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Internalizing and Externalizing Psychopathology, Stressful Life Events, and Trauma Exposure: Multivariate Structure and Shared Etiology

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Internalizing and Externalizing Psychopathology, Stressful Life Events, and Trauma Exposure: Multivariate Structure and Shared Etiology

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Master of Arts

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An abstract of
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Abstract

Internalizing and Externalizing Psychopathology, Stressful Life Events, and Trauma Exposure: Multivariate Structure and Shared Etiology
By Devon LoParo

Individuals who have experienced stressful life events (SLEs) or trauma are at a higher risk for both internalizing and externalizing psychopathology, although the strength of the association varies depending on the type of event, the form of psychopathology, and demographic characteristics such as ethnicity and gender. Though these relations are well documented, extant research has focused on relations between pairings of SLEs or trauma exposure and internalizing or externalizing disorders, rather than comprehensively evaluating their multivariate phenotypic or etiological structure, leading to several gaps in knowledge. In this study, we addressed these gaps by conducting a set of parallel analyses using data from two samples: 1) a low income, highly traumatized, primarily African American, adult nonclinical sample recruited at Grady Memorial Hospital in Atlanta, Georgia, (2) a primarily Caucasian, community sample of twin children from Georgia. First, we used confirmatory factor analysis (CFA) to determine whether SLEs and trauma exposure are separate constructs or lie on a single continuum of stressful experiences. Second, we used structural equation modeling (SEM) to test whether the relations of SLEs and trauma to internalizing and externalizing psychopathology can be equated and whether different types of SLEs or traumatic events are differentially related to internalizing and externalizing psychopathology. Third, we determined the univariate latent etiological structure of SLEs, trauma exposure, and internalizing and externalizing psychopathology and the multivariate etiological structure of the relations among them by performing univariate and multivariate behavior genetic analyses to quantify the degree to which SLEs and/or trauma exposure and internalizing and externalizing psychopathology share common genetic and environmental influences. Finally, we conducted genome wide association scan (GWAS) scans to conduct univariate single nucleotide polymorphism- (SNP) based and univariate and multivariate gene-based tests of association with SLEs, trauma, and internalizing and externalizing psychopathology. When possible, we compared results across samples to examine the robustness of the estimated relations to demographic factors (e.g., ethnicity, socioeconomic status).

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General Introduction

A basic finding in psychological research is that stressful events are related to increased levels of psychopathology. Several logical questions follow from this basic finding, such as (1) what types of stressful life events (SLEs) or trauma confer the most risk for psychopathology; (2) does that risk differ for internalizing versus externalizing psychopathology; (3) to what degree are these relations causal versus due to shared etiology; and (4) does the tendency to experience SLEs or trauma share genetic or biological etiology with internalizing or externalizing psychopathology?

The answers to these questions are unclear in extant research due to several limiting characteristics of studies conducted to date. First, although researchers have proposed several dimensions of SLEs and trauma, no research has established the construct validity of these dimensions (i.e., how well the proposed dimensions match how these events cluster).

Second, it is not clear the extent to which SLEs and trauma are differentiable, structurally or etiologically, as researchers have inconsistently included or separated trauma from measures of SLEs.

Third, most research includes only SLEs *or* trauma and either internalizing *or* externalizing psychopathology, and does not compare competing models of the structure of relations among these variables.

Fourth, although the tendencies to experience SLEs and trauma have been shown to be genetically influenced, few researchers have searched for specific genes associated with these tendencies and no researchers have searched for genes with multivariate associations across these

tendencies and psychopathology. Thus, the reasons for why and how stress and psychopathology are related are currently unclear.

To redress the limitations of the extant literature, we designed three studies which were performed sequentially so that results from prior studies informed the specific hypotheses tested in later studies. These analyses used data from two samples: 1) a low income, highly traumatized, primarily African American, adult population sample recruited at Grady Memorial Hospital in Atlanta, Georgia (Grady Sample), (2) a primarily Caucasian, community sample of twin children from Georgia (Twin Sample).

In Study 1 (both samples), we (1) tested alternative models of the structure of measures of SLEs and trauma exposure to determine how best to conceptualize these events; (2) tested alternative models of the relations between SLEs and trauma exposure to determine the degree to which these events represent partially separable phenomena; and (3) tested alternative models of the relations between internalizing and externalizing psychopathology, SLEs, and trauma exposure to determine whether different types or categories of stressful events are differentially related to internalizing versus externalizing psychopathology. We compared results across samples to examine the robustness of the estimated relations to demographic factors (e.g., age, ethnicity, socioeconomic status).

In Study 2 (Twin Sample only), we (1) conducted separate, univariate behavior genetic analyses of internalizing and externalizing psychopathology, SLEs, and trauma exposure to determine the degree to which each variable is explained by genetic and environmental influences; and (2) conducted multivariate behavior genetic analyses to determine the degree to which relations among these variables are explained by common etiological influences.

In Study 3 (Grady Sample only), we (1) conducted univariate single nucleotide polymorphism (SNP)-based genome-wide association studies (GWAS) of internalizing and externalizing psychopathology, SLEs, and trauma exposure in order to find genetic variants associated with these variables; (2) conducted univariate gene-based tests of these variables in order to find associated genes; and (3) conducted multivariate gene-based tests of variables that demonstrated common genetic influences in Study 2.

Each study is presented separately below followed by general conclusions.

Study 1: Structure of and Relations among Stressful Life Events, Trauma, and Psychopathology

Introduction

Individuals who have experienced stressful life events (SLEs) or trauma are at higher risk for many forms of psychopathology, although the strength of the association varies depending on the type of event, the form of psychopathology, and demographic characteristics such as ethnicity and gender (e.g. Dohrenwend, 1998; Copeland et al., 2007). SLEs and trauma exposure are associated with both internalizing and externalizing psychopathology (Dohrenwend, 1998; Anda et al., 2006). Although these relations are well documented, extant research has focused on relations between pairings of SLEs or trauma exposure and internalizing or externalizing psychopathology, rather than comprehensively evaluating their multivariate structure. Further, research on SLEs and trauma has tended to sum events across a given period of time rather than using latent variables to examine an underlying tendency to experience these events. The lack of research addressing these concerns has led to several gaps in knowledge.

First, researchers have proposed multiple dimensions of SLEs and trauma (e.g., Williamson et al., 1995; Stein et al., 2002) but use sum scores and have not used techniques such as Confirmatory Factor Analysis (CFA) to rigorously compare alternative models. Thus, it is unclear which dimensions best characterize how events tend to cluster together. Elucidating how events cluster could help researchers to standardize how these events are measured and classified as well as help to better predict and differentiate individuals' liability to experience SLEs or trauma.

Second, researchers tend to treat SLEs and trauma as categorically distinct, although the distinction between them is poorly defined. It is not clear whether trauma is an extreme form of SLEs or an at least partially distinct phenomenon with potentially unique etiology, correlates, or

outcomes. Elucidating this distinction could help researchers to measure SLEs and trauma more precisely and to determine the degree to which they have common or unique ramifications.

Third, research on the relation of SLEs and trauma to psychopathology tends to focus on particular disorders within either internalizing *or* externalizing psychopathology and has not taken into account the significant phenotypic overlap that exists both within and between internalizing and externalizing psychopathology (e.g. Lahey et al., 2012). In combination with the gaps in knowledge outlined above, it is unclear what types of SLEs or trauma are most strongly associated with psychopathology or whether that risk differs between internalizing and externalizing psychopathology. Further, although differential rates of SLEs and trauma exposure are found when comparing groups based on age, ethnicity, gender, and socioeconomic status (Hatch & Dohrenwend, 2007), it is not clear whether these differences translate to differences in the latent structure of the relations among SLEs, trauma exposure, and internalizing and externalizing psychopathology. In the current study, we aim to address these gaps in knowledge concerning the structure and etiology of SLEs, trauma exposure, and psychopathology.

Internalizing and Externalizing Psychopathology

Attempts to elucidate the latent structure of psychopathology in children and adults have revealed that rates of co-occurrence between disorders are quite high and roughly follow the rule of 50%: half of individuals who meet criteria for one disorder meet criteria for another, half of individuals with two disorders meet criteria for a third disorder, and so forth (Newman et al., 1998). Further, patterns of co-occurrence have been found to reflect two underlying core psychopathological processes in childhood (e.g., Achenbach & Edelbrock, 1981) and adulthood (e.g., Krueger et al., 2001): (1) an internalizing dimension that reflects liability to express distress inwards through mood and anxiety problems and (2) an externalizing dimension that

reflects liability to express distress outwards through antisocial behavior and substance use (reviewed by Caspi et al., 2014). Thus, behaviors and disorders within each dimension are more highly correlated with each other than with behaviors and disorders across dimensions (e.g., Hewitt et al., 1997). This basic finding has been replicated in multiple studies in different geographical locations, age groups, and types of populations (e.g., Forbush & Watson, 2013; Kendler, Prescott, Myers, & Neale, 2003; Krueger & Markon, 2006). Internalizing and externalizing dimensions are typically found to be correlated ~0.5, in adults (Caspi et al., 2013; Lahey et al., 2012) and youth (Lahey et al., 2011). Despite these findings, most research on correlates of psychopathology does not test whether these correlates are related to psychopathology generally or whether they have differentiable relations with internalizing versus externalizing psychopathology.

Stressful Life Events

Stressful life events (SLEs) have been defined as negative occurrences that are likely to cause readjustment or require changes in usual activities (Dohrenwind, 2006). SLEs are broadly defined and conceptualized differently across researchers (see Hatch & Dohrenwend, 2007). For example, SLEs are often sorted into dependent and independent SLEs. Dependent SLEs are characterized as being at least partially caused by the individual who experienced them (e.g., increasing arguments with parents, breaking up with a significant other) whereas independent SLEs are characterized as being unrelated to the actions of the individual who experienced them (e.g., death of a family member, parental divorce) (Williamson et al., 1995; Kendler, Karkowski, & Prescott, 1999). Some researchers also distinguish between minor SLEs (e.g., moving, being the victim of theft, expected death of a family member) and major SLEs (e.g., divorce, serious financial crisis, unexpected death of a family member) (e.g., McLaughlin et al., 2010). Another

conceptualization distinguishes between SLEs related to loss (e.g., death and separations), humiliation (e.g., rejection and delinquency of family members) entrapment (e.g., ongoing circumstances of difficulty with no resolution) (e.g., Brown et al., 1995; Kendler et al., 2003). Despite the common use of categorization in SLE research, researchers have opted to sum the number of events of a particular type, providing no information regarding whether events in a putative category actually tend to occur together. Stated differently, it is unclear whether these conceptualizations have construct validity. Further, no research to date has directly compared these alternative models of the underlying structure of SLEs, thus it is unclear which of these conceptualizations best describes how events tend to cluster within individuals.

Although SLEs are very common and most if not all individuals experience some form of SLE in their lifetime (e.g., Perris, 1984), individuals also reliably differ in the number of SLEs they experience. Among adults, SLEs are more common among African-Americans and other racial minorities, men, lower socioeconomic status individuals, and younger individuals, perhaps due to differential exposure to environments in which SLEs are likely to occur (reviewed by Hatch & Dohrenwend, 2007). SLEs are correlated with poor health outcomes including cardiovascular disease morbidity and mortality, progression of HIV to AIDS and AIDS-related clinical conditions, upper respiratory infections, asthma, herpes viral infections, autoimmune diseases, and wound healing (reviewed by Cohen, Janicki-Deverts, & Miller, 2007). Further, much research has established that SLEs are associated with psychopathology (reviewed by Brown & Harris, 1989; Dohrenwend, 1998).

SLEs and internalizing psychopathology. A robust field of research has linked SLEs with internalizing psychopathology in both adolescence (Rowe et al., 2006) and adulthood (Kendler, Gardner, & Prescott, 2002). The relation between SLEs and depression is the most well-

documented. SLEs are correlated with MDD and depressive symptoms such that 50-80% of depressed individuals experienced an SLE within the 6 months preceding the onset of depression, whereas only 20-30% of nondepressed individuals experienced an SLE within a 6 month period (reviewed by Monroe & Simons, 1991). Roughly 25% of people who experience a major SLE develop depression (van Praag, 2004), and more SLEs are also associated with longer duration of depressive episodes, higher symptom severity, relapse, and reduced treatment response (Hammen, 2005; Mazure, 1998). SLEs are more common in individuals who attempted suicide than nonsuicidal but depressed individuals (Adams et al., 1994).

SLEs are also associated with anxiety and eating disorders. High numbers of SLEs are associated with an 8.5 fold risk of onset of Generalized Anxiety Disorder (GAD) and one or more major SLE carries a 3 fold risk (Blazer et al., 1987). SLEs are associated with extreme weight-control behaviors and binge eating in men and women (Loth et al., 2008, Smyth et al., 2008), as well as risk for eating disorders or weight problems (Johnson et al., 2002) in adolescence and early adulthood. SLEs prior to (Brailey et al., 2007) and after (King et al., 1998) trauma exposure are both associated with higher rates of Post-Traumatic Stress Disorder (PTSD).

There is also evidence that different types of SLEs are differentially associated with increased risk of internalizing symptoms. For example, although independent and dependent SLEs are both associated with increased depression risk, dependent SLEs typically show a significantly stronger association (e.g., Kendler et al., 1999). Further, there is evidence that profiles of symptoms differ across types of SLEs both between individuals and within individuals with multiple episodes of depression (Keller et al., 2007), such that death of loved ones and romantic breakups are marked by sadness, anhedonia, and appetite loss, whereas failures are associated with fatigue and hypersomnia. Similarly, onset of major depression and

mixed major depression and generalized anxiety are predicted by SLEs related to loss and humiliation, onset of pure generalized anxiety is predicted by SLEs related to loss and danger, and onset of mixed depression and generalized anxiety is predicted by higher ratings of entrapment (Kendler et al., 2003). Taken together, SLEs seem to have a robust relation to internalizing symptoms that can differ depending on type of SLE and internalizing symptomology.

SLEs and externalizing psychopathology. SLEs are linked to increased externalizing psychopathology, although this relation is not as well studied as the relation between SLEs and internalizing symptoms. Research has demonstrated that SLEs are related to aggression and delinquency (Aseltine et al., 2000; Tolan, 1988; Suldo & Huebner, 2004; Oliva et al., 2009; Kim et al., 2003; Rowe et al., 2006), particularly when SLEs evoke anger and hostility (Aseltine et al., 2000), when individuals have low life satisfaction (Suldo & Huebner, 2004), or when individuals have poor family relationships (Oliva et al., 2009). SLEs are also related to higher levels of substance use, including cigarettes, alcohol, and marijuana (Hoffman & Sure, 1998; Wills et al., 1992), and criminal behavior (Eitle & Turner, 2002). Further, there is evidence that SLEs account in part for the continuity of externalizing problems throughout development, and that externalizing problems reciprocally increase the frequency of SLEs over time (Timmermans et al., 2010).

As reviewed above, researchers have thoroughly established that SLEs are related to both forms of psychopathology. Nevertheless, most research has focused on internalizing *or* externalizing psychopathology, ignoring the sizable overlap between them. Thus, it is unclear whether SLEs simply increase risk generally for psychopathology, whether risk differs for

internalizing versus externalizing psychopathology, and whether the tendency to experience particular types of trauma differ in the degree of associated risk.

Trauma Exposure

The fifth edition of *The Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; American Psychiatric Association, 2013) defines a traumatic event that can trigger PTSD as "exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: (1) Directly experiencing the traumatic event(s). (2) Witnessing, in person, the event(s) as it occurred to others. (3) Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental. (4) Experiencing repeated or extreme exposure to aversive details of the traumatic event(s)." Notably, the requirement for a response of intense fear, helplessness, or horror to the event was removed in *DSM-5* due to lack of additional predictive utility of the onset of PTSD (e.g., Bedard-Gilligan & Zoellner, 2008). The standard definition of a traumatic event is that used as a prerequisite for a diagnosis of PTSD, although particular events included in traumatic events inventories and questionnaires vary (reviewed by Goodman et al., 1998).

Trauma exposure is relatively common, although estimates of its prevalence vary: in one study 25% of children had been exposed to at least one traumatic event by age 13 (Costello et al. 2002), whereas another study found that 68% of children had been exposed to at least one traumatic event by age 16 (Copeland et al., 2007). Further, a sample of 34,075 United States residents found lifetime exposure rates to at least one traumatic event to be 84% for Caucasian, 76% for African-American, 66% for Asian, and 68% for Hispanic individuals, although minority groups tended to have higher rates of exposure to events with the highest risk of development of

PTSD, such as childhood maltreatment and violent victimization (Roberts et al., 2011). Generally, male, low SES, younger individuals are more likely to experience traumatic events, whereas there is conflicting evidence as to whether ethnic minorities are more or less likely to experience traumatic events than Caucasians (reviewed by Hatch & Dohrenwend, 2007). A survey of individuals included in the Grady Trauma Project, a sample of low-income, primarily African-American (>93%) women and men seeking care at an urban public hospital, found that 88% of individuals experienced some form of significant trauma in their lifetime, with the most common being accidents followed by interpersonal violence and sexual assault (Gillespie et al., 2009). Trauma exposure is associated with a variety of health problems including obesity (Felitti et al., 1998), cardiovascular disease (Goodwin & Stein, 2004), diabetes (Trief et al., 2006), cancer (Smith et al., 1999), and autoimmune disorders (Goodwin & Stein, 2004) (reviewed by Gillespie et al., 2009). Similar to research on SLEs, some attempts have been made to delineate categories of trauma (e.g., assaultive versus non-assaultive, Stein et al., 2002), but whether such conceptualizations have construct validity and which conceptualization best describes how and whether traumatic events are clustered has not been established.

Trauma exposure and internalizing psychopathology. A large field of research has linked trauma exposure to internalizing problems in childhood (e.g. McMillen et al., 2005) and adulthood (e.g. Anda et al., 2006). In a sample of children, trauma exposure was associated with increased risk of depressive and anxiety disorders (Copeland et al., 2007). In a large sample of adults, trauma exposure during childhood increased risk for panic, depressed affect, anxiety, and hallucinations in a dose-response manner (Anda et al., 2006). A prospective study following trauma exposure found that 19% of trauma exposed individuals met criteria for major depression at 1 month and 14% met criteria at 4 months (Shalev et al., 1998). There is also evidence that

different types of trauma carry differential risk for internalizing disorders. For example, Chapman et al. (2004) found in an adult sample that childhood emotional abuse increased lifetime risk of depressive disorders more than physical or sexual abuse. Some researchers have attempted to compare the effects of trauma involving child abuse and trauma not involving child abuse: Gillespie et al. (2009) found that both forms of trauma increased depressive symptoms but did not interact beyond their main effects. There is also robust evidence that childhood sexual abuse and other forms of trauma exposure are associated with increased risk for eating disorders (reviewed by Brewerton, 2007). Taken together, these studies provide clear evidence that trauma exposure is associated with increased risk of internalizing psychopathology throughout development.

Trauma exposure and externalizing psychopathology. Trauma exposure is also associated with increased risk of externalizing disorders and behavior. In children under 17, trauma exposure increased risk of conduct disorder and disruptive behavior disorders in general (Copeland et al., 2007). In adults, trauma exposure during childhood increased risk for alcoholism, illicit drug use, and intravenous drug use in a dose-response manner (Anda et al., 2006). Specific types of trauma also differentially predict externalizing problems. In a sample of patients with personality disorders, Bierer et al. (2003) found that childhood sexual and physical abuse, but not emotional abuse, predicted antisocial personality disorder.

Trauma researchers have typically ignored the overlap between internalizing and externalizing psychopathology, rendering unclear whether trauma increases risk generally or differentially or whether particular types of trauma are worth distinguishing.

SLEs and traumatic events. The distinction between SLEs and traumatic events also is not well established. Traumatic events are often narrowly defined as events that involve possibility

of death or threat to physical integrity of the self or others, whereas SLEs are more broadly defined as any negative events that would cause adjustments or require changes in usual activities. Although some researchers have excluded traumatic events from their research on SLEs (e.g., Lu & Chen, 2004), many have included them within counts of SLEs. For example, physical and sexual assault, robbery, and sudden family death were included as SLEs in the measure used by the Virginia Twin Register (e.g., Kendler et al., 1999; Kendler et al., 2002), whereas those same experiences have been included in many studies of trauma exposure (e.g., Stein et al., 2002). It is possible that traumatic events represent an extreme along the SLE severity spectrum or that they are distinguishable phenomena. Thus, it is unclear whether SLEs and trauma exposure should be examined separately when considering their relations with internalizing and externalizing psychopathology.

Current Study

We aimed to address three gaps in knowledge of the structure of and relations among SLEs, trauma exposure, and psychopathology. The first specific aim of this study was to determine the latent structure of the tendency to experience SLEs and trauma exposure. To accomplish this aim, we used CFA and latent variable modeling to compare alternative models representing proposed dimensions of SLEs (i.e., dependent versus independent, major versus minor, loss versus humiliation versus entrapment) and trauma exposure (i.e., assaultive versus non-assaultive, witnessed versus experienced). These analyses allowed us to determine whether individuals tend to experience certain dimensions of these events together, and thus whether these dimensions have construct validity.

The second specific aim of this study was to determine whether SLEs and trauma are the result of a single tendency to experience stress. In order to accomplish this aim, we used CFA to

compare alternative models of the relation between latent variables representing the tendency to experience SLEs and trauma. These analyses allowed us to clarify whether trauma is an extreme form of SLEs or an at least partially distinct phenomenon.

The third specific aim was to determine whether SLEs or trauma exposure have differentiable relations to internalizing and externalizing psychopathology. To accomplish this aim, we used CFA to compare alternative models of the relations among latent variables representing SLEs, trauma, and psychopathology. These analyses allowed us to clarify whether SLEs or trauma increase risk generally or whether certain types of events reliably predict internalizing versus externalizing psychopathology.

In order to assess the degree to which our findings were robust to demographic differences between individuals or due to methodology or measurement, we conducted parallel analyses in two very distinct samples: (1) a low income, highly traumatized, primarily African American, adult population sample recruited at Grady Memorial Hospital in Atlanta, Georgia, (2) a primarily Caucasian, child community sample of twins from Georgia.

Method

Participants

Participants included individuals from two samples. The first sample was comprised of several thousand urban, low-income, predominantly African American men and women (described by Gillespie et al., 2009). Data were available for 7,361 individuals, although any given variable was missing data for some portion of participants (methods for handling missing data are described below). Participants ranged in age between 18 and 90, with a mean of 40.2 (SD = 14.0). 73% of participants were female. 93% of participants identified as African American, 3% identified as Caucasian, 2% identified as Mixed, and 2% identified as Other,

Asian, or Hispanic/Latino. Initial interviews were performed with participants in the waiting rooms of primary care or obstetrical-gynecological clinics of Grady Memorial Hospital in Atlanta, Georgia starting in 2005. Participant recruitment took place Monday-Friday during regular clinic hours. Participants were approached while waiting for appointments in the primary care and obstetrical-gynecological clinics by a member of the research team and solicited for study participation. Participants were informed at the time of initial contact that the study in which they were being asked to participate examined trauma exposure during childhood and adulthood. Those participants who agreed to participate completed a battery of self-report measures obtained by verbal interview which took 45 to 75 minutes to complete. Participants also provided DNA samples via saliva collected in Oragene vials (DNA Genotek Inc., Ontario Canada). Participants who agreed to continue participation were invited to take part in a second, more in-depth phase of the study, but data collected beyond the first phase was not used in the current research. Data were pulled for these analyses in August of 2014.

The second sample was comprised of participants drawn from the Georgia Twin Registry, a population-based twin registry of monozygotic and dizygotic twins born in Georgia between 1980 and 1991. In 1992-1993, parents of twins were sent a request to join the Georgia Twin Registry along with a set of questionnaires. In 1996-1997, a second set of questionnaires was sent to the 1,567 twin families who joined the registry. Data was available for 461 sets of DZ twins and 382 sets of MZ twins (1,686 individuals). Participants ranged in age between 4 and 17, with a mean of 10.5 (SD = 3.2). 52% of participants were female. 82% of participants identified as European American, 11% identified as African American, 1% identified as Hispanic Americans, and 6% identified as Mixed/Other ethnicity.

The zygosity of the twins was determined based on parent reports of twins' physical similarity using an eight-item questionnaire (e.g., "are your twins mistaken for each other by people who know them?" "are your twins as alike as two peas in a pod?") with dichotomized responses (i.e., 1 indicates that the *twins are similar on a trait,* and 0 indicates that the *twins differ*) (Bonnelykke, Hauge, Holm, Kristofferson, & Gurtler, 1989). Responses across all items were averages. Twins were categorized as MZ if their average scores were 0.5 or above and as DZ if less than 0.5. The scores on this zygosity questionnaire showed good internal consistency in our community twin sample ($\alpha = .86$). This method of zygosity determination has been well validated against DNA test results, with at least 90% accuracy (Jackson, Sneider, Davis, & Treiber, 2001; Spitz et al., 1996).

Measures

Grady Sample.

Stressful Events Questionnaire II. The Stressful Events Questionnaire II (SEQ-II) is 16 item questionnaire designed for use in the Grady Trauma Project. Participants were prompted by the interviewer stating "I'm going to ask you some questions about stressful events people sometimes experience. Please tell me if the events have ever happened to you. If so, when was the most recent time?" Items include "loss of a confidant/loved one," "chronic health problems or life threatening illness," "home invasion/robbery/burglary," "murder of close friend/relative," "fired from job or had serious problems at work," "homeless, living in the shelter/on streets," "homeless with temporary or unplanned housing," "evicted from house or apartment," "inadequate financial resources or support to obtain food for family," "lived in a neighborhood you felt was unsafe," "child/spouse/significant other/other family member in prison/jail," "unplanned/unwanted pregnancy," "divorced," "cared or raised children other than your own

because their parents unable to care for them," "your children raised by others because you were not able to care for them," and "please describe most stressful event experienced in last month." The final item was not used in analyses. Participants were able to respond with "never happened to me," "within the last month," "within the last 6 months," "within the last year," "within the last 5 years," or "more than 5 years ago." Responses were dichotomized to represent the presence or absence of each SLE during each individual's lifetime.

Items from this measure were sorted by three independent raters into the following alternative dimensions: (1) independent or dependent; (2) loss, humiliation, or entrapment; (3) major or minor. Dependent and independent SLEs were sorted according to the following criteria (Kendler et al., 1999): Dependent SLEs are likely influenced by the individual's own behavior whereas independent SLEs are likely not influenced by the individual's own behavior.

Loss, humiliation, and entrapment were sorted according to the following criteria (Kendler et al., 2003): Rate which of these is the primary characteristic of the event. Loss: Diminution of a sense of connectedness or well-being potentially covering every aspect of life, including a real or realistically imagined loss of a person, material possessions, health, respect in the community, employment, or a cherished idea bout self or a close tie. Humiliation: feeling devalued in relation to others or to a core sense of self, usually with an element of rejection or a sense of role failure. Entrapment: Ongoing circumstances of marked difficulty of at least 6 months' duration that the individual can reasonably expect to persist or get worse, with little or no possibility that a resolution can be achieved as a result of anything that might reasonably be done.

Major and minor SLEs were sorted according to the following criteria (Conner et al., 2012): "Major events are expected to have a large and lasting impact on a given individual,

regardless of background and circumstances, whereas minor events are expected to have a smaller and more temporary impact on a given individual of average background and circumstances."

Consensus dimensions for dependent/independent and loss/humiliation/entrapment SLEs that were used in analyses are presented in Table 1.1. All events were sorted as major SLEs by all raters, and thus this conceptualization was not used in this sample. Each item was included as a separate, binary variable in analyses.

Traumatic Events Inventory. The Traumatic Events Inventory (TEI) is a screening instrument for lifetime history of traumatic events (Schwartz et al., 2005, 2006; Binder et al., 2008). The TEI assesses experiencing and witnessing of events separately when relevant. Participants were asked the number of times they have experienced or witnessed each event and their age at the first and most recent exposure. Traumatic events that are included in the TEI are natural disasters, serious accident or injuries, sudden life-threatening illnesses, military combat, close friend or family member murdered, attacked with a weapon, attacked without a weapon, violence between parents as a child, beaten as a child, insulted by parents as a child, sexual abuse as a child or teenager, and rape or sexual assault as an adult. The number of times each event was witnessed or experienced during the individual's lifetime was used in all analyses.

TEI Items were sorted by three independent raters into assaultive and non-assaultive. The distinction between witnessed and experienced events was explicit in the prompts presented to the individuals and thus did not need to be rated. The consensus dimensions used in analyses are presented in Table 1.2. Each item was included as a separate, ratio variable in analyses.

Internalizing Psychopathology Measures.

Beck Depression Inventory. Depressed mood was assessed with the 21-item Beck Depression Inventory, Second Edition (BDI-II) (Beck et al., 1988), a commonly used ordinal measure of level of depressive symptoms (Beck et al., 1988) over the last two weeks. The BDI-II assesses sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleeping patterns, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, and loss of interest in sex. Each item is scored on a 0-3 Likert scale and was treated as a separate, ordinal variable. In this sample, previously described by Gillespie et al., (2009), the BDI-II had a standardized alpha coefficient of .92 (M = 10.86, SD = 11.71).

Anxiety Sensitivity Inventory. Anxiety sensitivity was assessed using the 16-item Anxiety Sensitivity Inventory (ASI) (Reiss et al., 1986), a commonly used measure of the level of belief that anxiety experiences have negative implications and is predictive of but distinct from anxiety-related disorders and depression (reviewed by Deacon et al., 2003). The ASI items include “it is important for me not to appear nervous,” “when I cannot keep my mind on a task, I worry I might be going crazy,” “it scares me when I feel shaky,” “it scares me when I feel faint,” “it is important to me to stay in control of my emotions,” “it scares me when my heart beats rapidly,” “it embarrasses me when my stomach growls,” “it scares me when I am nauseous,” “when I notice that my heart is beating rapidly, I worry that I might have had a heart attack,” “it scares me when I become short of breath,” “when my stomach is upset, I worry that I might be seriously ill,” “it scares we when I am unable to keep my mind on a task,” “other people notice when I feel shaky,” “unusual body sensations scare me,” “when I am nervous, I worry that I might be mentally ill,” and “it scares me when I am nervous.” Items are scored on a 0-4 Likert

scale from “very little” to “very much.” Likert scale scores for each item were included as separate, ordinal variables.

Externalizing Psychopathology Measures.

BQ. The BQ is a measure developed for the Grady Trauma Project that measures violent behavior. Participants were prompted by the interviewer saying “No matter how well people get along, there are times when they disagree, get annoyed with another person, or have confrontations or fights for other reasons. Below is a list of things that might happen when you have differences, when you feel upset, or for other reasons. Please mark if you have ever done the following things in your lifetime.” The 6 included items are “pushed or shoved someone,” “pulled a knife or gun on someone,” “stabbed or shot someone,” “punched or hit someone with something that could hurt,” and “beat up someone.” Potential responses include “never,” “once,” “several times,” “many times,” and “more times than I can count.” Item responses were coded as ordinal variables and included separately in the analyses.

Alcohol Use Disorders Identification Test. The Alcohol Use Disorders Identification Test is a commonly used 10-item screening instrument for hazardous and harmful alcohol consumption that covers the domains of alcohol consumption, drinking behavior, and alcohol-related problems (Saunders et al., 1993). The AUDIT screens for drinking frequency, number of drinks per drinking episode, how often six or more drinks are consumed, frequency of inability to stop drinking, frequency of failure to meet expectations because of drinking, frequency of needing to drink in the morning, frequency of guilt or remorse after drinking, frequency of memory disturbances due to drinking, injuries related to drinking, and concerns of others about level of drinking. Each item is scored on a 0-4 scale and was included in the analyses as ordinal.

Drug Abuse Screening Test. The Drug Abuse Screening Test (DAST) is a commonly used 20-item screening instrument for problematic substance use (Skinner, 1982). The DAST screens for drug use, drug abuse, ability to stop using drugs, blackouts, guilt from drug use, family complaints about drug use, neglect of family because of drug use, illegal activities related to drug use, withdrawal symptoms from drug use, and medical problems related to drug use. Responses to the DAST were given as binary items and were included in the analyses as separate, binary variables.

Twin Sample Measures.

Life Events Scale. The Life Events Scale (LES) is a measure of 25 stressful life events that have occurred within the past year. Items include: "Suspended from school," "Broke up with boyfriend/girlfriend," "Broke up with close friend," "Close friend died," "Seriously ill or injured," "Mother/father seriously ill or injured," "Brother/sister seriously ill or injured," "Not accepted into important extracurricular activity," "Mother or father lost a job," "Favorite pet died," "Flunked a grade," "Brother or sister had serious trouble," "Was assaulted, robbed, or a victim of another violent crime," "Family member was victim of violence," "Close family member died," "Argued more with parents," "Family had serious financial trouble," "Parent spent much more time away from home," "Parents argued much more with each other," "Parents got divorced or separated," "Arrested or had serious law trouble," "Parent arrested or serious law trouble," "Dropped out of school," "Lost a job," and "Lost driver's license." Items were rated by parents of twins via mailed questionnaires. The item "was assaulted, robbed, or a victim of another violent crime" was included as a trauma item (see below) and removed from this measure. Responses were given as binary items. Items were sorted into (1) dependent or independent; (2) loss, humiliation, or entrapment; and (3) major or minor by three independent

raters SLEs using the criteria described above. Consensus dimensions of SLE items from this sample are presented in Table 1.3.

Trauma Measure. Traumatic events in the twin sample were measured by two related items. Parents were asked whether their child ever experienced or saw anything extremely frightening. If yes, parents were asked to describe the event. Item responses were coded by three independent raters as to whether the reported event meets criteria for a traumatic event as defined by *DSM-5*: "exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: (1) Directly experiencing the traumatic event(s). (2) Witnessing, in person, the event(s) as it occurred to others. (3) Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental. (4) Experiencing repeated or extreme exposure to aversive details of the traumatic event(s)." If so, a dichotomous variable indicating trauma exposure was coded as 1. If not, or if parents indicated the absence of trauma, responses were coded as 0. In addition, the LES item "was assaulted, robbed, or a victim of another violent crime" was deemed to be indicative of trauma and included as a separate, binary variable as an indicator of trauma.

