NEUROPSYCHOLOGY AND NEUROGENETICS OF MENTAL HEALTH:

RISK, RESILIENCE & WELLBEING

A Thesis Presented

by

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ABSTRACT

NEUROPSYCHOLOGY AND NEUROGENETICS OF MENTAL HEALTH:
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December 2018

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Experiences of childhood adversity have long been associated with poor mental health functioning (Anda et al., 2006) and with impairments in learning and memory (Homberg, Molteni, Calabrese, & Riva, 2014). How these experiences increase risk of mental illness and cognitive dysfunction remains an active area of research; much less is known about how protective factors alter trajectories and contribute to wellbeing. Participants (*N*=100) completed self-report measures of adverse childhood events, current wellbeing, emotional functioning, and neuropsychological tests of executive functioning. DNA samples were collected and analyzed for functional polymorphisms of the Serotonin Transporter Receptor (5-HTTLPR) and Brain-Derived Neurotrophic Factor (BDNF) genes. This study examined the moderating effect of candidate gene polymorphic variation in the associations between childhood adversity, mental health, and cognitive functioning. We hypothesized that greater exposure to adverse childhood

events would be associated with increased psychiatric symptomatology and lower levels of wellbeing. Significant associations were observed between experiences of childhood adversity and psychiatric symptomatology, such that endorsements of greater childhood adversity were correlated with lower levels of wellbeing, higher ratings of global psychiatric symptom severity and distress, as well as higher ratings of psychotic-like experiences. Additionally, adverse childhood events were negatively correlated with scores on measures of attention and working memory. Each genetic polymorphism was examined as a predictor and moderator of psychiatric symptomatology and wellbeing through Gene x Environment (G x E) interactions. Counter to our expectations, polymorphism group did not predict mental health functioning. Last, G x G x E interactions were tested to examine whether childhood adversity and polygenic susceptibility predicted symptoms and wellbeing. Three-way interaction of selected polymorphisms and adversity were not predictive of outcomes. However, endorsement of childhood adversity and being a carrier of the Short 5-HTTLPR alleles and Val/Met or Met/Met BDNF alleles each independently predicted both higher ratings on psychiatric symptoms and lower wellbeing. Taken together, these findings indicate strong evidence to support the influence of individual genetic variation in G x G models predicting psychiatric symptoms and wellbeing, although do not confirm the hypothesized G x E interactions with childhood adversity, despite strong evidence of adversity as predictor of outcomes.

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CHAPTER 1:

BACKGROUND & SIGNIFICANCE

Experiences of childhood adversity have long been associated with poor mental health functioning (Anda et al., 2006) and with impairments in learning and memory (Homberg et al., 2014). But how these experiences increase risk of mental illness and cognitive dysfunction remains a very active area of research. The classic diathesis-stress framework has emphasized increased genetic vulnerability to the negative consequences of early life stress. Central to the diathesis-stress model is that some individuals are posited to be particularly genetically vulnerable to environmental stress. Here, the genetic diathesis does not influence behavior directly, but rather its effects are moderated by specific environmental conditions or expressed in response to particular developmental experiences. Hence, the search for so-called vulnerability genes that has dominated the field of psychiatric genetics can be directly traced to the diathesis-stress model.

More recently, an alternative framework to the diathesis-stress model has been proposed that posits that genetically vulnerable people are more susceptible to environmental experiences and these experiences can be either positive or negative. In this differential-susceptibility model, the very same genes that lead individuals to be disproportionately vulnerable to childhood adversity may, simultaneously, bestow on them an advantage by making them more responsive to environmental support or

enrichment (Belsky & Pluess, 2009a). Hence, in this framework, the search for vulnerability genes is replaced by the search for plasticity genes; so-called, "vulnerable individuals" give way to "highly plastic or malleable individuals." The differential susceptibility model therefore predicts that that Gene x Environment (G x E) interactions likely dispose individuals to positive, as well as negative outcomes in the context of early childhood adversity (Belsky et al., 2009b; Ellis & Boyce, 2008). Aligning with the concept of differential susceptibility, this study sought to explore factors that contribute to resilience in outcomes of mental health functioning.

Molecular genetics provides a powerful approach to examine how emotion and cognition may be shaped or moderated by individual variation in responsiveness or plasticity to environmental influences. Traditionally, behavioral geneticists have relied on twin studies to estimate the heritability of a particular psychological construct, such as intelligence, by comparing the correlations of performance on an IQ test of identical and fraternal twins. More recent times have seen the development of two new molecular genetic methods: candidate gene (allelic association) and genome wide association studies (GWAS). These studies provide a different, yet complementary approach to the twin method (Parasuraman & Jiang, 2012). For example, the GWAS approach can now cover the entire human genotype, examining from 100,000 to more than one million single nucleotide polymorphisms (SNPs), and testing for associations between allelic variation and psychological phenotypes. The key advantage of the GWAS is that it offers an unbiased, hypothesis-free approach for discovering associations between behavioral phenotypes and all known genetic variation in the genome. The disadvantage is the risk

of Type II error. In contrast to GWAS, the candidate gene approach selects specific allelic variants based on prior empirical findings that have demonstrated gene-neural network associations. This approach aims to identify SNPs that are likely to influence brain networks that neural imaging studies have linked to specific cognitive and emotional functions.

Early childhood environments are critically important determinants of emotional and neurodevelopmental trajectories and predictors of outcomes across the lifespan. These critical periods of development have been identified as particularly sensitive to the effects of epigenetics, with an emphasis on the respective plasticity of earlier developmental stages (Gluckman, Hanson, Beedle, Buklijas, & Low, 2011; Hackman, Farrah, & Meaney, 2010). Epigenetics refer to environmental conditions that impact genetic expression, while maintaining the integrity of the DNA sequence (McEwen et al., 2015). Evidence of G x E influences on affective and neural development early in life is generally supported, identifying early childhood experiences and environmental factors as moderating long-term outcomes (Fagiolini, Jensen, & Champagne, 2009; Meaney, Szyf, & Seckl, 2007). Moreover, animal studies confirm the moderating effects of early life stressors of reduced maternal care (i.e., early life stress experienced by offspring) on chronic and functional impairment and subsequent brain (e.g., cellular modifications) and behavioral effects (e.g., environment/relational). Thus, the identification of candidate mechanisms may help to elucidate epigenetic cause-and-effect that in turn, may offer potential opportunities for mechanistic reversal or prevention (Hackman et al., 2010).

For example, recent studies have focused on the moderating effects of genetic variation in response to environmental events, in an attempt to elucidate the complex interactions that underlie aspects of resilience related to adult outcomes. Specifically, (Kaufman et al., 2006) explored the interaction effects of childhood adversity and both functional genotypes of 5-HTTLPR and BDNF genes, finding that the combined impact of these genetic polymorphisms increased risk for depression. Kaufman et al. (2006)'s landmark study evidenced associations between genetic susceptibility and psychopathology, in which environmental factors (i.e., early life stress; ELS) play a crucial role. Further, several studies have implicated subsequent supports (i.e., access and quality of social support) as having significant impacts on outcomes in the context of ELS; however, that these influences are different based on individual genetic variation (Charney & Manji, 2004; Curtis, Cicchetti, Luthar, & Becker, 2003). These supports proved more influential in promoting positive outcomes for carriers of the Short 5-HTT allele than when compared to counterparts also exposed to childhood adversity (Barbazanges et al., 1996; Huot, González, Ladd, Thrivikraman, & Plotsky, 2004; Kaufman et al., 2006). To this end, the current study adopts a multimodal approach to the investigation of differential susceptibility, defined in terms of the interactions between early childhood experiences, adult wellbeing, mental health functioning, and genetic variability.

Research independently exploring environmental and genetic predictors of mental illness has been predominantly inconclusive (Canli & Lesch, 2007) and some have argued that this is in part due to pursuing a theoretical dichotomy of risk versus resilience

(Belsky & Beaver, 2011). More complex analysis of combinations of risk and protective factors, the contexts (i.e., developmental stage, timing of exposures) in which they emerge, as well as individual susceptibility factors, may be necessary to predict the strength or direction of relations between individual risk and protective factors and mental health outcomes. One way to bridge the gap between environmental and genetic proponents of mental health outcomes is to explore the interactions of identified risk and resilience factors (e.g., exposure to childhood adversity; candidate genes; neuropsychological functioning) (Kuhn, Popovic, & Pezawas, 2014; Rabl et al., 2014).

Effects of Childhood Adversity

Childhood adversity can include experiences of child abuse (i.e., emotional, physical, or sexual contact) and exposure to household dysfunction (i.e., substance abuse, mental illness, mother treated violently, incarcerated household member, parental separation or divorce) before the age of 18 (Anda et al., 2006). There is strong evidence in support of significant neural alterations in the context of early life stress, particularly in areas of the brain responsible for cognitive and affective development (Caspi et al., 2003; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Uher & McGuffin, 2008; Nemeroff, 2004). Many have argued that detrimental effects of trauma relate to a concept of allostatic load, which presumes an additive impact of stress on neural development and functioning as a result of the accumulation of stressors and alterations to stress-response systems (McEwen & Stellar, 1993; Kuhn et al., 2014). Further, ELS-related neural alterations in regions responsible for emotional processing, stress-reactivity, and

executive functioning often result in psychiatric symptomatology and/or cognitive and functional impairment across the lifespan (Hackman et al., 2010; Pratt & Cullen, 2000). Among ELS-related brain changes are reductions in gray matter volume (GMV) in neural structures known to support executive functioning, learning and memory (e.g., prefrontal cortex; PFC, hippocampus) as well as enlargement in structures involved with emotional processes and regulation (e.g., amygdala). The combination of these alterations increases risk for psychopathology and functional impairment through disruption of stress-response and emotional, as well as behavioral regulation that results from environmental stressors (Teicher, 2002; Walsh et al., 2014).

