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Genetic Influence on Resilience to Potentially Traumatic Events

Kosuke Niitsu
University of Nebraska Medical Center

GENETIC INFLUENCE ON RESILIENCE TO POTENTIALLY TRAUMATIC EVENTS

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Kosuke Niitsu

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Supervisory Committee:

Michael J. Rice, Ph.D.	Scott F. Stoltenberg, Ph.D.
Cecilia R. Barron, Ph.D.	Kevin A. Kupzyk, Ph.D.

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Most individuals experience at least one potentially traumatic event (PTE), such as a natural disaster. When exposed to PTEs, some individuals are more vulnerable to develop psychopathology, such as Post-Traumatic Stress Disorder (PTSD). In contrast, others are less adversely affected by PTEs, who are often described as "resilient". A concept analysis of resilience (Manuscript #1) revealed: the antecedent is PTE; the defining attributes are ego-resiliency, emotion regulation, heredity, and social support; and the consequences are none to mild psychopathological symptoms and positive adaptation. Based on a systematic review of genetic influence on resilience (Manuscript #2), the following 10 polymorphisms were identified as candidate genes associated with resilience and selected in this study: rs25531 in *5-HTTLPR*, rs4680 in *COMT*, rs6265 in *BDNF*, rs1800955 in *DRD4*, rs1800497 in *DRD2*, rs53576 in *OXTR*, rs4606 in *RGS2*, rs1006737 in *CACNA1C*, rs9296158 in *FKBP5*, & rs7209436 in *CRHR1*. A total of 450 college students participated in this dissertation study (Manuscript #3), completed questionnaires, and donated their buccal cells to extract DNA for genotyping. The results indicated individuals exhibited lower resilience outcomes (*i.e.,* more psychological distress and less positive adaptation) as they experienced more PTEs. However, the effect of PTEs on resilience outcomes was weaker among individuals with high ego-resiliency, strong emotion regulation flexibility, high perceived social support, and the Val allele(s) of rs4680 in *COMT*. Additionally, the effect of unfavorable physical and sexual experiences on resilience outcomes was weaker among individuals with the G allele(s) of rs4606 in *RGS2*, the T allele(s) of rs7209436 in *CRHR1*, and higher scores (*i.e.,* more major alleles) of a Polygenic Susceptibility Score. Major limitation is the cross-sectional

design of this study because it cannot assess resilience over the time. In a future study, additional candidate genes associated with resilience need to be investigated, preferably with a longitudinal design among individuals exposed to more specific PTEs. Furthermore, if collaboration with other researchers is possible, a systematic approach, such as Genome-Wide Association Study (GWAS), can be considered.

DEDICATION

To individuals affected by the 2011 Great East Japan Earthquake (15,893 deaths, 2,553 missing, and 3,523 deaths related with the disaster to date) and those affected by other potentially traumatic events, doing their best to stay resilient.

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5-HTTLPR	serotonin-transporter-linked polymorphic region
BDNF	brain-derived neurotrophic factor
CACNA1C	calcium voltage-gated channel subunit alpha1 C
CD-RISC	Connor-Davidson Resilience Scale
COMT	catechol-o-methyltransferase
CRHR1	corticotropin releasing hormone receptor 1
DRD4	dopamine receptor D4
DRD2	dopamine receptor D2
ER89	Ego-Resiliency Scale
ERQ	Emotion Regulation Questionnaire
FKBP5	FK506 binding protein 5
MHI	Mental Health Inventory
OXTR	oxytocin receptor
PACT	Perceived Ability to Cope with Trauma
PSS	polygenic susceptibility score
PTEs	potentially traumatic events
RGS2	regulator of G-protein signaling 2
SNP	single-nucleotide polymorphism
SOC	sense of coherence
SSS	Social Support Survey
THQ	Trauma History Questionnaire
VNTR	variable number tandem repeat

INTRODUCTION

At 2:46 pm on Friday, March 11, 2011, the Great East Japan Earthquake occurred. It triggered the violent tsunami waves, caused nuclear accidents, and took away so many lives. When it happened, I did not know what I could do or how I could help. All I did was to join fundraising activities and donated money. My friends and colleagues kept asking me, a psychiatric-mental health nurse, about Post-Traumatic Stress Disorder (PTSD) and stress response syndromes. In my Master of Science in Nursing program, I focused my master's project on the psychological effect of indirect exposure associated with intense media coverage of the Great East Japan Earthquake (Niitsu, Watanabe-Galloway, Sayles, Houfek, & Rice, 2014). It motivated me to further study stress reactions in the Ph.D. program.

Two years later, during my Ph.D. coursework, I paid a visit to the affected area. The scenery was horrific and unbearable to imagine how it was like for local people to see their hometown destroyed. When I had an opportunity to interact with the local people, to my surprise, they were incredibly welcoming, warm, and kind. One gentleman told me that he lost his home, family, and friends. However, he smiled and thanked me for visiting his hometown. Not only he but also other local people were unexpectedly "resilient". This experience led me to further develop my knowledge and skills about resilience during my Ph.D. program, specifically for my dissertation.

This dissertation is formatted in the manuscript format consisting of an introduction, three manuscripts, and a synthesized discussion. In Manuscript #1, I explored what resilience is through a concept analysis by the Walker and Avant (2011) method and what may contribute to individual differences in resilience to potentially traumatic events, such as an earthquake. In Manuscript #2, I focused on the genetic aspect and described selected genes that are associated with resilience through a

systematic review. In Manuscript #3, I investigated resilience among students enrolled at a Midwestern university to examine the relationships between resilience, potentially traumatic events, genotypes, and intrapersonal (a personality trait, emotion regulation) and environmental (social support) variables. Finally, in the discussion, I synthesized the three manuscripts, reflected how they contributed to my research, and considered how this work informs my future research program.

MANUSCRIPT #1: A CONCEPT ANALYSIS OF RESILIENCE INTEGRATING GENETICS

Submitted for a publication:

Niitsu, K., Houfek, J. F., Barron, C. R., Stoltenberg, S. F., Kupzyk, K. A., & Rice, M. J. (2017). A concept analysis of resilience integrating genetics. *Issues in Mental Health Nursing*.

Abstract

Although clinicians and researchers are interested in the phenomenon of resilience, there is no agreed-upon definition of resilience. Scientific evidence suggests that resilience is influenced by intrapersonal (e.g. personality traits) and environmental (e.g. social support) variables. A concept analysis was conducted to better understand the meaning of resilience. In this analysis, the antecedent of resilience was a *potentially traumatic event*; the defining attributes were *ego-resiliency*, *emotion regulation*, *social support*, and *heredity*; and the consequences were *none to mild psychopathological symptoms* and *positive adaptation*. This analysis can help us better understand resilience and its relationships to both intrapersonal and environmental variables.

Keywords: resilience, concept analysis, genetics, trauma, adversity

Introduction

Resilience has been of increasing interest among both clinicians and researchers. However, there is no single agreed-upon definition of resilience in the clinical or scientific literature (Fletcher & Sarkar, 2013; Southwick & Charney, 2012b; Southwick, Litz, Charney, & Friedman, 2011) even among experts specializing in resilience research (Southwick, Bonanno, Masten, Panter-Brick, & Yehuda, 2014). For example, it has been debated if resilience is best categorized as an individual trait, a process, an outcome, a dynamic developmental process, or all of the above (Reich, Zautra, & Hall, 2010).

Concept analysis is the process of examining the basic elements of a concept to investigate its structure and function (Walker & Avant, 2011). According to Walker and Avant (2011), a concept has three components: antecedents, defining attributes, and consequences. Although the analysis itself must be rigorous and precise, the end product is always tentative and may be different than other analyses of the same concept, because a concept is constantly changing, influenced by cultural, contextual, and societal factors (Walker & Avant, 2011). Several investigators have conducted a concept analysis on resilience with somewhat different results. For example, Dyer and McGuinness (1996) identified antecedents of resilience as: (1a) *adversity*, and (1b) *the presence of at least one caring, emotionally available person at some point in the person's life*; defining attributes as (2a) *rebounding and carrying on*, (2b) *sense of self*, (2c) *determination*, and (2d) *prosocial attitude*; and consequences as (3a) *effective coping*, (3b) *toughening effect*, (3c) *sense of having overcome one situation*. In contrast, Gillespie, Chaboyer, and Wallis (2007) analyzed the antecedents of resilience as (1a) *adversity*, (1b) *interpretation of the situation as traumatic*, (1c) *cognitive ability*, and (1d) *realistic world-view*; defining attributes as (2a) *self-efficacy*, (2b) *hope*, and (2c) *coping*; and consequences as (3a) *integration*, (3b) *control*, (3c) *adjustment*, and (3d) *growth*.

Whereas Dyer and McGuinness (1996) considered coping, for example, as a consequence of resilience, Gillespie et al. (2007) identified coping a defining attribute.

In addition, recent advances in molecular genetics and genetic technologies enable us to investigate gene by environment interactions and the molecular mechanisms that promote resilience (Cicchetti, 2010). To our knowledge, none of the concept analyses on resilience have incorporated a genetic aspect. The purpose of this concept analysis is to better understand the broad meaning of resilience, including genetic influence on resilience.

Method

Using the Walker and Avant (2011) method, uses of the concept associated with resilience were identified first. Next, antecedents, defining attributes, and consequences of resilience were analyzed. To do so, the elements that are the most frequently associated with the concept and that allow the analyst to have the broadest insight into the concept were identified (Walker & Avant, 2011). Finally, cases (model, related, and contrary) based on the results of the concept analysis of resilience were developed. Empirical evidence was incorporated throughout the analysis.

Search engines, including PubMed, CINAHL, and Google Scholar were utilized to search for articles addressing resilience. The following keywords were used: “resilience”, “genetics”, “genes”, “polymorphisms”, “posttraumatic stress disorder (PTSD)”, “trauma”, and “adversity”. The publication date was not restricted to review comprehensively. Approximately 500 publications were reviewed, including book chapters and peer-reviewed articles. Although animal studies are essential in behavioral genetic research (Plomin, Defries, Knopik, & Neiderhiser, 2013), only human studies were reviewed.

Identifying Uses of the Concept of Resilience

One task at the initial stage of concept analysis is to identify the many uses of the concept by using resources, such as dictionaries, thesauruses, and interdisciplinary literature (Walker & Avant, 2011). The term, resilience, derives from the Latin verb *resilire*, which means "to leap back, spring back" (Simpson, 1959, p. 517). The Oxford English Dictionary defines resilience as "the (*or* an) act of rebounding or spring back; rebound, recoil" (Simpson & Weiner, 1989, p. 714). Another dictionary, the Webster's New World College Dictionary, defines resilience as "a) the ability to bounce or spring back into shape, position, etc. b) the ability to recover strength, spirits, good humor, etc." (Agnes, 2000, p. 1220). According to a thesaurus (Dictionaries, 1995), synonyms of resilience are:

> 1. The ability to recover quickly from depression or discouragement: bounce, buoyancy, elasticity, resiliency. 2. The quality or state of being flexible: bounce, ductility, elasticity, flexibility, flexibleness, give, malleability, malleableness, plasticity, pliability, pliableness, pliancy, pliantness, resiliency, spring, springiness, suppleness (p. 830).

Although *flexibility*, for example, is one of the synonyms for resilience, it is slightly different from resilience because *flexibility* does not necessarily require an object to return to its original shape, whereas resilience does.

In material sciences, resilience refers to the ability of certain materials, such as rubber, to withstand compression and return to their original shape or position (Denhardt & Denhardt, 2010). In engineering, resilience is "a return time to a single, global equilibrium" (Gunderson, 2000, p. 435). In ecological systems, resilience is considered as "the amount of disturbance that a system can absorb without changing stability domains" (Gunderson, 2000, p. 435). In physics, resilience is "the energy per unit volume absorbed by a material when it is subjected to strain, or the maximum value of

this when the elastic limit is not exceeded" (Simpson & Weiner, 1989, p. 714). Resilience per cubic inch in direct tension or compression may be formulated as $f/2E$ where f is the intensity of stress induced and E is the modulus of elasticity (Almedom & Glandon, 2007).

The concept of resilience was adapted to psychology to describe individuals who can "bounce back" when they face challenges (Denhardt & Denhardt, 2010). Analogous to material science of resilience to explain psychological resilience, one metaphor is *wrought iron* that is "soft, malleable, and bends without breaking (resilient)" in contrast to *cast iron* that is "hard, brittle, and breaks easily (not resilient)" (Tugade & Fredrickson, 2004, p. 320). However, the metaphor of "wrought iron" does not necessarily capture the quality of resilience to return to its original shape or state (*i.e.,* flexibility vs. resilience).

Because one of authors (KN) grew up in Japan, the resilience literature written in the Japanese language was also explored to describe its multicultural translatability. There is debate about how to define resilience in Japanese as well, especially because the science of resilience emerged from the Western countries (Ishihara & Nakamaru, 2007). In Western countries, the context of adversity and the cultural background of the study participants may be quite different from Japan (Ishihara & Nakamaru, 2007). Resilience is often translated into Japanese simply as "resilience" to imply that the term is imported from the West. In fact, one Japanese researcher who developed a scale to measures resilience named it "Bidimensional Resilience Scale (BRS)" (Hirano, 2010), without translating the term into Japanese. In this scale, Hirano (2010) operationalize resilience factors into two dimensions: (1) *innate resilience factors* that include optimism, control, sociability, and vitality, and (2) *acquired resilience factors* that include attempting to solve a problem, self-understanding, and understanding others. This conceptualization of resilience incorporates both trait (innate) and dynamic developmental (acquired) categories or views of resilience.

In contrast, other Japanese researchers have attempted to academically translate the word, resilience, into Japanese, although there is no single agreed-upon term. For example, Nishizono (2007) called resilience “Kaihuku-ryoku (回復力)”. “Kaifuku (回復)” means *recovery* or *healing*, and “ryoku (力)” means *ability*, *power*, or *strength*. Another proposed term is “Sippei-teikou-sei (疾病抵抗性)” or more simply, “Kou-byou-ryoku (抗病力)”, implying that the concept of resilience can occur in both health and illness: (1) the ability to withstand the onset of disease *while* healthy, and (2) the ability to recover, or the “restitutive” force, *after* becoming ill (Den, Yagi, Tanabe, & Watanabe, 2008; Yagi, Den, & Watanabe, 2007). More casually, the *Nippon Hoso Kyokai* (NHK, 2014), which is Japan’s national public broadcasting organization, has released a documentary about resilience, and they coined a new Japanese term, “Gyakkyou-ryoku (逆境力)”. “Gyakkyou (逆境)” means *adversity* or *challenge*, and “ryoku (力)” is the *ability*, *power*, or *strength*. This definition incorporates the idea that adversity is essential for resilience to occur.

Whether in the Western countries or in Japan, the definition of resilience varies greatly. Even in the cast vs. wrought iron example above, it is debatable if resilience is a trait (e.g. wrought iron being flexible), process (e.g. withstanding bending), or outcome (e.g. not broken). However, whether it is material science or engineering or psychology, it appears the presence of a force (e.g. to bend the iron) or a threat is required for resilience to emerge as a phenomenon and then an outcome follows as an evidence of resilience (e.g. not broken) influenced by characteristics (e.g. malleable) and other factors. In this sense, an antecedent must happen first and then consequences of resilience occur influenced by attributes of resilience. Overall, resilience could refer to

the dynamic process that comprehensively includes the trait, ability, process, *and* outcome.

Identifying Antecedents, Defining Attributes, and Consequences of Resilience

Antecedent of Resilience

Antecedents are events or incidents that occur prior to the manifestation of the concept (Walker & Avant, 2011). In order for resilience as a dynamic process to occur, an event that carries substantial threat of a negative outcome must happen (Carver, 1998; Davydov, Stewart, Ritchie, & Chaudieu, 2010; Rutten et al., 2013); such an extreme adversity is described as a potentially traumatic event (PTE) (Bonanno, 2004).

Potentially traumatic event (PTE). Historically, the science of resilience was established by the developmental researchers who investigated children who "did well" despite exposure to risk factors such as poverty (Garmezy, 1993), maternal mental illness (Rutter, 1987), and perinatal complications (Werner, 1994). The concept of resilience has evolved (Tusaie & Dyer, 2004), and participants in resilience studies have been expanded from children at risk to adults who are "in otherwise normal circumstances who are exposed to an isolated and potentially highly disruptive event" (Bonanno, 2004, p. 20). Regardless of the developmental stage, antecedent of resilience as a dynamic process is the presence of one or more significant stressors (Pangallo, Zibarras, Lewis, & Flaxman, 2015).

Trauma includes the "three E's" (Event, Experience, Effect) (Substance Abuse and Mental Health Services Administration, 2014):

> Individual trauma results from an *event*, series of events, or set of circumstances that is *experienced* by an individual as physically or emotionally harmful or threatening and that has lasting adverse *effects* on

> the individual's functioning and physical, social, emotional, or spiritual well-being (p. 7).

If an individual *experiences* a highly traumatic *event*, one lasting adverse *effect* may include a memory of the stressful event that becomes a central component of personal identity (Berntsen & Rubin, 2006). When individuals experience negative life events, they are at increased risk for psychopathologies (e.g. PTSD); some are less adversely affected by such events (Yehuda, 2004; Yehuda, Flory, Southwick, & Charney, 2006). Because the stressful events or adversity do not necessarily cause lasting adverse effects, it would be more appropriate to add the adjective, “potentially”, before “traumatic events”: *Potentially Traumatic Events* (PTEs). PTEs are defined as highly disruptive events that may potentially cause the exposed individual to develop psychopathology (Bonanno, 2004) (See Table 1 for the definitions of components of this concept analysis).

Defining Attributes of Resilience

The defining attributes of a concept are the characteristics of the concept that appear over and over again and “allow the analyst the broadest insight into the concept” (Walker & Avant, 2011, p. 162). The defining attributes of resilience are individual and environmental resources that facilitate positive adaptation (Pangallo et al., 2015). It is proposed in this concept analysis that the specific defining attributes of resilience are: (1) ego-resiliency, (2) emotion regulation, (3) social support, and (4) heredity.

Ego-resiliency. Ego-resiliency is a personality trait referring to the dynamic capacity to flexibly adapt to the changing demands of stressful experiences (Block & Kremen, 1996) (Table 1). To avoid confusion, *ego-resiliency* should be used when resilience is referred as a trait, whereas *resilience* as a dynamic process presupposes exposure to substantial adversity (Luthar, Cicchetti, & Becker, 2000). Individuals with high ego-resiliency may show better adjustment following exposure to PTEs because of adaptive flexibility (Letzring, Block, & Funder, 2005). For example, Fredrickson, Tugade,

Waugh, and Larkin (2003) measured ego-resiliency prior to the September 11th terrorist attacks among college students and found that those scoring high on ego-resiliency experienced more positive emotions and endured fewer depressive symptoms following the attacks. Similarly, Galatzer-Levy and Bonanno (2013) indicated that ego-resiliency played a role in healthy adjustment among college students exposed to distressing events.

According to Block and Kremen (1996), ego-resiliency is the first conceptual use of the term that describes the remarkable phenomenon of human adaptability in psychology and can subsume other characteristics associated with resilience. Although resilience is associated with other psychological variables, including personal competence (Ahern, 2006; Connor & Davidson, 2003; Friborg, Hjemdal, Rosenvinge, & Martinussen, 2003; Simmons & Yoder, 2013; Wagnild & Young, 1993; Windle, Markland, & Woods, 2008), self-enhancement (Gupta & Bonanno, 2010), self-efficacy (Earvolino-Ramirez, 2007; Garcia-Dia, DiNapoli, Garcia-Ona, Jakubowski, & O'Flaherty, 2013; Gillespie et al., 2007), hardiness (Bartone, 1999), ego-resiliency was selected as an attribute because it comprehensively and broadly captures the characteristics of resilient individuals. A review article indicates ego-resiliency is associated with flexibility, energy, assertiveness, humor, transcendent detachment, and a good capacity for affect regulation (Agaibi & Wilson, 2005).

Emotion regulation. Emotion regulation refers to the ability to shape which emotions one has, when emotions are generated, and to decide how one expresses or experiences those emotions (Gross, 2014) (Table 1). It involves two related strategies: (1) antecedent-focused *reappraisal*, which involves construing a potentially emotional situation to change its emotional impact, and (2) response-focused *suppression*, in which emotion expressive behavior is modified or inhibited (Gross & John, 2003). Emotion regulation is used to decrease or increase either the magnitude or the duration

of negative or positive emotion (Gross, 2014). Resilient individuals often use positive emotions, such as humor and optimism, to bounce back from stressful experiences (Tugade & Fredrickson, 2004). Empirical evidence indicates that resilient individuals benefit from positive emotions to adjust to PTEs, such as the 9/11 terrorist attacks (Fredrickson et al., 2003), spousal loss (Ong, Fuller-Rowell, & Bonanno, 2010), and captivity endured by Vietnam prisoners of war (Southwick & Charney, 2012a). It appears positive emotions protect against the unfavorable consequences of PTEs by decreasing the autonomic arousal provoked by negative emotions (Feder, Nestler, Westphal, & Charney, 2010). More specifically, according to the broaden-and-build theory (Fredrickson, 2001), "experiences of positive emotions broaden people's momentary thought-action repertoires, which in turn serves to build their enduring personal resources, ranging from physical and intellectual resources to social and psychological resources" (p. 218), which may help individuals stay resilient.

Emotion regulation is sometimes distinguished from *coping* because the predominant focus of coping is on decreasing negative affect for much larger periods of time (Gross, 2014). The literature certainly suggests that resilient individuals use active coping (Haglund, Cooper, Southwick, & Charney, 2007). Coping itself is also very complex, as "what works in one situation may not in another, what works for one individual may not for another, and what works at one point in time may not at another" (Norris et al., 2002, p. 238). For the purpose of conceptual clarification, coping (and the psychoanalytic literature including defensive mechanisms) may be considered as "historical antecedents to the contemporary study of emotion regulation" (Sheppes & Gross, 2013, p. 393). In addition, a newer concept, "regulatory flexibility" (Bonanno & Burton, 2013), which is defined as the matching of emotion regulation strategy (repertoire) to environmental circumstance (context) is emerging. In this paper, *emotion*

regulation is selected as a more comprehensive term rather than *defensive mechanisms* or *regulatory flexibility*.

Social support. There are three main types of social support: (1) *emotional support*, which supports esteem, affect, trust, concern, and listening, (2) *instrumental support*, which involves concrete actions that network members may perform, such as lending money, and (3) *informational support*, which consists of advice, suggestion, directives, and information (House & Kahn, 1985) (Table 1). Furthermore, social support has prominent facets, such as *received support*, which refers to actual behaviors that network members have performed, and *perceived support*, which refers to the subjective perception that network members are available to help if needed (Kaniasty & Norris, 2009). Evidence indicates that received and perceived social support may play a distinct role in adjustment to PTEs (Bonanno, Brewin, Kaniasty, & Greca, 2010). For example, perceived social support was found to be related to factors, such as age, education, and perceived community unity in addition to received social support in the aftermath of disaster (Kaniasty, 2012).

Social support helps individuals to remain resilient in the face of PTEs (Helgeson & Lopez, 2010; Perry, 1983; Yehuda et al., 2006). Research has shown that social support reduces the adverse psychological effects of PTEs, such as combat (Stretch, 1986), sexual assault (Golding, Siege, Sorenson, Burnam, & Stein, 1989), and terrorist attacks (Bonanno, Galea, Bucciarelli, & Vlahov, 2007), by decreasing negative cognitive reappraisal (Fontana, Kerns, Rosenberg, & Colonese, 1989). Correspondingly, a meta-analysis reveals that lack of social support is the second most important risk factor for predicting PTSD, following trauma severity (Brewin, Andrews, & Valentine, 2000). In addition, the importance of social support is validated by numerous longitudinal resilience studies around the world, including the Kauai Longitudinal Study, the British

Cohort Study, and the Australian Temperament Project (as cited in Werner, 2013). Therefore, social support can be considered as another defining attribute of resilience.

Heredity. Resilience has a heritable component and is influenced by more than one gene (Cicchetti & Blender, 2006). Heredity means inheriting genes with different alleles through reproduction that may influence individual variation in the observed traits, or phenotypes (Lemery-Chalfant, 2010) (Table 1). Because brain circuitries are involved in the stress response and reward experience (e.g. mesolimbic reward pathway), they may play an important role in resilience (Rutten et al., 2013). Several candidate genes involved in brain circuitry regulation include the *Serotonin-Transporter-Linked Polymorphic Region* (*5-HTTLPR*), *Brain-Derived Neurotrophic Factor* (*BDNF*), and *Catechol-O-Methyltransferase* (*COMT*) genes (Feder, Nestler, & Charney, 2009; Wu et al., 2013). In addition, other genes that regulate the hypothalamic-pituitary-adrenal (HPA) axis function, such as corticotrophin-releasing hormone receptor (*CRHR1*) gene and *FK506 Binding Protein 5* (*FKBP5*) gene, may also influence resilience to PTEs, including child maltreatment or abuse (Gillespie, Phifer, Bradley, & Ressler, 2009).

Variance in ego-resiliency was largely explained by additive genetic factors (77% in boys and 70% in girls) (Waaktaar & Torgersen, 2012). Taylor et al. (2014) investigated the development of ego-resiliency in relation to observed parenting and the serotonin transporter genes and found that the S10 haplotype of the serotonin transporter genes (*i.e.,* the combination of two variants: the S allele of *5-HTTLPR* and the 10-repeat allele of *Serotonin Transporter Intron 2* [*STin2*]) was negatively associated with initial levels of ego-resiliency. In addition to the serotonin transporter gene, other genes such as *CRHR1*, *Dopamine Receptor D4* (*DRD4*), and *Oxytocin Receptor* (*OXTR*) genes may also influence the development of ego-resiliency (Cicchetti & Rogosch, 2012).

Similarly, emotion regulation is also influenced by heredity. It is estimated that the heritability of emotion regulation is .45 to .55 (Weinberg, Venables, Proudfit, &

Patrick, 2015). Candidate genes associated with emotion regulation include *5-HTTLPR*, *COMT*, *MonoAmine Oxidase A* (*MAOA*), and *OXTR* (Canli, Ferri, & Duman, 2009; Hawn, Overstreet, Stewart, & Amstadter, 2015). Evidence also suggests that emotion regulation is developed through learning. For example, Ford, Mauss, Troy, Smolen, and Hankin (2014) found that children who learned effective emotion regulation did not exhibit increased depressive symptoms despite the fact that they were considered as "at-risk" due to the possession of the short allele of *5-HTTLPR*. Therapeutic interventions, such cognitive behavior therapy and mindful meditation, can enhance emotion regulation by strengthening the prefrontal cortex regulation of limbic and brainstem systems (Holzel et al., 2011; Southwick & Charney, 2012b), thereby promoting resilience (Feldman, Hayes, Kumar, Greeson, & Laurenceau, 2006; Henje Blom et al., 2014; McLaughlin, Mennin, & Farach, 2007; Southwick & Charney, 2012b; Thompson, Arnkoff, & Glass, 2011).

Gene expression is highly responsive to the environment (Lemery-Chalfant, 2010). Investigation of Gene by Environment (G x E) interaction has recently been incorporated in the field of resilience studies (Bowes & Jaffee, 2013; Kim-Cohen & Gold, 2009; Kim-Cohen & Turkewitz, 2012; Rutter, 2012). A G x E interaction occurs when the effect of exposure to an environmental risk factor on health and behavior is moderated by specific gene variants (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Moffitt, Caspi, & Rutter, 2006), or conversely, when the effect of specific genes is moderated by the environment (Caspi & Moffitt, 2006; Wermter et al., 2010). When resilience is investigated from the G x E interaction aspect, resilience can be conceptualized in terms of "reactivity" (Davydov et al., 2010). Namely, individuals who carry "reactive" alleles may be disproportionately influenced by *both* negative and positive environments ("differential susceptibility model") (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). To further conceptualize reactivity, Pluess (2015) identified that

maintaining the level of functioning when exposed to negative influence is called "resilience", whereas it is "vantage resistance" when exposed to positive influence. Worsening of the level of functioning when exposed to negative influence is called "vulnerability", whereas improving the level of functioning when exposed to positive influence is "vantage sensitivity" (Pluess, 2015) (Figure 1). A meta-analysis supports the differential susceptibility model that individuals with the reactive allele(s) of *5-HTTLPR*, S allele(s), are more negatively affected by adversity but also benefited more from positive environmental exposures (van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012). In other words, individuals with less reactive alleles (e.g. the L allele of *5-HTTLPR*) may be more "resilient" when exposed to PTEs, whereas the response of those with more reactive alleles (e.g. the S allele of *5-HTTLPR*) may depend on the environmental context.

Consequences of Resilience

Consequences are the events or incidents that arise as a result of the occurrence of the concept (*i.e.,* outcomes of the concept) (Walker & Avant, 2011). Some researchers (e.g. Luthar & Zelazo, 2003) argue that outcome of resilience cannot be directly measured but only inferred. For example, if a school-age child exposed to adversity meets developmental tasks (e.g. good academic performance) that are considered appropriate for his or her age, gender, culture, and period in history, then the child may be described as "resilient" (Masten, Monn, & Supkoff, 2011). Other investigators describe an individual as "resilient" if he or she remains free from mental health disorders or impairment following exposure to adversity (Alim et al., 2008; Bonanno, 2004). Furthermore, other scientists (e.g. Pangallo et al., 2015) propose that resilient outcomes are quantifiable and measurable by using psychometrically-validated instruments, such as CD-RISC (Connor & Davidson, 2003) and Sense of Coherence Scale (Antonovsky, 1993). Generally, the consequence of resilience is positive

adjustment or adaptation relative to developmental life stage (Pangallo et al., 2015). Because there is no simple method to determine what the outcomes of resilience are or no agreed upon outcome measures, two main consequences of resilience are proposed in this paper: (1) none to mild psychopathological symptoms, and (2) positive adaptation.

None to mild psychopathological symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) (American Psychiatric Association, 2013), the development of psychopathology may be suspected if the disturbance following exposure to PTEs "causes clinically significant distress or impairment in social, occupational, or other important areas of functioning" (p. 272). If the duration of psychopathological symptoms (e.g. avoidance) last three days to a month, it may be diagnosed as Acute Stress Disorder; if the duration lasts more than a month, it may be diagnosed as PTSD. Nonetheless, if the symptoms are not severe enough to cause disturbance in daily functioning, or if the symptoms resolve within a few days following exposure to PTEs, then the person may be described as resilient. In other words, a resilient outcome may be manifested as relatively stable and healthy levels of psychological and physical functioning following exposure to PTEs (Bonanno, 2004) (Table 1).

When resilience is considered as longitudinal consequences (e.g. measuring psychopathological symptoms at one, three, and six month after the exposure to PTEs), the severity and duration of psychopathological symptoms may be expressed as trajectories. Based on empirical evidence, Bonanno and Diminich (2013) identify the six most common prototypical outcome trajectories following PTEs: (1) *minimal-impact resilience* (consistently low levels of psychopathological symptoms before and after PTE exposure), (2) *recovery* (moderate-to-severe psychopathological symptoms occurring for several months after the PTE then gradually declining to baseline levels of adjustment over the course of one or two years), (3) *chronic* (psychopathological symptoms after the

occurrence of the PTE lasting several years or more), (4) *delayed* (increased psychopathological symptoms over time), (5) *continuous* (prior psychopathological symptoms that continue after PTE exposure), and (6) *improved* (psychopathological symptoms before PTE exposure that decrease greatly after the PTE). For example, deRoon-Cassini, Mancini, Rusch, and Bonanno (2010) investigated trajectories of resilience following traumatic injury (e.g. automobile crash) and identified four distinct patterns by measuring PTSD-like symptoms over six months: (1) minimal-impact resilience (*i.e.,* "low symptom", 59%), (2) recovery (13%), (3) chronic (22%), and (4) delayed (6%). Similar patterns of trajectories of resilience have been supported in a variety of PTEs, including the 1999 floods in Mexico and the terrorist attacks in New York (Norris, Tracy, & Galea, 2009), breast cancer among Chinese women (Lam et al., 2010), spinal cord injury (Bonanno, Kennedy, Galatzer-Levy, Lude, & Elfstrom, 2012), and campus mass shooting (Orcutt, Bonanno, Hannan, & Miron, 2014).

Positive adaptation. Comparable to the definition of health by World Health Organization (1948), which is "a state of complete physical, mental and social well-being and *not merely the absence of disease or infirmity*" (p. 1), resilience is *not simply the absence of psychopathology* (Almedom & Glandon, 2007; Vaillant, 2003). Rather than viewing resilience as dichotomy (*i.e.,* either one has it or not) or average scores (*i.e.,* comparing exposed to non-exposed) (Bonanno, Westphal, & Mancini, 2011), resilience may be considered as continuum of adaptation (Agaibi & Wilson, 2005; Simmons & Yoder, 2013). The presence of psychopathological symptoms may indicate negative adaptation. However, the absence of psychopathology does not necessarily mean positive adaptation.

Positive adaptation can be measured by other instruments (Davydov et al., 2010; Pangallo et al., 2015), such as Connor-Davidson Resilience Scale (Connor & Davidson, 2003) and Mental Health Inventory (Veit & Ware, 1983). However, Sense of Coherence

(SOC) was selected as an outcome in this concept analysis because SOC may be most inclusive of these similar measurements of positive adaptation (Almedom, 2005). SOC is defined as:

> …a global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence that (1) stimuli deriving from one's internal and external environments in the course of living are structured, predictable, and explicable; (2) the resources are available to one to offset the demands posed by these stimuli; and (3) these demands are challenges, worthy of investment and engagement (Antonovsky, 1987, p. 19) (Table 1).

SOC is quantifiable using the SOC Scale (Antonovsky, 1993), which consists of three subscales: (1) *comprehensibility* (cognitive), (2) *manageability* (behavioral), and (3) *meaningfulness* (motivational component). Although these three components are highly related to one another, *meaningfulness* may be considered as the most important, followed by *compressibility* and *manageability* (Horsburgh & Ferguson, 2012). Antonovsky (1993) emphasizes that SOC is not a personality trait or a coping strategy. Rather, SOC is shaped by life situation, such as culture and life experiences, and it ultimately functions as movement towards health (Antonovsky, 1979; Benz, Bull, Mittelmark, & Vaandrager, 2014; Horsburgh & Ferguson, 2012).

As an individual gains more life experiences, he or she will begin to view the world as coherent and predictable (Horsburgh & Ferguson, 2012). Although Antonovsky initially anticipated SOC to stabilize around the age of 30, emerging evidence suggests that SOC continuously develops until the mid-70s (Nilsson, Leppert, Simonsson, & Starrin, 2010). Systematic reviews reveal that stronger SOC is linked to better quality of life (Eriksson & Lindstrom, 2007) and better perceived health, especially mental health (Eriksson & Lindstrom, 2006).

Cases of Resilience

Walker and Avant (2011) encourage the concept analyst to apply the concept of interest and identify model, borderline, and contrary cases. A model case refers to an example of the concept that demonstrates all the defining attributes of the concept. A borderline case is an example that contains most defining attributes but not all of them. A contrary case is an example of "not the concept" (Walker & Avant, 2011, p. 166). The attributes of the concept of resilience are indicated within the parenthesis in each case.