Internalizing Psychopathology.

Depression Items. Symptoms of depression were assessed by parent-report of *DSM* depression symptoms over the past year. Items included "seems very sad or irritable" "lost interest in daily activities," "seems like nothing is fun," "lost noticeable amount of weight," "smaller appetite than usual," "put on noticeable amount of weight," "bigger appetite than usual," "trouble falling asleep, staying asleep, or sleeps less than usual," "trouble waking up or sleeps more than usual," "less active than usual," "fidgets or move around a lot more than usual,"

"more tired than usual," "less energy than usual," "feels worse about himself or herself than should," "feels more guilty than should," "more difficulty paying attention than usual," "feels hopeless," "thinks or talks a lot about death," and "tried to kill himself." These items were rated on a 0-4 scale of how well each item described the child from "not very well" to "very well." Item scores were included in the analyses as ordinal variables.

Anxiety Items. Symptoms of anxiety were assessed by parent-report of *DSM* GAD symptoms over the past six months. Items included "worries too much about doing well in school or sports," "worries too much about behaving well or being good," "worries too much about things he or she said or did," "gets headaches, stomachaches, or other physical symptoms even when not actually sick," "asks adults to reassure," "worries too much about health," "worries too much about getting to places on time," "worries too much about whether the family has enough money," "has trouble stopping worrying," "seems tense or nervous and can't relax," "worries too much about things that are coming up in the future," "has muscle tension," "has trouble falling asleep or doesn't sleep well," "seems irritable," "gets tired easily," and "can't concentrate or mind goes blank when trying to think." These items were rated on a 0-4 scale of how well each item described the child from "not very well" to "very well." Item scores were included in the analyses as ordinal variables.

Externalizing Psychopathology.

Oppositional Defiant Disorder (ODD) Symptoms. ODD symptoms were assessed by parent-reports of *DSM* ODD symptoms over the past 6 months. Items included "loses temper," "argues with adults," "actively disobeys rules," "does things on purpose to annoy others," "blames others for mistakes or misbehavior," "touchy or easily annoyed," "angry and resentful," "is spiteful or ties to get back at others," and "curses or uses bad language." These items were

rated on a 0-4 scale of how well each item described the child from "not very well" to "very well." Item scores were included in the analyses as ordinal variables.

Conduct Disorder (CD)Symptoms. CD symptoms were assessed by parent-report of *DSM* CD symptoms over the past year. Items included "starts fights with people who do not live at home," "skipped school or work," "ran away from home overnight," "used alcohol or drugs," "stole items worth more than $20," "destroyed property on purpose," "sets fires wanting to cause serious damage," "broke into someone else's house, building, or car," "physically cruel to animals," "physically cruel to people," "stole things from another person using force or threat," "used a weapon that could seriously harm others," "took part in sexual activities to get money or valuables," "forced someone into sexual activity," and "stayed out late against wishes." Parents were asked to report how many times their child has done these things, with possible responses of 0, 1, 2, 3, or more than 3. Item scores were included in the analyses as ordinal variables.

Analyses

Separate, parallel analyses were conducted in the Grady Sample and the Twin Sample. Prior to model-fitting, raw residuals with a mean of 0 and unconstrained variance for each item were generated by regressing each item (using linear, binary logistic, or ordinal logistic regression depending on the scale of each item) on age, age squared, sex, age X sex, and sex X age squared in SPSS (version 22.0) in order to account for mean level age and sex differences in the variables of interest (McGue & Bouchard, 1984). These values were used in all further analyses. All Confirmatory Factor Analyses (CFAs) were conducted in Mplus 7.2 (Muthén & Muthén, 2012) using the MLR estimator, which accounts for non-normality in the data. In the twin sample, the clustering of twins within family was accounted for using the "CLUSTER" function in Mplus, which adjusts standard errors to take into account the nonindependence of

observations within families. Missing data was handled using Full Information Maximum Likelihood (FIML), which has been shown to produce unbiased parameter estimates and standard errors by estimating a likelihood function for each individual based on the variables that are present so that all the available data are used (Graham, Cumsille, & Elek-Fisk, 2003).

We began by contrasting the fit of alternate models of the underlying structure of SLEs in both samples. In the Grady sample, we next tested alternative models of the underlying structure of traumatic events (this was not possible in the Twin Sample due to this sample only having two items assessing trauma). Next, we tested alternative models of the relation between SLEs and trauma in both samples. Finally, we tested alternative models of the relations among SLEs, trauma, and internalizing and externalizing psychopathology.

For all CFAs, goodness of fit was primarily judged using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), two commonly used indicators of model fit and parsimony (Akaike, 1974; Schwarz, 1978). Several additional fit indices, including Chi Square, the root mean square error of approximation (RMSEA), the comparative fit index (CFI), the Tucker Lewis Index (TLI), and the standardized root-mean square residual (SRMR) were also calculated to provide more complete information regarding model fit. We used the following criteria to evaluate model fit: RMSEA < .08 for adequate fit and < .05 for close fit (Browne & Cudeck, 1992), and CFI > 0.95, TLI > 0,95 and SRMR < .08 for good fit (Hu & Bentler, 1999). We also used a chi-square difference test with a Satorra-Bentler scaling correction (which is necessary when using the MLR estimator) to directly compare goodness of fit between models (Satorra & Bentler, 2011), where a *p*-value < .05 indicated a significant difference in goodness of fit. Notably, this chi square test is only appropriate if models are nested

(i.e., one model is nested in another if some of the coefficients in the first model can be restricted to obtain the second).

Results

Alternative Models of Stressful Life Events

We contrasted the goodness of fit of several models of the latent structure of SLEs in both samples (see Table 1.4 for Twin Sample and Table 1.5 for Grady Sample) in order to determine (1) whether participants simply differed in their tendency to experience SLEs in general or if they differed in their tendency to experience certain types of events; and (2) which conceptualization of SLEs was the best representation of how SLEs tended to be clustered. These analyses were conducted in parallel in both samples. We first fit a general factor model in which all items loaded onto one latent factor. Next we fit a series of models in which items loaded onto factors representing (1) dependent or independent SLEs; (2) loss, humiliation, or entrapment SLEs; and (3) major or minor SLEs (Twin Sample only) as specified in Tables 1.1 (Grady Sample) and 1.3 (Twin Sample). In addition, for each alternative, we fit one model in which the latent factors were allowed to correlate and one in which the latent factors were orthogonal. Finally, we fit models in which items were sorted by two of the three conceptualizations (e.g., independent major, independent minor, dependent major, and dependent minor).

As seen in Tables 1.4 and 1.5, the best fitting model in both samples was the correlated independent and dependent SLEs model. It was also the only model that fit better than a general factor model according to most fit statistics in both samples. The standardized factor loadings are presented in Tables 1.6 (Twin Sample) and 1.7 (Grady Sample) and a diagram of each model is presented in Figures 1.1 (Twin Sample) and 1.2 (Grady Sample). The latent dependent SLE and independent SLE factors were quite highly correlated in both samples (r = .86 in the Twin

Sample, r = .78 in the Grady Sample), indicating that the factors are not easily separable yet still distinguishable. The items all loaded significantly onto their respective factors, although standardized factor loadings ranged from 0.21-0.67 in the twin sample and from 0.07-0.57, indicating that a nontrivial amount of each item's variance remained unexplained by the latent SLE factors in both samples. Factor loadings for dependent SLEs tended to be higher than for independent SLEs in both samples, indicating that dependent SLEs are better represented by a latent tendency than independent SLEs.

Alternative Models of Trauma Exposure in the Grady Sample

Next, we contrasted the goodness of fit of several models of the latent structure of trauma exposure in the Grady sample (see Table 1.8) in order to determine (1) whether participants simply differed in their tendency to experience trauma in general or if they differed in their tendency to experience certain types of traumatic events; and (2) which conceptualization of trauma was the best representation of how trauma tended to be clustered. We were not able to test alternative models of the latent structure of trauma exposure in the twin sample due to the relative paucity of relevant items. We first fit a general factor model, in which all items loaded onto one latent factor. Next we fit a series of models in which items loaded onto factors representing (1) witnessed or experienced trauma; and (2) and assaultive or non-assaultive trauma as specified in Table 1.2. In addition, for each conceptualization, we fit one model in which the latent factors were allowed to correlate and one in which the latent factors were not allowed to be correlated. Finally, we fit a four way conceptualization model in which both conceptualizations were applied to the items to create latent factors (i.e., witnessed assault, experienced assault, witnessed non-assault, and experienced non-assault). Only one item fit into the witnessed non-assault category and thus it was represented by just this item.

As seen in Table 1.8, the best fitting model was the four way conceptualization model. The standardized factor loadings for the best fitting model are presented in Table 1.9 and a diagram of the model is presented in Figure 1.3. If one postulates a continuum of severity from experienced assault being the most severe to witnessed non-assault being the least severe as seen in Figure 1.3, factor correlations tended to be higher between events closer in severity than between those further apart in severity level. The items all loaded significantly onto their respective factors, although standardized factor loadings ranged from 0.06-0.62, indicating that a nontrivial amount of each item's variance remained unexplained by a latent trauma factor.

Alternative Models of the Relation between SLEs and Trauma in the Twin Sample

Next, we created a latent variable in the twin sample representing trauma exposure indicated by the trauma item and the "was assaulted, robbed, or a victim of another violent crime" SLE item. We then tested alternative models of the relation between trauma exposure, independent SLEs, and dependent SLEs (see Table 1.10) to determine (1) whether trauma is separable phenotypically from SLEs; and (2) whether trauma is differentially related to independent and dependent SLEs. We first fit a general stress factor model in which each of the three latent factors loaded onto a general stress latent factor. We then contrasted this model with (1) a model in which the trauma factor's correlations with independent and dependent SLEs were constrained to be equal; and (2) a model in which the relations among the trauma, independent SLEs, and dependent SLEs factors were freely estimated. Note that the correlation between the SLE variables was freely estimated in all models.

As seen in Table 1.10 and Figure 1.4, the best fitting model was one in which trauma was a separate factor and more strongly correlated with independent than dependent SLEs. This indicates that in this sample (1) the tendency to experience trauma is partially distinguishable

from the tendency to experience SLEs; and (2) the tendency to experience trauma does not equally predict the tendency to experience independent and dependent SLEs, but rather is slightly more strongly related to the tendency to experience independent SLEs.

Alternative Models of the Relation between SLEs and Trauma in the Grady Sample

Next, we tested alternative models of the relation between the four types of trauma, independent SLEs, and dependent SLEs in the Grady Sample (see Table 1.11) to determine (1) whether each type of trauma is separable phenotypically from SLEs; and (2) whether each type of trauma is differentially related to independent and dependent SLEs. We first fit a general stress factor model in which each of the six latent factors loaded onto a general stress latent factor. We then contrasted this model with (1) a model in which the correlations of each trauma factor with independent and dependent SLEs were constrained to be equal (i.e., four estimated correlations); (2) a model in which the correlations of independent and dependent SLE with all four trauma factors were fixed to be equal (i.e., two estimated correlations); and (3) a model in which the relations among the trauma, independent SLEs, and dependent SLEs factors were freely estimated (i.e., eight estimated correlations). Note that the correlations among the trauma variables and among the SLE variables were freely estimated in all models.

As seen in Table 1.11 and Figure 1.5, the best fitting model was one in which all correlations between the factors were freely estimated. In this model, correlations with both types of SLE generally increased as the severity of the trauma factor increased (from witnessed non-assault to experienced assault). Further, all trauma factors were more highly correlated with dependent than independent SLEs. This indicates that in this sample (1) the tendency to experience trauma is partially distinguishable phenotypically from the tendency to experience SLEs; (2) the tendency to experience trauma does not equally predict the tendency to experience

independent and dependent SLEs, but rather is more closely related to the tendency to experience dependent SLEs; and (3) the tendency to experience more severe trauma is more closely related to also experiencing both types of SLEs than the tendency to experience less severe trauma.

Relations among SLEs, Trauma, and Psychopathology in the Twin Sample

Next, we tested alternative models of the relations among independent and dependent SLEs, trauma, and internalizing and externalizing psychopathology. In the Twin Sample, we created a latent variable representing internalizing psychopathology indicated by *DSM* MDD and GAD symptoms. We also created a latent variable representing externalizing psychopathology indicated by *DSM* CD and ODD symptoms. These symptoms were chosen from a larger pool of *DSM* internalizing and externalizing symptoms in order to best match the measures available in the Grady Sample and thus increase comparability. We then compared alternative models of the relations among these variables and the trauma, independent SLEs, and dependent SLEs variables (see Table 1.12). Specifically, we fit the following models: (1) paths from trauma exposure, independent SLEs, and dependent SLEs to internalizing and externalizing psychopathology freely estimated (i.e., six estimated correlations); (2) paths from each stress variable equated across internalizing and externalizing psychopathology (i.e., three estimated correlations); and (3) all paths between psychopathology variables and stress variables equated (i.e., one estimated correlation). Note that the correlations among the stress variables and between the psychopathology variables were freely estimated in all models. As seen in Table 1.12, the third model fit significantly worse than the first model, but the second model did not. That is, the paths from each stress variable were able to be equated across internalizing and externalizing psychopathology without significantly worsening the fit. Thus, we selected this as the best fitting model (see Figure 1.6). In this model, the tendency to experience each form of

stress was equally correlated with both forms of psychopathology, and dependent SLEs were the most strongly related to psychopathology.

Relations among SLEs, Trauma, and Psychopathology in the Grady Sample

Finally, we tested alternative models of the relations among independent and dependent SLEs, all four types of trauma, and internalizing and externalizing psychopathology in the Grady Sample. We created a latent variable representing internalizing psychopathology in this sample indicated by depression and anxiety items from the BDI-II and ASI, respectively. We also created a latent variable representing externalizing psychopathology indicated by aggression, alcohol abuse, and drug abuse items from the BQ, AUDIT, and DAST, respectively. We then compared alternative models of the relations among these variables and the trauma, independent SLEs, and dependent SLEs variables (see Table 1.13). Specifically, we fit the following models: (1) paths from the four trauma variables, independent SLEs, and dependents SLEs to internalizing and externalizing psychopathology freely estimated (i.e., twelve estimated correlations); (2) paths from each stress variable equated across internalizing and externalizing psychopathology (i.e., six estimated correlations); and (3) all paths between psychopathology variables and stress variables equated (i.e., one estimated correlation). Note that the correlations among the stress variables and between the psychopathology variables were freely estimated in all models. As seen in Table 1.13, the best fitting model was the model in which all relations were freely estimated. Factor correlations in this model are presented in Table 1.14. In this sample, dependent SLEs were more strongly related to both forms of psychopathology than independent SLEs, relations with both forms of psychopathology increased with trauma severity, and all SLE and trauma variables were more strongly associated with externalizing than internalizing psychopathology.

Discussion

In this study, we used latent variable modeling to characterize and compare alternative models of SLEs and trauma, their relations with each other, and their relations with internalizing and externalizing psychopathology across two methodologically and demographically diverse samples. Briefly, we found that in both samples, the best fitting model of SLEs included correlated latent variables representing independent and dependent SLEs (i.e., SLEs not caused by the individual and SLEs at least partially caused by the individual). In the Grady Sample, the best fitting model for trauma consisted of four correlated latent variables representing witnessed assault, witnessed non-assault, experienced assault, and experienced non-assault. In both samples, allowing the correlations among SLEs and trauma to be freely estimated was the best fitting model. In the Twin Sample, correlations of trauma and both forms of SLEs with internalizing and externalizing psychopathology were able to be equated, whereas the best fitting model in the Grady Sample allowed these correlations to be freely estimated. These results have implications for our understanding of how individuals experience stress and trauma, how these experiences are related to psychopathology, and the potential role of demographic factors such as age, ethnicity, and socioeconomic status in these relations.

Latent Structure of Stressful Life Events

The best-fitting model of the latent structure of items from disparate SLE measures in demographically diverse samples consisted of correlated dependent and independent SLE factors. Several inferences can be made from this finding. First, these findings suggest that SLEs are not best represented by a single latent tendency to experience stress because a general factor model was not the best-fitting model. There appear to be multiple, differentiable tendencies to experience SLEs, with potentially separate etiologies, correlates, and outcomes. Thus, the

differentiation of types of SLEs may be important from both a research and clinical perspective. Researchers may be able to obtain more consistent results when investigating causes and effects of SLEs if their dependence is assessed. Clinicians also may benefit from assessing the dependence of SLEs that their clients experience in order to determine whether multiple approaches may be necessary to help clients reduce their exposure to dependent and independent SLEs.

Second, the tendencies to experience independent and dependent SLEs are correlated but distinguishable. In both samples, the correlation between dependent and independent SLEs was quite high (.86 in the Twin Sample and .78 in the Grady Sample). These correlations were higher than those reported in other studies (e.g., Kendler et al., 1999), all of which used sum scores to characterize SLEs. Correlations between sum scores in this sample were also appreciably lower than those between the latent variables (.43 in the Twin Sample and .38 in the Grady Sample), indicating that the higher correlations are due to using latent variables. Latent variable modeling provides an advantage over using sum scores by allowing researchers to isolate the variance in each item due to the commonalities among all the items, excluding residual variance in items due to measurement error or other item-specific factors. In this case, we are able to determine that while the number of SLEs experienced are only moderately correlated, the latent tendencies to experience dependent and independent SLEs are quite highly correlated. This is especially interesting because independent SLEs are supposedly not influenced by the individual, yet the tendency to experience such events is highly related to the tendency to experience dependent SLEs in both samples. Using latent variable modeling to study these tendencies may allow researchers to make clearer inferences regarding the etiology, correlates, and outcomes of SLEs.

Third, sorting SLEs into independent and dependent best represents the latent structure of the tendency to experience SLEs. Experiencing an independent or dependent SLE is more indicative of a likelihood to experience more independent or dependent SLEs, respectively, than the alternative conceptualizations. Thus, assessing the dependence of an SLE that an individual experiences may allow researchers and clinicians to more reliably predict the category of SLEs that individual is likely to have had in the past or will have in the future. It is important to note that although this was the best fitting model of the tendency to experience SLEs, this does not necessarily mean that other conceptualizations (e.g., major versus minor) are not worth considering in terms of correlates or outcomes.

Fourth, a nontrivial amount of the variance in each item remained unexplained by a latent SLE factor in both samples. This was expected, given the situation-specific factors that likely influence the endorsement of each item. This finding also further distinguishes between analyzing sum scores and latent variables, as latent variables allow researchers to model the degree to which the endorsement of each SLE reflects a latent tendency to experience SLEs rather than assuming each item contributes equally. Further, factor loadings in both samples for dependent SLEs tended to be higher than for independent SLEs, indicating that dependent SLEs are better represented by a latent tendency than independent SLEs. This was also expected, as independent SLEs are not expected to be influenced by the individual's own actions, and thus experiencing one independent SLE should be relatively less predictive of experiencing another.

Fifth, the striking similarity of results between the Twin and Grady Samples is an indicator of the stability of these results across populations. The implications reviewed above seem to apply across children and adults, primarily Caucasian and primarily African American samples, and middle-class and low-income individuals. There was little overlap in the particular

SLEs assessed by the measures across both samples, indicating the robustness of the distinction between independent and dependent SLEs regardless of the specific events themselves. One exception to the parallels between the results across the samples was that the model fit and standardized factor loadings were higher in the Twin Sample than the Grady Sample. This could be attributed to the impact of a restricted range of environments and lack of mobility between environments among children compared to adults, leading to SLEs being more highly correlated due to the relative inability of children to remove themselves from environments likely to cause SLEs.

Latent Structure of Trauma Exposure

We found that, in the Grady Sample, the best-fitting model of the tendency to experience trauma was to sort events into dimensions representing witnessed non-assault, witnessed assault, experienced non-assault, and experienced assault dimensions. Similar to the results for SLEs, this result indicates that (1) traumatic events are not best represented by a single latent tendency to experience trauma; (2) the tendencies to experience each of the four dimensions are correlated but distinguishable; (3) sorting trauma into both witnessed or experienced and assault and non-assault dimensions best represents the latent structure of the tendency to experience trauma. One way to conceptualize the differences between the four dimensions is to organize them by increasing likelihood of severity: witnessed non-assault, witnessed assault, experienced non-assault, and experienced assault. Doing so (as seen in Figure 1.3) revealed that each latent variable tended to be more highly correlated with variables more proximal in severity compared to those more distal in severity. This indicates that, although a tendency to experience any type of trauma increases one's tendency to experience trauma in general, partially separate factors likely influence one's tendency to experience different severities of trauma. Further, factor

loadings for each item indicated that a nontrivial amount of variance in each item was not explained by the latent factor onto which it loaded. Again, this was expected given the situation-specific factors beyond a general tendency to experience a particular trauma that likely influence the endorsement of each item.

Relations among SLEs and Trauma

In both samples, constraining the correlations among trauma variables and SLE variables to be equal resulted in significantly worsened fit, indicating that independent SLEs, dependent SLEs, and trauma are correlated but distinguishable factors with different degrees of relatedness among them. A general stress factor model also fit less well than freely estimated correlations among the variables. Taken together, these results indicate that trauma exposure is not simply a particularly severe SLE but a partially unique phenomenon with potentially unique etiology, correlates, and outcomes. As mentioned above, some researchers have excluded traumatic events from their research on SLEs (e.g., Lu & Chen, 2004), whereas many have included them within counts of SLEs (e.g., Kendler et al., 1999; Kendler et al., 2002). The current results results indicate that SLEs and trauma exposure should be separated when studied in order to determine whether particular etiological factors, correlates, and outcomes are common to both SLEs and trauma or are more closely related to one or the other. Thus, interventions could be targeted at reducing individuals' tendency to experience SLEs or trauma specifically, and research aimed at more consistently distinguishing the two could help clinicians to more accurately predict the causes or outcomes of their clients' experiences.

In the Twin Sample, trauma was more strongly related to independent than dependent SLEs, whereas in the Grady Sample, each form of trauma was more strongly related to dependent than independent SLEs. One interpretation of this pattern is that adults in the Grady

Sample are more capable of controlling their exposure to environments in which trauma is likely to occur, thus the tendency to experience trauma is more closely related to the tendency to experience dependent SLEs, which also indicates an individual's level of control. Conversely, the tendency to experience trauma among children in the Twin Sample may indicate the inability to escape dangerous environments due to their age and thus is more closely related to a tendency to experience independent SLEs.

Finally, relations with both dependent and independent SLEs were stronger as a function of increasing severity of trauma in the Grady Sample. This indicates that high levels of low-severity trauma may occur more randomly, whereas high levels of high-severity trauma may be predictive of a more consistent pattern of stressful experiences.

Relations among SLEs, Trauma, and Psychopathology

Although both independent and dependent SLEs were associated with both forms of psychopathology, dependent SLEs were more strongly associated with internalizing and externalizing psychopathology across samples. Thus, it appears that across diverse samples, the tendency to experience SLEs that emerge at least in part from an individual's characteristics or predispositions is more indicative of psychopathology than is the tendency to experience uncontrollable SLEs. This replicates findings in the literature regarding risk for depression (e.g., Kendler et al., 1999) but is a novel finding for externalizing psychopathology.

In the twin sample, each stress variable was equally related to internalizing and externalizing psychopathology, whereas in the Grady Sample, all stress variables were more strongly related to externalizing psychopathology. One explanation of these differences could be that internalizing and externalizing psychopathology are more highly co-occurring among children than among adults. Indeed, the correlation between internalizing and externalizing

psychopathology was appreciably higher in the Twin Sample (r = .48) than in the Grady Sample (r = .33). Another potential explanation is that the Grady Sample externalizing psychopathology variable included items assessing drug and alcohol use in adults, whereas the Twin Sample only had one item assessing these behaviors. As estimates of correlations between SLEs or trauma and disruptive behavior disorders tend to be lower than those between SLEs or trauma and alcohol and drug use (e.g., Anda et al., 2006; Copeland et al., 2007), it could be the case that this difference in measurement is responsible for the difference in results.

Finally, correlations between trauma and both forms of psychopathology increased as a function of trauma severity in the Grady Sample. This finding replicates studies that examined assaultive versus non-assault trauma (e.g., Clancy et al., 2006). Thus, individuals with a high tendency to experience severe trauma also tend to have a high tendency to experience SLEs and both forms of psychopathology. The direction and etiology of these relations is still unclear; future research should focus on elucidating these using longitudinal and genetically informed samples, respectively.

Limitations and Future Directions

Several limitations of the current study are worth noting. First, we cannot isolate the cause of differences in results between the Twin and Grady Samples. Although we speculated as to potential causes of those differences above, our current methodology did not allow us to directly assess whether differences in results were due to differences in age, ethnicity, socioeconomic status, methodology, or power between the samples. Further, in some cases, measures assessed for symptoms or events over different time periods (e.g., MDD symptoms within the last year in the Twin Sample versus BDI-II depression symptoms within the last two weeks in the Grady Sample). Although the degree of consistency in results between samples

indicates their robustness, future studies should examine the structure and relations among SLEs, trauma exposure, and psychopathology using the same measures so as to better assess the causes of the differences between these samples.

Second, we cannot establish causality or directionality between SLEs or trauma and psychopathology in these samples. The data was collected cross-sectionally and did not include dating of the occurrence or onset of each endorsed item beyond whether it had occurred within a certain period of time. Thus, we could not determine whether a particular event occurred before or after the onset of psychopathology. Further, the SLEs and traumatic events assessed in these samples could not be randomly assigned, thus noncausal relations among these events and psychopathology cannot be ruled out. Future studies using longitudinal samples could assess both the stability of these relations over development and the directionality of the effects. Multivariate behavior genetic analyses (see Study 2) can elucidate whether these relations are partially noncausal and due to common etiological factors such as common genetic or environmental influences.

Third, it is possible that relations between SLEs or trauma and psychopathology differ based on subcomponents of internalizing or externalizing psychopathology. We were interested in relations with higher-order factors in the current study, but future research may reveal that disorders within internalizing and externalizing psychopathology are worth distinguishing to best understand the multivariate structure among these variables. For example, there is evidence that internalizing disorders are best explained by symptom dimensions reflecting distress (e.g., MDD, GAD) versus fear (e.g., panic disorder, agoraphobia, specific phobias) (e.g., Krueger, 1999). Distinctions such as this may be important when considering the causes and effects of SLEs or trauma and should be examined in the future.

Study 2: Univariate and Multivariate Etiology of SLEs, Trauma, and Psychopathology

Introduction

There is considerable evidence that SLEs and trauma are associated with internalizing and externalizing psychopathology (e.g., Dohrenwend, 1998; Anda et al., 2006). Nevertheless, the etiology of these phenomena and the etiology of the associations between them are less definitively established. This is due in part to studies that quantify etiological influences on sum scores of one or two of these variables at a time. The current study aims to clarify and extend the current literature by using factors derived from CFA (see Study 1) to quantify common and unique etiological influences that may underlie the multivariate relations among internalizing and externalizing psychopathology, SLEs, and trauma. These analyses have the potential to help us understand why individuals differ in their tendencies to experience SLEs, trauma, or psychopathology, why individuals who experience one dimension of SLE are more likely to experience the other category of SLE and trauma, and why individuals who experience SLEs or trauma are more likely to exhibit internalizing and/or externalizing psychopathology.

Behavior genetic studies estimate the magnitude of genetic and environmental influences on the variance of traits and disorders in the population by exploiting the fact that monozygotic (MZ) twins share 100% of their genes identical-by-descent whereas dizygotic (DZ) twins, like ordinary siblings, share 50% of their genes on average. These studies typically partition influences into genetic (additive (a^2) or dominant (d^2) genetic variance components that influence behavior), shared environmental (environmental factors that both twins experience which make them similar for a trait or disorder (c^2)), and nonshared environmental (environmental factors that only one twin experiences which make them different for a trait or disorder, as well as measurement error (e^2)) influences. Some researchers also include estimates of rater contrasts or siblings' effects on each other (s). Multivariate behavior genetic studies

examine the etiology of co-occurring traits and disorders by characterizing genetic and environmental influences that are common across traits / disorders versus those that are unique to each. Researchers have applied these techniques to determine the magnitude of genetic and environmental influences on various traits, including SLEs, trauma, and psychopathology.

Etiology of Internalizing and Externalizing Psychopathology

Internalizing disorders such as major depressive disorder (MDD) and generalized anxiety disorder (GAD) tend to be highly correlated and to share etiological influences. A large review of 23 twin and 12 family bivariate behavioral genetic studies found that there were common genetic and nonshared environmental influences on anxiety and depression and that common genetic influences explained more variance than common nonshared environmental influences (Middeldorp et al., 2005). Shared environmental influences were not found to explain a significant amount of variance in the majority of anxiety or depression symptom dimensions, thus could not contribute to comorbidity among the traits. The correlation in the reviewed studies between genetic influences on MDD and GAD was high, ranging from 0.86 to 1.00. There is also evidence for a common internalizing genetic factor influencing disorders such as separation anxiety, GAD, MDD, and eating disorders (e.g., Silberg & Bulik, 2005). One study estimated that a latent internalizing factor explains 30-41% of the variance of individual internalizing disorders (Cosgrove et al., 2011). The latent internalizing factor itself was explained by genetic influences (60%) and nonshared environmental influences (40%), and the remaining variance in individual disorders was explained by unique nonshared environmental influences (Cosgrove et al., 2011). Kendler et al. (2011) found that genetic and nonshared environmental influences on somatoform disorder, panic disorder, MDD, agoraphobia, specific phobia, GAD, and eating disorders were largely common across these disorders. Further, in an analyses of combined adult

caretaker- and youth-reported dimensions of child and adolescent psychopathology, Lahey et al. (2011) found that a common genetic factor influenced separation anxiety, social phobia, obsessive-compulsive disorder, specific phobia, and agoraphobia. In the same study, genetic influences on MDD and GAD were primarily due to a general genetic factor that also influenced the aforementioned internalizing dimensions as well as externalizing psychopathology (Lahey et al., 2011). Nonshared environmental influences were less prominent, although internalizing dimensions were influenced slightly by a nonshared environmental factor unique to internalizing psychopathology and a general nonshared environmental factor that also influenced externalizing psychopathology (Lahey et al., 2011). Interestingly, one study found that common genetic vulnerability across depression and anxiety disorder symptoms emerged only in adolescence, continued into adulthood, and primarily accounted for comorbidity, whereas the nonshared environment was largely symptom-specific across development (Waszczuk et al., 2014). Thus, genetic influences on internalizing psychopathology seem to be largely common across disorders, whereas there are nonshared environmental influences that are common across disorders and also unique to each.

Externalizing disorders such as conduct disorder (CD), oppositional-defiant disorder (ODD), and substance use disorders also tend to be highly correlated and have been demonstrated to have common etiological influences. Researchers have found a highly heritable (84%) common factor that explained the covariance among novelty seeking, substance use, CD, and attention-deficit hyperactivity disorder (ADHD), suggesting that a general inability to regulate impulses may explain vulnerability to externalizing psychopathology (Young et al., 2000). Behavior genetic studies have provided evidence for common genetic influences on ADHD and CD (e.g., Thapar et al., 2001) and on CD, ADHD, and ODD (e.g., Waldman et al.,

2001; Dick et al., 2005). Common shared environmental influences on externalizing psychopathology are typically found to be small or nonexistent (e.g., Burt et al., 2001, Dick et al., 2005). One study estimated that a latent externalizing factor explains 26-52% of the variance of individual externalizing disorders (Cosgrove et al., 2011). The latent externalizing factor itself was explained by genetic influences (65%) and nonshared environmental influences (35%), and the remaining variance in individual disorders was explained by nonshared environmental influences, although CD had additional unique genetic influences (Cosgrove et al., 2011). Kendler et al. (2011) found that a common genetic factor influenced antisocial personality disorder, drug abuse/dependence, CD, and alcohol abuse/dependence in adults, whereas a common nonshared environment factor influenced antisocial personality disorder, CD, and drug abuse/dependence. In the study of child and adolescent psychopathology mentioned above, Lahey et al. (2011) found that externalizing dimensions of CD, ODD, hyperactivity/impulsivity, and inattention were each influenced by an externalizing genetic factor and a general genetic factor that also influenced internalizing psychopathology. Further, the externalizing dimensions were influenced slightly by an externalizing nonshared environment factor and had negligent loadings onto a general nonshared environment factor (Lahey et al., 2011). In another study of child and adolescent externalizing psychopathology, Singh & Waldman (2010) found that commonalities across ODD, CD, inattention, and hyperactivity were largely due to common additive and nonadditive genetic influences, whereas nonshared environmental influences were largely dimension-specific. Thus, similar to internalizing psychopathology, genetic influences on externalizing psychopathology are also largely shared across disorders, whereas there are nonshared environmental influences that are common across disorders and also unique to each.

As noted above, there is significant co-occurrence between internalizing and externalizing disorders, although behavior genetic studies examining the etiology of this co-occurrence have found inconsistent results. In a sample of adults, Kendler et al., (2003) found that two genetic risk factors influenced primarily internalizing disorders (MDD, GAD, and phobia) and externalizing disorders (alcohol dependence, drug abuse/dependence, antisocial behavior, and CD), respectively. The same group replicated these results in a similar sample (Kendler et al., 2011). Substance use disorders had disorder-specific genetic influences, and antisocial behavior and CD had common shared environmental influences. In contrast, Gjone and Stevenson (1997) found that in a sample of children and adolescents there were both common genetic and shared environmental influences on internalizing and externalizing psychopathology and little evidence of common nonshared environmental influences. Similarly, one study of adolescents found that the covariance between depression and antisocial behavior was explained by genetic (45%), shared environmental (30%), and nonshared environmental (25%) influences (O'Connor et al., 1998). Another study of adolescents found significant genetic and nonshared environmental influences on the covariance between MDD and CD (Subbarao et al., 2008). In the same sample, Cosgrove et al. (2011) found that the covariance between latent internalizing (including MDD, GAD, and separation anxiety disorder) and externalizing (including CD, ODD, and ADHD) factors was due to common genetic (62%) and nonshared environmental (38%) influences. Further, Lahey et al. (2011) and Tackett et al. (2013) found that internalizing and externalizing dimensions were influenced by a general genetic factor and an internalizing- or externalizing-specific genetic factor, whereas nonshared environmental influences tended to be dimension-specific. In a multivariate sibling study of the Swedish population, Pettersson et al. (2015) found that a general genetic factor influenced schizophrenia, schizoaffective disorder,

bipolar disorder, MDD, GAD, ADHD, alcohol abuse, drug abuse, and violent behavior, accounting for between 10% and 36% of the variance in each disorder. A nonshared environment factor also influenced mood problems, whereas the rest of the variance among these disorders was explained by genes or nonshared environment unique to each disorder (Pettersson et al., 2015). Thus, co-occurrence between internalizing and externalizing psychopathology seems to be primarily influenced by genetic factors.

