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Psychobiological Determinants of Stress Reactivity
in Schizophrenia

A dissertation submitted in partial satisfaction of the
Requirements for the degree Doctor of Philosophy
in Psychology

by

Gretchen Louise Sholty

2012

ABSTRACT OF THE DISSERTATION

Psychobiological Determinants of Stress Reactivity in Schizophrenia

by

Gretchen Louise Sholty

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2012

Professor Cindy Yee-Bradbury, Chair

Schizophrenia is a debilitating illness, characterized by significant impairment in functioning across the social, emotional, and cognitive domains. Although there is strong evidence to suggest that life stressors precede symptom exacerbation in schizophrenia, important gaps in the research literature still remain. First, the biological mechanisms through which stress may contribute to the onset and expression of clinical symptoms have not been well defined. Second, there is considerable variability across schizophrenia patients in terms of their susceptibility to an elevation in symptoms following life stress.

According to the neural-diathesis stress model of schizophrenia, cortisol interacts with a biological vulnerability for heightened dopamine neurotransmission to influence illness expression. Utilizing this framework, the present investigation sought to clarify whether the specific stressor and patient characteristics that lead to heightened cortisol release also place patients at greater risk for stress-induced relapse. Furthermore, this study was designed so as to

elucidate whether cortisol serves as one of the biological mechanisms through which life stress gets “under the skin” to influence symptom expression in schizophrenia.

Drawing upon data obtained from 125 schizophrenia patients and 95 healthy individuals, results indicated that clinical symptoms were most closely linked to acute and chronic stressors characterized by social evaluative content. Specific individual difference factors, including low trait positive affect, a reduced use of adaptive coping styles, early life adversity, and the *Met* allele of the catechol-O-methyltransferase Val¹⁵⁸Met (COMT) polymorphism, placed patients with schizophrenia at greater risk for symptom exacerbation following the experience of social evaluative stress. In healthy individuals, low trait positive affect and maladaptive coping styles moderated the relationship between life stress and depressive symptoms. Results also indicated that the specific individual characteristics moderating the relationships between social evaluative episodic stress and clinical symptoms also influenced the magnitude of the cortisol response to a laboratory psychosocial stressor, the Trier Social Stress Test. These findings have implications for not only furthering our understanding of the psychobiological determinants of stress reactivity in schizophrenia, but can contribute significantly to the development of specific treatment and management strategies aimed at resolving stress in the lives of individuals with this debilitating condition.

The dissertation of Gretchen Louise Sholty is approved.

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Although schizophrenia is largely conceptualized as a biological or genetic disorder of endogenous origins (Cannon et al., 1998; Kendler, 2000), research also highlights the influence of life stress in the etiology and course of the disorder. According to the diathesis-stress model of schizophrenia, environmental stressors interact with dispositional vulnerabilities to influence the onset and course of psychotic symptoms (e.g., Corcoran et al., 2003; Horan et al., 2005; Nuechterlein et al., 1992; Phillips et al., 2007). To date, the notion that life stress contributes to the clinical symptoms of schizophrenia has been well supported in the research literature. Early in life, the stressors include obstetric complications (Cannon et al. 2002), while later, psychosocial stressors appear to be especially potent in impacting illness expression. Among adults, previous research studies have consistently found that exposure to adverse life events (e.g., Norman & Malla, 1993; Ventura et al., 1989, 1992) or family environments characterized by high expressed emotion (EE; for a review, see Butzlaff & Hooley, 1998) are associated with increased psychotic symptoms in schizophrenia patients.

Despite the abundance of research studies documenting evidence in support of stress-symptom associations in schizophrenia, important questions still remain. Specifically, the biological mechanisms by which life stress contributes to symptom severity have yet to be clearly specified. Additionally, there is significant interindividual variability in patients' sensitivity to life stress (Norman & Malla, 1994). For example, some patients with schizophrenia do not relapse when exposed to psychosocial stressors (e.g., Docherty et al., 2009; Jacobs & Myers, 1976; Kavanagh, 1992; Ventura et al., 1989). Thus, the following set of studies aimed to elucidate the nature of the diathesis-stress interaction at both the biological and behavioral levels.

Neural-Diathesis Stress Model of Schizophrenia

In recent years, it has been suggested that the hypothalamic-pituitary-adrenal (HPA) axis may serve as one of the biological pathways by which life stress contributes to the onset and course of schizophrenia (Walker & Diforio, 1997; Walker, Mittal, & Tessner, 2008). According to the neural-diathesis stress model of schizophrenia, the HPA axis interacts with a biological vulnerability for heightened dopamine (DA) neurotransmission to influence illness expression (Walker & Diforio, 1997). Previous studies examining the DA system in schizophrenia have typically shown evidence of overactivation (Collip et al., 2008; Howes et al., 2004; Howes & Kapur, 2009), although the biological underpinnings of this hyperactivity are unclear. Furthermore, there is accumulating evidence that schizophrenia patients exhibit elevated DA responses to pharmacological, metabolic, and psychosocial stressors (Soliman et al., 2008). For example, Laruelle and colleagues (1996) reported that drug-naïve schizophrenia patients display greater DA release in the striatum relative to healthy controls when administered amphetamine. In addition, there is some suggestion that sensitivity to DA may stem from an abnormality in striatal DA receptors in patients with schizophrenia (Walker & Diforio, 1997). DA also appears to be related to clinical outcomes, as levels of homovanillic acid (HVA), a major DA metabolite, are positively correlated with symptom severity in schizophrenia (Davidson & Davis, 1985; Davis et al., 1985; Davis et al., 1991; Pickar et al., 1986). Several recent reviews of the research literature continue to suggest that there are abnormalities in DA neurotransmission in schizophrenia although the mechanisms by which these DA alterations lead to symptom expression have yet to be elucidated (Di Forti et al., 2007; Howes & Kapur, 2009; Jarskog et al., 2007; Seeman et al., 2006).

The neural-diathesis stress model posits that the HPA axis mediates the relationship between life stressors and symptom expression through the release of its end product, cortisol. Specifically, it is presumed that stress-related increases in cortisol levels exacerbate hyper-active DA circuits in schizophrenia patients to produce elevated symptom levels. Cortisol is a glucocorticoid that influences many biological systems, including the immune, metabolic, and central nervous systems (Charmandari et al., 2003; Sapolsky, 2003; Tsigos & Chrousos, 2002). This glucocorticoid also serves the important role of regulating physiological responses to stress (Raison & Miller, 2003). In stressful contexts, the HPA axis becomes activated and corticotropin releasing hormone is released from the periventricular nucleus of the hypothalamus, which then stimulates the anterior pituitary gland to release adrenocorticotrophic hormone (ACTH) into the bloodstream. ACTH then stimulates the adrenal cortex to secrete cortisol, which facilitates an individual's ability to adapt to a stressor, both physiologically and behaviorally (Lopez, Akil, & Watson, 1999; Sapolsky, Romero, & Munck, 2000; Vasquez, 1998). Although acute increases in cortisol levels in response to stress can be adaptive, unrestrained levels of this glucocorticoid often lead to adverse physical and mental health, and poor cognitive outcomes (e.g., Cicchetti & Rogosch, 2001; Kariyawasam et al., 2002; Lundberg, 2005, McEwen, 1998).

It is not entirely clear how the HPA axis is initially triggered, though there is evidence implicating the amygdala in the facilitation of the physiological stress response. For example, research has shown robust connections between the paraventricular nucleus of the hypothalamus and the amygdala (Ghashghaei & Barbas, 2002; Herman et al., 2003; Risold et al., 1997; Saphier & Feldman, 1986) and increased activation in the amygdala has been associated with increases in cortisol levels (Frankel et al., 1978). Conversely, the levels of cortisol in the body are typically down-regulated through a negative feedback cycle involving glucocorticoid receptors (GRs)

located in various regions throughout the brain. The hippocampus has been shown to contain a particularly high density of GRs, and thus, appears to play an important role in the regulation of cortisol (Sapolsky et al., 1990).

Previous research provides several lines of evidence to support the link between cortisol levels and psychosis. In particular, individuals suffering from illnesses associated with elevated cortisol levels, such as Cushing's syndrome, have been observed to exhibit psychotic symptoms (Saad et al. 1984; Gerson & Miclat 1985; Hirsch et al. 2000). Furthermore, researchers have directly examined the relationships between cortisol and DA release. These findings suggest that there is a synergistic relationship between cortisol activity and specific DA circuits that have been implicated in the production of psychotic symptoms. Specifically, it is suggested that cortisol exerts its effects on DA synthesis, reuptake, and receptor sensitivity primarily in the mesolimbic system (Walker & Diforio, 1997; Walker et al., 2008). The evidence for this synergistic relationship stems from three complementary approaches: 1) animal research, 2) studies using metabolic stressors in humans, and 3) investigations using psychosocial stressors in humans.

Regarding animal research, microdialysis studies have demonstrated that drugs that suppress corticosterone (the animal equivalent of cortisol) also inhibit DA release in the nucleus accumbens shell, both in basal conditions and in response to psychostimulants or stress (Barrot et al., 2000; Mittleman, Blaha, & Phillips, 1992; Piazza et al., 1996a; 1996b; Rothschild et al., 1985). These effects also appear to be corticosterone dependent as they are reversed by corticosterone administration. Additionally, tonic DA levels in the nucleus accumbens appear to moderate the DA-cortisol association; that is, there is a greater increase in corticosterone induced DA in the nucleus accumbens in rats with higher basal DA tone relative to those with lower tonic

levels of DA activity (Rouge-Pont et al., 1998). Research in animals also suggests that the administration of corticosterone significantly increases the synthesis of DA, with this increase partly due to the influence of corticosteroids on the chief enzyme involved in DA synthesis, tyrosine hydroxylase (Ortiz, DeCaprio, Kosten, & Nestler, 1995). Furthermore, Harfstrand and colleagues (1986) have shown that 40 to 75 percent of dopaminergic neurons of the ventral tegmental area have receptors for glucocorticoids, thus providing another possible mechanism for cortisol to act on the DA system.

Extending animal research to humans, researchers have investigated the influence of metabolic stressors on dopaminergic and cortisol reactivity using the intravenous infusion of 2-deoxy-D-glucose (2-DG). The infusion of this glucose analogue inhibits intracellular glucose metabolism and can induce heightened activation of the HPA axis and raise the levels of HVA. Using this methodology, Breier and colleagues (1993) determined that there was a positive correlation between the magnitude of the cortisol response and HVA release following 2-DG infusion in both schizophrenia patients and healthy individuals. Moreover, acute cortisol challenges have been shown to significantly raise HVA levels in normal human subjects (Rothschild et al., 1984; Schatzberg et al., 1985; Wolkowitz, 1994). Findings from a combined pharmacological and psychosocial stressor have also demonstrated that amphetamine-induced DA release in the striatum is positively associated with cortisol responses to a psychosocial stressor in healthy individuals (Wand et al., 2007). In a study conducted by Pruessner, Champagne, Meaney, and Dagher (2004), DA and cortisol responses were measured to the same psychosocial stressor and the authors found that psychosocial stress elicited both increased cortisol and dopamine in the ventral striatum; further, the magnitude of the cortisol response was positively correlated with the amount of DA release. Lastly, recent research has reported that

schizophrenia patients display both a sensitized dopaminergic and cortisol response to psychosocial stress relative to healthy individuals (Mizrahi et al., 2012).

In sum, previous research indicates that elevations in cortisol activity can lead to heightened activation of dysfunctional DA pathways in schizophrenia patients. This relationship, however, can also be bi-directional. Although DA antagonists, such as antipsychotics, can reduce cortisol release (Walker & Diforio, 1997), DA agonists have been reported to produce increases in cortisol release (Mokrani et al., 1995). Moreover, lesions of the ventral tegmental area result in a depletion of DA release as well as decrements in baseline and stress-induced corticosterone levels in rats (Casolini et al., 1993). Yet, despite these strong associations in the literature, the exact mechanisms underlying the close link between cortisol and DA remain to be clarified (Walker et al., 2008).

Cortisol Dysregulation in Schizophrenia

Further evidence for the role of cortisol in psychosis stems from research studies that highlight cortisol dysregulation in schizophrenia patients (for a review, see Bradley & Dinan, 2010). Considerable research demonstrates that patients exhibit higher resting levels of plasma, urinary, and salivary cortisol relative to healthy individuals (for a review, see Phillips et al., 2006). In reviewing the literature on resting cortisol levels in schizophrenia, Walker and Diforio (1997) computed an average effect size (Cohen's *d*) of .60. This moderate effect size is particularly striking given that only about one-third of the studies reporting a significant difference between schizophrenia patients and healthy individuals provided enough information to be incorporated into the effect size calculation. Thus, it appears that this effect size likely underestimates the true effect size in the population. Furthermore, group differences in resting cortisol levels cannot be attributed to medication effects, as elevated resting cortisol levels have

been found in drug naïve first-episode patients (Ryan et al., 2004) as well as medicated and chronic schizophrenia patients (Franzen, 1971; Gallagher et al., 2007; Ritsner et al., 2007; Yilmaz et al., 2007). Typical and atypical antipsychotics have also been shown to attenuate cortisol levels (Walker & DiForio, 1997).