Model Case

The story of Admiral Robert Shumaker (Southwick & Charney, 2012c) was analyzed as a model case because evidence of high ego-resiliency, adaptive emotion regulation, and strong perception of social support in a traumatic situation can be detected in his story. Admiral Shumaker was imprisoned as a prisoner of war (POW) in North Vietnamese prisons for 9 years (*PTE*). He understood the human's need to bond with one another (*strong social support*). From his solitary confinement cell, he was only able to see a fellow prisoner who was taken to the same latrine he used at a different time of day. To communicate with this prisoner, he wrote a message on toilet paper and left it for him since the guards rarely went in to his area. The message said: "Welcome to the Hanoi Hilton" (*high ego-resiliency*) and told him to show a shared signal on his way out of the latrine (Southwick & Charney, 2012c, p. 100). When Admiral Shumaker witnessed his fellow prisoner following this command, he felt, "…it was a happy day for me when I made contact" (Southwick & Charney, 2012c, p. 100). Judging from his selected word, "happy", it appears his emotions were well regulated by generating positive emotions (*adaptive emotion regulation*) even while in prison.

Despite such brutal conditions, his *psychopathological symptoms* were minimal. When three other POWs were added to his cell, Admiral Shumaker realized the importance of a communication method, that he later called the "Tap Code". When they

were separated into different cells, each one spread the code to other prisoners, which led to the formation of the Tap Code as the backbone of the prisoners' communication network within months. For his crucial role in communication among prisoners that prove to be a lifesaver for hundreds of POWs, Admiral Shumaker earned the name "Martini Mixer". It appears he had a strong SOC as he believed that social support and the Tap Code communication system was possible (*comprehensibility*), his mission to promote communications among POWs was important (*meaningfulness*), and the imprisonment was survivable (*manageability*). Although we do not have specific genetic information about Admiral Shumaker, we can hypothesize that, because he was in a very traumatic situation and was resilient, he had the less reactive alleles for genes that influence resilience (*heredity*).

Borderline Case

This is a fictional story to demonstrate a borderline case of resilience. Mike was an undergraduate pre-law student. After a significant disagreement, his girlfriend discontinued their relationship (*PTE*).

His mind was fixated on the loss of his girlfriend (*low ego-resiliency*). To suppress his sad feelings, Mike started to consume large amounts of alcohol (*maladaptive emotion regulation*). Although his family and friends attempted to console him (*strong social support*), he answered only a few of their phone calls and messages because it was too stressful to talk about the loss of this relationship.

He lost motivation to attend class and experienced depressive symptoms (*moderate psychopathological symptoms*). As a result, he received a low grade in several classes and was placed on academic probation. Even though he thought he could never find another girlfriend, he still viewed a law career as a meaningful goal (*moderate sense of coherence*). The notice of academic probation led him to seek counseling to address his depression. Mike was able to achieve better grades the

following semester and was in good academic standing. He started to date again, but continued to dwell on the loss of his previous romantic relationship. Although his genetic information is unknown, we can hypothesize that he had more susceptible alleles that were related to less resilience in a negative environment (*i.e.,* loss of a romantic partner) (*heredity*).

Contrary Case

This is a fictional story to demonstrate a contrary case of resilience. Sarah was a college student majoring in marketing. On a Friday night, she joined a party where she consumed too much alcohol and was sexually assaulted by an acquaintance (*PTE*).

She felt overwhelmed and remained passive (*low ego-resiliency*). She did not disclose this incident to her friends, family, school authorities, or police (*weak perceived social support*) because she was afraid of the consequences of reporting the assault. She suppressed her fearful feelings by being socially withdrawn (*maladaptive emotion regulation*).

She started experiencing flashbacks, panic attacks, and insomnia (*severe psychopathological symptoms*). She experienced significant guilt for drinking too much and not resisting her attacker, and she thought others would be better off without her (*weak sense of coherence*). Then, she overdosed with over-the-counter medications. She was later found by her roommate, taken to the Emergency Room, and hospitalized for treatment. Although no genetic information is available, we can hypothesize that she had more reactive alleles to the negative environment she encountered (*heredity*).

Discussion

There is no single agreed-upon definition of resilience in the clinical or scientific literature (Fletcher & Sarkar, 2013; Southwick & Charney, 2012b; Southwick et al., 2011). According to Walker and Avant (2011), the concept analyst identifies the purpose of the

analysis and identifies the elements that allow the analyst to have the broadest insight into the concept. Given that, the antecedent of resilience proposed is *PTE*; the defining attributes are *ego-resiliency*, *emotion regulation*, *social support*, and *heredity*; and the consequences are *none to mild psychopathological symptoms* and *positive adaptation* (Table 1). As a result of this analysis, resilience is defined as a dynamic process of positive adaptation following exposure to PTEs, facilitated by ego-resiliency, emotion regulation, social support, and heredity, and evidenced by none to mild psychopathological symptoms and positive adaptation through development of a SOC.

Most researchers who conducted a concept analysis on resilience identified one antecedent simply as “adversity” (Dyer & McGuinness, 1996; Earvolino-Ramirez, 2007; Felten & Hall, 2001; Garcia-Dia et al., 2013; Gillespie et al., 2007; Olsson, Bond, Burns, Vella-Brodrick, & Sawyer, 2003; Windle, 2011) or “life event” (Simmons & Yoder, 2013). In contrast, the term, “*potentially* traumatic event”, is applied in this paper, indicating individual variability in response to negative life events.

For the defining attributes of resilience, (1) ego-resiliency, (2) emotion regulation, (3) social support, and (4) heredity are proposed. *Ego-resiliency* is considered as a personality trait that contributes to *resilience*, a dynamic process, when exposed to PTEs. Individuals with high ego-resiliency would generate more positive emotions and set into motion a “resilience cascade” (Ong, Bergeman, & Boker, 2009, p. 1786), attracting even more social resources. In addition, heredity is identified as a defining attribute of resilience because genes may substantially influence behavioral health (Plomin et al., 2013), including resilience (Feder et al., 2009; Wu et al., 2013).

For the consequences, although psychological distress is considered as a normal reaction immediately following exposure to PTEs, resilient individuals would experience none to mild psychopathological symptoms and manage such symptoms in a relatively short period (Bonanno & Diminich, 2013). Because resilience is not merely the absence

of the psychopathological symptoms, SOC can be evidence of positive adaptation (Almedom & Glandon, 2007). Individuals are constantly in situations of stress, tension, challenge, response, and resolution (Horsburgh & Ferguson, 2012), and an individual's SOC would continue developing throughout the lifespan (Nilsson et al., 2010).

Three major limitations are identified. First, due to the tentativeness of concepts (Walker & Avant, 2011), usefulness of this concept analysis may change over time as the scientific and this analyst's knowledge develop. Second, this concept analysis may have failed to include some important components of resilience, especially the defining attributes, due to a reductionistic approach. For example, Pangallo et al. (2015) derived 16 themes associated with resilience, and Johnson et al. (2011) identified 26 related constructs to resilience. However, only four defining attributes (ego-resiliency, emotion regulation, social support, and heredity) were identified in this analysis because they gave the authors the broadest insight into the concept of resilience as a response to PTEs. Third, the antecedent of resilience in this concept analysis, PTEs, is described as a generic event that may commonly happen in the developed countries, such as the United States and Japan. It would be important to consider the context of PTEs (Masten & Narayan, 2012) as well as the cultural context unique to the individual to more comprehensively understand resilience (Bell, 2011; Block & Block, 2006; Castro & Murray, 2010).

Conclusions

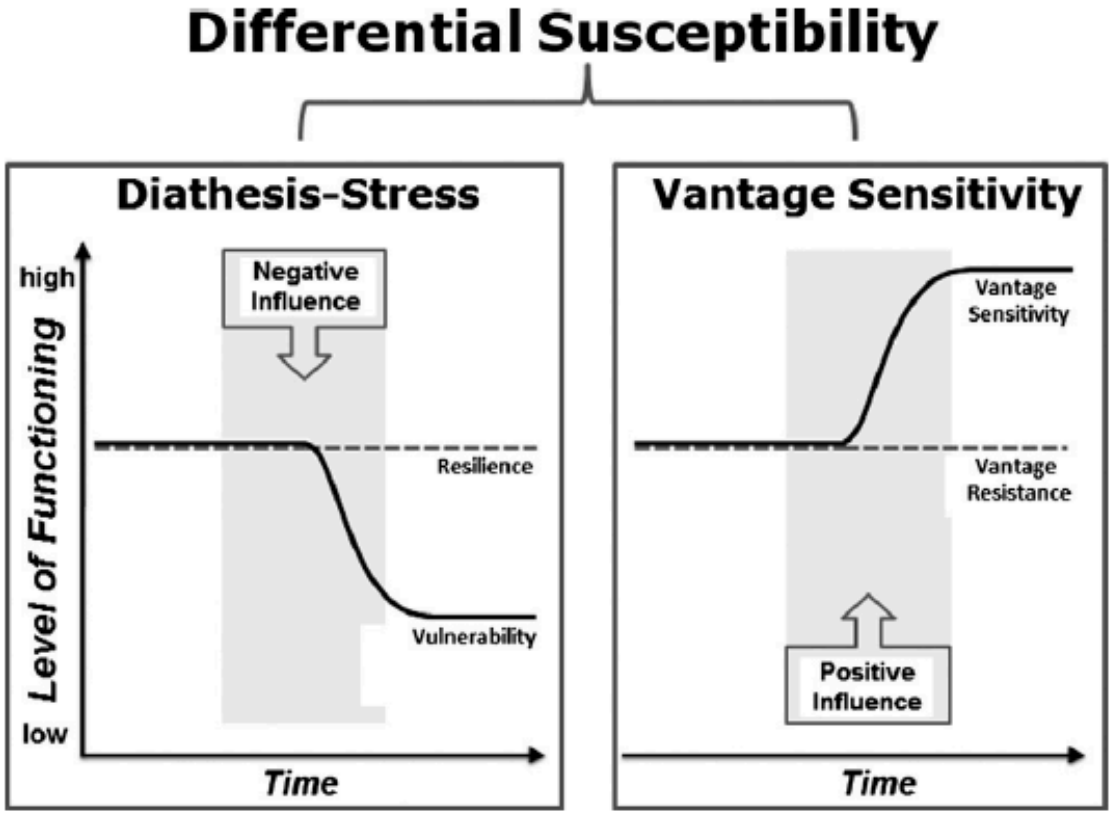
A concept analysis of resilience reveals: the antecedent is PTEs; the defining attributes are ego-resiliency, emotion regulation, social support, and heredity; and the consequences are none to mild psychopathological symptoms and positive adaptation that can be manifested as SOC (Table 1). To the authors' knowledge, this is the first concept analysis of resilience that includes ego-resiliency, emotion regulation, and heredity as defining attributes, and SOC as a consequence. As scientific knowledge

about resilience develops, the antecedent, defining attributes, and consequences may change. A better understanding of resilience and its relationship with intrapersonal (e.g. heredity, ego-resiliency) and environmental (e.g. social support) variables would help clinicians and researchers develop interventions that facilitate an individual's potential for resilience when exposed to PTEs.

Table 1: Proposed Components of Concept Analysis of Resilience and their Definitions

Components	Definition
Antecedent:	
Potentially traumatic event (PTE)	Highly disruptive event that may potentially cause the exposed individual to develop psychopathology (Bonanno, 2004).
Defining attributes:	
Ego-resiliency	A personality trait referring to the dynamic capacity to flexibly adapt to the changing demands of stressful experiences (Block & Kremen, 1996).
Emotion regulation	The capacity to shape which emotions one has, when one has emotions, and how one expresses or experiences these emotions (Gross, 2014).
Social support	Different aspects of social relationships, including emotional, instrumental, and informational support (House & Kahn, 1985). Social support has prominent facets, such as received (actual behaviors hat network members have performed) and perceived (the subjective perception that network members are available to help if needed) support (Kaniasty & Norris, 2009).
Heredity	Inheriting genes with different alleles through reproduction that may influence individual variation in the observed traits, or phenotypes (Lemery-Chalfant, 2010).
Consequences:	
None to mild psychopathological symptoms	Relatively stable and healthy levels of psychological and physical functioning following exposure to PTEs (Bonanno, 2004).
Positive adaptation (Sense of Coherence)	An indicator of positive adaptation is sense of coherence, which is a global orientation to view the world, consisting of comprehensibility, manageability, and meaningfulness (Antonovsky, 1987).

Figure 1: The Differential Susceptibility Model



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MANUSCRIPT #2: A SYSTEMATIC REVIEW OF GENETIC INFLUENCE ON PSYCHOLOGICAL RESILIENCE

Abstract

One of many determinants of psychological resilience is genetics. Because until recently the empirical study of resilience focused predominantly on behavioral and psychosocial variables, less is known about genetic contributions to resilience. A systematic review was conducted using search engines, PubMed and PsycINFO, with the combination of following keywords: “psychological resilience” AND “genotype”. Additional articles were identified from the HuGE Navigator and reference lists. The purposes of this review were to: (1) identify candidate genes associated with resilience, (2) identify alleles associated with resilience and less reactivity to the environment, and (3) review various methods to construct a Polygenic Susceptibility Score. A total of 24 studies were included in this review. The following candidate genes were associated with resilience: *5-HTTLPR*, *COMT*, *BDNF*, *DRD4*, *DRD2*, *DAT1*, *OXTR*, *RGS2*, *CACNA1C*, *FKBP5*, *CRHR1*, *MAOA*, *IL10*, *FGG*. Alleles associated with resilience and less reactivity to the environment largely varied by studies. Alternative methods to construct a Polygenic Susceptibility Score were reviewed. Factors that might contribute to inconsistent findings may include: (1) exclusion of rs25531 in *5-HTTLPR*, (2) assumption of different modes of inheritance, and (3) various methods and instruments to operationalize resilience. The review highlights the complexity of identifying genes with regard to reactivity to the environment, which is crucial for developing a polygenic susceptibility score.

Keywords: resilience, molecular genetics, differential susceptibility, polygenic susceptibility score, systematic review

Introduction

The majority of individuals in the United States experience at least one potentially traumatic event (PTE) during their lifetime (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). However, most individuals exposed to PTEs do not develop psychopathology, such as Post-Traumatic Stress Disorder (PTSD) (Kessler et al., 1995). Low rates of PTSD after exposure to PTEs are found not only in the United States (about 2.5%) but also in Japan (about 0.5%), France (about 1.5%), and other countries (reviewed by Yehuda et al., 2015). Resilience experts suggest the determinants of resilience needs to be approached from multiple levels of analysis, including genetic, epigenetic, developmental, demographic, cultural, economic, and social variables (Southwick et al., 2014). Among these variables, genetic contributions to resilience are less known because until recently the empirical study of resilience focused predominantly on behavioral and psychosocial variables (Cicchetti, 2010).

There is no universal definition of resilience (Southwick et al., 2014). From a genetic aspect, resilience can be conceptualized in terms of "reactivity" with an environment, known as the differential susceptibility model (Ellis et al., 2011; Pluess, 2015). If a level of functioning remains stable when exposed to negative influence, it is labeled as "resilience"; if the level of functioning worsens when exposed to negative influence, it is called "vulnerability" (Pluess, 2015) (Figure 1). Similarly, if the level of functioning stays the same when exposed to positive influence, it is described as "vantage resistance"; if the level of functioning improves when exposed to positive influence, it is "vantage sensitivity" (Pluess, 2015). Based on the Differential Susceptibility Model, if an individual experiences none to mild psychopathological symptoms (*i.e.,* less reactivity) after exposed to PTEs, he or she would be described as "resilient". However, resilience is not only the absence of psychopathology but also positive adaptation (Almedom & Glandon, 2007; Davydov et al., 2010). Because most

researchers measure resilience in terms of psychopathological symptoms following exposure to PTEs, less is known about positive adaptation to PTEs. In this systematic review, resilience is defined from two aspects: (1) reactivity to PTEs, and (2) positive adaptation. Resilience as positive adaptation is defined as an outcome associated with positive themes, such as adaptability, positive emotions, and mastery, and it can be operationalized using self-rating instruments (Pangallo et al., 2015). Combining concepts of stability from the differential susceptibility model and positive adaptation (vs. psychopathological symptoms), resilience for this review is defined as a stable level of functioning measured in terms of positive adaptation following exposure to PTEs.

Similar to common disorders, resilience is likely to be influenced by many genes with small effect and the environment (Feder et al., 2009; Plomin, Haworth, & Davis, 2009). A *polygenic risk score* refers to the combination of multiple DNA variants that are associated with a disorder and can be used for prediction of individual trait values (Dudbridge, 2013; Plomin et al., 2009). It is also known as *polygenic susceptibility scores*, *genomic profiles*, *SNP sets*, *genetic risk scores*, and *aggregate risk scores* (reviewed by Plomin et al., 2009). To be matched with the Differential Susceptibility Model (Pluess, 2015), the term “polygenic susceptibility score” is selected to describe an polygenic aggregate index in this review.

The purposes of this review are to: (1) identify candidate genes associated with resilience, (2) identify which alleles of these genes are associated with resilience (*i.e.,* main effect of positive adaption) or decreased reactivity (*i.e.,* gene x environment interaction with less reactivity described as resilient), and (3) review the various methods for constructing a polygenic susceptibility score.

Method

The literature review was conducted in January 2017 by using literature databases, PubMed, and PsycINFO. Keywords were: “psychological resilience” AND

"genotype" using MeSH Terms in PubMed and Thesaurus in PsycINFO. In addition, research articles associated with a phenotype of "Resilience, Psychological" in the HuGE (Human Genome Epidemiology) Navigator Phenopedia (Yu, Clyne, Khoury, & Gwinn, 2010) were identified. Additional studies were traced back from the reference lists of those articles. Published years were not restricted because the genetic study on resilience is relatively new.

The inclusion criteria for the articles analyzed in this manuscript were: (1) human subjects approved research, (2) written in English, (3) published in peer-reviewed journals, (4) operationalized resilience in terms of positive adaptation, and (5) molecular genetic studies.

The exclusion criteria were: (1) animal studies, (2) written in languages other than English, (3) non-peer-reviewed manuscripts (e.g. book chapters, dissertations), (4) resilience operationalized as only the absence of psychopathological symptoms (e.g. absence of PTSD symptoms), and (5) epigenetic and twin studies.

Results

A combination of the following two MeSH Terms in PubMed, "psychological resilience" and "genotype", revealed 46 articles. A combination of "resilience (psychological)" and "genotype" using Thesaurus in PsycINFO found nine articles. In addition, there were 26 articles associated with a phenotype of "Resilience, Psychological" in the HuGE Navigator Phenopedia (Yu et al., 2010). Therefore, a total of 81 (46 + 9 + 26) articles were initially identified. After removing duplicates (n = 22), articles that did not meet inclusion criteria (n = 45) were removed. While reviewing articles, additional 10 articles were traced back from reference lists because they were not identified through the search engines but met the inclusion criteria. In total, 24 research articles met the inclusion criteria and were analyzed for this review.

Overview of Candidate Genes Associated with Resilience

It is hypothesized that genes involved with the neurobiological mechanisms with stress responses, namely serotonergic, dopaminergic, and noradrenergic systems, and hypothalamic-pituitary-adrenal axis (HPA-axis), may influence resilience (Wu et al., 2013). For example, serotonin, which is a monoamine neurotransmitter in the central nervous system, regulates appetite, sleep, feelings of well-being, and happiness and affects mood and anxiety; therefore, polymorphisms in the serotonergic system may explain individual differences in stress responses and resilience (reviewed by Osorio, Probert, Jones, Young, & Robbins, 2016).

This systematic review from 24 research articles revealed a total of 14 candidate genes associated with resilience: *Serotonin-Transporter-Linked Polymorphic Region (5-HTTLPR) or* SLC6A4, *Catechol-O-methyltransferase (COMT)*, *Brain-Derived Neurotrophic Factor (BDNF)*, *Dopamine Receptor D4 (DRD4)*, *Dopamine Receptor D2 (DRD2)*, *Dopamine Transporter (DAT1)*, *Oxytocin Receptor (OXTR)*, *Regulator of G-Protein Signaling 2 (RGS2)*, *Calcium Voltage-Gated Channel Subunit Alpha1 C (CACNA1C)*, *FK506 Binding Protein 5 (FKBP5)*, *Corticotropin Releasing Hormone Receptor 1 (CRHR1)*, *Monoamine Oxidase A (MAOA), Interleukin 10 (IL10)*, and *Fibrinogen Gamma Chain (FGG)*. Descriptions of functional importance for each gene are summarized in Table 2.

All genes identified in this review play an important role to regulate the mental health by modulating neurotransmitters, except for *IL10* and *FGG* (Rana et al., 2014). Rana et al. (2014) selected 65 candidate genes associated with resilience based on a literature review and found strong associations between resilience operationalized by Connor-Davidson Resilience Scale (Connor & Davidson, 2003) and rs6323 in *MAOA*, and between optimism measured by Life Orientation Test (Scheier & Carver, 1985) and rs6323 in *MAOA*, rs1800896 in *IL10*, and rs1800792 in *FGG*. However, none of them

withstood a Bonferroni threshold for significant association (p = .00089). The authors discussed that their findings were only tentative and called for replication using larger samples (Rana et al., 2014).

The gene that was most frequently investigated was *SLC6A4* (solute carrier family 6 member 4), which encodes an integral membrane protein that transports serotonin from synaptic spaces into presynaptic neurons (National Center for Biotechnology Information, 2017j). Particularly, a Variable Number Tandem Repeat (VNTR) in *SLC6A4* known as *Serotonin-Transporter-Linked Polymorphic Region (5-HTTLPR)*, which contains a 43 base pair (bp) insertion or deletion in the 5' regulatory region of the gene (Heils et al., 1996), was the most frequently studied. In addition, rs6265 in *BDNF* and rs53576 in *OXTR* were also frequently investigated for their associations with resilience.

Alleles Associated with Resilience (Main Effect) and Less Reactivity (G x E Interaction)

Main effect. The alleles associated with resilience, which were measured in terms of positive adaptation, are summarized in Table 3. Consensus about the specific alleles associated with resilience were not determined due to the following three important issues that might contribute to inconsistent findings.

First, the majority of studies excluded a single base substitution (A>G), rs25531 in *5-HTTLPR*, from their analyses (Amstadter et al., 2012; Beaver, Mancini, DeLisi, & Vaughn, 2011; Carli et al., 2011; Cicchetti & Rogosch, 2012; Defrancesco et al., 2013; Gibbons et al., 2012; Hemmings et al., 2013; O'Hara et al., 2012; Stein, Campbell-Sills, & Gelernter, 2009), whereas others genotyped for rs25531 and recoded accordingly for statistical analyses (Dunn et al., 2014; Graham et al., 2013; Hankin et al., 2011; Nederhof et al., 2010; Reinelt et al., 2015). There is a single base substitution (A>G) known as rs25531 in the L allele (Hu et al., 2006), and the L_G (vs. L_A) allele is

functionally equivalent to the S allele of *5-HTTLPR* (Wendland, Martin, Kruse, Lesch, & Murphy, 2006). Consequently, based on the level of expression, the genotypes of *5-HTTLPR* can be reclassified as follows: L'/L' = L_A/L_A; L'/S' = L_A/S & L_A/L_G; and S'/S' = S/S & L_G/S & L_G/L_G (Parsey et al., 2006). This is known as the triallelic *5-HTTLPR* classification system. One study (Stein et al., 2009) found a significant association between CD-RISC and *5-HTTLPR* (L/L vs. L/S vs. S/S assuming the codominance as well as L/S vs. L/S & S/S assuming the S dominance) but not with the triallelic *5-HTTLPR* classification system (L'/L' vs. L'/S' vs. S'/S'). Another study (O'Hara et al., 2012) genotyped for rs25531 but excluded from the final results because only a few participants carried the L_G allele and the triallelic *5-HTTLPR* classification system did not impact the results.

Second, each study assumed the modes of inheritance differently. For example, Graham et al. (2013) assumed the dominance of the L' allele of *5-HTTLPR* by collapsing the L'/L' and L'/S' genotypes into a single group (*i.e.,* L'/L' & L'/S' vs. S'/S') in the statistical analyses. O'Hara et al. (2012) assumed the dominance of the S allele of *5-HTTLPR* by combining the L/S and S/S genotypes (*i.e.,* L/L vs. L/S & S/S). Reinelt et al. (2015) assumed the codominant mode of inheritance of *5-HTTLPR* (L'/L' vs. L'/S' vs. S'/S'). The same issue was observed for other polymorphisms. For example, Amstadter et al. (2012) assumed the dominance of the Val allele of rs4680 in *COMT* (*i.e.,* Val/Val & Val/Met vs. Met/Met), whereas Kang, Kim, Song, Namkoong, and An (2013) assumed the dominance of the Met allele (*i.e.,* Val/Val vs. Val/Met & Met/Met), although they both found the Met allele to be associated with resilience. Because these researchers assumed a different mode of inheritance, it is unclear whether individuals with the heterozygotes of rs4680 in *COMT* (*i.e.,* Val/Met carriers) may be associated with increased or decreased resilience.

Third, resilience in terms of positive adaptation was measured by various instruments. The most frequently used instrument was CD-RISC (Connor & Davidson, 2003) or the 10-item version of CD-RISC (Campbell-Sills & Stein, 2007), utilized in nine studies (Bradley, Davis, Wingo, Mercer, & Ressler, 2013; Carli et al., 2011; Das, Cherbuin, Tan, Anstey, & Easteal, 2011; Graham et al., 2013; Hemmings et al., 2013; Kang et al., 2013; O'Hara et al., 2012; Rana et al., 2014; Stein et al., 2009). Another frequently used instrument was the Sense of Coherence (SOC) scale (Antonovsky, 1993) which was utilized in three studies, although each selected a different version of SOC: the Swedish version of the 3-item SOC (Surtees et al., 2007), the unidimensional short version of SOC (Reinelt et al., 2015), and the original version of SOC (Strohmaier et al., 2013). Cicchetti and Rogosch (2012) measured resilience by accounting for self-report measures, peer measures, counselor measures, and school record data and composed a resilient functioning score.

G x E interaction. The alleles associated with less reactivity to the environmental effects were summarized in Table 4. Findings of genes investigated by more than two studies are described below.

5-HTTLPR. The most frequently investigated polymorphism (*n* = 16) was *5-HTTLPR* (or SLC6A4) examined by 11 studies (Table 4). Out of 11 studies, five studies (Amstadter et al., 2012; Cicchetti & Rogosch, 2012; Gibbons et al., 2012; Hankin et al., 2011; Nederhof et al., 2010) found the L or L' allele of *5-HTTLPR* to be less reactive, whereas 4 studies (Beaver et al., 2011; Carli et al., 2011; Graham et al., 2013; Reinelt et al., 2015) found the S or S' allele of *5-HTTLPR* to be less reactive. Two (Dunn et al., 2014; Stein et al., 2009) did not find any significant interactions between *5-HTTLPR* and other study variables, which were classified as environment.

Two studies investigated the interactions between *5-HTTLPR* and positive environments, namely, positive parenting (Hankin et al., 2011) and social support

(Reinelt et al., 2015). Alleles associated with less reactivity following exposure to positive influence are labeled as *vantage resistance* rather than *resilience* (Pluess, 2015). Because (Hankin et al., 2011) found the L allele of *5-HTTLPR* to be less reactive to positive parenting, whereas (Reinelt et al., 2015) found the S' allele to be less reactive to social support, the allele of *5-HTTLPR* associated with vantage resistance was unable to be determined. Due to inconsistent findings, the allele of *5-HTTLPR* associated with resilience (*i.e.,* less reactivity to negative environment) as well as vantage resistance (*i.e.,* less reactivity to positive environment) were not determined.

BDNF. Out of three studies that investigated rs6264 in *BDNF* and environment interactions, two studies (Nederhof et al., 2010; van Winkel et al., 2014) found the Val allele to be less reactive (*i.e.,* more resilient). However, van Winkel et al. (2014) assumed the codominant mode of inheritance (i.e., Val/Val vs. Val/Met vs. Met/Met), whereas Nederhof et al. (2010) assumed the dominant effect of the Met allele (i.e., Val/Val vs. Val/Met & Met/Met). Therefore, it was not clear whether the Val/Met carrier of rs6264 in *BDNF* would be less reactive to the environment. In addition, one study (Dunn et al., 2014) did not find a significant interaction.

DRD4. Four out of 24 studies investigated the interaction between *DRD4* and environment (Table 4). The effect of childhood adversity on CD-RISC was weaker (*i.e.,* less reactive and therefore more resilient) among individual with the 7r (7-repeat) allele of *DRD4* VNTR (Das et al., 2011), whereas the effect of racial discrimination on Life History Strategies (e.g. growth) was weaker among adolescents with the 4r allele of *DRD4* VNTR (Gibbons et al., 2012), producing a conflicting finding. Additionally, another study (Beaver et al., 2011) did not find any significant interaction between *DRD4* VNTR and victimization on resiliency. Cicchetti and Rogosch (2012) investigated a SNP (rs1800955) in *DRD4* instead of VNTR and found that the effect of child maltreatment on

resilient functioning was weaker among children with the C allele of rs1800955 in *DRD4*, assuming the dominant effect of the C allele (*i.e.,* C/C & C/T vs. T/T).

OXTR. Three out of 24 studies investigated the interactions between polymorphisms in *OXTR* (e.g. rs53576, rs2254298) and environments (Table 4). The effect of positive family environment on CD-RISC was weaker among individuals with the A alleles of rs53576 in *OXTR* assuming the dominant effect of the G allele (*i.e.,* G/G & G/A vs. A/A) (Bradley et al., 2013). Because positive family environment is considered a positive influence, the A allele of rs53576 in *OXTR* associated with less reactivity would be labeled as *vantage resistance* rather than *resilience* (Pluess, 2015). On the other hand, the effect of child maltreatment on resilient functioning was weaker among children with the G alleles of rs53576 in *OXTR* assuming the dominant effect of the A allele (*i.e.,* G/G vs. G/A & A/A) (Cicchetti & Rogosch, 2012). Because child maltreatment is negative influence, the A allele of rs53576 in OXTR associated with less reactivity is considered *resilient*. Dunn et al. (2014) did not find any significant interaction between polymorphisms in *OXTR* (rs53576 & rs2254298) and a hurricane on resilience measured by the Posttraumatic Growth Inventory (Tedeschi & Calhoun, 1996). Whether positive or negative environment, the alleles of polymorphisms in *OXTR* associated with less reactivity were not identified.

Polygenic Susceptibility Score

Two out of 24 articles analyzed in this review constructed a polygenic susceptibility score. First, Gibbons et al. (2012) formed “a measure of cumulative sensitivity” (p. 727) for *5-HTTLPR* and *DRD4* VNTR. Based on their literature review, the S allele of *5-HTTLPR* and the 7-repeat allele of *DRD4* were determined as “sensitivity” alleles (p. 724), and the codominant mode of inheritance (L/L vs. L/S vs. S/S of *5-HTTLPR*; 4r/4r vs. 4r/7r vs. 7r/7r of *DRD4*) was assumed. Their scoring system was: 0 = no sensitivity alleles (*i.e.,* L/L & 4r/4r); 1 = a sensitivity allele on either gene (*i.e.,* L/L &

4r/7r, L/L & 7r/7r, L/S & 4r/4r, S/S & 4r/4r); and 2 = sensitivity alleles on both genes (*i.e.,* L/S & 4r/7r, L/S & 7r/7r, S/S & 4r/7r, S/S & 7r/7r).

Second, Nederhof et al. (2010) coded the L'/L' genotype of *5-HTTLPR* and the Val/Val genotype of rs6265 in *BDNF* as reference categories given that they were less reactive (*i.e.,* resilient) alleles. Because the Met/Met genotype of rs6265 in *BDNF* was rare, the Met/Met and Val/Met genotypes were combined (*i.e.,* Met dominant mode), whereas the codominant mode of inheritance was taken for *5-HTTLPR*. Statistical analyses revealed that individuals with the L'/L' genotype of *5-HTTLPR* and the Val/Val genotype of rs6265 in *BDNF* (*i.e.,* L'/L' & Val/Val) were unaffected by childhood adversity, whereas those with the S' allele(s) of *5-HTTLPR* and/or the Met allele(s) of rs6265 in *BDNF* (*i.e.,* L'/L' & Val/Met, L'/L' & Met/Met, L'/S' & Val/Val, and S'/S' & Val/Val) exhibited "plasticity" (p. 968) or reactivity. The scoring system was not reported.

In addition, although not included when discussing the main and interaction effects of genotypes in this review, a study (Belsky & Beaver, 2011) conducted by one of the pioneers of the differential susceptibility model, Professor Jay Belsky, is potentially helpful to construct a polygenic susceptibility score. Based on a literature review (Belsky et al., 2009), Belsky and Beaver (2011) identified the followings as "plasticity alleles" (p. 622): the S allele of *5-HTTLPR*, the 7r allele of *DRD4*, the A1 allele of *DRD2*, the 10r allele of *DAT1*, and the 2r/3r alleles of *MAOA*. One point was assigned to each polymorphism if at least one plasticity allele was present. Then, "additive index of cumulative genetic plasticity" (p. 625) was created by summing these values, with the scores ranging from 0 to 5 for these 5 polymorphisms (Belsky & Beaver, 2011). In other words, the higher score would indicate the possession of more plasticity alleles and therefore imply greater plasticity or reactivity to the environment.

Discussion

The systematic review on genetic influence of psychological resilience was conducted to: (1) identify candidate genes associated with resilience, (2) identify alleles associated with resilience (main effect) and with less reactivity (G x E interaction), and (3) review various methods to construct a polygenic susceptibility score. A total of 14 genes were identified as candidate genes associated with resilience (Table 2): *5-HTTLPR*, *COMT*, *BDNF*, *DRD4*, *DRD2*, *DAT1*, *OXTR*, *RGS2*, *CACNA1C*, *FKBP5*, *CRHR1*, *MAOA*, *IL10*, *FGG*. Due to inconsistent findings, alleles of these genes associated with resilience (Table 3) or with less reactivity to the environment (Table 4) were not determined. Three methods to construct a polygenic index were reviewed.

According to the HuGE navigator (Centers for Disease Control and Prevention, 2017; Yu et al., 2010), there are 17 genes associated with a phenotype, "resilience, psychological", as of January 2017: *SLC6A4 (5-HTTLPR)*, *COMT*, *BDNF*, *DRD4*, *DRD2*, *OXTR*, *RGS2*, *CACNA1C*, *FKBP5*, *CRHR1*, *MAOA*, *IL10*, *FGG*, *ADAMTS16*, *PRTFDC1*, *HTR1A*, and *MTHFR*. All genes identified in this review are also identified by the HuGE Navigator except for *DAT1* (Beaver et al., 2011). In addition to candidate genes identified in this review, the HuGE Navigator adds the following four genes: *ADAMTS16*, *PRTFDC1*, *HTR1A*, *MTHFR*. The articles that the HuGE Navigator associated resilience with *ADAMTS16* (McGrath et al., 2013), *PRTFDC1* (Nievergelt et al., 2015), *HTR1A* (Benedetti et al., 2011), and *MTHFR* (Peerbooms et al., 2012) were excluded because they did not meet the inclusion criteria for this review. In addition, a review article (Wu et al., 2013) indicates, from the neurobiological perspective, *Neuropeptide Y gene (NPY)* and serotonin receptor genes (e.g. *HTR1A*, *HTR3A*, *HTR2C*) may also influence resilience. Although not considered in this review, epigenetics, which refers to stable changes in chromatin structure, such as altered acetylation, methylation of histones, and methylation of DNA itself, that underlie long-lasting alterations in gene expression and

that are not associated with changes in DNA sequence, may also contribute to resilience (Feder et al., 2009).

Given that resilience is a dynamic concept (Rutter, 2012) and is a quantitative trait likely influenced by numerous genes similar to common disorders (Plomin et al., 2009) and interacting with many variables. Therefore, failing to find a consensus about which alleles are associated with resilience and less reactivity to the environment is not surprising. From the genetic aspect, three main issues that may contribute to inconsistent findings are identified. First, rs25531 in *5-HTTLPR* is not often genotyped or is excluded from the statistical analyses. In general, it is recommended to genotype for rs25531 and reclassify the genotypes based on their transcriptional functionality (e.g. L'/L' = L_A/L_A; L'/S' = L_A/S & L_A/L_G; and S'/S' = S/S & L_G/S & L_G/L_G) (Murphy, Maile, & Vogt, 2013; Parsey et al., 2006).