Etiology of SLEs

Though SLEs are often assumed to occur randomly, there are several lines of research suggesting that such a model is unlikely (reviewed by Kendler & Prescott, 2006). First, the number of SLEs experienced by an individual in a given amount of time remains moderately stable over time (Andrews, 1981; Fergusson & Horwood, 1987). Second, the number of SLEs an individual experiences is related to characteristics such as SES, self-esteem, social support, mood, and personality (reviewed by Brett et al., 1990). Third, individuals consistently differ in their likelihood to experience specific SLEs (reviewed by Kendler & Prescott, 2006). Thus, the use of behavior genetic techniques to determine the underlying causes of individual differences in number of SLEs is warranted.

There is evidence that SLEs are primarily influenced by genetic and nonshared environmental factors. Specifically, research demonstrates that genetic factors account for 26-40%, shared environmental factors account for 1-18%, and nonshared environmental factors account for 50-60% of the variance of SLE frequency (Kendler et al., 1993; Lyons et al., 1993; McGue & Lykken, 1992; Plomin et al., 1990; Thapar & McGuffin, 1996). A review (Kendler & Baker, 2007) found that SLEs had a weighted mean heritability of 28% based on six studies, although there was variance in the estimate across types of SLEs. For example, independent

SLEs had a weighted mean heritability of 17% based on 6 studies, whereas dependent SLEs had a weighted mean heritability of 31% based on 5 studies. Although most studies examined the heritability of SLEs at only a single time point, one study (Foley et al., 1996) used data from two time points to separate the contribution of random or occasion-specific effects on SLEs from those that are stable over time. Their best-fitting model indicated that about 55% of the variation in SLEs result from occasion-specific effects and that the heritability of the stable tendency to experience SLEs was 65%. A recent multiwave longitudinal study (Johnson et al., 2013) found that genetic influences on dependent SLE exposure were mostly common across ages 9-16 (i.e. the same genes were relevant across these ages) and that the magnitude of the proportion of variance explained by genetic influences increased from around 14% at ages 9-11 to around 40% at ages 12-16. Further, shared environmental influences decreased from around 40% at ages 9-11 to around 10% at ages 12-16, indicating that the influence of family environment and dynamics on SLEs may decrease as children spend more time away from home. Genetic factors explained 0-40% of the variance of independent SLEs with an average of 18%. Shared environmental influence on independent SLEs also varied considerably across ages with an average of 20%. Using a method of estimating heritability from genome-wide data (Yang et al., 2013), one study estimated the heritability of experiencing any SLE at 30%, dependent SLEs at 30%, and independent SLEs at 26% (Power et al., 2013). Notably, most researchers have used sum scores rather than latent factors derived from CFA to characterize SLEs and thus have not separate the considerable event-specific variance (see Study 1) from the latent tendency to experience SLEs. Further, no researchers have quantified common versus unique etiological influences on independent and dependent SLEs, despite their considerable overlap. Thus it is unclear the

degree to which the same etiological factors actually influence both dimensions of SLEs. The same gaps in knowledge are present in research of the etiology of trauma exposure.

Etiology of Trauma Exposure

Trauma exposure has been found to be influenced by genetic, shared environmental, and nonshared environmental factors (reviewed by Afifi et al., 2010). In a community sample of adults (Stein et al., 2002), genetic influences explained 20%, shared environmental influences explained 21%, and nonshared environmental influences explained 58% of assaultive trauma (i.e., being held captive, being beaten up, sexual assault, and other life threatening events). Nonassaultive trauma (sudden death of a family member, car accident, fire, or environmental disaster) showed no genetic influence, and 39% and 61% of the variance was explained by shared and nonshared environmental influences, respectively. Similarly, Jang et al. (2003) found that 40% of the variance of assaultive trauma was explained by genetic influences and 60% was explained by nonshared environmental influences, whereas 28% and 72% of the variance of nonassaultive trauma was explained by shared and nonshared environmental influences, respectively. Using a unique design, Sartor et al. (2012) found that genetic and nonshared environmental influences explained 47% and 53% of the variance, respectively, of trauma exposure that carried a low risk of subsequent PTSD and 60% and 40% of the variance, respectively, of trauma exposure that had a high risk of subsequent PTSD. Another study (Lyons et al., 1993) found that genetic effects accounted for 35-47% of the variance of exposure to combat trauma in a sample of Vietnam veterans. Thus, there is convergent evidence that trauma exposure, particularly exposure to assaultive trauma, is influenced by genes, although nonshared environmental influences explain the majority of the variance of all types of trauma. No researchers have estimated common or unique influences among SLEs and trauma. Some

researchers have used multivariate behavior genetics techniques to do so between pairings of SLEs or trauma and psychopathology.

Etiological Overlap of SLEs, Trauma, and Psychopathology

Several competing, but not mutually exclusive, hypotheses have emerged regarding the relation between SLEs and psychopathology (see Kim et al., 2003; Kendler et al., 1999). One hypothesis is that SLEs are causal, and thus experiencing an SLE increases the risk of internalizing and externalizing problems. Another hypothesis, referred to as the social-selection hypothesis (e.g., Kim et al., 2003), is that emotional or behavioral problems lead to increases in SLEs. For example, adolescents with internalizing problems may be unsuccessful in social relations because they are unrewarding companions, whereas adolescents with externalizing problems may experience school failure, discordant relationships, or job losses due to their behavior. A third possibility is that the relation between SLEs and internalizing and externalizing problems is noncausal, and thus their relation is caused by shared etiological factors such as common genetic and environmental influences. Addressing the first two possibilities, longitudinal studies have demonstrated that internalizing and externalizing problems both predict later SLEs and are predicted by earlier SLEs (Kim et al., 2003; Rowe et al., 2006), suggesting that SLEs and internalizing and externalizing problems are reciprocally causal. Further, some studies have found that SLEs mediate the relation between externalizing and internalizing problems (Kendler, Gardner, & Prescott, 2002, Fergusson et al., 2003, Rowe et al., 2006) such that early conduct problems increase risk for SLEs which in turn leads to later depression, or vice versa.

There is also evidence that at least some portion of the relation between SLEs and psychopathology is noncausal. In particular, genetic liability to major depression was associated

with significantly increased risk for assault, serious marital problems, divorce/breakup, job loss, major financial problems, and trouble getting along with friends and relatives, an effect that was not due to SLEs occurring during depressive episodes (Kendler & Karkowski-Shuman, 1997; Kendler et al., 1999). Recent research attempting to disentangle the causal relations between SLEs and depression found that both causal paths and common etiology explained phenotypic correlations between SLEs and depressive symptoms, and further that the genetic factors that directly influence SLEs in turn had causal paths to depressive symptoms (Wichers et al., 2012). Thus, the shared genetic risk between depression and SLEs may be a result of genes that cause increased risk of SLEs, the experiencing of which in turn increase risk for depression. Conversely, shared environmental influences on depression indirectly increased risk for SLE exposure, whereas nonshared environmental influences on SLE and depression were separate but correlated. No research has examined etiological overlap between SLEs and any other form of internalizing psychopathology or any form of externalizing psychopathology.

There is some evidence that the genetic and environmental influences on trauma exposure are shared with internalizing and externalizing problems. Jang et al. (2003) found that 8% and 11% of the genetic influences on assaultive trauma exposure were shared with juvenile antisocial behavior and psychoticism, respectively, whereas there was no overlap between environmental influences on these traits and no overlap between genetic and environmental influences on nonassaultive trauma and these traits. In contrast, Koenen et al. (2005) found that there was no shared genetic vulnerability between conduct disorder and combat trauma exposure, although combat trauma may have a different etiology than civilian trauma. Sartor et al. (2012) found that 33% of the genetic influences on low-risk trauma exposure and major depressive disorder were shared, whereas 79% of the genetic influences and 23% of the nonshared environmental

influences on high-risk trauma exposure and major depressive disorder were shared. Thus, it appears that the etiological influences on trauma exposure are shared with at least some forms of internalizing and externalizing problems. Nevertheless, this research has not taken into account the overlap between SLEs and trauma or between internalizing and externalizing psychopathology.

Current Study

As reviewed above, most researchers have used sum scores to characterize these variables rather than latent factors derived from CFA, have not separated dimensions of SLEs, and have not examined these variables in a multivariate context. Thus, the degree to which the estimates of etiological influences on these variables across studies reflect common or unique influences remain unclear. In the current study, we aimed to address gaps in knowledge of common and unique influences on the tendency to experience SLEs, trauma, and psychopathology. Specifically, we aimed to (1) determine whether univariate behavior genetic analyses that quantify influences on SLEs, trauma, and psychopathology using factors derived from CFA replicate findings from research using sum scores; (2) determine the degree to which common genetic, shared environmental or nonshared environmental influences explain correlations among independent SLEs, dependent SLEs, and trauma; and (3) determine the degree to which common genetic, shared environmental or nonshared environmental influences explain correlations among SLEs, trauma, and psychopathology. These analyses have the potential to help us understand why individuals differ in their tendencies to experience SLEs, trauma, or psychopathology, why individuals who experience one category of SLE are more likely to experience the other category of SLE and trauma, and why individuals who experience SLEs or trauma are more likely to display internalizing and/or externalizing psychopathology.

Method

Participants

Participants were drawn from the Georgia Twin Registry, a population-based twin registry monozygotic and dizygotic twins born in Georgia between 1980 and 1991. In 1992-1993, parents of twins were sent a request to join the Georgia Twin Registry along with a set of questionnaires. In 1996-1997, a second set of questionnaires was sent to the 1,567 twin families who joined the registry. Data was available for 461 sets of DZ twins and 382 sets of MZ twins, although any given variable was missing data for some portion of participants (missing data methods are described below). Participants ranged in age between 4 and 17, with a mean of 10.5 (SD = 3.2). 52% of participants were female. 82% of participants identified as European American, 11% identified as African American, 1% identified as Hispanic Americans, and 6% identified as Mixed/Other ethnicity.

The zygosity of the twins was determined based on parent reports of twins' physical similarity using an eight-item questionnaire (e.g., "are your twins mistaken for each other by people who know then?" "are your twins as alike as two peas in a pod?") with dichotomized responses (i.e., 1 indicates that the *twins are similar on a trait*, and 0 indicates that the *twins differ*) (Bonnelykke, Hauge, Holm, Kristofferson, & Gurtler, 1989). Responses across all items were averages. Twins were categorized as MZ if their average scores were 0.5 or above and as DZ if less than 0.5. The scores on this zygosity questionnaire showed good internal consistency in our community twin sample ($\alpha = .86$). This method of zygosity determination has been well validated against DNA test results, with at least 90% accuracy (Jackson, Sneider, Davis, & Treiber, 2001; Spitz et al., 1996).

Measures

Life Events Scale. The Life Events Scale (LES) is a measure of 25 stressful life events that have occurred within the past year. Items include: "Suspended from school," "Broke up with boyfriend/girlfriend," "Broke up with close friend," "Close friend died," "Seriously ill or injured," "Mother/father seriously ill or injured," "Brother/sister seriously ill or injured," "Not accepted into important extracurricular activity," "Mother or father lost a job," "Favorite pet died," "Flunked a grade," "Brother or sister had serious trouble," "Was assaulted, robbed, or a victim of another violent crime," "Family member was victim of violence," "Close family member died," "Argued more with parents," "Family had serious financial trouble," "Parent spent much more time away from home," "Parents argued much more with each other," "Parents got divorced or separated," "Arrested or had serious law trouble," "Parent arrested or serious law trouble," "Dropped out of school," "Lost a job," and "Lost driver's license." Items were rated by parents of twins via mailed questionnaires. The item "was assaulted, robbed, or a victim of another violent crime" was included as a trauma item (see below) and removed from this measure. Responses were given as binary items. Based on the results of Study 1, items were sorted into dependent (i.e., events that the individual likely influenced) and independent (i.e., events that the individual likely did not influence) SLE dimensions.

Trauma Measure. Traumatic events in the twin sample were measured by two related items. Parents were asked whether their child ever experienced or saw anything extremely frightening. If yes, parents were asked to describe the event. Item responses were coded by three independent coders as to whether the reported event meets criteria for a traumatic event as defined by *DSM-5*: "exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: (1) Directly experiencing the traumatic event(s). (2) Witnessing, in person, the event(s) as it occurred to others. (3) Learning that the traumatic

event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental. (4) Experiencing repeated or extreme exposure to aversive details of the traumatic event(s).” If so, a dichotomous variable indicating trauma exposure was be coded as 1. If not, or if parents indicated the absence of trauma, responses were coded as 0. In addition, the LES item “was assaulted, robbed, or a victim of another violent crime” was deemed to be indicative of trauma and included as a separate, binary variable as an indicator of trauma.

Internalizing Psychopathology.

Depression Items. Depression symptoms were assessed by parent-report of *DSM* depression symptoms over the past year. Items included “seems very sad or irritable” “lost interest in daily activities,” “seems like nothing is fun,” “lost noticeable amount of weight,” “smaller appetite than usual,” “put on noticeable amount of weight,” “bigger appetite than usual,” “trouble falling asleep, staying asleep, or sleeps less than usual,” “trouble waking up or sleeps more than usual,” “less active than usual,” “fidgets or move around a lot more than usual,” “more tired than usual,” “less energy than usual,” “feels worse about himself or herself than should,” “feels more guilty than should,” “more difficulty paying attention than usual,” “feels hopeless,” “thinks or talks a lot about death,” and “tried to kill himself.” These items were rated on a 0-4 scale of how well each item described the child from “not very well” to “very well.” Item scores were included in the analyses as ordinal variables.

Anxiety Items. Anxiety symptoms were assessed by parent-report of *DSM* generalized anxiety disorder (GAD) symptoms over the past six months. Items included “worries too much about doing well in school or sports,” “worries too much about behaving well or being good,” “worries too much about things he or she said or did,” “gets headaches, stomachaches, or other

physical symptoms even when not actually sick," "asks adults to reassure," "worries too much about health," "worries too much about getting to places on time," "worries too much about whether the family has enough money," "has trouble stopping worrying," "seems tense or nervous and can't relax," "worries too much about things that are coming up in the future," "has muscle tension," "has trouble falling asleep or doesn't sleep well," "seems irritable," "gets tired easily," and "can't concentrate or mind goes blank when trying to think." These items were rated on a 0-4 scale of how well each item described the child from "not very well" to "very well." Item scores were included in the analyses as ordinal variables.

Externalizing Psychopathology.

Oppositional Defiant Disorder Symptoms. ODD symptoms were assessed by parent-reports of *DSM* ODD symptoms over the past 6 months. Items included "loses temper," "argues with adults," "actively disobeys rules," "does things on purpose to annoy others," "blames others for mistakes or misbehavior," "touchy or easily annoyed," "angry and resentful," "is spiteful or ties to get back at others," and "curses or uses bad language." These items were rated on a 0-4 scale of how well each item described the child from "not very well" to "very well." Item scores were included in the analyses as ordinal variables.

Conduct Disorder Symptoms. DSM CD symptoms present during the past year were assessed by parent-report. Items included "starts fights with people who do not live at home," "skipped school or work," "ran away from home overnight," "used alcohol or drugs," "stole items worth more than $20," "destroyed property on purpose," "sets fires wanting to cause serious damage," "broke into someone else's house, building, or car," "physically cruel to animals," "physically cruel to people," "stole things from another person using force or threat," "used a weapon that could seriously harm others," "took part in sexual activities to get money or

valuables," "forced someone into sexual activity," and "stayed out late against wishes." Parents were asked to report how many times their child has done these things, with possible responses of 0, 1, 2, 3, or more than 3. Item scores were included in the analyses as interval variables.

Analyses

Prior to model-fitting, raw residuals with a mean of 0 with their variance unconstrained ls for each item were generated by regressing each item (using linear, binary logistic, or ordinal logistic regression depending on the scale of each item) on age, age squared, sex, age X sex, and sex X age squared in SPSS version 22.0 in order to account for mean level age and sex differences in the variables of interest (McGue & Bouchard, 1984). All behavior genetic analyses were conducted in Mplus 7.2 (Muthén & Muthén, 2012) using the MLR estimator, which accounts for non-normality in the data. Missing data was handled using Full Information Maximum Likelihood (FIML), which has been shown to produce unbiased parameter estimates and standard errors by estimating a likelihood function for each individual based on the variables that are present so that all the available data are used (Graham, Cumsille, & Elek-Fisk, 2003). We used factor scores saved from the analyses in Study 1 because the focus of this study was not the estimation of latent variables, and to reduce the computational intensity of partitioning variance of up to five latent variables with several dozen indicators in total.

We began by conducting univariate behavior genetic analyses for each variable (i.e., independent SLEs, dependent SLEs, trauma exposure, internalizing psychopathology, and externalizing psychopathology) separately in order to estimate the proportion of variance explained by additive and nonadditive genetic, shared environmental, nonshared environmental, and sibling influences. A series of hierarchically nested models was used to determine the magnitude of each etiological influence (i.e., a^2, c^2 or d^2, e^2, and s) on the variance in each

variable. Next, we conducted a series of multivariate behavior genetic analyses using Cholesky decomposition (Loehlin, 1996; Neale & Cardon, 1992). A Cholesky factorization decomposes the genetic and environmental covariance matrices into triangular matrices of factor loadings in which the number of factors equals the number of variables (i.e., the first factor contributes to all five variables, the second factor contributes to the subsequent four variables, and so on). The genetic or environmental covariance matrix is calculated by the product of the triangular matrix and its transpose. Again, a series of hierarchically nested models was used to determine the magnitude of each common and specific etiological influence. Variables were ordered as follows: trauma exposure, independent SLEs, dependent SLEs, internalizing psychopathology, and externalizing psychopathology. We ordered the psychopathology variables last because, based on the extensive literature, we expected these variables to have additional etiological influences not shared with the stress variables which would be more difficult to cleanly estimate if the psychopathology variables were ordered first. We hypothesized that the SLE variables may share etiological influences with psychopathology that are not shared with trauma, and thus ordered trauma first in order to test this hypothesis. We first fit a full Cholesky model (see Figure 2.1), then tested a model in which nonsignificant paths were fixed to zero. We also fit a model only including etiological influences that were significant in the univariate models (e.g., if the best fitting univariate model did not include shared environmental influences, no paths from variables representing shared environment to that variable would be estimated).

Goodness of fit was primarily judged using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), two commonly used indicators of model fit and parsimony (Akaike, 1974; Schwarz, 1978). Several additional fit indices, including Chi Square, the root mean square error of approximation (RMSEA), the comparative fit index (CFI), the

Tucker Lewis Index (TLI), and the standardized root-mean square residual (SRMR) were also calculated to provide more complete information regarding model fit. We used the following criteria to evaluate model fit: RMSEA < .08 for adequate fit and < .05 for close fit (Browne & Cudeck, 1993), and CFI > 0.95, TLI > 0,95 and SRMR < .08 for good fit (Hu & Bentler, 1999). We also used a chi-square difference test with a Satorra-Bentler scaling correction (which is necessary when using the MLR estimator) to directly compare goodness of fit between models (Satorra & Bentler, 2011), where a *p*-value < .05 indicates a significant difference in goodness of fit. Notably, this chi square test is only appropriate if models are nested (i.e., one model is nested in another if some of the coefficients in the first model can be restricted to obtain the second).

Results

Univariate Behavior Genetic Analyses

***Trauma Exposure*.** We first estimated MZ and DZ twin correlations for the trauma exposure variable, which were rMZ = 0.84 and rDZ = 0.68. The MZ twin correlation being higher than the DZ correlation indicated the presence of genetic influences, whereas the high correlations between both MZ and DZ twins indicated high family resemblance in exposure to trauma regardless of zygosity. As seen in Table 2.1 and Figure 2.1, shared environmental, nonadditive genetic, and sibling influences were able to be dropped from the full model without significantly worsening fit. Thus, the best fitting model was the AE model, where additive genetic influences explained 73% of the variance and nonshared environmental influences explained 27% of the variance.

***Independent SLEs*.** We first estimated MZ and DZ twin correlations for the trauma exposure variable, which were rMZ = 0.74 and rDZ = 0.71. The lack of difference between MZ and DZ twin correlations indicated that shared environmental influences were more likely than

genetic influences, whereas the high correlations between both MZ and DZ twins indicate high family resemblance in exposure to trauma regardless of zygosity. As seen in Table 2.1 and Figure 2.2, additive genetic, nonadditive genetic, and sibling influences were able to be dropped from the full model without significantly worsening fit. Thus, the best fitting model was the CE model, where shared environmental influences explained 77% of the variance and nonshared environmental influences explained 23% of the variance.

***Dependent SLEs*.** We first estimated MZ and DZ twin correlations for the trauma exposure variable, which were rMZ = 0.68 and rDZ = 0.29. The MZ twin correlation being higher than the DZ correlation indicated the presence of genetic influences. As seen in Table 2.1 and Figure 2.3, shared environmental, nonadditive genetic, and sibling influences were able to be dropped from the full model without significantly worsening fit. Thus, the best fitting model was the AE model, where additive genetic influences explained 61% of the variance and nonshared environmental influences explained 39% of the variance.

***Internalizing Psychopathology*.** We first estimated MZ and DZ twin correlations for the trauma exposure variable, which were rMZ = 0.64 and rDZ = 0.38. The MZ twin correlation being higher than the DZ correlation indicated the presence of genetic influences. As seen in Table 2.1 and Figure 2.4, shared environmental, nonadditive genetic, and sibling influences were able to be dropped from the full model without significantly worsening fit. Thus, the best fitting model was the AE model, where additive genetic influences explained 68% of the variance and nonshared environmental influences explained 32% of the variance.

***Externalizing Psychopathology*.** We first estimated MZ and DZ twin correlations for the trauma exposure variable, which were rMZ = 0.77 and rDZ = 0.37. The MZ twin correlation being higher than the DZ correlation indicated the presence of genetic influences. As seen in

Table 2.1 and Figure 2.5, shared environmental, nonadditive genetic, and sibling influences were able to be dropped from the full model without significantly worsening fit. Thus, the best fitting model was the AE model, where additive genetic influences explained 77% of the variance and nonshared environmental influences explained 37% of the variance.

Multivariate Behavior Genetic Analyses

Next, we fit three alternative Cholesky decomposition models to determine the common and specific etiological influences on trauma exposure, independent SLEs, dependent SLEs, and internalizing and externalizing psychopathology (see Table 2.2). Correlations among the variables are presented in Figure 1.6. We first fit a full model in which each variable had an A, C, and E latent factor assigned to it (see Figure 2.6). We also fit a model in which all variables except independent SLEs had an A factor, only independent SLEs had a C factor, and each variable had an E factor assigned to it to mirror the findings from the univariate analyses. Finally, we fit a model in which the nonsignificant paths estimated in the first two models (the same paths were nonsignificant in both models) were equated to zero. As seen in Table 2.2 and Figure 2.7, this final model was the best fitting model. In this model, there were four additive genetic factors, one shared environmental factor, and five nonshared environmental factors.

The first genetic factor was defined by the trauma (57% variance explained) and internalizing psychopathology (5% variance explained) variables, whereas dependent SLEs, independent SLEs, and externalizing psychopathology did not load significantly onto it. After accounting for the variance explained by the first genetic factor, dependent SLEs (21% variance explained) and externalizing psychopathology (4% variance explained) loaded significantly onto the second genetic factor, whereas independent SLEs and internalizing psychopathology did not. After accounting for the variance explained by the first two factors, independent SLEs,

internalizing psychopathology, and externalizing psychopathology did not load significantly onto the third genetic factor and it was dropped from the best fitting model. After accounting for the variance explained by the first three genetic factors, internalizing (60% variance explained) and externalizing (33% variance explained) psychopathology loaded significantly onto the fourth genetic factor. After accounting for the variance explained by the first four genetic factors, externalizing psychopathology (42% variance explained) loaded significantly onto the fifth genetic factor.

Trauma (29% variance explained), independent SLEs (81% variance explained), and dependent SLEs (42% variance explained) loaded significantly onto the first shared environmental factor, whereas internalizing and externalizing psychopathology did not. Although trauma and dependent SLEs did not have shared environmental influences in the best fitting univariate models, multivariate behavior genetic models have greater power to detect such influences (Schmitz, Cherny, & Fulker, 1998), thus these results may more accurately reflect influences on trauma and dependent SLEs. After accounting for the variance explained by the first factor, no variables loaded significantly onto the second, third, fourth, or fifth shared environmental factor and each was dropped from the best fitting model.

Trauma (14% variance explained), independent SLEs (7% variance explained), dependent SLEs (9% variance explained), and internalizing psychopathology (4% variance explained) loaded significantly onto the first nonshared environmental factor, whereas externalizing psychopathology did not. After accounting for the variance explained by the first factor, independent SLEs (12% variance explained) loaded significantly onto the second nonshared environmental factor, whereas dependent SLEs, internalizing psychopathology, and externalizing psychopathology did not. After accounting for the variance explained by the first

two factors, dependent SLEs (28% variance explained) and externalizing psychopathology (5% variance explained) loaded significantly onto the third nonshared environmental factor, whereas internalizing psychopathology did not. After accounting for the variance explained by the first three factors, only internalizing psychopathology (31% variance explained) loaded onto the fourth nonshared environmental factors. After accounting for the variance explained by the first four factors, externalizing psychopathology (20% variance explained).

Discussion

In this study, we aimed to (1) determine whether univariate behavior genetic analyses that quantify influences on SLEs, trauma exposure, and psychopathology using factors derived from CFA replicate findings from research using sum scores; (2) determine the degree to which common genetic, shared environmental or nonshared environmental influences explain correlations among independent SLEs, dependent SLEs, and trauma; and (3) determine the degree to which common genetic, shared environmental or nonshared environmental influences explain correlations among SLEs, trauma, and psychopathology. Briefly, in the separate, univariate analyses of trauma exposure, independent SLEs, dependent SLEs, internalizing psychopathology, and externalizing psychopathology, we found that familial (i.e., genetic and/or shared environmental) influences explained the majority of the variance in each variable. Specifically, we found that genetic influences explained the majority of the variance in all variables except independent SLEs, the majority of which was explained by shared environmental influences. In the Cholesky decomposition of the variance among all the variables, it appeared that common shared environmental and nonshared environmental influences explained correlations among the tendencies to experience trauma, independent SLEs, and dependent SLEs. Further, it appeared that (1) the tendency to experience trauma and

internalizing psychopathology had common genetic influences; (2) the tendency to experience dependent SLEs and externalizing psychopathology had common genetic influences; (3) tendencies to experience trauma, independent SLEs, and dependent SLEs had common nonshared environmental influences; and (4) dependent SLEs and externalizing psychopathology had common nonshared environmental influences. The implications of these findings are discussed below.

Univariate Behavior Genetic Analyses

There are several inferences that can be made from our univariate behavior genetic findings that the variances of all five variables were primarily explained by familial influences. For internalizing (a^2 = .68) and externalizing (a^2 = .77) psychopathology, the best fitting models and the size of the estimates are in line with previous findings in adolescent and adult samples (e.g., Cosgrove et al., 2011; Young et al., 2000). Although we did not separately analyze the MDD, GAD, CD, and ODD symptoms that comprise the internalizing and externalizing psychopathology variables, these findings contribute to the literature reflecting that commonalities between these symptoms are largely due to heritable factors. Further, univariate analyses of internalizing and externalizing psychopathology often do not detect shared environmental influences on either variable (e.g., McGue & Bouchard, 1998). Nevertheless, there is a growing literature suggesting that shared environment does play a role in psychopathology, and that findings to the contrary are typically due to power limitations, as modest shared environmental influences are quite difficult to detect in the presence of both nonshared environmental and genetic influences (reviewed by Burt, 2009). For example, the sample size required to detect shared environmental influences of 10% in this context has been estimated as at least 7000 twin pairs (Martin et al., 1978). Thus, estimates of genetic influences

from univariate behavior genetic analyses in this study may be larger than in reality as they are likely to include difficult-to-detect shared environmental influences.

Conversely, although researchers have estimated etiological influences on SLEs and trauma much less frequently than on psychopathology, the estimates in the current study are quite discrepant from those found in other studies. Across dependent and independent SLEs, the nonshared environment is almost always the largest etiological influence in published studies, with estimates ranging between 46%-80% (e.g., Johnson et al., 2013; Kendler & Baker 2007). This same patterns holds true for trauma exposure, in which case estimates of nonshared environmental influence range between 40-72% (e.g., Jang et al., 2003; Stein et al., 2002; Sartor et al., 2012). Familial influences on independent SLEs are typically found to be primarily shared environmental (e.g., Johnson et al., 2013; Kendler & Baker 2007), whereas familial influences on dependent SLEs and trauma are typically found to be genetic (e.g., Jang et al., 2003; Johnson et al., 2013).

The discrepancies found in the current study may be attributable to several methodological distinctions between it and other research. First, no other studies have used factor scores on latent variables derived from CFA. As demonstrated in Study 1, there is a considerable amount of item-specific variance in measures of SLEs and trauma. Thus, estimates based on sum scores of SLEs or traumatic events are estimating influences on some combination of a latent tendency to experience these events and item-specific variance due to measurement error or other, occasion-specific factors. Our findings indicate that the latent, potentially more stable tendencies to experience SLEs or trauma are more strongly influenced by genetics or the shared environment. This is supported by findings from a longitudinal study that separated the contribution of occasion-specific from stable effects on SLEs, finding that genetic influences

explained 65% of the stable tendency to experience SLEs, roughly twice the standard heritability calculated from the same data (Foley et al., 1996). Second, most behavior genetic research on these events has been conducted in adult samples. It could be the case that because child twins have less control over their environment and are more likely to be in the same environment than are adult twins, child twins are more likely to experience similar levels of SLEs and trauma. This is supported by findings that familial influences on SLEs decreased as a function of age within a child sample (Johnson et al., 2013).

Multivariate Behavior Genetic Analyses of Trauma and SLEs

The results from the best fitting Cholesky decomposition model provide insight into the etiology of relations among SLEs, trauma, and psychopathology. Focusing on the relations between the tendencies to experience trauma, independent SLEs, and dependent SLEs, it appears that environmental influences predominantly cause their covariance. Specifically, a single shared environmental factor influenced all three variables with moderate to high proportions of variance explained (c^2 = .29-.81). This factor represents environmental factors that would affect both twins and influence trauma and both forms of SLEs. Potential influences that would fall under this category could range from parenting style to socioeconomic status to neighborhood or regional factors, all of which have been demonstrated to influence the tendency to experience SLEs and trauma (Dubow et al., 1991; Hatch & Dohrenwend, 2007). Importantly, these results suggest that the same set of shared environmental factors influence all three variables and thus cannot be used to differentiate between each tendency. That is, factors such as socioeconomic status increase one's chance to experience stress and trauma broadly.

Similarly, one nonshared environmental factor also influenced all three variables with low proportions of variance explained (e^2 = .07-.14). This factor represents environmental factors

that only one twin experienced and influence trauma and both forms of SLEs. Potential influences that would fall under this category could be differential peer groups or classrooms. Again, these results suggest that the same nonshared environmental factor influence all three variables and thus cannot be used to differentiate between each tendency. Taken together, these results suggest that environmental factors cause commonalities among these three stress variables, although shared environmental factors have more influence than nonshared environmental factors.

It is also worth noting that these multivariate results provide support for the argument that shared environmental influences are difficult to detect due to low power in univariate analyses (Burt, 2009). Researchers have demonstrated that power to detect both genetic and environmental influences increases not only with sample size but also with the number of correlated measurements in multivariate designs (Schmitz et al., 1998). When comparing the estimates from the multivariate analyses to those from the univariate analyses, it is clear that univariate estimates of genetic influences also contained shared environmental influences.

Whereas the environment causes commonalities among tendencies to experience stress, additional influences that separate each variable are primarily genetic. Genetic influences explained the majority of the variance in the tendency to experience trauma, and a separate genetic factor influenced dependent SLEs. Independent and dependent SLEs also each had unique nonshared environmental influences that differentiated them from the other stress variables. Although it is not difficult to imagine how environmental influences may cause differential tendencies to experience SLEs or trauma, understanding the pathway from genes to these experiences is less straightforward. The genes that cause an individual to be more likely to experience trauma or dependent SLEs likely influence an individual's tendency to select

themselves into high-risk environments. Such factors could include aspects of personality such as sensation seeking or negative affect, which may cause individuals to, for example, be more likely to get an a car accident (trauma) or lose a friend (dependent SLE). These personality factors are both correlated with SLEs and genetically influenced (Baker et al., 1992; Lauterbach & Vrana, 2001; Koopmans et al., 1995; Mroczek & Almeida, 2004; Smith, Ptacek, & Smoll, 1992). These factors also likely explain shared genetic influences with psychopathology.

Multivariate Behavior Genetic Analyses of Trauma, SLEs, and Psychopathology

The multivariate behavior genetic analyses demonstrated that trauma had common genetic influences with internalizing psychopathology, independent SLEs had common nonshared environmental influences with internalizing psychopathology, and dependent SLEs had common genetic and nonshared environmental influences with externalizing psychopathology and common nonshared environmental influences with internalizing psychopathology. Internalizing and externalizing psychopathology shared only genetic influences, a commonly found result (Kendler et al., 2003). These results indicate that etiological factors that influence tendencies to experience stress also influence internalizing *or* externalizing psychopathology, but not both. That is, the stress variables do not share etiology with psychopathology generally. This finding implies that, as specific genetic or environmental factors that constitute the estimates present in the current study are identified, we could use these factors to differentially predict tendencies to experience stress on the one hand and form of psychopathology on the other.