Abnormalities in diurnal changes in cortisol release have also been found in schizophrenia patients. In the absence of stressful conditions, the cortisol response normally displays a robust diurnal rhythm, with highest cortisol levels in the early morning and then a steady decrease throughout the remainder of the day (Kudielka, Schommer, Helhammer, & Kirschbaum, 2004). Kaneko et al. (1992), however, reported that the typical late-day drop in cortisol levels was reduced in schizophrenia patients relative to healthy individuals. Moreover, Van Cauter et al. (1991) showed that schizophrenia patients had higher cortisol levels throughout the day although in this study, the degree to which they differed from healthy individuals was only statistically significant at night. Two recent studies have demonstrated higher cortisol levels throughout the day in individuals with schizophrenia (Mondelli et al., 2010a,b).

In addition to measuring resting cortisol levels, investigators have examined schizophrenia patients' cortisol release in response to the Dexamethasone Suppression Test (DST). Although atypical basal levels of cortisol are strong indicators of abnormal HPA axis activity, DST-induced cortisol levels provide information regarding the integrity of the HPA axis feedback mechanism (Yeap & Thakore, 2005). Typically, cortisol release is reduced after the exogenous administration of the synthetic glucocorticoid, dexamethasone, via feedback inhibition of the HPA axis. In schizophrenia patients, however, there is a marked failure of cortisol suppression by dexamethasone. Although previous research reports a DST non-suppression incidence rate of 5% in healthy individuals (Yeragani, 1990), a survey of 44

published studies suggests that 36% of unmedicated schizophrenia patients and 20% of those in a medicated state fail to suppress their cortisol release in response to the DST pharmacological challenge (Tandon et al., 1991).

Only a few studies have examined cortisol reactivity among schizophrenia patients in response to physical or psychological stressors. Regarding physical stress, Breier, Wolkowitz, Doren, Bellar, and Pickar (1998) reported that schizophrenia patients show a diminished cortisol response to the stress of a lumbar puncture relative to healthy individuals and depressed patients. When presented with a variety of physical (i.e., cold pressor test, noise) and psychological (i.e., mental arithmetic) stress tasks, Albus, Ackenheil, Engel, and Muller (1982) found that acute, unmedicated schizophrenia patients showed elevated cortisol levels across all conditions. Similarly, Jansen, Gispen-de Wied, and Kahn (2000) conducted a study with both physiological (i.e., bicycle ergometry) and psychosocial (i.e., public speaking task) stressors. However, they reported that schizophrenia patients showed blunted cortisol responses to psychosocial stress and a normal increase in cortisol in response to the physical stressor. It is important to note that the psychosocial stressor used in the aforementioned study may have not been the most effective in eliciting a cortisol response given that it lacked strong social evaluative and uncontrollable components, which are important elicitors of the cortisol response (Dickerson & Kemeny, 2004). More recently, Brenner et al. (2009) examined the cortisol response to a modified version of the Trier Social Stress Test in chronic schizophrenia patients and healthy individuals and found that patients' cortisol responses did not differ from the healthy individuals immediately after the stressor or at the 30, 45, or 60 minute recovery time-points; however, they did display attenuated cortisol responses 15 minutes after the stressor terminated.

Taken together, it appears that schizophrenia patients exhibit abnormal patterns of cortisol activity. Although the resting cortisol and pharmacological findings suggest that patients may have heightened biological stress responsivity, interpretation of the findings in response to physical and psychosocial stressors in schizophrenia is less clear.

Cortisol Dysregulation and Clinical Symptoms in Schizophrenia

Previous research has also examined the association between patterns of cortisol release and symptom severity in medicated and non-medicated schizophrenia patients. While measuring daily urinary cortisol levels over a 2 to 3 month period, Sachar, Kanter, Buie, Engle, and Mehlman (1970) found that cortisol levels increased by 250% immediately preceding psychotic episodes, and then decreased to a level between that of the pre-episode and recovery during the actual psychotic state. This pattern of findings suggests that cortisol changes are not the result of an exacerbation of psychotic symptoms, but rather appear to predict significant increases in symptomatology. Cross-sectional and longitudinal studies investigating the clinical correlates of resting cortisol levels have also shown that increased cortisol levels are associated with more severe positive symptoms (Franzen, 1971; Kaneko et al., 1992; Walder et al., 2000). In addition, heightened cortisol levels have been linked to negative symptoms (Goyal et al., 2004; Newcomer et al. 1991; Zhang et al., 2005) and depressive symptomatology (Ritsner et al., 2004; Ventura et al., 2000). Walker and colleagues (2001) also examined HPA activity in adolescents over a ten-year period and its relationship with the progression of psychotic symptoms. Results from this study showed that a steeper increase in cortisol activity was linked to the progression of psychotic symptomatology in adolescents with schizotypal personality disorder. Furthermore, cortisol responses to pharmacological challenges have been associated with clinical symptom levels in schizophrenia. Increased cortisol responses to a serotonergic agonist (m-CPP) have

been associated with higher clinical symptom levels (Lindenmayer et al., 1997) and post-DST cortisol levels have been linked to symptom severity, with higher cortisol levels being associated with more severe negative and positive symptomatology (Keshavan et al., 1989; Tandon et al., 1991).

In sum, the neural-diathesis stress model provides an important foundation from which to elucidate the nature of stress sensitivity in schizophrenia at both the biological and behavioral levels. First, it provides a plausible biological mechanism by which psychosocial stressors can get “under the skin” to influence illness expression. Although cortisol dysregulation is not specific to schizophrenia, the neural-diathesis stress model suggests that cortisol activity contributes to psychotic symptomatology through its interactions with the neurotransmitter DA. Specifically, it is presumed that among individuals who have a diathesis consisting of DA over-activation, heightened cortisol activity may fuel elevations in clinical symptoms through its augmentation of DA release. At the same time, it is likely that there is a reciprocal effect, such that patients’ heightened sensitivity to DA may also influence their cortisol release, thus rendering patients more biologically responsive to stress.

Second, the neural-diathesis stress model encourages better identification of patients who are more likely to show elevations in clinical symptoms following the experience of life stress. Specifically, by identifying the patient and stressor characteristics that are most likely to be associated with increases in cortisol reactivity, it may be possible to better predict which patients with schizophrenia will be particularly sensitive to life stress given that symptom elevations are tightly linked to increases in cortisol secretion.

Study 1: Stressor Attributes That Influence Stress-Symptom Relationships

Stress-Symptom Relationships in Schizophrenia

As indicated above, there is a robust relationship between psychosocial stressors and the course of schizophrenia; however, there is also significant variability in patients' responsivity to life stress. Cross-sectional studies examining the frequency of stressful life events in schizophrenia patients and healthy individuals have not yielded consistent evidence to indicate that patients experience more psychosocial stressors than do healthy individuals. Although some studies report that patients experience a greater number of adverse life events relative to healthy individuals (Canton & Fracon; 1985; Jacobs & Meyers, 1976; Schwartz & Myers, 1977a), others have reported null effects (Al Khani et al., 1986; Dohrenwend et al., 1998) or an effect in the opposite direction (Gureje & Adewunmi, 1988; Horan et al., 2005). In addition to the frequency of life events, findings linking life stress and symptom expression have been mixed. A number of studies describe an increase in the frequency of stressful life events before elevations in clinical symptoms (Brown & Birley, 1968; Day et al., 1987; Nuechterlein et al., 1994; Pallanti et al., 1997; Schwartz & Myers, 1977b; Ventura et al., 1989), but this effect has not always been replicated for all patients (Chung et al., 1986; Docherty et al., 2009; Jacobs & Myers, 1976; Kavanagh, 1992).

The inconsistent findings in how psychosocial stressors impact illness expression may be partly due to varied conceptualizations of life stress. Specifically, previous studies have commonly viewed life stressors as a homogeneous construct and failed to distinguish among the many different dimensions in which events can be stressful. The studies that have differentiated among stressors have primarily focused on three stressor attributes: independence, magnitude, and the date of the stressful event. In terms of independence, investigators have assessed whether the onset of life stressors appear to be influenced by an individual's symptoms or behavior or can be considered independent of their illness. Results of these investigations have

tended to demonstrate that an increase in major independent life events immediately precedes psychotic exacerbations (Brown & Birley, 1968; Day et al., 1987; Hultman et al., 1997; Ventura et al., 1989). Jacobs and Myers (1976), however, reported that patients experienced significantly more dependent life events prior to elevations in clinical symptoms. Studies have also examined the influence of stressor magnitude on clinical symptoms. Norman and Malla (1994, 2001) determined that minor life events or chronic daily hassles, in addition to major life events, appear to predict increased symptom levels and subjective distress in schizophrenia patients. Regarding the date of the event, some research has found relationships between elevations in clinical symptoms and life stressors occurring in the preceding 12 months (Jacobs & Myers, 1976) while others have shown that stressors occurring in the preceding month are most potent in increasing risk for psychosis (Ventura et al., 2000). Taken together, these findings suggest that the degree to which patients express elevated symptom levels following life stress likely depends on the specific types of stressors that they experience. This further underscores the importance of specifying the nature of the stressor to more fully account for the heterogeneity inherent in understanding stress reactivity in schizophrenia.

In addition to independence level, date of the event, and stressor magnitude, Study 1 was designed to investigate other stressor dimensions that might account for more of the interindividual variability in stress-symptom relationships. Following from the neural-diathesis stress model of schizophrenia and results from basic behavioral research, two stressor domains appear to warrant particular attention: social evaluative threat and uncontrollability.

Social Self Preservation (SSP) Model

According to the Social-Self Preservation model (SSP; Dickerson, Gruenewald, & Kemeny, 2004; Kemeny, Gruenewald, & Dickerson, 2004), the stress associated with social

evaluation and uncontrollability threaten the human goal of preserving the “social self”. The SSP model posits that in addition to striving for physical self-preservation, preservation of the social self (e.g., social acceptance/inclusion) is also necessary for meeting human evolutionary goals. Specifically, it is argued that humans possess a fundamental need for social acceptance and inclusion because social status can be an important determinant in how social and physical resources are distributed (Baumeister & Leary, 1995; Gilbert, 1998). According to Gruenewald, Dickerson, and Kemeny (2007), prototypical threats to the social self involve circumstances in which an important aspect of one’s identity can be negatively judged by others. Previous research suggests that a variety of social situations may elicit social self threat. These include performance contexts in which individual abilities, competencies, or traits can be called into question in the presence of others, situations characterized by social rejection where an individual could be considered unworthy of social acceptance, as well as contexts where an uncontrollable and undesirable social identity is made salient.

Given the importance of preserving the social self and maintaining social acceptance, it is posited that humans have developed psychobiological responses to effectively cope with social self threats. The SSP model proposes that under conditions that threaten to demean one’s social image or standing, humans exhibit specific psychobiological reactions, such as shame and other negative self-evaluative emotions as well as the cortisol response. According to Denson, Spanovic, and Miller (2009), such increases in cortisol output may energize behaviors designed to aid in group reintegration. Furthermore, the degree to which the stressor is uncontrollable is also important. Specifically, uncontrollability is thought to further amplify the impact of social evaluative threat by creating a situation where individuals cannot succeed or avoid negative interpersonal consequences despite their best efforts.

Social Evaluative Threat, Uncontrollability, and the Cortisol Response

Consistent with the SSP model, laboratory studies have provided empirical evidence supporting the notion that increases in cortisol are a major component of the psychobiological response to social self threats. Beginning with animal studies, results indicate that social threat, such as social defeat and subordination, elicit heightened levels of corticosterone (Shively, Laber-Laird, & Anton, 1997). Extending this research to humans, Dickerson and Kemeny (2004) conducted a meta-analysis of 208 studies and determined the effects of different types of laboratory stressors on cortisol reactivity in healthy individuals. They showed that stressors characterized by social evaluative threat (i.e., an aspect of the self was perceived to be negatively judged by others) and uncontrollability (i.e., participants could not avoid negative consequences) were the most robust in eliciting a cortisol response. Specifically, an average effect size of $d = .67$ was found when social-evaluative threat was a component of the stress task as compared to $d = .15$ when social evaluative threat was absent. Additionally, uncontrollable stressor tasks elicited larger cortisol responses ($d = .52$) compared to controllable tasks ($d = .16$). As might be expected, the largest effect size occurred for tasks that contained both social evaluative threat and uncontrollable elements with $d = .92$. In a subsequent laboratory study, Gruenewald, Kemeny, Aziz, and Fahey (2004) found that tasks characterized by social evaluative threat elicited greater increases in cortisol relative to tasks without a social evaluative component. Furthermore, the authors identified a relationship between cortisol and the self-conscious emotion, shame, such that the magnitude of the cortisol response was greater in participants who experienced larger increases in shame to the social evaluative stressor.

In addition to performance-related stressors, previous research has shown that negative interpersonal evaluations are also potent elicitors of the cortisol response. According to

Dickerson and Kemeny (2004), relationships characterized by criticism or rejection are likely to create an uncontrollable, evaluative context which could activate the HPA axis. In support of this idea, Stroud, Salovey, and Epel (2002) reported elevations in cortisol levels following a social rejection task, especially in female participants. Furthermore, marital interaction studies have found that couples that respond to conflict provoking topics with greater levels of criticisms, “put-downs” and disapproval exhibit greater elevations in cortisol relative to couples with a more positive interactional style (Kiecolt-Glaser et al., 1997; Malarkey et al., 1994).