Second, the mode of inheritance is often assumed differently. Some researchers (e.g. Amstadter et al., 2012; Graham et al., 2013) examine both codominant and dominant models and explore which model produces a significant finding. Others (e.g. Cicchetti & Rogosch, 2012; Nederhof et al., 2010) combine the homozygote of the *minor* allele (e.g. A/A of *OXTR*) with the heterozygote (e.g. G/A of *OXTR*) to increase statistical power. In contrast, some investigators (e.g. Bradley et al., 2013; Graham et al., 2013) group the homozygote of the *major* allele (e.g. G/G of *OXTR*) with the heterozygote (e.g. G/A of *OXTR*). How to model a genotype for statistical purposes potentially obscures the complexity underlying the genetic model (Dick et al., 2015). In case of *5-HTTLPR*, Sharpley, Palanisamy, and McFarlane (2013) provide evidence that individuals with the L/S genotype of *5-HTTLPR* score significantly higher on depressive symptoms than the homozygotes and suggest that this may explain the inconsistent findings by the L vs. S dichotomy.

Third, resilience as positive adaptation is measured by a variety of methods and instruments. In this review, the most frequently used instrument was CD-RISC (Connor & Davidson, 2003). Although there are at least 15 measures of resilience, there is no current 'gold standard' (Windle, Bennett, & Noyes, 2011). Some instruments may be more appropriate to operationalize resilience in the adolescent population (Ahern, Kiehl, Sole, & Byers, 2006). A careful consideration must be taken to avoid the three "deadly sins of resilience research": conceptually hazy, empirically light, and methodologically lame (Panter-Brick & Leckman, 2013; Southwick et al., 2014).

There are various methods to construct a polygenic susceptibility score. Due to failing to find a consensus, the best or preferred method to assign a score to each genotype in terms of the reactivity to the environment based on a literature review cannot be determined at this time. Alternatively, a score may be given based on the allelic frequency: 0 = major allele, 1 = heterozygous, and 2 = minor allele (Rana et al., 2014). In cases of *5-HTTLPR*, rs6265 in *BDNF*, and rs53576 in *OXTR*, the score can be assigned as follows: 0 = L'/L', 1 = L'/S', 2 = S'/S'; 0 = Val/Val, 1 = Val/Met, 2 = Met/Met; and 0 = G/G, 1 = G/A, 2 = A/A. Each score can be summed up and divided by the number of polymorphisms to calculate the average score. If an individual carries only major alleles of these three polymorphisms, then the score would be (0 + 0 + 0) / 3 = 0. If an individual carries the S'/S' genotype of *5-HTTLPR*, unknown for rs6265 in *BDNF*, and the G/A genotype of rs53576 in *OXTR*, then the score would be (2 + 1) / 2 = 1.5. By calculating the average, all samples including the ones with unknown genotypes can be included to construct a polygenic susceptibility score for statistical analyses. However, this method fails to consider epistasis (*i.e.,* gene x gene interaction) and haplotype (*i.e.,* a pair of alleles). A significant epistatic effect between rs4680 in *COMT* and rs6265 in *BDNF* in relation with resilience measured by CD-RISC was reported (Kang et al., 2013), and the TAT haplotype of rs110402, rs242924, and rs7209436 in *CRHR1* significantly

moderated the relationship between child maltreatment and resilience functioning (Cicchetti & Rogosch, 2012).

This review is limited mainly because no sophisticated statistical analyses were applied as in a meta-analysis. The intension of this review was to systematically identify candidate genes associated with resilience and less reactivity to environment. Because a concept analysis (Niitsu, Houfek, Barron, et al., 2017) revealed that resilience outcomes include two components: (1) none to mild psychopathological symptoms, and (2) positive adaptation, these can be considered as the phenotypes of resilience. In this review, articles that operationalized resilience as the absence of psychopathological symptoms (e.g. PTSD) were excluded and articles that operationalized resilience as positive adaptation were included. However, because the absence of psychopathological symptoms is also an important consequence of resilience, this systematic review is limited by focusing only on positive adaptation. A systematic review to identify candidate genes associated with resilience whose phenotype is none to mild psychopathological symptoms following exposure to PTEs is a suggestion for a future investigation. Finally, although excluded from this review, animal studies and epigenetic studies are also critically important to reveal the complex mechanism of resilience (Feder et al., 2009; Franklin, Saab, & Mansuy, 2012).

Conclusion

At least 14 genes were identified as candidate genes associated with resilience: *5-HTTLPR*, *COMT*, *BDNF*, *DRD4*, *DRD2*, *DAT1*, *OXTR*, *RGS2*, *CACNA1C*, *FKBP5*, *CRHR1*, *MAOA, IL10*, and *FGG*. There are other potential candidate genes for resilience. Due to exclusion of rs25531 in *5-HTTLPR*, different assumptions of the mode of inheritance, and various methods to operationalize resilience, findings regarding which alleles are associated with resilience and less reactivity to environment were inconsistent. Consequently, a method to construct polygenic susceptibility score solely

on the findings in the genetic studies in this literature review was not evident. Therefore, the literature on genetic score construction was also reviewed. Additionally, epistasis and epigenetics may also contribute to the complexity of genetic influence on resilience.

Table 2: Description of Candidate Genes Associated with Resilience

Gene	Description
5-HTTLPR *(SLC6A4)*	The *5-HTTLPR* codes for the serotonin transporter (5-HTT), which removes serotonin from the synaptic cleft (Canli & Lesch, 2007). It is composed of the short "S" and the long "L" version so that the expression of the 5-HTT mRNA of the L allele is about three time that of the S allele (Heils et al., 1996). There is a single base substitution (A>G) known as rs25531 (Hu et al., 2006), producing a "L_G" allele, which is functionally equivalent to the S allele (Wendland et al., 2006).
COMT	The *COMT* encodes Catechol-O-methyltransferase (COMT) that metabolizes the neurotransmitters, such as dopamine, epinephrine, and norepinephrine (National Center for Biotechnology Information, 2017b). A SNP, rs4680, produces an amino acid substitution, Valine to Methionine, at codon 158 (National Center for Biotechnology Information, 2017g). The Met/Met homozygote has 3- to 4-fold lower enzymatic activity than the Val/Val homozygote, whereas the heterozygote (Val/Met) has intermediate activity (Chen et al., 2004).
BDNF	The *BDNF* gene encodes proteins in a member of the nerve growth factor, Brain-Derived Neurotrophic Factor (BDNF) (National Center for Biotechnology Information, 2017a). A SNP, rs6265, at nucleotide 196(G/A) produces an amino acid substitution, Valine to Methionine, at codon 66 (National Center for Biotechnology Information, 2017h), leading to lower levels of the protein BDNF than the Val allele (Bath & Lee, 2006).
DRD4	The *DRD4* gene codes the dopamine D4 receptor, which is most expressed in specific areas of the brain including the frontal cortex and amygdala (Murray et al., 1995). This gene contains a 48-bp sequence (VNTR), which is repeated between 2 and 11 repeats, on its third exon (Oak, Oldenhof, & Van Tol, 2000). *DRD4* molecules with 7 repeats are less efficient at inhibiting the enzyme adenylate cyclase compared to those carrying 4 copies (Asghari et al., 1995; Jovanovic, Guan, & Van Tol, 1999). In addition, a SNP in *DRD4*, rs1800955, describes -521 C/T, which is a Cytosine (C) to Thymine (T) transition at base -521 in the upstream promoter region (National Center for Biotechnology Information, 2017i). The -521C allele is associated with a 40% increase in DRD4 transcription in cultured cells (Okuyama et al., 2000).
DRD2 *(ANKK1)*	The Taq1A (rs1800497), a frequently investigated SNP, was originally associated with the *DRD2* gene, which was later discovered to be located within exon 8 of the adjacent gene, *ANKK1* (National Center for Biotechnology Information, 2016a). ANKK1 causes a non-conservative amino acid (National Center for Biotechnology Information, 2016a). A meta analysis supports significant association between rs1800497 (A1 allele) and PTSD (Li et al., 2016).
DAT1	The *DAT1* gene encodes a dopamine transporter (National Center for Biotechnology Information, 2016f), which plays a role in dopaminergic neurotransmission by mediating the re-uptake of synaptic dopamine back into the neurons (Stahl, 2013). It contains a 40 bp tandem repeat,

which can have 3 to 11 copies (National Center for Biotechnology Information, 2016f). The 10-repeat allele may contribute to symptoms of MDD and ADHD because it may cause the re-uptake process to be abnormally efficient (Mill, Asherson, Browes, D'Souza, & Craig, 2002) and underactive in the dopaminergic mesocorticolimbic and nigrostriatal pathways, implying reduced dopamine in mesolimbic and striatal pathways (Gatt, Burton, Williams, & Schofield, 2015).

OXTR The *OXTR* encodes the protein that belongs to the G-protein coupled receptor family and acts as a receptor for oxytocin (National Center for Biotechnology Information, 2016d). A meta-analysis found positive association between a SNP, rs53576, and general sociability (Li et al., 2015).

RGS2 The *RGS2* encode the Regulator of G-protein Signaling 2 (RGS2), which modulates neurotransmitter response by accelerating the deactivation of G proteins (National Center for Biotechnology Information, 2016e). RGS2 is highly expressed in the human brain, such as the hippocampus, amygdala, brain stem, and hypothalamus (Neubig & Siderovski, 2002), which are involved in anxiety and fear processing (Stahl, 2013).

CACNA1C The *CACNA1C* gene encodes an alpha-1 subunit of a voltage-dependent L-type gated calcium channel, which mediates the influx of calcium ions into the cell upon membrane polarization (National Center for Biotechnology Information, 2016b). A meta-analysis supports significant association between *CACNA1C* and MDD (Rao et al., 2016).

FKBP5 The *FKBP5* encodes the protein in the immunophilin protein family, which play a role in immunoregulation and basic cellular processes involving protein folding and trafficking (National Center for Biotechnology Information, 2017d). Polymorphisms in *FKBP5* (e.g. rs1306780) are associated with differential upregulation of FKBP5 following Glucocorticoid Receptor (GR) activation and differences in GR sensitivity and stress hormone system regulation (Binder, 2009).

CRHR1 The *CRHR1* encodes a G-protein coupled receptor that binds neuropeptides of the corticotropin releasing hormone family, which play a major role to regulate the hypothalamic-pituitary-adrenal (HPA) pathway (National Center for Biotechnology Information, 2016c). Resilience has been associated with the brain's ability to moderate stress-induced increases in cortisol and the corticotropin-releasing hormone in the HPA axis (reviewed by Osorio et al., 2016).

MAOA The *MAOA* encodes mitochondrial enzymes which catalyze the oxidative deamination of amines, including serotonin, dopamine, and norepinephrine (National Center for Biotechnology Information, 2017f). Significant association between *MAOA*, including rs6323, and anger-related traits (Antypa et al., 2013).

IL10 The *IL10* encodes a cytokine produced primarily by monocytes and by lymphocytes (National Center for Biotechnology Information, 2017e). The cytokine has pleiotropic effects in inflammation and immunoregulation (National Center for Biotechnology Information, 2017e).

FGG	The *FGG* encodes the gamma component of fibrinogen, which is a blood-borne glycoprotein comprised of three pairs of non-identical polypeptide chains (National Center for Biotechnology Information, 2017c).

ADHD = Attention-Deficit/Hyperactivity Disorder; MDD = Major Depressive Disorder; PTSD = Post-Traumatic Stress Disorder

Table 3: Main Effect of Genes with Resilience (Positive Adaptation)

Gene	rs#	Resilience Measure	Mode of Inheritance	Resilient Allele	Reference
5-HTTLPR	N/A	CD-RISC	Codominant	L	Stein et al. (2009)
5-HTTLPR	N/A	CD-RISC	S dominant	[a]L	O'Hara et al. (2012)
5-HTTLPR	N/A	BIRD	Codominant	L	Amstadter et al. (2012)
5-HTTLPR	rs25531	CD-RISC	L' dominant	S'	Graham et al. (2013)
5-HTTLPR	rs25531	SOC, RS	Codominant	S'	Reinelt et al. (2015)
5-HTTLPR	N/A	RS	Codominant	S	Defrancesco et al. (2013)
5-HTTLPR	N/A	CD-RISC	Codominant	N/S	Carli et al. (2011)
5-HTTLPR	rs25531	PTG	Codominant	N/S	Dunn et al. (2014)
5-HTTLPR	N/A	Resilient Functioning	Codominant	N/S	Cicchetti and Rogosch (2012)
5-HTTLPR *SLC6A4*	N/A	ER89	Haplotype	L/10-L/12	Taylor et al. (2014)
SLC6A4	rs25532 rs1042173	PTS	T dominant for rs25532; C dominant for rs1042173	C of rs25532; A of rs1042173	Resnick, Klinedinst, Yerges-Armstrong, Choi, and Dorsey (2015)
COMT	rs4680	CD-RISC	Met dominant	Met	Kang et al. (2013)
COMT	rs4680	BIRD	Val dominant	Met	Amstadter et al. (2012)
BDNF	rs6265	SOC	Codominant	Val	Surtees et al. (2007)
BDNF	rs6265	PTG	Codominant	N/S	Dunn et al. (2014)
COMT x *BDNF*	rs4680 in *COMT*;	CD-RISC	Met dominant	Val of *COMT* x Met of	Kang et al. (2013)

	rs6265 in *BDNF*		(Epistasis)	*BDNF*; Met of *COMT* x Val of *BDNF*	
DRD4	VNTR	CD-RISC	7r dominant	N/S	Das et al. (2011)
DRD4	rs1800955	Resilient Functioning	C dominant	N/S	Cicchetti and Rogosch (2012)
OXTR	rs53576	LOT	A dominant	G	Saphire-Bernstein, Way, Kim, Sherman, and Taylor (2011)
OXTR	rs53576	LOT	Codominant	N/S	Cornelis et al. (2012)
OXTR	rs53576 rs2254298	PTG	Codominant	N/S	Dunn et al. (2014)
OXTR	rs53576	CD-RISC	G dominant	N/S	Bradley et al. (2013)
OXTR	rs53576	Resilient Functioning	A dominant	N/S	Cicchetti and Rogosch (2012)
RGS2	rs4606	PTG	Codominant	N/S	Dunn et al. (2014)
CACNA1C	rs1006737	SOC	Codominant in males; G dominant in females	G in males; A in females	Strohmaier et al. (2013)
CACNA1C	rs1006737	PTG	Codominant	N/S	Dunn et al. (2014)
FKBP5	rs1306780 rs9296158 rs9470080	PTG	Codominant	T of rs1306780	Dunn et al. (2014)
CRHR1	rs12944712	PTG	Codominant	N/S	Dunn et al. (2014)
MAOA	rs6323	CD-RISC	Codominant	T	Rana et al. (2014)
MAOA	rs6323	LOT	Codominant	T	Rana et al.

					(2014)
IL10	rs1800896	LOT	Codominant	A	Rana et al. (2014)
FGG	rs1800792	LOT	Codominant	C	Rana et al. (2014)

Note. BIRD = Behavioral Indicator of Resilience to Distress; CD-RISC = Connor-Davidson Resilience Scale; ER89 = Ego-Resiliency Scale; LOT = Life Orientation Test (optimism); N/A = Not Applicable; N/S = Not Significant; PTG = Post-Traumatic Growth; PTS = Physical Resilience Scale; SOC = Sense of Coherence; RS = Resilience Scale; VNTR = Variable Number Tandem Repeat.
[a]Only in participants younger than 70 years old.

Table 4: Gene by Environment Interaction for Resilience (Less Reactivity)

Gene	rs#	Environment	Resilience Measurement	Mode of Heritability	Less Reactive Allele	Reference
5-HTTLPR	rs25531	Childhood adversity	Effortful Control	Codominant	L'	Nederhof et al. (2010)
5-HTTLPR	N/A	Emotional abuse	BIRD	Codominant	L	Amstadter et al. (2012)
5-HTTLPR	N/A	Discrimination	Life History Strategies	Codominant	L	Gibbons et al. (2012)
5-HTTLPR	N/A	Child maltreatment	Resilient functioning	Codominant	L	Cicchetti and Rogosch (2012)
5-HTTLPR	rs25531	[a]Positive parenting	Positive affect	Codominant	L	Hankin et al. (2011)
5-HTTLPR	rs25531	[a]Social support	SOC, RS	Codominant	S'	Reinelt et al. (2015)
5-HTTLPR	rs25531	TBI	CD-RISC	L dominant	S'	Graham et al. (2013)
5-HTTLPR	N/A	Childhood adversity	CD-RISC	Codominant	S	Carli et al. (2011)
5-HTTLPR	N/A	Victimization	Lifetime resiliency	Codominant	S	Beaver et al. (2011)
5-HTTLPR	rs25531	Hurricane	PTG	Codominant	N/S	Dunn et al. (2014)
5-HTTLPR	N/A	Childhood emotional abuse	CD-RISC	Codominant	N/S	Stein et al. (2009)
COMT	rs4680	Emotional abuse	BIRD	Val dominant	N/S	Amstadter et al. (2012)
BDNF	rs6265	Social stress	Positive affect	Codominant	Val	van Winkel et al. (2014)
BDNF	rs6265	Childhood adversity	Effortful Control	Val dominant	Val	Nederhof et al. (2010)

BDNF	rs6265	Hurricane	PTG	Codominant	N/S	Dunn et al. (2014)
DRD4	VNTR	Childhood adversity	CD-RISC	7r dominant	7r	Das et al. (2011)
DRD4	VNTR	Discrimination	Life History Strategies	Codominant	4r	Gibbons et al. (2012)
DRD4	VNTR	Victimization	Lifetime resiliency	Codominant	N/S	Beaver et al. (2011)
DRD4	rs1800955	Child maltreatment	Resilient functioning	C dominant	C	Cicchetti and Rogosch (2012)
DRD2	rs1800497	Victimization	Lifetime resiliency	Codominant	A2	Beaver et al. (2011)
DAT1	VNTR	Victimization	Lifetime resiliency	Codominant	10r	Beaver et al. (2011)
OXTR	rs53576	[a]Positive family environment	CD-RISC	G dominant	A	Bradley et al. (2013)
OXTR	rs53576	Child maltreatment	Resilient functioning	A dominant	G	Cicchetti and Rogosch (2012)
OXTR	rs53576 rs2254298	Hurricane	PTG	Codominant	N/S	Dunn et al. (2014)
RGS2	rs4606	Hurricane	PTG	Codominant	C	Dunn et al. (2014)
CACNA1C	rs1006737	Hurricane	PTG	Codominant	N/S	(Dunn et al., 2014)
FKBP5	rs1360780 rs9296158 rs9470080	Hurricane	PTG	Codominant	N/S	(Dunn et al., 2014)
CRHR1	rs110402 rs242924 rs7209436	Child maltreatment	Resilient functioning	Haplotype	1 & 2 copies of TAT	Cicchetti and Rogosch (2012)
CRHR1	rs12944712	Hurricane	PTG	Codominant	N/S	Dunn et al. (2014)

Note. BIRD = Behavioral Indicator of Resiliency to Distress; N/A = Not Applicable; N/S = Not Significant; PTG = Post-Traumatic Growth; SOC = Sense of Coherence; RS = Resilience Scale; TBI = Traumatic Brain Injury; VNTR = Variable Number Tandem Repeat.
[a]Positive environment.

MANUSCRIPT #3: RELATIONSHIPS BETWEEN RESILIENCE, POTENTIALLY TRAUMATIC EVENTS, GENOTYPES, AND INTRAPERSONAL AND ENVIRONMENTAL VARIABLES IN COLLEGE STUDENTS

Abstract

Background & Significance. Most individuals experience at least one Potentially Traumatic Event (PTE), such as natural disaster, in their lifetime. When exposed to PTEs, some individuals develop psychopathology, including Post-Traumatic Stress Disorder (PTSD). Others, who are less adversely affected, are often labeled as "resilient". The empirical study of resilience needs to be approached from multiple levels of analysis, including social, economic, cultural, demographic, developmental, epigenetic, and genetic variables. The purpose of this study was to examine the relationships between resilience outcomes, PTEs, selected polymorphisms, ego-resiliency, emotion regulation, and social support in college students. This study was guided by the Differential Susceptibility Model for genetic influences on resilience.

Aims & Hypotheses. Aim 1: Describe the relationships between PTEs and resilience outcomes. ***Hypothesis 1:*** Individuals who experienced more PTEs will exhibit lower resilience outcomes (*i.e.,* more psychological distress and less positive adaptation). **Aim 2:** Describe the relationships between selected polymorphisms (rs25531 in *5-HTTLPR*, rs4680 in *COMT*, rs6265 in *BDNF*, rs1800955 in *DRD4*, rs1800497 in *DRD2*, rs53576 in *OXTR*, rs4606 in *RGS2*, rs1006737 in *CACNA1C*, rs9296158 in *FKBP5*, & rs7209436 in *CRHR1*) and (1) intrapersonal variables (ego-resiliency & emotion regulation) and (2) resilience outcomes. ***Hypothesis 2:*** The major alleles will be associated with higher levels of ego-resiliency, adaptive emotion regulation strategies, and better resilience outcomes. **Aim 3:** Examine whether selected genotypes, ego-resiliency, emotion regulation, and/or perceived social support moderate the effect of PTEs on resilience outcomes. ***Hypothesis 3:*** Among individuals who carry the major alleles for selected polymorphisms, have higher levels of ego-resiliency, utilize adaptive emotion regulation strategies, and/or perceive more social support, the effects of PTEs on resilience outcomes will be lower.

Methods. A cross-sectional, correlational design was used. Participants (*N* = 450), who were enrolled in psychology courses at a Midwestern university, completed a one-time data collection session consisting of questionnaires and collection of buccal cells. Questionnaires measured demographics, PTEs [measured by Trauma History Questionnaire (THQ)], ego-resiliency [Ego-Resiliency Scale (ER89)], emotion regulation [Emotion Regulation Questionnaire (ERQ) & Perceived Ability to Cope with Trauma (PACT)], perceived social support [Social Support Survey (SSS)], and resilience outcomes [Connor-Davidson Resilience Scale (CD-RISC), Sense of Coherence (SOC), & Mental Health Inventory (MHI)]. DNA was extracted from buccal cells and genotyped at the University of Nebraska-Lincoln Behavior Genetics Laboratory. Data were analyzed with descriptive statistics, ANOVA, and bivariate and multiple linear regressions.

Results. Participants were mostly female (79.5%), single (98.0%), Caucasian (80.0%), non-Hispanic/Latino (91.0%), and Christian (76.0%). Bivariate linear regression revealed the THQ total score significantly predicted lower resilience outcomes measured by SOC [R^2 = .07, F(1, 429) = 32.33, p < .001], MHI Psychological Distress [R^2 = .09, F(1, 427) = 40.91, p < .001], MHI Psychological Well-Being [R^2 = .05, F(1, 428) = 23.87, p < .001], and MHI Index [R^2 = .09, F(1, 424) = 39.32, p < .001] but not CD-RISC [R^2 = .008, F(1, 424) = 3.58, p = .059], generally supporting Hypothesis 1. ANOVA analyses revealed significant differences among genotypes of rs4680 in *COMT* [F(2, 442) = 4.99, p = .007, η_p^2 = .022] and rs4606 in *RGS2* [F(2, 429) = 4.58, p = .011, η_p^2 = .021], partially supporting Hypothesis 2. The relationships between THQ and resilience outcomes were moderated by Ego-Resiliency [R^2 = .37, F(3, 413) = 79.63, p < .001, regarding CD-RISC], Emotion Regulation Flexibility [R^2 = .17, F(4, 414) = 20.46, p < .001, regarding SOC], social support [R^2 = .32, F(3, 421) = 65.36, p < .001, regarding MHI Psychological Well-Being], and rs4680 in *COMT* [R^2 = .10, F(4, 423) = 11.50, p < .001, regarding SOC]. Additionally, the relationships between THQ Physical & Sexual Experiences subscale

and resilience outcomes were moderated by rs4606 in *RGS2* [R^2 = .03, F(4, 421) = 3.59, p < .001, regarding CD-RISC], rs7209436 in *CRHR1* [R^2 = .05, F(4, 428) = 5.50, p < .001, regarding CD-RISC], and the Polygenic Susceptibility Score [R^2 = .04, F(4, 432) = 3.94, p = .004, regarding CD-RISC], partially supporting Hypothesis 3.

Conclusions. In general, when exposed to more PTEs, individuals may experience lower resilience manifested by more psychological distress and less positive adaptation. However, individuals with higher ego-resiliency, stronger emotion regulation flexibility, higher perceived social support, and/or certain genotypes may fare better when experiencing PTEs. To our surprise, the aggregate PSS score suggested that individuals with major (not minor) alleles may be at an elevated risk for less positive adaptation following exposure to PTEs, particularly physical and sexual experiences. Further study is needed to determine the effects of genotypes on resilience in relation to PTEs, especially with regard to using additive polygenic scores.

Keywords: resilience, genotype, potentially traumatic events, ego-resiliency, emotion regulation, social support

Introduction

Most individuals experience at least one potentially traumatic event (PTE), such as natural disaster, in their lifetime, (Kessler et al., 1995). Although the college environment provides many positive experiences, college students may be at increased risk for PTEs, such as sexual assault (Fedina, Holmes, & Backes, 2016) and alcohol misuse that can result in negative consequences (Zamboanga & Olthuis, 2016). Individuals exposed to PTEs may experience significant psychological distress, with some developing Post-Traumatic Stress Disorder (PTSD) (American Psychiatric Association, 2013). However, most individuals exposed to PTEs do not develop PTSD as evidenced by very low prevalence of PTSD globally (e.g. about 2.5% in the United States, about 0.5% in Japan) (reviewed by Yehuda et al., 2015).

To better understand the heterogeneous stress reactions, the field of resilience study has emerged (Luthar et al., 2000). Resilience is not merely the absence of psychopathology but is the dynamic process that enables the individual successfully adapt to PTEs over the life course (Rutten et al., 2013). The empirical study of this complex construct, resilience, needs to be approached from multiple levels of analysis, including social, economic, cultural, demographic, developmental, epigenetic, and genetic variables (Southwick et al., 2014). Based on a concept analysis of resilience (Niitsu, Houfek, Barron, et al., 2017), ego-resiliency, emotion regulation, social support, and heredity were proposed as selected variables that may contribute to resilience. *Ego-resiliency* is a personality trait describing a dynamic ability to adapt to constantly changing environmental demands (Block & Block, 2006) and is found to mitigate the effect of stressors on mental health (e.g. Galatzer-Levy & Bonanno, 2013). *Emotion regulation* refers to an ability to shape which emotions one generates, when one experiences emotions, and how one expresses these emotions (Gross, 2015) and includes strategies, such as reappraisal and suppression (Gross & John, 2003). In

general, *reappraisal* is considered as an effective emotion regulation strategy, whereas *suppression* is a relatively maladaptive and effortful emotion regulation strategy (Sheppes & Gross, 2013). In addition, *emotion regulation flexibility*, which is defined as the matching of emotion regulation strategy to environmental situation (Bonanno & Burton, 2013), is suggested as an important avenue for future emotion regulation research (Gross, 2015). Emerging evidence suggests that individuals low in emotion regulation flexibility may exhibit marked increases in PTSD symptoms at high levels of PTEs exposure, whereas those high in emotion regulation flexibility may show relatively little change in posttraumatic stress at higher levels of exposure (Bonanno & Diminich, 2013; Pinciotti, Seligowski, & Orcutt, 2016). Finally, meta-analyses indicate that *social support* can attenuate the risk to develop PTSD following exposure to PTEs (Brewin et al., 2000; Ozer, Best, Lipsey, & Weiss, 2003; Trickey, Siddaway, Meiser-Stedman, Serpell, & Field, 2012). Increased social support has buffering effects on mental and physical illness and fosters adaptive coping strategies, which leads to stress resilience (reviewed by Feder et al., 2009).

Resilience in terms of a positive mental health adaptation in response to PTEs can be quantitatively measured by self-rating instruments (Pangallo et al., 2015), including the *Connor-Davidson Resilience Scale (CD-RISC)* (Connor & Davidson, 2003) and the *Sense of Coherence (SOC)* Scale (Antonovsky, 1987). SOC is a global orientation shaped by life experiences, consisting of three dimensions: comprehensibility, meaningfulness, and manageability (Antonovsky, 1993). In general, the CD-RISC score is lower among individuals exposed to PTEs, such as childhood adversity (Campbell-Sills, Forde, & Stein, 2009; Simeon et al., 2007). Similarity, SOC may be reduced following exposure to PTEs, such as a severely injury accident or suffering from rheumatoid arthritis (Schnyder, Buchi, Sensky, & Klaghofer, 2000). Furthermore, psychological well-being, which is “positive mental health” and is the opposite side of

"negative mental health" or psychological distress, can be measured by combining general positive affect, emotional ties, and life satisfaction subscales (Veit & Ware, 1983, p. 731). More broadly, overall mental health can be assessed by combining both the positive and negative mental health (Veit & Ware, 1983). Psychological well-being and overall mental health may be reduced among individuals who experience PTEs, such as cancer (Salsman, Schalet, Andrykowski, & Cella, 2015).

Resilience is polygenic (Osorio et al., 2016). Candidate genes associated with resilience are the ones that play important roles in brain circuitries involved in the stress response and reward experience, including in serotonergic, noradrenergic, and dopaminergic systems, hypothalamic-pituitary-adrenal (HPA) axis, and Brain-Derived Neurotrophic Factor (BDNF) production (Rutten et al., 2013; Wu et al., 2013). Based on a literature review (Niitsu, Houfek, Stoltenberg, et al., 2017), a total of 10 polymorphisms were selected in this study: rs25531 in *5-HTTLPR* (serotonin-transporter-linked polymorphic region), rs4680 in *COMT* (Catechol-O-MethylTransferase), rs6265 in *BDNF*, rs1800955 in *DRD4* (Dopamine Receptor D4 gene), rs1800497 in *DRD2* (Dopamine Receptor D2 gene), rs53576 in *OXTR* (Oxytocin Receptor gene), rs4606 in *RGS2* (Regulator Of G-Protein Signaling 2 gene), rs1006737 in *CACNA1C* (Calcium Voltage-Gated Channel Subunit Alpha1 C gene), rs9296158 in *FKBP5* (FK506 Binding Protein 5 gene), and rs7209436 in *CRHR1* (Corticotropin Releasing Hormone Receptor 1 gene).

This study was guided by the *Differential Susceptibility Model* (Ellis et al., 2011; Pluess, 2015) (Figure 1). According to this model, some individuals are more susceptible to both negative (*i.e.,* risk-promoting) and positive (*i.e.,* development-enhancing) environmental conditions than others (Ellis et al., 2011; Pluess, 2015). More specifically, "resilience" refers to the less reactivity, which is experiencing a stable level of functioning after exposed to *negative* influence, whereas "vantage resistance" refers to the less reactivity after exposed to *positive* influence (Pluess, 2015). Additionally, the increased

reactivity in terms of level of functioning to *negative* influence is called “vulnerability”, whereas the increased reactivity to *positive* influence is named “vantage sensitivity” (Pluess, 2015). Factors that contribute individual differences in susceptibility to the environment may include genetics, in that certain alleles may be associated with increased reactivity to environmental influences (Ellis et al., 2011; Pluess, 2015, 2017).

The purpose of this study was to examine the relationships between resilience outcomes, PTEs, selected polymorphisms, ego-resiliency, emotion regulation, and social support in college students. This investigation was guided by the following aims and hypotheses (Figure 2).

Aim 1: Describe the relationships between PTEs and resilience outcomes.

Hypothesis 1: Individuals who experienced more PTEs will exhibit lower resilience outcomes (*i.e.,* more psychological distress and less positive adaptation).

Aim 2: Describe the relationships between selected polymorphisms (rs25531 in *5-HTTLPR*, rs4680 in *COMT*, rs6265 in *BDNF*, rs1800955 in *DRD4*, rs1800497 in *DRD2*, rs53576 in *OXTR*, rs4606 in *RGS2*, rs1006737 in *CACNA1C*, rs9296158 in *FKBP5*, & rs7209436 in *CRHR1*) and (1) intrapersonal variables (ego-resiliency & emotion regulation) and (2) resilience outcomes.

Hypothesis 2: The major alleles will be associated with higher levels of ego-resiliency, adaptive emotion regulation strategies, and better resilience outcomes.

Aim 3: Examine whether selected genotypes, ego-resiliency, emotion regulation, and/or perceived social support moderate the effect of PTEs on resilience outcomes.

Hypothesis 3: Among individuals who carry the major alleles for selected polymorphisms, have higher levels of ego-resiliency, utilize adaptive emotion regulation strategies, and/or perceive more social support, the effects of PTEs on resilience outcomes will be lower.

Method

Participants and Procedure

Undergraduate students (*N* = 450) enrolled at a Midwestern university were recruited from the Psychology Department's subject pool. The study was approved by the Institutional Review Boards of the University of Nebraska-Lincoln and the University of Nebraska Medical Center. Participants attended a one-time data collection session and completed a set of online questionnaires that measured demographics, PTEs, ego-resiliency, emotion regulation, social support, and resilience outcomes in a private data collection room. The questionnaires were accessed through the Research Electronic Data Capture ("REDCap"), a secure web application for building and managing online surveys and databases (Harris et al., 2009).

After completing online questionnaires, participants donated buccal cells for genotyping following the IRB-approved procedure. Students who completed this study earned one course credit for a half-hour participation. DNA samples were analyzed in the Behavior Genetics Laboratory at the University of Nebraska-Lincoln.

Instruments

Potentially traumatic events. PTEs were measured by the *Trauma History Questionnaire (THQ)* (Hooper, Stockton, Krupnick, & Green, 2011). It contains 24 items asking respondents to indicate if they experienced PTEs categorized into three categories: (1) Crime-Related Events (e.g. Has anyone ever tried to take something directly from you by using force or the threat of force, such as a stick-up or mugging?), (2) General Disaster and Trauma (e.g. Have you ever had a serious accident at work, in a car, or somewhere else?), and (3) Physical and Sexual Experiences (e.g. Has anyone ever made you have intercourse or oral or anal sex against your will?). In this study, the answer option was dichotomous (yes/no). The score was summed by assigning 1 to "yes"

and 0 to “no”, with the total score ranging from 0 to 24 so that a higher score indicates more exposure to PTEs.

Ego-resiliency. Ego-resiliency was measured by the *Ego-Resiliency Questionnaire* (Block & Kremen, 1996). It contains 14 items on a 4-point Likert scale (1 = does not apply at all; 4 = applies very strongly). It is unidimensional, and sample items are “I am generous with my friends” and “I quickly get over and recover from being startled”. The total score ranges from 14 to 56 where a higher score indicates higher ego-resiliency. Cronbach’s alpha for the ego-resiliency scale in this study was .77.

Emotion regulation strategies. Emotion regulation strategies were assessed by the *Emotion Regulation Questionnaire (ERQ)* (Gross & John, 2003). This is a 10-item self-report measure comprised of two subscales: Reappraisal (e.g. When I want to feel more positive emotion, such as joy or amusement, I change what I’m thinking about), and Suppression (e.g. I keep my emotions to myself), on a 7-point Likert scale (1 = strongly disagree; 7 = strongly agree). Reappraisal has six items and Suppression has four items. The scores are summed for each subscale and divided by the number of items to calculate an average. In this method, the score ranges from 1 to 7 where a higher average score indicates stronger use of each strategy. Cronbach’s alpha for this study was .81 for Reappraisal and .78 for Suppression.