As mentioned above, genetic factors shared between (1) trauma and internalizing psychopathology; and (2) dependent SLEs and externalizing psychopathology likely reflect influences on personality characteristics such as sensation seeking or negative affect. These

personality characteristics are not only genetically influenced and related to SLEs and trauma but also are related to internalizing and/or externalizing psychopathology (Beauchaine, Gatzke-Kopp, & Mead, 2007; Blonigen et al., 2005). Future research could investigate whether these personality characteristics mediate genetic effects on SLEs and trauma by controlling for measures of these characteristics to determine whether genetic estimates are reduced or become nonsignificant.

Limitations and Future Directions

Several limitations to the current study are worth considering. First, we used a child sample, and although there is evidence that age moderates the magnitude of etiological influences on at least some of the variables of interest (Bergen, Gardner, & Kendler, 2007; Johnson et al., 2013), we did not have a large enough sample size to conduct multivariate analyses while testing age as a moderator. It could be the case that the magnitude or nature of the influences on each variable separately or their shared etiology could differ between younger and older children, and between children and adults. Further, these relations may differ as a function of gender. Research with more substantial sample sizes could examine age, gender, and their interaction as moderators to expand and clarify the results from the current study.

Second, the bivariate correlations of SLEs and trauma with internalizing and externalizing psychopathology were relatively low (ranging between r = .09-.20) compared with other estimates found in the literature (e.g., Kendler et al., 1999). Thus, we had less covariance available to decompose in the multivariate analyses. We encourage researchers to attempt to replicate these analyses in samples with stronger correlations among these variables to determine whether the magnitudes of our estimates are consistent.

Finally, we were interested in shared etiology among general measures of internalizing and externalizing psychopathology, but it could be the case that SLEs or trauma share etiological factors with only certain aspects of each form of psychopathology (i.e., just with MDD or just with CD). Researchers interested in differentiating disorders could conduct similar analyses to ours while focusing on disorders within one higher-order dimension of psychopathology rather than across both.

Study 3: Gene-Based Tests of GWAS Data on SLEs, Trauma, and Psychopathology

Introduction

Genome-Wide Association Studies (GWAS) are currently the primary tool used to identify genetic variants underlying phenotypic variation. Although GWAS require large sample sizes, the potential to search the entire genome for variants associated with any given variable on

which individuals differ has led researchers to conduct GWAS of many traits. Researchers often conduct GWAS of aspects of internalizing and externalizing psychopathology that behavior genetic analyses have shown to be genetically influenced, such as MDD or CD (e.g. Dick et al., 2011; Wray et al., 2012). It is much rarer for researchers to conduct GWAS of the tendency to experience events such as stressful life events (SLEs) or trauma, even though exposure to these events is genetically influenced, as demonstrated in Study 2. Further, due to the analytic and computational complexity of GWAS, most researchers treat both sides of the genotype-phenotype causal model of these traits as univariate and comprised of additive components. Nevertheless, (1) single nucleotide polymorphisms (SNPs) tend to cluster together in patterns called linkage disequilibrium (LD) within genes, (2) measures of phenotypes often characterized using sum scores often are better characterized as differential indicators of latent traits (as seen in Study 1), and (3) phenotypes are often correlated and have common genetic influences (as seen in Study 2). The use of gene-based tests with multivariate phenotypes is a novel approach to handling these complexities that has demonstrated increased power to detect sources of genetic variation over traditional GWAS methods (Li et al., 2011; van der Sluis et al, 2013; van der Sluis et al., 2015). In the current study, we aimed to apply these techniques to the tendency to experience SLEs, trauma, and internalizing and externalizing psychopathology.

Molecular Genetic Studies of Psychopathology, SLEs, and Trauma

Researchers have used molecular genetic techniques to identify genetic variants associated with aspects of internalizing and externalizing psychopathology, although no studies have used factors derived from CFA to measure these variables in search for associated variants within or across forms of psychopathology. Within internalizing psychopathology, MDD has been a particular focus; many studies of candidate genes (reviewed by Bosker et al., 2011) and

GWAS (reviewed by Wray et al., 2012) have been conducted. Though there have been many positive findings reported by candidate gene studies, none have replicated consistently in meta-analyses (e.g., Risch et al., 2009) or in GWAS (Bosker et al., 2011). GWAS methods have also yet to identify replicable risk loci for MDD (e.g., Wray et al., 2012). The largest GWAS of MDD thus far, which included 18,759 individuals, had no genome-wide significant SNPs (Ripke et al., 2013). Similarly, candidate gene studies of anxiety generally have not stood the test of replication and GWAS methods have returned limited evidence (reviewed by Sokolowska & Hovatta, 2013; Trzaskowski et al., 2013). Some researchers have investigated multivariate associations across disorders or used samples of individuals co-occurring internalizing disorders. For example, there is limited evidence that SNPs associated with MDD may also be associated with bipolar disorder (McMahon et al., 2010; Ripke et al., 2013). Another study found evidence suggestive of SNPs associated with comorbid anxiety and MDD, though the study was relatively underpowered (Schosser et al., 2013). Further, one study found and replicated associations between SNPs in the *PPARGC1A* gene, which encodes a transcriptional coactivator concentrated in GABAergic interneurons that may provide neuroprotection, and internalizing psychopathology using evidence from mouse linkage scans and knockout studies, human linkage scans, and human GWAS (Hettema et al., 2011).Taken together, molecular genetic evidence suggests that particular variants may be associated with risk for internalizing psychopathology broadly, though there has yet to be a genome-wide study that has used a latent internalizing psychopathology factor as a phenotype.

Externalizing psychopathology has also been studied using molecular genetic methods. Similar to studies of internalizing disorders, candidate gene studies of particular externalizing disorders and general externalizing psychopathology have reported several positive results that

have failed to replicate consistently (reviewed by Dick et al., 2011; Ficks & Waldman, 2014; Gizer et al., 2009; Vassos et al., 2013). A GWAS of CD symptoms found four markers that met criteria for genome-wide significance along with several other suggestive signals (Dick et al., 2011). A GWAS of antisocial personality disorder symptoms did not find any significant associations and did not replicate the findings of Dick et al. (2011) (Tielbeek et al., 2012). Promisingly, one study found that polygenic risk scores were associated with externalizing disorders broadly in young adults and adolescents (Salvatore et al., 2014) In contrast, GWAS of various aspects of substance use and abuse have successfully detected and replicated SNP associations, including SNPs within genes for nicotinic receptors and enzymes (Saccone et al., 2010; Thorgeirsson et al., 2008) and other loci (Schumann et al., 2011). Most studies have not tested multivariate associations across externalizing phenotypes. Nevertheless, one study that conducted a GWAS of nicotine use, alcohol consumption, alcohol dependence, illicit drug use, and non-substance related behavioral disinhibition found 13 SNPs that demonstrated suggestive but not genome-wide significant association across multiple phenotypes (McGue et al., 2013). Thus, though behavior genetic studies have demonstrated a latent externalizing factor that is primarily genetic, no GWAS have directly tested the association of SNPs with a latent externalizing factor.

Few studies have used molecular genetic techniques to investigate the genetic correlation between internalizing and externalizing disorders. One GWAS in a small sample of individuals with comorbid alcohol dependence and MDD (467 cases and 407 controls) found several suggestive SNPs and reported that the degree of overlap of nominally significant SNPs between a comorbid phenotype and univariate MDD or alcohol dependence was modest (Edwards et al., 2012). A large scale GWAS meta-analysis in a sample of 33,332 cases and 27,888 controls of

autism spectrum disorder, ADHD, bipolar disorder, MDD, and schizophrenia found that SNPs at four loci were genome-wide significant and aggregate polygenic risk scores showed cross-disorder associations with bipolar disorder, MDD, and schizophrenia (Smoller et al., 2013). Pathway analysis of these results indicated a role for genes involved in calcium channel signaling for all five disorders, and genes with evidence of cross-disorder association were likely to be expressed in the brain. A follow-up study examined whether there were copy number variants with multivariate associations with depression, schizophrenia, and autism spectrum disorders, with no significant associations (O'Dushlaine et al., 2014). Another follow-up study estimated the genetic correlations explained by common SNPs among autism spectrum disorder, ADHD, bipolar disorder, MDD, and schizophrenia, finding that genetic correlations were high between schizophrenia and bipolar disorder, moderate between schizophrenia and MDD, bipolar disorder and MDD, and ADHD and MDD, low between schizophrenia and autism spectrum disorders, and non-significant for other pairs of disorders (Lee et al., 2013). Thus, there is limited but promising evidence that molecular genetic techniques can identify variants underlying common genetic influence on internalizing and externalizing disorders.

By contrast, the molecular genetic literature examining SLEs or trauma is in its infancy. In fact, there is only one study in which GWAS of SLEs were conducted (Power et al., 2013). The researchers found one SNP on Chromosome 1 (rs4927134) that demonstrated genome-wide significance in association with dependent SLEs (and none with independent SLEs) in a sample of 2,578 individuals. This finding did not replicate in smaller samples (Power et al., 2013). There are no published research reports on GWAS of trauma exposure. Thus, the genetic makeup of how individuals differ in their exposure to SLEs and trauma, and whether those genes also predispose individuals to exhibiting psychopathology, remains essentially unknown.

Although researchers have used multivariate behavior genetic techniques to identify traits that share genetic influences and quantify the magnitude of influences shared between them, GWAS are generally univariate in nature. Due to the difficulty of reliably detecting genetic variants significantly associated with one trait, researchers have tended to assume that multivariate GWAS would prove even more difficult (van der Sluis et al., 2013). Nevertheless, recently developed methods have demonstrated that multivariate GWAS methods are actually more powerful than univariate methods when the actual causal model is phenotypically and genetically complex, as is almost always the case (van der Sluis et al., 2013; van der Sluis et al., 2015). Further, these methods are sensitive to both genetic variants common to multiple phenotypes and genetic variants specific to a single phenotype, thus providing a more comprehensive view of the genetic architecture of complex traits (van der Sluis et al., 2013; van der Sluis et al., 2015).

Current Study

In the current study, we expanded upon previous GWAS of SLEs, trauma exposure, and internalizing and externalizing psychopathology in several major ways. First, we used a latent variable approach to modeling each variable across multiple items. This approach allowed us to measure the commonalities among items on each measure while excluding item-specific variance and measurement error. Latent variable modeling frameworks tend to be more powerful than simply summing items (e.g., Muthén & Curran, 1997), but are rarely used in combination with GWAS methods.

Second, we conducted omnibus gene-based tests of multiple markers within each gene and its flanking regions. Gene-based tests maximize the amount of genetic variation analyzed simultaneously and can provide substantially increased power to detect association, particularly

in moderate sample sizes (e.g., Li, et al., 2011; Liu et al., 2010). Genes are the functional unit of the genome, as individual SNPs' effects are expressed jointly upon the gene as a whole. Thus, gene-based tests may provide a more biologically and conceptually relevant framework than SNP-based tests. Further, this method greatly reduces the number of tests conducted, reducing the degree to which results must be corrected for multiple testing.

Third, we used a novel multivariate approach to the analysis of GWAS data that has been shown to be more powerful than constituent univariate approaches and rival multivariate methods (van der Sluis et al., 2013; van der Sluis et al., 2015). This method is particularly appropriate for traits that are not only correlated but have demonstrated common genetic influences, such as trauma and internalizing psychopathology, dependent SLEs and externalizing psychopathology, and internalizing and externalizing psychopathology (see Study 2).

In summary, these analyses have the potential to identify starting points of biological pathways between genetic variation and behavior, clarify how individual differences in biology can influence differential exposure to stressful events, and provide a model for how those individual differences in biology could also influence psychopathology.

Method

Participants

The sample is comprised of several thousand urban, low-income, predominantly African American men and women (described by Gillespie et al., 2009). Full genetic and phenotype data was available for 4,647 individuals. Participants ranged in age between 18 and 90, with a mean

of 40.2 (SD = 14.0), 73% of participants were female, and 93% of participants identified as African American, 3% identified as Caucasian, 2% identified as Mixed, and 2% identified as Other, Asian, or Hispanic/Latino. Initial interviews were performed with participants approached in the waiting rooms of primary care or obstetrical-gynecological clinics of Grady Memorial Hospital in Atlanta, Georgia starting in 2005. Participant recruitment took place Monday-Friday during regular clinic hours. Participants were approached while waiting for appointments in the primary care and obstetrical-gynecological clinics by a member of the research team and solicited for study participation. Participants were informed at the time of initial contact that the study in which they were being asked to participate examined trauma exposure during childhood and adulthood. Those participants who agreed to participate completed a battery of self-report measures obtained by verbal interview which took 45 to 75 minutes to complete. Participants also provided DNA samples via salvia collected in Oragene vials (DNA Genotek Inc., Ottawa, Ontario Canada). Participants who agreed to continue participation were invited to take part in a second, more in-depth phase of the study, but data collected beyond the first phase was not used in the current research. Data was pulled for these analyses in August of 2014, although data collection continues through the present.

Measures

Stressful Events Questionnaire II

The Stressful Events Questionnaire II (SEQ-II) is a 16 item questionnaire designed for use in the Grady Trauma Project. Participants were prompted by the interviewer stating “I’m going to ask you some questions about stressful events people sometimes experience. Please tell me if the events have ever happened to you. If so, when was the most recent time?” Items include “loss of a confidant/loved one,” “chronic health problems or life threatening illness,”

"home invasion/robbery/burglary," "murder of close friend/relative," "fired from job or had serious problems at work," "homeless, living in the shelter/on streets," "homeless with temporary or unplanned housing," "evicted from house or apartment," "inadequate financial resources or support to obtain food for family," "lived in a neighborhood you felt was unsafe," "child/spouse/significant other/other family member in prison/jail," "unplanned/unwanted pregnancy," "divorced," "cared or raised children other than your own because their parents unable to care for them," "your children raised by others because you were not able to care for them," and "please describe most stressful event experienced in last month." The final item was used in analyses. Participants were able to respond with "never happened to me," "within the last month," "within the last 6 months," "within the last year," "within the last 5 years," or "more than 5 years ago." Responses were dichotomized to represent the presence or absence of each SLE during each individual's lifetime.

Based on the results of Study 1, SLEs were sorted into dependent and independent SLE dimensions (see Table 1.1).

Traumatic Events Inventory

The Traumatic Events Inventory (TEI) is a screening instrument for lifetime history of traumatic events (Schwartz et al., 2005, 2006; Binder et al., 2008). For each traumatic event, the TEI assesses experiencing and witnessing of events separately. Participants were asked the number of times they have experienced or witnessed each event and their age at the first and most recent exposure. Traumatic events that are included in the TEI are natural disasters, serious accident or injuries, sudden life-threatening illnesses, military combat, close friend or family member murdered, attacked with a weapon, attacked without a weapon, violence between parents as a child, beaten as a child, insulted by parents as a child, sexual abuse as a child or

teenager, and rape or sexual assault as an adult. The number of times each event was witnessed or experienced during the individual's lifetime was used in all analyses.

Traumatic events were sorted into witnessed assault, experienced assault, witnessed non-assault, and experienced non-assault dimensions based on the results of Study 2 (see Table 1.2).

Internalizing Psychopathology Measures

Beck Depression Inventory. Depressed mood was assessed with the 21-item Beck Depression Inventory, Second Edition (BDI-II) (Beck et al., 1996), a commonly used ordinal measure of level of depressive symptoms (Beck et al., 1996) over the last two weeks. The BDI-II assesses sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleeping patterns, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, and loss of interest in sex. Each item is scored on a 0-3 Likert scale and was treated as a separate, ordinal variable.

Anxiety Sensitivity Inventory. Anxiety sensitivity was assessed using the 16-item Anxiety Sensitivity Inventory (ASI) (Reiss et al., 1986), a commonly used measure of the level of belief that anxiety experiences have negative implications and is predictive of but distinct from anxiety-related disorders and depression (reviewed by Deacon et al., 2003). The ASI items include "it is important for me not to appear nervous," "when I cannot keep my mind on a task, I worry I might be going crazy," "it scares me when I feel shaky," "it scare me when I feel faint," "it is important to me to stay in control of my emotions," "it scares me when my heart beats rapidly," "it embarrasses me when my stomach growls," "it scares me when I am nauseous," "when I notice that my heart is beating rapidly, I worry that I might have had a heart attack," "it scares me when I become short of breath," "when my stomach is upset, I worry that I might be

seriously ill," "it scares we when I am unable to keep my mind on a task," "other people notice when I feel shaky," "unusual body sensations scare me," "when I am nervous, I worry that I might be mentally ill," and "it scares me when I am nervous." Items are scored on a 0-4 Likert scale from "very little" to "very much." Likert scale scores for each item were included as separate, ordinal variables.

Items from the BDI-II and ASI loaded onto a single internalizing psychopathology latent variable as reported in Study 1.

Externalizing Psychopathology Measures

***BQ*.** The Behavior Questionnaire (BQ) is a measure developed for the Grady Trauma Project that measures violent behavior. Participants were prompted by the interviewer saying "No matter how well people get along, there are times when they disagree, get annoyed with another person, or have confrontations or fights for other reasons. Below is a list of things that might happen when you have differences, when you feel upset, or for other reasons. Please mark if you have ever done the following things in your lifetime." The 6 included items are "pushed or shoved someone," "pulled a knife or gun on someone," "stabbed or shot someone," "punched or hit someone with something that could hurt," and "beat up someone." Potential responses include "never," "once," "several times," "many times," and "more times than I can count." Item responses were coded as ordinal variables and included separately in the analyses.

Alcohol Use Disorders Identification Test. The Alcohol Use Disorders Identification Test is a commonly used 10-item screening instrument for hazardous and harmful alcohol consumption that covers the domains of alcohol consumption, drinking behavior, and alcohol-related problems (Saunders et al., 1993). The AUDIT screens for drinking frequency, number of drinks per drinking episode, how often six or more drinks are consumed, frequency of inability

to stop drinking, frequency of failure to meet expectations because of drinking, frequency of needing to drink in the morning, frequency of guilt or remorse after drinking, frequency of memory disturbances due to drinking, injuries related to drinking, and concerns of others about level of drinking. Each item is scored on a 0-4 scale and was included in the analyses as ordinal.

Drug Abuse Screening Test. The Drug Abuse Screening Test (DAST) is a commonly used 20-item screening instrument for problematic substance use (Skinner, 1982). The DAST screens for drug use, drug abuse, ability to stop using drugs, blackouts, guilt from drug use, family complaints about drug use, neglect of family because of drug use, illegal activities related to drug use, withdrawal symptoms from drug use, and medical problems related to drug use. Responses to the DAST were given as binary items and were included in the analyses as separate, binary variables.

Items from the BQ, AUDIT, and DAST loaded onto a single externalizing psychopathology latent variable as reported in Study 1. Factor scores on that latent variable for each individual were estimated and saved from the analyses in Study 1 and used in the genetic association analyses.

DNA Extraction and Genotyping

DNA from saliva was collected in Oragene vials (DNA Genotek Inc., Ottawa, Ontario, Canada) and extracted using the DNAdvance extraction kit (Beckman Coulter Genomics, Danvers, MA). All DNA for genotyping was quantified by gel electrophoresis with Quantity One (Bio-Rad, Hercules, CA) and then normalized to 400 ng. Using the Illumina Human Omni1-Quad BeadChip (Illumina Inc.), SNP genotyping was performed according to instructions by the manufacturer.

Sample and SNP Quality Control

First, SNPs with a callrate < 98% (i.e., successful genotyping rate), a minor allele frequency (MAF) below 1% and deviation from Hardy-Weinberg-Equilibrium (p-value < e-06) were removed from further analysis. This step removes SNPs that were not well genotyped or have such low MAFs that they are susceptible to genotyping errors. Individuals with a callrate below 95% across all SNPs were also removed. In this dataset, we checked for relatedness and multidimensional scaling (MDS)-outliers. This process, similar to principal components analysis, helps to identify individuals who may be genetically related and thus may contribute to spurious associations due to lack of independence of observations. Any individual deviating more than 6 SD from the mean on any of the first ten MDS-components was not taken further into analysis. Afterwards, any outliers on heterozygosity, defined as deviating more than 5 SD from the mean heterozygosity over all individuals, were also removed. This removes individuals that have too high or too low levels of heterozygosity, the fraction of non-missing genotype calls that are heterozygous, which may indicate contaminated DNA samples. This cleaned dataset was prepared for imputation by removing AT and CG SNPs (further described below). Removing AT and CG SNPs helps with imputation because these SNPs are difficult to align between strands and not all SNPs are required for imputation.

Imputation

Imputation is a process that infers sporadic missing genotypes and genotypes for ungenotyped markers that have been genotyped in a reference panel. Essentially, imputation allows researchers to make an educated guess at individuals' genotypes at ungenotyped markers or when there is missing data by using correlation patterns between SNPs in a large, heavily genotyped reference panel. This process allows researchers to test associations with many more SNPs than were directly genotyped. Imputation was performed using shapeit2

(https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html) and impute2 (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html) using the 1000 Genomes Project database as a reference sample (Phase I integrated haplotypes sample released in June 2014). This provided dosage values for each of these markers. Dosage values are defined as 0xP(AA) + 1xP(AB) + 2xP(BB), where A is the major allele, B is the minor allele, and P(AA), P(AB), P(BB) are the probabilities of having two major alleles, one major and one minor allele, and two minor alleles, respectively. This process also outputs an INFO score, which is a measure of imputation quality defined as the estimated squared correlation between the estimated allele dosage with the highest posterior probability and the true allele dosage for the marker. After imputation, imputed genotypes underwent another quality control step using qctool (http://www.well.ox.ac.uk/~gav/qctool) removing any markers with INFO scores below 0.8 and HWE deviation (p-value < e-06). Finally, SNPs with a MAF below 3% were removed. These final steps were taken in order to ensure that only well-imputed SNPs that are less susceptible to error due to low MAF were included in the analyses.

The total number of genotyped and imputed quality controlled SNPs was 9,939,746. To control for population stratification, a systemic difference in allele frequencies between ethnic populations that can produce spurious associations, we conducted principle components analyses and generated eight principle components which were controlled for in all analyses.

Analyses

Univariate Genome Wide Association Analyses of SNPs. As in Study 1, raw residuals with means of 0 and unconstrained variance for each item were generated by regressing each item on age, age squared, sex, age X sex, and sex X age squared in SPSS version 22.0 in order to account for mean level age and sex differences in the variables of interest (McGue & Bouchard,

1984). Factor scores on each latent variable for each individual were estimated and saved from the analyses in Study 1 and used in the genetic association analyses. Eight univariate SNP-based association analyses were conducted using PLINK version 1.9 (Purcell et al., 2007) to search for SNPs associated with witnessed assault trauma, experienced assault trauma, witnessed non-assault trauma, experienced non-assault trauma, independent SLEs, dependent SLEs, internalizing psychopathology, and externalizing psychopathology. It is important to note that these univariate GWASs were used as a prelude to conducting the multivariate GWASs of interest. Imputed data in dosage format were used in the analyses, thus the 'dosage' option in plink was used, which treats dosage data as continuous and regresses phenotype data on these values. Eight principle components were controlled for in all analyses in order to control for the effects of population stratification. We used the standard genome-wide significance cutoff of $p < 5x10^{-8}$ as an index of statistical significance. In addition to nominal significance, critical thresholds for significance were evaluated using False Discovery Rate (FDR; Benjamini & Hochberg, 1995).

Gene-Based Tests of Association. We used the statistical genetics package KGG (Li et al., 2011; Li et al., 2012) to test whether there were any genes associated with any of the eight outcome variables. Gene-based tests, such as those used in this study, combine the association statistics (e.g., p-values) for each of the constituent markers within a gene and its flanking region with the linkage disequilibrium (LD) among those markers. These tests can have advantages over more conventional SNP-based tests, including higher effect sizes if multiple markers within the gene contribute to its association with a trait and a lower threshold for assessing statistical significance due to a reduction in number of tests conducted (Li et al., 2011; Li et al., 2012; Neale & Sham, 2004). Specifically, in this study we used the HYST gene-based test (hybrid set-

based test for genome-wide association studies; Li et al., 2012). This test first combines the independent statistics of SNPs within regions of high LD (i.e., LD blocks) and then combines results across the different LD blocks within each gene using a scaled chi-square test (Li et al., 2012). In the gene-based tests, we evaluated SNPs within each gene and 10 kilobases of its 5' and 3' flanking regions.

We also conducted multivariate gene-based tests of association using MGAS (Multivariate Gene-based Association test by extended Simes procedure) (van der Sluis et al., 2015). MGAS combines SNP p-values obtained from standard univariate GWAS results of multiple correlated traits to construct a multivariate gene-based p-value. Analogous to the univariate HYST gene-based test, MGAS combines the association statistics for each trait considering the phenotypic correlations among the multiple traits included in the multivariate gene-based analysis. In order to reduce the number of tests conducted and to apply a more conservative analytic strategy given we only had one sample, we only conducted MGAS analyses on combinations of variables that demonstrated common genetic influences in Study 2 (i.e., trauma and internalizing psychopathology, dependent SLEs and externalizing psychopathology, and internalizing and externalizing psychopathology) and on the four trauma variables given the lack of information about common genetic influences based on the available trauma measure in Study 2.

Results

Univariate Genome Wide Association Analyses of SNPs

We conducted eight univariate, SNP-based genome-wide association studies to search for SNPs associated with witnessed assault trauma, experienced assault trauma, witnessed non-assault trauma, experienced non-assault trauma, independent SLEs, dependent SLEs,

internalizing psychopathology, and externalizing psychopathology. We calculated the genomic inflation factor, the ratio of the median of the observed distribution of the GWAS test statistics to the expected median, for each phenotype. Extreme deviations in the genomic inflation factor indicate an excess false-positive rate in a GWAS, which may be attributed to technical issues or uncontrolled population stratification. There was no evidence of genomic inflation for any of the phenotypes, as the inflation factor values were < 1.01. SNP association results uncorrected for genomic inflation were thus interpreted and used in the gene-based tests of association.

Results are shown in the SNP QQ-plots in Figures 3.1 through 3.8. Results for all SNPs with $p < 1x10^{-6}$ are presented in Table 3.1 through Table 3.8. For internalizing psychopathology, there were no genome-wide significant SNPs by nominal significance or FDR (threshold = $1.75x10^{-7}$). The minimum *p*-value = $2.21x10^{-7}$ for rs200174320 at position 75042981 on chromosome 2.

For externalizing psychopathology, there were no genome-wide significant SNPs by nominal significance, but eight significant SNPs by FDR (threshold = $5.86x10^{-7}$). The minimum *p*-value = $7.65x10^{-8}$ for rs9984249 at position 19044655 on chromosome 21.

For dependent SLEs, there were no genome-wide significant SNPs by nominal significance, but one significant SNP by FDR (threshold = $7.70x10^{-8}$). The minimum *p*-value = $7.03x10^{-8}$ for rs62126043 at position 49039858 on chromosome 19.

For independent SLEs, there were no genome-wide significant SNPs by nominal significance or FDR (threshold = $1.24x10^{-7}$). The minimum *p*-value = $1.29x10^{-7}$ for rs645295 at position 4400680 on chromosome 20.

For witnessed non-assault trauma, there were no genome-wide significant SNPs by nominal significance, but two significant SNPs by FDR (threshold = 1.76×10^{-7}). The minimum *p*-value = 7.31×10^{-8} for rs11872391 at position 77303624 on chromosome 18.

For witnessed assault trauma, there were nine genome-wide significant SNPs by nominal significance and six by FDR (threshold = 7.23×10^{-9}). The minimum *p*-value = 3.96×10^{-9} for rs149978953 at position 9557833 on chromosome 4.

For experienced non-assault trauma, there was one genome-wide significant SNP by nominal significance and FDR (threshold = 3.61×10^{-8}). The minimum *p*-value = 2.98×10^{-8} for rs56389657 at position 38771365 on chromosome 2.

For experienced assault trauma, there were four genome-wide significant SNPs by nominal significance and twelve by FDR (threshold = 1.16×10^{-7}). The minimum *p*-value = 1.62×10^{-8} for rs142711911 at position 2571763 on chromosome 1.

Univariate Gene-Based Tests of Association

We then conducted gene-based tests of association, which combine results across SNPs within and near each gene, for each phenotype separately using the HYST test in the program KGG (Li et al., 2012). We used FDR to evaluate significance of genes. Results are shown in the gene QQ plots in Figures 3.1 through 3.8 and the gene Manhattan plots in Figures 3.9 through 3.16. Results for all genes with $p < .0001$ are presented in Tables 3.9 through 3.16.

For internalizing psychopathology, independent SLEs, witnessed non-assault trauma, and experienced non-assault trauma, no genes were genome-wide significant by FDR.

For externalizing psychopathology, one gene was genome-wide significant by FDR (see Table 3.10), which was *SDK2* (*p*-value = 6.25×10^{-7}), starting at position 71330522 on chromosome 17.

For dependent SLEs, six genes were genome-wide significant by FDR (see Table 3.11). The most strongly associated gene was *CGB5* (*p*-value = 9.93×10^{-7}), starting at position 49547101 on chromosome 19.

For witnessed assault trauma, one gene was genome-wide significant by FDR (see Table 3.14), which was *MIR548I2* (*p*-value = 9.24×10^{-8}), starting at position 9557788 on chromosome 4.

For experienced assault trauma, six genes were genome-wide significant by FDR (See Table 3.16). The most strongly associated gene was *LOC100996583* (*p*-value = 2.36×10^{-7}), starting at position 2497973 on chromosome 1.

Multivariate Gene-Based Tests of Association

Finally, we conducted multivariate gene-based tests of association using the MGAS feature of KGG (van der Sluis et al., 2015). We chose to perform multivariate gene-based tests only on combinations of variables that demonstrated common genetic influences in Study 2 (i.e., trauma and internalizing psychopathology, dependent SLEs and externalizing psychopathology, and internalizing and externalizing psychopathology) in order to reduce the number of tests conducted. We also performed a multivariate gene-based test of the four trauma variables (i.e., witnessed assault, witnessed non-assault, experienced assault, experienced non-assault), as Study 2 was only able to estimate influences on a general trauma variable. We used FDR to evaluate the significance of the multivariate association of genes with combinations of phenotypes. Results are shown in the gene Manhattan plots in Figures 3.17 through 3.20.

For the four trauma variables, five genes were significant by FDR (threshold = 7.86×10^{-6}). The minimum p-value = 5.62×10^{-7} for *MIR548I2* starting at position 9557788 on chromosome 4. Results for all genes with $p < .0001$ are presented in Table 3.17.

For the four trauma variables and internalizing psychopathology, five genes were significant by FDR (threshold = 9.19×10^{-6}). The minimum p-value = 7.03×10^{-7} for *MIR548I2* starting at position 9557788 on chromosome 4. Results for all genes with $p < .0001$ are presented in Table 3.18.

For dependent SLEs and externalizing psychopathology, six genes were significant by FDR (threshold = 8.44×10^{-6}). The minimum p-value = 1.40×10^{-6} for *SNAR-G2* starting at position 49534925 on chromosome 19. Results for all genes with $p < .0001$ are presented in Table 3.19.

For internalizing and externalizing psychopathology, no genes were significant by FDR (threshold = 1.08×10^{-4}). The minimum p-value = 1.10×10^{-4} for *OR1I1* starting at position 15197876 on chromosome 19. Results for the genes with the five lowest *p*-values are presented in Table 3.20.

Discussion

In the current study, we used a latent variable modeling approach to characterize aspects of SLEs, trauma, and psychopathology and performed univariate SNP-based GWAS analyses, univariate gene-based GWAS analyses, and multivariate gene-based GWAS analyses. In the univariate SNP-based analyses, we found no SNPs associated with internalizing psychopathology or independent SLEs. There were eight SNPs associated with externalizing psychopathology, one SNP associated with dependent SLEs, two SNPs associated with witnessed non-assault trauma, six SNPs associated with witnessed assault trauma, one SNP associated with experienced non-assault trauma, and twelve SNPs associated with experienced assault trauma. In the univariate gene-based analyses, there were no genes associated with internalizing psychopathology, independent SLEs, witnessed non-assault trauma, or experience

non-assault trauma. One gene was associated with externalizing psychopathology, six genes were associated with dependent SLEs, one gene was associated with witnessed assault trauma, and six genes were associated with experienced assault trauma. In the multivariate gene-based analyses, there were five genes associated with the four trauma variables, five genes associated with the four trauma variables and internalizing psychopathology, six genes associated with dependent SLEs and externalizing psychopathology, and no genes associated with internalizing and externalizing psychopathology.

We considered the univariate SNP-based analyses to be a pre-processing step for the more powerful and novel univariate gene-based analyses and thus did not interpret the results beyond noting that (1) variables with more significant SNP-based associations tended to also have more significant gene-based associations; and (2) we found more significant SNPs than the typical GWAS of similar sample size of these variables, providing support for the utility of latent variable modeling in GWAS.

Univariate Gene-Based Results

The sole gene associated with externalizing psychopathology was *SDK2*, a protein-coding gene on chromosome 17 that encodes Sidekick Cell Adhesion Molecule 2, a protein that guides axonal terminals to specific synapses in developing neurons. This protein is a member of the immunoglobulin superfamily. Interestingly, a SNP in this gene (rs3816995) was found to be associated with panic disorder in a GWAS in the Japanese population (Otowa et al., 2009). This same SNP approached significance in another study of candidate SNPs for panic disorder (Subaran et al., 2012). Further, upregulation of Sidekick Cell Adhesion Molecule 1, a related protein, occurs after chronic cocaine use in rodent models and promotes both cocaine's behavioral effects and induction of dendritic plasticity in the nucleus accumbens (Scobie et al.,

2014). Thus, this gene has been implicated in several aspects of psychopathology, including aspects of externalizing psychopathology, using diverse methods. Future studies should focus on determining the degree to which this gene is truly involved in human behavior.

