0.638	-0.0626 (-0.34, 0.22)
Physical Neglect	-.10 (-.25, .05)	0.171	-0.16 -(0.41, 0.09)
Emotional Neglect	.05 (-.13, .22)	0.606	0.07 (-0.23, 0.36)

Table 14. Aim 1 regression analysis attention domain

(n=305)	β 95% CI	p- value	Effect size 95% CI
Physical Abuse	-.06 (-.38, .26)	0.714	-0.08 (-0.41, 0.25)
Sexual Abuse	.08 (-.24, .39	0.626	0.10 -0.29, 0.50
Emotional Abuse	-.13 (-.34, .09)	0.254	-0.17 (-0.46, 0.12)
Physical Neglect	-.08 (.29, .12)	0.421	-0.11 (-0.37, 0.14)
Emotional Neglect	.09 (-.15, .33)	0.453	0.12 (-0.18, 0.43)

Table 15. HPA axis SNPs included in addiction array

CRH	CRHBP	CRHR1	CRHR2	NR3C1
rs12721511	rs3792738	rs9900679	rs8192492	rs13306585
rs3176921	rs32897	rs4792887	rs3779250	rs864082
rs6472257	rs6453267	rs110402	rs2240403	rs33391
rs5030875	rs7718461	rs242924	rs973002	rs10482672
	rs1875999	rs16940655	rs8192498	rs33389
	rs10474485	rs81189	rs8192495	rs852982
	rs7704995	rs242939	rs2190242	rs17339455
	rs1500	rs173365	rs2284217	rs7730946
		rs17689918	rs2267717	rs2918419
			rs6967702	rs6877893
			rs4723002	rs6861962
			rs255102	rs6195
			rs255105	rs6192
			rs255125	rs6190

Table 16. Functional SNPs

CRH	**rs12721511***			
CRHR1	rs16940655*			
CRHR2	rs8192492^	rs2240403*	**rs8192498**	rs8192495*
NR3C1	rs33391*	rs6195*	rs6192^	rs6190*

*Data missing in dataset

^No allelic variation in dissertation dataset

Table 17. SNPs implicated in the literature

CRHBP	**r**s3792738	**r**s6453267	rs1875999	rs10474485	rs7704995	rs150**0**	
CRHR1	rs4792887	rs110402	rs242924	rs81189	rs242939	rs173365	rs17689918
CRHR2	rs2190242	rs2267717^					
NR3C1	rs10482672	rs2918419					

^No allelic variation in dissertation dataset

Table 18. Linkage disequilibrium (LD)

Gene	SNPs	Distance	R^2
CRHBP	rs7704995	2301	1.000
	rs1500		
CRHR1	rs110402	5329	0.967
	rs242924		
	rs242924	9432	0.967
	rs81189		
	rs81189	14761	0.934
	rs110402		

Table 19. Complete list of SNPs included in analysis

CRHBP	rs3792738	rs6453267	rs1875999	rs10474485	rs7704995*	rs1500*	
CRHR1	rs4792887	rs110402*	rs242924*	rs81189*	rs242939	rs173365	rs17689918
CRHR2	rs2190242	rs8192498					
NR3C1	rs10482672	rs2918419					

*in LD

Table 20. Allele Frequencies

	Allele Frequency 1000 Genomes	Allele Frequency Fam Path (all)	Allele Frequency Dissertation Dataset
CRHBP			
rs3792738	C=0.9065	C= 0.9196	C= 0.8945
	A=0.0935	A= 0.0804	A= 0.1055
rs6453267	G=0.9163	G= 0.9478	G= 0.9324
	A=0.0837	A= 0.0522	A= 0.0676
rs1875999	T=0.5725	A= 0.6023	A= 0.6396
	C=0.4275	G= 0.3977	G= 0.3604
rs10474485	C=0.7067	C= 0.7222	C= 0.7387
	A=0.2933	A=0.2778	A= 0.2613
rs7704995*	C=0.5058	T= 0.5514	T= 0.4685
	T=0.4942	C= 0.4486	C= 0.5315
rs1500*	C=0.5094	C= 0.4535	C= 0.5270
	G=0.4906	G= 0.5465	G= 0.4730
CRHR1			
rs4792887	C=0.8700	C= 0.8397	C= 0.7864
	T=0.1300	T= 0.1603	T= 0.2136
rs110402*	G=0.4389	C=0.6072	C= 0.6351
	A=0.5611	T= 0.3928	T= 0.3649
rs242924*	G=0.4363	C=0.6194	C= 0.6532
	T=0.5637	A= 0.3806	A= 0.3468
rs81189*	G=0.4283	G= 0.5799	G= 0.5766
	C=0.5717	C= 0.4201	C= 0.4234
rs242939	C=0.1130	A= 0.8582	A= 0.8378
	T=0.8870	G= 0.1418	G= 0.1622
rs173365	A=0.3480	C= 0.5259	C= 0.5318
	G=0.6520	T= 0.4741	T= 0.4682
rs17689918	G=0.9103	G= 0.8106	G= 0.8227
	A=0.0897	A= 0.1894	A= 0.1773
CRHR2			
rs8192498	C=0.9864	G= 0.9818	G= 0.9820
	T=0.0136	A= 0.0182	A= 0.0180
rs2190242	C=0.3277	C= 0.2152	C= 0.1955
	A=0.6723	A= 0.7848	A= 0.8045
NR3C1			
rs10482672	G=0.8253	C= 0.8404	C= 0.8010
	A=0.1747	T= 0.1596	T= 0.1990
rs2918419	T=0.8830	A= 0.8760	A= 0.8874
	C=0.1170	G= 0.1240	G= 0.1126

Table 21. Aim 2 summary of significant regression models

Gene	SNP	Domain	β (95% CI)	p	q	Std β (95% CI)
CRHBP	rs3792738	Abstract/Contingent Learning (n=102)	.31 (.08, .54)	0.008	0.118	.18 (.05, .31)
CRHBP	rs7704995	Impulse Control[1] (n=62)	.52 (.19, .85)	0.003	0.044	.47 (.17, .76)
CRHR1	rs4792887	Attention[2] (n=96)	-.21 (-.42, .01)	0.04	.588	-.15 (-.29, -.004)
CRHR1	rs242939	Attention[3] (n=94)	-.46 (-.68, .23)	0.000	.059	-.31 (-.46, -.16)
CRHR2	rs8192498	Language Fluency (n=68)	.65 (.08, 1.21)	0.03	.441	.13 (.02, .24)
NR3C1	rs2918419	Memory[4] (n=68)	-.67 (-1.24, -.10)	0.02	.294	-.30 (-.55, -.04)

All models controlled for age, race/ethnicity, sex, and IQ.