The hippocampus has been identified as particularly vulnerable to environment in early development and given its critical role in learning and memory processes (McEwen, 2003; Kuhn et al., 2014), can have quite detrimental effects on cognitive trajectories and subsequent functioning overall. Additionally, studies have suggested that the hippocampus, particularly the dentate gyrus, is one of the few sites in the adult brain that shows, which shows neurogenesis (i.e., the brain's ability to create new neurons, a process that is integral for learning and memory) (Kraus et al., 2014; Homberg et al., 2014). In support of Belsky's theory of, "for better *and* for worse", studies have found that environments of deprivation or early enrichment impact neurogenesis throughout the lifespan. In the context of adversity, neurogenesis is inhibited as a protective factor against the effects of environmental stressors (Gluckman et al., 2011). Kuhn et al. (2014) describe structural changes in the PFC such as dendritic de-branching and hypertrophy, cell proliferation, synaptic remodeling and epigenetic modifications in response to

chronic, particularly early stress, which demonstrates various forms of neural plasticity relevant to understanding mechanisms of ELS-effects. Alternatively, supportive and enriching environments appear to have the opposite effect and enhance neurogenesis (Barr et al., 2003; Dranovsky & Hen, 2006; Kempermann & Gage, 1999; Warner-Schmidt, & Duman, 2006).

Overall psychological wellbeing and mental health is significantly impacted by cognitive abilities, perhaps most importantly, by domains of executive functioning. Executive functioning allows us to successfully participate in many aspects of daily life (e.g., facilitating problem solving, multi-tasking, social competence) and can have deleterious effects on social and role functioning when impaired. For example, working memory, one aspect of executive functioning modulated by activity in the prefrontal cortex, has emerged as a key component in neuropsychological functioning among clinical and healthy samples and is predictive of academic success and overall executive functioning (Nestor, Niznikiewicz, & McCarley, 2010; Ohtani et al., 2014).

In an effort to understand the factors that contribute to negative effects of childhood adversity on mental health functioning, severity, type of adversity, frequency, and individual differences have been investigated. To this end, age of exposure has emerged as a consistently implicated factor in the predictive validity of childhood adversity effects on mental health outcomes (Hackman et al., 2010; Loman & Gunnar, 2010). Similarly, increased risk for psychosis related to childhood adversity appears to depend on age of exposure, rather than type (Varese et al., 2012). Other studies have found that the experience of adverse events in childhood were associated with increased

likelihood of exposure to subsequent adversity (Anda et al., 2006), which is representative of the cyclical and perpetual nature of adversity across one's own lifespan. There is also evidence to support the intergenerational transference of susceptibility to stress from both the biological and social perspectives (Meaney et al., 2007; Hackman et al., 2010). Mothers exposed to trauma and stress while pregnant are more likely to pass on altered stress response systems to their fetuses, which predisposes the children to disrupted stress reactivity from the earliest stage of life. Exacerbating these biological effects of maternal stress and early fetal development are the social factors that often entrench individuals in systems of perpetual trauma and deprivation (i.e., low SES, barriers in access to resources, abuse, neglect, malnutrition). With these biological and psychosocial factors in mind, the need to explore the effects of ELS from a multimodal perspective is abundantly clear and will likely have the greatest potential impact for altering these trajectories and improving functional outcomes.

Gene x Environment Interactions

Genes that regulate affective, emotional and cognitive processes in the brain have been explored in the context of G x E interactions and have been found to be sensitive to environmental stressors (e.g., childhood adversity), such that structural, functional, and epigenetic changes have been observed (Alonoso et al., 2005; Payton et al., 2005). Thus, genes play a role in mental health functioning, which can be active, passive, and/or dependent on certain factors (e.g., developmental stage, environmental context, sex) (Beutel et al., 2017).

The serotonin system (5-HT) has long been implicated in the etiology of stress-related personality traits and psychopathology (Caspi et al., 2003). The Serotonin Transporter (SLC6A4) functional promoter polymorphism (5-HTTLPR or 5-HTT) regulates serotonin function in the brain and is associated with emotion-related processes (Gasic et al., 2009; Hariri, Mattay, Tessitore, & Kolachana, 2002). Functional variation of this polymorphism is dependent on genotypic composition of Short (S) and Long (L) allele pairs. The (S) allele (e.g., S/S or S/L) has been associated with reduced functional capacity of 5-HTTLPR (Lesch et al., 1996). In the context of ELS, carriers of the Short allele have been linked with increased risk for depression and suicidality (Kalueff, Wheaton, Ren-Patterson, & Murphy, 2007; Caspi et al., 2003). The risk conferred by the Short 5-HTT allele has been replicated in studies with children (Kaufman et al., 2006), adolescents (Eley et al., 2004) and adults (Jacob et al., 2006; Kendler et al., 2005; Taylor et al., 2006) indicating strong G x E interactions. As mentioned, it is not only that the presence of the Short 5-HTTLPR genotype is more strongly associated with ELS-related functional impairment, but that these "susceptible individuals" are also more responsive to supportive and enriching environments, more so than their Long genotype peers, also with exposure to early life stress (Barbazanges et al., 1996; Huot et al., 2004; Kaufman et al., 2006; Drury et al., 2012).

The Brain-Derived Neurotrophic Factor (BDNF) gene influences intracellular processing and secretion of BDNF proteins, which promote neurogenesis and other forms of neural plasticity, which support healthy social and emotional development, learning and memory (Kraus et al., 2014; Gratacòs et al., 2007). A single nucleotide

polymorphism (SNP) of this gene includes the substitution of a Valine (Val) to Methionine (Met) allele at codon 66 (Val66Met). Val genotypes show increased BDNF secretion in comparison to Met carriers (e.g., Val/Met or Met/Met) (Egan et al., 2003). Many studies have suggested that the Met genotype is associated with increased sensitivity to environmental stressors, resulting in poor mental health/cognitive functioning (e.g., increased risk for depression, working memory impairment) (Bath et al., 2012; Kraus et al., 2014; Masi & Brovedani, 2011; Wichers et al., 2008). Other studies have found increased sensitivity to environment for homozygous Val carriers; specifically, Val genotypes have been linked with increased activation to emotional stimuli and risk for depression, suicidality and substance abuse disorders (Berton et al., 2006; Gasic et al., 2009; Gratacòs et al., 2007; Perroud et al., 2008; Pezawas et al., 2005).

Direct gene effects on psychopathological and cognitive outcomes have produced mixed results, with more consistency across studies that look at specific environmental influences (e.g., childhood adversity). Gene x Gene interactions may reflect a similar phenomenon; however, appear to be strengthened when examined through interactions with environmental factors. The complex interaction of genes has been examined through a process known as epistasis, which is the action of one gene on another, in which genetic variation in one gene can suppress or promote the expression of another gene (Wang, Ashley-Koch, Steffens, Krishnan, & Taylor, 2012). For example, a three-way interaction between BDNF, 5-HTTLPR, and maltreatment was found to be associated with depression in children (Kaufman et al., 2006) as well as with healthy subjects and adults with Major Depressive Disorder (MDD) (Kuhn et al., 2014). Research suggests that

individual variation in both of these genes differentially impact neural and functional mechanisms of emotional processing and wellbeing (Paaver et al., 2007; Rabl et al., 2014; Schofield et al., 2009), which appears to be sensitive to environmental stressors early in development. Investigations into the epistatic effects of 5-HTTLPR and BDNF on affective and cognitive functioning have been inconclusive due to the lack of studies that have investigated both genes in both domains (Wang et al., 2012). Therefore, this study seeks to contribute to a gap in the literature regarding the main and epistatic effects of both candidate genes on cognitive and emotional outcomes.

In summary, we expected that the findings from this research would contribute to more advanced understanding of the role of psychological, neurological and genetic components of mental health and wellbeing. It combined methodologies in genetics with emerging theoretical approaches in neurocognition pertaining to the role of functional meaning in our lives, which has the potential to be of benefit across multiple contexts, including clinical, occupational, education and general social and life situations. On the one hand, identifying correlations and/or patterns of genetic risk and childhood adversity as they relate to symptom presentation, we may be able to diminish risk with increased identification capacity, thus paving the way for the development of novel preventative treatments for psychopathology. This study was set in a framework that posits risk for poor mental health functioning as a multidimensional construct that is differentially influenced by the presence of plasticity genes, childhood experiences, and cognitive abilities.

CHAPTER 2:

SPECIFIC AIMS

Current Study

The current study examined the unique, shared, and interacting influences of childhood adversity, neuropsychological functioning, and genes in the expression of mental health risk and resilience among young adults.

Specific Aim I: To investigate the effects of childhood adversity on adult mental health and cognitive functioning.

Specific Aim II: To examine main and interaction effects of childhood adversity and executive functioning on mental health functioning.

Specific Aim III: To examine the associations between childhood adversity and mental health functioning related to individual genetic variation.

Specific Aim IV: To explore epistatic effects of 5-HTTLPR and BDNF polymorphisms on mental health functioning and investigate whether G x G interaction with adversity moderated mental health functioning.

Hypotheses

I. AIM I: Adverse childhood events would correlate with a higher frequency and severity of self-reported symptoms of general psychopathology and psychotic-like experiences and, more specifically, childhood adversity would predict clinically significant psychiatric symptomatology. Further, childhood adversity would be negatively associated with scores on neuropsychological and cognitive assessments, as well as lower levels of self-reported wellbeing.

II. AIM II: The interaction of childhood adversity and adult executive functioning (i.e., scores on measures of working memory and set-shifting) would significantly moderate severity of psychiatric symptoms and wellbeing such that individuals with childhood adversity would show stronger associations between adult executive functioning and both psychiatric symptom severity and wellbeing.

III. AIM III: Distinct profiles would emerge for carriers of Short 5-HTT and Met BDNF alleles, such that childhood adversity would be differentially associated with wellbeing and mental health functioning between genotype groups. More specifically, Short 5-HTT and Met BDNF genotypes would predict greater psychiatric symptomatology and lower wellbeing in the context of childhood adversity.

IV. AIM IV: Gene x Gene susceptibility groups would be differentiated by the strength of associations between childhood adversity and poorer mental health outcomes and that

the Short/Met group membership would show stronger associations between childhood adversity and symptoms, compared to their counterparts for whom, associations between adversity and mental health functioning may not be predicted by their genetics.