Lastly, although most studies have investigated cortisol release to acute stressors with social evaluative threat content, chronic social self threats also appear to be tightly linked to the HPA axis. In a meta-analysis, Miller, Chen, and Zhou (2007) observed that chronic stressors that were likely to threaten the social self (e.g., stressors that could diminish a person’s social standing or interrupt a major social role occupied by the individual) were positively correlated with greater cortisol output. A recent study by Friedman and colleagues (2012) similarly reported cortisol dysregulation throughout the day for individuals who reported greater social strain.

Furthermore, individual difference factors that render participants to be more sensitive to negative social evaluation can amplify cortisol responses to stressors. For example, individuals low in social competence and self esteem show greater cortisol responses to laboratory stress tasks (Schmidt et al., 1999; Pruessner et al., 1999; Seeman et al., 1995). Gruenewald and colleagues (2004) further demonstrated that subjective social status can influence cortisol reactivity to a social evaluative stressor, with individuals who perceived themselves to be of high status showing heightened cortisol reactivity to the stressor while individuals of low social status did not mount a significant cortisol response to the stressor. Although this finding was contrary

to their original predictions, the authors suggest that heightened cortisol reactivity in the high social status group might reflect greater sensitivity to the social evaluative threat given that they may have had more to lose in terms of a change in their perceived social status.

Social Evaluative Threat and Uncontrollability in Schizophrenia

Although there do not appear to be any previous studies that have directly investigated associations between social evaluative or uncontrollable life stressors and clinical symptom levels, indirect evidence suggests that these stressor domains may be particularly relevant to schizophrenia. Regarding social evaluation, a strong and consistent association has been observed between increased clinical symptom levels and the degree to which schizophrenia patients are exposed to critical and challenging interpersonal environments. In a meta-analysis of 27 studies examining clinical outcomes and EE (i.e., level of criticism, hostility and emotional overinvolvement) in the family environment, 89% of studies showed a significant relationship between level of EE and more severe clinical symptomatology in schizophrenia (Butzlaff & Hooley, 1998). Additionally, a study conducted by Myin-Germeys and colleagues (2001) demonstrated that individuals with a psychotic disorder reported experiencing more stressful events that were social in nature relative to healthy comparison subjects.

A large body of research also supports the notion that patients experience an increased rate of social evaluative threat in the form of stigmatization. Stigmatizing attitudes towards schizophrenia patients have become so pronounced that Torrey (1995) describes schizophrenia as the modern-day equivalent of leprosy. There is also evidence to suggest that stigma experiences influence symptom levels in schizophrenia. Using a cross-sectional design, Ertugrul and Ulug (2004) found that patients who reported greater stigmatization exhibited more positive symptoms and a tendency for more negative symptoms. Janssen, Hanssen, and Bak (2003)

demonstrated prospectively that perceived social discrimination is a risk factor for developing psychotic symptoms. Furthermore, past research has shown that stigma predicted increases in depressive symptoms at a 4-month follow-up after controlling for baseline symptoms (Ritsher & Phelan, 2004).

There is also evidence that schizophrenia patients report more uncontrollable life events (Horan et al., 2005), and such uncontrollable stressors may be linked to an increased risk for schizophrenia. Frenkel and colleagues (1995), for instance, showed that adolescents who attribute negative events to external, uncontrollable causes are more likely to develop schizophrenia later in life.

Summary and Hypotheses

Given previous findings suggesting that psychosocial stressors vary in their effectiveness in triggering cortisol reactivity, it is important to consider different stressor attributes when evaluating stress-symptom relationships in schizophrenia. Based on clear demonstrations of increases in cortisol reactivity to social evaluative threat and uncontrollable stressors in healthy individuals and the hypothesized role of cortisol in the course of schizophrenia, it appears likely that these stressor domains are closely linked to elevated positive, negative, and depressive symptoms in schizophrenia patients. Thus, Study 1 examined the frequency with which schizophrenia patients experience social evaluative and uncontrollable life stress in addition to the previously established domains of stressor independence and magnitude. Another primary aim of the study was to assess the degree to which episodic and chronic social evaluative stressors are associated with positive, negative, and depressive symptoms in schizophrenia patients. Based on prior research indicating that cortisol is also associated with depressive symptoms in healthy individuals (Pruessner et al., 2003), the relationship between these domains

of life stress and depressive symptoms was also examined within the healthy comparison subject group.

Hypothesis 1a: Frequency of stressors characterized by social evaluative threat and uncontrollability. Given that the stigma associated with schizophrenia or an undesirable social status position may operate to increase the frequency of social evaluative threat experiences, it was hypothesized that patients would report more uncontrollable and socially evaluative episodic life events as well as chronic social stress relative to healthy comparison subjects.

Hypothesis 1b: Relationships between episodic stressors characterized by social evaluative threat and uncontrollability and clinical symptom levels in schizophrenia patients. Within the patient group, it was hypothesized that stronger positive associations would be found between clinical symptoms and episodic stressors with uncontrollable and social-evaluative content relative to other categories of stressful life events. Because increased cortisol levels have been associated with positive, negative, and depressive symptoms, all three symptom domains were predicted to be elevated following social evaluative and uncontrollable stressors.

Hypothesis 1c: Relationships between interpersonal chronic stress and clinical symptoms in schizophrenia patients. It was also expected that there would be stronger positive relationships between the interpersonal chronic stress domains and clinical symptoms (i.e., positive, negative, and depressive) relative to the non-interpersonal domains of chronic stress.

Hypothesis 1d: Relationships between social evaluative stress and depressive symptoms in healthy individuals. Given that cortisol is positively correlated with depressive symptoms in healthy individuals, it was hypothesized that healthy comparison subjects would display stronger relationships between acute and chronic social evaluative stressors with depressive symptoms relative to the other stressor domains.

Study 2: Patient Characteristics that Influence Stress-Symptom Relationships

In addition to specific stressor attributes, characteristics of the patient may differentiate those more likely to show elevated symptom levels following life stress. According to the neural-diathesis stress model of schizophrenia (Walker & Diforio, 1997; Walker et al., 2008), the strength of the association between the constitutional diathesis and symptom expression in patients may vary as a function of the level of cortisol activation to life stressors. Thus, schizophrenia patients characterized by individual difference factors that amplify the impact of daily stressors and heighten cortisol reactivity might be at greater risk for increased symptom expression following life stress.

There is substantial research indicating that trait affect, coping style, early life adversity, and genetic variation all exert a considerable impact on the cortisol response in healthy individuals. To date, however, only a handful of studies have investigated such potential moderators of stress reactivity in patients with schizophrenia. Thus, Study 2 was designed to extend these basic research findings to schizophrenia and to examine whether enduring psychosocial and genetic factors might moderate stress-symptom relationships in schizophrenia.

Trait Affect

One individual difference factor that appears to play a potent role in moderating the stress response is trait affect. As noted by Horan and colleagues (2008), affective traits represent stable individual differences in the tendency to experience emotional states. By influencing how individuals orient and appraise external events, these traits have the potential to affect physiological responses. Specifically, different trait-like emotional styles might alter amygdala activation to external stimuli (Etkin et al., 2004), which in turn, may influence cortisol reactivity

via connections between amygdala nuclei and the hypothalamus (Frankel et al., 1978; Ghashghaei & Barbas, 2002; Herman et al., 2003; Risold et al., 1997; Saphier & Feldman, 1986).

Basic behavioral research has commonly conceptualized trait affect as reflecting two domains: negative affect (NA) and positive affect (PA). While NA is associated with an increased likelihood of experiencing intense, aversive or distressing emotional states (Watson & Clark, 1984), PA refers to an orthogonal dimension of trait affect reflecting the dispositional tendency to experience positive or rewarding emotional states. In addition to moderating stress-mood relationships (Bolger & Schilling, 1991), trait affect appears to be associated with daily cortisol concentrations in healthy individuals (Polk, Cohen, Doyle, Skoner, & Kirschbaum, 2005). Specifically, high levels of trait NA in males were associated with higher daily cortisol output while low levels of PA were related to a relatively high but flat diurnal cortisol profile. Women scoring high in trait PA, however, exhibited reduced cortisol output throughout the day. Furthermore, Steptoe and colleagues have reported inverse associations between trait positive affect and cortisol concentrations throughout the day (Steptoe, Wardle, & Marmot, 2005; Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008). The influence of trait affect on cortisol reactivity has also been investigated using laboratory stressors. Results of a meta-analysis suggest that positive psychological traits (e.g., happiness, positive mood, etc.) are associated with reduced cortisol reactivity to laboratory-induced stressors (Chida & Hamer, 2008). Moreover, a recent study by Bostock and colleagues (2012) demonstrated that trait positive affect was associated with a lower cortisol response to a laboratory stress task. In contrast, trait NA has been associated with greater activation of the cortisol response to a laboratory psychosocial stressor in healthy individuals (Habra, Linden, Anderson, & Weinberg, 2003).

Trait Affect in Schizophrenia. Although previous studies examining state changes in emotional reactivity suggest that patients with schizophrenia experience positive and negative emotions in a manner similar to that of healthy individuals (Kring et al., 2008; Yee et al., 2010), it appears that patients display abnormalities in trait emotional reactivity. In a review by Horan, Blanchard, Clark, and Green (2008), it was shown that across international samples, schizophrenia patients are generally characterized by elevated levels of trait NA and lower levels of trait PA across different dependent measures. Furthermore, when comparing patient groups to healthy individuals, the effect sizes were large for NA and medium to large for PA. This pattern of high NA and low PA in schizophrenia patients also appears to remain across changes in symptom status as well as different phases of illness (Blanchard et al., 2001). Moreover, a pattern of high NA and low PA can be found in the healthy biological relatives of schizophrenia probands, suggesting that these affective disturbances are not primarily consequences of developing the illness (Horan et al., 2008). Yet, despite these overall group findings, Horan and colleagues (2008) highlight the large amount of variability in trait affect among individuals with schizophrenia.

There is also evidence that trait emotional reactivity is an important moderator of stress reactivity in schizophrenia. In examining the influence of trait affect on the subjective stress response to a laboratory stressor, Horan and Blanchard (2003) found that chronic patients with higher levels of trait NA reported more negative mood following an interpersonal stressor relative to those with low trait NA. Additionally, higher levels of trait NA have been associated with increased exposure to negative dependent life events in patients (Horan et al., 2005). The association between trait affect and stressful life events exposure may also extend to PA. Horan and colleagues (2008) speculate that patients low on PA may exhibit diminished emotional

expressivity and engagement during social exchanges and, therefore, may be more likely to experience social rejection from others. However, empirical studies examining such an association between trait PA and social evaluative stress have yet to be conducted.

In sum, it appears that schizophrenia patients are generally characterized by a pattern of affective traits that may increase the frequency or amplify the effects of negative psychosocial stressors. Given that these affective traits have been related to heightened cortisol output in healthy individuals, it was presumed that trait affect would also play a significant role in influencing stress-symptom relationships in schizophrenia patients.

Coping Styles

Another individual difference factor that likely influences patients' vulnerability to stress is their use of different coping styles. As conceptualized by Lazarus and Folkman (1984), coping is the process of attempting to manage the internal and external demands of stressful situations that are appraised as taxing or exceeding personal resources. Although there are a variety of frameworks for examining coping styles, two approaches have commonly been used in the schizophrenia literature. The first approach examines the degree to which individuals engage in problem-focused coping (e.g., attempting to resolve the stressful situation causing the distress) or emotion-focused coping (e.g., attempting to reduce emotional distress evoked by the stressor; Lazarus & Folkman, 1984). The second approach investigates whether the individual approaches or avoids the stressful event (i.e., approach versus avoidance coping; Suls & Fletcher, 1985). Examples of coping through avoidance would be emotional, cognitive, or behavioral strategies that lead the individual away from the stressor (e.g., withdrawal, distraction). Conversely, approach-oriented strategies attempt to directly change the nature of the stressor or how one responds to it (e.g., problem solving, seeking social support; Taylor & Stanton, 2007).

In addition to influencing a variety of mental health outcomes (for a review, see Taylor & Stanton, 2007), the manner in which individuals regulate their behaviors, cognitions, and emotions can have implications for physiological reactivity to real-life and laboratory stressors (Gross & Levenson, 1997). Upon contrasting the effects of approach versus avoidant coping in healthy individuals, Arnetz and colleagues (1991) found that cortisol responses to unemployment stress were amplified by an avoidant style and reduced by direct or problem focused coping styles. Similarly, research indicates that among individuals undergoing knee surgery, avoidant coping (e.g., behavioral disengagement, substance use, denial, self-distraction) was positively associated with cortisol activity measured one hour before surgery (Rosenberger, Ickovics, Epel, D'Entermont, & Jokl, 2004). O'Donnell and colleagues (2008) have also examined coping styles in relation to daily cortisol output and found that coping by seeking social support and problem engagement (e.g., planning and positive reframing) were related to lower cortisol output throughout the day. In response to a laboratory stressor, Bohnen, Nicolson, Sulon, and Jolles (1991) observed attenuation in cortisol reactivity through the use of an emotion-focused coping style that reframes the adverse situation in a positive and self-encouraging manner; furthermore, there tended to be an inverse relationship between the coping style "seeking social support" and cortisol reactivity.