1: Also controlled for lifetime history of depression and ADHD
2: Also controlled for lifetime history of anxiety
3: Also controlled for lifetime history of depression and ADHD
4: Also controlled for site

Table 22. Aim 3 interactions between maltreatment and rs3792738 on abstract contingent learning

	β (95% CI)	**p-value**
Physical Abuse	.01 (-.35, .37)	0.94
rs3792738	**.30 (.03, .58)**	**0.03**
Interaction	-.05 (-.67, .58)	0.88
Sexual Abuse	*	*
rs3792738	*	*
Interaction	*	*
Emotional Abuse	**.39 (.09, .69)**	**0.04**
rs3792738	**.30 (.01, .58)**	**0.01**
Interaction	-.15 (-.55, .26)	0.47
Physical Neglect	-.03 (-.38, .33)	0.89
rs3792738	**.37 (.01, .73)**	**0.04**
Interaction	-.19 (-.66, .27)	0.41
Emotional Neglect	.05 (-.23, .32)	0.74
rs3792738	**.33 (.09, .56)**	**0.01**
Interaction	-.14 (-1.05, .77)	0.76

Covariates: Age, race/ethnicity, sex, IQ
*Interaction Model would not run for sexual abuse

Table 23. Aim 3 interactions between maltreatment and rs7704995 on impulse control

	β (95% CI)	p-value
Physical Abuse	.05 (-.64, .73)	0.89
rs7704995	**.59 (.15, 1.03)**	**0.01**
Interaction	-.07 (-.90, .76)	0.86
Sexual Abuse	*	*
rs7704995	*	*
Interaction	*	*
Emotional Abuse	-.10 (-.89. .69)	0.80
rs7704995	**.60 (.16, 1.05)**	**0.01**
Interaction	-.08 (-.67, .50)	0.79
Physical Neglect	.09 (-.52, .70)	0.77
rs7704995	**.58 (.08, 1.08)**	**0.03**
Interaction	-.04 (-.80, .72)	0.91
Emotional Neglect	-.23 (-1.05, .60)	0.58
rs7704995	**.62 (.164, 1.08)**	**0.01**
Interaction	-.12 (-.76, .51)	0.70

Covariates: Age, race/ethnicity, sex, IQ, lifetime history of depression and anxiety
*Interaction Model would not run for sexual abuse

Table 24. Aim 3 interactions between maltreatment and rs4792887 on attention

	β (95% CI)	p-value
Physical Abuse	-.40 (-1.31, .51)	0.38
rs4792887	**-.29 (-.56, -.02)**	**0.04**
Interaction	.01 (-.65, .67)	0.98
Sexual Abuse	.15 (-.23, .52)	0.44
rs4792887	**-.28 (-.54, -.02)**	**0.04**
Interaction	.10 (-.32, .51)	0.64
Emotional Abuse	.08 (-.62, .77)	0.82
rs4792887	-.25 (-.58, .06)	0.11
Interaction	-.11 (-.74, .53)	0.74
Physical Neglect	.05 (-.48, .58)	0.86
rs4792887	-.26 (-.56, .04)	0.09
Interaction	.02 (-.52, .56)	0.94
Emotional Neglect	-.03 (-.53, .47)	0.89
rs4792887	**-.31 (-.58, -.04)**	**0.03**
Interaction	.13 (-.36, .62)	0.60

Covariates: Age, race/ethnicity, sex, IQ, lifetime history of anxiety

Table 25. Aim 3 interaction between maltreatment and rs242939 on attention

	β (95% CI)	p-value
Physical Abuse	-.29 (-.98, .40)	0.40
rs242939	**-.42 (-.77, -.07)**	**0.02**
Interaction	-.04 (-.58, .49)	0.87
Sexual Abuse*	*	*
rs242939	*	*
Interaction	*	*
Emotional Abuse	.18 (-.48, .84)	0.59
rs242939	**-.37 (-.74, -.01)**	**0.05**
Interaction	-.26 (-.90, .39)	0.43
Physical Neglect	.14 (-.42, .69)	0.63
rs242939	**-.40 (-.71, -.09)**	**0.01**
Interaction	-.10 (-.70, .49)	0.73
Emotional Neglect	-.09 (-.59, .40)	0.71
rs242939	**-.47 (-.76, -.18)**	**0.002**
Interaction	.17 (-.41, .74)	0.56

Covariates: Age, race/ethnicity, sex, IQ, lifetime history of anxiety and ADHD
*Interaction Model would not run for sexual abuse

Table 26. Aim 3 interaction between maltreatment and rs2918419 on memory

	β (95% CI)	p-value
Physical Abuse	**-.67**	**0.02**
	(-1.23, -.10)	
rs2918419	**-.76**	**0.03**
	(-1.43, -.09)	
Interaction	.46	0.36
	(-.55, 1.48)	
Sexual Abuse	*	*
rs2918419	*	*
Interaction	*	*
Emotional Abuse	*	*
rs2918419	*	*
Interaction	*	*
Physical Neglect	.32	0.24
	(-.22, .86)	
rs2918419	**-.61**	**0.03**
	(-1.16, -.07)	
Interaction	-.24	0.79
	(-2.03, 1.55)	
Emotional Neglect	.00	1.00
	(-.80, .80)	
rs2918419	**-.73**	**0.03**
	(-1.39, -.06)	
Interaction	.56	0.54
	(-1.26, 2.39)	

*Interaction Model would not run for sexual or emotional abuse
Covariates: Age, race/ethnicity, sex, IQ, and site

APPENDIX B

UNIVERSITY OF PITTSBURGH IRB'S APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Mrs. Jamie Zelazny

From: Christopher Ryan , Ph.D., Vice Chair

Date: 4/23/2013

IRB#: PRO13040476

Subject: Effects of Childhood Trauma on Neuropsychological Functioning

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The above-referenced project has been reviewed by the Institutional Review Board. Based on the information provided, this project meets all the necessary criteria for an exemption, and is hereby designated as "exempt" under section
45 CFR 46.101(b)(4) Existing data, documents, or records

Please note the following information:

- If any modifications are made to this project, use the "**Send Comments to IRB Staff**" process from the project workspace to request a review to ensure it continues to meet the exempt category.
- Upon completion of your project, be sure to finalize the project by submitting a "**Study Completed**" report from the project workspace.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX C

UNPUBLISHED MANUSCRIPT 1

The effects of childhood abuse and neglect on executive function and memory-a review of the literature

Background. Exposure to childhood maltreatment has long lasting effects, including poor academic performance and increased risk for psychiatric disorders and suicide.