Emotion regulation flexibility. Emotion regulation flexibility was measured by the *Perceived Ability to Cope with Trauma (PACT)* scale (Bonanno, Pat-Horenczyk, & Noll, 2011). This is a 20-item self-report scale comprised of two subscales: Forward-focus (e.g. Keep myself serious and calm), and Trauma-focus (e.g. Pay attention to the distressing feelings that result from the event), on a 7-point Likert scale (1 = not at all able, 7 = extremely able). Emotion regulation flexibility can be calculated by subtracting Polarity (|Forward-focus – Trauma-focus|) from Sum (Forward-focus + Trauma-focus) (details described in Bonanno, Pat-Horenczyk, et al., 2011). A higher score indicates

more flexibility in emotion regulation. Cronbach's alpha for this study was .85 for Forward-focus and .80 for Trauma-focus.

Perceived social support. Perceived social support was measured by the Medical Outcomes Study *Social Support Survey (SSS)* (Sherbourne & Stewart, 1991). This is a 19-item self-report measure comprised of four subscales: Emotional/Informational Support (e.g. Someone you can count on to listen to you when you need to talk), Tangible Support (e.g. Someone to help you in you were confined to bed), Affectionate Support (e.g. Someone who shows you love and affection), and Positive Social Interaction (e.g. Someone to have a good time with), on a 5-point Likert scale (1 = None of the time, 5 = All of the time). There is an additional item that does not belong to any subscales: Someone to do things with to help you get your mind off things. This additional item was included in this study to detect a broader variety of perceived social support. The total score ranges 19 to 95 where a higher score indicates stronger perceived social support. Cronbach's alpha for this study was: .94 for Emotional/Informational Support, .93 for Tangible Support, .91 for Affectionate Support, .93 for Positive Social Interaction, and .96 for the total.

Resilience outcomes. One of resilience outcomes addressing positive adaptation was measured by the ***Connor-Davidson Resilience Scale (CD-RISC)*** (Connor & Davidson, 2003). This is a 25-item self-report scale comprised of five subscales: Personal competence/tenacity (e.g. You work to attain your goals), Trust in one's Instincts/tolerance of negative affect (e.g. Have to act on a hunch), Positive acceptance of change/secure relationships (e.g. Able to adapt to change), Control (e.g. In control of your life), and Spiritual influences (e.g. Sometimes fate or God can help), on a 5-point Likert scale (0 = Not true at all, 4 = True nearly all of the time). The total score ranges from 0 to 100 where a higher score indicates higher resilience. Cronbach's alpha

for this study was: .87 for Personal Competence, .73 for Trust, .74 for Positive Acceptance, .79 for Control, .64 for Spiritual Influences, and .92 for the total score.

Another resilience outcome was measured by *the* ***Sense of Coherence (SOC) scale*** (Antonovsky, 1987). This is a 29-item self-report measure comprised of three subscales: Comprehensibility (e.g. When you talk to people, do you have the feeling that they don't understand you?), Manageability (e.g. Has it happened that people whom you counted on disappointed you?), and Meaningfulness (e.g. Do you have the feeling that you don't really care about what goes on around you?), on a 7-point scale (e.g. 1 = Never, 7 = Always have this feeling, for the sample item for Comprehensibility above). Some items are reverse-coded so that a higher score indicates stronger SOC. The total score ranges from 29 to 203. Cronbach's alpha for this study was .75 for Comprehensibility, .77 for Manageability, .81 for Meaning, and .89 for the total.

Overall mental health was measured by *the* ***Mental Health Inventory (MHI)*** (Veit & Ware, 1983). This is a 38-item self-report scale comprised of six subscales: *Anxiety* (e.g. How often did you become nervous or jumpy when faced with excitement or unexpected situations during the past month?), *Depression* (e.g. Did you feel depressed during the past month?), *Loss of Behavioral/Emotional Control* (e.g. During the past month, have you had any reason to wonder if you were losing your mind, or losing control over the way you act, talk, think, feel, or of your memory?), *General Positive Affect* (During the past month, how much of the time have you felt that the future looks hopeful and promising?), *Emotional Ties* (e.g. During the past month, how much of the time have you felt loved and wanted?), and *Life Satisfaction* (e.g. How happy, satisfied, or pleased have you been with your personal life during the past month?), on 5 or 6-point scale, which varies by item (e.g. 1 = Always, 6 = Never). Additionally, three MHI global scores can be generated: *Psychological Distress* (Anxiety + Depression + Loss of Behavioral/Emotional Control), *Psychological Well-Being* (General Positive Affect +

Emotional Ties + Life Satisfaction), and *Mental Health Index* (combination of six subscales). Some items were reverse-coded so that a higher score indicates favorable (e.g. higher well-being) or unfavorable (e.g. more distress) mental health symptoms. The MHI Index score ranges from 38 to 226 where a higher score indicates greater psychological well-being and relatively less psychological distress. Cronbach's alpha for this study was: .88 for Anxiety, .87 for Depression, .86 for Loss of Behavioral/Emotional Control, .91 for General Positive Affect, .86 for Emotional Ties, not applicable for Life Satisfaction (one item only), .94 for Psychological Distress, .93 for Psychological Well-Being, and .96 for MHI Index.

Genotyping

DNA was extracted from buccal cells following the Gentra Puregene DNA Isolation Kit Protocol (Qiagen, Valencia, CA, USA) in the Behavior Genetics Laboratory at the University of Nebraska-Lincoln.

The *5-HTTLPR* Variable Number Tandem Repeat (VNTR) and rs25531 single-nucleotide polymorphism (SNP) were amplified using primers: F: 5'–TCCTCCGCTTTGGCGCCTCTTCC–3' and R: 5'–TGGGGGTTGCAGGGGAGATCCTG–3' (Wendland et al., 2006). The Polymerase Chain Reaction (PCR) was performed in 25 μl reactions containing 20 ng of DNA, 1X GoTaq Green Master Mix (Promega, Madison, WI, USA), and 10 μM of each primer. Cycling conditions consisted of (1) a 3 min denaturation at 95.0 °C, (2) 30 cycles of 30 sec denaturation at 95.0 °C, (3) 30 sec annealing at 61.3 °C, (4) 60 sec extension at 72.0 °C, and (5) a final cycle of 72.0 °C for 5 min. The PCR product (15 μl) was digested with *Hpa*II (New England BioLabs, Ipswich, MA, USA) for the rs25531 polymorphism overnight at 37.0 °C. The PCR product and digested product were separated by electrophoresis on a 2.5% agarose gel at 130 V for 90 min and visualized under UV light with SybrSafe stain. Forty-five samples (10% of *N*

= 450) were randomly selected and re-genotyped for *5-HTTLPR* and rs25531 to check for genotyping errors. In addition, samples that produced invisible/faint bands were rerun. Genotype calls were independently scored by two trained researchers, and no discrepancies were found. According to the level of expression, the genotypes of *5-HTTLPR* were reclassified as follows: L'/L' = L_A/L_A; L'/S' = L_A/S & L_A/L_G; and S'/S' = S/S & L_G/S & L_G/L_G (Parsey et al., 2006). Call rate for *5-HTTLPR*/rs25531 was 97.6%.

Other SNPs including rs4680 (Assay #: C_25746809_50) in *COMT*, rs6265 (C_11592758_10) in *BDNF*, rs1800955 (C_7470700_30) in *DRD4*, rs1800497 (C_7486676_10) in *DRD2*, rs53576 (C_3290335_10) in *OXTR*, rs4606 (C_2498717_10) in *RGS2*, rs1006737 (C_2584015_10) in *CACNA1C*, rs9296158 (C_1256775_10) in *FKBP5*, and rs7209436 (C_1570087_10) in *CRHR1* were genotyped by the TaqMan SNP Genotyping Assays following the manufacturer's protocol (Applied Biosystems, Foster City, CA, USA). PCR was performed in 5 μl reactions containing 20 ng of DNA, 1X TaqMan Master Mix, and 2X TaqMan primers/probes. Cycling conditions for all polymorphisms, except for rs53576 in *OXTR*, consisted of an initial 10 min denaturation at 95.0 °C, followed by 40 cycles of 95.0 °C for 15 sec and 60.0 °C for 60 sec. Cycling conditions for rs53576 in *OXTR* were an initial 10 min denaturation at 95.0 °C, followed by 50 cycles of 92.0 °C for 15 sec and 60.0 °C for 60 sec. Reactions were run on the StepOnePlus Real-Time PCR System, and end point FAM and VIC fluorescence levels were analyzed using the ABI Sequence Detection Software v1.2.3. (Applied Biosystems, Foster City, CA, USA). Forty-five samples (10% of *N* = 450) were randomly selected and re-genotyped for each SNP to check for genotyping errors. In addition, samples that were unable to be genotyped were rerun. No discrepancies were found. Call rate for each polymorphism was as follows: 99.1% for rs4680 in *COMT*; 99.6% for rs6265 in *BDNF*; 99.6% for rs1800955 in *DRD4*; 99.1% for rs1800497 in *DRD2*; 99.6% for rs53576

in *OXTR*; 97.1% for rs4606 in *RGS2*; 98.7% for rs1006737 in *CACNA1C*; 99.1% for rs9296158 in *FKBP5*; and 99.1% for rs7209436 in *CRHR1*.

Statistical Analysis

All statistical analyses were performed with IBM SPSS version 24. The data were examined for outliers and missing values, and summary statistics for demographics were computed. Continuous variables (age, intrapersonal and environmental variables, and resilience outcomes) were analyzed with t-tests to determine group differences in gender. To examine the relationships between PTEs and resilience (Aim 1), bivariate linear regressions were performed. To examine the relationships between genotypes and intrapersonal variables (ego-resiliency, emotion regulation strategies, emotion regulation flexibility) and resilience outcomes (Aim 2), analysis of variance (ANOVA) models and bivariate linear regressions were applied. To examine the moderation effects of intrapersonal and environmental variables on the relationship between PTEs and resilience outcomes (Aim 3), multiple linear regression analysis was used.

Scoring. The genetic variants were coded additively as the number of minor alleles (Rana et al., 2014): no minor allele (*i.e.,* homozygous of major alleles) = 0, one minor allele (*i.e.,* heterozygous) = 1, two minor alleles (*i.e.,* homozygous of minor alleles) = 2, except for *5-HTTLPR*/rs25531 and rs1800955 in *DRD4*. Although there were more participants who carried the S'/S' (*n* = 116) allele of *5-HTTLPR* than L'/L' (*n* = 100) carriers in this sample, a score was given as follows in line with previous literature (e.g. Stein et al., 2009): L'/L' = 0, L'/S' = 1, and S'/S' = 2. Similarly, there were more participants who carried the T/T genotype (*n* = 129) than those with the C/C genotype (*n* = 105) in this sample. Because rs1800955 in *DRD4* describes -521 C/T, which is a Cytosine (C) to Thymine (T) transition at base -521 in the upstream promoter region (National Center for Biotechnology Information, 2017i), and the -521 T allele is associated with a 40% decrease in DRD4 transcription in cultured cells (Okuyama et al.,

2000), a score was assigned as follows: C/C = 0, C/T = 1, T/T = 2. To test evocative Gene – Environment correlations (rGE), chi-square analyses (a 3 × 2 contingency table) were conducted.

Constructing a polygenic susceptibility score. To better understand a genetic contribution of a set of DNA aggregating the small effects of each DNA variant, an aggregate genetic index, which is known as "Polygenic Risk Score" or "Polygenic Susceptibility Score" (Plomin et al., 2009, p. 875), can be constructed. Because reactive alleles may be associated to not only negative but also positive environments, the name *Polygenic Susceptibility Score* (PSS) instead of *Polygenic Risk Score* was selected to describe an aggregate genetic index where a higher score indicates more susceptibility to both negative and positive environments.

PSS was constructed by summing assigned scores for each polymorphism and dividing by the numbers of polymorphisms included for each participant. For example, if an individual carried homozygotes of minor alleles (e.g. A/A of rs53576 in *OXTR*) for 10 polymorphisms, then a score of 2 was given [*i.e.,* (2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2) / 10 = 2]. Similarly, if an individual carried homozygotes of minor alleles for 8 polymorphisms with 2 unknown genotypes, then a score of 2 was given [(2 + 2 + 2 + 2 + 2 + 2 + 2 + 2) / 8 = 2]. In this study, PSS ranged from .20 to 1.50 (n = 450, M = .75, SD = .23). A total of 28 samples had one or more polymorphisms that were unable to be genotyped, and the denominator was adjusted accordingly for these samples to calculate PSS.

Results

Sample Characteristics

Demographics. Sociodemographic characteristics of participants are described in Table 5. A total of 450 college students participated in this study. The majority of

participants were female (79.5%), single (98.0%), Caucasian (80.0%), non-Hispanic/Latino (91.0%), and Christian (76.0%). Participants were young (*M* = 20.35, *SD* = 1.87 for males; *M* = 20.42, *SD* = 2.82 for females), and 49.2% of them were freshmen or sophomore. More than half (56.4%) had a family income of $60,000 or above.

Major study variables. The mean (*M*) and standard deviation (*SD*) of PTEs and the intrapersonal and environmental variables stratified by gender are described in Table 6. Participants generally experienced 3 or 4 PTEs (*M* = 4.10, *SD* = 2.62 for males; *M* = 3.79, *SD* = 2.67 for females). Males, however, were significantly more likely to experience crime-related events than females (*t* = 2.65, *p* = .008, *d* = .28). The ego-resiliency score, which ranged from 24 to 56 in this sample, was generally high (*M* = 42.67, *SD* = 5.42 for males; *M* = 41.82, *SD* = 5.75 for females). Males in this study used the suppression emotion regulation strategy more than females, but the difference did not reach significance (*t* = 1.78, *p* = .075, *d* = .22). There were no significant differences between males and females in reappraisal (*t* = -1.45, *p* = .147, *d* = -.18) and emotion regulation flexibility (*t* = .39, *p* = .694, *d* = .05). For social support, females perceived significantly more tangible (*t* = -2.27, *p* = .024, *d* = -.26) and affectionate (*t* = -2.27, *p* = .024, *d* = -.25,) support than males. In addition, females scored significantly higher on the Spiritual Influence subscale of CD-RISC (*t* = -2.82, *p* = .005, *d* = -.32) and the Anxiety subscale of MHI (*t* = -2.62, *p* = .009, *d* = -.33) than males.

Genotypic distribution. The distribution of genotypes of each polymorphism is described in Table 7. Hardy-Weinberg Equilibrium (HWE) was calculated by using the Online Encyclopedia for Genetic Epidemiology studies (Rodriguez, Gaunt, & Day, 2009). The genotypic distributions of polymorphisms were in accordance with HWE except for rs1800497 in *DRD2* (χ^2 = 4.90, *p* = .03) and rs9296158 in *FKBP5* (χ^2 = 3.96, *p* = .05). Deviation from HWE in a population may be due to genotyping error, stratification, and chance (Ebrahimi & Bilgili, 2007; Rodriguez et al., 2009). Regarding genotyping error,

10% of samples (*n* = 45) were randomly selected and re-genotyped for all polymorphisms, and no discrepancies were found. When HWE was recalculated by including only participants who self-identified themselves as White to explore stratification, rs1800497 in *DRD2* was in HWE (G/G = 228, G/A = 110, A/A = 18, χ^2 = 0.97, *p* = .32), whereas rs9296158 in *FKBP5* was not (G/G = 182, G/A = 134, A/A = 40, χ^2 = 3.91, *p* = .05). Additionally, the significance was relatively marginal for both rs1800497 in *DRD2* (*p* = .03) and rs9296158 in *FKBP5* (*p* = .05), and the sample size was relatively small (*N* = 450), implying that deviation from HWE may be due to chance. Overall, it was unlikely that genotyping error was the cause; stratification might partially explain deviation from HWE in rs1800497 in *DRD2* but not in rs9296158 in *FKBP5*; and the significant findings might be due to chance. Therefore, being mindful with deviation from HWE, both rs1800497 in *DRD2* and rs9296158 in *FKBP5* were included in further statistical analyses.

Gene – Environment Correlation (rGE)

Chi-square analyses were conducted to examine differences between participants who experienced low PTEs and those with high PTEs on frequency distributions of each polymorphism. Chi-square analyses were used following the method Banny, Cicchetti, Rogosch, Oshri, and Crick (2013) applied. In this study sample, the THQ scores were not normally distributed; therefore, chi-square analyses were more appropriate than t-tests. A score of 6.52 of THQ (*M* + 1*SD* = 3.86 + 2.66 = 6.52) or above was categorized as high PTEs, whereas a score of less than 6.52 was categorized as low PTEs. Chi-square analyses revealed that the distributions of genotypes did not differ between high PTEs and low PTEs in *5-HTTLPR*/rs25531 (χ^2 = .55, *p* = .76), rs4680 in *COMT* (χ^2 = .27, *p* = .88), rs6265 in *BDNF* (χ^2 = 1.39, *p* = .50), rs1800955 in *DRD4* (χ^2 = 4.37, *p* = .11), rs1800497 in *DRD2* (χ^2 = .65, *p* = .72), rs53576

in *OXTR* (χ^2 = .95, *p* = .62), rs4606 in *RGS2* (χ^2 = .76, *p* = .68), rs1006737 in *CACNA1C* (χ^2 = .53, *p* = .77), and rs9296158 in *FKBP5* (χ^2 = .16, *p* = .92). However, the finding in rs7209436 in *CRHR1* was marginal (χ^2 = 5.908, *p* = .052). For the low PTEs vs. high PTEs, respectively, the frequencies were as follows: C/C = 90.3% vs. 9.7%; C/T = 81.4% vs. 18.6%; and T/T = 88.5% vs. 11.5%. Therefore, no strong evidence of an evocative gene – environment correlation as an explanation for PTEs was found in all polymorphisms investigated in this study.

Aim 1: Relationships between PTEs and Resilience Outcomes

Hypothesis 1: *Individuals who experienced more PTEs will exhibit lower resilience outcomes (i.e., more psychological distress and less positive adaptation).*

Bivariate linear regression was performed to examine the linear relationship between PTE subscales and the total scale (THQ Crime-Related Events, THQ General Disaster, THQ Physical & Sexual Experience, and THQ Total) and resilience outcomes (CD-RISC, SOC, MHI Psychological Distress, MHI Well-Being, and MHI Index) (Table 8). CD-RISC Total [R^2 = .008, F(1, 435) = 3.72, p = .054] was predicted by only the THQ Physical & Sexual Experiences subscale (b = -1.24, t = -1.93, p = .054, η_p^2 = .008) but not other THQ subscales or the total score. Higher THQ total scores (as well as other subscales, see Table 8) significantly predicted lower resilience outcomes measured by SOC Total [R^2 = .07, F(1, 429) = 32.33, p < .001], MHI Psychological Distress [R^2 = .09, F(1, 427) = 40.91, p < .001], MHI Psychological Well-Being [R^2 = .05, F(1, 428) = 23.87, p < .01], and MHI Index [R^2 = .09, F(1, 424) = 39.32, p < .01]. The significant associations between the THQ total score and resilience outcomes measured by SOC (Figure 3) and MHI Psychological Distress (Figure 4) were depicted. Thus, overall, Hypothesis 1, that individuals who experience more PTEs will have more psychological

distress as measured by MHI Psychological Distress and less positive adaptation as measured by SOC, MHI Psychological Well-Being, and MHI Index, was supported.

Aim 2: Relationships between Genotypes and Intrapersonal Variables & Resilience Outcomes

Hypothesis 2: *The major alleles will be associated with higher levels of ego-resiliency, adaptive emotion regulation strategies, and better resilience outcomes.*

Intrapersonal variables (ego-resiliency and emotion regulation) and resilience outcomes were stratified for genotype groups of each polymorphism, and the differences among three genotypes were compared (Table 9). ANOVA revealed significant differences among individuals with the Val/Val vs. Val/Met vs. Met/Met genotypes of rs4680 in *COMT* on the ERQ Suppression subscale [$F(2, 442) = 4.99$, $p = .007$, $\eta_p^2 = .022$]. Subsequently, a post hoc Tukey test indicated that the mean score of the ERQ Suppression subscale in individuals with the Val/Val genotype of rs4680 in *COMT* was significantly higher than the mean score in Val/Met carriers ($p = .008$), but there were no significant differences between Val/Val and Met/Met ($p = .650$) and between Val/Met and Met/Met ($p = .120$) carriers (Figure 5).

In addition, ANOVA revealed significant differences among individuals with the C/C vs. C/G vs. G/G genotypes of rs4606 in *RGS2* on SOC scores [$F(2, 429) = 4.58$, $p = .011$, $\eta_p^2 = .021$]. A post hoc Tukey test indicated that the mean score of SOC in individuals with the C/C genotype of *RGS2* was significantly higher than the mean score in C/G carriers ($p = .027$), but there were no significant differences between C/C and G/G ($p = .067$) and between C/G and G/G ($p = .815$) carriers (Figure 6).

ANOVA analyses did not find significant differences on any intrapersonal variables and resilience outcomes in the following polymorphisms: rs25531 in *5-HTTLPR*, rs6265 in *BDNF*, rs1800955 in *DRD4*, rs1800497 in *DRD2*, rs53576 in *OXTR*,

rs1006737 in *CACNA1C*, rs9296158 in *FKBP5*, and rs7209436 in *CRHR1*. Overall, based on the finding of rs4606 in *RGS2* on SOC scores, Hypothesis 2 was partially supported.

Aim 3: The Moderating Effect between PTEs and Resilience Outcomes

Hypothesis 3: *Among individuals who carry the major alleles for selected polymorphisms, have higher levels of ego-resiliency, utilize adaptive emotion regulation strategies, and/or perceive more social support, the effects of PTEs on resilience outcomes will be lower.*

Multiple regression analysis was applied to examine the moderating effect of intrapersonal and environmental variables and genotypes on the relationships between PTEs and resilience outcomes. In each model, gender, age, and race (recoded as 1 = Caucasians, 2 = Non-Caucasians) were included as covariates. Non-automated backward selection was used; namely, a variable was deleted one by one until all remaining variables were significant at the .05 level.

Intrapersonal and environmental variables as moderators. Final models of intrapersonal and environmental variables as moderators between PTEs and resilience outcomes are presented in Table 10.

Ego-resiliency. Multiple linear regression analyses were used to test if THQ, Ego-Resiliency, and the interaction between THQ and Ego-Resiliency predicted participants' resilience outcomes, which were measured by CD-RISC Total, SOC Total, MHI Psychological Distress, MHI Psychological Well-Being, and MHI Index scores, respectively. Regarding CD-RISC Total, the results of the regression indicated three predictors (THQ: b = -3.86, t = -2.74, p = .006, η_p^2 = .018; Ego-Resiliency: b = 1.08, t = 6.94, p < .001, η_p^2 = .104; THQ x Ego-Resiliency: b = .08, t = 2.48, p = .014, η_p^2 = .015) explained 37% of the variance [R^2 = .37, $F(3, 413) = 79.63$, p < .001] (Table 10).

Regarding SOC Total, the results of the regression indicated that four predictors (THQ: *b* = -8.99, *t* = -3.94, *p* < .001, η_p^2 = .036; Ego-Resiliency: *b* = 1.07, *t* = 4.30, *p* < .001, η_p^2 = .042; THQ x Ego-Resiliency: *b* = .16, *t* = 2.98, *p* = .003, η_p^2 = .021; Age: *b* = .85, *t* = 2.18, *p* = .030, η_p^2 = .011) explained 31% of the variance [R^2 = .31, *F*(4, 417) = 47.13, *p* < .001] (Table 10). To create interaction plots for interpretations, the Ego-Resiliency score was dichotomized: a score of 36.29 (*M* – 1*SD* = 41.98 – 5.69 = 36.29) and below as low Ego-Resiliency, and a score greater than 36.29 as high Ego-Resiliency. The effect of THQ on CD-RISC Total (see Figure 7; linear regressions for each group listed) and SOC Total (see Figure 8; linear regressions for each group listed) was stronger among individuals with low Ego-Resiliency. No significant interactions between THQ and Ego-Resiliency on other resilience outcomes measured by MHI Psychological Distress, MHI Psychological Well-Being, and MHI Index emerged.

Emotion regulation reappraisal & suppression. No significant moderating effects of the Emotion Regulation Reappraisal and Suppression subscale scores between THQ and any resilience outcomes were found.

Emotion regulation flexibility. SOC Total [R^2 = .17, *F*(4, 414) = 20.46, *p* < .001] was significantly predicted by THQ (*b* = -1.91, *t* = -4.90, *p* < .001, η_p^2 = .055), Flexibility (*b* = 1.58, *t* = 2.06, *p* = .040, η_p^2 = .010), THQ x Flexibility (*b* = .29, *t* = 1.94, *p* = .053, η_p^2 = .009), and Age (*b* = 1.08, *t* = 2.55, *p* = .011, η_p^2 = .015) (Table 10). To create an interaction plot, the Emotion Regulation Flexibility (measured by PACT) score was dichotomized: a score of -2.95 (*M* – 1*SD* = -.98 – 1.97 = -2.95) and lower as weak flexibility; a score of -2.95 or greater as strong flexibility. The effect of THQ on SOC Total was stronger among individuals with weak emotion regulation flexibility (Figure 9). No significant moderating effects of emotion regulation flexibility was found between THQ

and other resilience outcomes measured by CD-RISC Total, MHI Psychological Distress, MHI Psychological Well-Being, and MHI Index.

Perceived social support. MHI Psychological Well-Being [R^2 = .32, F(3, 421) = 65.36, p < .001] was significantly predicted by THQ (b = -2.88, t = -2.93, p = .004, η_p^2 = .096), Perceived Social Support (b = .30, t = 4.77, p < .001, η_p^2 = .051), and THQ x Social Support (b = .03, t = 2.41, p = .016, η_p^2 = .014) (Table 10). Similarly, MHI Index [R^2 = .28, F(4, 416) = 40.17, p < .001] was significantly predicted by THQ (b = -6.75, t = -2.84, p = .005, η_p^2 = .019), Social Support (b = .58, t = 3.88, p < .001, η_p^2 = .035), THQ x Social Support (b = .58, t = 1.98, p = .048, η_p^2 = .009), and Gender (b = -5.57, t = -1.96, p = .050, η_p^2 = .009) (Table 10). To visualize the moderation effect, the Social Support score was dichotomized: a score of 65.88 (M – 1SD = 79.99 – 14.11 = 65.88) and below as weak social support, and a score greater than 65.88 as strong social support. The effect of THQ on MHI Psychological Well-Being (see Figure 10; linear regressions for each group listed) and MHI Index (see Figure 11; linear regressions for each group listed) was stronger among individuals with weak perceived social support. No significant interactions between THQ and social support on other resilience outcomes measured by CD-RISC Total, SOC Total, and MHI Psychological Distress were found.

Genotypes as moderators. Final multiple linear regression models of genotypes as moderators are displayed in Table 11. No significant interactions between THQ and any polymorphisms on any resilience outcomes were found except for the moderation effect of rs4680 in *COMT* on the relationship between THQ and SOC Total. SOC Total [R^2 = .10, F(4, 423) = 11.50, p < .001] was significantly predicted by THQ (b = -1.29, t = -1.96, p = .051, η_p^2 = .009), rs4680 in *COMT* (b = 5.44, t = 2.20, p = .029, η_p^2 = .011), THQ x rs4680 in *COMT* (b = -1.10, t = -2.02, p = .044, η_p^2 = .010), and Age (b = 1.23, t = 2.76, p = .006, η_p^2 = .018). The effect of THQ on SOC was stronger among individuals with the

Met allele(s) of rs4680 in *COMT* than those with the Val/Val genotype (see Figure 12; linear regressions for each group listed).

PSS as a moderator. Multiple regression analysis was applied to examine the moderating effects of PSS between PTEs and resilience outcomes. In each model, gender, age, and race were included as covariates, and non-automated backward selection was used as described above. Multiple linear regression analyses revealed no significant moderation effects of PSS on the relationships between PTEs and any resilience outcomes.

Additional Analyses: Moderation Effects of Genotypes on the Relationships between Physical & Sexual Experiences and Resilience Outcomes

Based on the results of bivariate linear regressions indicating stronger effects of the THQ Physical and Sexual Experience subscale on resilience outcomes (Table 8), the moderating effects of genotypes and PSS on the relationships between the THQ Physical & Sexual Experiences subscale (instead of the THQ total score) and resilience outcomes were examined.

Genotypes as moderators. The moderation effects of selected polymorphisms on the relationships between the THQ Physical & Sexual Experiences subscale and resilience outcomes are summarized in Table 12. Multiple linear regression revealed CD-RISC Total [R^2 = .03, F(4, 421) = 3.59, p < .001] was significantly predicted by THQ Physical & Sexual Experiences (b = -2.83, t = -3.16, p = .002, η_p^2 = .023), rs4606 in *RGS2* (b = -2.12, t = -1.98, p = .049, η_p^2 = .009), THQ Physical & Sexual Experiences x rs4606 in *RGS2* (b = 1.86, t = 2.19, p = .029, η_p^2 = .011), and Age (b = .55, t = 2.23, p = .026, η_p^2 = .012). The effect of THQ Physical & Sexual Experiences on CD-RISC Total was stronger among individuals with the C allele(s) of rs4606 in *RGS2* (see Figure 13; linear regressions for each group listed). In addition, the interaction between THQ

Physical & Sexual Experiences and rs7209436 in *CRHR1* significantly predicated CD-RISC Total [R^2 = .05, F(4, 428) = 5.50, p < .001], SOC Total [R^2 = .09, F(3, 434) = 14.70, p < .001], MHI Psychological Distress [R^2 = .09, F(4, 430) = 10.14, p < .001], MHI Psychological Well-Being [R^2 = .07, F(3, 433) = 11.35, p < .001], and MHI Index [R^2 = .09, F(3, 429) = 13.35, p < .001]. The effect of the THQ Physical and Sexual Experiences subscale on resilience outcomes measured by CD-RISC Total (see Figure 14; linear regressions for each group listed), SOC Total (see Figure 15; linear regressions for each group listed), MHI Psychological Distress (see Figure 16; linear regressions for each group listed), MHI Psychological Well-Being (see Figure 17; linear regressions for each group listed), and MHI Index (see Figure 18; linear regressions for each group listed) was stronger among individuals with the C allele(s) of rs7209436 in *CRHR1*.

PSS as a moderator. The final regression models examining moderations effects of PSS on the relationships between the THQ Physical & Sexual Experiences subscale and resilience outcomes are presented in Table 13. The results of the multiple linear regression indicated the four predictors explained 4% of the variance to predict CD-RISC Total [R^2 = .04, F(4, 432) = 3.94, p = .004]: THQ Physical & Sexual (b = -6.32, t = -2.82, p = .005, η_p^2 = .018), PSS (b = -6.85, t = -2.22, p = .027, η_p^2 = .011), THQ Physical & Sexual x PSS (b = 6.49, t = 2.20, p = .028, η_p^2 = .011), and Age (b = .51, t = 2.07, p = .039, η_p^2 = .010). Additionally, SOC Total [R^2 = .07, F(3, 438) = 10.34, p < .001] was significantly predicted by THQ Physical & Sexual (b = -11.96, t = -3.53, p < .001, η_p^2 = .028), PSS (b = -10.65, t = -2.30, p = .022, η_p^2 = .012), THQ Physical & Sexual x PSS (b = 9.87, t = 2.23, p = .027, η_p^2 = .011). Furthermore, MHI Index [R^2 = .06, F(3, 433) = 9.09, p < .001] was significantly predicted by THQ Physical & Sexual (b = -15.71, t = -3.44, p = .001, η_p^2 = .027), PSS (b = -14.66, t = -2.36, p = .019, η_p^2 = .013), THQ Physical

& Sexual x PSS (b = 13.56, t = 2.27, p = .024, η_p^2 = .012). To visualize the interaction, PSS was dichotomized: a score of .70, which was the median, and above as high PSS; a score less than .70 as low PSS. The effect of the THQ Physical and Sexual Experiences subscale on resilience outcomes measured by CD-RISC Total (see Figure 19; linear regressions for each group listed), SOC Total (see Figure 20; linear regressions for each group listed), and MHI Index (see Figure 21; linear regressions for each group listed) was stronger among individuals with low PSS. Based on the interaction effects of the intrapersonal and environmental variables and genotypes, including PSS, Hypothesis 3 was partially supported.

Discussion

The relationships of PTEs, ego-resiliency, emotion regulation, social support, and 10 polymorphisms with resilience outcomes were examined (Figure 2). Overall, Hypothesis 1 was generally supported, whereas Hypotheses 2 and 3 were partially supported. Although the effect size was relatively small, genetic influence on resilience was detected.

Aim 1: Relationships between PTEs and Resilience Outcomes

Although the THQ Physical and Sexual Experiences subscale significantly predicted CD-RISC Total, the other THQ subscales (*i.e.,* THQ Crime-Related Events, THQ General Disaster & Trauma, and THQ Total) did not (Table 8). The lack of a significant relationship between participants' scores on the THQ and CD-RISC Total was an unexpected finding. Possible reasons for this result are: (1) lack of variability on the instruments used (*i.e.,* overall low scores on the THQ indicating that students did not have significant trauma and high scores on CD-RISC indicating that students were resilient based on this instrument), and (2) the scale items were all worded positively, which may have encouraged respondents to indicate higher scores on the items (*i.e.,*

response bias) except for the Spiritual Influence subscale. This subscale, which contains only two items, also had lower internal consistency (r = .64) compared to the other CD-RISC subscales.

Otherwise, increased THQ subscale scores including the total score significantly predicted reduced resilience outcomes measured by SOC Total, MHI Psychological Distress, MHI Well-Being, and MHI Index (Table 8). Therefore, Hypothesis 1 that individuals who experienced more PTEs will exhibit lower resilience outcomes was *generally* supported. This is in line with the Diathesis-Stress framework of the Differential Susceptibility Model (Figure 1) that describes vulnerability for developing problematic outcomes following exposure to adversity (Pluess, 2015).

Aim 2: Relationships between Genotypes and Intrapersonal Variables and Resilience Outcomes

ANOVA analyses revealed significant associations between rs4680 in *COMT* and the ERQ subscale and between rs4606 in *RGS2* and the SOC total score but no significant associations between other polymorphisms and other intrapersonal variables and resilience outcomes. Therefore, Hypothesis 2 that the major alleles will be associated with higher levels of ego-resiliency, adaptive emotion regulation strategies, and better resilience outcomes was *partially* supported.

rs4680 in *COMT*. The mean score of the ERQ Suppression subscale in individuals with the Val/Val genotype of rs4680 in COMT was significantly higher than those with the Val/Met genotype (Table 9 & Figure 5). Because Hypothesis 2 assumed the major allele (the Val allele in this case) would be associated with adaptive emotion regulation, which is less suppression, Hypothesis 2 was not supported with rs4680 in *COMT*. Transcriptionally, individuals with homozygosity for the Val allele (*i.e.,* Val/Val) yield a three- to four-fold increase in *COMT* activity relative to Met homozygotes (*i.e.,* Met/Met), whereas individuals with heterozygosity (*i.e.,* Val/Met) have intermediate

activity (Syvanen, Tilgmann, Rinne, & Ulmanen, 1997). Accordingly, it is expected that the Val allele carriers would result in lower prefrontal dopamine level compared with the Met allele carriers (Bilder, Volavka, Lachman, & Grace, 2004). Given that suppression can be considered as a maladaptive emotion regulation strategy (Sheppes & Gross, 2013), this study's data may imply that carrying the heterozygotes (*i.e.,* not homozygotes) of rs4680 in *COMT* may be advantageous by regulating the prefrontal dopamine at the optimal level. Interestingly, a meta-analysis (Costas et al., 2011) also supports a protective effect for heterozygosity of rs4680 in *COMT* among individuals with schizophrenia and suggests both too high and too low levels of dopamine signaling may be risk factors. However, the association between rs4680 in *COMT* and suppression in this study may be due to chance because no significant differences among genotypes of rs4680 in *COMT* on emotion regulation reappraisal or flexibility were found.

rs4606 in *RGS2*. *RGS2* is a member of Regulator of G protein signaling (RGS) regulatory molecules that act as GTPase activating proteins (GAPs) for G alpha subunits of heterotrimeric G proteins and deactivate G protein subunits of the Gi alpha, Go alpha and Gq alpha subtypes (National Center for Biotechnology Information, 2016e). In this study, the mean score of SOC Total was significantly higher in individuals with the C/C genotype of rs4606 in *RGS2* than the mean score in C/G carriers (Table 9 & Figure 6). Because the C allele of rs4606 in *RGS2* is the major allele, this finding supports Hypothesis 2.