Coping Styles in Schizophrenia. When examining coping styles in schizophrenia patients, research suggests that individuals with schizophrenia often demonstrate significant difficulty coping with life stressors (Corrigan & Toomey, 1995). A recent review of the coping literature in schizophrenia indicates that patients tend to display a diminished ability to actively cope with life stressors and show a preference for avoidant coping styles relative to healthy individuals (Phillips, Francey, Edwards, & McMurray, 2009). Investigations examining the

frequency of emotion versus problem-focused coping styles in patients, however, have provided less consistent results (Phillips et al., 2009). In addition to reporting overall group findings, a number of empirical studies state that there is considerable variability in the types of coping styles used by schizophrenia patients to handle stressful life events (Ventura, Nuechterlein, Subotnik, Green, & Gitlin, 2004). Moreover, coping styles may change over the course of the illness although such a possibility has not always been supported in the literature. Some studies suggest that chronic schizophrenia patients engage in more coping styles relative to earlier phases of the illness (Thurm & Haefner, 1987) while other research has failed to find an effect of duration of illness on coping styles (Carter et al., 1996).

In addition to measuring the types and frequency of coping styles employed by schizophrenia patients, a limited number of studies have examined the influence of coping on stress reactivity. In a sample of chronic schizophrenia patients, Hultman, Wieselgren, and Ohman (1997) reported that patients characterized by a social-oriented coping style had lower rates of relapse after the experience of a stressful life event. More recently, Horan and Blanchard (2003) examined the influence of coping styles on subjective emotional responses to a psychosocial stressor in first-episode schizophrenia patients. Results from this study indicated that patients who reported using more maladaptive coping styles (i.e., denial, mental and behavioral disengagement) also reported experiencing greater negative mood after the interpersonal stressor.

Taken together, it appears that the examination of coping styles may help explain the substantial heterogeneity in stress-symptom relationships among patients with schizophrenia. Given that different coping styles can alter cortisol activity in healthy individuals, the manner in

which a patient copes with life stressors may promote physiological changes that ultimately lead to the expression of psychotic symptoms.

Early Life Adversity

Another critical factor that may heighten sensitivity to current life stress in patients with schizophrenia is the experience of early life adversity. Risky families characterized by either cold and unaffectionate, conflict-ridden, or neglectful parenting can produce deficits in the control and expression of emotions as well as social competence in youth, that ultimately may exacerbate or produce disturbances in the physiological stress response (Repetti, Taylor, & Seeman, 2002; Taylor, Lerner, Sage, Lehman, & Seeman, 2004, Taylor, Karlamangla, Friedman, & Seeman, 2011). There is also evidence to suggest that constant or recurrent exposure to early life adversity may lead to alterations in a variety of physiological profiles, such as cortisol reactivity and dopaminergic functioning.

Regarding the cortisol response, converging evidence from animal research suggests that adverse childhood experiences can lead to permanent alterations in the HPA axis. Given that the HPA system is not fully mature at birth and that developing brain circuits are shaped by early experience (Gunnar & Vazquez, 2006), early life adversity can greatly impact the development, basal rhythms, and reactivity of the HPA axis (Tarullo & Gunnar, 2006). Findings from rodent and primate models suggest that adverse experiences are associated with long-term changes in cortisol reactivity, brain development, and emotional and behavioral regulation (Nemeroff, 2004; Sanchez et al., 2001). For example, infant rat pups that receive warm maternal care following a brief separation from their mothers have more hippocampal glucocorticoid receptors and less glucocorticoid secretion during a stressor relative to pups receiving lower levels of maternal care (Caldji et al., 1998; Liu et al., 1997; Francis, Diorio, Liu, & Meaney, 1999). Hyper-reactivity of

the HPA axis also appears to extend to later in life, as heightened responses to stress have been observed in adult nonhuman primates raised by mothers who are psychologically unavailable (Rosenblum et al., 1994).

Previous research on childhood maltreatment in humans has also examined different aspects of early rearing experiences and their impact on cortisol release. Child abuse appears to be associated with disrupted HPA axis activity, with a variety of atypical cortisol patterns depending on the type of transgression (e.g., sexual, physical, emotional abuse, and neglect) or a combination of multiple forms (Cicchetti & Rogosch, 2001). When examining families characterized by physical abuse, Hart, Gunnar, and Cicchetti (1996) found that children who had been abused exhibited elevated afternoon cortisol concentrations relative to non-maltreated children. Similarly, Flinn and England (1995) reported that family conflict during childhood was associated with abnormal patterns of cortisol release, including chronically-elevated cortisol or low basal cortisol levels with unusually high spikes in response to conflict. Regarding parental loss, children who experienced permanent or long-term separation from parents or parental death demonstrated elevations in resting cortisol levels (Flinn et al., 1996; Pfeffer et al., 2007). Previous research has also examined the moderating influence of early life adversity on cortisol reactivity to laboratory stressors. Gunnar and Donzella (2002), for example, reported findings of higher cortisol reactivity to stressors in children with poor caregiving and insecure attachment relationships. Chorpita and Barlow (1998) have also shown that children raised by families characterized by low levels of warmth and high levels of social control displayed hypercortisolism in response to stress.

Lastly, there is data to suggest that early life adversity sensitizes the cortisol response to stressors experienced during adulthood (Liu et al., 1997; Nemeroff, 2004). Specifically, adults

who describe poor family relationships earlier in life exhibit greater cortisol responses to a laboratory stressor relative to individuals with less adversity earlier in life (Luecken et al., 1998). Cortisol dysregulation has also been found in adult men who experienced a parental death in childhood and subsequently displayed higher cortisol levels relative to control subjects who did not experience a loss (Nicolson, 2004).

In addition to extensive research highlighting the effects of adverse childhood experiences on cortisol, early life adversity can produce disturbances within the DA system. Findings from animal studies suggest that early social isolation and maternal deprivation are associated with alterations in DA concentrations in the nucleus accumbens and with DA receptor sensitivity (Lewis et al., 1990; Kehoe, Shoemaker, Arons, Triano, & Suresh, 1998). Furthermore, there is evidence to indicate that early adversity can reprogram the rodent brain to release more DA in the nucleus accumbens following stress (Cabib et al., 2002). More recently, studies have investigated the moderating effect of early life adversity on the dopamine response to stress in healthy individuals using PET methodology. Pruessner, Champagne, Meaney, and Dagher (2004) observed that healthy individuals reporting low parental care displayed heightened levels of DA release in the ventral striatum following a psychosocial stressor.

Early Life Adversity in Schizophrenia. Recent reviews evaluating retrospective and prospective studies of early life adversity in schizophrenia are suggestive of a link between early childhood stressors and increased risk for psychosis in adulthood (Read et al., 2005; Bendall et al., 2008; Fisher et al., 2011). This relationship appears to be dose-dependent and remains after controlling for a variety of potential confounds (Janssen et al., 2004). When examining the childhood family characteristics of patients who later developed schizophrenia, evidence of conflict, parental neglect or loss, and low levels of parental care have been found (Parker et al.,

1982). Regarding conflict, prior research suggests that the childhood environments of many schizophrenia patients are characterized by elevated levels of parental violence, hostility, and criticism (Bebbington et al., 2004; Heads, Taylor, & Leese, 1997; Honig et al., 1998).

Schizophrenia patients also report a fourfold increase in parental loss as compared to controls (Agid et al., 1999) and reduced levels of parental care (Parker et al., 1982). Heightened levels of neglect during childhood have also been demonstrated. Results from a 30-year prospective study indicated that 35% of adult schizophrenia patients were removed from their homes during childhood due to neglect, which was twice the level of neglect recorded from other diagnostic groups in the study (Robins, 1966). Adoption studies further highlight the importance of the family context, as high-risk children are more likely to develop schizophrenia if they are raised by adoptive families that are characterized as “dysfunctional” (Tienari et al., 1991) or show “communication deviance” (Wahlberg et al., 1997). Lastly, there is evidence to suggest that greater levels of childhood adversity are associated with more frequent relapses in schizophrenia patients during the chronic phase of illness (Goff, Brotman, Kindlon, Waites, & Amico, 1991).

Taken together, there is substantial evidence to indicate that schizophrenia patients experience more early life adversity relative to healthy individuals. Although no studies have explicitly examined the moderating role of early life adversity on stress-symptom relationships in schizophrenia, there is strong biological evidence to suggest that early life adversity can lead to the development of an overactive subcortical dopamine system and an exaggerated cortisol response. Thus, this neurobiological response profile may render schizophrenia patients characterized by early life adversity at greater risk for exhibiting elevations in clinical symptom levels following the experience of adult psychosocial stress.

Catechol-*O*-methyltransferase (COMT) polymorphism

In addition to psychosocial factors, certain biological factors might also influence an individual's vulnerability to stress. One particular genetic variant that has received much attention in the research literatures on stress reactivity and on schizophrenia is the catechol-*O*-methyltransferase *Val*¹⁵⁸*Met* (COMT) polymorphism. COMT is a functional polymorphism of the catechol-*O*-methyltransferase gene, which codes for an enzyme that degrades catecholamines, such as dopamine. COMT results in a change from the amino acid, Valine (*Val*) to Methionine (*Met*), which reduces the enzyme's activity. Chen and colleagues (2004) reported that individuals with the *Val/Val* genotype have a 40% higher enzyme activity rate than individuals with the *Met/Met* genotype, with heterozygotes (i.e., *Val/Met* genotype) demonstrating intermediate activity. The COMT enzyme plays a particularly crucial role in the regulation of DA in the prefrontal cortex (PFC) as there are fewer DA transporters in this region (Lewis et al., 2001). Based on this pattern of COMT activity, individuals with the *Val* allele have lower prefrontal extracellular DA compared with those with the *Met* allele (Chen et al., 2004).

A recent meta-analysis indicates that the COMT polymorphism has a pleiotropic effect on cognition, emotion, and behavior (Mier, Kirsch, & Meyer-Lindenberg, 2010). Following the Warrior/Worrier model of COMT (Stein et al., 2006), the *Val* allele appears to be a risk factor for cognitive dysfunction but a protective factor in stressful situations (warrior) while the *Met* allele reflects enhanced performance on cognitive tasks but results in exaggerated reactivity to aversive stimuli (worrier). This pattern of activity has been supported in animal models examining the effects of experimentally induced COMT activity on a range of cognitive and stressful tasks (Papaleo et al., 2008). When extending this research to humans, there is evidence that the *Val* allele is associated with worse cognitive performance (Bearden et al., 2004; Meyer-Lindenberg

et al., 2005) especially on working memory tasks, while the *Met* allele is associated with heightened responsivity to aversive stimuli when assessed by functional magnetic resonance imaging (fMRI). For example, Smolka and colleagues (2005) reported that the *Met* allele was associated with increased reactivity of the limbic system (e.g., amygdala) to emotionally unpleasant stimuli, with no genotype effect for pleasant stimuli. Similarly, Drabant and colleagues (2006) found increased corticolimbic activation during the viewing of negative faces in individuals homozygous for the *Met* allele.

Of particular relevance to schizophrenia, previous research has also investigated the influence of COMT on the cortisol response as well as striatal activity. In a study examining longitudinal changes in cortisol among healthy and at-risk individuals, the *Met/Met* genotype was associated with a greater increase in mean cortisol level over a 1-year period as compared to the individuals with the *Val/Met* or *Val/Val* genotypes (Walder et al., 2010). Using a laboratory psychosocial stressor, Jabbi and colleagues (2007) found that healthy individuals homozygous for the *Met* allele exhibited larger cortisol and subjective stress responses to the stressor relative to *Val* carriers. Oswald and colleagues (2004) also examined the influence of COMT on HPA axis activity in response to the opioid receptor antagonist, naloxone, and found cortisol responses were greater for the participants with the *Met/Met* genotype as compared to the group consisting of individuals with *Met/Val* or *Val/Val* genotypes. Lastly, Schmack and colleagues (2008) reported that individuals homozygous for the *Met* allele had greater ventral striatal reactivity to the anticipation of monetary loss, but not gain, relative to the *Val* allele carriers.

Although there is accumulating evidence to suggest that the *Met* allele might increase emotional reactivity to negatively valenced stimuli, the mechanisms underlying this effect remain to be elucidated. One potential pathway appears to involve the functioning of the PFC,

given its significant role in modulating the amygdala response to aversive stimuli (Hariri et al., 2000; 2003; Nomura et al., 2003). Furthermore, COMT is an important determinant of DA neurotransmission, which has been shown to be critical for cognitive processing in the PFC (Mattay et al., 2003).

It is not entirely clear, however, how DA release impacts PFC efficiency. One theory suggests that cortical DA levels are related to PFC efficiency through an inverted U-shaped dose response curve, where too little and too much dopamine exert deleterious effects on cognition (Mattay et al., 2003; Vijayraghavan et al., 2007). Thus, COMT may impact prefrontal cognitive processing by placing individuals at specific points along this curve. Specifically, it is posited that individuals who are homozygous for the *Val* allele are placed to the left of *Met* allele carriers who are believed to be at the peak of the inverted U-shaped curve with high levels of DA release in the PFC. During baseline conditions, placement at the peak of the curve allows *Met* allele carriers to perform better at cognitive tasks. However, under conditions of increased DA release, *Val* allele individuals continue to move up the curve to a more optimal level and improve their prefrontal efficiency while individuals with the *Met* allele genotype move beyond the optimal peak of the U-shaped curve and demonstrate worse prefrontal cognitive performance (Mattay et al., 2003). In turn, such prefrontal inefficiency may make it difficult to down-regulate amygdala responses, further sustaining heightened levels of emotional reactivity. Ultimately, an over-activated amygdala response can lead to increases in the HPA axis given connections between the amygdala and the hypothalamus (Ghashghaei & Barbas, 2002; Herman et al., 2003; Risold et al., 1997; Saphier & Feldman, 1986).