Objective(s). The aim of this literature review was to synthesize the body of literature on studies of the effects of early childhood trauma on neuropsychological outcomes.

Design. A search was conducted of MEDLINE, PUBMED, CINAHL and PsycINFO for empirically based articles published since 1990 searching on childhood maltreatment and a validated neuropsychological testing battery.

Results. Thirty-three articles met the criteria. Neuropsychological domains most frequently affected were memory and executive function.

Conclusions. Individuals with a history of early childhood trauma exhibit deficits in memory and executive function. This effect was found across psychiatric diagnoses. There is some evidence that an earlier age of exposure to childhood trauma may produce more severe deficits and this may be related to disruption of neural development during critical periods of development.

Based on data from the Department of Health and Human Services, in 2012, there were approximately 686,000 victims of child abuse and neglect in the United States. This equates to a rate of 9.2 victims per 1,000 children in the US population. Of the children who were maltreated, 78.3% were neglected, 18.3% were physically abused, and 9.3% were sexually abused. Child abuse and neglect occurred across all races with higher rates of maltreatment found in African Americans, American Indians or Alaska Natives and those of multiple racial descent. Children under one year of age, had the highest rates of maltreatment (21.9 victims per 1,000). From ages one to four years of age, the rates were approximately 11 – 11.9 victims per 1,000 with rates of victimization generally decreasing with age. (US DHHS, 2012).

The effects of early childhood trauma can have profound effects on the developing brain. Critical periods of brain development have been identified. These are thought to be windows during which the brain experiences heightened plasticity allowing neural connections to form. After birth, a critical period for sensory development is experienced, during which vision and hearing connections are formed in the visual and auditory cortexes. This is followed by a critical period for motor and language development, which includes receptive language and speech production. These are followed by a critical period for developing higher cognition. (Hensch, 2005) The young, developing brain is highly vulnerable to environmental experiences occurring during these critical periods. The experience of adverse life events in early childhood can lead to a disruption in the formation of neural connections, and can weaken the brain's architecture resulting in deficits in neurocognitive functioning. The purpose of this literature review is to synthesize the body of literature on the effects of early childhood trauma on neuropsychological outcomes.

Methods

Searches were conducted of Medline, PsychInfo, CINAHL, and Pub Med for articles published after the year 2000. The search terms used were "Child Abuse" or "Child Maltreatment" or "Early Life Trauma" with "Executive Function" or "Mental Recall" or "Problem Solving" or Neuropsychological Tests". Published articles that met the following were included: Empirically based paper, childhood maltreatment including child abuse and/or neglect, and a validated neuropsychological testing battery that included measures of memory, attention, problem solving and/or executive function. Studies addressing autobiographical memory and repressed memories were excluded.

Results

A total of 299 unique articles were identified and the abstracts were reviewed. A total of 33 studies met inclusion criteria. There were differences across the studies in the manner in which childhood abuse, trauma or maltreatment were assessed. In order to compare the findings across these various studies, it is important to first examine the methods in which childhood abuse and trauma were measured.

Assessment of childhood abuse and trauma

The most widely used measure across the studies was Childhood Trauma Questionnaire (CTQ), which was cited in 17 articles. The CTQ is a 28-item self-report questionnaire which is widely considered to be the gold standard for assessing exposure to childhood trauma. (Bernstein et al, 2003) It has been psychometrically tested and shown to be a reliable and valid method for assessing childhood trauma. The CTQ assesses five types of maltreatment: emotional, physical, and sexual abuse, and emotional and physical neglect. Three studies used the KSADS PTSD

screening section, an interview which inquires about physical and sexual abuse as well as a number of other types of childhood trauma (Kaufman et al 2001). Two studies used Conflict Tactics Scale (CTS) as part of a multimodal assessment (Straus, 1979). The CTS assesses exposure to family violence including physical and sexual abuse. The following assessments were also used in single studies. The Childhood Experience of Care and Abuse (CECA-Q) is a questionnaire that was modeled after the CECA interview and has shown satisfactory validity and reliability as a self-report measure for adverse childhood experiences. (Bifulco et al, 2005) The CECA-Q assesses the following types of maltreatment: parental neglect, parental physical abuse and sexual abuse by any adult before the age of 17. The Child Abuse Questionnaire (Levitan et al, 1998) is a questionnaire that was created for epidemiological research and assesses for physical and sexual abuse. The Early Trauma Inventory (Bremner et al, 2004), assesses for physical, sexual and emotional abuse as well as other types of general childhood trauma such as being in an accident. The History of Victimization Form (HVF) was completed with parents and therapists about children suspected of having been maltreated. This is 65-item instrument assessing five subscales: sexual abuse, physical abuse, neglect, witness to family violence and psychological abuse (Wolfe et al,

Two assessments appeared to be created specifically for the reviewed studies. The Childhood Adversity Questionnaire is a 17 item self-report focusing on parental adversity. It appears that the assessment was created specifically for use in the reviewed study as psychometric data was provided as part of the article. Five factors are described: abusive parenting, loss, poverty and sexual abuse, neglectful parenting, dysfunctional parenting and sibling loss. The Child Maltreatment Survey is a self-report that inquires about physical maltreatment, sexual maltreatment and child neglect across three age rages (0-6, 7-12, and 13-18). Five studies did not

use psychometrically tested instruments but identified childhood trauma through Child Protective services. Another study identified child maltreatment via chart review.

Findings

Executive function

Executive function is a set of higher-order cognitive processes that are used to integrate and process information to modify thoughts and behaviors in response to contextual or environmental changes. Executive function includes cognitive skills responsible for planning, cognitive flexibility, inhibitory control and working memory (Stuss, 1992). Executive function has been described as the air traffic control system of the brain. The three domains most commonly described as part of executive function are cognitive flexibility, inhibitory control, and working memory (Center on the Developing Child at Harvard University, 2011).

Cognitive flexibility

Cognitive flexibility is the ability to shift cognitive strategies based on changes in the environment. The Wisconsin Card Sorting Test and the Stroop are examples of neuropsychological tests commonly used to assess cognitive flexibility. A history of moderate to severe childhood trauma was associated with poorer cognitive flexibility in a sample of adult cocaine abusers (Narvaez et al, 2012), but not in a sample of post-partum mothers recruited from a maternity ward (Gonzalez, 2012). Gould et al, 2012 found that moderate to severe abuse and neglect were strongly associated with deficits in cognitive flexibility in a sample of adults with and without major depression. These deficits were found across all types of neglect and abuse, emotional, physical and sexual. Similar results were found in a study of borderline personality

disordered patients where a history of childhood abuse was significantly correlated with impairment in an executive function domain score (Minzenberg et al, 2008).