Findings from previous studies with rs4606 in *RGS2* are incongruent. Some studies indicate that the C allele of rs4606 in *RGS2* is associated with an increased risk of having current suicidal ideation (Amstadter et al., 2009b) and an increased risk of General Anxiety Disorder (Koenen et al., 2009). In contrast, other studies suggest the G allele of rs4606 in *RGS2* is associated with anxiety phenotypes including increased limbic activation during emotion processing (Smoller et al., 2008) and with reduced

sertraline (one of Selective Serotonin Reuptake Inhibitors) response (Stein et al., 2014). Because SOC is an indication of positive adaptation, this study's finding implies the C allele of rs4606 in *RGS2* may associated with increased resilience. In this sense, this study's result is in line with findings by Smoller et al. (2008) and Stein et al. (2014) that the G allele of rs4606 in *RGS2* may be associated with decreased resilience.

Aim 3: Moderating Effects of Intrapersonal and Environmental Variables and Genotypes on the Relationships between PTEs and Resilience Outcomes

Some of intrapersonal (ego-resiliency, emotion regulation flexibility) and environmental (social support) variables and genotypes (rs4680 in *COMT*, rs4606 in *RGS2*, rs7209436 in *CRHR1*, and PSS) moderated the relationships between PTEs and Resilience Outcomes (Table 10, 11, 12, & 13). However, other intrapersonal variables (emotion regulation reappraisal and suppression strategies) and other genotypes (rs25531 in *5-HTTLPR*, rs6265 in *BDNF*, rs1800955 in *DRD4*, rs1800497 in *DRD2*, rs53576 in *OXTR*, rs1006737 in *CACNA1C*, and rs9296158 in *FKBP5*) did not moderate the relationships between PTEs and any resilience outcomes. Therefore, Hypothesis 3 that, among individuals who carry the major alleles for selected polymorphisms, have higher levels of ego-resiliency, utilize adaptive emotion regulation strategies, and/or perceive more social support, the effect of PTEs on resilience outcomes will be lower, was *partially* supported.

Intrapersonal and environmental variables. Ego-resiliency, emotion regulation flexibility, and social support moderated the relationships between PTEs and resilience outcomes.

***Ego-resiliency*.** In this study, the effect of PTEs measured by THQ Total on resilience outcomes measured by CD-RISC Total (Figure 7) and SOC Total (Figure 8) was stronger among individuals with low Ego-Resiliency than those with high Ego-Resiliency. In contrast, a meta-analysis (Hu, Zhang, & Wang, 2015) indicates adversity

moderates the relationship between trait resilience and mental health measured by both positive and negative indicators. In other words, the stronger ego-resiliency, the higher on positive and the lower on negative indicators of mental health, but adversity moderates these relationships (Hu et al., 2015). Based on their finding, Hu et al. (2015) suggest that "…trait resilience may comprise both innate and acquired contents, both relatively stable and influenced by environmental factors" (p. 25). Participants in this study were young (Table 5) with experiencing a few PTEs in average (Table 6). In addition, PTEs were assessed with a binary answer (*i.e.,* Yes or No) without further measuring the severity, duration, and nature of events. If an event is severely stressful or traumatic, it may become a central component of personal identity and life story (Berntsen & Rubin, 2006). Therefore, ego-resiliency may be protective to certain severity, duration, and/or frequency of PTEs (*i.e.,* innate contents) but not to severely traumatic events that may influence an individual's identity (*i.e.,* acquired contents).

Furthermore, in addition to ego-resiliency, the participant's age significantly and positively predicted resilience outcomes measured by SOC Total (Table 6). This is consistent with the finding by Nilsson et al. (2010) that SOC improves with age.

***Emotion regulation flexibility*.** Individuals who had weak emotion regulation flexibility had less SOC when they reported more PTEs measured by THQ Total (Figure 9). Emotion regulation flexibility is adaptive when it is more likely to result in achieving personally meaningful goals (Aldao, Sheppes, & Gross, 2015). In addition, the original model explicitly indicates that strong SOC and "coping strategy: rational, *flexible*, and farsighted" would be related (Antonovsky, 1979, pp. 184-185). Given that SOC consists of Comprehensibility, Manageability, and Meaningfulness (Antonovsky, 1993), individuals with strong emotion regulation flexibility may be able to make a cognitive sense, perceive the demands as challenges rather than burdens, and find a meaning more easily when exposed to PTEs. Similar to ego-resiliency, the participant's age also

positively predicted SOC (Table 10), supporting that SOC improves with age (Nilsson et al., 2010). This may imply that an individual may become more resilient by understanding, managing, and making sense of PTEs better as one grows older. Overall, this finding provides additional evidence that emotion regulation flexibility may be protective in the face of PTEs, contributing to stronger SOC.

***Social support*.** The effect of PTEs measured by THQ Total on resilience outcomes measured by MHI Psychological Well-Being (Figure 10) and MHI Index (Figure 11) was stronger among individuals with weak social support than those with strong social support. The literature suggests that social support can be protective to stressful events among medical (Thompson, McBride, Hosford, & Halaas, 2016), dental (Harrison, Shaddox, Garvan, & Behar-Horenstein, 2016), nursing (Horgan, Sweeney, Behan, & McCarthy, 2016), and other college students (Mason, Zaharakis, & Benotsch, 2014). Social support moderated the relationships between PTEs and MHI Psychological Well-Being and MHI Index but not other resilience outcomes measured by CD-RISC Total, SOC Total, and MHI Psychological Distress, which is an area for future research. In addition to social support, the participant's gender (coded as 1 = Males, 2 = Females) significantly and negatively predicted MHI Index (*i.e.,* overall mental health) in this study (Table 10). Meta-analyses suggest that females tend to ruminate more (Johnson & Whisman, 2013) and exhibit greater activation in the left amygdala for negative emotion (Stevens & Hamann, 2012) than males, which may partially explain the gender difference in overall mental health.

Genotypes. Genotypes of rs4680 in *COMT*, rs4606 in *RGS2*, rs7209436 in *CRHR1*, and PSS moderated the relationships between PTEs and resilience outcomes.

***rs4680 in COMT*.** According to the *warrior/worrier model* (Goldman, Oroszi, & Ducci, 2005), individuals with the Val allele of rs4680 in *COMT* may control stress better under high pressure (therefore "warrior") but with moderately diminished executive

cognitive performance under mild pressure. In comparison, individuals with the Met allele may experience increased anxiety under high pressure (therefore "worrier") but with better cognitive performance under mild pressure. In addition to emotion regulation suppression, rs4680 in *COMT* was associated with the interaction between PTEs and resilience outcome measured by SOC Total (Figure 12). The effect of PTEs on SOC Total was stronger among individuals with the Met allele(s) of rs4680 in *COMT* than those with the Val/Val genotype. This finding may be in agreement with the *warrior/worrier model* (Goldman et al., 2005) that individuals with the Met allele ("worrier") of rs4680 in *COMT* may experience increased anxiety under high pressure (*i.e.,* more PTEs), which may diminish their cognitive performance (*i.e.,* comprehensibility of SOC). In contrast, those with the Val allele ("warrior") may not focus on comprehensibility or meaningfulness as much as the Met allele carriers do and could perform better behaviorally under high pressure (*i.e.,* more PTEs).

Furthermore, this study provides additional evidence for the differential susceptibility model (Pluess, 2015) that individuals with reactive alleles (the Met allele of rs4680 in *COMT* in this case) may function worse when exposed to negative influence as demonstrated in Figure 12. In this study, participants became more reactive with an increase of the Met allele of rs4680 in *COMT* (*i.e.,* Val/Val < Val/Met < Met/Met). A study (Agnafors et al., 2016) investigated the relationships between SOC and rs4680 in *COMT* but did not find any significant association or moderating effect. To this authors' knowledge, this is the first study to find the moderating effect of rs4680 in *COMT* on the relationship between PTEs and SOC.

***rs4606 in RGS2*.** The effect of THQ Physical and Sexual Experiences on resilience outcome measured by CD-RISC was stronger among individuals with the C/C genotype of rs4606 in *RGS2* (Figure 13). In other words, the C/C genotype of rs4606 in *RGS2* was found to be more reactive to PTEs related to physical and sexual

experiences when resilience outcome was measured by CD-RISC. This finding is congruent with the report by Amstadter et al. (2009a) who found that the effect of hurricanes on PTSD symptoms was stronger among individuals with the C/C genotype of rs4606 in *RGS2* (and with low social support and high lifetime PTEs in their study) than G allele(s) carriers. Overall, this study's findings indicate that individuals with the C/C genotype of rs4606 in *RGS2* may exhibit stronger SOC when not controlling for PTEs (Figure 6); however, as they experience more PTEs related to undesirable physical and sexual experiences, they may experience lower resilience outcome measured by CD-RISC (Figure 13). This may imply that these instruments (*i.e.,* SOC and CD-RICS) measure similar but distinct resilience outcomes. Further investigation is needed.

rs7209436 in CRHR1. *CRHR1* encodes a G-protein coupled receptor that binds neuropeptides of the corticotropin releasing hormone family, which play an important role in regulating the hypothalamic-pituitary-adrenal pathway and in activating signal transduction pathways that regulate diverse physiological processes, including stress, reproduction, immune response, and obesity (National Center for Biotechnology Information, 2016c). This study revealed the effect of THQ Physical & Sexual Experiences on resilience outcomes measured by CD-RISC Total (Figure 14), SOC Total (Figure 15), MHI Psychological Distress (Figure 16), MHI Psychological Well-Being (Figure 17), and MHI Psychological Index (Figure 18) was stronger among individuals with the C allele(s) of rs7209436 in *CRHR1* than those with the T/T genotype. Therefore, Hypothesis 3 that the effect of PTEs on resilience outcomes will be lower among individuals with the major allele or the C allele in rs7209436 in *CRHR1* was not supported. However, convergent evidence suggests that the effect of child abuse (Bradley et al., 2008) or childhood/adolescent physical assault/attack (Ben-Efraim, Wasserman, Wasserman, & Sokolowski, 2011) on depressive symptoms is stronger

among individuals with the C allele(s) of rs7209436 in *CRHR1*. Therefore, this study's findings that individuals with the C allele(s) of rs7209436 in CRHR1 were more vulnerable to PTEs related to undesirable physical and sexual experiences are congruent with the literature. However, this interpretation needs caution because SNPs in *CRHR1* are often investigated as a haplotype, such as a TAT haplotype formed by rs7209436, rs110402, and rs242924 in *CRHR1* (e.g. Cicchetti & Rogosch, 2012; Laucht et al., 2013; Polanczyk et al., 2009).

***PSS*.** To investigate the polygenic effect on resilience, PSS (Polygenic Susceptibility Score) was constructed. Because PSS is the average of scores where "0" is assigned for the major alleles, 1 for the heterozygotes, and 2 for the minor alleles, the lower score indicates possession of more major alleles, whereas the higher score indicates possession of more minor alleles. Results revealed that the effect of THQ Physical and Sexual Experiences was stronger among individuals with the low PSS (*i.e.,* more major alleles) on resilience outcomes measured by CD-RISC Total (Figure 19), SOC Total (Figure 20), and MHI Index (Figure 21) than those with the high PSS (*i.e.,* more minor alleles). Because individuals with more minor alleles (e.g. the S' allele of *5-HTTLPR*) were assumed to be more reactive to the environmental influence, these findings did not support Hypothesis 3. Although there is no study that constructs a polygenic score with the same 10 selected polymorphisms to this authors' knowledge, several researchers have investigated relationships between some of these selected polymorphisms and resilience outcomes. For example, there are evidence that the effect of PTEs, such as traumatic brain injury (Graham et al., 2013) and childhood trauma (Carli et al., 2011), on CD-RISC is stronger among individuals with the L or L' (accounting for rs25531) allele(s) of *5-HTTLPR*. These findings are consistent with this study's finding that the effect of THQ Physical & Sexual Experiences on CD-RISC Total was stronger among individuals with low PSS (*i.e.,* more major alleles such as the L'

allele of *5-HTTLPR*) than those with high PSS (Figure 19). However, no significant interaction effect of *5-HTTLPR* on the relationships between PTEs measured by THQ Total and THQ Physical & Sexual Experience subscale and CD-RISC Total was observed in this study.

Limitations

Four main limitations are identified in this study. First, a cross-sectional, quantitative study cannot determine changes in resilience over time. Ideally, a longitudinal design (Bonanno & Diminich, 2013; Masten, 2011) may be preferred so that changes in resilience over time can be examined. Additionally, in this study, the lifetime cumulative PTEs were assessed by asking participants to recall whether PTEs had happened to them or not (*i.e.,* yes or no). In other words, the nature of PTEs, including frequency, severity, duration, and how recent/old was not addressed.

Second, the use of a convenience sample utilizing college students limits generalizability. In addition, most participants in this study were females (79.5%), which also limits generalizability. However, this population was chosen for the preliminary study because college students are developmentally mature enough to complete questionnaires regarding their past PTEs and variables related to resilience, likely to have been exposed to at least some PTEs, and mostly homogeneous regarding race/ethnicity (*i.e.,* predominantly Caucasians), which limits the confounding issues related to polymorphisms. Nonetheless, several significant differences in gender emerged, such as that males were more likely to experience crime-related events than females, and that females were more likely to feel anxious than males (Table 6).

Third, the score assignment to construct PSS was based on the genotypic distribution (*i.e.,* 0 = major allele, 1 = heterozygotes, 2 = minor allele), not on the literature support or biological plausibility. Based on the preliminary results from this study, PSS may need to be reconstructed.

Forth, because this was a preliminary/exploratory study, inflated alpha or multiple significance tests (e.g. Bonferroni correction) was not controlled. In other words, all statistical significance levels were kept at the .05 level. Bonferroni corrections are widely known to be overly conservative corrections, and these multiple comparison procedures were originally intended to correct alpha when multiple group comparisons were being made on the same variable (K. A. Kupzyk, personal communication, April 7, 2017). Alternatively, the False Discovery Rate (Benjamini & Hochberg, 1995), instead of the Bonferroni correction, can be considered for a correction procedure in future studies.

Conclusion

The relationships between PTEs, selected polymorphisms, intrapersonal (ego-resiliency and emotion regulation) and environmental (perceived social support) variables, and resilience outcomes as measured by CD-RISC, SOC, and MHI were investigated. In general, participants who reported more PTEs were less resilient. The effect of PTEs on resilience outcomes was lower among participants with high ego-resiliency, strong emotion regulation, strong perceived social support, and/or certain genotypes (e.g. Val/Val of rs4680 in *COMT*). This study provides additional support for the differential susceptibility model (Pluess, 2015) that individuals with certain genotypes may be more reactive to environmental influences. Against our hypothesis, individuals with more major (not minor) alleles were more reactive to PTEs.

Table 5: Sociodemographic Characteristics of Participants (*N* = 450)

Variable	*M*	*SD*
Age	20.41	2.65
Demographics	**Frequency**	**Percent**
Gender		
Male	92	20.5%
Female	357	79.5%
Marital Status		
Single/never married	441	98.0%
Married	6	1.3%
Separated	0	0%
Divorced	3	0.7%
Widowed	0	0%
Grade		
Freshmen	61	13.6%
Sophomore	160	35.6%
Junior	133	29.6%
Senior	92	20.4%
Already have a bachelor's degree	4	0.9%
Family Income		
Under $20,000	39	8.7%
$20,000 - $39,999	41	9.1%
$40,000 - $59,999	46	10.2%
$60,000 - $79,999	59	13.1%
$80,000 - $99,999	60	13.3%
$100,000 or more	135	30.0%
Don't know	70	15.6%
Racial Group		
American Indian/Alaska Native	1	0.2%
Asian	33	7.3%
Black/African American	22	4.9%
Hispanic/Latino	25	5.6%
Native Hawaiian/Other Pacific Islander	1	0.2%
White/Caucasian	360	80.0%
Other	8	1.8%
Ethnic Group		
Hispanic/Latino	40	9.0%
Non-Hispanic/Latino	406	91.0%
Religious Background		
Christian	342	76.0%
Muslim	9	2.0%
Jewish	1	0.2%
Buddhist	6	1.3%
Hindu	1	0.2%
Others	19	4.2%
None	72	16.0%

Note. *M* = Mean; *SD* = Standard Deviation.

Table 6: Major Study Variables Stratified by Gender

	Males		Females			
Variable	*M*	*SD*	*M*	*SD*	*t*	*p*
Trauma History Questionnaire (THQ)						
Crime-Related Events	.63	.91	.40	.70	2.65	.008**
General Disaster & Trauma	2.92	1.85	2.61	1.73	1.52	.128
Physical & Sexual Experiences	.37	.85	.57	1.01	-1.77	.077
Total	4.10	2.62	3.79	2.67	.981	.327
Ego-Resiliency						
Total	42.67	5.42	41.82	5.75	1.26	.207
Emotion Regulation Questionnaire (ERQ)						
Reappraisal (average)	4.88	.92	5.04	.90	-1.45	.147
Suppression (average)	3.87	1.11	3.61	1.27	1.78	.075
Perceived Ability to Cope with Trauma (PACT)						
Flexibility	-.91	1.78	-1.00	2.01	.39	.694
Social Support Survey (SSS)						
Emotional/Informational Support	31.78	7.06	32.78	6.62	-1.26	.209
Tangible Support	15.77	4.05	16.77	3.67	-2.27	.024*
Affectionate Support	12.59	3.01	13.30	2.56	-2.27	.024*
Positive Social Interaction	13.01	2.46	13.37	2.28	-1.31	.190
Total	77.53	14.99	80.62	13.84	-1.87	.062
Connor-Davidson Resilience Scale (CD-RISC)						
Personal Competence	23.78	5.06	24.06	5.04	-.47	.641
Trust	19.34	3.77	18.56	4.20	1.62	.106
Positive Acceptance	15.17	2.70	15.42	2.86	-.76	.448
Control	8.79	2.39	8.94	2.50	.51	.614
Spiritual Influences	5.21	2.19	5.90	2.07	-2.82	.005**
Total	72.49	12.83	72.91	13.50	-.27	.789
Sense of Coherence (SOC)						
Comprehensibility	44.34	7.99	43.45	8.94	.87	.386
Manageability	50.86	7.24	49.97	8.33	.92	.356
Meaning	41.49	7.28	43.12	7.22	-1.91	.056
Total	136.88	18.43	136.54	21.04	.14	.891
Mental Health Inventory (MHI)						
Anxiety	22.77	6.12	25.08	7.70	-2.62	.009**
Depression	8.73	3.29	9.06	3.48	-.79	.429
Loss of Behavioral/Emotional Control	17.91	6.26	18.97	6.51	-1.39	.165
General Positive Affect	38.09	8.06	38.82	8.29	-.74	.457
Emotional Ties	8.45	2.68	8.77	2.66	-1.03	.304
Life Satisfaction	4.16	1.06	4.29	1.09	-.96	.339
Psychological Distress	55.38	15.17	59.29	17.67	-1.90	.058
Psychological Well-Being	54.49	11.43	55.41	11.72	-.66	.510
Mental Health Index	164.87	25.07	162.08	27.97	.85	.398

* $p < .05$. ** $p < .01$.

Table 7: Genotypic Distribution and Hardy Weinberg Equilibrium (HWE)

Gene	SNP	Common HZ	Heterozygotes	Rare HZ	HWE χ^2	*p*
5-HTTLPR	rs25531	S'/S' = 116	L'/S' = 223	L'/L' = 100	0.13	0.72
COMT	rs4680	V/V = 120	V/M = 211	M/M = 115	1.29	0.26
BDNF	rs6265	V/V = 293	V/M = 138	M/M = 17	0.02	0.89
DRD4	rs1800955	T/T = 129	C/T = 214	C/C = 105	0.79	0.37
DRD2	rs1800497	G/G = 264	G/A = 147	A/A = 35	4.90	0.03*
OXTR	rs53576	G/G = 202	G/A = 187	A/A = 59	2.22	0.14
RGS2	rs4606	C/C = 217	C/G = 175	G/G = 46	1.43	0.23
CACNA1C	rs1006737	G/G = 209	G/A = 189	A/A = 46	0.11	0.74
FKBP5	rs9296158	G/G = 219	G/A = 174	A/A = 53	3.96	0.05*
CRHR1	rs7209436	C/C = 128	C/T = 208	T/T = 110	1.93	0.16

Note. HZ = homozygotes; M = Methionine; SNP = Single-Nucleotide Polymorphism; V = Valine.

* $p < .05$.

Table 8: Results of Bivariate Linear Regression between THQ and Resilience Outcomes

Outcome	Predictor	*b*	*SE*	β	*t*	*p*	η_p^2
CD-RISC Total	THQ Crime	-.68	.85	-.04	-.79	.429	.001
CD-RISC Total	THQ General	-.26	.37	-.03	-.71	.477	.001
CD-RISC Total	THQ Physical	-1.24	.64	-.09	-1.93	.054*	.008
CD-RISC Total	THQ Total	-.46	.24	-.09	-1.89	.059	.008
SOC Total	THQ Crime	-3.61	1.30	-.13	-2.77	.006**	.017
SOC Total	THQ General	-1.86	.55	-.16	-3.37	.001**	.025
SOC Total	THQ Physical	-4.70	.97	-.23	-4.87	<.001**	.051
SOC Total	THQ Total	-2.05	.36	-.27	-5.69	<.001**	.070
MHI Distress	THQ Crime	2.33	1.10	.10	2.12	.035*	.010
MHI Distress	THQ General	2.27	.46	.23	4.95	<.001**	.054
MHI Distress	THQ Physical	3.58	.81	.21	4.40	<.001**	.042
MHI Distress	THQ Total	1.90	.30	.30	6.40	<.001**	.087
MHI Well-Being	THQ Crime	-1.46	.75	-.09	-1.96	.051*	.009
MHI Well-Being	THQ General	-1.00	.31	-.15	-3.20	<.001**	.023
MHI Well-Being	THQ Physical	-2.09	.55	-.18	-3.79	<.001**	.032
MHI Well-Being	THQ Total	-1.00	.21	-.23	-4.89	<.001**	.053
MHI Index	THQ Crime	-3.96	1.76	-.11	-2.25	.025*	.012
MHI Index	THQ General	-3.35	.73	-.22	-4.58	<.001**	.047
MHI Index	THQ Physical	-5.73	1.29	-.21	-4.43	<.001**	.043
MHI Index	THQ Total	-2.98	.48	-.29	-6.27	<.001**	.085

Note. *b* = Unstandardized coefficient; β = Standardized coefficient; CD-RISC = Connor-Davidson Resilience Scale; MHI = Mental Health Inventory (Psychological Distress, Psychological Well-Being, Index); *SE* = Standard Error; SOC = Sense of Coherence; THQ = Trauma History Questionnaire (Crime-Related Events, General Disaster & Trauma; Physical & Sexual Experience, and total).
* $p < .05$. ** $p < .01$.

Table 9: Major Variables Stratified for Selected Polymorphism by Genotype Group

rs4680 in *COMT*	Val/Val		Val/Met		Met/Met				
	(n = 120)		(n = 211)		(n = 115)				
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	η_p^2
Ego-Resiliency	41.77	6.32	42.04	5.20	42.09	5.93	.11	.893	.001
ERQ Reappraisal	5.11	.92	4.99	.84	4.93	.98	1.20	.301	.005
ERQ Suppression	3.89	1.19	3.46	1.27	3.75	1.19	4.99	.007**	.022
PACT Flexibility	-.92	2.09	-.94	1.96	-1.16	1.87	.59	.556	.003
CD-RISC Total	71.27	15.39	73.27	12.32	73.60	12.67	1.11	.328	.005
SOC Total	134.72	20.94	138.02	19.49	136.03	21.99	1.03	.357	.005
MHI Distress	57.51	17.65	57.91	16.32	60.30	18.16	.93	.396	.004
MHI Well-Being	55.20	12.37	55.57	10.87	54.90	12.07	.13	.876	.001
MHI Index	163.43	28.36	163.71	25.54	160.47	29.07	.56	.574	.003
rs4606 in *RGS2*	C/C		C/G		G/G				
	(n = 217)		(n = 175)		(n = 46)				
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	η_p^2
Ego-Resiliency	42.34	5.76	41.27	5.62	42.64	5.65	2.06	.129	.010
ERQ Reappraisal	4.96	.89	4.98	.93	5.25	.79	2.03	.132	.009
ERQ Suppression	3.69	1.28	3.54	1.21	4.03	1.16	2.92	.055	.013
PACT Flexibility	-.93	2.08	-1.21	1.87	-.46	1.71	2.81	.062	.013
CD-RISC Total	73.76	12.96	71.32	13.53	72.62	13.95	1.61	.202	.007
SOC Total	139.41	20.45	134.03	20.00	131.96	21.13	4.58	.011*	.021
MHI Distress	57.08	17.34	59.92	16.95	61.14	17.46	1.82	.164	.008
MHI Well-Being	56.42	11.84	53.72	11.14	54.04	11.89	2.82	.061	.013
MHI Index	165.21	27.91	159.78	26.30	158.84	27.67	2.30	.101	.011

Note. CD-RISC = Connor-Davidson Resilience Scale; ERQ = Emotion Regulation Questionnaire; MHI = Mental Health Inventory; PACT = Perceived Ability to Cope with Trauma; SOC = Sense of Coherence.

No significant findings were found among genotypes of the following polymorphisms: rs25531 in *5-HTTLPR*, rs6265 in *BDNF*, rs1800955 in *DRD4*, rs1800497 in *DRD2*, rs53576 in *OXTR*, rs1006737 in *CACNA1C*, rs9296158 in *FKBP5*, and rs7209436 in *CRHR1*.

* $p < .05$. ** $p < .01$.

Table 10: Moderating Effects of Intrapersonal and Environmental Variables between THQ and Resilience Outcomes

Variable	*b*	*SE*	*t*	*p*	η_p^2
Ego-Resiliency (predictor)					
CD-RISC Total [R^2 = .37, F(3, 413) = 79.63, p < .001]					
(Constant)	28.86	6.57	4.40	.000	.045
THQ	-3.86	1.41	-2.74	.006	.018
Ego-resiliency	1.08	.16	6.94	<.001	.104
THQ x Ego-resiliency	.08	.03	2.48	.014	.015
SOC Total [R^2 = .31, F(4, 417) = 47.13, p < .001]					
(Constant)	83.00	13.03	6.37	.000	.089
THQ	-8.99	2.28	-3.94	<.001	.036
Ego-resiliency	1.07	.25	4.30	<.001	.042
THQ x Ego-resiliency	.16	.05	2.98	.003	.021
Age	.85	.39	2.18	.030	.011
Emotion Regulation Flexibility (predictor)					
SOC Total [R^2 = .17, F(4, 414) = 20.46, p < .001]					
(Constant)	124.90	8.39	14.88	.000	.348
THQ	-1.91	.39	-4.90	<.001	.055
Flexibility	1.58	.77	2.06	.040	.010
THQ x Flexibility	.29	.15	1.94	.053	.009
Age	1.08	.42	2.55	.011	.015
Social Support (predictor)					
MHI Psychological Well-Being [R^2 = .32, F(3, 421) = 65.36, p < .001]					
(Constant)	33.91	5.08	6.68	.000	.096
THQ	-2.88	.98	-2.93	.004	.020
Social Support	.30	.06	4.77	<.001	.051
THQ x Social Support	.03	.01	2.41	.016	.014
MHI Index [R^2 = .28, F(4, 416) = 40.17, p < .001]					
(Constant)	134.61	12.80	10.52	.000	.210
THQ	-6.75	2.38	-2.84	.005	.019
Social Support	.58	.15	3.88	<.001	.035
THQ x Social Support	.06	.03	1.98	.048	.009
Gender	-5.57	2.84	-1.96	.050	.009

Note. CD-RISC = Connor-Davidson Resilience Scale; MHI = Mental Health Inventory; SOC = Sense of Coherence; THQ = Trauma History Questionnaire. Gender coded as: 1 = Males, 2 = Females.
Only significant findings were displayed in Table 10.
No significant interactions between THQ and Emotion Regulation Questionnaire (both Suppression & Reappraisal) on any resilience outcomes were found.

Table 11: Moderating Effects of Polymorphisms between THQ and Resilience Outcomes

Variable	*b*	*SE*	*t*	*p*	η_p^2
rs4680 in *COMT* (predictor)					
SOC Total [R^2 = .10, $F(4, 423) = 11.50$, $p < .001$]					
(Constant)	115.70	9.10	12.71	.000	.276
THQ	-1.29	.66	-1.96	.051	.009
COMT	5.44	2.48	2.20	.029	.011
THQ x *COMT*	-1.10	.54	-2.02	.044	.010
Age	1.23	.44	2.76	.006	.018

Note. SOC = Sense of Coherence; THQ = Trauma History Questionnaire.
Only significant findings were displayed in Table 11.
No significant interactions were found in the following polymorphisms: rs25531 in *5-HTTLPR*, rs6265 in *BDNF*, rs1800955 in *DRD4*, rs1800497 in *DRD2*, rs53576 in *OXTR*, rs4606 in *RGS2*, rs1006737 in *CACNA1C*, rs9296158 in *FKBP5*, and rs7209436 in *CRHR1*.

Table 12: Moderating Effects of Polymorphisms between THQ Subscale: Physical & Sexual Experiences and Resilience Outcomes

Variables	*b*	*SE*	*t*	*p*	η_p^2
rs4606 in *RGS2* (predictor)					
CD-RISC Total [R^2 = .03, $F(4, 421) = 3.59$, $p < .001$]					
(Constant)	63.61	5.03	12.66	.000	.276
THQ P & S	-2.83	.90	-3.16	.002	.023
RGS2	-2.12	1.08	-1.98	.049	.009
THQ P & S x *RGS2*	1.86	.85	2.19	.029	.011
Age	.55	2.23	.03	.026	.012
rs7209436 in *CRHR1* (predictor)					
CD-RISC Total [R^2 = .05, $F(4, 428) = 5.50$, $p < .001$]					
(Constant)	66.20	5.04	13.13	.000	.287
THQ P & S	-4.79	1.15	-4.16	<.001	.039
CRHR1	-2.58	.97	-2.65	.008	.016
THQ P & S x *CRHR1*	3.41	.98	3.47	.001	.027
Age	.48	.24	1.96	.051	.009
SOC Total [R^2 = .09, $F(3, 434) = 14.70$, $p < .001$]					
(Constant)	142.53	1.75	81.36	.000	.938
THQ P & S	-11.09	1.73	-6.40	<.001	.086
CRHR1	-3.68	1.46	-2.51	.012	.014
THQ P & S x *CRHR1*	6.56	1.48	4.44	<.001	.043
MHI Psychological Distress [R^2 = .09, $F(4, 430) = 10.14$, $p < .001$]					
(Constant)	46.69	3.86	12.09	.000	.254
THQ P & S	8.52	1.46	5.85	<.001	.074
CRHR1	3.08	1.23	2.50	.013	.014
THQ P & S x *CRHR1*	-5.24	1.25	-4.21	<.001	.039
Gender	4.04	2.00	2.03	.043	.009
MHI Psychological Well-Being [R^2 = .07, $F(3, 433) = 11.35$, $p < .001$]					
(Constant)	57.99	.99	58.80	.000	.889
THQ P & S	-5.67	.98	-5.77	<.001	.071
CRHR1	-1.94	.83	-2.34	.020	.012
THQ P & S x *CRHR1*	3.70	.84	4.42	<.001	.043
MHI Index [R^2 = .09, $F(3, 429) = 13.35$, $p < .001$]					
(Constant)	170.00	2.32	73.17	.000	.926
THQ P & S	-14.23	2.30	-6.18	<.001	.082
CRHR1	-4.96	1.95	-2.55	.011	.015
THQ P & S x *CRHR1*	8.80	1.97	4.48	<.001	.045

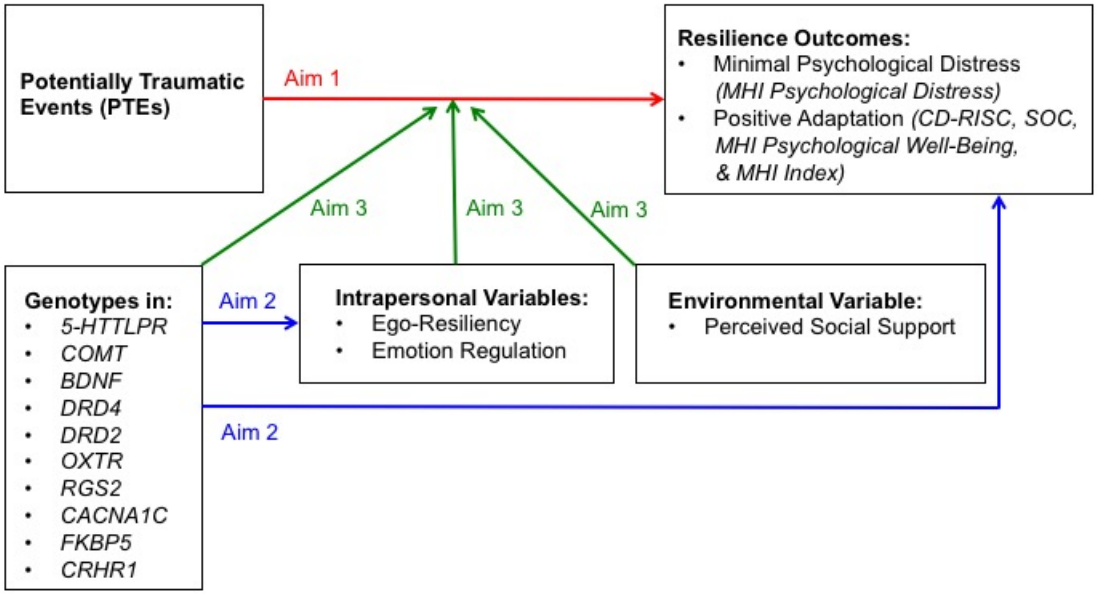
Note. CD-RISC = Connor-Davidson Resilience Scale; MHI = Mental Health Inventory; SOC = Sense of Coherence; THQ P & S = Trauma History Questionnaire Physical & Sexual Experiences. Gender coded as: 1 = Males, 2 = Females.
Only significant findings were displayed in Table 12.
No significant interactions were found in the following polymorphisms: rs25531 in *5-HTTLPR*, rs4680 in *COMT*, rs6265 in *BDNF*, rs1800955 in *DRD4*, rs1800497 in *DRD2*, rs53576 in *OXTR*, rs1006737 in *CACNA1C*, and rs9296158 in *FKBP5*.