CHAPTER 3:

RESEARCH DESIGN & METHODS

Participants

Participants were recruited from the greater Boston area, primarily at the University of Massachusetts, Boston (UMB). A description of the study and eligibility criteria was sent to the undergraduate student body at UMB via email and a public post was created to attract non-UMB potential participants. Participants were between the ages of 18 and 25 (*M*=21.22, *SD*=1.99) and were identified as English speaking for at least five years prior to study enrollment (*N*=100). Briefly, 70% of participants identified as biologically female, 42% racially identified as White, 72% reported the United States of America as their country of origin, and 63% endorsed 1-3 years of college as their level of education. See Table A1 (in appendix) for a description of participant characteristics.

Procedures

The Institutional Review Board (IRB) at UMB approved all research study procedures. Prior to enrollment in the study, participants were provided with a summary of the study's tasks and an opportunity to ask any questions. They were subsequently asked to read and voluntarily sign a consent form. Consenting participants then completed a series of paper and pencil measures that included a demographics

questionnaire, the Brief Symptom Inventory (Derogatis & Melisaratos, 1983), Prodromal Questionnaire-Brief Version (Loewy, Pearson, Vinogradov, Bearden, & Cannon, 2011), Adverse Childhood Experiences scale (Anda et al., 2006), and the Mental Health Continuum-Short Form (Keyes, 2002). Participants were asked to provide a DNA sample via a cheek swab for the assaying of genotypes. Consenting individuals had the option to participate in all aspects of the present study or decline to provide genetic samples; all participants agreed to genetic sampling (N=100). Participants were also administered a battery of cognitive measures that assessed general intelligence, attention, working memory, processing speed and set-shifting. Subjects were informed that their participation was voluntary and they could discontinue any task or their participation in the study at any time. Participants were compensated $25 for their time.

Measures

Demographics Questionnaire

A self-report questionnaire was administered to gather demographic and background information. Items included inquiries about age, gender identity, racial identity, ethnic identity, income, immigration status (of self and parents/caregivers), languages spoken, education level, employment status, housing situation, income, relationship status, and parent status.

Self-Report Measures

Adverse Childhood Experiences

The Adverse Childhood Experiences scale (ACE; Anda et al., 2006) is a 10-item measure that assesses eight categories of adverse experiences in childhood, including: emotional, physical and sexual abuse, and household dysfunction (i.e., substance abuse, mental illness, mother treated violently, and incarcerated household member). Participants are asked to provide "Yes" or "No" responses to each of the 10 items. Total ACE scores are the sum of affirmative responses to questions such as: "Were your parents ever separated or divorced?" "Did a parent/adult in your household often or very often push, grab, slap, or throw something at you?" "Did a member of your household go to prison?" Each question falls under an initial prompt, specifying the timeframe as the first 18 years of the participants' life. Scores range from 0-10, as responses are recorded as dichotomous and represent endorsement of experiences falling within each of the 8 categories. Higher scores were indicative of greater childhood adversity.

Mental Health Continuum – Short Form

The Mental Health Continuum – Short Form (MHC-SF; Keyes, 2002) is a 14-item scale, which measures social, emotional and psychological domains of wellbeing. Scores range from 0-70 with 70 indicating the highest wellbeing. Participants were asked to indicate how frequently, within the past month, they identified with statements such as, "I have something important to contribute to society" and "I feel satisfied with life." Responses were indicated on a five-point scale ranging from 0 (never) to 5 (everyday).

Level of wellbeing is characterized by three sub-categories: languishing (greatest wellbeing), moderately mentally healthy, and flourishing (lowest wellbeing).

Brief Symptom Inventory

The Brief Symptom Inventory (BSI) is a 53-item scale that measures psychiatric symptoms status across nine distinct symptom dimensions: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism (Derogatis & Melisaratos, 1983). Participants rated how much they identified with statements regarding symptoms of psychopathology on a five-point scale ranging from 0 (not at all) to 4 (extremely). Higher ratings indicated the presence of more symptoms of psychopathology and subsequent distress. In addition to the nine symptom domain scores, the scale includes global indices that reflect the total number of symptoms endorsed (PST; positive symptom total), severity of symptoms endorsed (GSI; global severity index), as well as the level of distress caused by symptoms (PSDI; positive symptom distress index). This inventory will be used as a measure of general risk for psychiatric symptoms and related distress. All raw scores were converted to age and gender normed T scores with a mean of 50 and a standard deviation of 10 within an adult, non-patient population. Clinical significance can be determined by meeting 1 of 2 criterion: GSI T score $\geq$ 63 or T score $\geq$ 63 in 2 or more specific symptom domains.

Prodromal Questionnaire – Brief Version

Prodromal Questionnaire – Brief Version (PQ-B) is a 21-item questionnaire that assesses the presence of symptoms/experiences associated with psychosis-risk syndromes (Loewy et al., 2011) and was adapted from the Structured Interview for Prodromal Syndromes (SIPS, Miller et al., 2003). The items on the PQ-B assess psychotic-like experiences within the last month and include two scores: presence of symptom and related distress. Participants responded to items with statements about the experience of positive symptoms of psychosis within the past month (0=no, 1=yes). Every affirmative symptom response is followed by an additional question regarding levels of distress caused by the symptom, which is rated on a five-point scale (0=strongly disagree, 1=disagree, 2=neutral, 3=agree, 4=strongly agree). For example, item 18 reads: "Do you find yourself feeling mistrustful or suspicious of other people?" "If yes, when this happens, I feel frightened, concerned, or it causes problems for me: strongly agree, disagree…" A total score is calculated on a scale of 0-21, and distress score is calculated on a scale of 0-105 with higher numbers on both subscales representing more psychotic-like experiences and greater distress.

Neuropsychological Measures

Estimated IQ was measured by an oral word-reading test (Wide Range Achievement Test - 4th Edition; WRAT4-Blue Form Word Reading Subtest, Wilkinson & Robertson, 2006). Age-matched normative data was utilized to calculate Standard Scores

(SS), which have a mean of 100 and standard deviation of 15, thus, scores in the average range fall between 86 and 114.

Various aspects of attention and processing speed were also explored. Specifically, basic auditory attention, psychomotor processing speed, working memory, and set-shifting was explored through performances on select subtests of the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008) and on the Trail Making Test (TMT*; Army individial test battery: Manual of directions and scoring*., 1944; Reitan, 1955). Specifically, we examined performance on the WAIS-IV Digit Span (Forward & Backward) subtests, which measure attention and working memory. Raw scores were converted to scaled scores (ss) that range from 1 to 19 (M=10, SD=3); scores between 8 and 12 fall within the average range. Finally, aspects of psychomotor processing speed and set-shifting were evaluated by performances on Trail Making Test, Part A & B (i.e., Trails A & Trails B). Trails A & B was represented in seconds (i.e., completion time raw scores, representative of psychomotor processing speed) and were also converted to Z Scores, using normative data. Z Scores indicate the number of standard deviations from the mean.

The WAIS-IV Digit Span subtest measures the storage and manipulation of orally presented strings of numbers, which increase in sequence length. There are two conditions to the test: Digit Span Forward (numbers are read aloud and participants are required to repeat the sequence in the same order) and Digit Span Backward (taxes higher-order executive functioning by requiring participants to mentally manipulate digit sequences and repeat them in the opposite order in which they were presented). For the

purpose of this study, we examined participants' Longest Digit Span for both forward (LDSF) and backward tasks (LDSB), which is indicative of attention and working memory capacity.

The Trail Making Test is a pencil-and-paper measure that is widely used in clinical neuropsychology to assess abilities related to attention and executive function. It consists of two distinct tasks, Trails A & Trails B. In each task, participants are given a piece of paper with 25 randomly arranged circles with numbers in each circle. In Trails A, participants are required participants to draw lines, without lifting their pencil from the page, connecting the numbers in ascending order; in Trails B, the circles are labeled with both numbers and letters and participants are asked to draw lines connecting the ascending (alternating) numbers and letters, (e.g., 1-A-2-B-3-C). Trails A measures psychomotor processing speed and Trails B provides a measure of executive functions related to shifting mental set and response inhibition (Lezak, Howieson, Bigler, & Tranel, 2012).

Genetic Sampling

A detailed description of the PCR protocol used for this study has been previously published (Shen, Adbullah, & Wang, 2009). Buccal cells were collected via cheek swabs and genetic polymorphisms (e.g., 5-HTTLPR & BDNF Val66Met) were assayed. Both of these single nucleotide polymorphisms (SNPs) have been linked to specific aspects of psychological well-being (a) BDNF Val66Met is linked to emotional regulation (e.g., (Hayden et al., 2010); (b) 5-HTTLPR is linked to stress reactivity and vulnerability

(Caspi et al., 2003). Taken together, these genetic polymorphisms may have a moderating effect via G x E and/or G x G x E interactions, in cases of childhood adversity and the emergence of psychopathology in adulthood (Aguilera et al., 2009).

DNA Collection and Extraction

Cytobrush swabs (Coopersurgical Inc.) were used to collect buccal cells. Participants were instructed to brush the swab 30 times against the inside of their cheek while slowly rotating the swab. Swabs were immediately placed on ice and stored at -80°C until DNA extraction. Buccal samples were extracted using a Zymo Quick DNA Universal Kit per the manufacturer's instructions (Zymo Research). DNA yield from buccal samples ranged from 0.48µg to 14.4µg of DNA. Extracted DNA was stored in molecular biology-grade water at -80°C until genotyping analysis.