To provide support for this model of PFC inefficiency, Mattay and colleagues (2003) examined the influence of increased DA on prefrontal cortical function in healthy individuals by

administering amphetamine prior to a working memory task. According to results from animal studies, higher working memory loads lead to increases in DA release in the PFC (Floresco & Phillips, 2001), and thus, can further affect an individual's placement on the U-shaped curve. Results from this study confirmed the U-shaped hypothesis, such that amphetamine-induced DA release enhanced the efficiency of the PFC in individuals with the *Val/Val* genotype at all levels of task difficulty. In participants with the *Met/Met* genotype, amphetamine caused deterioration in prefrontal functioning during the high working memory load condition (Mattay et al., 2003). Thus, it appears that prefrontal efficiency greatly depends on the cognitive demands of the environment, with more demanding situations leading to improved efficiency in the *Val* allele carriers and inefficiency in the *Met/Met* genotype.

COMT and Psychosis. Although recent meta-analyses examining the association between COMT and schizophrenia have revealed minimal to no effects (Fan et al., 2005; Munafo et al., 2005), there is increasing evidence to suggest that COMT may produce larger effects when examined from a gene-environment perspective. Similar to results of research conducted with healthy individuals, the *Met* allele appears to increase stress sensitivity in schizophrenia. Specifically, van Winkel and colleagues (2008) examined the influence of COMT on the relationship between stress and psychotic symptoms in a sample of schizophrenia patients. Using experience sampling methodology, the authors found that patients with the *Met/Met* genotype reported more negative affect and psychotic experiences following daily life stress relative to the *Val* allele carriers. Similarly, Collip and colleagues (2011) reported that patients homozygous for the *Met* allele showed significantly increased psychotic symptoms and negative affect to daily life stress relative to patients with *Val/Met* and *Val/Val* genotypes. Furthermore, there is evidence to suggest that the *Met* allele may be associated with a worse clinical course

among individuals with schizophrenia, given that individuals genotyped with the *Met* allele exhibit greater severity of symptoms and more frequent hospitalizations (Herken & Erdal, 2001).

Although the biological mechanisms by which the *Met* allele can increase stress-sensitivity in schizophrenia patients remain to be elucidated, findings from healthy individuals as described above provide possible pathways that are consistent with the neural-diathesis stress model (Walker & Diforio, 1997; Walker et al., 2008). For example, using the inverted U-shaped curve model (Mattay et al., 2003), the processing of a challenging stressor would cause the *Met* allele's placement to be shifted to the right of the optimal peak, ultimately resulting in decreased prefrontal efficiency and a heightened amygdala and cortisol response. Furthermore, elevations in psychotic symptoms might stem directly from heightened striatal activity given previous findings demonstrating increased ventral striatal reactivity to the anticipation of loss in *Met/Met* homozygotes (Schmack et al., 2008).

Despite accumulating evidence to suggest that the *Met* allele is associated with greater psychotic symptom elevations following life stress, this effect has not always been replicated. In particular, research investigating the role of COMT on stress-induced psychotic reactions in healthy individuals has shown that *Val* allele carriers are particularly sensitive to life stressors. In a study of males undergoing mandatory military training, Stefanis and colleagues (2007) found that *Val* allele carriers showed greater increases in "paranoid ideation" and "psychoticism" following the stress associated with entering the military as compared to those with the *Met/Met* genotype. Furthermore, in a general population sample of female twins, it was reported that individuals homozygous for the *Val* allele displayed more feelings of paranoia in response to event-related stress relative to the *Met* allele carriers (Simons et al., 2008). It should also be noted that past research has suggested that the *Val* allele places individuals at greater risk for the

development of schizophrenia (Li et al., 1996, 2000; Kunugi et al., 1997; Egan et al., 2001). For example, according to the DA hypothesis proposed by Weinberger and colleagues (2001), schizophrenia patients are characterized by a brain pattern of hypodopaminergic activity in the PFC and hyper-activation of DA in subcortical regions, which closely parallels the DA response observed in carriers of the *Val* allele.

Overall, it appears that despite the well-documented effect that the *Met* allele increases stress and emotional reactivity in healthy individuals, the role that COMT plays in moderating stress-symptom relationships in schizophrenia is less clear. Although preliminary data suggest that the *Met* allele may be more potent in eliciting symptom elevations following life stress for patients, the *Val* allele appears to place individuals in the general population at greater risk for psychotic symptomatology. Thus, further research examining the specific influence of COMT on stress-symptom relationships and the biological mechanisms underlying these relationships is greatly warranted.

Summary and Hypotheses

Consistent with the neural-diathesis stress model of schizophrenia (Walker & Diforio, 1997; Walker et al., 2008), it appears that patients characterized by psychosocial and genetic factors that heighten cortisol reactivity and DA subcortical dysfunction will more likely exhibit elevated clinical symptom levels following the experience of life stressors. Thus, Study 2 extended findings from basic behavioral research to the schizophrenia population and examined the moderating effects of these factors on stress-symptom relationships in patients. Furthermore, Study 2 focused primarily on the relationships between social evaluative episodic stressors and interpersonal chronic stress with clinical symptoms, given research associated with Study 1 demonstrating that these stressor attributes elicit the greatest cortisol response. The degree to

which these variables moderated the relationship between life stress and depressive symptoms within the healthy normal comparison subject group was also explored.

Hypothesis 2a: Group differences in psychosocial vulnerability. It was hypothesized that schizophrenia patients would display more avoidant and less approach-oriented coping styles, heightened levels of trait negative affect and lower levels of trait positive affect, and greater levels of early life adversity relative to healthy comparison subjects.

Hypothesis 2b: The influence of psychosocial vulnerability on stress-symptom relationships in schizophrenia patients. Within the patient group, it was predicted that there would be stronger associations between social evaluative episodic stress and clinical symptom levels in patients characterized by greater psychosocial vulnerability (i.e., greater maladaptive coping, less adaptive coping, greater trait negative affect, less trait positive affect, more early life adversity) as compared to patients with more protective/resilient traits. Similar effects were also hypothesized when examining the moderating influence of these variables on the relationships between interpersonal chronic stress and clinical symptoms.

Hypothesis 2c: Genetic vulnerability as a moderator of the relationship between life stress and clinical symptoms in schizophrenia patients. Based on research indicating that carriers of the *Met* allele of the COMT^{Val158Met} polymorphism demonstrate greater biological stress reactivity to aversive stimuli, it was hypothesized that there would be positive associations between episodic and chronic social evaluative stress with clinical symptoms for carriers of the *Met* allele; however, no associations would be found for individuals homozygous for the *Val* allele.

Hypothesis 2d: The influence of psychosocial and genetic vulnerability on stress-symptom relationships in healthy individuals. Similar to schizophrenia patients, it was

hypothesized that there would be stronger relationships between social evaluative stress and depressive symptoms in healthy normal comparison subjects who were carriers of the *Met* allele and who were characterized by more psychosocial vulnerability.

Study 3: Biological Mechanisms Underlying Stress-Symptom Relationships

Although a large body of research has examined both the behavioral and biological aspects of stress reactivity in schizophrenia, much of this research has been conducted independently. Thus, Study 3 aimed to synthesize these two levels of analyses and elucidate the biological mechanisms by which life stressors lead to elevated clinical symptom levels in schizophrenia. Specifically, Study 3 investigated the role of cortisol by examining whether the individual difference factors that increased patients' vulnerability to social evaluative stress as identified in Study 2 also increased the magnitude of the cortisol response to a laboratory psychosocial stressor. Given the evidence outlined in Study 1, the influence of these variables on cortisol reactivity was investigated using a standard laboratory stressor, the Trier Social Stress Test (TSST; Kirschbaum et al., 2003) which is characterized by both social evaluative threat and uncontrollable elements.

As stated previously, a variety of individual difference factors can influence cortisol reactivity in healthy individuals. While avoidant coping styles tend to increase the cortisol response, approach-oriented coping styles attenuate cortisol output (e.g., Arnetz et al., 1991). Cortisol levels also appear to be enhanced by heightened amounts of trait NA in males and reduced by high trait PA in females (Polk et al., 2005). Furthermore, given its role in the development of the HPA axis, early life adversity can also enhance cortisol reactivity later in life (e.g., Lueken et al., 1998). Lastly, there is evidence that specific genetic variants, such as the

Met allele of the COMT^{Val158Met} polymorphism, increase physiological reactivity to aversive stimuli (e.g., Jabbi et al., 2007; Smolka et al., 2005).

Although no studies to date have explicitly examined the influence of these characteristics on cortisol reactivity in schizophrenia patients, there is behavioral evidence to suggest that these domains are important to consider. For example, in addition to reporting higher levels of trait NA and lower levels of trait PA, schizophrenia patients characterized by higher trait NA show greater subjective stress responses to a laboratory social stressor. Furthermore, patients characterized by more maladaptive coping styles also report greater increases in negative mood following an interpersonal stressor (e.g., Horan & Blanchard, 2003). Regarding early life adversity, patients with schizophrenia tend to experience heightened levels of childhood stressors that are associated with greater relapse rates (e.g., Goff et al., 1991). Lastly, the *Met* allele of COMT appears to place schizophrenia patients at greater risk for experiencing psychotic symptoms following daily life stress (e.g., van Winkel et al., 2008).

Summary and Hypotheses

Study 3 attempted to bridge the gap between biological and behavioral research by examining whether the cortisol response serves as a potential mechanism through which life stress contributes to illness expression in schizophrenia. Specifically, this study tested whether the individual difference factors found to amplify clinical symptom levels following social evaluative stress in Study 2 also increased cortisol levels in response to a social evaluative and uncontrollable stressor (Study 1). The relationships between individual difference factors and the cortisol response were also examined within the healthy individual group.

Hypothesis 3a: Psychosocial vulnerability would influence the cortisol response to a psychosocial stressor. It was predicted that schizophrenia patients characterized by greater

psychosocial vulnerability (i.e., greater maladaptive coping, less adaptive coping, greater trait negative affect, less trait positive affect, more early life adversity) would exhibit heightened cortisol reactivity to the laboratory stressor as compared to patients with more protective or resilient traits.

Hypothesis 3b: The influence of genetic vulnerability on the cortisol response to a psychosocial stressor in schizophrenia patients. Based on prior research indicating that carriers of the *Met* allele of the COMT^{Val158Met} polymorphism demonstrate greater biological stress reactivity to aversive stimuli, it was hypothesized that carriers of the *Met* allele would display increased cortisol responses to the laboratory psychosocial stressor relative to patients homozygous for the *Val* allele.

Hypothesis 3b: The influence of psychosocial and genetic vulnerability on the cortisol response to a psychosocial stressor in healthy individuals. Similar to schizophrenia patients, it was predicted that healthy individuals who were carriers of the *Met* allele and who were characterized by more psychosocial vulnerability would show greater cortisol reactivity to the psychosocial stress task.

Method

Participants

A total of 125 schizophrenia patients (76 first-episode and 49 chronic) and 95 healthy comparison subjects were included in the present research. Their data were obtained as part of an ongoing project examining emotion and stress reactivity (PI: C. Yee-Bradbury) within the NIMH-funded Center for Neurocognition and Emotion in Schizophrenia (PI: K. Nuechterlein).

First-episode schizophrenia patients were recruited from the UCLA Aftercare Research Program. All first-episode schizophrenia patients met Diagnostic and Statistical Manual of

Mental Disorders criteria (First et al., 1995; Ventura et al., 1998) for schizophrenia, schizophreniform disorder, or schizoaffective disorder and experienced their first psychotic episode within the previous 24 months before testing. The average duration of illness was 1.40 ($SD = .88$) years, and all patients were receiving risperidone. Chronic schizophrenia patients were former participants of the UCLA Aftercare Research Program. These patients met DSM-IV criteria for schizophrenia or schizoaffective disorder, with their first psychotic episode occurring at least five years prior to participation in the study. The chronic schizophrenia patients had an average duration of illness of 9.96 ($SD = 4.98$) years. The type of antipsychotic medication varied although chronic patients treated with first-generation antipsychotic medications were excluded from the present study. Any first-episode or chronic schizophrenia patient with a history of a known neurological disorder, significant alcohol/substance abuse within the past 6 months, or mental retardation were excluded from participation.

Healthy normal comparison subjects were recruited through flyers and advertisements posted at community sites and in local newspapers. The normal comparison group consisted of 43 older and 52 younger adults matched to the first-episode and chronic schizophrenia patients in age, gender, handedness, and parental educational level (see Table 1). Exclusion criteria included a personal history of a schizophrenia-spectrum disorder, bipolar disorder, recurrent major depression, obsessive-compulsive disorder, neurological disorder, significant head injury, alcohol/substance dependency, and/or presence of a psychotic disorder among first-degree relatives. All participants provided informed consent after receiving oral and written information describing the study.