Table 13: Moderating Effects of PSS between THQ Subscale: Physical & Sexual Experiences and Resilience Outcomes

Variables	*b*	*SE*	*t*	*p*	η_p^2
CD-RISC Total [R^2 = .04, $F(4, 432) = 3.94$, $p < .001$]					
(Constant)	68.33	5.55	12.31	.000	.260
THQ Physical & Sexual	-6.32	2.24	-2.82	.005	.018
PSS	-6.85	3.08	-2.22	.027	.011
THQ Physical & Sexual x PSS	6.49	2.95	2.20	.028	.011
Age	.51	.25	2.07	.039	.010
SOC Total [R^2 = .07, $F(3, 438) = 10.34$, $p < .001$]					
(Constant)	147.02	3.61	40.73	.000	.791
THQ Physical & Sexual	-11.96	3.39	-3.53	<.001	.028
PSS	-10.65	4.62	-2.30	.022	.012
THQ Physical & Sexual x PSS	9.87	4.44	2.23	.027	.011
MHI Index [R^2 = .06, $F(3, 433) = 9.09$, $p < .001$]					
(Constant)	176.34	4.85	36.38	.000	.753
THQ Physical & Sexual	-15.71	4.57	-3.44	.001	.027
PSS	-14.66	6.21	-2.36	.019	.013
THQ Physical & Sexual x PSS	13.56	5.97	2.27	.024	.012

Note. CD-RISC = Connor-Davidson Resilience Scale; MHI = Mental Health Inventory; PSS = Polygenic Susceptibility Score; SOC = Sense of Coherence; THQ = Trauma History Questionnaire.
Only significant findings were displayed in Table 13.

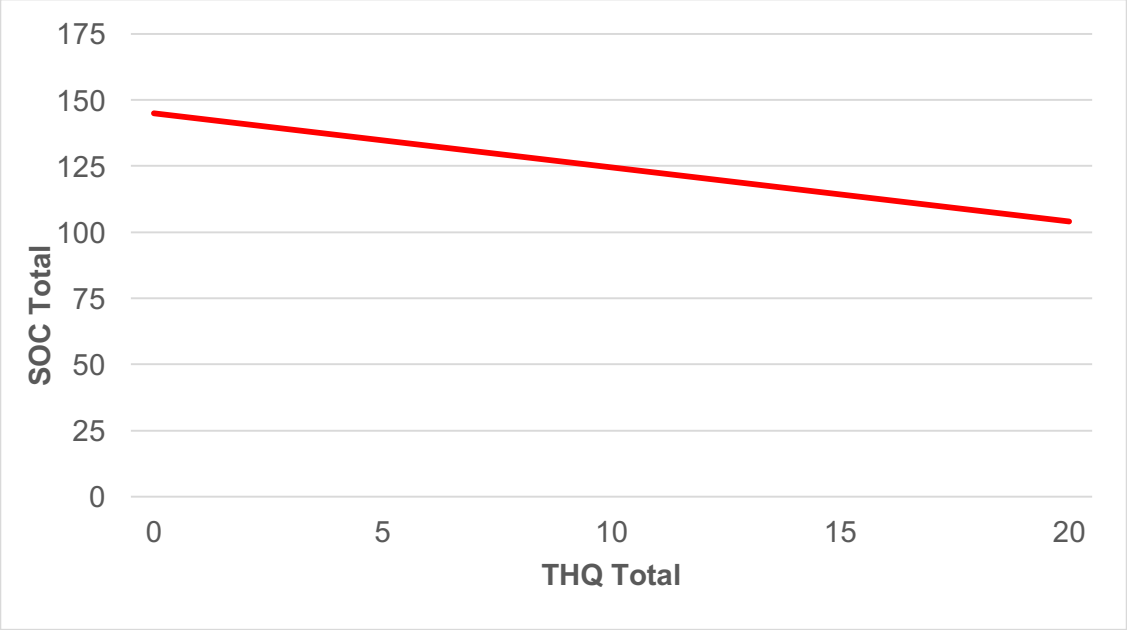
Figure 2: Hypothesized Relationships between Resilience, PTEs, Genotypes, and Intrapersonal and Environmental Variables



Instruments to measure:

- PTEs: *Trauma History Questionnaire (THQ)*
- Ego-Resiliency: *Ego-Resiliency Scale (ER89)*
- Emotion Regulation Strategies: *Emotion Regulation Questionnaire (ERQ)*
- Emotion Regulation Flexibility: *Perceived Ability to Cope with Trauma (PACT)*
- Perceived Social Support: *Social Support Survey (SSS)*
- Psychological Distress: *Mental Health Inventory (MHI) Psychological Distress*
- Positive Adaptation:
    - *Connor-Davidson Resilience Scale (CD-RISC)*
    - *Sense of Coherence (SOC)*
    - *MHI Psychological Well-Being*
    - *MHI Index*

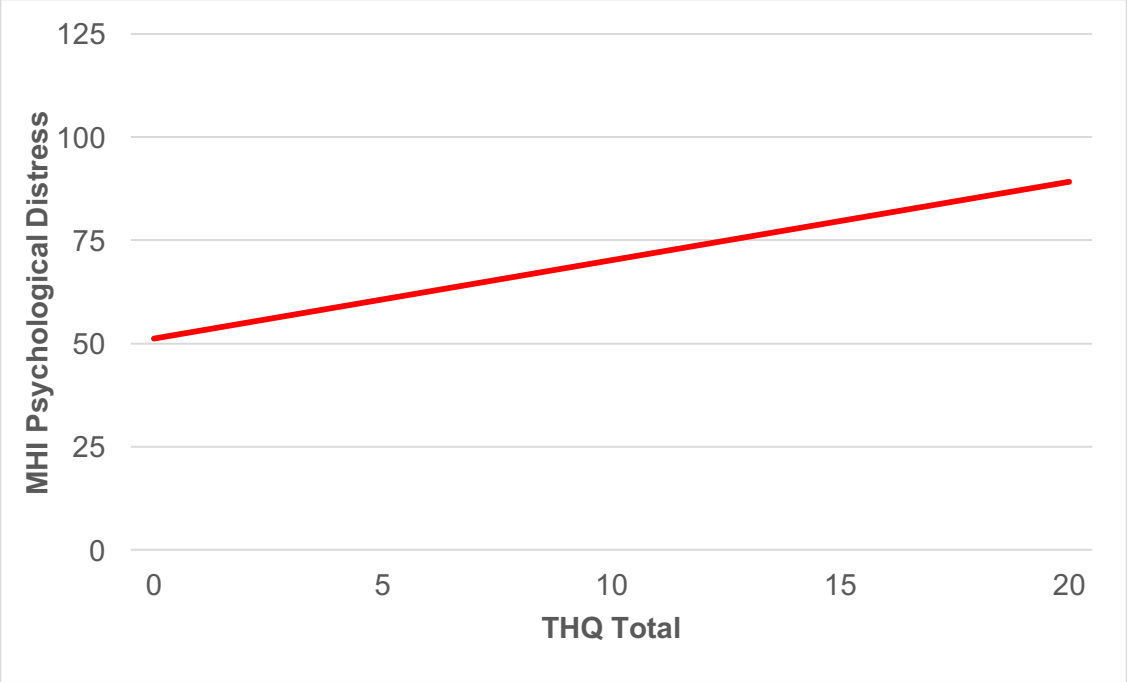
Figure 3: Bivariate Relationship between THQ Total and SOC Total



Note. SOC = Sense of Coherence; THQ = Trauma History Questionnaire.

SOC = 144.65 – 2.05 (THQ), [R^2 = .07, F(1, 429) = 32.33, p < .01**].

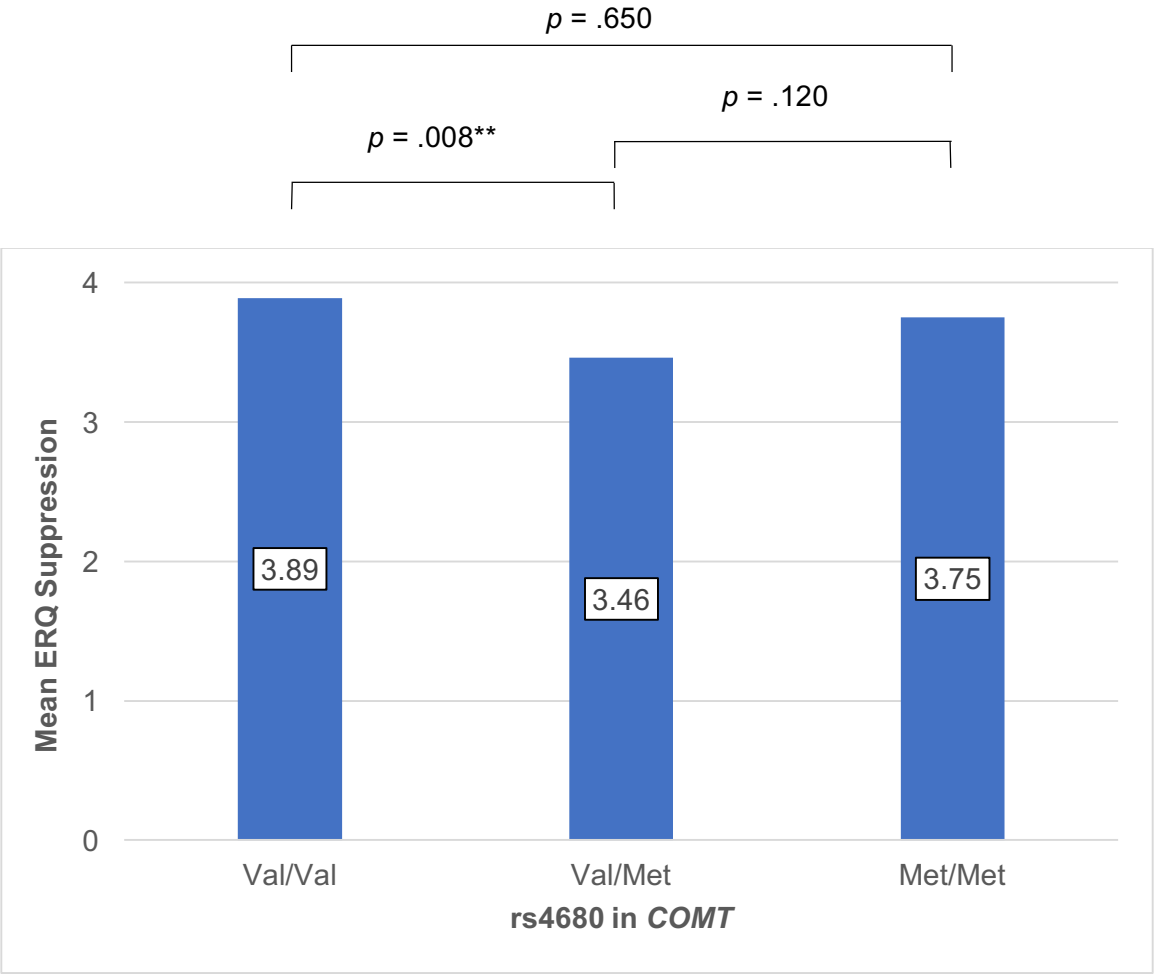
Figure 4: Bivariate Relationship between THQ Total and MHI Psychological Distress



Note. MHI = Mental Health Inventory; THQ = Trauma History Questionnaire.

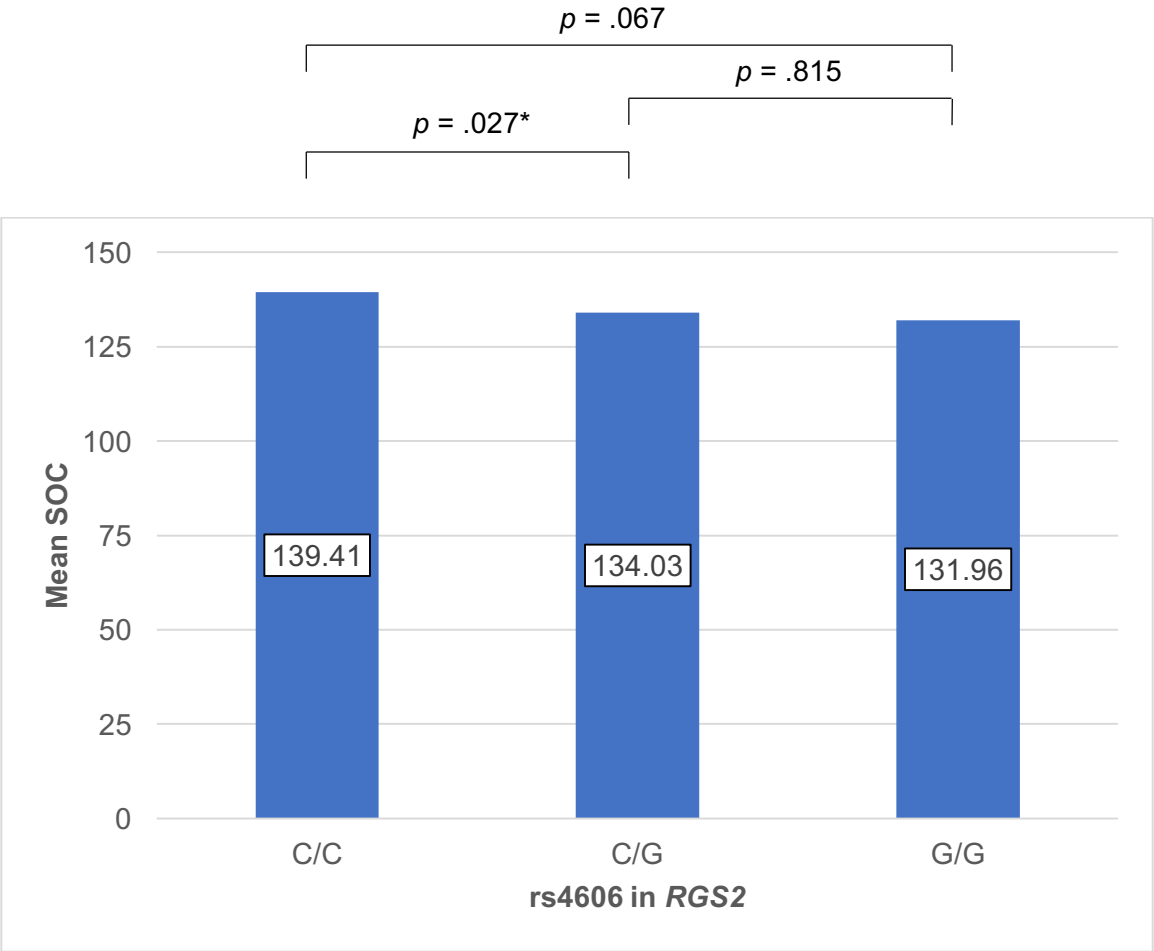
MHI Psychological Distress = 51.14 + 1.90 (THQ), [R^2 = .09, F(1, 427) = 40.91, p < .01**].

Figure 5: Comparison of Mean ERQ Suppression Scores among Val/Val vs. Val/Met vs. Met/Met Genotypes of rs4680 in *COMT*



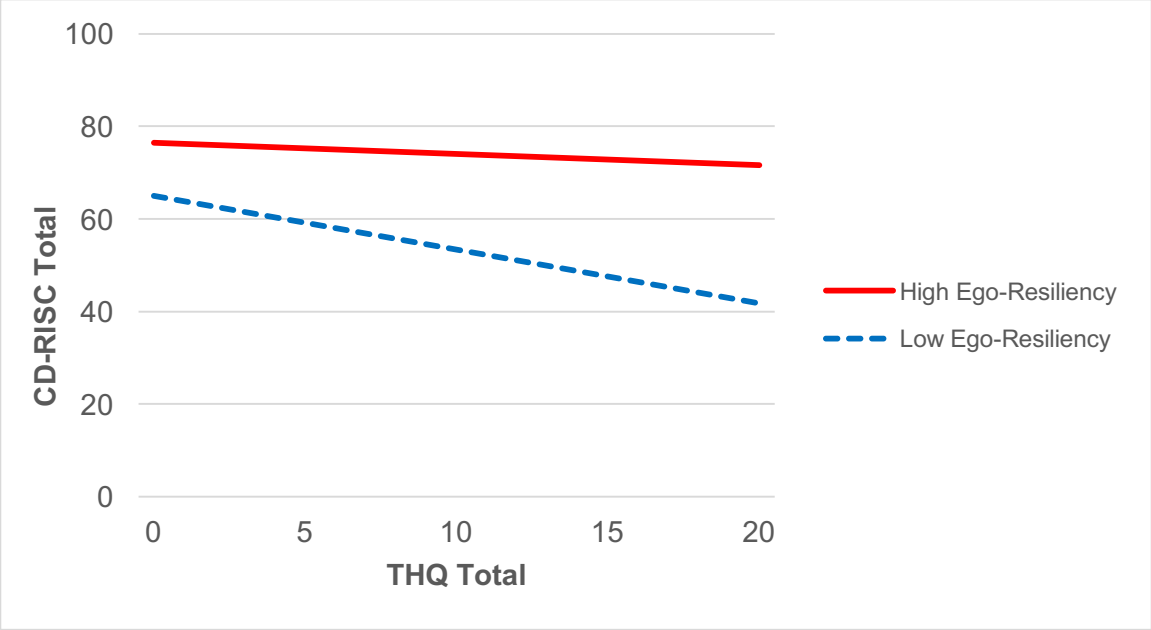
Note. ERQ = Emotion Regulation Questionnaire.
ANOVA revealed significant differences among genotypes of rs4680 in *COMT* on the ERQ Suppression mean scores [$F(2, 442) = 4.99$, $p = .007$, $\eta_p^2 = .022$]. Post hoc Tukey test indicated that the mean score of the ERQ Suppression subscale in participants with the Val/Val genotype of rs4680 in *COMT* was significantly higher than the mean score in Val/Met carriers ($p = .008$), but there were no significant differences between Val/Val and Met/Met ($p = .650$) and Val/Met and Met/Met ($p = .120$) carriers.

Figure 6: Comparison of Mean SOC Scores among C/C vs. C/G vs. G/G Genotypes of rs4606 in *RGS2*



Note. SOC = Sense of Coherence.
ANOVA revealed significant differences among individuals with the C/C vs. C/G vs. G/G genotypes of rs4606 in *RGS2* on the mean SOC scores [$F(2, 429) = 4.58$, $p = .011$, $\eta_p^2 = .021$]. Post hoc Tukey test indicated that the mean score of SOC in individuals with the C/C genotype of rs4606 in *RGS2* was significantly higher by the mean score in C/G carriers ($p = .027$), but there were no significant differences between C/C and G/G ($p = .067$) and between C/G and G/G ($p = .815$) carriers.

Figure 7: Moderation Effect of Ego-Resiliency between THQ Total and CD-RISC Total

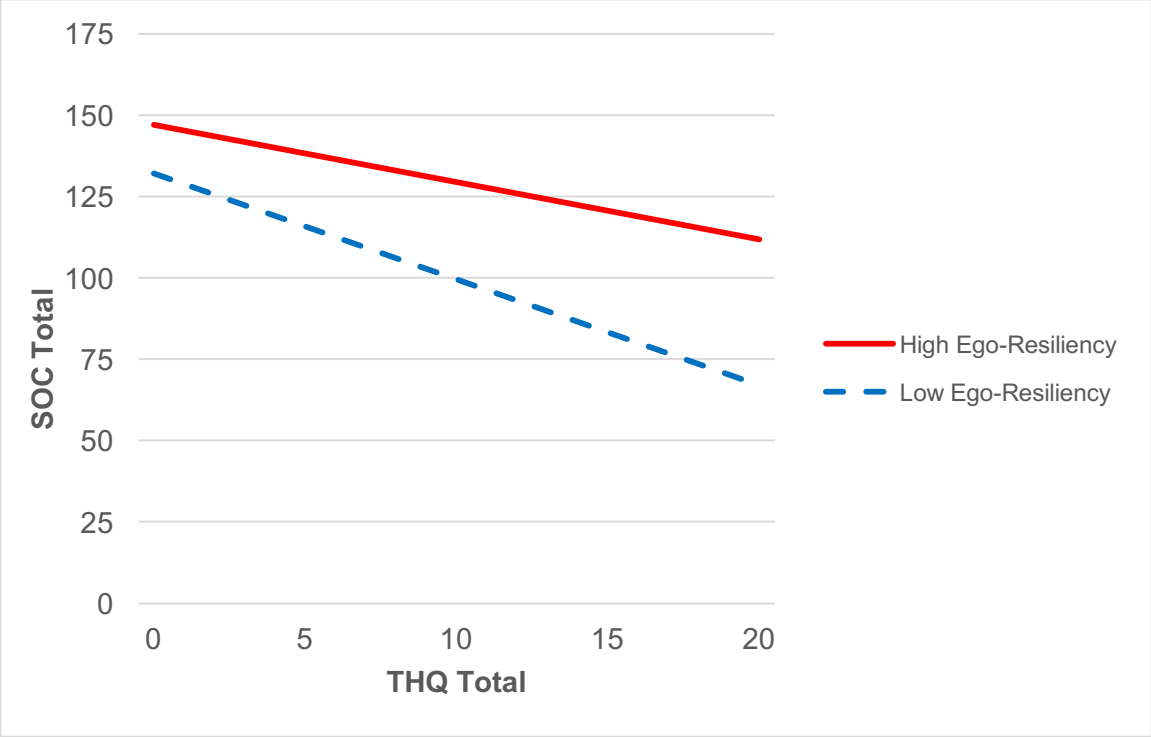


Note. CD-RISC = Connor-Davidson Resilience Scale; THQ = Trauma History Questionnaire.

High Ego-Resiliency: CD-RISC = 76.40 – 0.24 (THQ), [R^2 < .01, F(1, 339) = 1.04, p = .31].

Low Ego-Resiliency: CD-RISC = 64.94 – 1.16 (THQ), [R^2 = .05, F(1, 74) = 4.01, p = .05*].

Figure 8: Moderation Effect of Ego-Resiliency between THQ Total and SOC Total

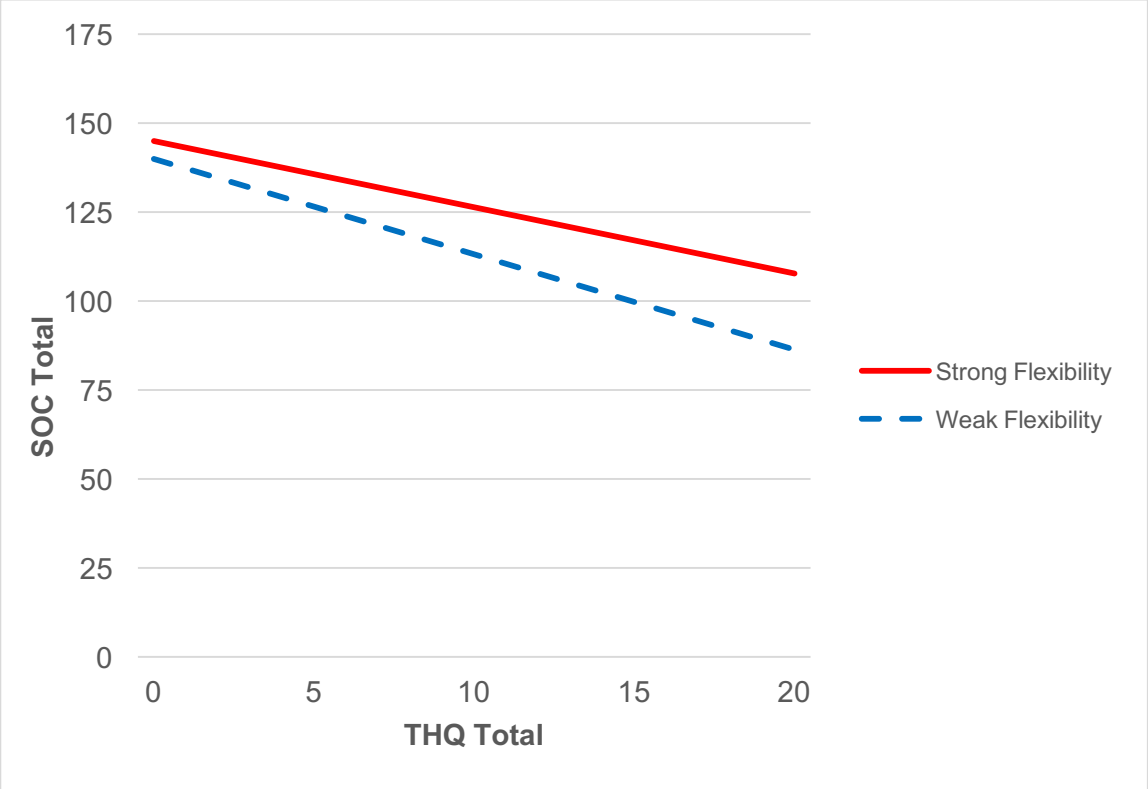


Note. SOC = Sense of Coherence; THQ = Trauma History Questionnaire.

High Ego-Resiliency: SOC = 147.27 – 1.76 (THQ), [R^2 = .06, F(1, 344) = 23.67, p < .01**].

Low Ego-Resiliency: SOC = 132.44 – 3.25 (THQ), [R^2 = .17, F(1, 74) = 14.88, p < .01**].

Figure 9: Moderation Effect of Emotion Regulation Flexibility between THQ Total and SOC Total

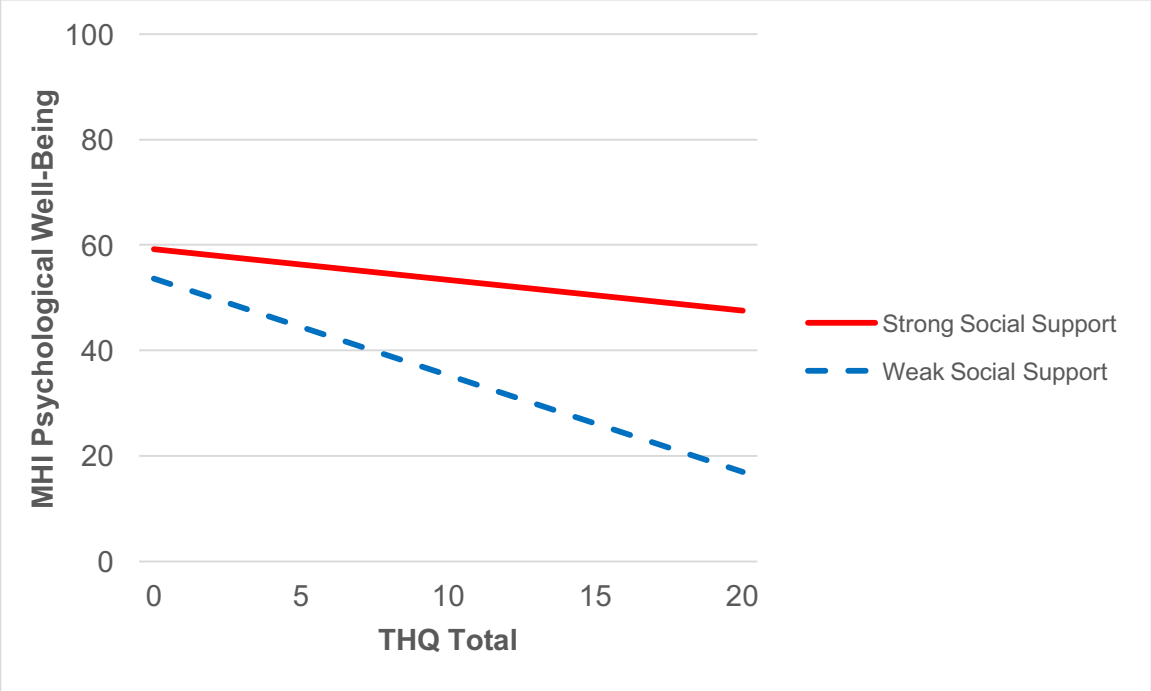


Note. PACT = Perceived Ability to Cope with Trauma (to measure emotion regulation flexibility); SOC = Sense of Coherence; THQ = Trauma History Questionnaire.

Strong Flexibility: SOC = 144.95 – 1.86 (THQ), [R^2 = .07, F(1, 359) = 25.69, p < .01**].

Low Ego-Resiliency: SOC = 140.32 – 2.68 (THQ), [R^2 = .08, F(1, 56) = 5.13, p = .03*].

Figure 10: Moderation Effect of Social Support between THQ Total and MHI Psychological Well-Being

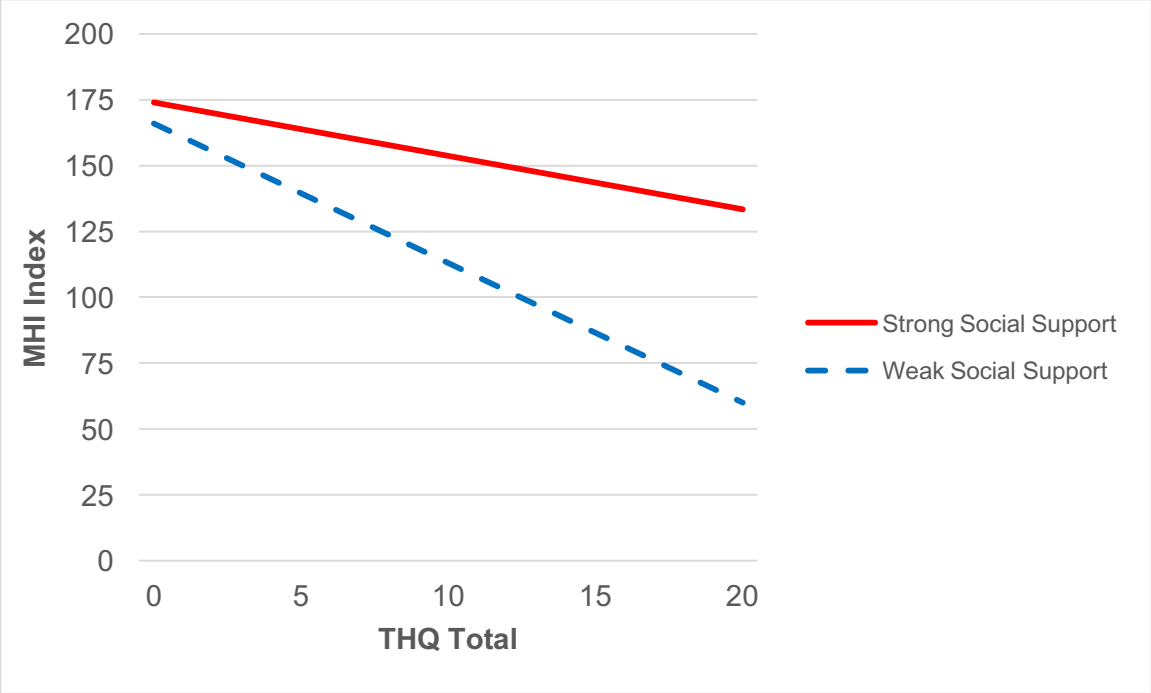


Note. MHI = Mental Health Inventory; THQ = Trauma History Questionnaire.

Strong Social Support: MHI Psychological Well-Being = 59.16 – .58 (THQ), [R^2 = .02, $F(1, 362) = 7.64$, $p < .01$**].

Weak Social Support: MHI Psychological Well-Being = 53.59 – 1.83 (THQ), [R^2 = .18, $F(1, 59) = 12.59$, $p < .01$**].

Figure 11: Moderation Effect of Social Support between THQ Total and MHI Index

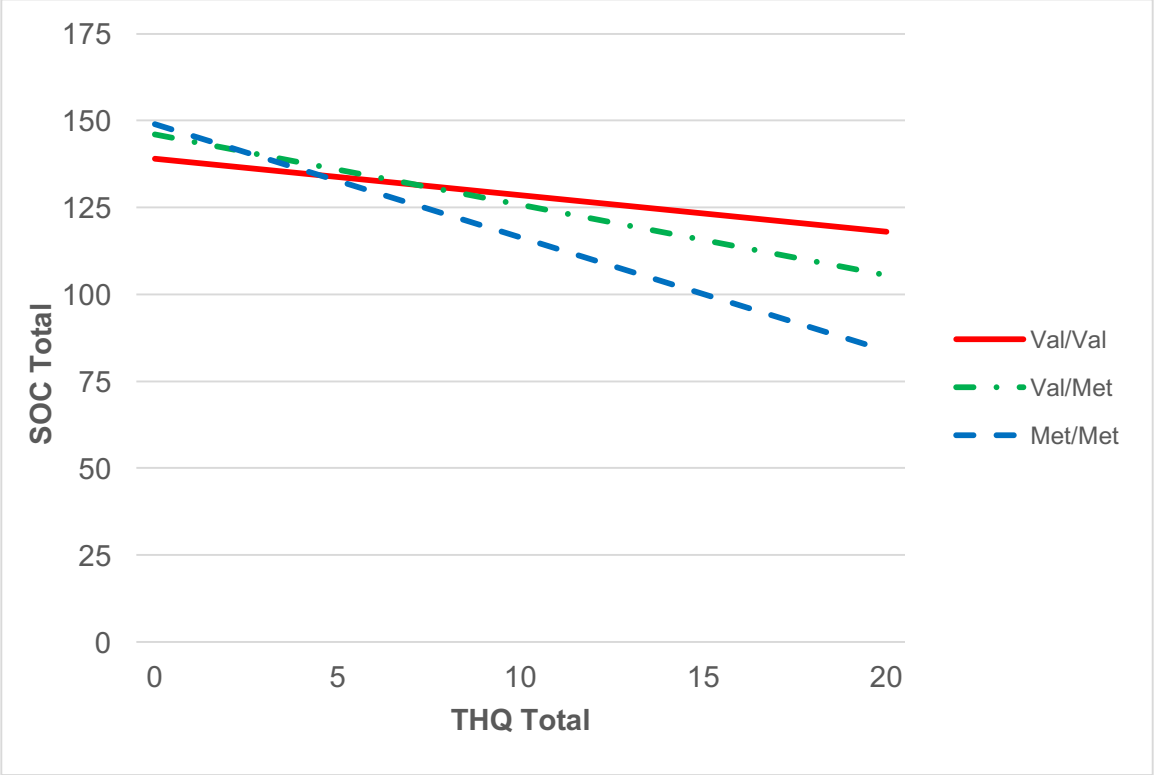


Note. MHI = Mental Health Inventory; THQ = Trauma History Questionnaire.

Strong Social Support: MHI Index = 173.94 – 2.03 (THQ), [R^2 = .05, F(1, 361) = 17.76, p < .01**].

Weak Social Support: MHI Index = 166.36 – 5.30 (THQ), [R^2 = .22, F(1, 57) = 16.29, p < .01**].

Figure 12: Moderation Effect of rs4680 in *COMT* between THQ Total and SOC Total



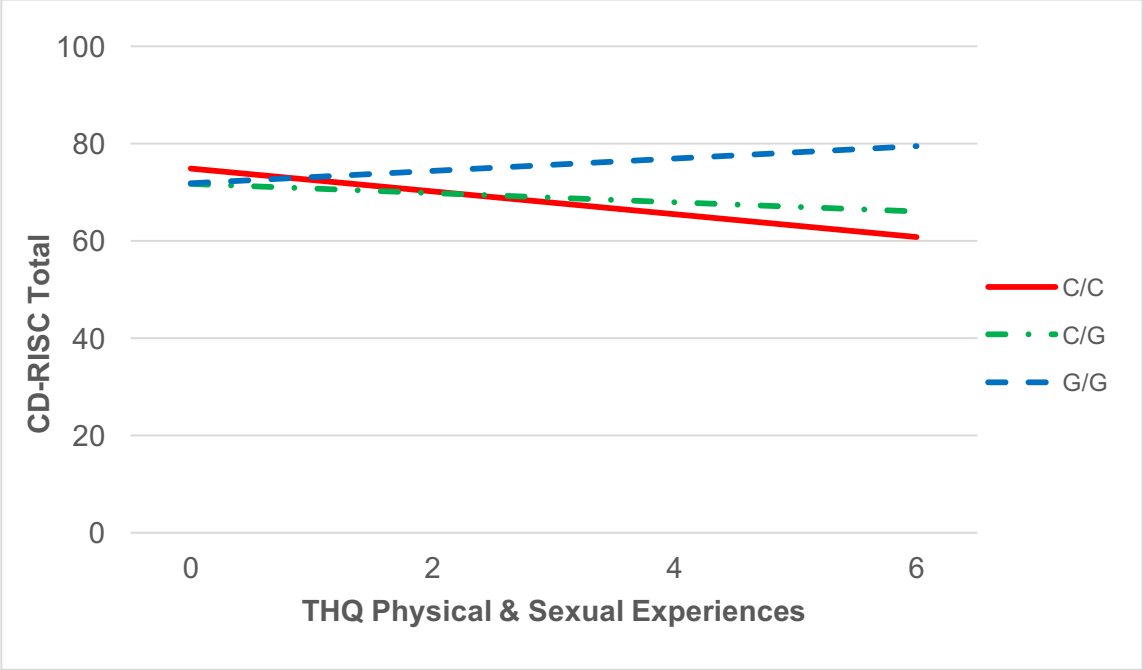
Note. SOC = Sense of Coherence; THQ = Trauma History Questionnaire.