In a sample of adolescents aged 12-17 with no history of psychiatric disorder, more severe physical abuse and physical neglect were significantly associated with deficits in cognitive flexibility (Spann et al, 2012). Similar results were found in a small study of children with a documented history of physical or emotional abuse or neglect compared with controls (Perna and Kiefner, 2013). In another study of children with a history of child sexual abuse involved in legal action against their abusers exhibited poorer performance on the Stroop test that controls (Barrera et al, 2013). The effects of neglect on executive function, including cognitive flexibility, were found even in children as young as 3-6 years of age in foster care (Pears and Fisher, 2005)

Problem solving

In a study of suicidal and non-suicidal college students, Yang et al (2010) found that a history of childhood maltreatment was significantly associate with poorer performance on a problem solving test. In a sample with widespread low socioeconomic status, neglected children who were also physically abused performed significantly poorer in the domain of problem solving than children who were neglected but not physically abused. Surprisingly, children who were neglected but not physically abused performed significantly higher than controls. The authors posit that perhaps the neglected children were forced to become more resourceful and to "fend for themselves" but the additive effects of physical abuse to low socioeconomic status may have been too overwhelming for the development of these higher level cognitive processes. In 10-12 year old Hispanic children, physical abuse was marginally negatively associated with problem

solving skills, but in multivariate analyses, the results were no longer significant (Fishbein et al, 2009)

Working memory

Working memory is the active part of the memory system and involves a combination of short term memory and processing. It involves the temporary storage and manipulation of information needed for complex cognitive tasks such as learning and reasoning (Baddeley, 1992).

Processing, Attention, and Inhibition

In a sample of adults with schizophrenia spectrum disorders, those with a history of childhood sexual abuse had impaired working memory and poorer processing speed compared to those with no history of abuse (Lysaker et al, 2001). However, another study of a similar sample of inpatients with schizophrenia spectrum disorders found no relationship between childhood maltreatment and processing speed (Schenkel et al, 2005). It should be noted however, that childhood maltreatment was assessed in this study by chart review looking for recorded history of childhood sexual abuse, physical abuse and neglect and only 18 subjects had a history of childhood maltreatment. College women with a history of repeated sexual abuse exhibited increased response latency variability and decreased inhibition capacity compared with controls (Navalta et al, 2006). In a study of individuals experiencing a first episode of psychosis, a history of childhood trauma was associated with a significant decrease in cognitive function in the domains of verbal intelligence, language, attention, concentration and mental speed, predominantly in affective psychoses and in males (Aas et al, 2011). Physical abuse, sexual abuse and physical neglect were significantly associated with working memory, executive

function and verbal performance tasks in a sample of bipolar and schizophrenic patients (Aas et al, 2012)

A small sample of children with maltreatment related PTSD performed more poorly than controls on attention tasks (Beers and DeBellis, 2002). However, a larger study of children with PTSD and a history of childhood maltreatment trended towards poorer performance on attention tasks than those without a history of maltreatment, but the results did not reach significance (DeBellis et al, 2010). A notable difference between the two studies is that the smaller study compared children with PTSD and maltreatment with controls while all of the children in the larger study had PTSD and those with a history of maltreatment were compared to those without a history of maltreatment. Children who were both neglected and physically abused performed significantly poorer than controls in domains of manual dexterity, attention, visual-motor integration. They also performed significantly lower than those who were neglected but not abused in domains of control self- regulation and problem solving. (Nolan and Ethier, 2007) Children with a history of exposure to trauma (physical or sexual abuse or neglect) before 4 years of age performed more poorly than controls on tests of attention and working memory (Bucker et al, 2012). Earlier age of exposure to neglect was significantly associated with poorer visuospatial processing in a study of 3-6 year olds in foster care (Pears and Fisher, 2005). This could be attributed to disruption during the early critical periods of sensory and motor development.

Visual, Verbal and Spatial Working Memory

Moderate to severe childhood abuse and neglect was strongly associated with deficits in visual memory and spatial working memory in adults. Childhood sexual abuse was associated with an additional visual working memory deficit than the physical or emotional forms of abuse in this

sample (Gould et al, 2012). Women with a history of early childhood penetrating sexual abuse and PTSD performed significantly worse on measures of declarative memory than women with a similar abuse history without PTSD or controls. There were also significant findings in this study between severity of abuse and declarative memory (Bremner et al, 2004). A strong, but not statistically significant association was found between duration of sexual abuse and poorer scores on memory tests, including short term, verbal, visual and global memory scores in college women with a history of repeated sexual abuse (Navalta et al, 2006). Adult schizophrenics with a history of moderate to severe childhood adversity exhibited significantly poorer working memory and episodic narrative memory than schizophrenics with none to low childhood adversity (Shannon et al, 2011). In a family study of bipolar disorder, a history of emotional and sexual abuse were associated with poorer cognitive performance on verbal and visual recall memory tests (Savitz et al, 2008). Adults with borderline personality disorder and a history of abuse showed a significantly lower percentage of recalled words on a memory test than borderline adults without a history of abuse and controls (Sala et al, 2009). In adult borderlines, the correlation between a history of childhood abuse and lower scores on recall and learning trended towards but did not reach significance (Minzenberg et al, 2008). A study of highly traumatized adults defined "resiliency" as having at least one trauma with the absence of psychiatric disorder and found no differences in verbal memory between those with or without psychiatric disorders. The "nonresilient" group (or those with a psychiatric disorder) exhibited significantly poorer nonverbal memory scores (Wingo et al, 2010). The definition of resiliency is more often based on an individual's capability to recover from or bounce back after adversity, not simply the presence of a psychiatric disorder.

A small study of 8-14 year old children with a documented history of sexual abuse did not find significant differences compared to healthy controls on performance on memory tests after controlling for IQ and socioeconomic status (Porter et al, 2013) However, in a similar larger study, children with a documented history of physical or emotional abuse performed significantly poorer on measures of working memory (Perna and Kiefner, 2013). Neglected children also performed significantly lower on measures of language, learning and memory (DeBellis et al, 2009). A study of incarcerated violent offenders found an association between exposure to childhood trauma and deficits in spatial working memory, but these results did not reach statistical significance (Zou et al, 2013).