Measures

Assessment of life stress. The UCLA Life Stress Interview (Hammen, 1987) was utilized to assess chronic stress levels across eight domains of functioning (i.e., best friendships, social circle, romantic relationships, family relationships, school, work, finances, and health) over the preceding six-month period. Using standard probes, each of the domains was discussed with the participant and rated by the interviewer on a scale from 1 (exceptionally good circumstances) to 5 (extremely stressful and maladaptive circumstances). A general chronic stress score was calculated by summing across the eight chronic stress domains, with higher scores representing more chronic stress in the lives of participants. Following previous research (Marin et al., 2007), an interpersonal chronic stress score was obtained by summing across the four interpersonal domains (i.e., best friend, social circle, romantic and family relationships), with higher scores demonstrating more interpersonal distress. A non-interpersonal chronic stress score was also created by summing across the remaining non-interpersonal domains (i.e., school, work, finances, and health). Agreement among the 4 raters, who were all advanced graduate students in clinical psychology, across the chronic stress domains ranged from acceptable to very good: ICC = .88 (best friend), .89 (social circle), .90 (romantic partner), and .80 (family), .96 (school), .71 (work), .78 (finances), .72 (health of self), all p 's < .01.

Episodic life events were also assessed using the UCLA Life Stress Interview. Interviewers gathered information regarding the nature of stressful life events occurring in the past six months and the circumstances surrounding their occurrence. Participants provided subjective stress ratings based on a Likert scale, ranging from 1 (no negative impact) to 5 (extremely negative impact). Following the interview, the same rating scale was used by a team of raters who reached a consensus on an objective stress rating for each reported stressful life

event. The objective stress ratings were based on how much impact an event would have for a typical person under the same conditions, ignoring any information regarding the individual's subjective perception of the event. Raters were blind to diagnostic information.

Stressful life events were coded for social evaluative threat and uncontrollable content using guidelines based on the SSP model and the coding scheme included in the meta-analysis conducted by Dickerson and Kemeny (2004). Based on this coding scheme, the events were separated into one of four stressor categories: 1) social evaluative threat events (SET events), 2) uncontrollable events (UNC events), 3) social evaluative threat and uncontrollable events (COM events), and 4) all life events (ALL events). Events in the social evaluative threat category reflected instances where an important aspect of the self (e.g., trait or ability) could be negatively judged by other people. The uncontrollable category consisted of events where individuals were unable to end the stressor or avoid negative consequences.

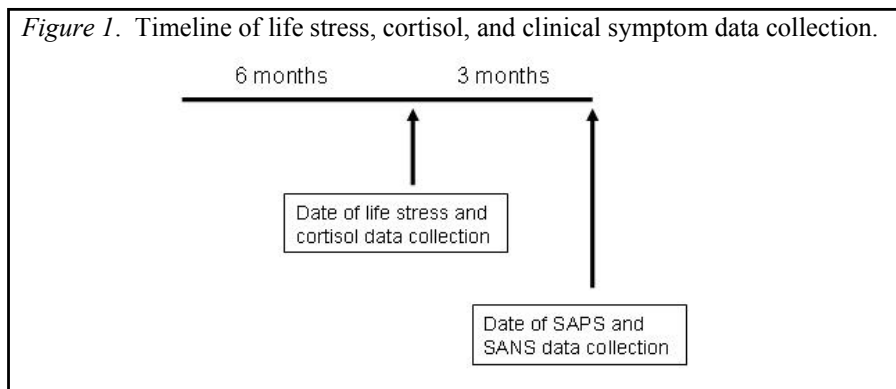
Comment [CY1]: Include specific examples in the methods section rather than here.

Within each stressor category, three episodic life stress measures were calculated for each participant: the number of life events, a sum of the subjective impact ratings, and a sum of the objective impact ratings. Fleiss' kappa was .78 (for social evaluative threat events) and .81 (for uncontrollable events), indicating good agreement between the coders.

Given prior research highlighting the importance of considering the life event's magnitude, independence level, and date of occurrence when examining stress-symptom relationships, these stressor attributes were also assessed. Life events were categorized into these additional stressor domains following established recommendations (Hammen, 1987). For the stressor magnitude criteria, life events that were given an objective impact rating above 3 were considered to be major and life events that were rated a 3 or below were categorized as minor. Regarding independence level, life events were divided into three separate categories

based on a team rating of 1 or 2, for independent life events, 3 for mixed life events, and 4 or 5 for dependent events. Lastly, the date of the event was calculated as the time interval between the life event date and the clinical symptoms assessment date. Events were then placed into 1 of 6 time interval categories (e.g., one-month interval, two-month interval, etc.). The three episodic life stress measures (i.e., number of events, sum of objective impact ratings, sum of subjective impact ratings) were also calculated for the additional stressor categories of magnitude, independence, and time interval.

Assessment of clinical symptoms. The Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984a), and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984b) were administered once every 3 months to the patient participants. The SAPS and SANS data used in the present study were selected to coincide with the date of the UCLA Life Stress Interview and when cortisol data were obtained (see Figure 1). To minimize Type I error, total and global scores from these clinical measures were examined rather than individual symptom ratings. For the SAPS, a total SAPS score was calculated by summing across all of the global subscales: Hallucinations, Delusions, Bizarre Behavior, and Positive Formal Thought Disorder, whereas the global Affective Flattening, Alogia, Avolition/Apathy, Anhedonia/Asociality, and Inattention subscales were summed to form a total SANS score.



Based on previous findings that stressful life events are also implicated in depressive symptomatology in healthy individuals (Pruessner et al., 2003) and schizophrenia patients (Ritsner et al., 2004; Ventura et al., 2000), the Beck Depression Inventory (BDI; Beck & Steer, 1993) was administered on the same day as the Life Stress Interview. The reliability of this measure was acceptable for healthy individuals ($\alpha = .77$) and was good for schizophrenia patients ($\alpha = .86$).

Trait affect and state anxiety. Trait levels of negative and positive affect were assessed through the Positive Affect/Negative Affect Scales (PANAS; Watson et al., 1988). Participants rated the extent to which they generally experience a particular emotion on a scale from 1 (very slightly or not at all) to 5 (extremely). Trait Positive Affect (PA) was calculated by summing across the following emotions: interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, and active. The trait Negative Affect (NA) score was a sum of the emotions: distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, and afraid. Internal consistency reliabilities for the trait NA and PA scales were very good in both the schizophrenia ($\alpha = .89$ and $.91$, respectively) and healthy comparison ($\alpha = .84$ and $.84$, respectively) groups.

The State Trait Anxiety Inventory (STAI; Spielberger & Krasner, 1987) was used to assess state anxiety levels at baseline and after the psychosocial stressor task. The questionnaire consists of 40 items that asks participants to rate the extent to which they experience symptoms of anxiety on a 4-point scale from 1 (not at all) to 4 (very much so). The first 20 items were used to generate a state anxiety score. Coefficient alpha for the state anxiety scores during the baseline and post-psychosocial stressor conditions were very good for schizophrenia patients ($\alpha = .91$ and $.92$, respectively) and healthy individuals ($\alpha = .89$ and $.93$, respectively).

Coping styles. Coping styles were assessed using the Brief COPE (Carver, 1997), an abbreviated version of the COPE Inventory (Carver, Scheier, & Weintraub, 1989). The Brief COPE consists of 14 subscales representing different ways of coping with stressful experiences. Each scale is comprised of two items each, and participants rate how often they rely on each coping style within the past 6-month period. Response options ranged from 0 (I usually do not do this at all) to 3 (I usually do this a lot). To reduce the number of coping variables, three composite scales were selected on the basis of factor analysis and previous research using the COPE and Brief COPE with schizophrenia patients (Blanchard et al., 1999; Horan & Blanchard, 2003; Meyer et al., 2001). For the factor analysis, four factors were specified for extraction using principal axis factoring with Promax rotation. This analysis yielded three factors, which combined to explain 45.65% of the variance of the 28 items.

The first factor yielded an “adaptive” coping style, which was calculated by summing across the following subscales:

1. active coping (i.e., taking action to improve the situation)
2. planning (i.e., devising strategies to improve the situation)
3. positive reframing (i.e., making events seem more positive)
4. acceptance (i.e., learning to live with reality)

The second factor yielded a “maladaptive” coping style, which was derived by summing across the following subscales:

1. denial (i.e., refusing to believe what has happened)
2. venting (i.e., verbally expressing negative feelings)
3. behavioral disengagement (i.e., giving up the attempt to cope)
4. self-blame (i.e., criticizing and blaming oneself)

The third factor yielded a “supportive” coping style, which was calculated by summing across the following subscales:

1. emotional support (i.e., getting comfort or understanding from someone)
2. instrumental support (i.e., getting help and advice from other people)

In the present sample, the factor loadings for the items that loaded onto the “adaptive” coping scale ranged from .41 to .64. Coefficient alpha was acceptable for both healthy individuals and schizophrenia patients with alpha = .70 and .76, respectively. For the “maladaptive” coping scale items, the factor loadings ranged from .33 to .63. Internal consistency was also acceptable for healthy individuals (alpha = .71) and schizophrenia patients (alpha = .77). Lastly, the factor loadings for the items that loaded onto the “supportive” coping scale ranged from .65 to .85, with internal consistency in the good range for both groups (.82 for healthy subjects and .85 for patients).

Early life adversity. The childhood home environment prior to age 15 was assessed using the structured Early Home Environment Interview (EHEI; Lizardi, Klein, & Ouimette, 1995). The EHEI consists of 21 items that are either rated on a yes/no or 3-point rating scale. Specific examples were also elicited from the participant when the interviewer concluded that additional information was needed to substantiate the participant’s ratings. Five primary outcome variables of early life adversity were generated from this interview:

1. loss (i.e., parental death, divorce, or separation from either parent for over six months)
2. physical abuse (i.e., being hit hard or often enough to leave bruises, draw blood, or require medical attention)
3. sexual abuse (i.e., non-voluntary sexual experiences and sexual contact between relatives and the participant)

4. quality of relationship with mother (i.e., time spent with mother, ability to confide in mother, consistency of mother's behavior, feeling loved, criticized, or rejected by mother)
5. quality of relationship with father (i.e., same as #4 but referring to father)

Due to the low prevalence of loss and abusive experiences, items referring to these content areas were scored dichotomously (i.e., presence or absence of abuse and loss). Items related to the quality of relationship with mother were summed together to produce an overall score; the same method was used to generate the overall score for relationship with father. Higher scores indicated a poor quality relationship with a parent.

DNA extraction and genotyping. DNA was isolated from previously collected saliva samples by a commercial vendor (Salimetrics, LLC, State College, PA). Total DNA was isolated from one milliliter of saliva using the QIAmp Blood and Body Fluid protocol described in the QIAmp Blood Kit. Previous research reports that this kit provides a fast, easy, and reproducible method for genomic DNA isolation from saliva samples (van Schie & Wilson, 1997). A similar protocol has also been conducted at the UCLA Biological Samples Processing Core in the Department of Human Genetics, verifying that high quantity and quality DNA can be extracted from our previously collected saliva samples. The COMT^{Val158Met} polymorphism was genotyped using a Taqman SNP Genotyping Assay designed by Applied Biosystems (Applied Biosystems, Foster City, CA, USA). Genotyping was performed using the 7900HT Sequence Detection System according to manufacturer's instructions (Applied Biosystems, Foster City, CA, USA). To ensure the quality of the genotyping, consistent results were required for eight control samples before the proposed study's results were released to the study investigator.

Participants were classified into one of three genotype groups: *Val/Val*, *Val/Met*, and *Met/Met*. For the total sample, the frequencies of the three genotypes were: *Met/Met* = 21, *Met/Val* = 72, and *Val/Val* = 51, which did not deviate from Hardy-Weinberg equilibrium, $\chi^2 (2, N = 144) = .13, p = .94$.

Cortisol assessment. Three saliva samples were obtained using Wheaton Cryule vials to assess cortisol levels. Saliva samples were obtained at baseline, again at approximately 20 minutes after the initiation of the psychosocial stress task, in accordance with when cortisol shows peak increases following a stressor (Dickerson & Kemeny, 2004), as well as 20 minutes following the collection of the second sample. After the samples were collected, they were stored in a freezer at -20 degrees Celsius until batched and shipped on dry-ice overnight to a commercial vendor (Salimetrics, LLC) where they were brought to room temperature and centrifuged at 3,000 RPM for 15 minutes. The clear top-phase of the saliva samples were then pipetted out of the Cryule vials and assayed for salivary cortisol. The test uses 25 μ l of saliva, has a range of sensitivity from .007 to 1.8 μ g/dl, and average intra- and inter-assay coefficients of variation of less than 10% and 15%, respectively (Hibel, Granger, Kivlighan, & Blair, 2006). All samples were assayed in duplicate and the average of the duplicates was used in all analyses.

To maintain the integrity of the cortisol data, participants were instructed to avoid alcohol consumption and dental work during the 24 hours prior to the study. Subject to physician consent, anticholinergic medications were withheld for 48 hours prior to testing. Participants were also told to refrain from exercising and taking non-prescription medications on the day of the study. The experimental sessions were scheduled to avoid school exams on the day of testing and any acute medical illness within the past week. Participants were also instructed to refrain from caffeine consumption, nicotine use, consuming a major meal, dairy products, chips, and

acidic or high sugar foods, and brushing their teeth during the hour before the session. During the session, compliance with these instructions was assessed using a health behavior questionnaire. All test sessions were also scheduled in the mid-afternoon to avoid diurnal variations. Additional factors that have been shown to influence the cortisol response, including age, gender, phase of menstrual cycle, and oral contraceptive use (Kajantie & Phillips, 2006; Kirschbaum et al., 1992b; Kudielka et al., 2004; Seeman et al., 2001; Van Cauter et al., 1996; Wilkins et al., 1982;) were also assessed for further examination.