Val/Val: SOC = 138.62 – 1.05 (THQ), [R^2 = .02, F(1, 112) = 1.66, p = .20].

Val/Met: SOC = 145.94 – 2.02 (THQ), [R^2 = .09, F(1, 203) = 20.23, p < .01**].

Met/Met: SOC = 149.15 – 3.26 (THQ), [R^2 = .13, F(1, 107) = 15.97, p < .01**].

Figure 13: Moderation Effect of rs4606 in *RGS2* between THQ Physical & Sexual Experiences and CD-RISC Total



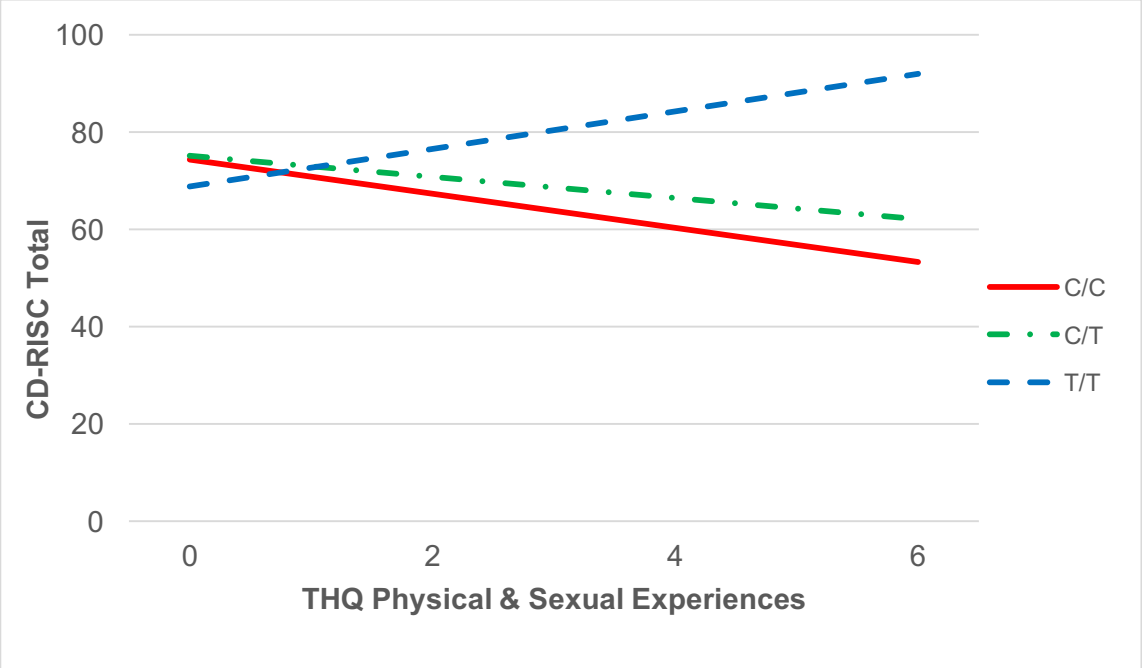
Note. CD-RISC = Connor-Davidson Resilience Score; THQ = Trauma History Questionnaire.

C/C: CD-RISC = 74.91 – 2.35 (THQ Physical & Sexual), [R^2 = .03, F(1, 208) = 6.74, p = .01**].

C/G: CD-RISC = 71.73 – 0.94 (THQ Physical & Sexual), [R^2 < .01, F(1, 169) = .70, p = .40].

G/G: CD-RISC = 71.76 + 1.29 (THQ Physical & Sexual), [R^2 = .02, F(1, 43) = .65, p = .43].

Figure 14: Moderation Effect of rs7209436 in *CRHR1* between THQ Physical & Sexual Experiences and CD-RISC Total



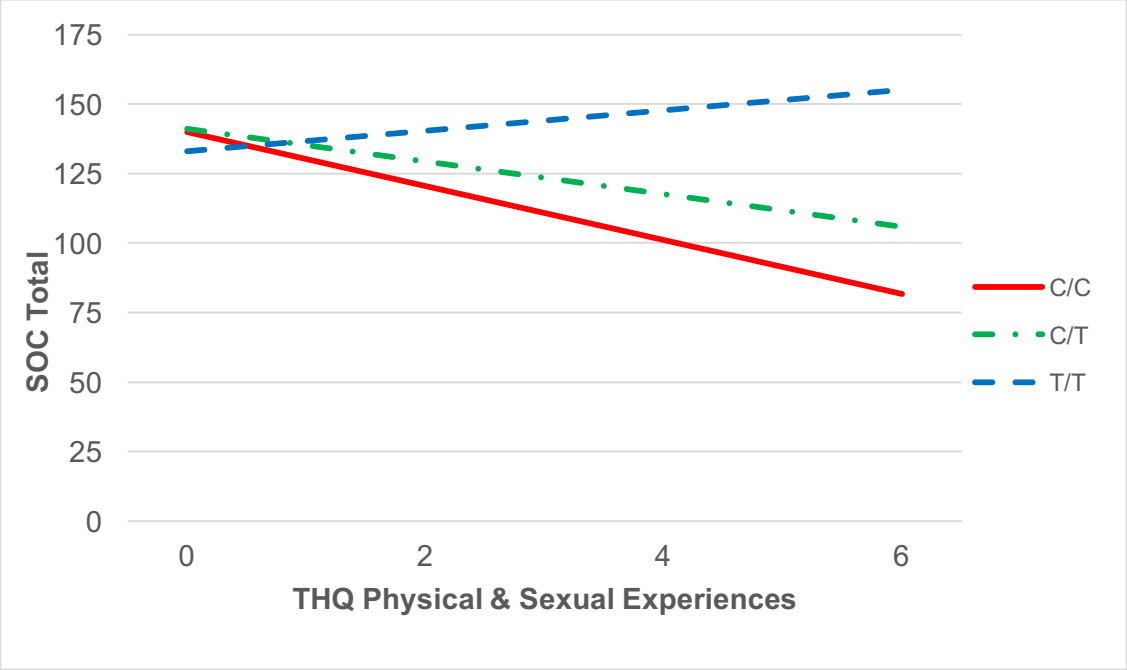
Note. CD-RISC = Connor-Davidson Resilience Scale; THQ = Trauma History Questionnaire.

C/C: CD-RISC = 74.30 – 3.51 (THQ Physical & Sexual), [R^2 = .05, F(1, 120) = 6.48, p = .01**].

C/T: CD-RISC = 75.08 – 2.16 (THQ Physical & Sexual), [R^2 = .04, F(1, 200) = 8.14, p < .01**].

T/T: CD-RISC = 68.76 + 3.86 (THQ Physical & Sexual), [R^2 = .05, F(1, 107) = 5.92, p = .02*].

Figure 15: Moderation Effect of rs7209436 in *CRHR1* between THQ Physical & Sexual Experiences and SOC Total



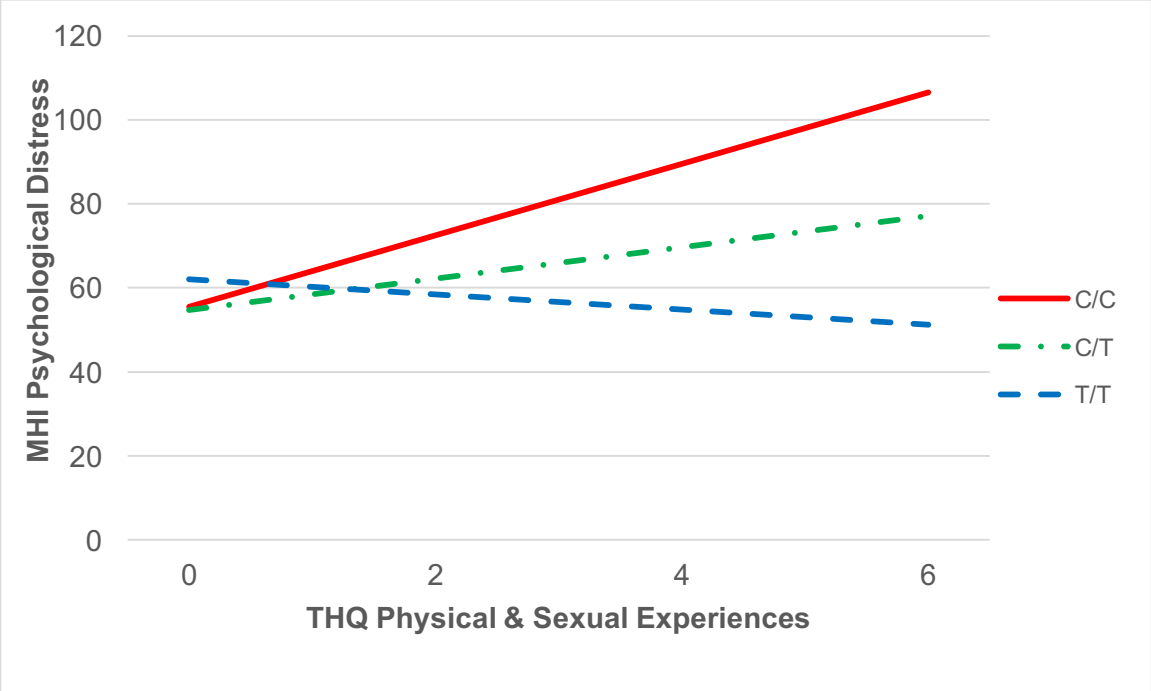
Note. SOC = Sense of Coherence; THQ = Trauma History Questionnaire.

C/C: SOC = 140.45 – 9.71 (THQ Physical & Sexual), [R^2 = .18, F(1, 123) = 27.32, p < .01**].

C/T: SOC = 141.48 – 5.85 (THQ Physical & Sexual), [R^2 = .10, F(1, 203) = 22.77, p < .01**].

T/T: SOC = 132.63 + 3.68 (THQ Physical & Sexual), [R^2 = .02, F(1, 106) = 2.39, p = .13].

Figure 16: Moderation Effect of rs7209436 in *CRHR1* between THQ Physical & Sexual Experiences and MHI Psychological Distress



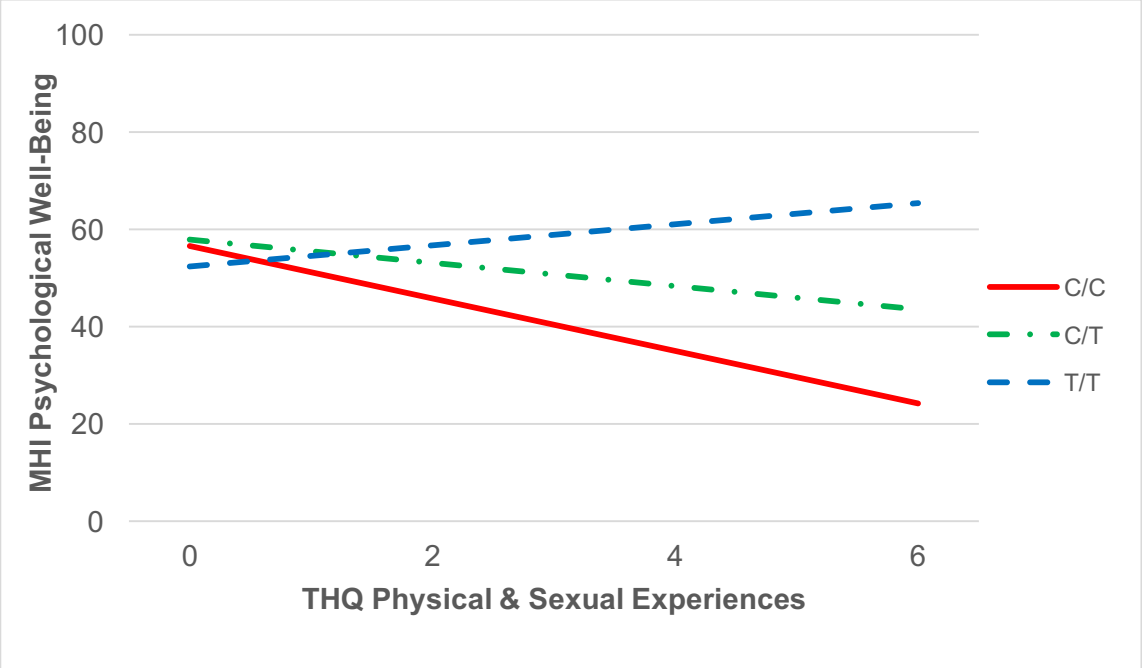
Note. MHI = Mental Health Inventory; THQ = Trauma History Questionnaire.

C/C: Distress = 55.51 + 8.50 (THQ Physical & Sexual), [R^2 = .19, F(1, 124) = 28.83, p < .01**].

C/T: Distress = 54.79 + 3.71 (THQ Physical & Sexual), [R^2 = .07, F(1, 201) = 14.47, p < .01**].

T/T: Distress = 61.97 – 1.80 (THQ Physical & Sexual), [R^2 < .01, F(1, 105) = .70, p = .40].

Figure 17: Moderation Effect of rs7209436 in *CRHR1* between THQ Physical & Sexual Experiences and MHI Psychological Well-Being



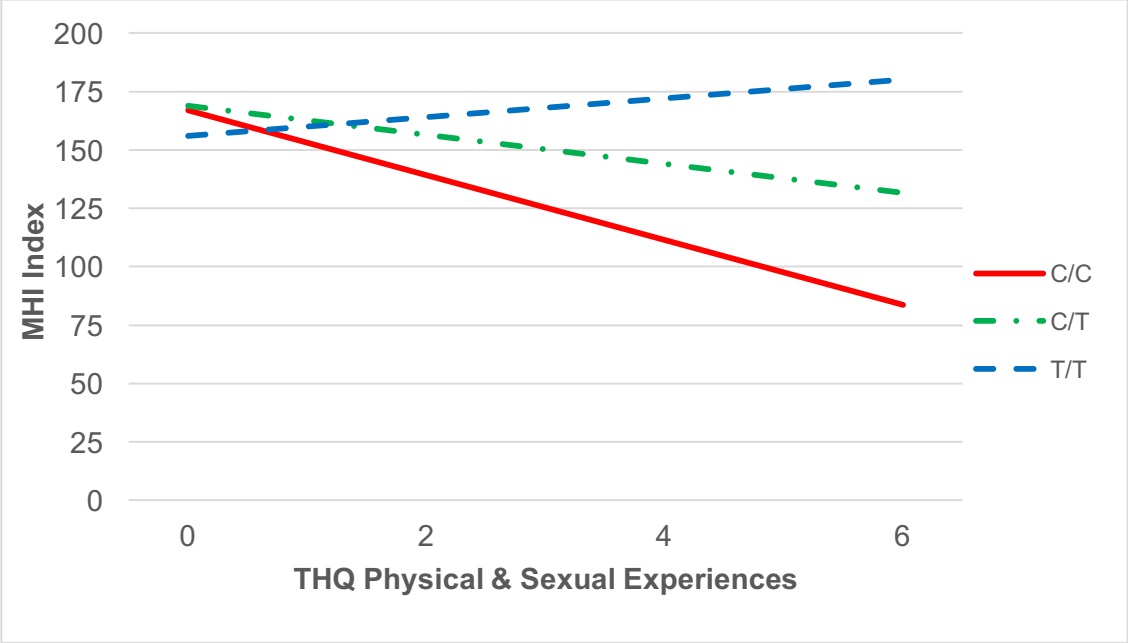
Note. MHI = Mental Health Inventory; THQ = Trauma History Questionnaire.

C/C: Well-Being = 56.59 – 5.41 (THQ Physical & Sexual), [R^2 = .16, F(1, 125) = 23.49, p < .01**].

C/T: Well-Being = 57.92 – 2.41 (THQ Physical & Sexual), [R^2 = .06, F(1, 202) = 12.40, p < .01**].

T/T: Well-Being = 52.36 + 2.16 (THQ Physical & Sexual), [R^2 = .03, F(1, 104) = 2.73, p = .10].

Figure 18: Moderation Effect of rs7209436 in *CRHR1* between THQ Physical & Sexual Experiences and MHI Index



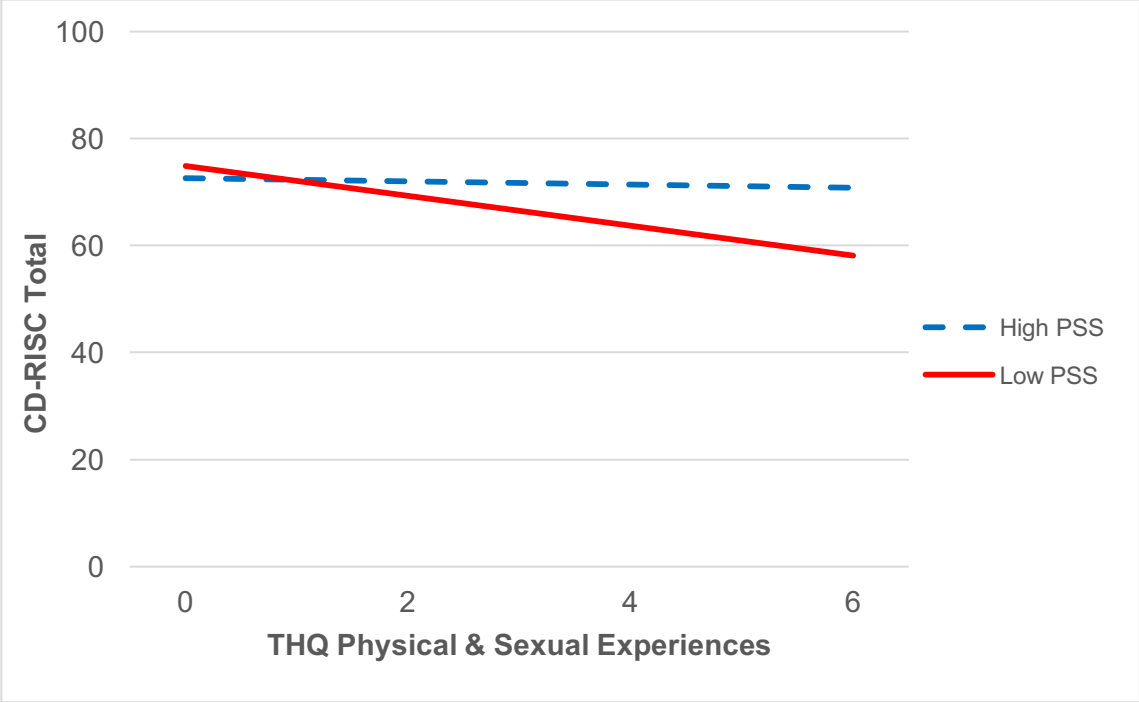
Note. MHI = Mental Health Inventory; THQ = Trauma History Questionnaire.

C/C: Index = 167.08 – 13.91 (THQ Physical & Sexual), [R^2 = .20, F(1, 124) = 30.71, p < .01**].

C/T: Index = 169.04 – 6.24 (THQ Physical & Sexual), [R^2 = .07, F(1, 199) = 16.01, p < .01**].

T/T: Index = 156 + 4.01 (THQ Physical & Sexual), [R^2 = .01, F(1, 104) = 1.45, p = .23].

Figure 19: Moderation Effect of PSS between THQ Physical & Sexual Experiences and CD-RISC Total

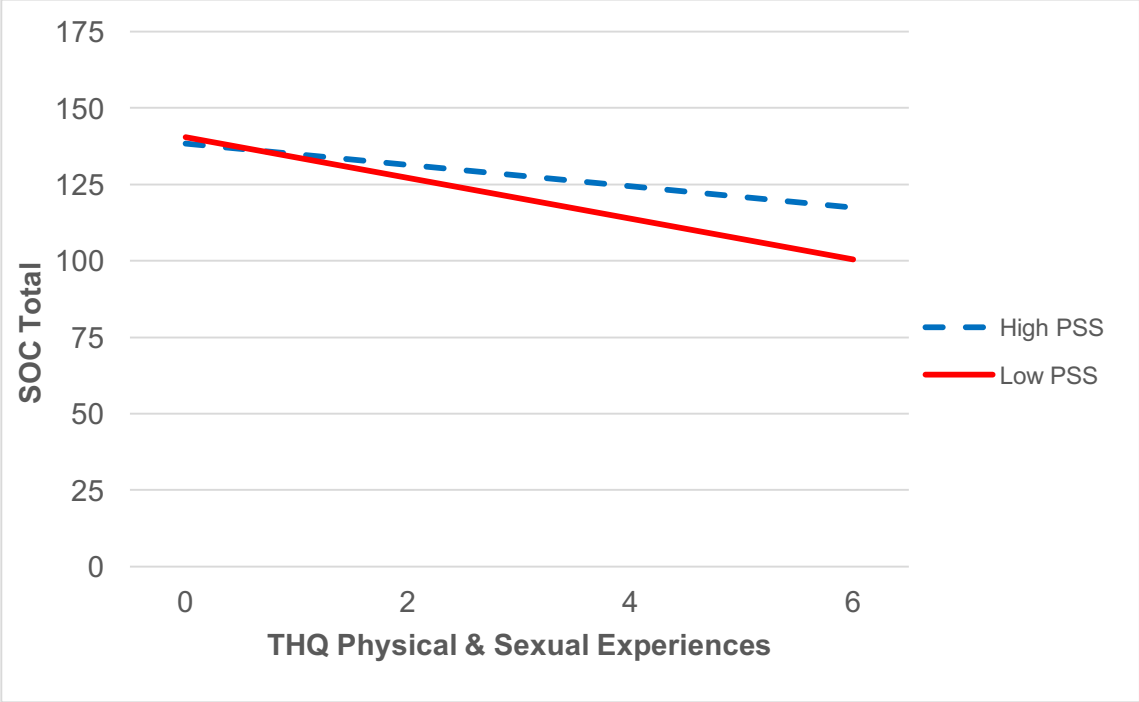


Note. CD-RISC = Connor-Davidson Resilience Scale; PSS = Polygenic Susceptibility Score; THQ = Trauma History Questionnaire.

High PSS (more minor alleles): CD-RISC = 72.58 – .29 (Physical & Sexual), [R^2 < .01, F(1, 274) = .13, p = .72].

Low PSS (more major alleles): CD-RISC = 74.83 – 2.78 (Physical & Sexual), [R^2 = .04, F(1, 159) = 6.61, p = .01**].

Figure 20: Moderation Effect of PSS between THQ Physical & Sexual Experiences and SOC Total

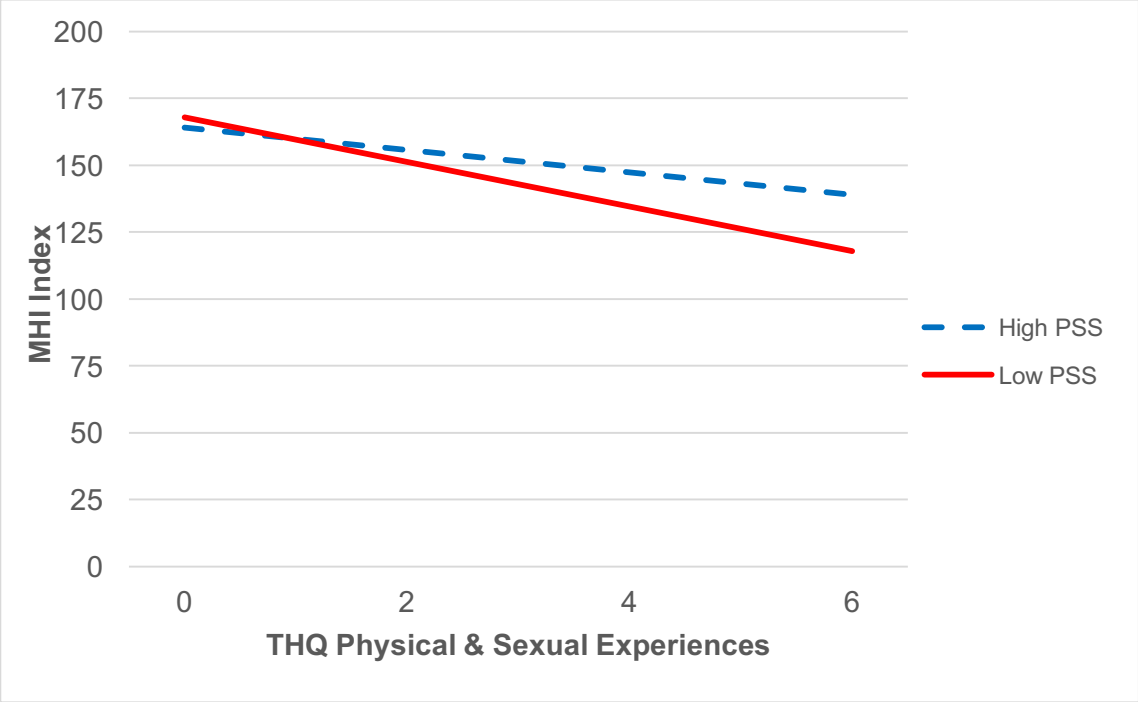


Note. PSS = Polygenic Susceptibility Score; SOC = Sense of Coherence; THQ = Trauma History Questionnaire.

High PSS (more minor alleles): SOC = 138.36 – 3.50 (Physical & Sexual), [R^2 = .03, F(1, 278) = 7.95, p < .01**].

Low PSS (more major alleles): SOC = 140.39 – 6.65 (Physical & Sexual), [R^2 = .11, F(1, 160) = 18.86, p < .01**].

Figure 21: Moderation Effect of PSS between THQ Physical & Sexual Experiences and MHI Index



Note. MHI = Mental Health Inventory; PSS = Polygenic Susceptibility Score; THQ = Trauma History Questionnaire.

High PSS: MHI Index = 164.00 – 4.16 (Physical & Sexual), [R^2 = .02, F(1, 276) = 6.20, p = .01**].

Low PSS: MHI Index = 167.95 – 8.34 (Physical & Sexual), [R^2 = .10, F(1, 157) = 16.95, p < .01**].

DISCUSSION

In Manuscript #1, based on the Walker and Avant (2011) method, a concept analysis on resilience to potentially traumatic events (PTEs) was conducted to explore the defining attributes of resilience. In Manuscript #2, a systematic review was performed to (1) identify candidate genes associated with resilience, (2) identify which alleles are associated with higher resilience in terms of positive adaptation (main effect) and with less reactivity to environmental influences (Gene x Environment Interaction), and (3) explore various methods to construct a Polygenic Susceptibility Score (PSS). In Manuscript #3, the results of data collected from college students (*N* = 450) enrolled at a Midwestern university to investigate the relationships between resilience, PTEs, genotypes, and intrapersonal (ego-resiliency, emotion regulation) and environmental (social support) variables were reported.

Reflecting Manuscript #1: A Concept Analysis of Resilience

A concept analysis of resilience to potentially traumatic events (Manuscript #1) contributes to the field of resilience science from the three aspects: (1) inclusion of heredity, (2) clarification of terminology and concept of resilience, and (3) two components of resilience outcomes.

Inclusion of heredity. To this candidate's knowledge, this is the first concept analysis to include heredity as a defining attribute of resilience. Walker and Avant (2011), the nurse scientists who developed the concept analysis method used, identified technologic changes in patient care as a significant trend in 21st Century nursing. Increasingly, genetics and genetic technologies are informing nursing care. Nurse scientists are encouraged to conduct genetic/genomic research (International Society of Nurses in Genetics, 2016) because nurses have a holistic perspective on human health and play an important role in applying genomic discoveries to improve methods for patient assessment and intervention (Lee, Gill, Barr, Yun, & Kim, 2017). Because

emerging evidence indicate resilience is influenced by genetics (Feder et al., 2009), heredity was included in this concept analysis of resilience. If there is interest in psychological concepts that are influenced by genetics, then future concept analysists are encouraged to consider heredity as a defining attribute of the concept.

When this concept analysis of resilience was conducted, heredity was originally thought as one of the antecedents. However, it was later changed as one of the defining attributes. According to Walker and Avant (2011), *antecedents* are events or incidents that arise prior to the occurrence of the concept, and *defining attributes* are the characteristics of the concept that appear over and over again and let the analyst have the broadest insight into the concept. Because we are born with a certain set of genes (*i.e.,* before the occurrence of the concept), categorizing heredity as an antecedent appeared appropriate. However, as more insight toward resilience was gained, it could be considered that heredity would be similar to ego-resiliency (a personality trait) because both would be present prior to the occurrence of the concept of resilience, which in this concept analysis required the occurrence of a PTE as an antecedent for the concept to be fully evident.

Clarification of terminology and concept of resilience. It has been debated if resilience is best categorized as an individual trait, a process, an outcome, or all of the above (Reich et al., 2010). While performing this concept analysis, it was found that resilience as an individual trait and resilience as a process/outcome is used interchangeably in the literature, causing a troublesome confusion among researchers. This concept analysis made it clearer that, when referring to a personality trait, the term *resiliency* or more specifically *ego-resiliency* instead of *resilience* is best used (Luthar et al., 2000; Mancini & Bonanno, 2010).

Mancini and Bonanno (2010) state, "… it is meaningless to assess resilience in the absence of adversity" (p. 259). Based on this concept analysis, their statement can

be supported because adversity or a PTE is the antecedent of resilience. In this case, resilience is referred as a process or outcome. In contrast, it *can* be meaningful to assess *ego-resiliency* as a personality trait (vs. resilience as a process/outcome) in the absence of adversity. This concept analysis illuminates the distinctions between ego-resiliency as a personality trait and resilience as a process/outcome.

In the Differential Susceptibility Model (Pluess, 2015), "resilience" refers to the stable level of functioning following exposure to negative influence (Figure 1). Because resilience is used as a process or outcome (*i.e.,* antecedent = negative influence; consequence = stable functioning, or this process), this concept analysis supports the use of the terminology as a process/outcome. Although there are at least 13 concept analyses of resilience to this candidate's knowledge, only this concept analysis clarified the conceptual use and terminology of resilience.

Two components of resilience outcomes. This concept analysis identified that resilience outcomes may include two components: (1) none to mild psychopathological symptoms, and (2) positive adaptation. The rationale for this conceptualization is because resilience is not merely the absence of psychopathology but also is positive adaptation (Almedom & Glandon, 2007). This concept analysis emphasizes that, if only none to mild psychopathological symptoms are the focus, it tells only part of the story of resilience.

None to mild psychopathological symptoms are usually the definition of resilience especially for the bench scientists. For example, in the Porsolt Swim Test (*i.e.,* a measure of stress), the rodents that exhibit escape-directed behaviors, such as active swimming, are described as *resilient*, whereas those that exhibit helpless behaviors, such as passive floating which is a measure of depressive-like behaviors, are considered as *non-resilient* (Franklin et al., 2012). Animal studies are crucial in the search for biological determinants of resilience because they help us identify neural

circuits and molecular pathways that mediate resilient phenotypes (Feder et al., 2009). However, this kind of findings can be limited when translating animal studies into human resilience.

According to Freud, if a patient is free from psychopathological symptoms, then he or she would be considered as “happy” (Seligman, 2015). It appears this view is still prevalent in the research as well as in the current psychiatric practice by focusing exclusively on controlling the psychopathological symptoms. Psychiatric nurses are encouraged to assist individuals to improve the ability to live a fulfilling and productive life (American Nurses Association, 2014). In this candidate’s opinion, to achieve this, psychiatric nurses need to implement interventions not only to reduce psychopathological symptoms but also to facilitate positive adaptation. It is this candidate’s hope to send a message through this concept analysis to the research and clinical community about the importance of investigating and facilitating positive adaptation in addition to reduction of psychopathological symptoms.

Reflecting Manuscript #2: A Systematic Review of Genetic Influence on Resilience

This systematic review of genetic influence on resilience contributes to the study of resilience from two aspects: (1) clearer selection of candidate genes associated with resilience, and (2) issues related to constructing a PSS based on known knowledge of resilience-related candidate genes.

Clearer selection of candidate genes associated with resilience. A candidate gene is a gene whose function suggests it might be associated with a phenotype (Plomin et al., 2013). In this dissertation, from a genetic perspective, the phenotype of interest was resilience. There are several ways to identify candidate genes associated with resilience. One is a review article of biological mechanisms that facilitate resilience. For example, because the neural circuitry of reward may contribute to resilience, genes whose function are involved with the reward circuitry, such as *COMT*, can be considered

as candidate genes associated with resilience (Feder et al., 2009). Another way is the HuGE Navigator (Yu et al., 2010). The HuGE Navigator recognizes “Resilience, Psychological” as a phenotype and lists it in the Phenopedia (Centers for Disease Control and Prevention, 2017). However, as discussed in the concept analysis paper, the use of the term, “resilience”, in these resources is confusing by referring to a trait, process, and/or outcome.

The concept analysis revealed that resilience outcomes include two components: (1) none to mild psychopathological symptoms, and (2) positive adaptation. These can be considered as the phenotypes of resilience. This systematic review made a distinction between these two components by *excluding* articles that operationalized resilience as the absence of psychopathological symptoms (e.g. PTSD) and *including* articles that operationalized resilience as positive adaptation. Therefore, candidate genes associated with resilience that were identified in this systematic review are conceptually “clearer” in selecting articles that measured resilience in terms of positive adaptation. However, the absence of psychopathological symptoms is also an important consequence of resilience. A systematic review to identify candidate genes associated with resilience whose phenotype is none to mild psychopathological symptoms following exposure to PTEs is suggested for a future manuscript.

Issues related to constructing a PSS. An original intention in this systematic review was to construct a PSS based on the findings from the literature. For example, if the majority of the research articles found the S’ allele of *5-HTTLPR* to be more susceptible to environment, then the following scoring system would gain more confidence: 0 = L’/L’, 1 = L’/S’, and 2 = S’/S’. Similarly, if the majority of the literature found the Met allele of rs4680 in *COMT* to be more susceptible to environment, then a score could be confidently assigned as follows: 0 = Val/Val, 1 = Val/Met, and 2 = Met/Met. Accordingly, a higher score of the PSS, which is the average of these scores,

would indicate more susceptibility to environment based on the literature. However, this systematic review revealed inconsistent findings (Table 3 & 4). Therefore, constructing PSS based on the literature to date was not feasible.

Alternatively, the score could be assigned based on the biological plausibility. For example, there is evidence that the Met/Met homozygote rs4680 in *COMT* has 3- to 4-fold lower enzymatic activity than the Val/Val homozygote, whereas the heterozygote (Val/Met) has intermediate activity (Chen et al., 2004). If this is true, then the scoring system described above would be logical. However, the biological contribution of other polymorphisms, such as rs53576 in *OXTR*, is largely unknown to date. Therefore, constructing PSS based on the biological mechanism was also a challenge.