5-HTTLPR Genotyping

Genotyping for 5-HTTLPR polymorphisms was performed using polymerase chain reaction and resolution using gel electrophoresis (adapted from Smith *et al.,* 2004). 25µL PCR reactions were set up to contain 1X Green GoTaq Flexi Buffer, 1.5mM $MgCl_2$, 0.25mM PCR Nucleotide Mix, 2.5ng of DNA sample, and 0.15µM of both forward and reverse primers (FW: 5' TGA ATG CCA GCA CCT AAC CC 3' and RV: 5'TTC TGG TGC CAC CTA GAC GC 3'). DNA amplification was achieved used the following thermocycler programming: initial denaturation was run for 11 minutes at 95°C, followed by 40 cycles of 45 seconds (s.) at 95°C, 45 s. at 60°C, 45 s. at 72°C, and a

final elongation step of 72°C for 10 minutes. The two amplicon products varied by 44 base pairs (515 base pairs for the long allele and 471 base pairs for the short allele) and were visualized by running the DNA samples on a 1.5% agarose gel stained with 1.5% Ethidium Bromide. Length of amplicon was determined by comparing sample bands to a reference DNA ladder (Promega, USA; ref: G695A) using Molecular Imaging ChemiDoc XRS+. Heterozygous 5-HTTLPR genotype was visibly detected by the presence of two bands in the lane approximately 44 base pairs apart.

BDNF Genotyping

TaqMan SNP genotyping was used to determine BDNF val66met genotype (rs6265). 25µL PCR reactions were performed using a pre-designed 1X Taqman allelic discrimination assay (Applied Biosystems, USA; assay number: C__11592758_10), containing forward and reverse primers and allele-specific probe with 5ng of sample DNA. Genotypic amplification was achieved using the StepOne Plus Real-Time (Applied Biosystems) PCR System with programming as follows: 95°C for 10 minutes, followed by 42 cycles of 95°C for 15 s. and 60°C for 60 s. Genotype was determined from the resulting allelic discrimination plot.

Statistical Methods

First, correlational and regression analyses tested relations of adverse childhood experiences with symptom outcomes. Prior to analyses, all outcome and predictor variables were centered and/or transformed to standard scores using normative data. All

included measures were determined to be normally distributed. Data analyses included Pearson's correlations evaluating the associations between standardized scores representing childhood adversity, wellbeing, psychiatric symptoms (general and psychosis-risk), as well as scores on neuropsychological assessments. Binomial regression analyses tested whether childhood adversity predicted clinically significant psychiatric symptomatology.

Second, a series of hierarchical regressions were performed to allow for the parsing of the unique, shared, and interacting influences of childhood adversity and executive functioning. Specifically, ACE total scores and standardized scores on two measures of executive function (i.e., working memory via Digit Span Backward; set-shifting via Trails B) were entered as predictors of clinically significant psychiatric symptomatology and wellbeing.

Next, differences related to individual genetic variation are presented below through descriptive data. Correlational analyses were conducted to examine associations between childhood adversity, mental health and cognitive functioning for each genotype. Independent sample t tests were conducted to evaluate group differences between genotypes. Hierarchical regressions were run to examine childhood adversity and single gene group as predictors of psychiatric symptoms and wellbeing.

Lastly, descriptive data, one-way ANOVA, correlational analyses, and regressions were conducted to characterize G x G groups, examine within and between group differences, and explore whether polygenetic susceptibility interacts with environmental

risk (i.e., childhood adversity) to predict clinically significant psychiatric symptomatology and wellbeing.

CHAPTER 4:

RESULTS

Descriptive Data

Descriptive data for each of the self-report and cognitive measures for the entire sample (*N*=100) is presented in Table A2. Participants reported a mean of 2.17 (*SD=2.31*) adverse events in childhood. Approximately 76% (*N*=76) of the full sample had fewer than 4 adverse childhood experiences and 24% (*N* =24) experienced 4 or more adverse events in childhood, which is considered the cutoff for clinical significance (i.e., ≥4 ACEs). Continuous ACE total score was non-normally distributed with a skewness of .979 (*SE=.241*) and kurtosis of -.063 (*SE=.478*).

Mental health functioning is represented by two interrelated, yet distinct constructs: wellbeing and psychiatric symptomatology. Overall, participants reported moderate to high levels of wellbeing, as measured by the MHC-SF (*M*=46.24, *SD*=13.49). Within the full sample, only 7% fell within the "languishing" range (the lowest level of wellbeing), 45% were considered "moderately mentally healthy" and 48% were "flourishing" (greatest wellbeing). Wellbeing was normally distributed with a skewness of -.496 (*SE=.241*) and kurtosis of -.550 (*SE=.478*).

Clinically significant symptoms of psychopathology (T $\geq$ 63) were endorsed on each of the 9 symptom domains on the BSI. Additionally, scores representing Global Symptom Severity reached clinical significance for 49% of the full sample, also represented by a standard score of 63 or greater. Among the 71 participants that endorsed significant symptomatology, 16% (*N* =11) had ratings above the clinical cutoff for a single symptom domain, while 84% (*N* =60) indicated significant symptomatology on 2 or more domains. Overall, mean GSI was 60.11 (*SD=12.53*). GSI T scores were normally distributed with skewness -.269 (*SE=.241*) and kurtosis -.591 (*SE=.478*).

Turning to the PQ-B, rates of psychotic-like experiences (*M*=4.08, *SD*=4.11) and subsequent distress (*M*=12.06, *SD*=14.21) were relatively low, as would be expected in a non-clinical sample. Frequency of "Yes" responses ranged from 0 to 18, with 79% of the entire sample reporting at least 1 affirmative response. PQ-B scores were normally distributed with skewness .072 (*SE=.241*) and kurtosis -.598 (*SE=.478*).

Estimated general intellectual ability, as measured by the WRAT4 oral reading was within the high end of the average range for the entire sample (*M*=105.80, *SD*=15.33). Performances on measures of attention, processing speed, working memory, and set-shifting, were comparable to one another and within the expected ranges, compared to age-derived normative data. Descriptive data of performances on neuropsychological assessments can be seen in Table A2. All scores on cognitive measures were normally distributed with the exception of Trails A and Trails B, which were both slightly negatively skewed and kurtoic. The dataset was complete with data

points for each participant on each of the included measures (i.e., there was no missing data).

Test of Specific Aims

Specific Aim I:

Consistent with our Aim I hypothesis, childhood adversity was significantly correlated with wellbeing, such that greater adversity was correlated with lower levels of current wellbeing, $r(98) = -.244$, $p < .05$. In addition, as shown in Table A3, childhood adversity was significantly associated with higher symptom ratings on five of the nine BSI symptom clusters (i.e., obsessive-compulsive, depression, anxiety, hostility, and phobic anxiety). Similarly, the total number of psychiatric symptoms endorsed, symptom severity and related distress were all also significantly correlated with childhood adversity, indicating that reports of greater incidents of early life stress were correlated with higher domain-specific psychiatric symptom ratings, severity and subsequent distress. Additionally, symptoms associated with psychosis-risk increased significantly with elevations in incidents of childhood adversity. Lastly, significant, negative associations between WAIS-IV measures of attention (Digit Span Forward) and working memory (Digit Span Backward) were established, indicating that reports of more adversity in early development is associated with weaker performance in these cognitive domains in young adulthood.

A binomial logistic regression was performed to determine the effects of childhood adversity on the likelihood that participants fall within the clinically significant

range for psychiatric symptomatology (i.e., T ≥ 63 in 2 or more BSI symptom domains); X^2 6.065(1) = $p < .05$. First, Hosmer and Lemeshow test confirmed goodness of fit of the model ($p = .657$). The explained variation in clinically significant psychiatric symptomatology, based on the model, was approximately 8% (Nagelkerke $R^2 = .080$). The percentage accuracy in classification indicated that the ACE (as measured by a continuous ACE total score) correctly classified 66% of cases into psychiatric symptom groups (i.e., below and above cutoff for clinical significance). Of all cases predicted to fall within the clinical group, 69% were correctly predicted. Childhood adversity increased the odds of falling within the clinically significant symptom group by 1.731 ($p < .05$).

Specific Aim II:

To evaluate the impact of two central components of executive functioning (e.g., working memory & set-shifting), correlation and regression analyses were conducted. More specifically, standardized scores on two neuropsychological measures, WAIS-IV: Digit Span Backward and Trails B were examined as moderators in the association between childhood adversity and psychiatric symptomatology and wellbeing. As mentioned, significant, negative associations were found between childhood adversity and scores on Digit Span Forward and Digit Span Backward, such that greater incidences of adverse events were associated with poorer performance on the selected measures of attention and working memory.

A series of hierarchical multiple regressions was run to determine if the addition

of working memory and set-shifting ability represented by standard scores on WAIS-IV: Digit Span Backward and Trails B, respectively, improved the prediction of psychiatric symptoms over and above childhood adversity alone. See Table A4 for full details on each model. BSI global severity index T scores and standardized total ACE scores represented psychiatric symptoms and childhood adversity. The full model of childhood adversity, working memory, and set-shifting (Model 4) was statistically significant, R^2 = .127, $F(5, 94) = 2.731$, $p < .05$; adjusted R^2 = .080. Significant main effects of ACE and LDSB were observed in Model 2.

A second series of regressions was conducted to determine whether childhood adversity and cognitive abilities predicted wellbeing. Wellbeing was represented by standardized total scores on the MHC-SF. The full model of childhood adversity, working memory and set-shifting (Model 4) was not statistically significant, nor was the preceding Model 3. Model 2, which included only the ACE and LDSB showed significant main effects for the ACE and was statistically significant, R^2 = .060, $F(2, 97) = 3.091$, $p < .05$; adjusted R^2 = .041.

Specific Aim III:

First, each gene was examined discretely through a comparison of group characteristics across two genotype groups (i.e., 5-HTT Long, 5-HTT Short & BDNF Val, BDNF Met). For the 5-HTT or SERT gene, the first group was composed of 5-HTT Long homozygotes (5-HTT Long, i.e., L/L) and the second group was represented by 5-HTT Short homo- and heterozygotes (5-HTT Short, i.e., S/L, S/S). For the BDNF gene,

the first of two groups was represented by BDNF Val homozygotes (BDNF Val, i.e., V/V), the second by BDNF Met homo- and heterozygotes (BDNF Met, i.e., V/M, M/M). See Tables 1 & 2 below for genotype frequencies.