To calculate cortisol reactivity, the three cortisol values were first log-transformed to correct for non-normality. Two area under the curve (AUC) measures were then derived from these log-transformed cortisol values to quantify the magnitude of the cortisol response to the psychosocial stressor. The AUC is derived from the trapezoid formula, and is often used in endocrinology research to determine the overall secretion of a hormone over any number of measurements (Pruessner, Kirschbaum, Meinlschmind, & Hellhammer, 2003). The two AUC measures that were calculated from the three cortisol time-points were: 1) AUC with respect to ground (AUC_g) which captures total hormone output and 2) AUC with respect to increase (AUC_i) which represents reactivity of the HPA axis.

Procedure

After becoming familiarized with the laboratory equipment and protocols, participants completed the STAI, BDI, trait version of the PANAS, Brief COPE, as well as other self-report measures not included in this study. They were then administered the UCLA Life Stress and EHEI interviews by trained graduate students in clinical psychology. Following tasks unrelated to the present study, saliva was collected to assess resting levels of cortisol. Participants next completed the Trier Social Stress Test (Kirschbaum et al., 1993), which consists of both social

evaluative and uncontrollable elements. After being given 10 minutes to prepare a speech, participants were asked to deliver a 5-minute speech without relying on any notes. After delivering the speech, participants performed a 5-minute series of mental arithmetic tasks involving serial subtraction; they were told to perform quickly and accurately, and they were instructed to restart a series if any errors were made. Both activities were performed while being tape recorded and in the presence of three audience members (males and females) who asked challenging questions, and took notes so as to appear engaged in monitoring and judging the participant's behavior. Immediately following the completion of the stressor, the second saliva sample was obtained and state anxiety levels were assessed. Subjects then completed a variety of health behavior questionnaires for the next 20 minutes before their third saliva sample was collected. Following the last saliva collection, participants were debriefed about the purpose of the present study and compensated for their time.

Results

Data Analysis

Group differences were examined using univariate analyses of variance (ANOVAs) with the Greenhouse-Geisser method to adjust degrees of freedom. Hierarchical linear regression analyses and Pearson correlations along with the Bonferroni-adjusted level of significance were conducted to determine relationships between life stress, individual characteristics, and cortisol data. As reflected in the degrees of freedom, behavioral and clinical data were not always available for all participants due to missing data or procedural constraints. Cortisol data obtained from participants reporting pregnancy or breast feeding, use of steroid-based medications, disorders affecting the neuroendocrine system (e.g., autoimmune disease, cancer, diabetes, etc.), gum disease, oral infection, and night-shift work were also excluded.

Demographic and Clinical Characteristics

Before combining first-episode and chronic schizophrenia patients into a single group to maximize statistical power, the groups were compared on the primary demographic variables. As might be expected, patients in the chronic phase were significantly older ($M = 34.80$, $SD = 7.99$) than those in their first-episode ($M = 22.90$, $SD = 4.21$), $F(1, 123) = 118.25$, $p < .001$, and they were ill for a longer period ($M = 9.96$, $SD = 4.98$) than first-episode patients ($M = 1.40$, $SD = .71$), $F(1, 115) = 156.54$, $p < .001$. However, age and duration of illness did not correlate with any of the dependent measures, and no group differences were found in parental education levels or in the distribution of gender and ethnicity. Moreover, the groups did not differ in their clinical state, as evaluated with the SAPS and SANS, depressive symptoms, or medication dosage, using chlorpromazine (CPZ) equivalents of the antipsychotic medications. Lastly, group differences were not observed for any of the primary dependent measures, with the exception of adaptive coping style, $F(1, 115) = 6.67$, $p = .01$ and supportive coping style, $F(1, 115) = 7.41$, $p < .01$. Thus, the two patient groups were collapsed into one schizophrenia patient group, except when statistical analyses involved coping styles.

The younger and older matched healthy comparison subjects were evaluated on the demographic and primary dependent measures to assess whether they could similarly be combined into one group. As expected, comparison subjects matched to chronic patients were significantly older ($M = 33.23$, $SD = 4.98$) than first-episode comparison subjects ($M = 21.25$, $SD = 2.59$), $F(1, 93) = 227.18$, $p < .001$. There was also a significant difference in years of education, $F(1, 93) = 6.09$, $p < .05$, with chronic comparison subjects reporting higher education levels ($M = 15.00$, $SD = 1.99$) relative to their younger counterparts ($M = 13.93$, $SD = 2.19$). However, subject education level and age did not correlate with any of the dependent measures.

No differences in parental education level, the distribution of ethnicity, or the proportion of male to female participants were observed across the two healthy comparison groups. Furthermore, the two healthy comparison groups did not differ on any of the primary dependent variables. Thus, older and younger healthy adults were collapsed to form one normal comparison group.

As shown in Table 1, schizophrenia patients and healthy comparison subjects significantly differed in subject education level and in the distribution of ethnicity. However, these variables were not significantly related to the primary dependent variables and the study results remained after statistically controlling for ethnicity and subject education levels. The results presented do not include these variables as covariates.

Table 1. *Demographic and Clinical Characteristics of Participants*

Characteristic	Schizophrenia Patients (<i>n</i> = 125)		Healthy Comparison Subjects (<i>n</i> = 95)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age (years)	27.56	8.33	26.67	7.12
Education (years)**	13.31	2.26	14.48	2.06
Parental Education (years)	14.21	3.31	15.00	3.37
Illness Duration (years)	4.48	5.12	-	-
Medication Dosage (mg/day, in Cpz equiv)	237.84	213.51	-	-
SAPS Total Score	4.28	3.62	-	-
SANS Total Score	9.06	4.76	-	-
BDI Score***	9.11	8.38	3.03	3.62
	<i>n</i>		<i>n</i>	
Gender (Female/Male)	38/87		35/60	
Ethnicity**				
African American	32		11	
Asian American	15		7	
Caucasian	34		50	
Hispanic	37		21	
Mixed	7		6	

p* < .01. *p* < .001

Notes: Cpz equiv = chlorpromazine equivalents; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; BDI = Beck Depression Inventory

Study 1: Stressor Attributes That Influence Stress-Symptom Relationships

Group differences in episodic life stress. As shown in Table 2, schizophrenia patients reported fewer stressful life events overall and they had lower subjective and objective impact ratings relative to healthy comparison subjects. The groups did not differ, however, in episodic stress that was characterized by social evaluation, uncontrollability, or a combination of the two attributes (i.e., social evaluative + uncontrollable).

Table 2. *Group Differences in Episodic Life Stress Measures*

	Schizophrenia Patients (<i>n</i> = 125)			Healthy Individuals (<i>n</i> = 95)			<i>F</i> value	Cohen's <i>d</i>
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>		
<i>ALL Category</i>								
Number of life events	109	1.72	1.07	85	2.31	1.51	10.10	0.46**
Subjective impact ratings	97	5.30	3.26	76	7.17	4.98	8.87	0.46**
Objective impact ratings	97	5.65	2.96	76	7.32	4.38	8.81	0.46**
<i>SET Category</i>								
Number of life events	109	0.72	0.81	85	0.91	1.03	2.08	0.21
Subjective impact ratings	57	4.17	2.60	47	4.81	3.21	1.27	0.22
Objective impact ratings	57	4.06	1.86	47	4.76	2.77	2.32	0.34
<i>UNC Category</i>								
Number of life events	109	0.76	0.84	85	0.87	1.02	0.67	0.12
Subjective impact ratings	59	4.19	2.77	46	5.42	4.03	3.42	0.36
Objective impact ratings	59	4.21	1.87	46	4.82	3.08	1.54	0.25
<i>COM Category</i>								
Number of life events	109	0.24	0.53	85	0.24	0.50	0.02	0.00
Subjective impact ratings	21	4.19	2.18	17	4.68	1.99	0.50	0.23
Objective impact ratings	21	3.55	1.19	17	3.71	1.16	0.17	0.14

** $p < .01$.

Notes: ALL = all life events; SET = social evaluative threat events; UNC = uncontrollable events; COM = combined (SET + UNC) events.

Given that prior studies have examined episodic stress according to the life event's magnitude, independence level, and date of event, potential group differences in episodic stress were also evaluated across these domains. Although the groups did not differ in episodic stress for major life events, healthy comparison subjects reported a greater number of minor life events ($M = 1.65$, $SD = 1.21$) relative to schizophrenia patients ($M = 1.16$, $SD = 1.02$), $F(1, 193) = 9.65$, $p < .01$, Cohen's $d = .45$. When examining episodic stress based on independence level and date of the event, no group differences were found.

Associations between episodic life stress and clinical symptoms. Because objective and subjective impact ratings for each stressor category were highly correlated (r 's $> .70$ for patients and healthy comparison subjects) and yielded similar findings, the following regression

analyses only report findings for the objective impact ratings. Given that gender differences were found for the SAPS and SANS measures, gender was covaried out of all regression analyses involving positive and negative symptoms.

Episodic stress-symptom associations in schizophrenia patients. Although significant stress-symptom relationships were not found when stressful life events were considered as a single category, stressors characterized by social evaluation were strong predictors of positive and negative symptoms in schizophrenia patients. As indicated in Tables 3 and 4, these effects were primary driven by the Hallucinations, Delusions, and Bizarre Behavior subscales for positive symptoms as well as the Affective Flattening and Anhedonia/Asociality subscales for negative symptoms.

Table 3. Regression Model of Objective Impact Ratings for Social Evaluative Stressors Predicting Positive Symptoms in Schizophrenia Patients ($n = 55$)

Variable	Total Positive Symptoms Score			Global Hallucinations subscale		
	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β
<i>Step 1</i>						
Gender	-1.28	0.98	-0.16	-0.55	0.35	-0.20
SET objective impact ratings	0.81	0.25	0.40**	0.24	0.09	0.34**
R^2	0.19			0.16		
Variable	Global Delusions subscale			Global Bizarre Behavior subscale		
	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β
<i>Step 1</i>						
Gender	-0.09	.38	-0.03	-0.27	-.26	-0.13
SET objective impact ratings	0.27	1.00	0.36**	0.18	0.07	0.35**
R^2	0.14			0.14		

** $p < .01$.

Note: SET = social evaluative threat

Table 4. *Regression Model of Objective Impact Ratings for Social Evaluative Stressors Predicting Negative Symptoms in Schizophrenia Patients (n = 55)*

Variable	Total Negative Symptoms Score			Affective Flattening subscale			Anhedonia/Asociality subscale		
	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β
<i>Step 1</i>									
Gender	-2.55	1.03	-0.30*	-0.40	0.31	-0.17	-0.79	0.31	-0.32*
SET objective impact ratings	0.78	0.27	0.36**	0.20	0.08	0.32*	0.20	0.08	0.30*
R^2	0.22			0.13			0.20		

* $p < .05$. ** $p < .01$.
 Note: SET = social evaluative threat

To examine whether social evaluative stressors continued to predict clinical symptoms after controlling for baseline clinical data, hierarchical linear regression analyses were conducted on a subset of 24 schizophrenia patients who had clinical symptom data available before and after the occurrence of the stressor. Gender was not covaried due to the restricted sample size. Results continued to indicate a positive relationship between social evaluative stress and negative symptoms ($\beta = .59$, $t(21) = 2.42$, $p = .03$), even after controlling for initial level of negative symptomatology, R^2 change = .29, $F(1, 22) = 5.86$, $p = .03$. The reliable association between positive symptoms and social evaluative stress was also demonstrated but weakened ($\beta = .50$, $t(21) = 2.05$, $p = .06$) after controlling for initial positive symptom levels, R^2 change = .23, $F(1, 22) = 4.21$, $p = .06$.

Regarding the life event category combining social evaluative and uncontrollable content, Table 5 shows that impact ratings were significantly associated with positive symptoms. Follow-up analyses revealed that these effects were mainly driven by the subscales of Hallucinations and Delusions. A similar relationship was found for total negative symptoms although this stress-symptom association was only marginally significant (see Table 6). Because there were only four patients with combined life event data and baseline clinical data, follow-up analyses covarying out baseline data could not be conducted.

Table 5. *Regression Model of Objective Impact Ratings for Combined Events Predicting Positive Symptoms in Schizophrenia Patients (n = 20)*

Variable	Total Positive Symptoms Score			Global Hallucinations subscale			Global Delusions subscale		
	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β
<i>Step 1</i>									
Gender	3.43	1.84	0.35	-0.10	0.78	-0.03	1.34	0.64	0.40
COM objective impact ratings	0.89	0.34	0.44*	0.34	0.14	0.49*	0.30	0.12	0.49*
R^2	0.36			0.24			0.38		

* $p < .05$.

Note: COM = combined (social evaluative threat + uncontrollable) events

Table 6. *Regression Model of Objective Impact Ratings for Combined Events Predicting Negative Symptoms in Schizophrenia Patients (n = 20)*

Variable	Total Negative Symptoms Score		
	<i>B</i>	<i>SE B</i>	β
<i>Step 1</i>			
Gender	-1.58	2.13	-.16
COM objective impact ratings	.78	.39	.42 [†]
R^2	0.20		

[†] $p = .06$.

Note: COM = combined (social evaluative threat + uncontrollable) events

No significant stress-symptom relationships were found when the magnitude of life events was considered or the date of their occurrence. However, life events rated as dependent, such that the individual contributed to the stressor's occurrence, predicted depressive symptoms ($\beta = .33$, $t(43) = 2.30$, $p < .03$) and explained a significant proportion of variance in depressive symptoms, $R^2 = .20$, $F(1, 44) = 5.28$, $p < .03$, in patients with schizophrenia.