Of the six genes associated with dependent SLEs, five genes are close in genetic distance on chromosome 19. Four of these genes, *CGB1*, *CGB2*, *CGB5*, and *CGB8*, encode for the beta 5, 1, 2, and 8 subunits of chorionic gonadotropin. Chorionic gonadotropin is produced by the placenta during pregnancy and stimulates the ovaries to synthesize the steroids that are essential for the maintenance of pregnancy. The beta subunit of chorionic gonadotropin is encoded by 6 genes on chromosome 19q13.3, four of which were significantly associated with dependent SLEs. Several studies have found variants in these genes to be associated with recurrent miscarriages (Rull et al., 2008; Rull et al., 2013) and maternal breast cancer (Chen et al., 2008). The connection between these phenotypes and the tendency to experience dependent SLEs is not immediately clear. Interestingly, *CGB5* was also significantly associated with experienced assault trauma in this sample (see below). The other associated gene in this region of chromosome 19, *SNAR-G2* is a noncoding RNA gene thought to include transcription factors that affect the expression of chorionic gonadotropin genes (Parrott et al., 2010). The sixth associated gene, *LOC100996583*, is a gene of unknown function on chromosome 1. Interestingly, this gene and others around it on chromosome 1 were associated with experienced assault trauma and showed suggestive signals for associated with independent SLEs and experienced non-assault trauma. As mentioned in Study 2, it is highly unlikely that these genes directly influence an individual's tendency to experience stressful events; it is more likely that their effects are mediated by personality characteristics which in turn influence an individual's likelihood to self-select into risky environments. More research is needed to determine how these genes may be

connected to personality characteristics such as sensation seeking or negative affect (Baker et al., 1992; Lauterback & Vrana, 2001; Koopmans et al., 1995; Mroczek & Almeida, 2004; Smith, Ptacek, & Smoll, 1992). This work could illuminate both biological processes underlying personality and gene-environment correlation.

One gene, *MIR548I2* on chromosome 4, was associated with witnessed assault trauma. This gene encodes microRNA 548i-2. MicroRNAs are short non-coding RNAs that are involved in post-transcriptional regulation of gene expression by affecting both the stability and translation of messenger RNA. This particular microRNA has not been found to have associations with any traits and its target genes have not yet been identified, but microRNAs generally have been identified as potent regulators of gene expression and implicated various biological development processes and disease progression (Duan et al., 2009). More research is needed to determine the targets of microRNA 548i-2 and its pathway to behavior affecting the likelihood of witnessing assault.

There were 6 genes associated with experienced assault trauma, 5 of which, *LOC100996583, TTC34, TNFRSF14, MMEL1,* and *FAM213B*, fall in close proximity to each other on chromosome 1. As mentioned above, *LOC100996583* was also associated with dependent SLEs, and several of these genes had suggestive association signals with independent SLEs and experienced non-assault trauma. *TTC34* encodes Teratricopeptide Repeat Domain 34. There is evidence that this protein may be associated with Systemic Lupus Erythematosus, an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue, including brain (Ross, 2014). *TNFRSF14* encodes Tumor Necrosis Factor Receptor Superfamily, Member 14, a protein that functions in signal transduction pathways to activate inflammatory and inhibitory T-cell immune response. It binds herpes simplex virus, mediating its entry into

cells. It also has been associated with follicular lymphoma (e.g., Cheung et al., 2010), rheumatoid arthritis and coeliac disease (Coenen et al., 2009). Thus, it is clear that this gene plays a role in physical health problems, yet it remains to be clarified how it influences differential exposure to experienced assault trauma. *MMEL1* encodes Membrane Metallo-Endopeptidase-Like 1. This protein is a member of a family of proteins that plays an important role in pain perception, arterial pressure regulation, phosphate metabolism and homeostasis. It is expressed mainly in testis but also in the brain, kidney, and heart. It has also been associated with primary biliary cirrhosis and multiple sclerosis (Ban et al., 2010; Hirschfield et al., 2010). Pain perception may influence a patient's likelihood to remember trauma and thus their likelihood to report it. *FAM213B* encodes Family With Sequence Similarity 213, Member B. This protein catalyzes the reduction of prostaglandin-ethanolamide H(2) to prostamide F(2alpha), a process involved in inflammatory signaling (Vasilache, Qian, & Blomqvist, 2015). This protein has demonstrated association with syndromic obesity (Vuillaume et al., 2014) and intellectual disability (Waltl, 2015). These genes on chromosome 1 are quite close in proximity and likely in high LD, and thus determining the true source of the signal is difficult. Due to their apparent involvement in distinct aspects of differential stress exposure, future research should disentangle these LD patterns in order to locate more precisely the source of these associations. This argument also applies to *CGB5* on chromosome 19, which was also significantly associated with experienced assault trauma and dependent SLEs.

Looking across these results, it appears that regions on chromosome 1 and chromosome 19 are associated with the tendency to experience several different forms of stress. Although dependent SLEs and trauma exposure did not show common genetic influences in Study 2, it could be the case that different genetic influences are in effect in adults, African Americans, or

highly traumatized individuals. Further, it could be the case that differences in power due to differences in sample size between the samples are responsible for this discrepancy. Regardless, suggestive or significant signals from these regions across multiple related forms of stressful event suggests that these regions are involved in the tendency to experience stress generally.

Multivariate Gene-Based Test Results

The multivariate gene-based results generally support inferences made from the univariate results. Multivariate analyses of all four forms of trauma revealed that *MIR548I2, TNFRSF14, LOC1000996583,* and *FAM213B,* all genes with at least one significant univariate association, were significantly related to the multivariate trauma phenotype. *GEMIN6*, a gene on chromosome 2 that encodes Gem Associated Protein 6, also demonstrated a multivariate association. This protein is part of a large macromolecular complex, localized to both the cytoplasm and nucleus of cells, which plays a role in the assembly of proteins involved in RNA splicing. Defects in this gene appear to affect rates of motor neuron issues, birth defects, and muscular atrophy (Ma et al., 2005; Pellizzoni et al., 2002; Wirth, Brichta, & Hahnen, 2006).

Multivariate analyses of all four trauma variables and internalizing psychopathology yielded the same five significant genes (*MIR548I2*, *TNFRSF14, LOC1000996583, GEMIN6*, and *FAM213B*) in the same rank order as the multivariate analyses of just the four trauma variables. As noted above, univariate analyses of internalizing psychopathology yielded no significant associations. Further, each p-value from these analyses were slightly higher than those from the analyses of just the four trauma variables. In fact, all of the significant genes in these analyses had *p*-values > .20 in the internalizing psychopathology univariate analyses. Thus, it is highly likely that these results do not reflect genes that truly influence internalizing psychopathology. The MGAS algorithm used to conduct these analyses is powerful in detecting multivariate

signals and perhaps uncovering some signals that were not apparent in univariate analyses (such as *GEMIN6*), but is likely to produce the pattern of results seen here when only one of five variables included in multivariate analyses has null results.

Multivariate analyses of dependent SLEs and externalizing psychopathology yielded six significant genes clustered on chromosome 19, 5 of which (*SNAR-G2, CGB2, CGB5, CGB1,* and *CGB8*) had univariate associations with dependent SLEs. *SNAR-G2* is in the same region of chromosome 19 as the other associated genes and has a similar function to *SNAR-G1*. Each of this genes had *p*-values < .07 in the externalizing psychopathology univariate analyses, indicating that these genes may represent a true multivariate influence on dependent SLEs and externalizing psychopathology. These results suggest that disruptions in chorionic gonadotropin influence both the tendency to experience dependent SLEs and externalizing psychopathology, perhaps by influencing risk-taking behavior.

Finally, multivariate analyses yielded no significant genes associated with internalizing and externalizing psychopathology. This results is surprising given that internalizing and externalizing psychopathology have been found to have common genetic influences in a multitude of behavior genetic analyses (e.g., Cosgrove et al., 2011; Kendler et al., 2003). Nevertheless, univariate associations have been difficult to find and replicate in GWAS of aspects of internalizing and externalizing psychopathology (e.g., Dick et al., 2011; Wray et al., 2012). It may be the case that genetic variants influencing psychopathology are too rare or their genetic architecture too complex to be detected with the sample sizes found in this study and others. As researchers continue to increase sample sizes and willingness to collaborate, more significant and replicable findings will likely emerge due to increased power to examine rare and

complex genetic phenomena, as demonstrated by recent advances in discovering the genetics of schizophrenia (Sekar et al., 2016).

Taken together, our results provide an argument for the value of using univariate and multivariate gene-based tests as a method of learning more from standard GWAS analyses. Further, we detected more significant associations for SLE and trauma variables than for psychopathology variables. Although the genetics of psychopathology are far more frequently examined, elucidating the genetics of SLEs and trauma may not only provide insight into the biological process underlying differential exposure to the environment but also uncover biological pathways that lead to psychopathology. In addition, far more individuals have experienced SLEs and/or trauma than are able to endorse significant psychopathology, thus the sample size needed for adequate power is lower. We suggest that the viability of this approach be examined in further research.

Limitations and Future Directions

There are several limitations to this study that should be noted. First, although the sample size used in this study was fairly large, comprising 4,647 participants, it is still relatively underpowered to detect genome-wide associated SNPs with plausible effect size (e.g., that account for only ~.5% of the variance in the phenotype). Future studies with larger sample sizes are necessary to find reliable SNP associations that are likely to be replicated. Second, the results are based solely on analyses conducted in a single sample. Replication samples are becoming increasingly important before trusting GWAS results given the number of tests required. The use of gene-based and multivariate tests attenuate this concern somewhat, but replications of the associations reported in this study are necessary before considering them trustworthy. Beyond replication using GWAS, other methods of validating genetic associations include resequencing

of putatively associated genes, using animal models to examine the effects of silencing or amplifying genes or their products on relevant phenotypes. These methods could help to overcome the difficulty of finding the specific genes that contribute etiologically to SLEs, trauma, and psychopathology.

General Conclusions

We conducted three studies to attempt to answer the following questions: (1) what types of stressful life events (SLEs) or trauma confer the most risk for psychopathology; (2) does that risk differ for internalizing versus externalizing psychopathology; (3) to what degree are these relations causal versus due to shared etiology; and (4) does the tendency to experience SLEs or trauma share genetic or biological etiology with internalizing or externalizing psychopathology? It appears that dependent SLEs and experienced assault trauma confer the most risk for psychopathology. In the Twin Sample, SLEs and trauma conferred risk generally for psychopathology, whereas SLEs and trauma conferred more risk for externalizing than internalizing psychopathology in the Grady Sample. Trauma exposure and internalizing psychopathology shared genetic influences in the Twin Sample, although there were no significant SNPs or genes associated with internalizing psychopathology in the Grady Sample. Dependent SLEs and externalizing psychopathology also shared genetic influences in the Twin Sample and genes influencing chorionic gonadotropin demonstrated multivariate associations with these variables in the Grady Sample.

Although the results of Study 3 cannot be considered a replication of Study 2, their results provide convergent evidence. For example, of the four variables that demonstrated genetic influence in Study 2, three (trauma exposure, dependent SLEs, and externalizing psychopathology) were significantly associated with genes. Further, independent SLEs did not demonstrate genetic influence in Study 2 nor were associated with any genes in Study 3. The two variables (dependent SLEs and externalizing psychopathology) that demonstrated common genetic influences in Study 2 that had significant univariate GWAS findings in Study 3 also had significant multivariate associations with genes. Beyond providing convergent evidence, these

results demonstrate robustness to the demographic and methodological discrepancies between the samples.

Further, the results of Study 2 and Study 3 provide etiological evidence for the structural findings of Study 1. For example, although dependent and independent SLEs were highly correlated in both samples, each category of SLE was found to have primarily unique etiological influences in Study 2 and demonstrate different levels of genetic association in Study 3, lending support for the importance of distinguishing between them. This same pattern applies to the distinction between SLEs and trauma.

The structure, etiology, and causal nature of the relations among SLEs, trauma exposure, and psychopathology are complex, yet disentangling these complexities is essential to improving our ability to predict, differentiate, and treat psychopathology. Although much more research is needed to extend upon the current research, these findings suggest (1) that distinguishing between dimensions of SLEs and trauma is important; (2) that relations among SLEs, trauma, and psychopathology are primarily due to environmental influences, secondarily due to common genetic influences, and are primarily differentiated by unique genetic influences; and (3) several biological pathways that may uniquely or jointly influence these variables.

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Tables and Figures

Table 1.1: Alternative Dimensions of Stressful Life Events from the Stressful Events Questionnaire II in the Grady Sample

Stressful Life Event	Ind/Dependent	Loss/Humiliation/Entrapment
Lived in a neighborhood you felt was unsafe	Dependent	Entrapment
Unplanned/unwanted pregnancy	Dependent	Entrapment
Inadequate financial resources or support to obtain food for family	Dependent	Humiliation
Your child(ren) raised by others because unable to care	Dependent	Humiliation
Fired from job OR had serious problems at work	Dependent	Loss
Evicted from house or apartment	Dependent	Loss
Divorced	Dependent	Loss
Chronic health problems or life threatening illness	Independent	Entrapment
Homeless, living in shelter/on streets	Independent	Entrapment
Homeless with temporary or unplanned housing	Independent	Entrapment
Cared or raised children other than your own because their parents unable to care	Independent	Entrapment
Child/spouse/spouse/other family member in prison/jail	Independent	Humiliation
Loss of a confidant/loved one	Independent	Loss
Home invasion/robbery/burglary	Independent	Loss
Murder of close friend/relative	Independent	Loss

Table 1.2: Alternative Dimensions of Trauma Items from the Traumatic Events Inventory in the Grady Sample

Event	Experienced/Witnessed	Assaultive vs. Non-Assaultive
Experienced Natural Disaster	Experienced	Non-Assaultive
Experienced Serious Accident/Injury	Experienced	Non-Assaultive
Experienced Sudden Life-Threatening Illness	Experienced	Non-Assaultive
Experienced Childhood Emotional Abuse	Experienced	Non-Assaultive
Experienced Military Combat/Service in Warzone	Experienced	Assaultive
Experienced Attack with Weapon by Romantic Partner	Experienced	Assaultive
Experienced Attack with Weapon by Other	Experienced	Assaultive
Experienced Attack without Weapon by Romantic Partner	Experienced	Assaultive
Experienced Attack without Weapon by Other	Experienced	Assaultive
Experienced Childhood Physical Abuse	Experienced	Assaultive
Experienced Sexual Contact before 13	Experienced	Assaultive
Experienced rape between 14 and 17	Experienced	Assaultive
Experienced rape after 17	Experienced	Assaultive
Witnessed Serious Accident/Injury	Witnessed	Non-Assaultive
Witnessed Close Friend/Family Murder	Witnessed	Assaultive
Confronted with Close Friend/Family Murder	Witnessed	Assaultive
Witnessed Family Member/Friend attacked with Weapon	Witnessed	Assaultive
Witnessed Nonfamily Member attacked with Weapon	Witnessed	Assaultive
Witnessed Family Member/Friend attacked without Weapon	Witnessed	Assaultive
Witnessed Nonfamily Member attacked without Weapon	Witnessed	Assaultive
Witnessed Violence between parents	Witnessed	Assaultive

Table 1.3: Alternative Dimensions of Stressful Life Events from the Life Events Scale in the Twin Sample

Stressful Life Event	Ind/Dependent	Major/Minor	Loss/Humiliation/Entrapment
Flunked a grade	Dependent	Major	Humiliation
Arrested or had serious law trouble	Dependent	Major	Humiliation
Dropped out of school	Dependent	Major	Humiliation
Lost driver's license	Dependent	Major	Loss
Lost a job	Dependent	Major	Loss
Not accepted into important extracurricular activity	Dependent	minor	Humiliation
Suspended from school	Dependent	minor	Humiliation
Argued more with parents	Dependent	minor	Humiliation
Broke up with boyfriend/girlfriend	Dependent	minor	Loss
Broke up with close friend	Dependent	minor	Loss
Family had serious financial trouble	Independent	Major	Entrapment
Seriously ill or injured	Independent	Major	Entrapment
Mother or father lost a job	Independent	Major	Entrapment
Parent arrested or serious law trouble	Independent	Major	Humiliation
Mother/father seriously ill or injured	Independent	Major	Loss
Brother/sister seriously ill or injured	Independent	Major	Loss
Family member was victim of violence	Independent	Major	Loss
Close family member died	Independent	Major	Loss
Parents got divorced or separated	Independent	Major	Loss
Close friend died	Independent	Major	Loss
Parents argued much more with each other	Independent	minor	Entrapment
Favorite pet died	Independent	minor	Loss
Brother or sister had serious trouble	Independent	minor	Loss
Parent spent much more time away from home	Independent	minor	Loss

Table 1.4: Fit Statistics of Alternative Models of Stressful Life Events in the Twin Sample

Model	ChiSq	df	RMSEA	CFI	TLI	SRMR	ChiSqTest p	AIC	BIC
General Factor	398.4	252	.017	.865	.852	.049	--	136725	137132
Uncorrelated Dep/Independent	572.7	252	.023	.755	0.733	0.108	N/A	142395	142818
Correlated Dep/Independent	**380.3**	**251**	**.016**	**.881**	**0.869**	**0.048**	**1.62-08**	**136578**	**136991**
Uncorrelated Major/Minor	694.5	252	0.027	0.655	0.623	0.127	N/A	142918	143342
Correlated Major/Minor	433.6	251	0.017	0.869	0.856	0.048	1	141648	142078
Uncorrelated Loss/Hum/Entrapment	944.2	252	0.034	0.449	0.399	0.146	N/A	144350	144773
Correlated Loss/Hum/Entrapment	451.1	250	0.018	0.853	0.837	0.05	1	141817	142258
Dep/Indep*Major/Minor	422.1	242	0.016	0.875	0.861	0.056	1	141526	141978
Dep/Indep*Loss/Hum/Entrapment	535.5	242	0.022	0.781	0.757	0.081	1	142430	142882
Major/Minor*Loss/Hum/Entrapment	469.6	238	0.019	0.832	0.811	0.063	1	141856	142331

Note: Bolded model is the best fitting model. ChiSq = Chi Square statistic. Df= degrees of freedom. RMSEA = Root Mean Square Error of Approximation. CFI = Comparative Fit Index. TLI = Tucker Lewis Index. SRMR = Squared Root Mean Residual. ChiSqTest p = *p*-value of the Chi Square test with Satorra-Bentler correction. AIC = Aikaike Information Criterion. BIC = Bayesian Information Criterion. All Chi Square Test *p*-values are comparing each model to the General Factor model.

Table 1.5: Fit Statistics of Alternative Models of Stressful Life Events in the Grady Sample

Model	**ChiSq**	**df**	**RMSEA**	**CFI**	**TLI**	**SRMR**	**ChiSqTest p**	**AIC**	**BIC**
General Factor	338.4	90	0.035	0.676	0.622	0.036	--	91974	92231
Ind/Dep Uncorrelated	513.2	90	0.046	0.449	0.357	0.053	N/A	92204	92461
Ind/Dep Correlated	**328.3**	**89**	**0.035**	**0.688**	**0.632**	**0.035**	**0.004**	**91962**	**92225**
Loss/Hum/Entr Uncorrelated	466.7	90	0.043	0.509	0.427	0.052	N/A	92147	92404
Loss/Hum/Entr Correlated	350.3	88	0.037	0.658	0.592	0.044	1	92001	92269
Ind/Dep*Loss/Hum/Entr	478.5	80	0.049	0.498	0.391	0.060	1	92890	92943

Note: Bolded model is the best fitting model. ChiSq = Chi Square statistic. Df= degrees of freedom. RMSEA = Root Mean Square Error of Approximation. CFI = Comparative Fit Index. TLI = Tucker Lewis Index. SRMR = Squared Root Mean Residual. ChiSqTest p = *p*-value of the Chi Square test with Satorra-Bentler correction. AIC = Aikaike Information Criterion. BIC = Bayesian Information Criterion. All Chi Square Test *p*-values are comparing each model to the General Factor model.

Table 1.6: Standardized Factor Loadings of Life Event Scale Items onto Dependent and Independent Stressful Life Event Latent Variables in the Twin Sample

Dependent SLEs	**Beta**	**SE**	**Beta/SE**	***p*-value**
Suspended from school	0.561	0.062	9.112	<.001
Broke up with boy/girlfriend	0.35	0.043	8.213	<.001
Broke up with close friend	0.353	0.059	6.031	<.001
Flunked a grade	0.43	0.075	5.695	<.001
Argued more with parents	0.304	0.042	7.197	<.001
Arrested or had serious law trouble	0.664	0.116	5.744	<.001
Dropped out of school	0.668	0.122	5.458	<.001
Lost a job	0.614	0.088	6.957	<.001
Lost driver's license	0.611	0.125	4.876	<.001
Independent SLEs				
Close friend died	0.369	0.071	5.218	<.001
Seriously ill or injured	0.353	0.077	4.597	<.001
Parent seriously ill or injured	0.27	0.088	3.075	0.002
Sibling seriously ill or injured	0.388	0.11	3.522	<.001
Not accepted into important extracurricular activity	0.205	0.042	4.853	<.001
Parent lost job	0.362	0.077	4.673	<.001
Favorite pet died	0.273	0.033	8.253	<.001
Sibling had serious trouble	0.37	0.056	6.615	<.001
Family member was victim of violence	0.631	0.193	3.265	0.001
Close family member died	0.259	0.071	3.639	<.001
Family had serious financial trouble	0.407	0.058	6.965	<.001
Parent spent much more time away	0.279	0.034	8.149	<.001
Parents argued more	0.37	0.042	8.74	<.001
Parented got divorced	0.414	0.079	5.237	<.001
Parent had serious law trouble	0.596	0.203	2.935	0.003

Table 1.7: Standardized Factor Loadings of Life Event Scale Items onto Dependent and Independent Stressful Life Event Latent Variables in the Grady Sample

Dependent SLEs	**Beta**	**SE**	**Beta/SE**	***p*-value**
Lived in an unsafe neighborhood	0.117	0.039	2.982	0.003
Unplanned/unwanted pregnancy	0.376	0.055	6.824	<.001
Inadequate financial resources to obtain food	0.466	0.051	9.161	<.001
Children raised by others because unable to care	0.243	0.041	5.901	<.001
Fired or had serious work problems	0.068	0.034	1.98	0.048
Evicted from home	0.096	0.046	1.868	0.042
Divorced	0.147	0.044	3.299	0.001
Independent SLEs				
Chronic health problem or life threatening illness	0.063	0.032	0.729	0.046
Homeless, living in shelter/on streets	0.15	0.032	4.673	<.001
Homeless with temporary or unplanned outfits	0.052	0.028	0.44	0.049
Took in children because parents couldn't	0.089	0.033	0.857	0.039
Family member in prison/jail	0.567	0.042	13.513	<.001
Loss of a confidant/loved one	0.617	0.043	14.439	<.001
Home invasion/robbery/burglary	0.094	0.029	1.502	0.013
Murder of close friend/relative	0.105	0.034	3.135	0.002

Table 1.8: Fit Statistics of Alternative Models of Traumatic Events in the Grady Sample

Model	**ChiSq**	**df**	**RMSEA**	**CFI**	**TLI**	**SRMR**	**ChiSqTest p**	**AIC**	**BIC**
General Factor	4364.5	189	0.055	0.660	0.622	0.065	--	404261	404696
Experienced vs. Witnessed	3856.1	188	0.051	0.701	0.666	0.063	1.41E-112	403337	403778
Assault vs Non-Assault	4335	188	0.055	0.662	0.623	0.065	5.59E-08	404212	404654
Experienced/Witnessed* Assault/Non-Assault	**3745.5**	**184**	**0.051**	**0.710**	**0.669**	**0.062**	**1.58E-131**	**403101**	**403571**

Note: Bolded model is the best fitting model. ChiSq = Chi Square statistic. Df= degrees of freedom. RMSEA = Root Mean Square Error of Approximation. CFI = Comparative Fit Index. TLI = Tucker Lewis Index. SRMR = Squared Root Mean Residual. ChiSqTest p = *p*-value of the Chi Square test with Satorra-Bentler correction. AIC = Aikaike Information Criterion. BIC = Bayesian Information Criterion. All Chi Square Test *p*-values are comparing each model to the General Factor model.

Table 1.9: Standardized Factor Loading of Items from the Traumatic Events Inventory onto Latent Variables in the Grady Sample

Experienced Non-Assault	**Beta**	**SE**	**Beta/SE**	***p*-value**
Experienced Natural Disaster	0.272	0.02	13.559	<.001
Experienced Serious Accident/Injury	0.439	0.02	21.703	<.001
Experienced Sudden Life-Threatening Illness	0.198	0.018	11.224	<.001
Experienced Childhood Emotional Abuse	0.440	0.021	21.434	<.001
Experienced Assault				
Attacked with Weapon by Romantic Partner	0.459	0.023	20.222	<.001
Attacked with Weapon by Other	0.477	0.034	14.169	<.001
Experienced Military Combat/Service in Warzone	0.062	0.021	2.992	0.003
Attacked Without Weapon by Romantic Partner	0.469	0.025	18.414	<.001
Attacked Without Weapon by Other	0.449	0.031	14.285	<.001
Experienced Childhood Physical Abuse	0.478	0.02	23.419	<.001
Experienced Sexual Contact before 13	0.425	0.029	14.757	<.001
Experienced Rape between 14 and 17	0.349	0.029	11.892	<.001
Experienced Rape after 17	0.326	0.027	11.892	<.001
Witnessed Assault				
Witnessed Close Friend/Family Murder	0.402	0.021	19.106	<.001
Witnessed Family Member Attacked with Weapon	0.539	0.017	31.23	<.001
Witnessed Nonfamily Member attacked with Weapon	0.619	0.016	37.67	<.001
Witnessed Family Member attacked without Weapon	0.570	0.015	38.632	<.001
Witnessed Nonfamily Member attacked without Weapon	0.613	0.014	44.013	<.001
Witnessed Violence Between Parents	0.288	0.018	16.406	<.001
Confronted with the Murder of Close Friend/Family	0.432	0.018	23.601	<.001

Table 1.10: Fit Statistics of Alternative Models of the Relations among Stressful Life Events and Trauma in the Twin Sample

Model	**ChiSq**	**df**	**RMSEA**	**CFI**	**TLI**	**SRMR**	**ChiSqTest p**	**AIC**	**BIC**
General Stress Factor	6465.3	594	0.037	0.64	0.618	0.051	6.06E216	496386	497132
Paths fixed across Trauma	5508.4	586	.034	.698	.676	.052	1.71E-18	494951	495752
Paths fixed across SLEs	5444.6	584	0.034	0.702	0.678	0.05	1.91E-06	494859	495694
4 Trauma Factors and Ind/Dep Correlated	**5412.3**	**580**	**0.034**	**0.702**	**0.677**	**0.05**	**--**	**494851**	**495674**

Note: Bolded model is the best fitting model. ChiSq = Chi Square statistic. Df= degrees of freedom. RMSEA = Root Mean Square Error of Approximation. CFI = Comparative Fit Index. TLI = Tucker Lewis Index. SRMR = Squared Root Mean Residual. ChiSqTest p = *p*-value of the Chi Square test with Satorra-Bentler correction. AIC = Aikaike Information Criterion. BIC = Bayesian Information Criterion. All Chi Square Test *p*-values are comparing each model to the correlations freely estimated model.

Table 1.11: Fit Statistics of Alternative Models of the Relations among Stressful Life Events and Trauma in the Grady Sample

Model	ChiSq	Df	RMSEA	CFI	TLI	SRMR	ChiSqTest p	AIC	BIC
General Stress Factor	447.4	275	.017	.859	.846	.049	1.37E-09	143505	143929
Trauma Paths fixed across Dependent/Independent SLEs	426.8	274	.016	.875	.863	.047	.009	143351	143780
Trauma Freely Estimated with Dependent/Independent SLEs	**420.4**	**273**	**.016**	**.880**	**.868**	**.047**	**--**	**143320**	**143755**

Note: Bolded model is the best fitting model. ChiSq = Chi Square statistic. Df= degrees of freedom. RMSEA = Root Mean Square Error of Approximation. CFI = Comparative Fit Index. TLI = Tucker Lewis Index. SRMR = Squared Root Mean Residual. ChiSqTest p = *p*-value of the Chi Square test with Satorra-Bentler correction. AIC = Aikaike Information Criterion. BIC = Bayesian Information Criterion. All Chi Square Test *p*-values are comparing each model to the correlations freely estimated model.

Table 1.12: Fit Statistics of Alternative Models of the Relations among Stressful Life Events, Trauma, and Psychopathology in the Twin Sample

Model	ChiSq	Df	RMSEA	CFI	TLI	SRMR	ChiSqTest p	AIC	BIC
All Relations Equated	14211.4	3567	0.038	0.571	0.561	0.065	0.009	472928	474398
Paths from Stress Variables Equated Across Internalizing/Externalizing	**13958.6**	**3565**	**0.038**	**0.571**	**0.56**	**0.065**	**0.17**	**472931**	**474412**
All Relations Freely Estimated	14197	3562	0.038	0.572	0.56	0.065	--	472919	474428

Note: Bolded model is the best fitting model. ChiSq = Chi Square statistic. Df= degrees of freedom. RMSEA = Root Mean Square Error of Approximation. CFI = Comparative Fit Index. TLI = Tucker Lewis Index. SRMR = Squared Root Mean Residual. ChiSqTest p = *p*-value of the Chi Square test with Satorra-Bentler correction. AIC = Aikaike Information Criterion. BIC = Bayesian Information Criterion. All Chi Square Test *p*-values are comparing each model to the correlations freely estimated model.

Table 1.13: Fit Statistics of Alternative Models of the Relations among Stressful Life Events, Trauma, and Psychopathology in the Grady Sample

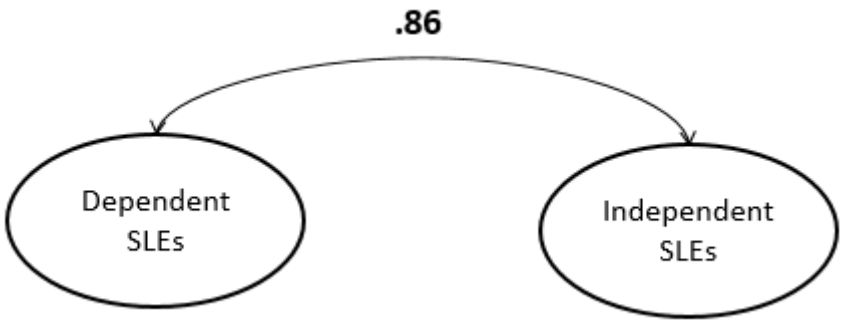
Model	ChiSq	df	RMSEA	CFI	TLI	SRMR	ChiSqTest	AIC	BIC
All Paths Equated	6275.4	652	0.034	0.687	0.658	0.052	2.59E-54	584181	585111
Paths fixed across Internalizing/Externalizing	6112.4	647	0.033	0.696	0.669	0.052	5.67E-18	583978	584894
All Correlations Freely Estimated	**6018.9**	**641**	**0.033**	**0.701**	**0.672**	**0.051**	**--**	**583862**	**584819**

Note: Bolded model is the best fitting model. ChiSq = Chi Square statistic. Df= degrees of freedom. RMSEA = Root Mean Square Error of Approximation. CFI = Comparative Fit Index. TLI = Tucker Lewis Index. SRMR = Squared Root Mean Residual. ChiSqTest p = *p*-value of the Chi Square test with Satorra-Bentler correction. AIC = Aikaike Information Criterion. BIC = Bayesian Information Criterion. All Chi Square Test *p*-values are comparing each model to the correlations freely estimated model.

Table 1.14: Correlations among Stressful Life Events, Trauma, and Psychopathology in the Grady Sample

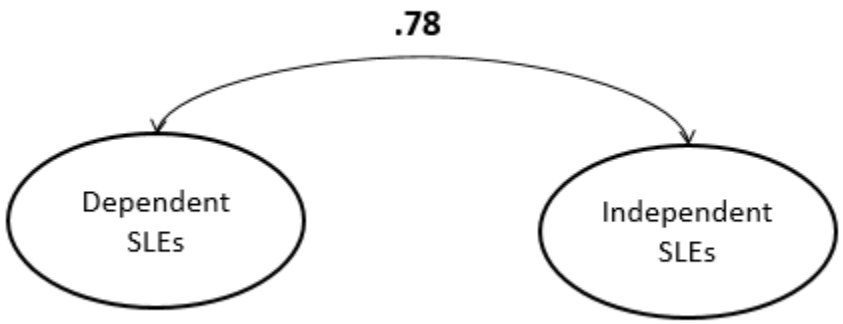
	Correlations	
Events	**Internalizing**	**Externalizing**
Independent SLEs	0.13	0.22
Dependent SLEs	0.25	0.41
Witnessed Non-Assaultive Trauma	0.07	0.12
Witnessed Assaultive Trauma	0.18	0.30
Experienced Non-Assaultive Trauma	0.25	0.42
Experienced Assaultive Trauma	0.26	0.43

Figure 1.1: Diagram of the Relation between Dependent and Independent SLEs in the Twin Sample



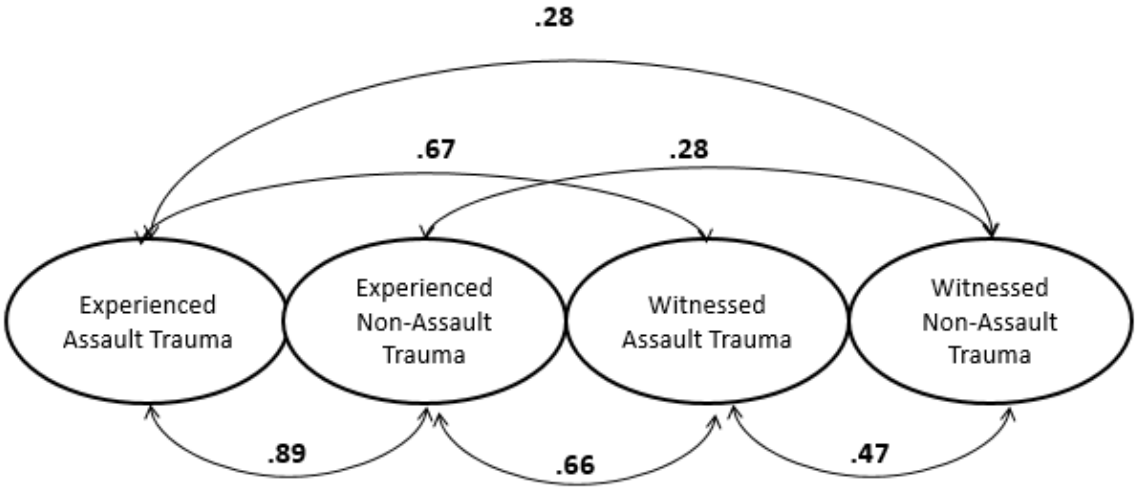
Note: Correlation coefficients are presented over paths. Bolded correlations are significant. Paths to items that indicate each latent variable are omitted for legibility.