Table 1. 5-HTT & BDNF Variants

5-HTT Variants				BDNF Variants		
Variant	L/L	S/L	S/S	Val/Val	Val/Met	Met/Met
Total N	41	43	16	72	22	6

Table 2. 5-HTT & BDNF Genotypes

	5-HTT Genotypes		BDNF Genotypes	
Genotype	Long (L/L)	Short (S/L, S/S)	Val (Val/Val)	Met (Val/Met, Met/Met)
Total N	41	59	72	28

Descriptive statistics for each gene group are presented on Table A5. Independent sample t tests were conducted to examine within-group differences in primary predictors and outcomes. Specifically, genotype groups were examined for differences in ratings of adverse childhood events, psychiatric symptoms, and level of wellbeing. First, 5-HTT Long and Short groups were compared (see Table A6). 5-HTT Long and 5-HTT Short groups did not differ significantly on any of the mental health measures. However, a significant difference in estimated IQ derived from the WRAT4 (SS) was observed between the 5-HTT groups, such that Short carriers exhibited higher IQ scores (M=108.47, SD=15.76) when compared to their Long counterparts (M=102.02, SD=14.03); t (98)= -2.10, $p < .05$. Then, BDNF groups were compared and it was indicated that Val homozygotes reported higher symptom ratings in interpersonal

sensitivity (t (98)= 2.27, $p < .05$), depression (t (98)= 2.11, $p < .05$.), and anxiety (t (98)= 2.17, $p < .05$.), when compared to Met carriers. No other significant differences were present between the BDNF groups on the remainder of the study measures (Table A7).

To further explore single genotype associations, a series of hierarchical regressions were conducted to examine whether the interaction of ACE and gene group predicted psychiatric symptom severity and wellbeing. The first step of the model included the ACE (continuous total score converted to Z Score), and 5-HTT genotypes (two levels; 0=LL and 1=SL & SS). In the second, final step, an interaction term for ACE x 5-HTT was created and entered into the model. Psychiatric symptom severity (continuous standardized GSI score) and wellbeing (continuous standardized MHC-SF total score) were not predicted by the interaction of ACE and 5-HTT genotype. In the first step of the two regression models, there were significant main effects of the ACE on both outcomes. Regression models were run with the same variables, but instead, included the BDNF genotypes (two levels: 0=VV and 1=VM & MM). There were not significant interaction effects of the ACE and BDNF genotype on symptoms or wellbeing; however, significant main effects of the ACE on both outcomes were observed in the first model, which did not include the interaction term. Overall, genotype group status did not predict associations observed between the ACE and psychiatric symptoms or wellbeing (see Table 3 & 4 below).

Table 3. Hierarchical Multiple Regression Predicting Psychiatric Symptoms from ACE & Genotype

	Model 1		Model 2		Model 3	
Variable	B	*β*	B	*β*	B	*β*
ACE Total	1.599	.294**	1.526	.281**	.906	.167
5-HTT Genotype			-.362	-.014	-.591	-.023
BDNF Genotype			4.620	.166	4.181	.151
ACE x 5-HTT					2.219	.130
ACE x BDNF					.296	.020
R^2	.086		.115		.122	
F	9.276**		4.163**		2.621**	
R^2 change	.086		.029		.007	
F Change	9.276**		1.555		.387	

Note. N=100. * p <.05, ** p <.01

Table 4. Hierarchical Multiple Regression Predicting Wellbeing from ACE & Genotype

	Model 1		Model 2		Model 3	
Variable	B	*β*	B	*β*	B	*β*
ACE Total	-1.428	-.244**	-1.415	-.242*	-1.356	-.232
5-HTT Genotype			-.820	-.030	-.781	-.029
BDNF Genotype			-3.293	-.110	-3.419	-.114
ACE x 5-HTT					.526	.029
ACE x BDNF					-.588	-.037
R^2	.059		.071		.072	
F	6.199**		2.452		1.458	
R^2 change	.059		.012		.000	
F Change	6.199**		.604		.041	

Note. N=100. * p < .05, ** p < .01

While group status did not predict association between ACE and symptom ratings, wellbeing or cognitive performance, notable trends emerged from correlational analyses for each genotype when examined separately. Pearson's correlation coefficients between ACE and wellbeing, symptoms and cognition revealed several significant associations for carriers of the 5-HTT Short allele (i.e., S/S, S/L) across nearly all domains (see Table A8 in appendix). For 5-HTT Short carriers, there was a significant, negative correlation between childhood adversity and wellbeing, $r(98) = -.254$, $p < .05$). Additionally, 7 of the 9 symptom domains were positively correlated with childhood adversity, relating higher symptom ratings to greater experiences of adversity in childhood. For 5-HTT Short carriers, experiences of childhood adversity were significantly correlated with symptoms of psychosis-risk, $r(98) = .326$, $p < .05$, and related distress, $r(98) = .345$, $p < .01$). By contrast, among 5-HTT Long carriers, only one significant, positive correlation was observed between childhood adversity and obsessive-compulsive symptoms on the BSI, $r(98) = .308$, $p < .05$. For neuropsychological measures, ACE scores did not correlate with any cognitive measures for either 5-HTT group with the lone exception of a negative association of childhood adversity and performance on a measure of attention, $r(98) = .335$, $p < .05$ for 5-HTT Long carriers. Overall, these correlations indicated that for 5-HTT Short carriers, childhood adversity correlated with lower levels of current wellbeing and increased psychiatric symptoms and related distress, as well as increased risk of psychosis.

Similarly, Table A9 presents correlations of childhood adversity with wellbeing, psychiatric symptoms, and cognition for each BDNF group. Pearson's correlation

coefficients revealed several significant associations for homozygous carriers of the BDNF Val allele across nearly all domains. Among BDNF Val homozygotes, a significant, negative correlation between experiences of childhood adversity and wellbeing was found, $r(98) = -.240$, $p < .05$; an association that was not observed in Met carriers. Additionally, 4 of the 9 psychiatric symptom domains were positively correlated with ACE scores, relating higher symptoms to greater number of experiences of adversity in childhood. Global indices for symptom severity and distress were also significantly correlated with childhood adversity for BDNF Val carriers, as well as with symptoms of psychosis-risk, $r(98) = .299$, $p < .01$ and related distress, $r(98) = .302$, $p < .01$. BDNF Val also showed significant associations between childhood adversity and weaknesses in performance on measures of attention, working memory, and processing speed/set-shifting. A single significant correlation emerged for BDNF Met carriers between early adversity and hostility on the BSI, $r(98) = .393$, $p < .05$. There were no significant associations between adversity and performances on neuropsychological measures for BDNF Met genotypes.

Specific Aim IV:

Table 5 below presents three G x G groups, which represent 3 of 4 possible genotype combinations. These groups were determined based on evidence put forth by previous studies and informed by trends in associations between ACE and symptoms when each genotype was examined individually. As mentioned above, group status for 5-HTT and BDNF alone did not predict outcomes, nor did group status contribute to

associations between ACE and mental health outcomes. Given the consistency with which significant associations between ACE and mental health measures emerged for 5-HTT Short and BDNF Val groups, three gene x gene groups were established and did not include carriers of the homozygous 5-HTT Long and BDNF Met alleles. Thus, three gene x gene groups were identified as: Short/Val (5-HTT SS, SL & BDNF VV), Long/Val (5-HTT LL & BDNF VV), and Short/Met (5-HTT SS, SL & BDNF VM, MM). Further explanation will follow in the discussion section.

Table 5. BDNF Group * 5-HTT Group Cross-tabulation

		5-HTT Group (Long=LL and Short=SL, SS)		
		Long	**Short**	**Total**
BDNF Group	**Val**	34	38	72
(Val=VV and Met=VM, MM)	**Met**	7	21	28
Total		41	59	100

A one-way ANOVA was conducted to determine if reported childhood adversity, psychiatric symptomatology and wellbeing was different for the gene x gene groups. As mentioned above, three groups were comprised of Short/Met (S/M; *N*=21), Long/Val (L/V; *N* =34) and Short/Val (S/V; *N* =38). Levene's test of homogeneity of variances indicated adequate homogeneity for each of the three measures. Data is presented as (M, *SD*). Psychiatric symptoms (GSI T score) was statistically significantly different for different gene x gene groups, $F(2, 90) = 4.814$, $p < .01$. Psychiatric symptoms increased from the lowest ratings for Short/Met carriers (*M*=52.52, *SD*=13.27), to the Long/Val group's ratings (*M*=60.24, *SD*=10.04) to highest psychiatric symptom ratings for the Short/Val group (*M*=62.76, *SD*=13.42). There were no statistically significant differences

in ACE score, $F(2, 90) = 1.544$, $p = .219$. Level of wellbeing was statistically significantly different for different gene x gene groups, Welch's $F(2, 56.926) = 3.658$, $p < .05$, as was psychiatric symptom severity, Welch's $F(2, 49.569) = 4.053$, $p < .05$. A Games-Howell post hoc test was conducted to further understand group differences. There was a decrease in wellbeing from Short/Met group (M=51.76, SD=9.47) compared to the Short/Val group (M=43.76, SD=13.08), with a mean decrease of -7.99 (SE=*2.96*), which was statistically significant ($p < .05$). Additionally, there was an increase in psychiatric symptoms endorsed by the Short/Val group compared to the Short/Met group, with a mean increase of 10.24 (SE=*3.62*), which was also statistically significant ($p < .05$).

A series of regressions was conducted to determine whether childhood adversity and gene x gene groups predicted psychiatric symptoms. BSI global severity index T scores represented psychiatric symptomatology and standardized total ACE scores represented childhood adversity. In the first step of the model, ACE main effects were observed. Model 2 included the addition of the three gene x gene groups and remained significant overall, with significant main effects for ACE and Short/Met. The full Model 3 included the addition of three interaction terms that represented the ACE x each of the three gene x gene groups (e.g., ACE x Short/Met). The full model was statistically significant and included significant main effects for the Short/Met group, $R^2 = .196$, $F(7, 92) = 3.196$, $p < .01$; adjusted $R^2 = .134$ (see Table 6).