Biological Implications

The literature search also yielded several studies which included both neuropsychological testing and biological testing. In post-partum mothers, the direct path from childhood maltreatment to spatial working memory was not significant, but was indirectly related through hypothalamic-pituitary-adrenal cortex (HPA) function (Gonzalez, 2012). In adult women with a history of prepubertal physical or sexual abuse, no differences in hippocampal volumes or memory performance were found between with those with PTSD and those without PTSD. However, the authors noted that the PTSD symptoms were notably lower than other similar studies suggesting an overall healthier sample (Pederson et al, 2004). A study of maltreated children and adolescents with and without PTSD found no significant findings with regards to hippocampal volume but the presence of PTSD symptoms were associated with poorer visual memory performance (DeBellis et al, 2010). Because decreases in hippocampal volumes may occur over time, these changes may be more difficult to detect in younger samples. In a study of recurrently depressed females with and without physical neglect, multivariate analyses found that

impaired immediate verbal recall was predicted by the severity of childhood physical neglect and low plasma BDNF; delayed recall was predicted by childhood physical neglect and depression; and, memory retention was predicted by PTSD severity (Grassi-Oliveira et al, 2008). In a family study of bipolar disorder, childhood sexual abuse was negatively associated with memory performance. Additionally, this study found interactions between the low acting allele of the BDNF gene and the 4 allele of apolipoprotein-E (APO-E) gene with sexual abuse which resulted in poorer performance on memory tests (Savitz et al, 2007).

The effects of exposure to childhood trauma on the development of psychopathology are now being studied in the context of gene environment interactions. Functional polymorphisms in the serotonin transporter gene were found to moderate the effects of stressful life events on the development of depression and suicide attempts (Caspi et al, 2003). Since that groundbreaking study, further studies have also found that functional polymorphisms in the serotonin transporter gene moderate the relationship between childhood maltreatment and chronic depression (Brown et al, 2013) and recurrent depression (Fisher et al, 2013) but not with single episode depression (Uher et al, 2011). This again illustrates the long lasting impact of early childhood trauma. Another exciting area of study is the investigation of epigenetic mechanisms of early life trauma on the HPA axis. While there are challenges that must be overcome to pursue this area of study, animal models and studies of deceased suicide completers suggest that exposure to trauma early in life can lead to epigenetic changes and recent technological advances may facilitate further study of epigenetics (McGowan, 2013)

Summary

This literature review provides evidence that individuals with a history of early childhood trauma exhibit deficits in executive function and working memory. There is some evidence that

an earlier age of exposure to childhood trauma may produce more severe deficits and this may be related to disruption of neural development during critical periods of development. There is also data to suggest that the severity of trauma and the number of traumas experienced may be associated with more severe deficits in executive function and working memory. In general, these findings held across psychiatric diagnoses of Schizophrenia spectrum Disorders, Bipolar Disorder, Major Depression, Borderline Personality Disorder and PTSD. In some cases, the effects of PTSD and Major Depression appeared to contribute to poorer cognitive performance independently of early childhood trauma. This might be due, in part, to ineffective coping mechanisms, the experience of stress and activation of the HPA axis.

The experience of childhood abuse and neglect can have profound effects of the developing brain during critical periods of development. This can cause long lasting impairments in executive function and working memory, affecting the ability to learn and to problem solve during childhood and adolescence, which can lead to poorer functioning and increased risk for psychiatric disorders into adulthood. While the focus of this literature review was not on the biological effects of early childhood maltreatment, it seems that the effects on neuropsychological development may be mediated through biological pathways. Exciting areas for further study include further investigation of BDNF and the hippocampus as well as studies of the HPA axis. As noted above, there is likely to be prolonged activation of the HPA axis not only in reaction to the abuse or neglect itself, but also in response to impaired executive function and problem solving. Genetic variability appears to play a role in the function of the HPA axis. Therefore, genes as well the environment and their interactions are areas for continued research. Further study of this pathway, including gene-environment interactions and epigenetic mechanisms are warranted.

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Article	Trauma Measure	Domains assessed	Sample Size	Study Population
Narvaez et al, 2012	CTQ	Executive Function; Cognitive Flexibility	84	Substance Dependence
Gonzalez et al, 2012	CTQ	Executive Function; Cognitive Flexibility; Working Memory; Attentional Set Shifting	89	Post partum women
Gould et al, 2012	CTQ	Memory; Attention; Reasoning; Planning; Psychomotor Coordination; Motor Speed	93	Major Depressive Disorder and Controls
Minzenberg et al, 2008	CTQ	Executive Function; Short Term Recall	69	Borderline Personality Disorder
Spann et al, 2012	CTQ	Executive Function; Cognitive Flexibility	30	Ninth graders with no history of psychiatric disorder
Perna & Kiefer, 2013	Medical Record or Child Protective Service Case File	Executive Function	41	Abused children without PTSD
Pears & Fisher, 2005	Child Protective Service Case Files	Executive Function; Langage; "general cognitive function"	133	Foster children and community controls
Yang et al, 2000	Child Maltreatment Survey	Problem Solving	181	Suicidal and non-suicidal college students
Fishbein et al, 2009	CTQ	Problem Solving; Cognitive Flexibility	553	10-12 year old public school students
Lysaker et al. 2001	Child Abuse Questionnaire	Working memory; Information processing speed	43	Schizophrenia spectrum disorders
Schenkel et al, 2005	Medical record review and clinical interview	Executive Function; Verbal Fluency; Verbal Processing Speed; Visual Perceptual Organization	40	Schizophrenia spectrum disorders
Navalta et al, 2006	Traumatic Antecedents	Memory; Attention	45	College students

	Questionnaire			
Beers & DeBellis, 2002	KSADS	Language; Attention; Abstract Reasoning; Executive Function; Learning; Memory; Visual Spatial Processing	29	Post Traumatic Stress Disorder and Controls
DeBellis et al, 2010	KSADS CAPA	Visual Memory; Verbal Reasoning; Attention	216	Post Traumatic Stress Disorder and Controls
Nolin &Ethier, 2007	Child Protective Services Files; Conflict Tactic Scale; Child Abuse Potential Inventory	Motor Performance; Attention; Memory; Learning; Visual Motor Integration; Language; Executive Function	142	Age 6-12 receiving Child Protective Services due to maltreatment and community controls
Bremner et al, 2004	Early Trauma Inventory	Memory	43	Post traumatic stress disorder and controls
Shannon et al, 2011	CTQ	Verbal Memory; List Learning; Working Memory	85	Chronic Schizophrenia
Wingo et al, 2010	CTQ; Traumatic Events Inventory	Verbal and nonverbal memory; Verbal and nonverbal reasoning	226	Traumatized Community Sample
DeBellis et al, 2009	Child Protective Service Records	Language; Visual Spatial Processing; Memory; Learning; Attention; Executive Function	106	Post Traumatic Stress Disorder and Controls
Zou et al, 2013	CTQ	Memory; Executive Function	321	Juvenile Violent Offenders
Pederson et al, 2004	CTQ	Auditory immediate and delayed memory; Visual immediate and delayed memory; Working memory	51	Post Traumatic Stress Disorder and Controls
DeBellis et al, 2010	Child Protective Service Records	Visual memory; Verbal memory; Attention regulation; Inhibitory Control	216	Post Traumatic Stress Disorder and Controls
Grassi-Oliveira et al, 2008	CTQ	Verbal memory	49	Major Depression; Controls
Driessen et al, 2004	CTQ	Memory	12	Borderline Personality