Figure 1.2: Diagram of the Relation between Dependent and Independent SLEs in the Grady Sample



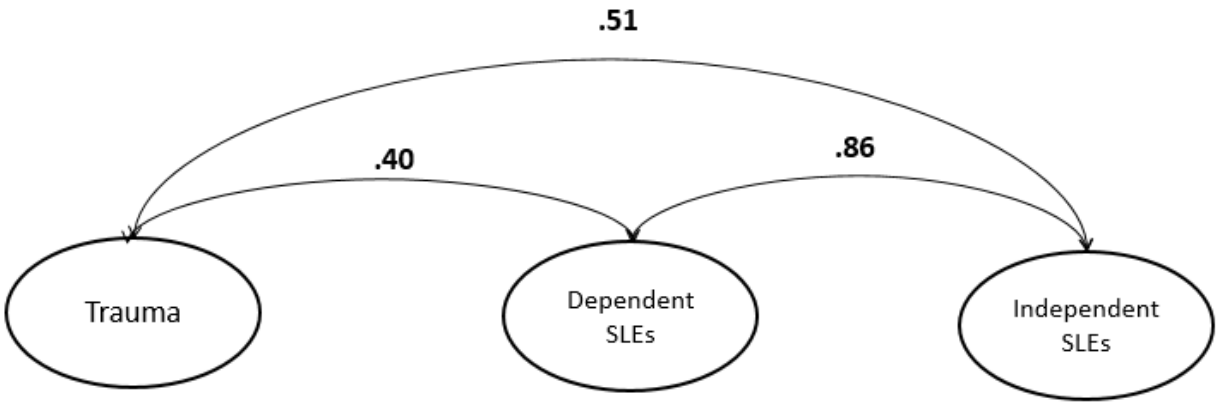
Note: Correlation coefficients are presented over paths. Bolded correlations are significant. Paths to items that indicate each latent variable are omitted for legibility.

Figure 1.3: Diagram of the Relations among Latent Trauma Variables in the Grady Sample



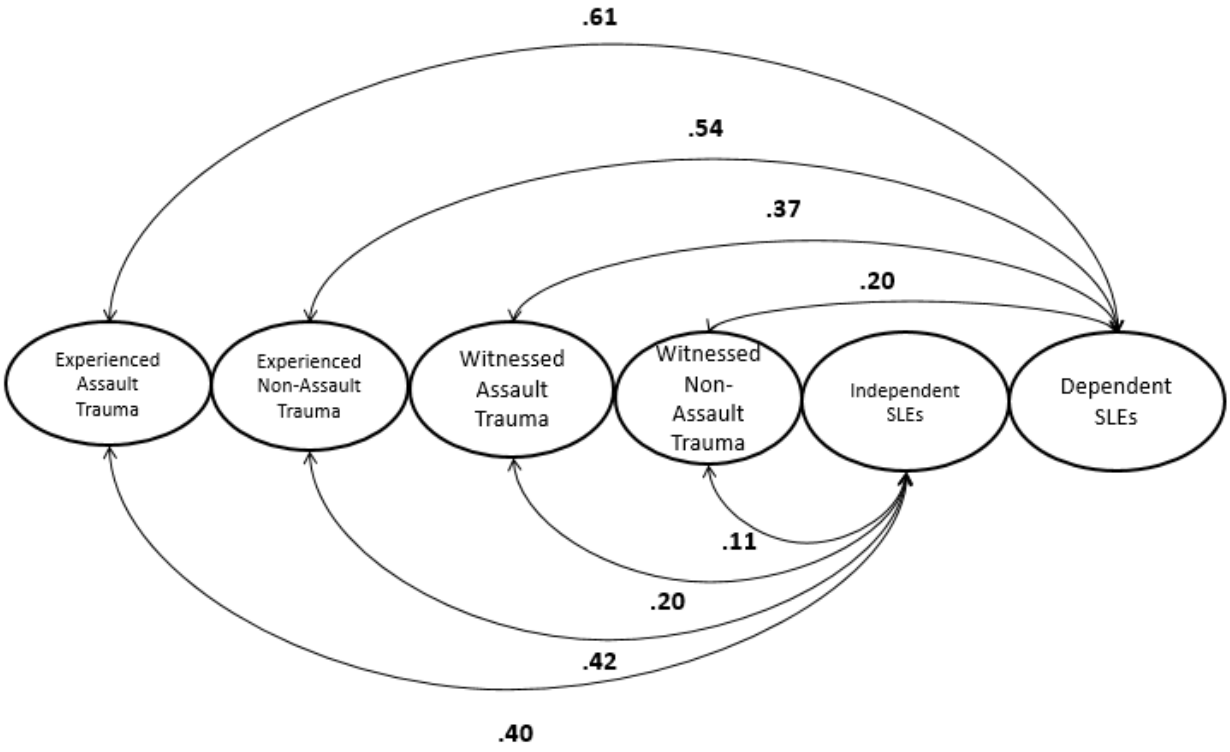
Note: Correlation coefficients are presented over paths. Bolded correlations are significant. Paths to items that indicate each latent variable are omitted for legibility.

Figure 1.4: Diagram of the Relations among Latent Stressful Life Events and Trauma Variables in the Twin Sample



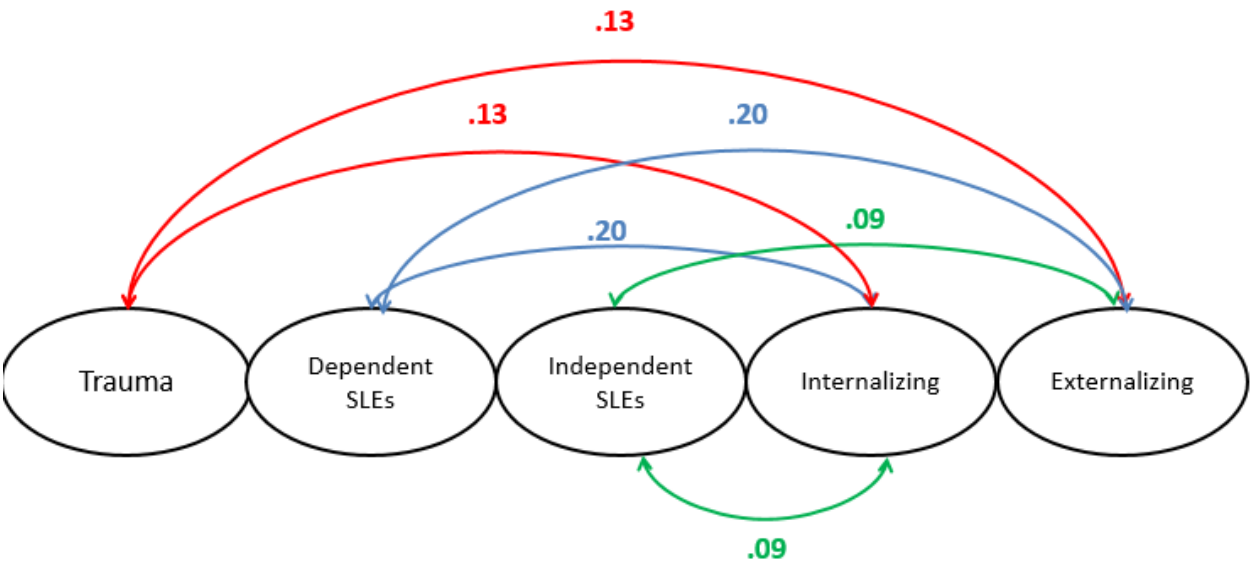
Note: Correlation coefficients are presented over paths. Bolded correlations are significant. Paths to items that indicate each latent variable are omitted for legibility.

Figure 1.5: Diagram of the Relations among Latent Stressful Life Events and Trauma Variables in the Grady Sample



Note: Correlation coefficients are presented over paths. Bolded correlations are significant. Paths to items that indicate each latent variable and correlations presented in previous figures are omitted for legibility.

Figure 1.6: Diagram of the Relations among Latent Stressful Life Events, Trauma, and Psychopathology Variables in the Twin Sample



Note: Correlation coefficients are presented over paths. Bolded correlations are significant. Paths to items that indicate each latent variable and correlations presented in previous figures are omitted for legibility. Paths of the same color are constrained to have equal values.

Table 2.1: Fit Statistics of Univariate Behavior Genetics Models of Trauma, Stressful Life Events, and Psychopathology

Model	**ChiSq**	**df**	**RMSEA**	**CFI**	**TLI**	**SRMR**	**ChiSqTest p**	**AIC**	**BIC**
Trauma									
ACE+s	7.58	5	0.035	0.57	0.828	0.18	--	3341	3365
ADE+s	4.9	5	0	1	1.006	0.181	--	3342	3365.1
ACE	4.95	6	0	1	1.006	0.181	1	3340	3358
ADE	4.91	6	0	1	1.006	0.181	1	3340	3358
AE	**5.15**	**7**	**0**	**1**	**1.009**	**0.181**	**1**	**3338**	**3352**
CE	6.29	7	0	1	1.034	1.98	1	3406	3420
Independent SLEs									
ACE+s	27.8	5	0.104	0.629	0.652	0.44		1645	1669
ADE+s	41.6	5	0.132	0.407	0.441	0.397		1639	1663
ACE	33.3	6	0.104	0.629	0.652	0.44	0.32	1643	1662
ADE	127.6	6	0.219	-0.327	-0.549	0.378	0.00004	1816	1835
AE	44.4	7	0.167	0.485	0.511	0.47	0.03	1639	1658
CE	**38.9**	**7**	**0.104**	**0.631**	**0.652**	**0.44**	**0.11**	**1641**	**1655**
Dependent SLEs									
ACE+s	15.9	5	0.072	0.691	0.876	0.515	--	3063	3086
ADE+s	16.9	5	0.067	0.73	0.893	0.495	--	3056	3079
ACE	15.4	6	0.061	0.734	0.911	0.516	1	3061	3080
ADE	17.1	6	0.066	0.687	0.896	0.513	0.42	3060	3079
AE	**17.9**	**7**	**0.061**	**0.69**	**0.911**	**0.516**	**0.37**	**3058**	**3073**
Internalizing									

ACE+s	5.19	5	0.01	0.997	0.999	0.123	--	1994	2017
ADE+s	6.39	5	0.026	0.979	0.991	0.122	--	1999	2023
ACE	7.13	6	0.02	0.983	0.994	0.122	0.15	1997	2016
ADE	6.39	6	0.013	0.994	0.998	0.123	0.32	1998	2016.3
AE	**7.46**	**7**	**0.013**	**0.993**	**0.998**	**0.123**	**0.32**	**1996**	**2010**
Externalizing									
ACE+s	1.086	5	0	1	1.004	0.043	--	1313	1336
ADE+s	2.204	5	0	1	1.003	0.042	--	1313	1336
ACE	1.15	6	0	1	1.004	0.043	0.91	1311	1330
ADE	1.19	6	0	1	1.004	0.042	0.89	1311	1329
AE	**1.34**	**7**	**0**	**1**	**1.004**	**0.043**	**0.87**	**1309**	**1323**

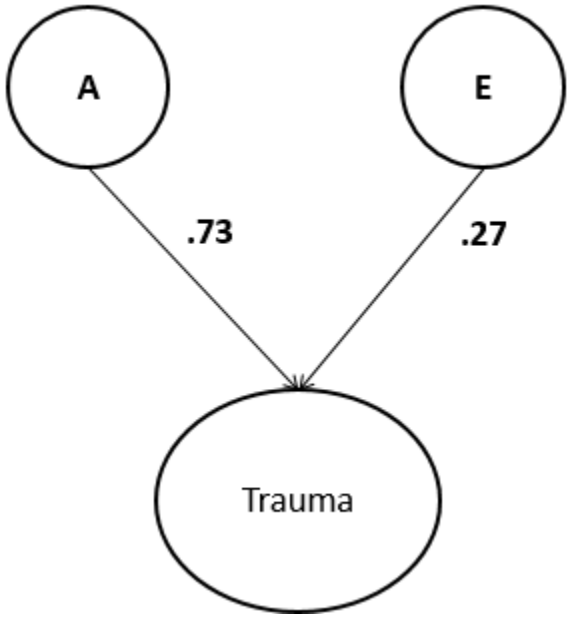
Note: Bolded model is the best fitting model. Models labeled with A, C, D, E, and S estimated additive genetic, nonadditive genetic, shared environmental, nonshared environmental, and sibling influences respectively. ChiSq = Chi Square statistic. Df= degrees of freedom. RMSEA = Root Mean Square Error of Approximation. CFI = Comparative Fit Index. TLI = Tucker Lewis Index. SRMR = Squared Root Mean Residual. ChiSqTest p = *p*-value of the Chi Square test with Satorra-Bentler correction. AIC = Aikaike Information Criterion. BIC = Bayesian Information Criterion. All Chi Square Test *p*-values are comparing each model to the ACE+s model.

Table 2.2: Fit Statistics of Multivariate Behavior Genetics Models of Trauma, Stressful Life Events, and Psychopathology

Model	**ChiSq**	**df**	**RMSEA**	**CFI**	**TLI**	**SRMR**	**ChiSqTest p**	**AIC**	**BIC**
Full ACE	728.2	81	0.138	0.784	0.760	0.986	--	13768	14000
Paths Match Univariate	490.8	99	0.097	0.864	0.864	0.253	1	12681	12828
Nonsignificant Paths Dropped	**517.0**	**110**	**0.094**	**0.869**	**0.869**	**0.250**	**1**	**12798**	**12703**

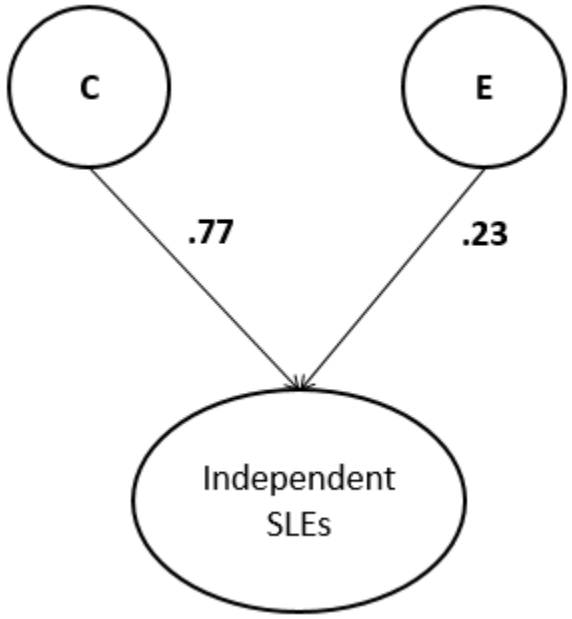
Note: Bolded model is the best fitting model. ChiSq = Chi Square statistic. Df= degrees of freedom. RMSEA = Root Mean Square Error of Approximation. CFI = Comparative Fit Index. TLI = Tucker Lewis Index. SRMR = Squared Root Mean Residual. ChiSqTest p = *p*-value of the Chi Square test with Satorra-Bentler correction. AIC = Aikaike Information Criterion. BIC = Bayesian Information Criterion. All Chi Square Test *p*-values are comparing each model to the Full ACE Model.

Figure 2.1: Path Diagram of Etiological Influences on Trauma Exposure



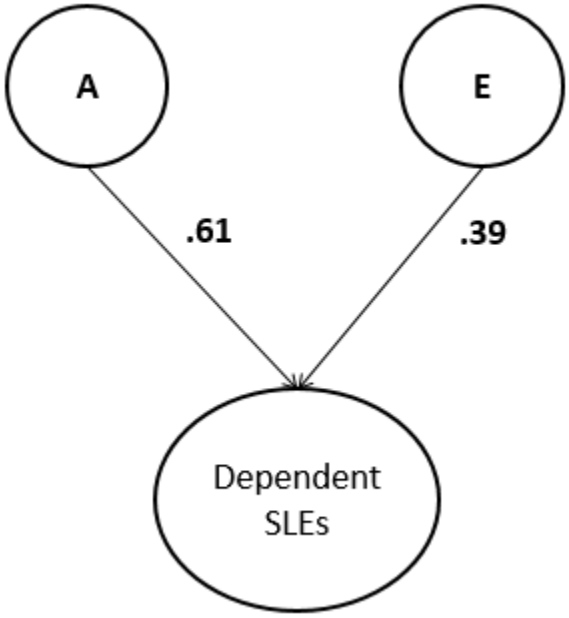
Note: A and E represent additive genetic and nonshared environmental influences, respectively. Path estimates are standardized and squared to represent proportion of variance explained.

Figure 2.2: Path Diagram of Etiological Influences on Independent Stressful Life Events



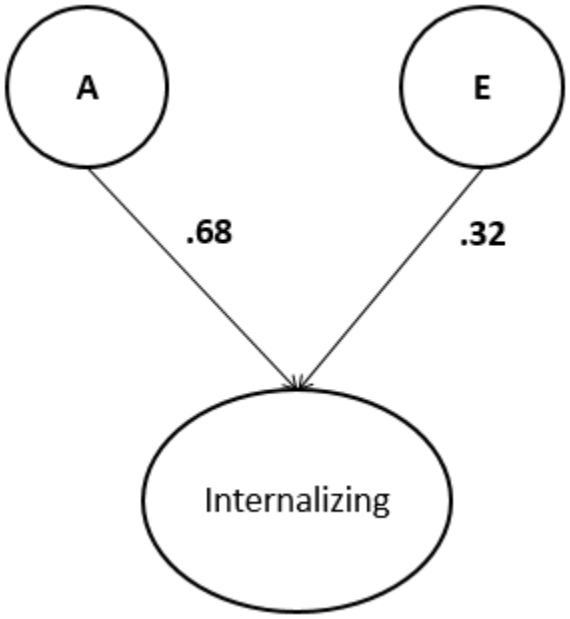
Note: C and E represent shared and nonshared environmental influences, respectively. Path estimates are standardized and squared to represent proportion of variance explained.

Figure 2.3: Path Diagram of Etiological Influences on Dependent Stressful Life Events



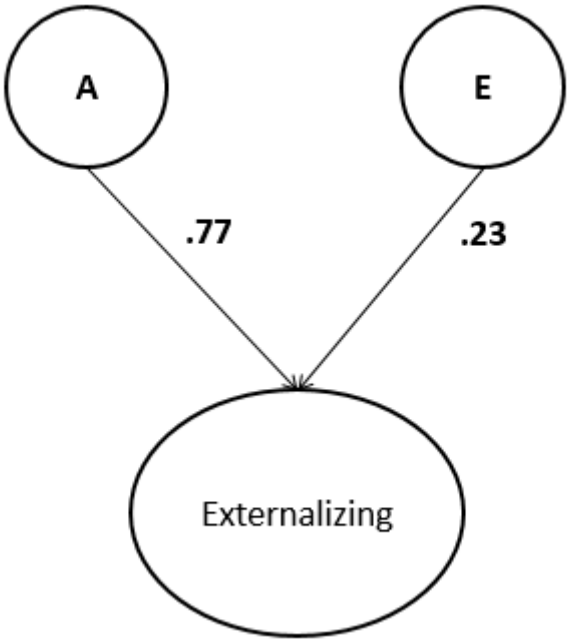
Note: A and E represent additive genetic and nonshared environmental influences, respectively. Path estimates are standardized and squared to represent proportion of variance explained.

Figure 2.4: Path Diagram of Etiological Influences on Internalizing Psychopathology



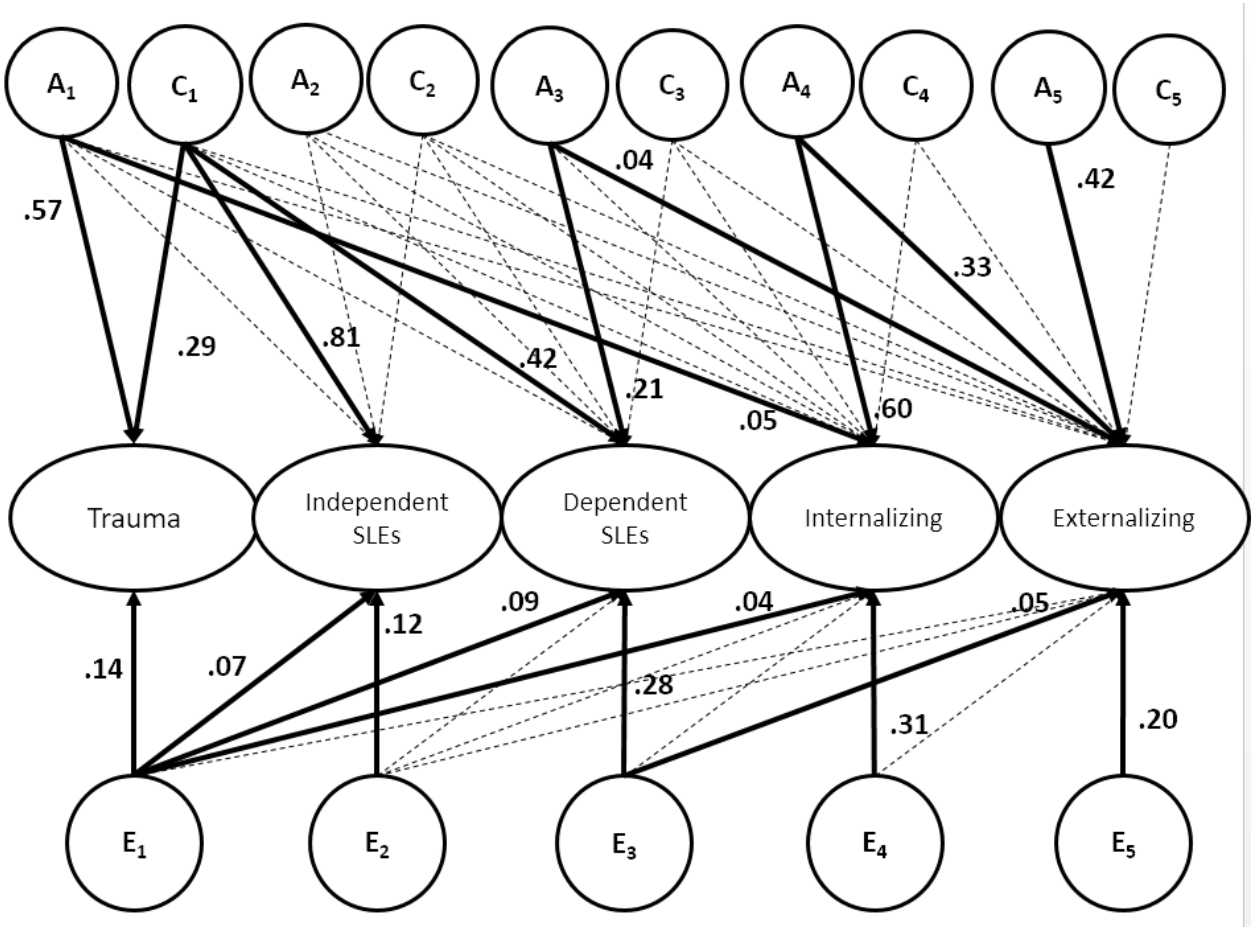
Note: A and E represent additive genetic and nonshared environmental influences, respectively. Path estimates are standardized and squared to represent proportion of variance explained.

Figure 2.5: Path Diagram of Etiological Influences on Externalizing Psychopathology



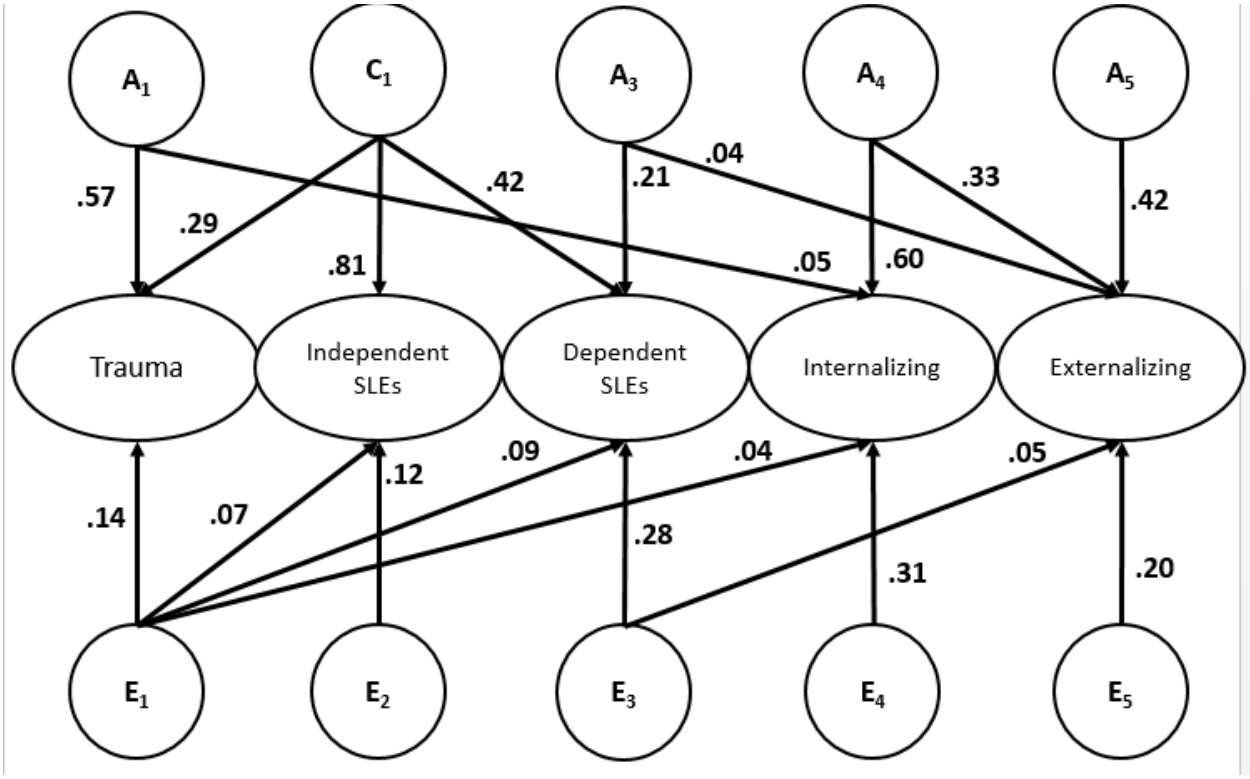
Note: A and E represent additive genetic and nonshared environmental influences, respectively. Path estimates are standardized and squared to represent proportion of variance explained.

Figure 2.6: Path Diagram of the Full Model of the Cholesky Decomposition of Etiological Influences on Trauma, Stressful Life Events, and Psychopathology



Note: A, C, and E represent additive genetic, shared environmental, and nonshared environmental influences, respectively. Dotted arrows represent nonsignificant paths. Path estimates are standardized and squared to represent proportion of variance explained.

Figure 2.7: Path Diagram of the Cholesky Decomposition of Etiological Influences on Trauma, Stressful Life Events, and Psychopathology



Note: A, C, and E represent additive genetic, shared environmental, and nonshared environmental influences, respectively. Path estimates are standardized and squared to represent proportion of variance explained.

Table 3.1: Univariate Genome Wide Association Results for Internalizing Psychopathology

Chromosome	Position	SNP	MAF	INFO	Beta	SE	p
2	75042981	rs200174320	0.8331	0.9577	2.7039	0.5211	2.21E-07
13	97314029	rs72643881	0.9227	0.9336	3.7726	0.7373	3.24E-07
13	97317870	rs140011589	0.9229	0.9321	3.7784	0.7386	3.26E-07
8	97764622	rs10955082	0.9482	0.8735	-4.6163	0.9183	5.18E-07
17	31482040	rs9895456	0.5078	1.0111	1.8955	0.3786	5.75E-07

Note: Table include SNPs with *p*-values below $1x10^{-6}$. MAF = Minor Allele Frequency. INFO = INFO score, a measure of imputation quality ranging from 0 to 1. SE = standard error.

Table 3.2: Univariate Genome Wide Association Results for Externalizing Psychopathology

Chromosome	Position	SNP	MAF	INFO	Beta	SE	p
21	**19044655**	**rs9984249**	**0.9089**	**1.0065**	**-2.3573**	**0.4375**	**7.65E-08**
9	**78950368**	**rs148270179**	**0.9446**	**0.9081**	**3.0744**	**0.5799**	**1.23E-07**
2	**174748387**	**rs2255918**	**0.4397**	**0.9421**	**1.3461**	**0.2647**	**3.90E-07**
19	**48537304**	**rs115570521**	**0.94**	**0.9266**	**2.8095**	**0.5531**	**4.03E-07**
2	**174736163**	**rs10497429**	**0.8471**	**0.9992**	**-1.7686**	**0.3518**	**5.25E-07**
8	**19842084**	**rs59979174**	**0.9127**	**0.9648**	**2.2955**	**0.4566**	**5.25E-07**
19	**48539141**	**rs144570613**	**0.9399**	**0.9257**	**2.7736**	**0.5528**	**5.54E-07**
8	**19786203**	**rs73594434**	**0.943**	**0.9426**	**2.818**	**0.5626**	**5.80E-07**
8	19836607	rs80168484	0.9129	0.9616	2.2921	0.4579	5.89E-07
4	36648789	rs61798575	0.7363	0.985	1.4411	0.2892	6.63E-07
4	36648301	rs6850300	0.7363	0.985	1.4408	0.2892	6.65E-07
4	36647514	rs16988294	0.7362	0.9839	1.4401	0.2893	6.82E-07
4	36647308	rs16988292	0.7362	0.9836	1.4399	0.2894	6.87E-07
4	36647255	rs16992542	0.7362	0.9835	1.4398	0.2894	6.88E-07
4	36647023	rs61797904	0.7362	0.9833	1.4395	0.2894	6.93E-07
4	36646576	rs61522500	0.7361	0.9828	1.4389	0.2895	7.05E-07
19	15090902	rs78758412	0.9591	0.8681	-3.3951	0.6834	7.13E-07
4	36646832	rs58569945	0.7359	0.982	1.4382	0.2895	7.15E-07
4	36644839	rs56356148	0.736	0.9815	1.4356	0.2896	7.56E-07
4	36644696	rs16992534	0.736	0.9815	1.4353	0.2896	7.61E-07
4	36644383	rs55912256	0.736	0.9814	1.4346	0.2896	7.70E-07
4	36643773	rs56938313	0.736	0.9812	1.4334	0.2896	7.87E-07
4	36643623	rs60669009	0.7359	0.9812	1.4331	0.2896	7.91E-07
4	36643566	rs16992529	0.7359	0.9812	1.433	0.2896	7.93E-07
4	36643467	rs60635579	0.7359	0.9812	1.4328	0.2896	7.95E-07

4	36643232	rs56894985	0.7359	0.9812	1.4324	0.2896	8.01E-07
4	36642836	rs147771325	0.7359	0.9812	1.4317	0.2896	8.11E-07
4	36642475	rs61797894	0.7359	0.9812	1.4309	0.2896	8.21E-07
2	174736830	rs16862818	0.8468	0.996	-1.7377	0.3522	8.48E-07
8	19828234	rs77750306	0.917	0.9551	2.3056	0.4694	9.52E-07
8	19833125	rs73599573	0.9129	0.9481	2.2633	0.4612	9.71E-07
4	87916553	rs4693909	0.4641	0.9692	-1.2624	0.2574	9.83E-07
19	48544899	rs147863378	0.9396	0.9238	2.7086	0.5522	9.85E-07

Note: Table include SNPs with *p*-values below $1x10^{-6}$. MAF = Minor Allele Frequency. INFO = INFO score, a measure of imputation quality ranging from 0 to 1. SE = standard error. Bolded SNPs are significant by FDR (threshold = $5.86x10^{-7}$).

Table 3.3: Univariate Genome Wide Association Results for Dependent Stressful Life Events

Chromosome	Position	SNP	MAF	INFO	Beta	SE	p
19	**49039858**	**rs62126043**	**0.8797**	**0.8495**	**-0.1261**	**0.0234**	**7.03E-08**
19	49039594	rs200979533	0.8801	0.8488	-0.1258	0.0234	8.06E-08
19	49039762	rs74385812	0.8801	0.8487	-0.1258	0.0234	8.07E-08
19	49041173	rs12609121	0.8688	0.8137	-0.1227	0.023	9.95E-08
19	49042965	rs4801788	0.855	0.8224	-0.1158	0.0219	1.36E-07
19	49038821	rs4002456	0.8762	0.8574	-0.1211	0.023	1.43E-07
1	227912016	rs147140827	0.9487	0.8911	-0.1741	0.0337	2.38E-07
15	50729989	rs115862220	0.9488	0.9364	-0.1698	0.0328	2.38E-07
3	118122040	rs79099625	0.9452	0.9459	-0.1618	0.0317	3.34E-07
15	50760555	rs114576871	0.9448	0.8916	-0.1659	0.0325	3.36E-07
15	50761903	rs116646026	0.9458	0.8793	-0.168	0.033	3.65E-07
15	50762062	rs114349696	0.946	0.8783	-0.1681	0.033	3.74E-07
9	132990767	rs8193004	0.7598	0.9588	-0.085	0.0168	4.61E-07
1	229015144	rs10916408	0.7324	0.8923	-0.0844	0.0167	4.71E-07

Note: Table include SNPs with *p*-values below $1x10^{-6}$. MAF = Minor Allele Frequency. INFO = INFO score, a measure of imputation quality ranging from 0 to 1. SE = standard error. Bolded SNPs are significant by FDR (threshold = $7.70x10^{-8}$).