A second series of hierarchical multiple regressions was run to determine if the addition of the three gene x gene groups improved the prediction of wellbeing over and

above childhood adversity alone. See Table 7 for full details on each model. Wellbeing was represented by standardized total scores on the MHC-SF. The model of childhood adversity, Short/Met, Long/Val, and Short/Val (Model 2) was statistically significant, R^2 = .104, $F(4, 95) = 2.766$, $p < .05$; adjusted R^2 = .067. Significant main effects of ACE were observed in Models 1 & 2; however, when G x E interaction terms were added in the full Model 3, only significant main effects of Short/Met were identified as a predictor of wellbeing.

Table 6. Hierarchical Multiple Regression Predicting Psychiatric Symptoms from ACE & Gene x Gene Groups

	Model 1		Model 2		Model 3	
Variable	B	*β*	B	*β*	B	*β*
ACE Total	1.599	.294**	1.273	.234*	-.224	-.041
Short/Met			-12.304	-.402*	-15.157	-.495**
Long/Val			-5.964	-.227	-8.172	-.310
Short/Val			-3.080	-.120	-5.353	-.208
ACE x S/M					1.955	.065
ACE x L/V					2.466	.115
ACE x S/V					5.732	.277
R^2	.086		.173		.196	
F	9.276**		4.977**		3.196**	
R^2 change	.086		.087		.022	
F Change	9.276**		3.324*		.852	

Note. N=100. * $p < .05$, ** $p < .01$

Table 7. Hierarchical Multiple Regression Predicting Wellbeing from ACE & Gene x Gene Groups

	Model 1		Model 2		Model 3	
Variable	B	β	B	β	B	β
ACE Total	-1.428	-.244**	-1.209	-.207*	2.003	.342
Short/Met			8.884	.270	13.701	.416*
Long/Val			5.308	.187	10.466	.369
Short/Val			1.850	.067	6.816	.246
ACE x S/M					-7.800	-.242
ACE x L/V					-9.292	-.402
ACE x S/V					-7.085	-.328
R^2	.059		.104		.135	
F	6.199**		2.766*		2.051	
R^2 change	.059		.045		.031	
F Change	6.199**		1.584		1.088	

Note. N=100. * $p < .05$, ** $p < .01$

CHAPTER 5:

DISCUSSION

The current study explored the effects of childhood adversity and the main and epistatic effects of 5-HTTLPR and BDNF polymorphisms on wellbeing and psychiatric symptoms. Inconsistency within the literature related to the genetic mechanisms underlying the effects of childhood adversity on mental health functioning have encouraged investigators to build upon the current diathesis-stress model and explore how the interacting influences of genes and environmental factors may confer both risk and protection in cognitive and emotional functioning. This investigation sought to better understand a concept of differential susceptibility by examining genetic variability as moderators of environmental effects on mental health.

I hypothesized that the ACE would be positively correlated with psychiatric symptoms, and negatively correlated with wellbeing and cognitive functioning. That is, higher ACE scores would be associated with higher psychiatric symptom severity, lower levels of wellbeing, and lower performance on cognitive measures of attention and executive functioning.

The current study aimed to replicate the extensive literature linking childhood adversity with many poor mental health and health outcomes (Kaufman et al., 2006; Caspi et al., 2003), first, along a spectrum of wellbeing and in relation to psychiatric symptom presentation. These two constructs were explored intentionally in an effort to capture the nature of mental health as it is related to wellbeing (e.g., emotional, psychological, and social) as well as through the experience of symptoms of psychopathology. These concepts are conceptually interrelated, although examined as separate constructs to elucidate respective impacts of symptomatology on wellbeing and vice versa (Westerhof & Keyes, 2010).

Consistent with an extensive literature in support of the moderating effects of childhood adversity on neurobiological development and emotional, psychological and social functioning across the lifespan (Beutel et al., 2017; Brown & Harris, 2008; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; McEwen, 2008) our results suggest that the ACE is negatively correlated with wellbeing and positively correlated with clinically significant symptoms of psychopathology (see Table A3).

Additionally, significant associations between the ACE and measures of attention and working memory were identified. Specifically, higher ACE scores were negatively correlated with basic auditory attention (WAIS-IV Digit Span Forward) and working memory ability (WAIS-IV Digit Span Backward). When measures of executive functioning were examined as moderators of the effects of childhood adversity on psychiatric symptoms and wellbeing, only childhood adversity and working memory alone predicted higher symptoms and lower wellbeing. There was no evidence of

moderation of childhood adversity and executive functioning. Wellbeing and symptoms were examined as separate outcomes to evaluate whether hypothesized adversity-related cognitive deficits differentially impacted each construct; the majority of investigations have focused on psychiatric symptoms rather than level of subjective wellbeing. It is possible that the sample, which was comprised of 100 college, undergraduate and graduate students, who are expected to differ to some degree from clinical samples, presented with cognitive profiles that lacked variability within- and between-subjects. It is also possible that associations between mental health outcomes and cognition are evident among patients with more significant cognitive decline/impairment. It may be that other cognitive abilities that remain intact for this non-clinical sample either confound or compensate for any potential moderating effect of these two measures on the effects of childhood adversity and adult mental health functioning.

Studies have long explored the neuroscience of childhood adversity, specifically, the structural and functional repercussions of exposure to stress during critical stages of cognitive and affective development (Hackman et al., 2010; Hunter & McEwen, 2013; McEwen & Stellar, 1993). Brain dysfunction impacts wellbeing across the lifespan and differences in functioning and structure of particular brain regions are thought to underlie the majority of psychiatric illnesses (Hackman et al., 2010; McEwen et al., 2015; Meloni, 2014). Thus, it is unsurprising that our results indicate mild impairments in domains of attention and executive functioning in the context of childhood adversity, particularly given the observed brain-related changes associated with early life stress (e.g., volume reductions in hippocampal and PFC grey matter, amygdalar enlargement) (Deoni et al.,

2016). These findings are significant in that they provide further evidence for the effects of childhood adversity on mental health and cognitive functioning across the lifespan within a population considered, from a developmental perspective, at-risk for mental health issues.

I hypothesized that main effects of Short 5-HTTLPR and Met BDNF genotypes would predict greater psychiatric symptomatology and lower wellbeing in the context of childhood adversity, above and beyond the contribution of adversity alone. I hypothesized that epistatic effects of Short 5-HTTLPR and Met BDNF on mental health outcomes would indicate that genetic variation and adversity predicted wellbeing and functioning in the expected directions and uniquely for Short/Met, additionally, that these associations would persist above and beyond the contribution of G x G alone or ACE alone.

Several studies have indicated that BDNF plays a mediating role in the effects of 5-HTT on neural mechanisms that underlie cognitive and affective functioning that are impacted by environmental stressors (Bath et al., 2012). Studies have associated BDNF Met with increased risk for psychopathology in the context of adversity (Kaufman et al., 2006; Aguilera et al., 2009; Wichers et al., 2008; Wells, Beevers, & McGeary, 2010) while others suggest Met alleles serve to protect against the effects of 5-HTT (Pezawas, et al., 2008). However, others have presented findings that suggest increased susceptibility is associated with Val carriers (Gatt et al., 2009; Pezawas et al., 2008; Perroud et al., 2003). Specifically, Val carriers showed increased GMV in the amygdala and associated medial PFC when exposed to early life stress. These same individuals

reported higher ratings of anxiety-traits and emotional dysregulation (Pezawas et al., 2008; Gatt et al., 2009; Dougherty, Klein, Congdon, Canli, & Hayden, 2009). Met carriers from this same sample presented with GMV reductions in the hippocampus and amygdala, declines in working memory ability and decreased BDNF secretion. These Met carriers reported higher rates of depressive symptoms, which was significantly predicted by allelic variation and ELS. Taken together, these findings suggest differential susceptibility resulting from allelic differences in the BDNF Val66Met genotype. That is, both alleles seem to be implicated, however, differentially and depending on several other factors.

Gene group status did not predict psychiatric symptomatology or wellbeing independently or through interaction with childhood adversity. Childhood adversity was the only predictor of symptoms and wellbeing when examined with each of the gene groups. The hypothesized association between Short 5-HTTLPR carriers and childhood adversity was not established. Neither was the hypothesized relation between the ACE and BDNF Met carriers. These findings likely reflect similar results presented by (Kaufman et al., 2006; Wichers et al., 2008), which suggested that the respective susceptibility conferred by each genotype failed to increase sensitivity to environmental stressors (e.g., childhood trauma) and predict outcomes (e.g., depression) unless both vulnerable genotypes were present. With this in mind, clear associations between the ACE, psychiatric symptoms and wellbeing for the Short 5-HTTLPR carriers and Val BDNF carriers were observed. Correlations between the ACE and mental health

functioning were not statistically significantly different when each gene group was compared.

Epistatic effects of Short 5-HTTLPR and Met BDNF and childhood adversity were examined as predictors of psychiatric symptomatology and wellbeing. Three susceptibility groups were determined based on theoretical constructs: "Short/Met" (5-HTT SS, SL & BDNF VM, MM), "Short/Val" (5-HTT SS, SL & BDNF VV), and "Long/Val" (5-HTT LL & BDNF VV). It was hypothesized that childhood adversity and epistatic effects of Short 5-HTTLPR and BDNF Met would represent the strongest associations between ACE and mental health functioning. Regression analyses indicated that childhood adversity and Short/Met group membership predicted psychiatric symptoms and wellbeing. There were no differences in exposure to adversity across the gene x gene groups; however, Short/Met participants endorsed lower psychiatric symptoms and higher levels of wellbeing when compared to Short/Val carriers, who reported higher symptoms and lower levels of wellbeing. Short/Met group membership was the only gene x gene group that predicted symptoms or wellbeing. Post hoc testing suggested that the presence of the Met allele (hetero- or homozygous) predicted lower symptom severity and higher wellbeing for this group compared to Short/Val carriers, which may indicate that the interaction of these genes may play a protective role in mental health functioning. However, this association was not impacted by childhood adversity, as hypothesized. Further, while differences in symptom ratings and wellbeing emerged between two of the gene x gene groups, the combination of Short/Val did not uniquely predict outcomes. Sample characteristics likely impacted associations between

the ACE and outcomes, particularly when examining the moderating effects of gene groups. The current study sample reported relatively mild exposure to adversity; it is possible that degree of adversity reported may differentially position individuals along the spectrum of susceptibility; in other words, epistatic effects of Short 5-HTTLPR and Met BDNF may not have been sensitive to mild adversity.