				Disorder
Sala et al, 2009	Soloff Child Abuse Scale	Cognitive Memory Control	38	Borderline Personality Disorder
Savitz et al, 2007	CTQ	Executive Function; Verbal and Visual Memory	350	Bipolar Disorder families
Savitz et al, 2008	CTQ	Visual and Verbal Memory; Verbal Fluency; Cognitive Flexibility	230	Bipolar Disorder families
Porter et al, 2005	Wolfe's History of Victimization	Memory, Learning	24	Sexually abused children and matched controls
Jakubczyk et al,		Impulsivity	304	Alcohol dependence
Barrera et al, 2013	Legal records	Attentional inhibition; (check for cognitive flexibility and EF)	76	Child victims of sexual abuse involved in legal action against abusers
Aas et al, 2011	CECA-Q	Learning; Memory; Executive Function; Working Memory; Attention; Concentration; Mental Speed; Visuoconstruction; Perceptual abilities; Verbal Intelligence	276	First episode affective and non-affective psychosis
Aas et al, 2012	CEQ	Learning; Memory; Executive Function; Working Memory; Attention; Concentration; Mental Speed; Visuoconstruction; Perceptual abilities; Verbal intelligence	406	Schizophrenia spectrum or bipolar disorder
Bucker et al, 2012	KSADS-E	Executive Function; Working Memory; Attention	60	School age children with history of early trauma and matched controls

APPENDIX D

UNPUBLISHED MANUSCRIPT 2

The effects of childhood maltreatment on neuropsychological functioning

Abstract

Exposure to childhood maltreatment has been shown to have detrimental and long lasting effects on functioning and to increase risk for psychiatric disorders and suicide. The aim of this secondary data analysis was to examine the effects of childhood maltreatment on executive function and memory in offspring of parents with mood disorders. A total of 299 subjects between the ages of 10-21 were included in the analyses. History of childhood maltreatment was assessed using the Childhood Trauma Questionnaire (CTQ). Subjects underwent an extensive neuropsychological testing battery. Standard research interviews were conducted for demographic information and psychiatric diagnoses. Multiple linear regression was used to test the hypotheses. After controlling for age, history of head injury, site, household income and lifetime history of major depression, anxiety disorders and ADHD, exposure to moderate to severe physical abuse significantly predicated poorer scores on tests of memory (p=.006). However, after FDR correction, physical abuse was no longer significant (q=0.081) and none of the covariates approached significance. Further study of this sample, including gene-environment interactions, is warranted.

Key Words: Child maltreatment, Executive Function, Memory

Introduction. Exposure to maltreatment during childhood can have detrimental and long lasting effects on functioning and can increase the risk for psychiatric disorders and suicide (Porter et al, 2005; Navalta et al, 2006; Minzenberg et al, 2008). Children with post-traumatic stress disorder (PTSD) from exposure to physical or sexual abuse exhibit deficits in attention and executive function (Beers and DeBellis, 2002). A significant association was found between exposure to abuse or neglect before age 13 years and poorer performance on measures of memory and executive function (Gould et al, 2012). Cognitive deficits in abused or neglected children have been found to persist into adulthood (Majer et al, 2010). Children with a documented history of physical or emotional abuse performed significantly poorer on measures of working memory (Perna and Kiefner, 2013).

The aim of this secondary data analysis was to examine the effect of childhood maltreatment on neuropsychological outcomes of executive function, memory and attention in a sample of offspring of parents with mood disorders to determine if a history of child abuse or neglect is associated with decreased performance on neuropsychological tests of executive function, memory, and attention.

Methods. This is a cross sectional analysis of baseline data collected from offspring participating in the Familial Pathways to Early Onset Suicide Attempt Study. The parent study is a "high risk" longitudinal study of the offspring of depressed parents. Depressed adults were recruited from inpatient psychiatric units and outpatient treatment programs in Pittsburgh, PA and New York, NY. Adults were eligible for the study if they met DSM-IV criteria for an Axis I Mood Disorder (Major Depressive Disorder or Bipolar Disorder) and had at least one biological offspring age 10 years or older who was willing to participate in the study. Probands were not

required to live with the offspring under study. The primary aim of the parent study was to compare the offspring of depressed suicide attempters with the offspring of depressed non-attempters at baseline and at yearly follow-ups over a period of 15 years to determine whether the offspring of suicide attempters were more likely to attempt suicide than the offspring of nonattempters. Complete psychiatric assessments including diagnostic interviews were conducted on all subjects at baseline and follow-up. All subjects underwent baseline neuropsychiatric testing. Offspring who were under 18 years at the time of baseline assessment also underwent an additional neuropsychiatric assessment battery at least 2 years later.

The dataset for this secondary analysis includes the baseline demographic, clinical and neuropsychiatric data from 299 offspring aged 10-21. This analysis will examine the effects of childhood abuse and/or neglect on neuropsychological functioning, controlling for demographic and clinical characteristics.

***Neuropsychological battery*.** Neuropsychological testing assessed the following domains: (1) attention (computerized Continuous Performance Test (CPT) and Stroop Color Word test); (2) memory (Buschke Selective Reminding Task (SRT) and Benton Visual Retention Test (VRT); (3) executive function (Wisconsin Card Sorting Test); (4) working memory (N-back and A, Not B) ; (5) language fluency (Letter and Category Fluency); (6) impulse control (Time production and Go- No Go), and (7) Psychomotor functioning (WAIS-III Digit Symbol and Trail Making). Neuropsychological testers for both sites were trained at Columbia University and weekly meetings were held between the two sites with in-person re-training occurring yearly. Test scores were adjusted for age, education, and gender based on available norms. Aggregate domain scores were computed according to the algorithm described by Keilp et al 2013 in which the principal measure from each task was averaged with others within each domain.