Finally, the following scoring system was considered: 0 = the major allele, 1 = heterozygote, and 2 = the minor allele (Rana et al., 2014). Because the literature or the biological mechanism for many polymorphisms to date cannot support this scoring system where a higher score indicates more susceptibility to environment, this is a limitation. It is this candidate's hope to stimulate discussion among scientists through this systematic review so that PSS can be better constructed based on more consistent and biologically-sound evidence in the future.

Reflecting Manuscript #3: Results of Resilience Study among College Students

The results of this preliminary study informed the field by identifying two important considerations that can guide future studies: (1) candidate genes worthwhile investigating further, and (2) operationalization of resilience outcomes. In addition, this study provided support for the hypothesis that PTEs are related to resilience outcomes. It also provided partial support for the relationships between selected polymorphisms and defining attributes of resilience as well as that selected genotypes moderated the relationships between PTEs and resilience outcomes.

Candidate genes worthwhile investigating further. The systematic review (Manuscript #2) revealed 14 candidate genes associated with resilience: *5-HTTLPR*, *COMT*, *BDNF*, *DRD4*, *DRD2*, *OXTR*, *RGS2*, *CACNA1C*, *FKBP5*, *CRHR1*, *DAT1*, *MAOA, IL10*, and *FGG.* Based on this result, the following 10 polymorphisms were investigated in this dissertation study (Manuscript #3): rs25531 in *5-HTTLPR*, rs4680 in *COMT*, rs6265 in *BDNF*, rs1800955 in *DRD4*, rs1800497 in *DRD2*, rs53576 in *OXTR*, rs4606 in *RGS2*, rs1006737 in *CACNA1C*, rs9296158 in *FKBP5*, and rs7209436 in *CRHR1*. Of these 10 polymorphisms, rs4680 in *COMT*, rs4606 in *RGS2*, and rs7209436 in *CRHR1* may be worthwhile investigating further because they produced significant findings (Table 11 & 12). Among these three, rs4680 in *COMT* is the most interesting because it was found to be significant in both Aim 2 (Figure 5) and Aim 3 (Figure 12). In addition, although not included in Manuscript #3 because it was not part of aims (Figure 2), a secondary analysis revealed that individuals with the Met allele(s) of rs4680 in *COMT* were more susceptible to not only the negative environment (*i.e.,* PTEs, see Figure 12) but also the positive environment (*i.e.,* social support). This finding supports both the diathesis-stress and the vantage sensitivity components of the Differential Susceptibility Model (Pluess, 2015). It is this candidate's plan to publish this finding as a secondary analysis as well as the findings of the primary analysis described in Manuscript #3.

It was disappointing for this candidate that *5-HTTLPR* did not produce any significant findings. Originally, it was intended to investigate only *5-HTTLPR* because this is the most well-studied polymorphism. However, this candidate was advised to investigate more than one polymorphism because resilience is polygenic. Accordingly, rs4680 in *COMT* and rs6265 in *BDNF* were added because they appeared promising to this student, and research grant proposals were prepared by listing these three polymorphisms. Fortunately, this study was funded by three organizations (see Financial Support in page vii), and additional seven polymorphisms (rs1800955 in *DRD4*,

rs1800497 in *DRD2*, rs53576 in *OXTR*, rs4606 in *RGS2*, rs1006737 in *CACNA1C*, rs9296158 in *FKBP5*, and rs7209436 in *CRHR1*) could be afforded. If only *5-HTTLPR* was investigated, this study's genetic contribution likely would not have been informative.

It is debatable whether *5-HTTLPR* is worth investigating in a future study. In general, findings of candidate gene associations have been difficult to replicate (Tabor, Risch, & Myers, 2002). Even meta-analyses found conflicting results of *5-HTTLPR* in relation to depression (Karg, Burmeister, Shedden, & Sen, 2011; Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009; Sharpley, Palanisamy, Glyde, Dillingham, & Agnew, 2014; Uher & McGuffin, 2010) or PTSD (Gressier et al., 2013; Navarro-Mateu, Escamez, Koenen, Alonso, & Sanchez-Meca, 2013). Although this dissertation study did not find any significant findings with *5-HTTLPR*, it appears *5-HTTLPR* should be investigated again because this is one of the most frequently studied polymorphisms and is involved in regulating the serotonin neurotransmitter, which biologically plays an important role in mental health and positive adaptation. The future study can be strengthened if additional genes involved in the serotonergic system, such as serotonin receptor genes (e.g. *HTR1A*, *HTR3A*, *HTR2C*) (Wu et al., 2013), are also investigated.

Operationalization of resilience outcomes. The concept analysis revealed that resilience outcomes have two components: (1) none to mild psychopathological symptoms, and (2) positive adaptation. None to mild psychopathological symptoms were assessed by the Mental Health Inventory (MHI) Psychological Distress subscale (Veit & Ware, 1983). Because this was a preliminary/exploratory study, positive adaptation was measured by four scales: the Connor-Davidson Resilience Scale (CD-RISC) total score (Connor & Davidson, 2003), the Sense of Coherence (SOC) total score (Antonovsky, 1993), the MHI Psychological Well-Being subscale, and the MHI Index (Veit & Ware, 1983). Because CD-RISC and SOC were the frequently used instruments in the systematic review (Manuscript #2), these two were selected. In addition, MHI was

selected because it can measure mental health in general populations (Davydov et al., 2010; Veit & Ware, 1983), such as college students. To determine which instrument(s) can be recommended to measure positive adaptation for the future study, the following two aspects are discussed: (1) reliability, and (2) significant findings in relation with polymorphisms.

Reliability. The scale with the best Cronbach's alpha was MHI Index (r = .96), followed by MHI Psychological Well-Being subscale (r = .93), CD-RISC Total (r = .92), and SOC Total (r = .89). Therefore, from the aspect of reliability, this study can suggest MHI may be the best. However, because these Cronbach's alpha values are all high, any of them can be recommended. It is note-worthy that the Cronbach's alpha of the CD-RISC Spiritual Influence was low (r = .64) as discussed in Manuscript #3.

Significant findings in relation with polymorphisms. Aim 3 investigated the moderating effect of polymorphisms on the relationships between PTEs (especially unfavorable physical and sexual experiences) and resilience outcomes. The most frequently and significantly associated resilience outcomes with genetic polymorphisms (Table 11 – 13) were CD-RISC Total (rs4606 in *RGS2*, rs7209436 in *CRHR1*, & PSS) and SOC Total (rs4680 in *COMT*, rs7209436 in *CRHR1*, & PSS), followed by MHI Index (rs7209436 in *CRHR1*, & PSS), and MHI Psychological Well-Being subscale (rs7209436 in *CRHR1*). Based on these results, CD-RISC and SOC may be better instrument choices to consider for the future use when the focus of studies is the genetic contributions to resilience. These instruments may best capture cognitions, emotions, and behaviors associated with resilience (or a resilience phenotype) that may be related to genetic influences. The congruence of psychometrically-developed instruments, their ability to operationalize the resilience phenotype, and the genes that may underline the phenotype is an area for future research.

Future Directions

Based on this dissertation study, the future directions in terms of (1) study design and (2) interventions are considered.

Study design. To investigate genetic influence on resilience, a large sample size is required. For typical candidate studies, the sample size of less than 1,000 may be considered small and be underpowered for detecting genetic influences with small effect sizes (Dick et al., 2015). There are other genomic approaches, such as *genome-wide association studies (GWAS)* (Conley et al., 2013). However, GWAS requires even a larger sample size (e.g. a few thousands) for the statistically significant discovery (Ahlqvist, van Zuydam, Groop, & McCarthy, 2015). To address the sample size issue, the Psychiatric Genomic Consortium (PGC) was organized in 2007 to investigate the genetic basis of mental disorders, such as major depressive disorder, schizophrenia, and bipolar disorder (Gain Collaborative Research Group et al., 2007). Recently, PGC-PTSD was formed to bring PTSD researchers together for large-scale GWAS studies of PTSD (Logue et al., 2015). Although there is no consortium to investigate resilience to this candidate's knowledge, a collaboration with other researchers is required to conduct genetic studies. Additionally, the phenotype can be selected following the Research Domain Criteria (RDoC), such as *approach motivation* in Positive Valence Systems, to investigate the relationships between genes and resilience (Insel et al., 2010; Kaufman, Gelernter, Hudziak, Tyrka, & Coplan, 2015).

One limitation of this dissertation study was the cross-sectional design because it cannot detect the dynamic process of resilience changing over time. Therefore, a longitudinal study design is preferred to investigate resilience. One longitudinal statistical method to capture the change of resilience over time is *latent growth modeling* (LGM) techniques, which identify heterogeneous subpopulations that comprise distinct response trajectories across time (Bonanno & Diminich, 2013). It would be ideal if data

can be collected before a PTE, immediately after the event, and a few more times in the following a few months, as Orcutt et al. (2014) investigated before and after a campus mass shooting. However, encouraging participants to complete questionnaires at multiple time points and determining feasible methods to facilitate longitudinal data collection, especially with a large sample size would be a challenge.

Another limitation of this dissertation study was the lack of specificity with PTEs because lifetime events were assessed. This can be improved if more specific PTEs are selected. If a tornado, for example, strikes a town and if its effect can be investigated, then the study population would be individuals exposed to the tornado. However, recruiting a large number of participants, asking them to donate DNA, and collecting data at multiple points would be challenging. A genetic and longitudinal study with a large sample size would not be feasible without collaborating with other researchers.

Interventions. If more evidence support that emotion regulation and social support are important factors that contribute to resilience, then nurses can focus on these to facilitate resilience among individuals exposed to PTEs. If mindful meditation, for example, facilitates emotion regulation (Chambers, Gullone, & Allen, 2009), then nurses can implement interventions to teach the mediation skill. The presence of nurses itself can be served as perceived as well as received social support. For example, nurses can implement a social support intervention to identify resources that individuals might benefit from and ways to obtain these resources following a PTE, when additional resources may be helpful.

We are aware that there are no one-size-fits-all interventions. The main question in modern clinical practice is, “What works for whom?”, and genetic information may partially answer this question (Belsky & van Ijzendoorn, 2015). For example, accumulating evidence indicate that individuals with the L allele of *5-HTTLPR* have a faster and better response to Selective Serotonin Reuptake Inhibitor (SSRI)

antidepressants compared to the S allele carriers (Karlovic & Karlovic, 2013). In contrast, individuals with the S allele of *5-HTTLPR* responded better to the Cognitive Behavioral Therapy (CBT) and showed a greater reduction in anxiety symptom severity (Eley et al., 2012). If there are enough evidence to support these findings, then it would be more efficient to have individuals with the L allele of *5-HTTLPR* receive SSRI and assign the S allele carriers into the CBT group.

Thibodeau, August, Cicchetti, and Symons (2016) propose that individuals who are more sensitive to environmental influence may be more responsive to intervention in general and thus need only a brief-type program to benefit. On the other hand, those who are less susceptible to environmental influence may require more comprehensive or intensive treatment for optimal responsiveness (Thibodeau et al., 2016). This implies that the duration or the intensity of an intervention can vary based on the sensitivity. Alternatively, individuals who are more susceptible to negative influence can be prioritized to receive an intervention when resources are limited (e.g. immediately after a tornado strikes). If an intervention serves as positive influence, then those who are more reactive to environment may have the potential to function better because they may more susceptible to *both* negative (“vulnerability) and positive (“vantage sensitivity) environments (Pluess, 2015). Those who are less susceptible to negative influence may function fine without any intervention. If more evidence support the Differential Susceptibility Model and variables that contribute to environmental sensitivity (e.g. genotype) are better identified, then the type of interventions, the intensity/duration of interventions, and/or recipients of interventions can be adjusted based on the individual’s sensitivity.

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APPENDIX A: DEMOGRAPHICS

The background information you provide here will help us describe, in general terms, the people who participated in this study and will also help us compare our results with other studies.

Please answer the following questions by indicating the response that best describes you.

Subject ID? _____

Gender?
- ◯ Male
- ◯ Female

Age? _____ (e.g. 20)

Marital status?
- ◯ Single or never married
- ◯ Married
- ◯ Separated
- ◯ Divorced
- ◯ Widowed

Which grade are you in?
- ◯ Freshman
- ◯ Sophomore
- ◯ Junior
- ◯ Senior
- ◯ Already have a bachelor's degree

Please indicate your annual family income:
- ◯ Under $20,000
- ◯ $20,000 - $39,999
- ◯ $40,000 - $59,000
- ◯ $60,000 - $79,999
- ◯ $80,000 - $99,999
- ◯ $100,000 or more
- ◯ Don't know

Please indicate the racial group that you identify with:
- ◯ American Indian / Alaska Native
- ◯ Asian
- ◯ Black / African American
- ◯ Hispanic / Latino
- ◯ Native Hawaiian / Other Pacific Islander
- ◯ White
- ◯ Other

Please indicate the ethnic group that you identify with:
- ◯ Hispanic / Latino
- ◯ Not Hispanic / Latino

What is your religious background?
- ◯ Christian
- ◯ Muslim
- ◯ Jewish
- ◯ Buddhism
- ◯ Hindu
- ◯ Others
- ◯ None

APPENDIX B: TRAUMA HISTORY QUESTIONNAIRE (THQ)

The following is a series of questions about serious or traumatic life events. These types of events actually occur with some regularity, although we would like to believe they are rare, and they affect how people feel about, react to, and/or think about things subsequently. Knowing about the occurrence of such events will help us to develop programs for prevention, education, and other services.

The questionnaire is divided into questions covering crime experiences, general disaster and trauma questions, and questions about physical and sexual experiences.

For each event, please indicate whether it happened (Yes / No).

Has anyone ever tried to take something directly from you by using force or the threat of force, such as a stick-up or mugging?	◯ Yes ◯ No
Has anyone ever attempted to rob you or actually robbed you (i.e., stolen your personal belongings)?	◯ Yes ◯ No
Has anyone ever attempted to or succeeded in breaking into your home when you WERE NOT there?	◯ Yes ◯ No
Has anyone ever attempted to or succeed in breaking into your home while you WERE there?	◯ Yes ◯ No
Have you ever had a serious accident at work, in a car, or somewhere else?	◯ Yes ◯ No
Have you ever experienced a natural disaster such as a tornado, hurricane, flood or major earthquake, etc., where you felt you or your loved ones were in danger of death or injury?	◯ Yes ◯ No
Have you ever experienced a "man-made" disaster such as a train crash, building collapse, bank robbery, fire, etc., where you felt you or your loved ones were in danger of death or injury?	◯ Yes ◯ No
Have you ever been exposed to dangerous chemicals or radioactivity that might threaten your health?	◯ Yes ◯ No
Have you ever been in any other situation in which you were seriously injured?	◯ Yes ◯ No
Have you ever been in any other situation in which you feared you might be killed or seriously injured?	◯ Yes ◯ No
Have you ever seen someone seriously injured or killed?	◯ Yes ◯ No
Have you ever seen dead bodies (other than at a funeral) or had to handle dead bodies for any reason?	◯ Yes ◯ No
Have you ever had a close friend or family member murdered, or killed by a drunk driver?	◯ Yes ◯ No

Have you ever had a spouse, romantic partner, or child die?	◯ Yes ◯ No
Have you ever had a serious or life-threatening illness?	◯ Yes ◯ No
Have you ever received news of a serious injury, life-threatening illness, or unexpected death of someone close to you?	◯ Yes ◯ No
Have you ever had to engage in combat while in military service in an official or unofficial war zone?	◯ Yes ◯ No
Has anyone ever made you have intercourse or oral or anal sex against your will?	◯ Yes ◯ No
Has anyone ever touched private parts of your body, or made you touch theirs, under force or threat?	◯ Yes ◯ No
Other than incidents mentioned in previous two questions, have there been any other situations in which another person tried to force you to have an unwanted sexual contact?	◯ Yes ◯ No
Has anyone, including family members or friends, ever attacked you with a gun, knife, or some other weapon?	◯ Yes ◯ No
Has anyone, including family members or friends, ever attacked you without a weapon and seriously injured you?	◯ Yes ◯ No
Has anyone in your family ever beaten, spanked, or pushed you hard enough to cause injury?	◯ Yes ◯ No
Have you experienced any other extraordinarily stressful situation or event that is not covered above?	◯ Yes ◯ No

Source. Hooper, L. M., Stockton, P., Krupnick, J. L., & Green, B. L. (2011). Development, use, and psychometric properties of the Trauma History Questionnaire. *Journal of Loss and Trauma, 16*(3), 258-283. doi:10.1080/15325024.2011.572035

APPENDIX C: EGO-RESILIENCY SCALE (ER89)

Please read the below statements about yourself and indicate how well it applies to you by indicating the answer to the right from 1 (does not apply at all) to 4 (applies very strongly). Let us know how true the following characteristics are as they apply to you generally:

	Does not apply at all	Applies slightly	Applies somewhat	Applies very strongly
I am generous with my friends.	○	○	○	○
I quickly get over and recover from being startled.	○	○	○	○
I enjoy dealing with new and unusual situations.	○	○	○	○
I usually succeed in making a favorable impression on people.	○	○	○	○
I enjoy trying new foods I have never tasted before.	○	○	○	○
I am regarded as a very energetic person.	○	○	○	○
I like to take different paths to familiar places.	○	○	○	○
I am more curious than most people.	○	○	○	○
Most of the people I meet are likable.	○	○	○	○
I usually think carefully about something before acting.	○	○	○	○
I like to do new and different things.	○	○	○	○
My daily life is full of things that keep me interested.	○	○	○	○
I would be willing to describe myself as a pretty "strong" personality.	○	○	○	○
I get over my anger at someone reasonably quickly.	○	○	○	○

Source. Block, J., & Kremen, A. M. (1996). IQ and ego-resiliency: Conceptual and empirical connections and separateness. *Journal of Personality and Social Psychology, 70*(2), 349-361.

APPENDIX D: EMOTION REGULATION QUESTIONNAIRE (ERQ)

We would like to ask you some questions about your emotional life, in particular, how you control (that is, regulate and manage) your emotions.

The questions below involve two distinct aspects of your emotional life. One is your emotional experience, or what you feel like inside. The other is your emotional expression, or how you show your emotions in the way you talk, gesture, or behave. Although some of the following questions may seem similar to one another, they differ in important ways.

For each item, please answer using the following scale:

	Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat agree	Agree	Strongly agree
When I want to feel more POSITIVE emotion (such as joy or amusement), I CHANGE WHAT I'M THINKING ABOUT.	○	○	○	○	○	○	○
I keep my emotions to myself	○	○	○	○	○	○	○
When I want to feel less NEGATIVE emotion (such as sadness or anger), I CHANGE WHAT I'M THINKING ABOUT.	○	○	○	○	○	○	○
When I am feeling POSITIVE emotions, I am careful not to express them.	○	○	○	○	○	○	○
When I'm faced with a stressful situation, I make myself THINK ABOUT IT in a way that helps me stay calm.	○	○	○	○	○	○	○
I control my emotions by NOT EXPRESSING THEM.	○	○	○	○	○	○	○
When I want to feel more POSITIVE emotion, I CHANGE THE WAY I'M THINKING about the situation.	○	○	○	○	○	○	○
I control my emotions by CHANGING THE WAY I THINK about the situation I'm in.	○	○	○	○	○	○	○
When I am feeling NEGATIVE emotions, I make sure not to express them.	○	○	○	○	○	○	○
When I want to feel less NEGATIVE emotion, I CHANGE THE WAY I'M THINKING about the situation.	○	○	○	○	○	○	○

Source. Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology, 85*(2), 348-362.

APPENDIX E: PERCEIVED ABILITY TO COPE WITH TRAUMA (PACT)

Sometimes we must contend with difficult and upsetting events. Unfortunately, sometimes we are confronted with events that might be traumatic and disruptive to the course of our lives. Examples of such events include the death or injury of someone close to us, a natural disaster, a serious accident or illness, sexual and physical assault, and terrorist attack.

Below you will find a list of different kinds of behaviors and strategies that people sometimes use in the weeks following potentially traumatic events. This questionnaire asks which of these behaviors and strategies you might be able to use.

Please rate the extent that you would be able to use each of these behaviors and strategies following a potentially traumatic event if you needed to.

	Not at all able	Low able	Slightly able	Neutral	Moderately able	Very able	Extremely able
Keep myself serious and calm	○	○	○	○	○	○	○
Stay focused on my current goals and plans	○	○	○	○	○	○	○
Remind myself that things will get better	○	○	○	○	○	○	○
Look for a silver lining	○	○	○	○	○	○	○
Try to lessen the experience of painful emotions	○	○	○	○	○	○	○
Keep my schedule and activities as constant as possible	○	○	○	○	○	○	○
Distract myself to keep from thinking about the event	○	○	○	○	○	○	○
Find activities to help me keep the event off my mind	○	○	○	○	○	○	○
Enjoy something that I would normally find funny or amusing	○	○	○	○	○	○	○
Comfort other people	○	○	○	○	○	○	○
I would be able to laugh	○	○	○	○	○	○	○
Focus my attention on or care for the needs of other people	○	○	○	○	○	○	○
Pay attention to the distressing feelings that result from the event	○	○	○	○	○	○	○
Reflect on the meaning of the event	○	○	○	○	○	○	○

Let myself fully experience some of the painful emotions linked with the event	○	○	○	○	○	○	○
Spend time alone	○	○	○	○	○	○	○
Remember the details of the event	○	○	○	○	○	○	○
Face the grim reality head on	○	○	○	○	○	○	○
Reduce my normal social obligations	○	○	○	○	○	○	○
Alter my daily routine	○	○	○	○	○	○	○

Source. Bonanno, G. A., Pat-Horenczyk, R., & Noll, J. (2011). Coping flexibility and trauma: The Perceived Ability to Cope with Trauma (PACT) scale. *Psychological Trauma: Theory, Research, Practice, and Policy, 3*(2), 117-129.

APPENDIX F: SOCIAL SUPPORT SURVEY (SSS)

People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to you if you need it?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Someone you can count on to listen to you when you need to talk	○	○	○	○	○
Someone to give you information to help you understand a situation	○	○	○	○	○
Someone to give you good advice about a crisis	○	○	○	○	○
Someone to confide in or talk to about yourself or your problems	○	○	○	○	○
Someone whose advice you really want	○	○	○	○	○
Someone to share your most private worries and fears with	○	○	○	○	○
Someone to turn to for suggestions about how to deal with a personal problem	○	○	○	○	○
Someone who understands your problems	○	○	○	○	○
Someone to help you if you were confined to bed	○	○	○	○	○
Someone to take you to the doctor if you needed it	○	○	○	○	○
Someone to prepare your meals if you were unable to do it yourself	○	○	○	○	○
Someone to help with daily chores if you were sick	○	○	○	○	○
Someone who shows you love and affection	○	○	○	○	○
Someone to love and make you feel wanted	○	○	○	○	○
Someone who hugs you	○	○	○	○	○
Someone to have a good time with	○	○	○	○	○
Someone to get together with for relaxation	○	○	○	○	○
Someone to do something enjoyable with	○	○	○	○	○
Someone to do things with to help you get your mind off things	○	○	○	○	○

Source. Sherbourne, C. D., & Stewart, A. L. (1991). The MOS social support survey. *Social Science and Medicine, 32*(6), 705-714.

APPENDIX G: CONNOR-DAVIDSON RESILIENCE SCALE (CD-RISC)

CD-RISC is a copyrighted material. Permission to use CD-RICS was obtained from Dr. Jonathan Davidson. Further information about the scale and terms of use can be found at www.cd-risc.com.

Source. Connor, K. M., & Davidson, J. R. (2003). Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). *Depression and Anxiety, 18*(2), 76-82. doi:10.1002/da.10113

APPENDIX H: SENSE OF COHERENCE SCALE (SOC)

Here is a series of questions relating to various aspects of your lives.

Each question has seven possible answers. Please indicate the number, which expresses your answer, with number 1 and 7 being the extreme answers. If the words under 1 are right for you, indicate 1: if the words under 7 are right for you, indicate 7. If you feel differently, indicate the number which best expresses your feeling.

Please give only one answer to each question.

When you talk to people, do you have the feeling that they don't understand you?	◯ 1. Never ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Always have this feeling
In the past, when you had to do something which depended upon cooperation with others, did you have the feeling that it:	◯ 1. Surely wouldn't get done ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Surely would get done
Think of the people with whom you come into contact daily, aside from the ones to whom you feel closest. How well do you know most of them?	◯ 1. You feel that they're strangers ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. You know them very well
Do you have the feeling that you don't really care about what goes on around you?	◯ 1. Very seldom or never ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Very often
Has it happened in the past that you were surprised by the behavior of people whom you thought you knew well?	◯ 1. Never happened ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Always happened

Has it happened that people whom you counted on disappointed you?	◯ 1. Never happened ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Always happened
Life is:	◯ 1. Full of interest ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Completely routine
Until now your life has had:	◯ 1. No clear goals or purpose at all ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Very clear goals and purpose
Do you have the feeling that you're being treated unfairly?	◯ 1. Very often ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Very seldom or never
In the past ten years your life has been:	◯ 1. Full of changes without your knowing what will happen next ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Completely consistent and clear
Most of the things you do in the future will probably be:	◯ 1. Completely fascinating ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Deadly boring
Do you have the feeling that you are in an unfamiliar situation and don't know what to do?	◯ 1. Very often ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Very seldom or never

What best describes how you see life:

- ◯ 1. One can always find a solution to painful things in life
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. There is no solution to painful things in life

When you think about your life, you very often:

- ◯ 1. Feel how good it is to be alive
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. Ask yourself why you exist at all

When you face a difficult problem, the choice of a solution is:

- ◯ 1. Always confusing and hard to find
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. Always completely clear

Doing the things you do every day is:

- ◯ 1. A source of deep pleasure and satisfaction
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. A source of pain and boredom

Your life in the future will probably be:

- ◯ 1. Full of changes without knowing what will happen next
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. Completely consistent and clear

When something unpleasant happened in the past your tendency was:

- ◯ 1. "To eat yourself up" about it
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. To say "ok that's that, I have to live with it" and go on

Do you have very mixed-up feelings and ideas?

- ◯ 1. Very often
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. Very seldom or never

When you do something that gives you a good feeling:

- ◯ 1. It's certain that you'll go on and feeling good
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. It's certain that something will happen to spoil the feeling

Does it happen that you have feelings inside you would rather not feel?

- ◯ 1. Very often
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. Very seldom or never

You anticipate that your personal life in the future will be:

- ◯ 1. Totally without meaning or purpose
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. Full of meaning and purpose

Do you think that there will always be people whom you'll be able to count on in the future?

- ◯ 1. You're certain there will be
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. You doubt there will be

Does it happen that you have the feeling that you don't know exactly what's about to happen?

- ◯ 1. Very often
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. Very seldom or never

Many people - even those with a strong character - sometimes feel like sad sacks (losers) in certain situations. How often have you felt this way in the past?

- ◯ 1. Never
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. Very often

When something happened, have you generally found that:

- ◯ 1. You overestimated or underestimated its importance
- ◯ 2.
- ◯ 3.
- ◯ 4.
- ◯ 5.
- ◯ 6.
- ◯ 7. You saw things in the right proportion

When you think of the difficulties you are likely to face in important aspects of your life, do you have the feeling that:	◯ 1. You will always succeed in overcoming the difficulties ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7.You won't succeed in overcoming the difficulties
How often do you have the feeling that there's little meaning in the things you do in your daily life?	◯ 1. Very often ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Very seldom or never
How often do you have feelings that you're not sure you can keep under control?	◯ 1. Very often ◯ 2. ◯ 3. ◯ 4. ◯ 5. ◯ 6. ◯ 7. Very seldom or never

Source. Antonovsky, A. (1993). The structure and properties of the sense of coherence scale. *Social Science and Medicine, 36*(6), 725-733.

APPENDIX I: MENTAL HEALTH INVENTORY (MHI)

Please read each question and indicate the one statement that best describes how things have been for you during the past month. There are no right or wrong answers.

How happy, satisfied, or pleased have you been with your personal life during the past month?	◯ Extremely happy, could not have been more satisfied or pleased ◯ Very happy most of the time ◯ Generally, satisfied, pleased ◯ Sometimes fairly satisfied, sometimes fairly unhappy ◯ Generally dissatisfied, unhappy ◯ Very dissatisfied, unhappy most of the time
How much of the time have you felt lonely during the past month?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ None of the time
How often did you become nervous or jumpy when faced with excitement or unexpected situations during the past month?	◯ Always ◯ Very often ◯ Fairly often ◯ Sometimes ◯ Almost never ◯ Never
During the past month, how much of the time have you felt that the future looks hopeful and promising?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ None of the time
How much of the time, during the past month, has your daily life been full of things that were interesting to you?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ None of the time
How much of the time, during the past month, did you feel relaxed and free from tension?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ None of the time
During the past month, how much of the time have you generally enjoyed the things you do?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ None of the time

During the past month, have you had any reason to wonder if you were losing your mind, or losing control over the way you act, talk, think, feel, or of your memory?

- ◯ No, not at all
- ◯ Maybe a little
- ◯ Yes, but not enough to be concerned or worried about
- ◯ Yes, and I have been a little concerned
- ◯ Yes, and I am quite concerned
- ◯ Yes, I am very much concerned about it

Did you feel depressed during the past month?

- ◯ Yes, to the point that I did not care about anything for days at a time
- ◯ Yes, very depressed almost every day
- ◯ Yes, quite depressed several times
- ◯ Yes, a little depressed now and then
- ◯ No, never felt depressed at all

During the past month, how much of the time have you felt loved and wanted?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

How much of the time, during the past month, have you been a very nervous person?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

When you have got up in the morning, this past month, about how often did you expect to have an interesting day?

- ◯ Always
- ◯ Very often
- ◯ Fairly often
- ◯ Sometimes
- ◯ Almost never
- ◯ Never

During the past month, how much of the time have you felt tense or "high-strung"?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

During the past month, have you been in firm control of your behavior, thoughts, emotions or feelings?

- ◯ Yes, very definitely
- ◯ Yes, for the most part
- ◯ Yes, I guess so
- ◯ No, not too well
- ◯ No, and I am somewhat disturbed
- ◯ No, and I am very disturbed

During the past month, how often did your hands shake when you tried to do something?

- ◯ Always
- ◯ Very often
- ◯ Fairly often
- ◯ Sometimes
- ◯ Almost never
- ◯ Never

During the past month, how often did you feel that you had nothing to look forward to?

- ◯ Always
- ◯ Very often
- ◯ Fairly often
- ◯ Sometimes
- ◯ Almost never
- ◯ Never

How much of the time, during the past month, have you felt calm and peaceful?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

How much of the time, during the past month, have you felt emotionally stable?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

How much of the time, during the past month, have you felt downhearted and blue?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

How often have you felt like crying, during the past month?

- ◯ Always
- ◯ Very often
- ◯ Fairly often
- ◯ Sometimes
- ◯ Almost never
- ◯ Never

During the past month, how often have you felt that others would be better off if you were dead?

- ◯ Always
- ◯ Very often
- ◯ Fairly often
- ◯ Sometimes
- ◯ Almost never
- ◯ Never

How much of the time, during the past month, were you able to relax without difficulty?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

How much of the time, during the past month, did you feel that your love relationships, loving and being loved, were full and complete?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

How often, during the past month, did you feel that nothing turned out for you the way you wanted it to?

- ◯ Always
- ◯ Very often
- ◯ Fairly often
- ◯ Sometimes
- ◯ Almost never
- ◯ Never

How much have you been bothered by nervousness, or your "nerves", during the past month?

- ◯ Extremely so, to the point where I could not take care of things
- ◯ Very much bothered
- ◯ Bothered quite a bit by nerves
- ◯ Bothered some, enough to notice
- ◯ Bothered just a little by nerves
- ◯ Not bothered at all by this

During the past month, how much of the time has living been a wonderful adventure for you?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

How often, during the past month, have you felt so down in the dumps that nothing could cheer you up?

- ◯ Always
- ◯ Very often
- ◯ Fairly often
- ◯ Sometimes
- ◯ Almost never
- ◯ Never

During the past month, did you think about taking your own life?

- ◯ Yes, very often
- ◯ Yes, fairly often
- ◯ Yes, a couple of times
- ◯ Yes, at one time
- ◯ No, never

During the past month, how much of the time have you felt restless, fidgety, or impatient?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

During the past month, how much of the time have you been moody or brooded about things?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

How much of the time, during the past month, have you felt cheerful, lighthearted?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

During the past month, how often did you get rattled, upset or flustered?

- ◯ Always
- ◯ Very often
- ◯ Fairly often
- ◯ Sometimes
- ◯ Almost never
- ◯ Never

During the past month, have you been anxious or worried?

- ◯ Yes, extremely to the point of being sick or almost sick
- ◯ Yes, very much so
- ◯ Yes, quite a bit
- ◯ Yes, some, enough to bother me
- ◯ Yes, a little bit
- ◯ No, not at all

During the past month, how much of the time were you a happy person?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

How often during the past month did you find yourself trying to calm down?	◯ Always ◯ Very often ◯ Fairly often ◯ Sometimes ◯ Almost never ◯ Never
During the past month, how much of the time have you been in low or very low spirits?	◯ All of the time ◯ Most of the time ◯ A good bit of the time ◯ Some of the time ◯ A little of the time ◯ None of the time
How often, during the past month, have you been waking up feeling fresh and rested?	◯ Always, every day ◯ Almost every day ◯ Most days ◯ Some days, but usually not ◯ Hardly ever ◯ Never wake up feeling rested
During the past month, have you been under or felt you were under any strain, stress or pressure?	◯ Yes, almost more than I could stand or bear ◯ Yes, quite a bit of pressure ◯ Yes, some more than usual ◯ Yes, some, but about normal ◯ Yes, a little bit ◯ No, not at all

Source. Veit, C. T., & Ware, J. E., Jr. (1983). The structure of psychological distress and well-being in general populations. *Journal of Consulting and Clinical Psychology, 51*(5), 730-742.

APPENDIX J: IRB APPROVAL LETTER

University of Nebraska Medical Center
NEBRASKA'S HEALTH SCIENCE CENTER

Office of Regulatory Affairs (ORA)
Institutional Review Board (IRB)

August 19, 2015

Kosuke Niitsu, BSN, RN
CON-Omaha Division
UNMC - 5330

IRB # 610-15-ET

TITLE OF PROPOSAL: Life Experiences, Genes, and Resilience

DATE OF REVIEW: 08/06/2015

DATE OF FINAL ACCEPTANCE: 08/19/2015 **VALID UNTIL:** 08/06/2020

The UNMC IRB has completed its review of the above-titled external protocol. Please be advised that the UNMC IRB has accepted approval from the University of Nebraska-Lincoln (UNL) IRB under the provisions of 45 CFR 46.114.

It is understood that the UNL IRB is responsible for oversight of the above-titled research project in accordance with HHS regulations at 45 CFR 46 and FDA regulations at 21 CFR 50, 56 as applicable. Such oversight includes: 1) continuing review no less often than annually, 2) approval of any protocol amendments, 3) reporting to the Office for Human Research Protections (OHRP), and FDA as applicable, 4) unanticipated problems involving risk to subjects or others, and 5) serious and continuing non-compliance, as well as suspensions. Should any reports be filed with OHRP and/or FDA, the UNMC IRB should be provided with copies of such correspondence.

Finally, please be advised that acceptance by the UNMC IRB of the UNL IRB approval is valid for a period of **five years** from the initial date of review. If the study continues beyond the five year period, the project must be resubmitted in order to maintain an active status.

On Behalf of the IRB,

Signed on: 2015-08-19 15:39:00.000

Gail Paulsen, RN, BSN, CIP
IRB Administrator III
Office of Regulatory Affairs