Questions surrounding a developmental or temporal specificity of ELS exposure are worth exploring, particularly given findings put forth by Failla et al. (2016), which suggest Met carriers are more susceptible when injury is experienced earlier in development, but that Met alleles serve as a protective factor later in life (i.e., among older adults when compared to younger adults). In addition to developmental factors, sex differences have been explored in the context of genetic risk and differential susceptibility. One study found that Val homozygote boys rated higher on measures of loneliness, a precursor for depression, than their female counterparts (Verhagen, Van Roekel, & Engels, 2014). Taken together, our results fit nicely with both a developmental and sex-based model of differential susceptibility and thus, might explain some of the inconsistency in the literature. Overall, presence of Short/Met genes predicted lower symptoms and higher wellbeing, which suggests that genetic variability influenced outcomes and was not dependent on adversity for this sample.

Gene x Gene (i.e., Short/Met) group membership predicted psychiatric symptoms and wellbeing. Short/Met was comprised of carriers of Short 5-HTTLPR and Val/Met or Met/Met BDNF alleles. While single gene group membership did not predict outcomes, correlations between ACE and mental health functioning that arose for Val/Val carriers

may implicate the Val allele in particular. That is, the presence of the Val allele in the Short/Met carrier group may be of importance in understanding the mechanisms that underlie the prediction of symptoms and wellbeing differentially for the Short/Met group. While our results did not identify significant G x G x E interactions, G x G effects and significant main effects of childhood adversity were found.

Strengths & Limitations

The present study utilized a convenience sample of undergraduate and graduate students aged 18-25. This period of young adulthood has been established as a critical developmental stage, during which vocational, social, and emotional trajectories are being set, which therefore, constitutes as a developmentally "at risk" population. Additionally, the present sample represents a considerably diverse population in terms of racial and ethnic identity, which is beneficial for the generalizability of the studies findings to diverse populations.

An important consideration for the study's limitations is that most study measures were self-report based, which may be subject to recall bias and/or not capture the multifaceted nature of many aspects of psychological functioning. However, it is possible that this method of data collection may have also reduced the impact of social desirability, as participants were able to complete questionnaires without direct interaction with research staff. The chosen measure of childhood adversity captured experiences from birth to 18 years of age, which did not take into account earlier versus later childhood adverse events or recent trauma/adversity in early adulthood. Cultural

factors influencing self-report and performance on cognitive measures would also require further investigation. With regard to the cognitive measures, given the diversity represented in this sample, particularly in terms of nation of origin and English as a second language speakers, it is possible that performance on some of the verbal measures underrepresents the cognitive abilities of the sample. However, each measure chosen was validated for use within diverse populations, although this remains a consideration in interpreting the results of the present study. Unequal distribution of G x G groups and small sample size for the Long/Val (n=7) group may limit the generalizability of these findings.

Future Directions

Future studies may benefit from a multimodal approach to ELS effects on mental health functioning, specifically, by incorporating neuroimaging and/or behavioral activation paradigms. Additionally, future investigations may include semi-structured or interview-based assessments of psychopathology to either supplement or replace self-report questionnaires, allowing for a more complex assessment of mental health functioning. Additionally, with regards to the PQ-B, as this measure was created as a screening tool for youth exhibiting signs of risk for psychosis, it likely over-represented or pathologized normative experiences that may also be culturally-based and thus, interpretation of this measure within this non-clinical population should be cautioned. Future projects may benefit from exploring positive childhood experiences and social

support as potential moderators of the effects of ELS on mental health functioning, particularly to investigate the concept of differential susceptibility.

Further investigation into the complex social and cultural factors that impact developmental trajectories and wellbeing across the lifespan is imperative for future studies. Specifically, acknowledgement of the limitations of many clinical diagnostic and cognitive assessments in terms of their lack of cultural sensitivity and use of standardized normative data collected from a diverse and therefore, widely representative sample, is imperative. Relatedly, examination of recent life stressors and trauma exposure should be included in future studies to evaluate the impact of ongoing stressors as they impact mental health functioning both in addition to and outside of the context of childhood trauma. Experiences of intergenerational trauma and lived experiences of individuals from marginalized backgrounds should be well integrated into conceptualizing how trauma and adversity are operationalized and constructed.

APPENDIX

Table A1. Demographic Information for Full Sample

	N		M *(SD)*
Biological Sex		Age	21.22 *(1.99)*
Male	30	Country of Origin	N
Female	70	Belarus	1
Gender Identity		Brazil	1
Man	29	China	2
Woman	66	El Salvador	1
Transgender	2	Haiti	3
Other	3	India	9
Sexual Orientation *(n=98)*		Iran	1
Bisexual	9	Jamaica	1
Gay/Lesbian	4	Kenya	2
Heterosexual	81	Nepal	2
Other	4	Nigeria	1
Racial Identity		Pakistan	1
Asian	20	Saudi Arabia	1
African American/Black	16	Taiwan	1
African American/Indian	1	United States of America	72
Brown	3	Venezuela	1
Caribbean	2	Highest Level of Education	
Latin(x)	8	1-3 years of high school	2
Middle Eastern	1	High school diploma	15
Native American	1	1-3 years of college	63
White	42	College degree (BA, BS)	19
White/Latin(x)	4	Graduate degree (MA, MS)	1
White/Middle Eastern	1		
White/Native American	1		

Note. N=100

Table A2. Descriptive Statistics – Full Sample

MEASURE	M	SD
Adverse Childhood Experiences		
ACE Total	2.17	2.31
Wellbeing		
MHC-SF Total	46.24	13.49
Brief Symptom Inventory-Domain & Index Scores		
Somatization	55.32	11.83
Obsessive-Compulsive	61.49	12.67
Interpersonal Sensitivity	59.79	12.21
Depression	60.45	11.12
Anxiety	56.43	13.16
Hostility	57.07	10.96
Phobic Anxiety	57.40	10.86
Paranoid Ideation	58.33	11.79
Psychoticism	61.72	11.96
Global Severity Index	60.11	12.53
Positive Symptom Total	59.04	12.37
Positive Symptom Distress Index	58.55	9.25
Prodromal Questionnaire – Brief		
PQ-B "Yes" Total	4.08	4.11
PQ-B Distress Total	12.06	14.21
Neuropsychological/Cognitive Measures		
WRAT4 (SS)	105.80	15.33
WAIS-IV: LDSF (ss)	9.93	3.02
WAIS-IV: LDSB (ss)	10.19	3.24
Trails A (seconds)	26.88	12.28
Trails A (z score)	-0.37	1.59
Trails B (seconds)	67.36	33.74
Trails B (z score)	-0.71	1.75

Note. N=100

Table A3. Correlations Between ACE and Wellbeing, Symptoms & Cognition

MEASURE	
Wellbeing	
MHC-SF Total	-.244*
Brief Symptom Inventory – Domain Totals & Index Scores	
Somatization	.172
Obsessive-Compulsive	.337**
Interpersonal Sensitivity	.169
Depression	.259**
Anxiety	.257**
Hostility	.285**
Phobic Anxiety	.255**
Paranoid Ideation	.150
Psychoticism	.171
Global Severity Index	.294**
Positive Symptom Total	.274**
Positive Symptom Distress Index	.328**
BSI Clinical Cutoff	.239*
Prodromal Questionnaire – Brief	
PQ-B "Yes" Total	.294**
PQ-B Distress Total	.300**
Neuropsychological/Cognitive Measures	
WRAT4	-.156
WAIS-IV: Digit Span Forward	-.233*
WAIS-IV: Digit Span Backward	-.250*
Trails A	-.041
Trails B	-.102

Note. N=100.

*. Correlation is significant at the 0.05 level (2-tailed)

**. Correlation is significant at the 0.01 level (2-tailed)

Standard Scores: BSI (T score); WRAT4 (SS); WAIS-IV: Digit Span (ss); Trail Making Test (z score)

Table A4. Hierarchical Multiple Regression Predicting Psychiatric Symptoms from Executive Functioning

	Model 1		Model 2		Model 3		Model 4	
Variable	B	*β*	B	*β*	B	*β*	B	*β*
ACE Total	3.686	.294**	4.331	.346**	4.335	.346**	4.445	.355**
Working Memory			2.393	.206**	2.327	.200	2.315	.199
Set-Shifting					.120	.017	.140	.020
ACE x Working Memory							-.195	-.015
ACE x Set-Shifting							.139	.023
R^2	.086		.126		.126		.127	
F	9.276**		7.003**		4.631**		2.731*	
R^2 change	.086		.040		.000		.000	
F Change	9.276**		4.408*		.027		.022	

Note. N=100. * p <.05, ** p <.01. Working Memory: LDSB z score; Set-Shifting: Trails B z score.