Psychiatric assessments. Subjects who were 18 years and older at the time of baseline assessment were assessed for the presence of lifetime and current Axis I disorders using the Structured Clinical Interview for DSM-IV Diagnoses (SCID-I) (Spitzer et al., 1990). The SCID-I is a semi-structured interview designed for assessment and differential diagnosis of Axis I psychiatric disorders, using DSM-IV criteria. At baseline, subjects were assessed for lifetime and current disorders. Subjects who were 10-17 years of age at the time of baseline assessment were assessed for Axis I psychopathology using the School Aged Schedule for Affective Disorders and Schizophrenia: Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The K-SADS-PL is a widely used diagnostic instrument designed to obtain both lifetime and current DSM-IV Axis I diagnoses administered as a semi-structured interview. The age of onset and the chronicity of major depression and anxiety were assessed and documented for all subjects. According to standard assessment procedures, both parental and child reports were integrated for offspring age 10-17 years. Interviews were conducted by master's or doctorally prepared psychologists, social workers or nurses across two sites. Inter-rater reliability was routinely assessed, both within each site and across sites, for the variables under study in this secondary data analysis, namely the diagnostic interviews, assessment of abuse and depression/anxiety.

Abuse and neglect. Exposure to childhood abuse and neglect was assessed using the Child Trauma Questionnaire (CTQ), a 28-item self-report, which provides a brief, reliable and valid screening for a history of child abuse and neglect (Bernstein et al, 1994). The CTQ assesses for five types of maltreatment: emotional, physical, and sexual abuse, and emotional and physical neglect. The data are scored on a continuous scale for each type of trauma. Additionally,

thresholds for moderate to severe exposure are provided for each type of trauma. Internal consistency of the CTQ in this study was acceptable with alpha ranging from .68-.96.

Demographic Data. A general demographic form was used to collect age, gender, race, ethnicity, and socioeconomic status. The same form also included general medical questions, including past history of head injury. ***Data Analysis.*** The sample was characterized with regards to demographic and clinical variables using descriptive statistics. T-tests were used to check for site differences in the variables of interest and in the covariates (age, race, ethnicity, income, IQ, depression, anxiety, and head injury). Bivariate correlations were run between the CTQ subscales and the neuropsychological domains. Multiple linear regression was used to test the hypothesis. Each domain was examined separately as the dependent variable. The domain scores were z-scores and were normally distributed. The independent variables of interest were exposure to abuse or neglect before the age of 18 according to the CTQ. Moderate to severe abuse or neglect was entered into the regression model as a dichotomous variable using the scoring procedure described by Bernstein et al. Site, socioeconomic status, history of head injury, and presence of lifetime mood, anxiety, or attention deficit hyperactivity disorder were entered as covariates in each model. The covariates were selected based on both the published literature and on study specific factors, including site differences. There were significant site differences in the sample with lower household income at the Pittsburgh site ($p=.001$); higher numbers of Hispanic subjects at the NY site ($p<.001$); and, a higher frequency of head injuries at the NY site ($p=.002$). Site, household income, history of head injury, age and lifetime history of major depression, anxiety disorders and attention deficit hyperactivity disorder were included as covariates when modeling.

Because the original study was a family study, this sample of offspring included siblings. To control for family relationships, a cluster effect for family membership was included in all models. To control for multiple comparisons for correlated test statistics, Yekutieli's False Discovery Rate (FDR) analyses were run and no significant findings were noted (Yekutieli & Benjamini, 1999).

Results. Demographic and clinical characteristics of the sample are presented in Tables 1-4. A total of 299 subjects underwent baseline neuropsychological assessments. The number of subjects evaluated for each domain varied depending on the time point at which the test was added and whether the subject completed all of the tests. The average age was 14.9 years at the time of the neuropsychiatric assessment and the sample included nearly equal numbers of males and females (47.5%). Childhood abuse and/or neglect was reported by 44.4% of subjects.

Significant negative correlations were found between emotional neglect and the memory domain ($r=-.18$, $p<.05$) and between physical neglect and the executive function domain ($r=-.20$, $p<.05$) (Table 5). However, multiple regression analyses did not find significant independent associations between the variables of interest and these domains.

Memory domain

Significant negative correlations were found between physical abuse and the memory domain ($r=-0.28$, $p<.01$) (Table 5). Multiple regression was run with memory domain z-score as the dependent variable, moderate to severe physical abuse as the independent variable, and controlling for covariates of age, history of head injury, site, household income and lifetime history of major depression, anxiety disorders and ADHD. In the full regression model, a history of moderate to severe physical abuse predicted poorer scores in the memory domain ($p=.006$) (Table 6). A backward stepwise regression was run, and physical abuse ($p=.002$), household

income (p=.005), and site (p=.037) remained significant. However, after FDR correction, physical abuse was no longer significant (q=.081) and none of the covariates approached significance.

Discussion

The results of this study are consistent with the body of literature suggesting that individuals with a history of childhood physical abuse exhibit deficits in measures of memory. The literature also suggests that the severity of trauma and the number of traumas experienced may be associated with more severe deficits in executive function (Spann et al, 2012; Nolan and Ethier, 2007). There is evidence in the literature that an earlier age of exposure to childhood trauma may produce more severe deficits (Pears and Fisher, 2005; Bucker et al, 2012). This may be related to disruption of neural development during critical periods of development (Hensch, 2005). In our study, we know that the exposure to trauma occurred prior to age 18, but the exact age of exposure to trauma was not ascertained. The profound effects of childhood trauma on the developing brain can cause long lasting impairments in executive function and working memory and can impact the ability to learn and to problem solve during childhood and adolescence, which can lead to poorer functioning and increased risk for psychiatric disorders into adulthood. These impairments in memory and executive function can have implications on treatment response. A history of childhood abuse was found to be a significant moderator of both short-term and long-term response to cognitive behavioral therapy (CBT) combined with antidepressant therapy (Asarnow et al, 2009; Vitiello et al, 2011) This might be due, in part, to ineffective coping mechanisms, the experience of stress and activation of the HPA axis.

Limitations. All of the subjects in this study were offspring of depressed parents. This sample endorsed a rather high prevalence of neglect, which may be the result of having a chronically

depressed parent. These results may not be generalizable to individuals without mood-disordered parents. A larger proportion of those who experienced moderate to severe physical abuse also experienced emotional abuse and/or neglect. There were significant intercorrelations between memory domain scores and predictor variables (See Table 7). The study is underpowered due to multiple comparisons and results were no longer significant after FDR correction.

Implications: Although the results did not maintain significance after FDR correction, further exploration of the effects of moderate to severe physical abuse on memory is warranted. While the focus of this secondary data analysis was not on the biological effects of early childhood maltreatment, the literature suggests that at least some of the effects of early childhood trauma on neuropsychological development may be mediated through biological pathways (Heim & Nemeroff, 1999; Gonzalez et al, 2012; McGowan 2013). There is likely to be prolonged activation of the HPA axis not only in reaction to the abuse or neglect itself, but also in response to ongoing impairments in executive function and memory. Genetic variability appears to play a role in the function of the HPA axis. Polymorphisms in the CRHR1 and CRHR2 genes were found to interact with childhood sexual abuse and neglect in decision-making in a sample of suicide attempters (Guillaume et al, 2013). There is a growing body of evidence suggesting that genes and their interactions with the environment are areas for continued research. Further study of this pathway, including gene-environment interactions and epigenetic mechanisms are warranted.