Table 3.4: Univariate Genome Wide Association Results for Independent Stressful Life Events

Chromosome	Position	SNP	MAF	INFO	Beta	SE	P
20	4400680	rs645295	0.087	0.8473	0.1122	0.0212	1.29E-07
1	227912016	rs147140827	0.9487	0.8911	-0.1324	0.0265	5.85E-07
2	162842402	rs201382967	0.6152	0.9767	0.0572	0.0115	6.71E-07
2	162842399	rs139424279	0.6152	0.9767	0.0572	0.0115	6.72E-07
1	17707512	rs10749623	0.5632	0.9815	0.0558	0.0112	6.81E-07
9	132990767	rs8193004	0.7598	0.9588	-0.0658	0.0132	6.92E-07
4	5469030	rs185806545	0.9686	0.8846	-0.166	0.0336	7.88E-07
1	229015144	rs10916408	0.7324	0.8923	-0.0646	0.0132	9.41E-07

Note: Table include SNPs with *p*-values below $1x10^{-6}$. MAF = Minor Allele Frequency. INFO = INFO score, a measure of imputation quality ranging from 0 to 1. SE = standard error.

Table 3.5: Univariate Gene-Based Association Results for Witnessed Non-Assault Trauma

Chromosome	Position	SNP	MAF	INFO	Beta	SE	p
18	**77303624**	**rs11872391**	**0.9444**	**0.9311**	**-0.2553**	**0.0473**	**7.31E-08**
8	**2573563**	**rs79579302**	**0.9312**	**0.88**	**-0.231**	**0.0441**	**1.73E-07**
5	121532349	rs145479012	0.9679	0.9601	-0.3112	0.0619	5.15E-07
8	124873864	rs7461817	0.9899	0.8755	-0.5653	0.1125	5.25E-07
7	19607688	rs10232959	0.3151	0.9393	-0.1157	0.0235	8.75E-07
14	25868936	rs1954159	0.0457	0.8126	0.2734	0.0556	9.05E-07
10	60050522	rs10821663	0.942	0.9778	-0.2232	0.0455	9.81E-07

Note: Table include SNPs with *p*-values below $1x10^{-6}$. MAF = Minor Allele Frequency. INFO = INFO score, a measure of imputation quality ranging from 0 to 1. SE = standard error. Bolded SNPs are significant by FDR (threshold = $1.76x10^{-7}$).

Table 3.6: Univariate Genome Wide Association Results for Witnessed Assault Trauma

Chromosome	Position	SNP	MAF	INFO	Beta	SE	p
4	***9557833***	***rs149978953***	***0.9555***	***0.8896***	***-0.2753***	***0.0467***	***3.96E-09***
4	***9557062***	***rs137929824***	***0.9555***	***0.8898***	***-0.2749***	***0.0467***	***4.13E-09***
4	***9545699***	***rs149768045***	***0.9547***	***0.9003***	***-0.2705***	***0.046***	***4.36E-09***
4	***9554441***	***rs188058760***	***0.9555***	***0.8906***	***-0.2739***	***0.0467***	***4.65E-09***
4	***9566740***	***rs141580469***	***0.9537***	***0.887***	***-0.2682***	***0.0458***	***5.25E-09***
4	***9560465***	***rs192581973***	***0.9537***	***0.8809***	***-0.2674***	***0.046***	***6.67E-09***
4	*9543638*	*rs141559791*	*0.9529*	*0.8739*	*-0.2601*	*0.0459*	*1.51E-08*
4	*9548322*	*rs140528306*	*0.9567*	*0.8703*	*-0.2614*	*0.0478*	*4.88E-08*
4	*9550452*	*rs140045821*	*0.9639*	*0.8729*	*-0.2846*	*0.0521*	*4.98E-08*
4	65392555	rs1376416	0.1891	1.0047	-0.1236	0.0234	1.27E-07
4	65392174	rs1451174	0.1892	1.0009	-0.1235	0.0234	1.36E-07
4	65393800	rs9790816	0.1851	0.9894	-0.1233	0.0237	2.19E-07

Note: Table include SNPs with *p*-values below $1x10^{-6}$. MAF = Minor Allele Frequency. INFO = INFO score, a measure of imputation quality ranging from 0 to 1. SE = standard error. Bolded SNPs are significant by FDR (threshold = $7.23x10^{-9}$). Italicized SNPs are significant at a nominal level (threshold = $5x10^{-8}$).

Table 3.7: Univariate Genome Wide Association Results for Experienced Non-Assault Trauma

Chromosome	Position	SNP	MAF	INFO	Beta	SE	P
2	***38771365***	***rs56389657***	***0.9355***	***0.9533***	***-0.2122***	***0.0382***	***2.98E-08***
19	49042965	rs4801788	0.855	0.8224	-0.1493	0.0287	2.12E-07
19	49039858	rs62126043	0.8797	0.8495	-0.1543	0.0306	4.80E-07
19	49041173	rs12609121	0.8688	0.8137	-0.1516	0.0301	5.00E-07
19	49039762	rs74385812	0.8801	0.8487	-0.1537	0.0307	5.57E-07
19	49039594	rs200979533	0.8801	0.8488	-0.1537	0.0307	5.58E-07
11	81652071	rs11232764	0.9019	0.9757	0.1562	0.0313	6.09E-07
4	159603823	rs17038523	0.9288	0.8904	-0.1861	0.0378	9.05E-07
1	158854475	rs115202892	0.968	0.9105	-0.2686	0.0546	9.05E-07
22	19611713	rs116240313	0.9042	0.8333	-0.1677	0.0341	9.29E-07
6	6826071	rs201956852	0.2698	0.8607	0.1096	0.0223	9.33E-07
3	118122040	rs79099625	0.9452	0.9459	-0.2036	0.0415	9.38E-07

Note: Table include SNPs with *p*-values below $1x10^{-6}$. MAF = Minor Allele Frequency. INFO = INFO score, a measure of imputation quality ranging from 0 to 1. SE = standard error. Bolded SNPs are significant by FDR (threshold = $3.61x10^{-8}$). Italicized SNPs are significant at a nominal level (threshold = $5x10^{-8}$).

Table 3.8: Univariate Genome Wide Association Results for Experienced Assault Trauma

Chromosome	Position	SNP	MAF	INFO	Beta	SE	p
1	***2571763***	***rs142711911***	***0.9697***	***0.9855***	***-0.4438***	***0.0784***	***1.62E-08***
1	***2572543***	***rs146341786***	***0.9351***	***0.9856***	***-0.4437***	***0.0784***	***1.63E-08***
1	***2572801***	***rs145199907***	***0.8577***	***0.9856***	***-0.4436***	***0.0784***	***1.63E-08***
1	***2575813***	***rs143506860***	***0.8625***	***0.9861***	***-0.4431***	***0.0784***	***1.66E-08***
1	***2800197***	***rs61733554***	***0.8199***	***0.9464***	***-0.442***	***0.081***	***5.14E-08***
1	***2787241***	***rs192840628***	***0.9559***	***0.9751***	***-0.4292***	***0.0796***	***7.43E-08***
1	***2788714***	***rs139034606***	***0.9483***	***0.975***	***-0.4292***	***0.0796***	***7.44E-08***
1	***2783146***	***rs141994131***	***0.6943***	***0.9755***	***-0.429***	***0.0796***	***7.45E-08***
1	***2768201***	***rs186739969***	***0.9298***	***0.9766***	***-0.4283***	***0.0795***	***7.60E-08***
1	***2627257***	***rs139870187***	***0.8087***	***0.9871***	***-0.4229***	***0.0789***	***8.88E-08***
1	***2613208***	***rs150481818***	***0.2473***	***0.9903***	***-0.422***	***0.0788***	***9.01E-08***
1	***2601222***	***rs189980295***	***0.9039***	***0.9917***	***-0.4216***	***0.0789***	***9.46E-08***
22	19611713	rs116240313	0.9042	0.8333	-0.1771	0.0338	1.71E-07
3	118122040	rs79099625	0.9452	0.9459	-0.2131	0.0411	2.22E-07
2	38771365	rs56389657	0.9355	0.9533	-0.1959	0.0379	2.42E-07
5	153689654	rs78827897	0.9139	0.9457	-0.1675	0.0333	5.20E-07
19	49042965	rs4801788	0.855	0.8224	-0.1429	0.0285	5.40E-07
3	118146388	rs78336596	0.9458	0.9501	-0.2068	0.0412	5.47E-07
19	49041173	rs12609121	0.8688	0.8137	-0.1492	0.0298	6.00E-07
19	49039858	rs62126043	0.8797	0.8495	-0.1512	0.0303	6.43E-07
19	49039762	rs74385812	0.8801	0.8487	-0.1509	0.0304	7.12E-07
19	49039594	rs200979533	0.8801	0.8488	-0.1509	0.0304	7.12E-07

Note: Table include SNPs with *p*-values below $1x10^{-6}$. MAF = Minor Allele Frequency. INFO = INFO score, a measure of imputation quality ranging from 0 to 1. SE = standard error. Bolded SNPs are significant by FDR (threshold = $1.16x10^{-7}$). Italicized SNPs are significant at a nominal level (threshold = $5x10^{-8}$).

Table 3.9: Univariate Genome Wide Association Gene-Based Results for Internalizing Psychopathology

Gene	Chromosome	Start Position	p	Function
LINC01448	7	42701325	0.0000527	non-coding RNA
MCAM	11	119179233	0.0000713	protein-coding gene
LRRC74B	22	21400248	0.000084	protein-coding gene

Note: Table includes genes with *p*-values below .0001.

Table 3.10: Univariate Genome Wide Association Gene-Based Results for Externalizing Psychopathology

Gene	Chromosome	Start Position	p	Group
SDK2	**17**	**71330522**	**6.25E-07**	**protein-coding gene**
ARHGEF10	8	1772141	1.88E-05	protein-coding gene
OR1I1	19	15197876	3.21E-05	protein-coding gene
INTS10	8	19674917	3.99E-05	protein-coding gene
C9orf92	9	16203932	4.71E-05	protein-coding gene
LOC102723828	4	31999000	6.51E-05	unknown
ERC1	12	1136913	8.37E-05	protein-coding gene

Note: Table includes genes with *p*-values below .0001. Bolded genes are significant by FDR (threshold = 6.26×10^{-7}).

Table 3.11: Univariate Genome Wide Association Gene-Based Results for Dependent Stressful Life Events

Symbol	Chromosome	Start_Position	NominalP	Group
CGB5	**19**	**49547101**	**9.93E-07**	**protein-coding gene**
SNAR-G2	**19**	**49534925**	**2.06E-06**	**non-coding RNA**
CGB2	**19**	**49535129**	**2.07E-06**	**protein-coding gene**
CGB1	**19**	**49538825**	**3.60E-06**	**protein-coding gene**
LOC100996583	**1**	**2497973**	**5.15E-06**	**unknown**
CGB8	**19**	**49550894**	**5.77E-06**	**protein-coding gene**
LINC-PINT	7	130628918	1.67E-05	non-coding RNA
SNAR-G1	19	49540276	1.93E-05	non-coding RNA
WNT9A	1	228109164	2.46E-05	protein-coding gene
SPPL2A	15	50999736	4.08E-05	protein-coding gene
MMEL1	1	2522080	4.23E-05	protein-coding gene
TTC34	1	2572806	5.51E-05	protein-coding gene
FAM213B	1	2518188	7.04E-05	protein-coding gene

Note: Table includes genes with *p*-values below .0001. Bolded genes are significant by FDR (threshold = 5.77×10^{-6}).

Table 3.12: Univariate Genome Wide Association Gene-Based Results for Independent Stressful Life Events

Symbol	Chromosome	Start_Position	NominalP	Group
KCNH7	2	163279756	2.07E-05	protein-coding gene
FAM213B	1	2518188	2.42E-05	protein-coding gene
WNT9A	1	228109164	2.47E-05	protein-coding gene
LOC100996583	1	2497973	2.89E-05	unknown
ZNF90	19	20188802	4.91E-05	protein-coding gene
NPTX1	17	78440632	6.41E-05	protein-coding gene
ZMIZ1	10	80828791	6.44E-05	protein-coding gene
CCNI	4	77969176	6.67E-05	protein-coding gene
MMEL1	1	2522080	7.52E-05	protein-coding gene
EVI5L	19	7911385	8.16E-05	protein-coding gene
ZNF486	19	20278022	9.50E-05	protein-coding gene

Note: Table includes genes with *p*-values below .0001.

Table 3.13: Univariate Genome Wide Association Gene-Based Results for Witnessed Non-Assault Trauma

Symbol	Chromosome	Start_Position	NominalP	Group
RHPN2	19	33469497	8.01E-06	protein-coding gene
PRSS23	11	86511281	1.34E-05	protein-coding gene
MFSD10	4	2932287	1.49E-05	protein-coding gene
SGCZ	8	13947372	2.11E-05	protein-coding gene
PVT1	8	128806778	2.71E-05	non-coding RNA
SNX13	7	17830384	3.85E-05	protein-coding gene
GPATCH1	19	33571785	5.15E-05	protein-coding gene
CD8A	2	87011727	5.93E-05	protein-coding gene
XKR5	8	6666040	6.01E-05	protein-coding gene
CWF19L2	11	107197071	8.01E-05	protein-coding gene

Note: Table includes genes with *p*-values below .0001.

Table 3.13: Univariate Genome Wide Association Gene-Based Results for Witnessed Assault Trauma

Symbol	Chromosome	Start_Position	NominalP	Group
MIR548I2	**4**	**9557788**	**9.24E-08**	**non-coding RNA**
SPPL2A	15	50999736	3.54E-05	protein-coding gene
ANK1	8	41510743	6.11E-05	protein-coding gene
FLJ37505	12	128366161	7.60E-05	Unknown
MBD1	18	47797838	9.04E-05	protein-coding gene

Note: Table includes genes with *p*-values below .0001. Bolded genes are significant by FDR (threshold = 9.25×10^{-8}).

Table 3.15: Univariate Genome Wide Association Gene-Based Results for Experienced Non-Assault Trauma

Symbol	Chromosome	Start_Position	NominalP	Group
CGB5	19	49547101	3.08E-06	protein-coding gene
GEMIN6	2	39005326	8.89E-06	protein-coding gene
LOC100996583	1	2497973	9.30E-06	unknown
MMEL1	1	2522080	1.47E-05	protein-coding gene
FAM213B	1	2518188	1.51E-05	protein-coding gene
CGB1	19	49538825	2.08E-05	protein-coding gene
SNAR-G2	19	49534925	2.14E-05	non-coding RNA
CGB2	19	49535129	2.16E-05	protein-coding gene
MIR548I2	4	9557788	3.30E-05	non-coding RNA
TNFRSF14	1	2487803	5.66E-05	protein-coding gene
TTC34	1	2572806	7.87E-05	protein-coding gene
CGB8	19	49550894	8.61E-05	protein-coding gene

Note: Table includes genes with *p*-values below .0001.

Table 3.16: Univariate Genome Wide Association Gene-Based Results for Experienced Assault Trauma

Symbol	Chromosome	Start_Position	NominalP	Group
LOC100996583	**1**	**2497973**	**2.36E-07**	**unknown**
TTC34	**1**	**2572806**	**7.67E-07**	**protein-coding gene**
TNFRSF14	**1**	**2487803**	**1.00E-06**	**protein-coding gene**
MMEL1	**1**	**2522080**	**1.11E-06**	**protein-coding gene**
FAM213B	**1**	**2518188**	**5.06E-06**	**protein-coding gene**
CGB5	**19**	**49547101**	**6.96E-06**	**protein-coding gene**
CGB2	19	49535129	1.72E-05	protein-coding gene
EML1	14	100259744	1.83E-05	protein-coding gene
ZNF532	18	56530060	1.96E-05	protein-coding gene
AKR1B15	7	134233848	2.36E-05	protein-coding gene
SNAR-G2	19	49534925	2.78E-05	non-coding RNA
CGB1	19	49538825	3.40E-05	protein-coding gene
VAPA	18	9913954	6.93E-05	protein-coding gene
ATOX1	5	151122382	8.04E-05	protein-coding gene

Note: Table includes genes with *p*-values below .0001. Bolded genes are significant by FDR (threshold = 6.96×10^{-6}).

Table 3.17: Multivariate Genome Wide Association Gene-Based Results for All Trauma Variables

Symbol	Chromosome	Start_Position	NominalP	Group
MIR548I2	**4**	**9557788**	**5.62E-07**	**non-coding RNA**
TNFRSF14	**1**	**2487803**	**1.59E-06**	**protein-coding gene**
LOC100996583	**1**	**2497973**	**3.32E-06**	**unknown**
GEMIN6	**2**	**39005326**	**6.13E-06**	**protein-coding gene**
FAM213B	**1**	**2518188**	**7.86E-06**	**protein-coding gene**
TTC34	1	2572806	1.22E-05	protein-coding gene
SNAR-G2	19	49534925	1.76E-05	non-coding RNA
CGB5	19	49547101	2.09E-05	protein-coding gene
CGB2	19	49535129	2.16E-05	protein-coding gene
CGB1	19	49538825	2.16E-05	protein-coding gene
MMEL1	1	2522080	2.94E-05	protein-coding gene
CGB8	19	49550894	3.51E-05	protein-coding gene
SNAR-G1	19	49540276	5.01E-05	non-coding RNA
EML1	14	100259744	5.92E-05	protein-coding gene

Note: Table includes genes with *p*-values below .0001. Bolded genes are significant by FDR (threshold = 7.86×10^{-6}).

Table 3.18: Multivariate Genome Wide Association Gene-Based Results for All Trauma Variables and Internalizing Psychopathology

Symbol	Chromosome	Start_Position	NominalP	Group
MIR548I2	**4**	**9557788**	**7.03E-07**	**non-coding RNA**
TNFRSF14	**1**	**2487803**	**1.94E-06**	**protein-coding gene**
LOC100996583	**1**	**2497973**	**4.00E-06**	**unknown**
GEMIN6	**2**	**39005326**	**7.83E-06**	**protein-coding gene**
FAM213B	**1**	**2518188**	**9.19E-06**	**protein-coding gene**
SNAR-G2	19	49534925	1.52E-05	non-coding RNA
TTC34	1	2572806	1.57E-05	protein-coding gene
CGB2	19	49535129	2.64E-05	protein-coding gene
CGB5	19	49547101	2.66E-05	protein-coding gene
CGB1	19	49538825	2.71E-05	protein-coding gene
MMEL1	1	2522080	3.10E-05	protein-coding gene
CGB8	19	49550894	4.50E-05	protein-coding gene
SNAR-G1	19	49540276	6.33E-05	non-coding RNA
EML1	14	100259744	7.72E-05	protein-coding gene

Note: Table includes genes with *p*-values below .0001. Bolded genes are significant by FDR (threshold = 9.19×10^{-6}).

Table 3.19: Multivariate Genome Wide Association Gene-Based Results for Dependent Stressful Life Events and Externalizing Psychopathology

Symbol	Chromosome	Start_Position	NominalP	Group
SNAR-G2	**19**	**49534925**	**$1.40x10^{-6}$**	**non-coding RNA**
CGB2	**19**	**49535129**	**$3.14x10^{-6}$**	**protein-coding gene**
CGB5	**19**	**49547101**	**$5.10x10^{-6}$**	**protein-coding gene**
CGB1	**19**	**49538825**	**$5.43x10^{-6}$**	**protein-coding gene**
CGB8	**19**	**49550894**	**$6.57x10^{-6}$**	**protein-coding gene**
SNAR-G1	**19**	**49540276**	**$8.44x10^{-6}$**	**non-coding RNA**
WNT9A	1	228109164	$3.84x10^{-5}$	protein-coding gene
SPPL2A	15	50999736	$4.88x10^{-5}$	protein-coding gene
TNFRSF14	1	2487803	$9.84x10^{-5}$	protein-coding gene

Note: Table includes genes with *p*-values below .0001. Bolded genes are significant by FDR (threshold = $8.44x10^{-6}$).

Table 3.20: Multivariate Genome Wide Association Gene-Based Results for Internalizing and Externalizing Psychopathology

Symbol	Chromosome	Start_Position	NominalP	Group
OR1I1	19	15197876	0.00011	protein-coding gene
INTS10	8	19674917	0.00011	protein-coding gene
LOC102723544	12	362607	0.00018	unknown
WSCD1	17	5973933	0.00022	protein-coding gene
LINC01448	7	42701325	0.00024	non-coding RNA

Note: Table includes genes with *p*-values below .0001.

Figure 3.1: QQ-Plot of SNP and Gene *p*-values for Internalizing Psychopathology

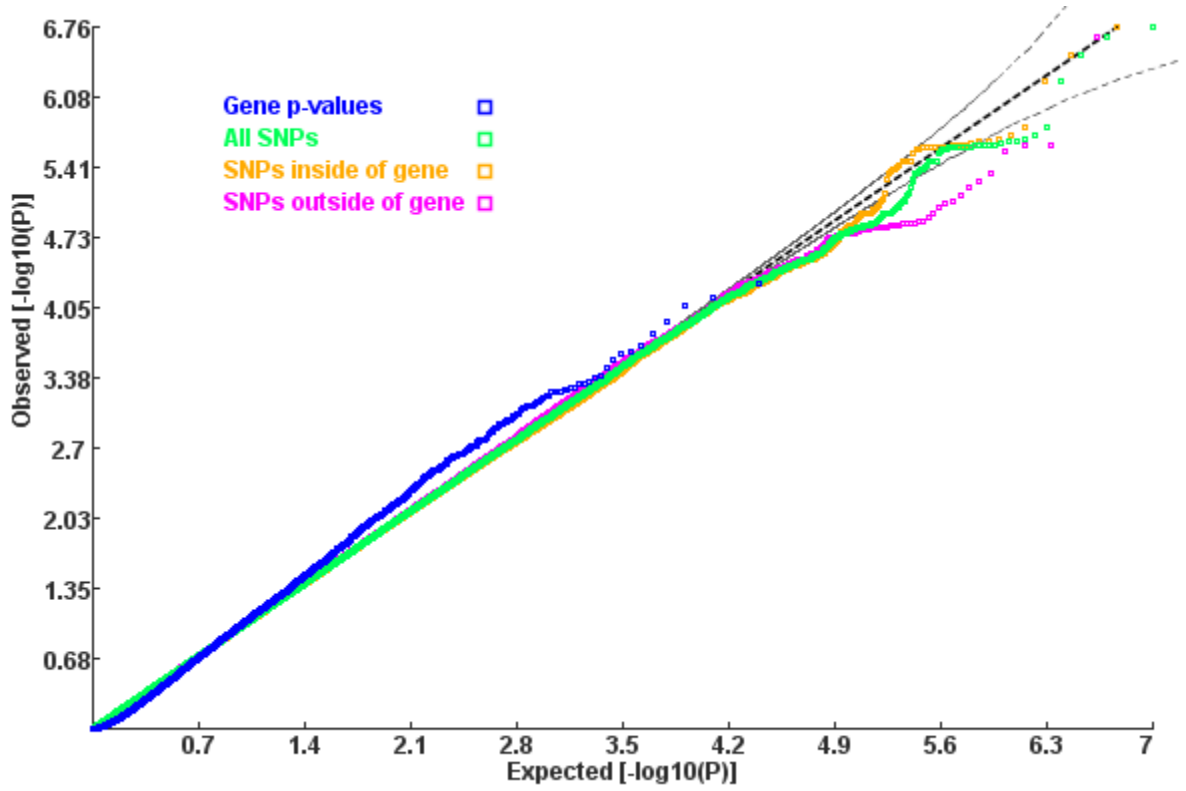


Figure 3.2: QQ-Plot of SNP and Gene *p*-values for Externalizing Psychopathology

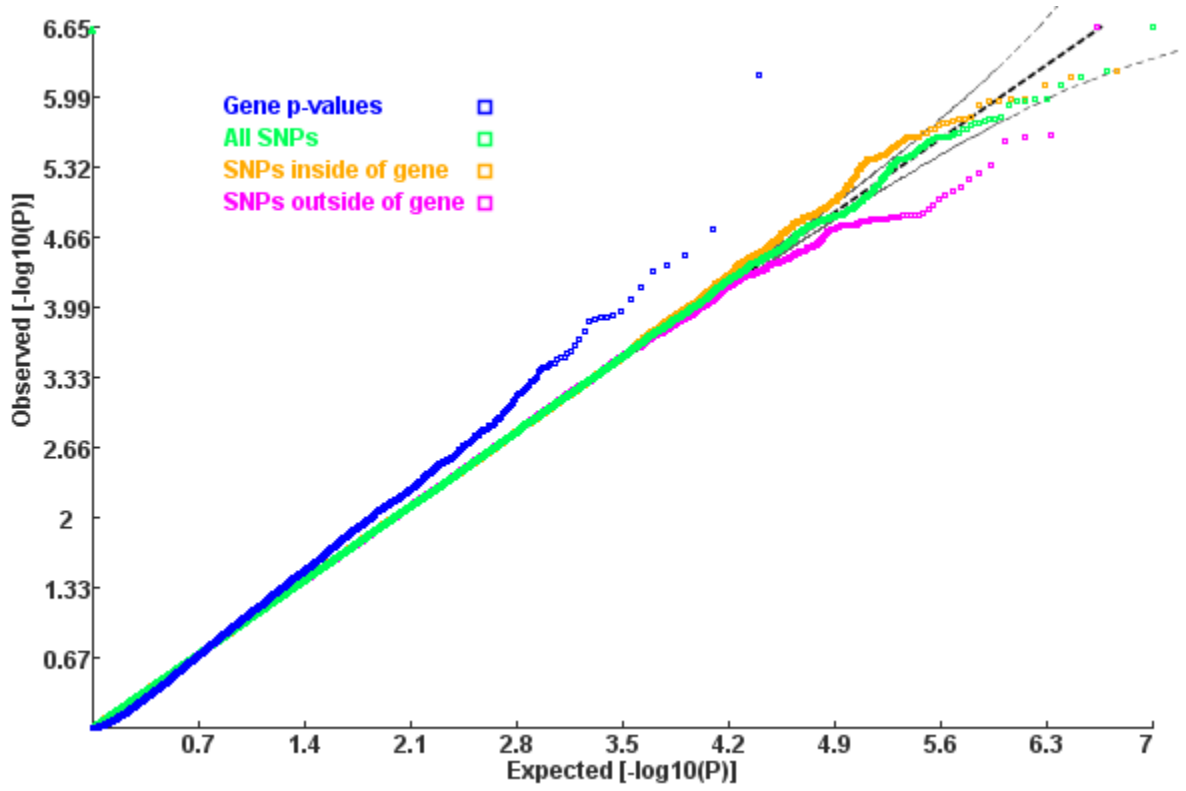


Figure 3.3: QQ-Plot of SNP and Gene *p*-values for Dependent Stressful Life Events

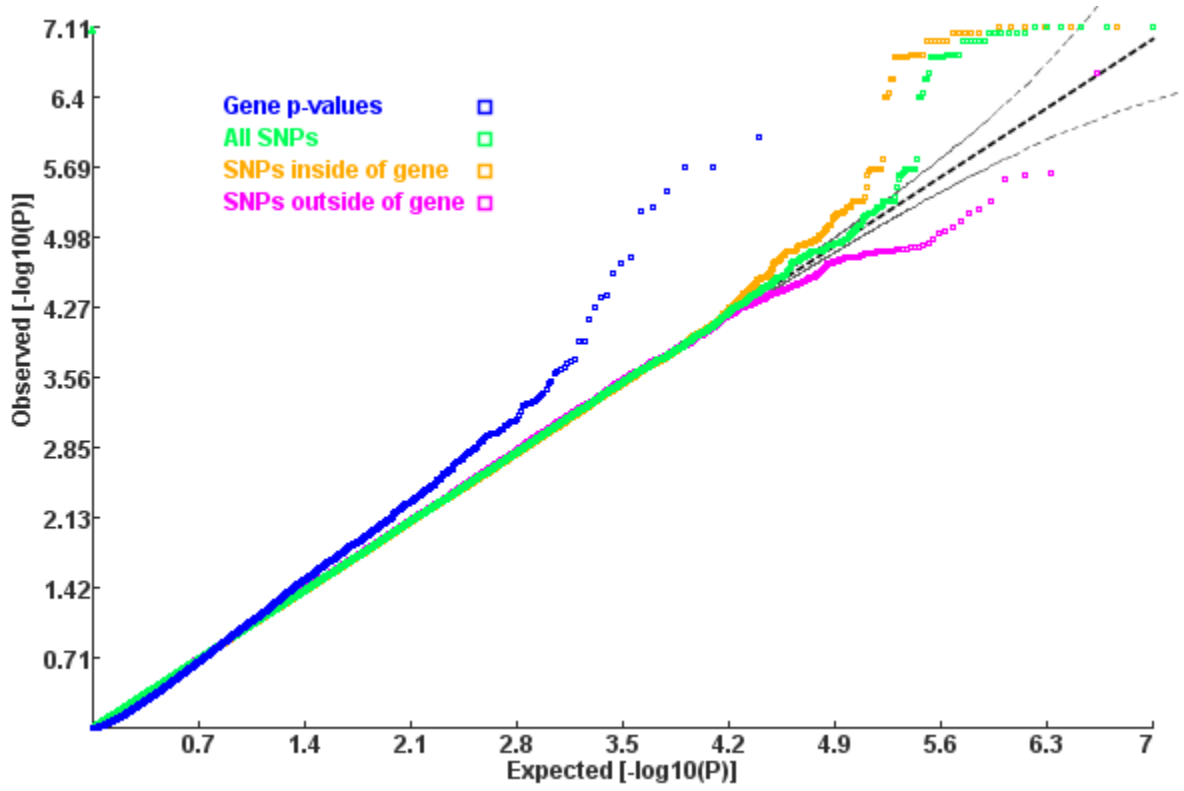


Figure 3.4: QQ-Plot of SNP and Gene *p*-values for Independent Stressful Life Events