Table A5. Descriptive Statistics by 5-HTT & BDNF Genotype

MEASURES	5-HTT				BDNF			
	Long/Long		Short/Long & Short/Short		Val/Val		Val/Met & Met/Met	
	M	SD	M	SD	M	SD	M	SD
Adverse Childhood Experiences								
ACE Total	2.63	2.40	1.85	2.20	2.26	2.29	1.93	2.37
Wellbeing								
MHC-SF Total	45.71	15.01	46.61	12.45	45.24	14.11	48.82	11.58
Brief Symptom Inventory – Domain Total & Index Scores								
Somatization	54.90	10.43	55.61	12.79	56.04	11.88	53.46	11.70
Obsessive-Compulsive	61.71	12.37	61.34	12.95	61.82	12.49	60.64	13.28
Interpersonal Sensitivity	61.27	10.94	58.76	13.01	61.49	12.33	55.43	10.93
Depression	61.34	9.51	59.83	12.15	61.89	10.95	56.75	10.87
Anxiety	57.61	11.71	55.61	14.11	58.18	13.23	51.93	12.04
Hostility	58.22	10.28	56.27	11.43	58.36	10.83	53.75	10.78
Phobic Anxiety	59.00	10.62	56.29	10.98	57.82	11.40	56.32	9.46
Paranoid Ideation	59.83	11.10	57.29	12.24	59.63	11.80	55.00	11.29
Psychoticism	62.49	11.46	61.19	12.37	62.51	12.36	59.68	10.81
Global Severity Index	61.54	9.76	59.12	14.14	61.57	11.93	56.36	13.48
Positive Symptom Total	60.93	10.52	57.73	13.45	60.53	11.81	55.21	13.18
Positive Symptom Distress Index	59.49	8.39	57.90	9.82	58.96	9.62	57.50	8.28
Prodromal Questionnaire - Brief								
PQ-B “Yes” Total	4.46	4.05	3.81	4.16	4.04	4.16	4.18	4.06
PQ-B Distress Total	13.12	12.59	11.32	15.30	12.44	14.99	11.07	12.18
Neuropsychological/Cognitive Measures								
WRAT4	102.02	14.03	108.47	15.76	106.89	15.50	102.89	14.75
WAIS-IV: LDSF	9.98	3.04	9.90	3.04	10.07	3.13	9.57	2.76
WAIS-IV: LDSB	9.95	3.24	10.36	3.26	10.21	3.26	10.14	3.26
Trails A (seconds)	26.81	10.38	26.92	13.53	27.15	10.27	26.18	16.57
Trails B (seconds)	67.38	34.22	67.34	33.70	66.62	32.22	69.26	37.95

Note. 5-HTT Long (N =41); Short (N =59); BDNF Val (N =72); Met (N =28).

Standard Scores: BSI (T score); WRAT4 (SS); WAIS-IV: Longest Digit Span (ss); Trail Making Test (seconds).

Table A6. Independent Samples T-Test for All Measures & 5-HTT Groups

	t	df	p
ACE Total	1.69	98	.093
MHC-SF Total	-.328	98	.744
Wellbeing Groups	-.264	98	.792
BSI Domains & Index Scores			
Somatization	-.293	98	.770
Obsessive-Compulsive	.142	98	.887
Interpersonal Sensitivity	1.01	98	.315
Depression	.667	98	.507
Anxiety	.746	98	.458
Hostility	.873	98	.385
Phobic Anxiety	1.23	98	.221
Paranoid Ideation	1.06	98	.292
Psychoticism	.533	98	.595
Global Severity Index	.948	98	.345
Positive Symptom Total	1.28	98	.205
Positive Symptom Distress Index	.844	98	.401
BSI Clinical Cutoff	.576	98	.566
PQ-B "Yes" Total	.776	98	.439
PQ-B Distress Total	.621	98	.536
WRAT4 (SS)	-2.10	98	.039*
WAIS-IV: LDSF (ss)	.125	98	.901
WAIS-IV: LDSB (ss)	-.612	98	.542
Trails A (seconds)	-.045	98	.964
Trails B (seconds)	.005	98	.996

Note. N=100.

*. Correlation is significant at the 0.05 level (2-tailed)

**. Correlation is significant at the 0.01 level (2-tailed)

Table A7. Independent Samples T-Test for All Measures & BDNF Groups

	t	df	p
ACE Total	.651	98	.516
MHC-SF Total	-1.196	98	.235
Wellbeing Groups	-1.634	98	.105
BSI Domain & Index Scores			
Somatization	.978	98	.331
Obsessive-Compulsive	.416	98	.679
Interpersonal Sensitivity	2.274	98	.025*
Depression	2.111	98	.037*
Anxiety	2.173	98	.032*
Hostility	1.914	98	.059
Phobic Anxiety	.617	98	.539
Paranoid Ideation	1.780	98	.078
Psychoticism	1.065	98	.290
Global Severity Index	1.891	98	.062
Positive Symptom Total	1.955	98	.053
Positive Symptom Distress Index	.706	98	.482
BSI Clinical Cutoff	.360	98	.719
PQ-B "Yes" Total	-.149	98	.882
PQ-B Distress Total	.432	98	.667
WRAT4 (SS)	1.158	97	.250
WAIS-IV: LDSF (ss)	.738	98	.462
WAIS-IV: LDSB (ss)	.090	98	.928
Trails A (seconds)	.352	98	.726
Trails B (seconds)	-.350	98	.727

Note. N=100.

*. Correlation is significant at the 0.05 level (2-tailed)

**. Correlation is significant at the 0.01 level (2-tailed)

Table A8. Correlations Between ACE and Wellbeing, Symptoms & Cognition by 5-HTT

MEASURE	Long (L/L)	Short (S/L, S/S)
Wellbeing		
MHC-SF Total	-.230	-.254*
Brief Symptom Inventory – Domain Total & Index Scores		
Somatization	.032	.274*
Obsessive-Compulsive	.308*	.363**
Interpersonal Sensitivity	.056	.219
Depression	.121	.334**
Anxiety	.192	.287*
Hostility	.118	.382**
Phobic Anxiety	.054	.374**
Paranoid Ideation	-.015	.236
Psychoticism	.024	.263*
Global Severity Index	.213	.330*
Positive Symptom Total	.162	.320*
Positive Symptom Distress Index	.248	.369**
Prodromal Questionnaire – Brief		
PQ-B "Yes" Total	.232	.326*
PQ-B Distress Total	.219	.345**
Neuropsychological/Cognitive Measures		
WRAT4	-.159	-.105
WAIS-IV: Digit Span Forward	-.315*	-.178
WAIS-IV: Digit Span Backward	-.279	-.218
Trails A	-.269	.089
Trails B	-.215	-.021

Note. 5-HTT Long n=41; 5-HTT Short n=59.

*. Correlation is significant at the 0.05 level (2-tailed), **. Correlation is significant at the 0.01 level (2-tailed).

Standard Scores: BSI (T score); WRAT4 (SS); WAIS-IV: Digit Span (ss); Trail Making Test (z score).

Table A9. Correlations Between ACE and Wellbeing, Symptoms & Cognition by BDNF

MEASURE	Val (V/V)	Met (V/M, M/M)
Wellbeing		
MHC-SF Total	-.240*	-.236
Brief Symptom Inventory – Domain Total & Index Scores		
Somatization	.181	.131
Obsessive-Compulsive	.377**	.237
Interpersonal Sensitivity	.186	.080
Depression	.217	.339
Anxiety	.219	.334
Hostility	.232*	.393*
Phobic Anxiety	.277*	.179
Paranoid Ideation	.251*	-.154
Psychoticism	.160	.181
Global Severity Index	.296*	.270
Positive Symptom Total	.301**	.191
Positive Symptom Distress Index	.341**	.283
Prodromal Questionnaire – Brief		
PQ-B "Yes" Total	.299*	.286
PQ-B Distress Total	.302**	.290
Neuropsychological/Cognitive Measures		
WRAT4	-.203	-.054
WAIS-IV: Digit Span Forward	-.309**	-.045
WAIS-IV: Digit Span Backward	-.245*	-.257
Trails A	-.166	.163
Trails B	-.239*	.180

Note. BDNF Val n=72; BDNF Met n=28.

*. Correlation is significant at the 0.05 level (2-tailed),

**. Correlation is significant at the 0.01 level (2-tailed).

Standard Scores: BSI (T score); WRAT4 (SS); WAIS-IV: Digit Span (ss); Trail Making Test (z score).

Table A10. Descriptive Statistics for All Measures - Gene x Gene Groups

	Long/Val		Short/Val		Short/Met	
MEASURE	M	SD	M	SD	M	SD
Adverse Childhood Experiences						
ACE Total	2.41	2.32	2.13	2.28	1.33	2.01
Low ACE (0-3)	*N=24 (70.6%)*		*N=30 (78.9%)*		*N=19 (90.5%)*	
High ACE (4+)	*N=10 (29.4%)*		*N=8 (21.1%)*		*N=2 (9.5%)*	
Wellbeing						
MHC-SF Total	46.88	15.22	43.76	13.08	51.76	9.47
Languishing	*N=4 (11.8%)*		*N=2 (5.3%)*		*N=0 (0%)*	
Moderately Mentally Healthy	*N=11 (32.4%)*		*N=24 (63.2%)*		*N=6 (28.6%)*	
Flourishing	*N=19 (55.9%)*		*N=12 (31.6%)*		*N=15 (71.4%)*	
BSI – Domain Total & Index Scores						
Somatization	54.03	10.07	57.84	13.17	51.57	11.27
Obsessive-Compulsive	59.56	12.32	63.84	12.45	56.81	12.89
Interpersonal Sensitivity	60.74	11.51	62.16	13.15	52.62	10.49
Depression	60.03	9.52	63.55	11.98	53.10	9.43
Anxiety	56.91	11.95	59.32	14.35	48.90	11.10
Hostility	57.12	10.75	59.47	10.92	50.48	10.17
Phobic Anxiety	58.82	10.78	56.92	11.99	55.14	9.02
Paranoid Ideation	59.26	11.23	59.95	12.43	52.48	10.51
Psychoticism	61.32	11.98	63.58	12.76	56.86	10.57
Global Severity Index	60.24	10.04	62.76	13.42	52.52	13.27
Positive Symptom Distress Index	58.26	8.66	59.58	10.49	54.86	7.83
Clinically Significant Symptomatology						
$\geq$2 T scores > 63	*N=19 (55.9%)*		*N=25 (65.8%)*		*N=9 (42.9%)*	
Prodromal Questionnaire - Brief						
PQ-B "Yes" Total	3.94	3.64	4.13	4.62	3.24	3.21
PQ-B Distress Total	11.82	11.67	13.00	17.575	8.29	9.603
Neuropsychological/Cognitive Measures						
WRAT4	102.65	13.96	110.68	16.00	104.25	14.78
WAIS-IV: DS Forward	9.97	2.93	10.16	3.33	9.43	2.42
WAIS-IV: DS Backward	9.76	3.11	10.61	3.38	9.90	3.06
Trails A	27.40	10.59	26.92	10.12	26.93	18.47
Trails B	69.66	34.76	63.90	29.97	73.58	39.62

Note. N=93; Long/Val n=34; Short/Val n=38; Short/Met n=21. **Trails A & B time in seconds*

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