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Table 1
Demographic Characteristics

	Baseline
Number of subjects	299
Age in years, mean (SD), (range)	14.91 (3.38) (10-21)
Female gender, Number, percent of sample	122, 47.47%
Caucasian race Number, percent of sample	152, 60.56%
Hispanic ethnicity Number, percent of sample	29, 11.37%
Income (US dollars), mean (SD), (range)	10,438 (14,823), (0-140,000)

Table 2

Clinical Characteristics

	Current (number, percent)	**Lifetime (number, percent)**
Major Depressive Disorder	36, 14.01%	84, 32.81%
Bipolar disorder	6, 2.33%	8, 3.13%
Anxiety disorder	39, 15.23%	78, 30.47%
Post-Traumatic Stress Disorder	5, 1.95%	15, 5.86%
Attention Deficit Hyperactivity Disorder	38, 15.08%	44, 17.74%
Alcohol or Substance Use Disorder	9, 3.53%	20, 7.84%
Lifetime History of head trauma		36, 14.88%
Lifetime History of Suicide Attempt		12, 9.68%

Table 3
History of Abuse and Neglect

Any CTQ	114, 44.36%
Any Abuse	75, 29.18
Any Neglect	80, 31.13%
Physical (abuse or neglect)	85, 33.07%
Emotional (abuse or neglect)	72, 28.02%
Moderate to Severe Emotional Abuse	51, 19.84%
Moderate to Severe Physical Abuse	39, 15.18%
Moderate to Severe Sexual Abuse	24, 9.34%
Moderate to Severe Emotional Neglect	41, 15.95%
Moderate to Severe Physical Neglect	67, 26.07%

Table 4
Exposure to multiple categories of maltreatment

Count CTQ	0	143, 55.64%
	1	56, 21.79%
	2	27, 10.51%
	3	16, 6.23%
	4	11, 4.28%
	5	4, 1.56%

Figure 1.

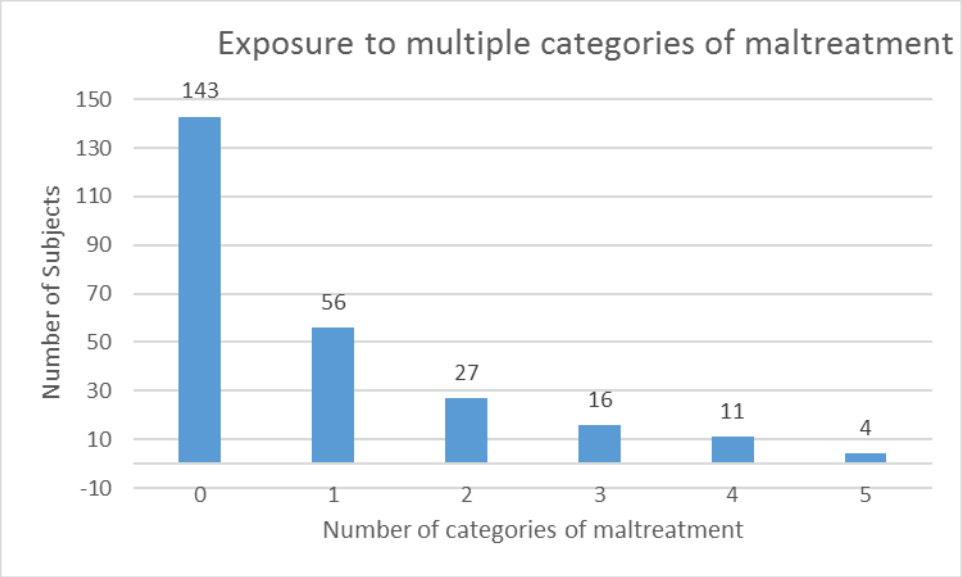

Table 5
Bivariate Correlations

Domain	Physical Abuse	Sexual Abuse	Emotional Abuse	Physical Neglect	Emotional Neglect
Memory	**-.281 ****	-.071	-.041	-.081	**-.177***
Working Memory	-.052	-.0966	-.069	-.028	.005
Attention	-.039	.003	-.107	-.034	-.052
Psychomotor Functioning	-.004	.106	-.007	-.016	.014
Language Fluency	**-.155***	.011	.033	.008	-.028
Executive Function	-.029	.068	-.068	**-.196***	-.025
Impulse Control	-.034	.005	-.023	.041	-.106

* p<.05
**p<.01

Table 6

Regression Model Predicting Memory Domain (Moderate to Severe Physical Abuse)

Variable	β	p-value	SE(β)	95% CI
Site (Pitt)	0.432	.034	0.201	.033 .831
Head injury	0.102	.599	0.193	-.282, .486
Sex (Female)	0.044	.800	0.175	-.303, .392
Household Income	0.042	.173	0.030	-.019, .102
Age	-0.020	.549	0.034	-.088, .047
IQ (Peabody Picture Vocabulary Test)	0.003	.650	0.007	-.010, .016
Current depression	-0.199	.354	0.213	-.622, .225
Current anxiety	-0.088	.652	0.194	-.472, .297
Current Attention Deficit Hyperactivity	-0.113	.673	0.267	-.644, .418
Moderate to Severe Physical Abuse	-0.673	.005**	0.234	-1.140, -.208

R-squared=.164, p=.0047**

**p<.01

Table 7

Intercorrelations for Memory Domain Scores and Predictor Variables

Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Memory domain score	.163*	.033	.07	.211*	-.122	.200*	-.163*	-.081	-.044	-.281*
Predictor Variables										
1. Site		-.02	-.05	-.19*	-.089	.113	.023	-.067	.082	.014
2. Head Injury			-.15	.16*	.132	.119	.084	-.032	.021	-.035
3. Sex				.045	.005	-.097	-.007	-.012	-.201*	-.051
4. SES					.069	.461*	-.055	.056	-.123	-.186*
5. Age						-.069	.35*	.198*	-.084	-.003
6 IQ (PPVT[+])							.001	-.039	-.008	-.096
7. Lifetime depression								.287*	.156*	.097
8. Current anxiety									.019	.074
9. Current ADHD[++]										.144*
10. Physical Abuse										

*p<.05

[+]PPVT: Peabody Picture Vocabulary Test

[++]ADHD: Attention Deficit Hyperactivity Disorder

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