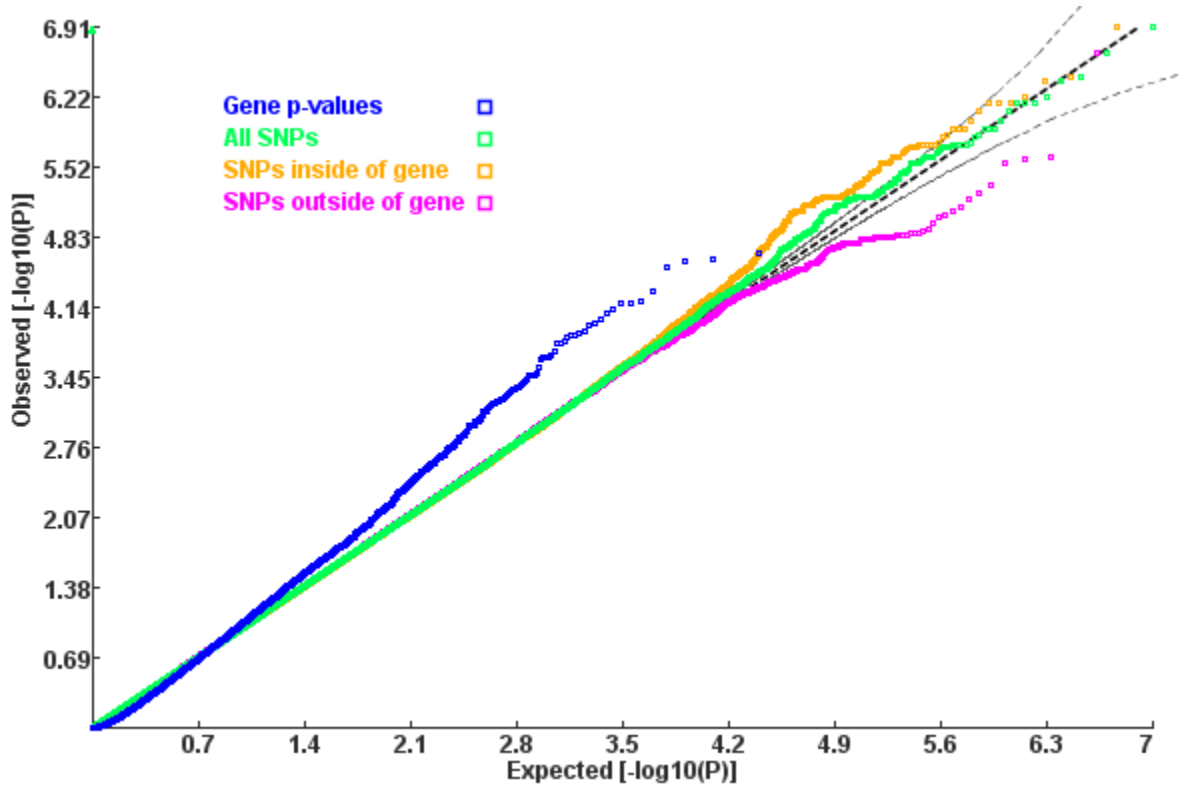


Figure 3.5: QQ-Plot of SNP and Gene *p*-values for Witnessed Non-Assault Trauma

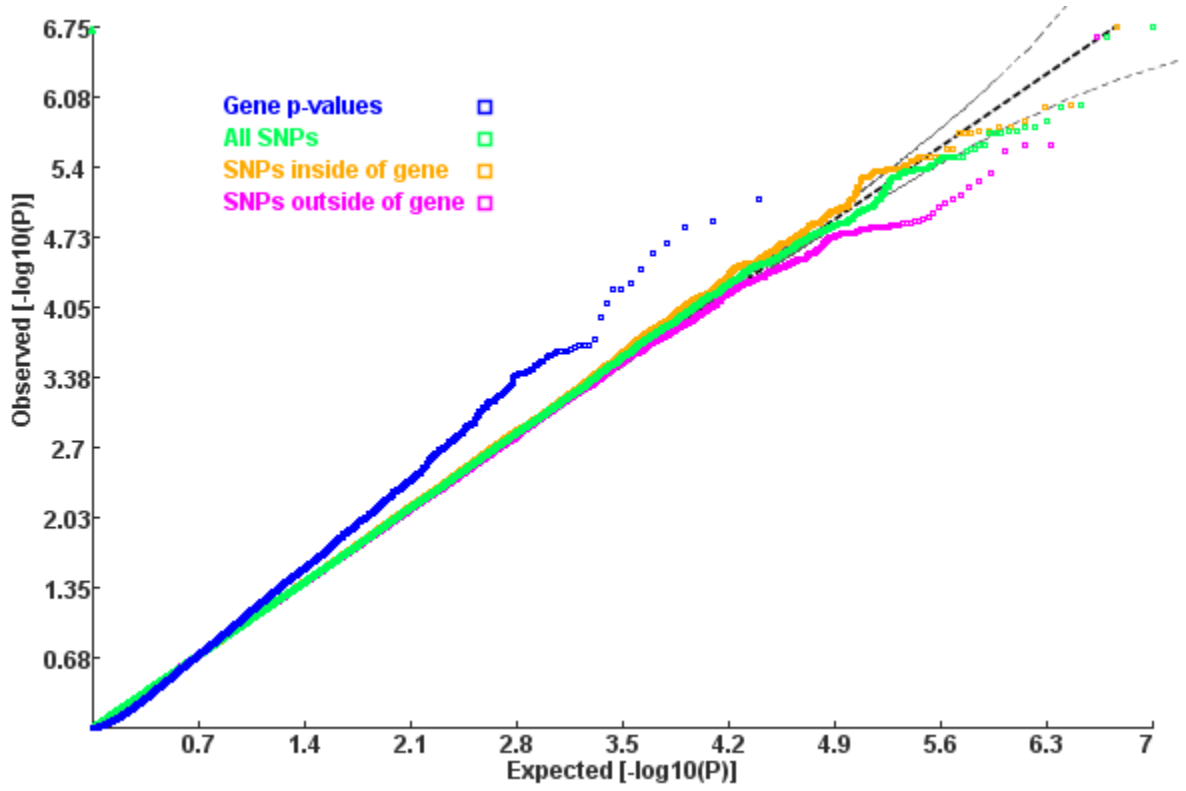


Figure 3.6: QQ-Plot of SNP and Gene *p*-values for Witnessed Assault Trauma

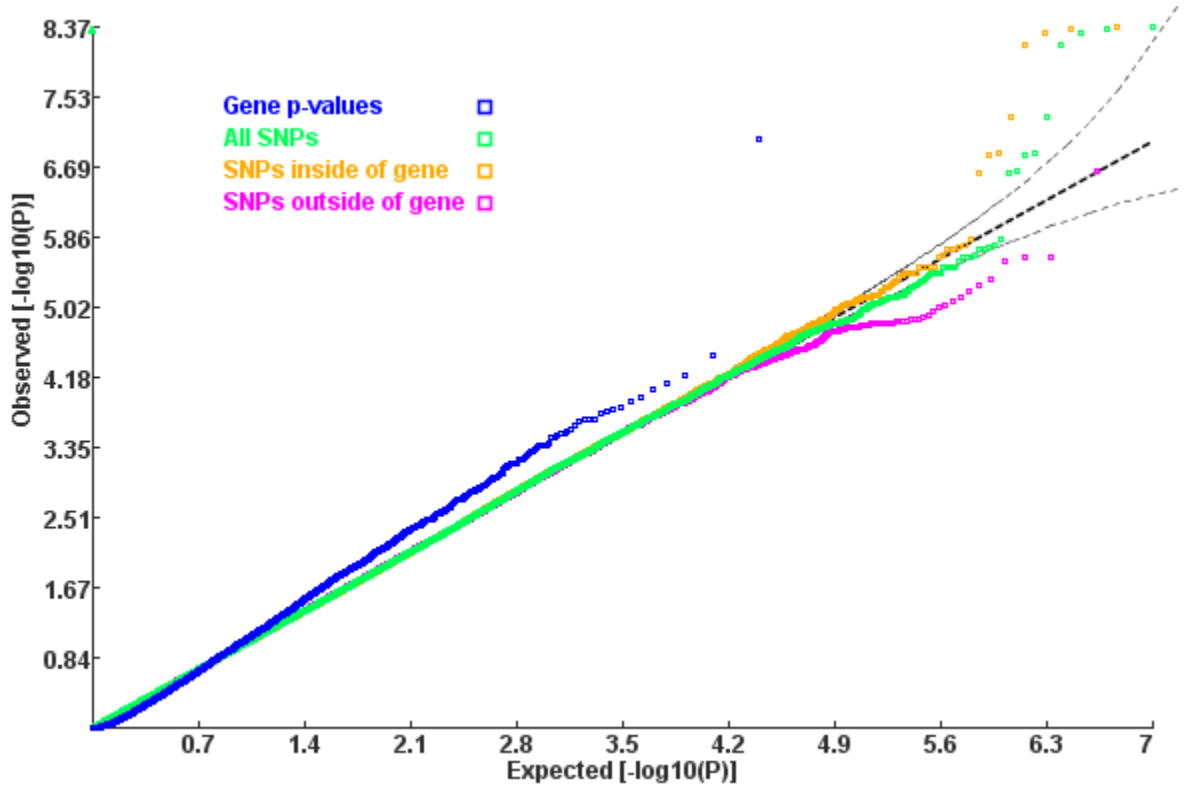


Figure 3.7: QQ-Plot of SNP and Gene *p*-values for Experienced Non-Assault Trauma

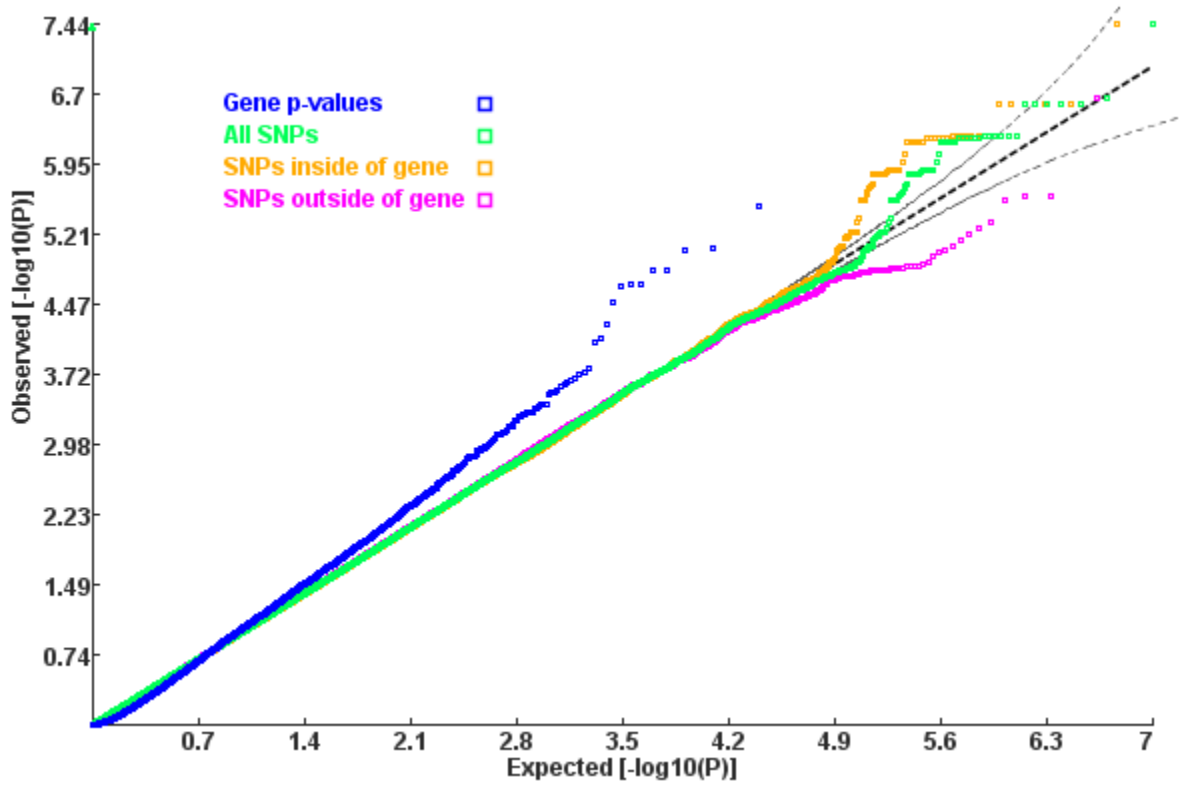


Figure 3.8: QQ-Plot of SNP and Gene *p*-values for Experienced Assault Trauma

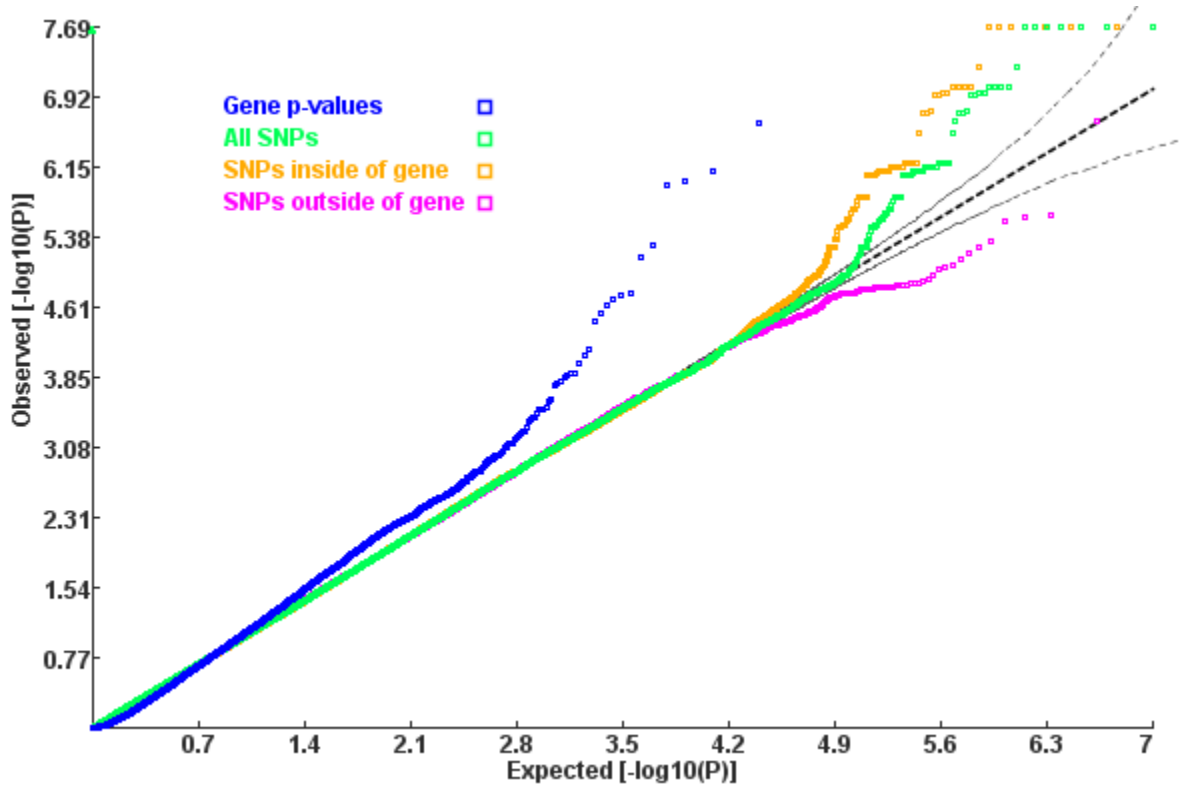


Figure 3.9: Manhattan Plot of Gene *p*-values for Internalizing Psychopathology

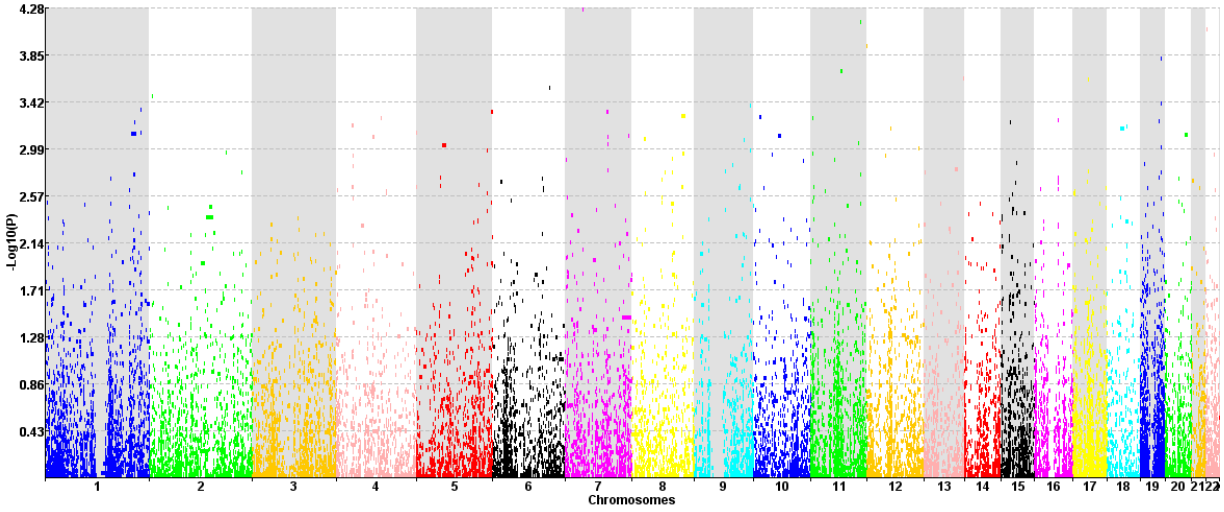


Figure 3.10: Manhattan Plot of Gene *p*-values for Externalizing Psychopathology

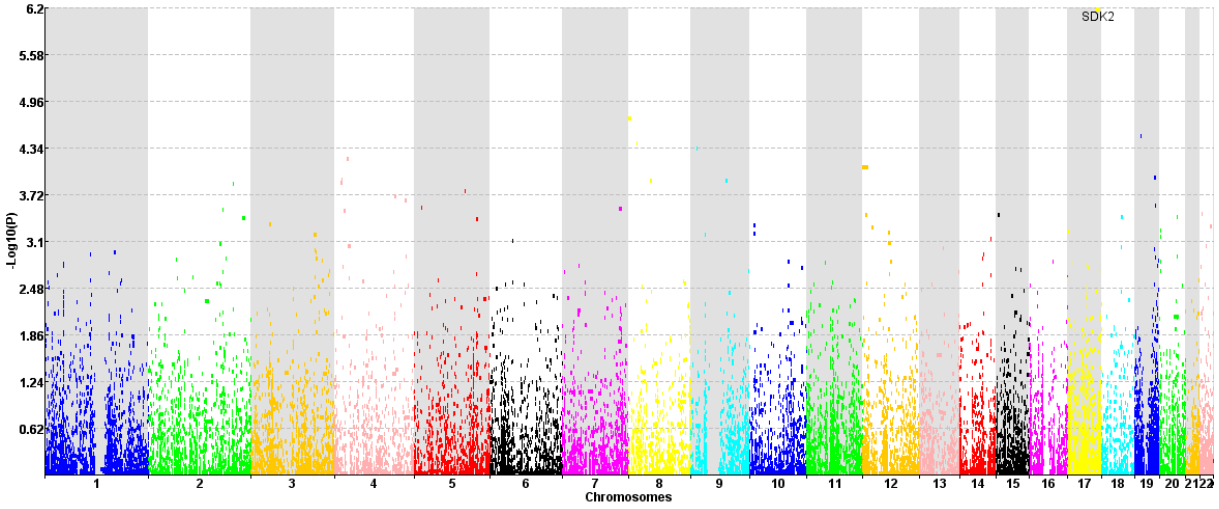


Figure 3.11: Manhattan Plot of Gene *p*-values for Dependent Stressful Life Events

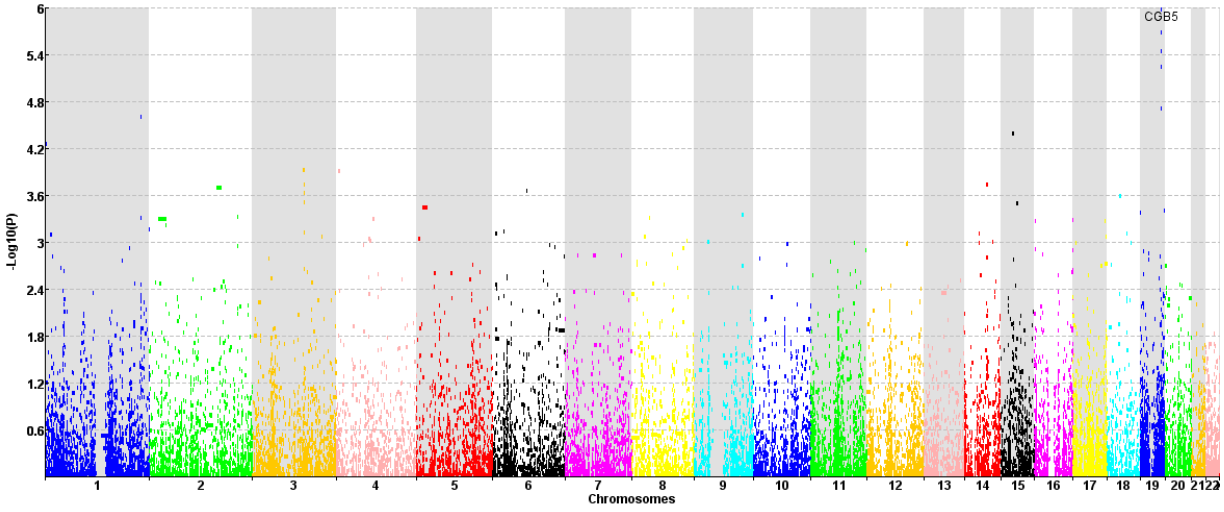


Figure 3.12: Manhattan Plot of Gene *p*-values for Independent Stressful Life Events

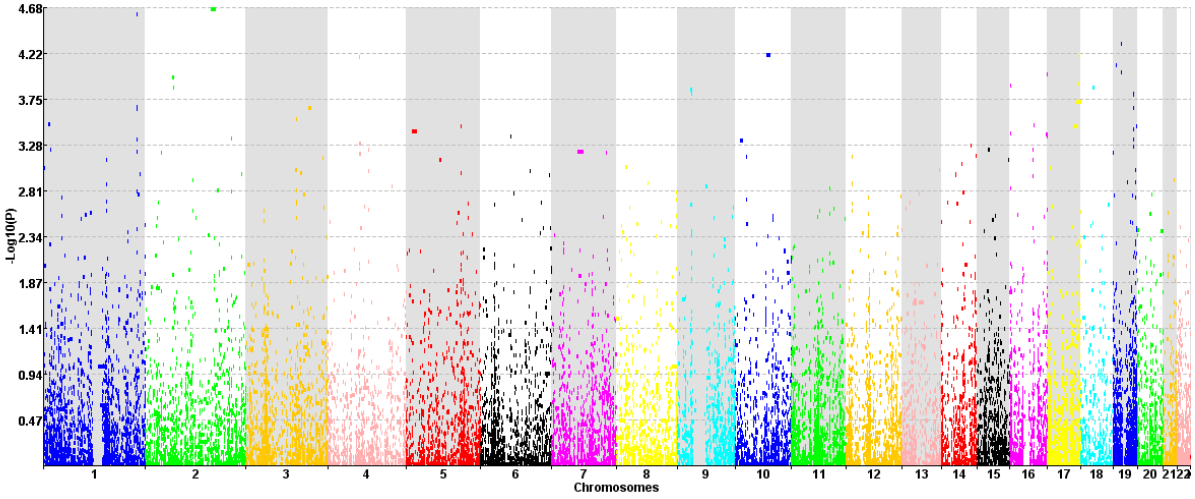


Figure 3.13: Manhattan Plot of Gene *p*-values for Witnessed Non-Assault Trauma

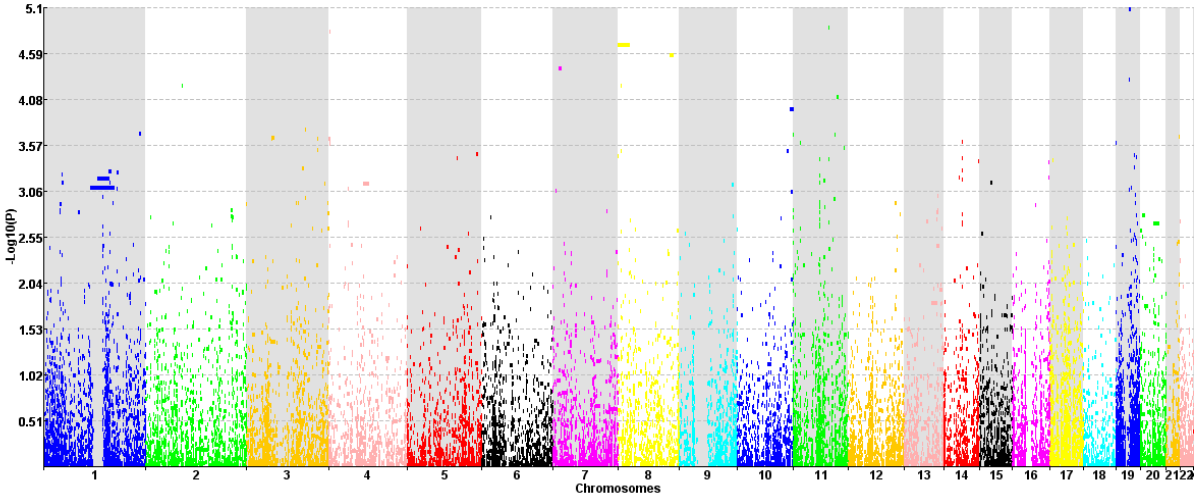


Figure 3.14: Manhattan Plot of Gene *p*-values for Witnessed Assault Trauma

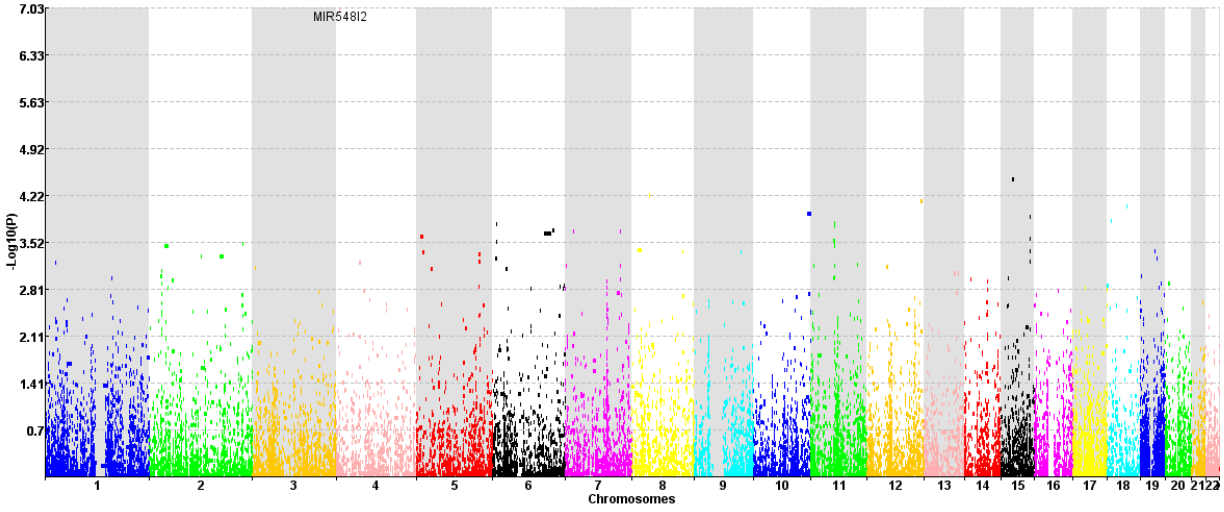


Figure 3.15: Manhattan Plot of Gene *p*-values for Experienced Non-Assault Trauma

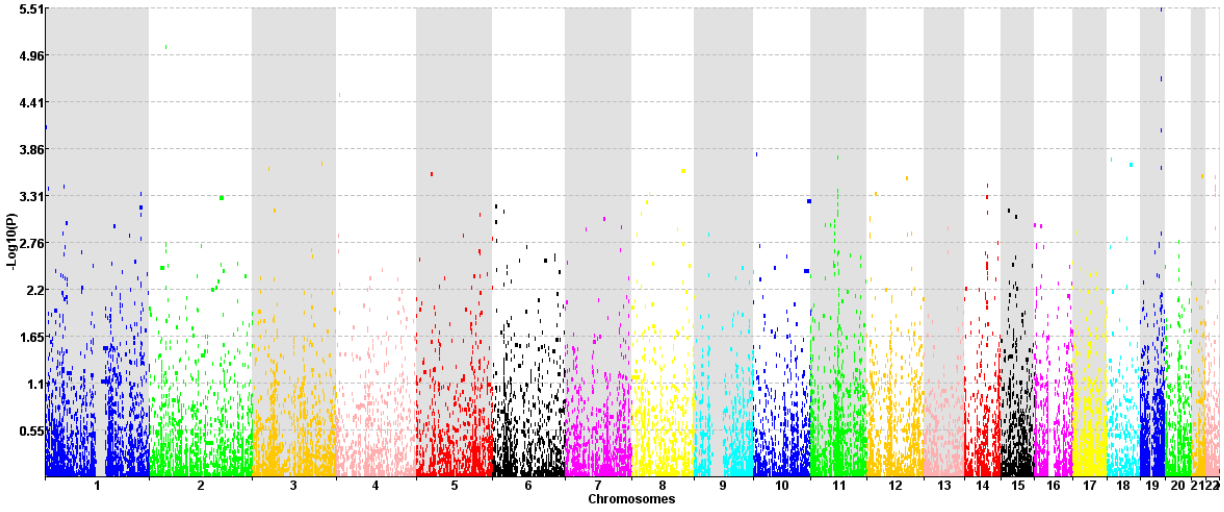


Figure 3.16: Manhattan Plot of Gene *p*-values for Experienced Assault Trauma

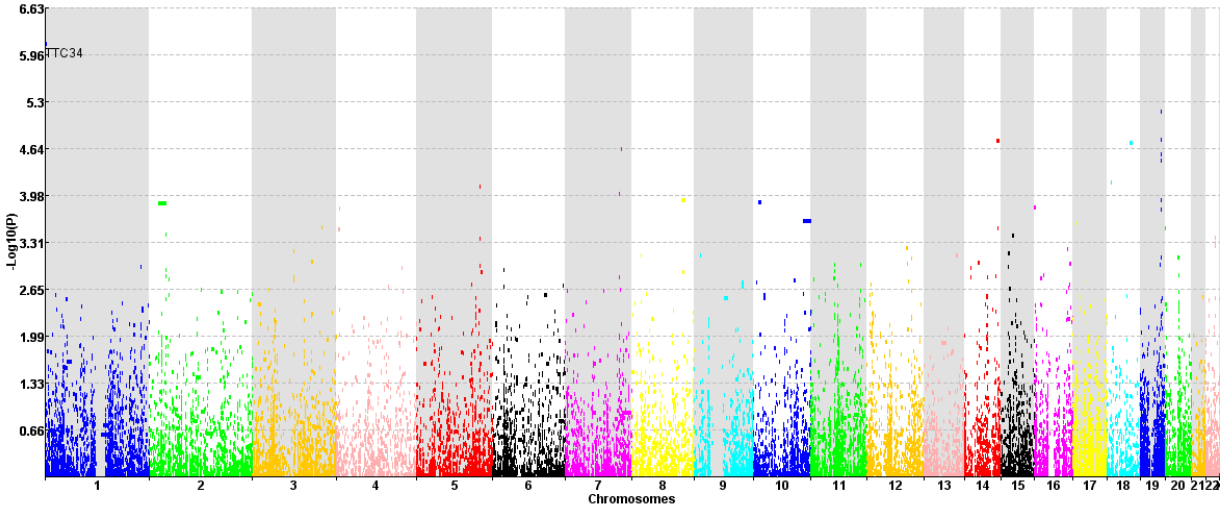


Figure 3.17: Manhattan Plot of Gene *p*-values for All Forms of Trauma

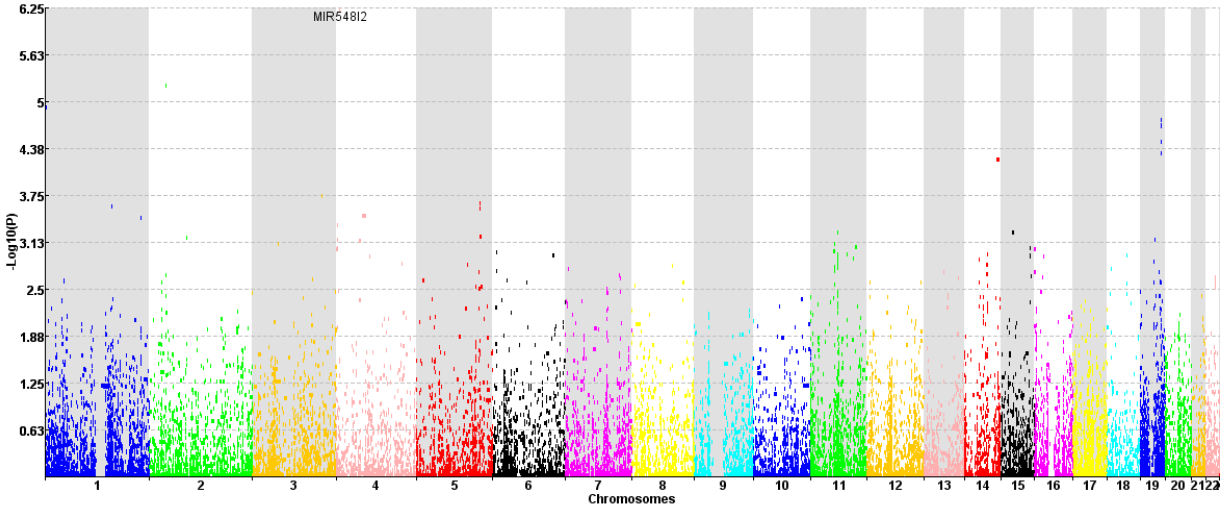


Figure 3.18: Manhattan Plot of Gene *p*-values for All Forms of Trauma and Internalizing Psychopathology

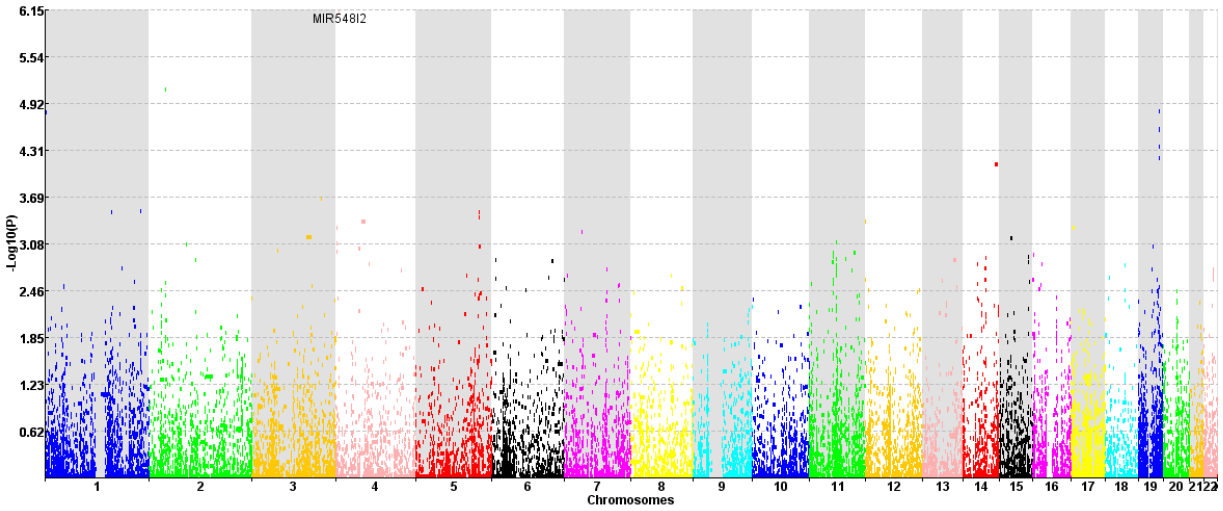


Figure 3.19: Manhattan Plot of Gene *p*-values for Dependent Stressful Life Events and Externalizing Psychopathology

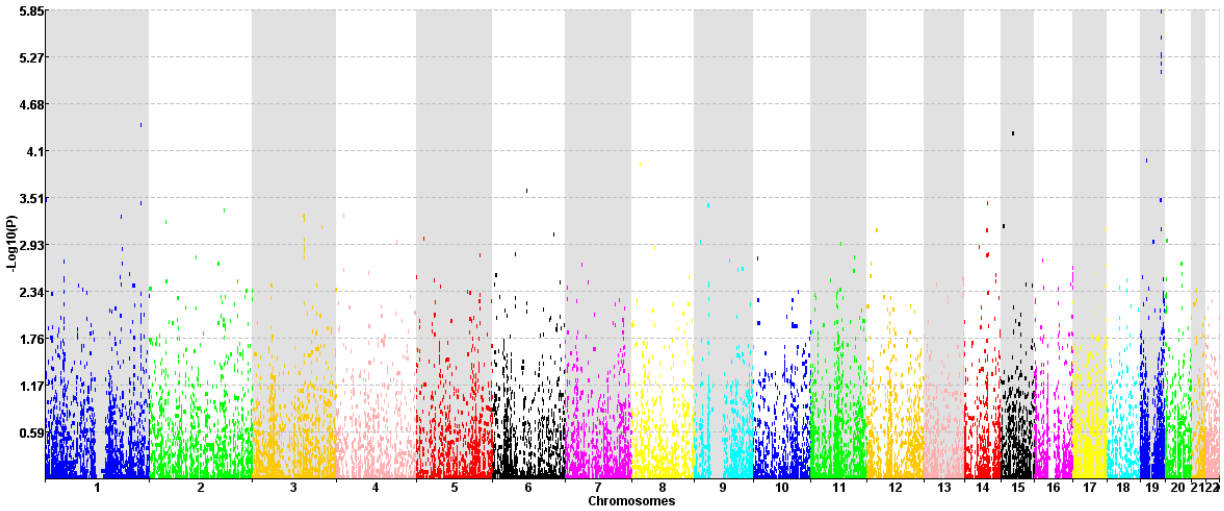


Figure 3.20: Manhattan Plot of Gene *p*-values for Internalizing and Externalizing Psychopathology