Episodic stress-symptom associations in healthy comparison subjects. Similar to schizophrenia patients, social evaluative stressors were linked to depressive symptoms in healthy individuals, $\beta = 0.28$, $t(41) = 1.89$, $p = .06$ and explained a proportion of the variance in depressive symptoms, $R^2 = .08$, $F(1, 42) = 3.56$, $p = .06$, although falling short of statistical significance in both instances. Further paralleling the findings for patients, dependent events

also predicted depressive symptoms in the healthy comparison subject group ($\beta = .32, t(39) = 2.14, p < .04$) and accounted for 13% of the variance in depressive symptoms $R^2 = .13, F(1, 40) = 4.59, p < .04$. However, depressive symptoms were not related to any of the other episodic stress categories, the magnitude of the stressor, or its date of occurrence.

Group differences in chronic life stress. In contrast to overall episodic stress, schizophrenia patients reported higher levels of chronic stress relative to healthy comparison subjects across all chronic stress domains, with the possible exception of family relationships (see Table 7). Furthermore, higher levels of chronic stress in patients were present in both the interpersonal and non-interpersonal domains.

Table 7. *Group Differences in Chronic Stress Domains.*

	Schizophrenia Patients (<i>n</i> = 111)		Healthy Individuals (<i>n</i> = 85)		<i>F</i> value	Cohen's <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
<i>Chronic Stress Domains</i>						
Best Friend	2.79	1.23	2.02	0.81	25.33	0.72***
Social Circle	3.25	0.97	2.17	0.83	67.36	1.18***
Romantic Relationships	2.73	0.81	2.45	0.88	5.31	0.33*
Family Relationships	2.51	0.95	2.28	0.87	2.99	0.25 [†]
School	2.48	0.79	1.83	0.71	36.03	0.86***
Work	2.51	0.89	2.13	0.73	10.44	0.46**
Finances	2.36	0.84	2.04	0.61	10.96	0.43**
Physical Health of Self	2.14	0.50	1.89	0.50	11.84	0.50**
<i>Sum of All Chronic Stress Domains</i>	20.68	3.46	16.69	3.34	65.51	1.17***
<i>Sum of Interpersonal Chronic Stress Domains</i>	11.25	2.51	8.85	2.35	46.57	0.98***
<i>Sum of Non-interpersonal Chronic Stress Domains</i>	9.47	1.85	7.84	1.70	40.11	0.91***

[†]*p* = .08. **p* < .05. ***p* < .01. ****p* < .001

Chronic stress-symptom associations in schizophrenia patients. Consistent with the results for episodic stress, positive and negative symptoms were only related to the interpersonal

domains of chronic stress in patients with schizophrenia. As indicated in Tables 8 and 9, patients experienced greater symptoms in the Affective Flattening, Anhedonia/Asociality, and Hallucination global subscales following the experience of interpersonal chronic stress.

Table 8. *Regression Model of Interpersonal Chronic Stress Predicting Negative Symptoms in Schizophrenia Patients (n = 108)*

Variable	Total Negative Symptoms Score			Affective Flattening subscale			Anhedonia/ Asociality subscale		
	B	SE B	β	B	SE B	β	B	SE B	B
<i>Step 1</i>									
Gender	-1.79	0.98	-0.17	-0.44	0.26	-0.16	-0.58	0.25	-0.21*
Interpersonal Chronic Stress	0.46	0.18	0.24**	0.14	0.05	0.26**	0.14	0.05	0.28**
R^2	0.09			0.09			0.12		

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

Table 9. *Regression Model of Interpersonal Chronic Stress Predicting Positive Symptoms in Schizophrenia Patients (n = 108)*

Variable	Total Positive Symptoms Score			Global Hallucinations subscale		
	B	SE B	β	B	SE B	β
<i>Step 1</i>						
Gender	-0.90	0.71	-0.12	-0.48	0.32	-0.14
Interpersonal Chronic Stress	0.25	0.13	0.18 [†]	0.11	0.06	0.18 [†]
R^2	0.05			0.05		

[†] $p = .06$.

Interpersonal chronic stress ($\beta = .37, t(20) = 2.16, p = .04$) continued to predict negative symptoms after controlling for initial levels of symptomatology ($\beta = .47, t(20) = 2.74, p = .01$) within the subset of 23 schizophrenia patients, R^2 change = .11, $F(1, 21) = 4.67, p = .04$. For positive symptoms, interpersonal chronic stress also remained a significant predictor ($\beta = 0.42, t(20) = 2.25, p < .04$) after controlling for baseline symptom levels, R^2 change = .16, $F(1, 21) = 5.05, p < .04$.

Chronic stress-symptom associations in healthy comparison subjects. Although the overall measure of chronic stress predicted depressive symptoms in healthy individuals, $R^2 = .11$,

$F(1, 78) = 9.98, p < .01$, this effect was primarily driven by the interpersonal domains of chronic stress. Similar to the findings within the schizophrenia patient group, healthy individuals displayed a strong relationship between interpersonal chronic stress and depressive symptoms ($\beta = .33, t(77) = 3.08, p < .01, R^2 = .11, F(1, 78) = 9.51, p < .01$), and no significant stress-symptom relationship when utilizing the non-interpersonal chronic stress measure.

Study 2 Analyses: Patient Characteristics that Influence Stress-Symptom Relationships

To test the hypothesized moderating effects of trait affect, coping styles, early life adversity, and COMT on the relationship between social evaluative stress and clinical symptoms, hierarchical linear regression analyses were limited to two of the life stress measures: (1) the sum of the objective impact ratings for episodic life events characterized by social evaluative threat content and (2) interpersonal chronic stress. Due to an insufficient sample size, moderation analyses were not conducted on impact ratings for the combined life events category.

Trait Affect

Schizophrenia patients reported significantly higher levels of trait negative affect ($M = 1.62, SD = .67$) as compared to healthy individuals ($M = 1.39, SD = .44, F(1, 198) = 8.06, p < .01, Cohen's d = .41$). Lower levels of trait positive affect, a potential protective factor, were also observed within the patient group ($M = 2.92, SD = .98$) relative to healthy individuals ($M = 3.55, SD = .59, F(1, 198) = 27.37, p < .001$).

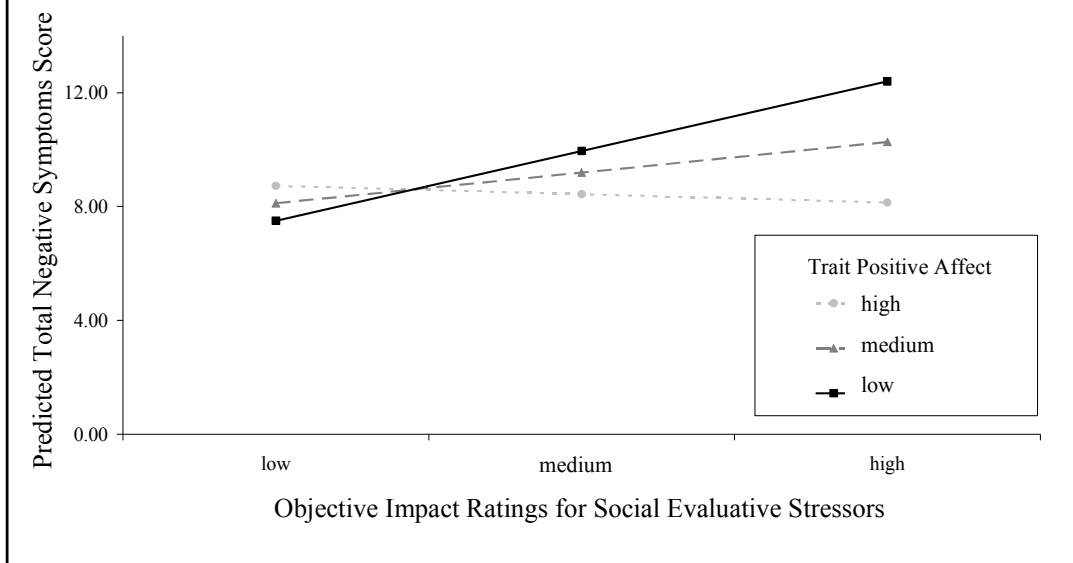
Trait affect as a moderator of stress-symptom associations in schizophrenia patients. Trait positive affect tended to moderate the relationship between social evaluative episodic stressors and negative symptoms in schizophrenia patients, R^2 change = .05, $F(1, 45) = 3.64, p = .06$ (see Table 10).

Table 10. Hierarchical Linear Regression Model of Trait Positive Affect Moderating the Relationships between Objective Impact Ratings for Social Evaluative Stressors and Negative Symptoms in Schizophrenia Patients ($n = 49$)

Variable	Total Negative Symptoms Score			Affective Flattening subscale			Anhedonia/Asociality subscale		
	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β
<i>Step 1</i>									
Gender	-2.68	1.02	-0.32**	-0.28	0.29	-0.12	-0.85	0.32	-0.33
<i>Step 2</i>									
SET objective impact ratings	2.78	1.01	1.20**	0.80	0.29	1.23**	0.87	0.32	1.23**
Positive Affect	2.28	1.53	0.57	0.51	0.44	0.46	0.86	0.49	0.71
<i>Step 3</i>									
SET ratings x Positive Affect	-0.75	0.39	-1.03 [†]	-0.24	0.11	-1.18*	-0.26	0.13	-1.16*
R^2	0.36			0.34			0.31		
[†] $p = .06$. * $p < .05$. ** $p < .01$. Note: SET = social evaluative threat									

To tease apart the interaction, follow-up regression analyses were conducted. As displayed in Figure 2, the association between social evaluative episodic stressors and negative symptoms was strongest in patients who were low in trait positive affect, $t(1,45) = 3.84, p < .001$; stress-symptom relationships were not significant, however, in patients characterized by greater levels of this protective factor.

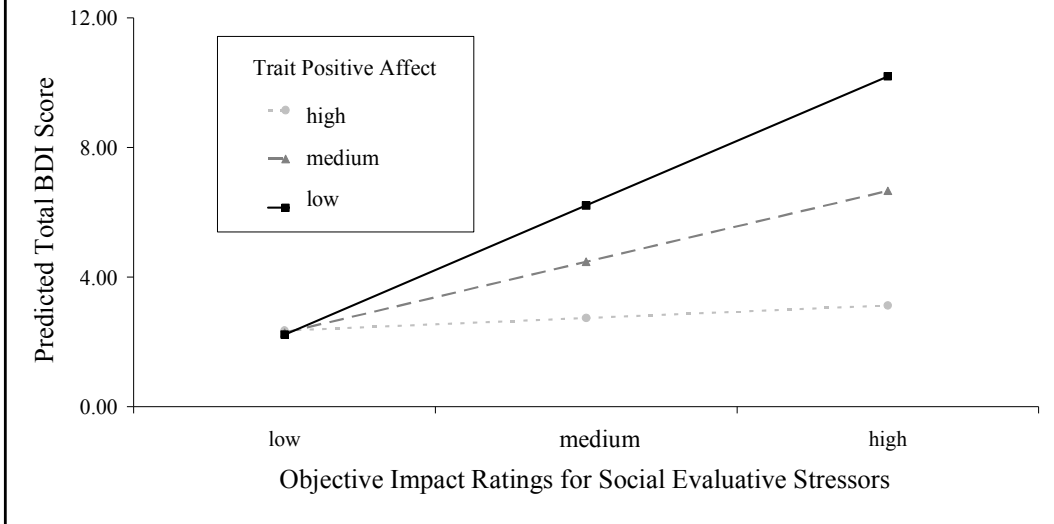
Figure 2. Moderating influence of trait positive affect on the relationship between episodic social evaluative stress and negative symptoms in schizophrenia patients ($n = 49$). This stress-symptom association was only significant for schizophrenia patients with low levels of trait positive affect.



Trait affect as a moderator of stress-symptom associations in healthy individuals.

Trait positive affect also appeared to serve a protective function in the healthy group and moderated the relationship between social evaluative episodic stressors and depressive symptoms, R^2 change = .20, $F(1, 37) = 11.31, p < .01$. Follow-up analyses indicated that episodic social evaluative stress predicted depressive symptoms but only in healthy individuals characterized by low, $t(1, 36) = 4.18, p < .001$, and medium, $t(1, 36) = 3.27, p < .01$, levels of trait positive affect (see Figure 3).

Figure 3. Moderating influence of trait positive affect on the relationship between episodic social evaluative stress and depressive symptoms in healthy comparison subjects ($n = 40$). This stress-symptom association was only significant for healthy individuals who reported low and medium levels of trait positive affect.



Coping Styles

Group differences in coping styles. Due to significant differences between chronic and first-episode schizophrenia patients in adaptive and supportive coping styles, the patient groups were considered by phase of illness in the following analyses. As indicated in Table 11, schizophrenia patients and healthy individuals differed in adaptive, supportive, and maladaptive coping styles as well as on most individual coping subscales.

Table 11. *Group Differences in Coping Styles*

Variable	First-episode Schizophrenia Patients (<i>n</i> = 73)		Chronic Schizophrenia Patients (<i>n</i> = 44)		Healthy Individuals (<i>n</i> = 91)		<i>F</i> value
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
<i>Maladaptive Coping Style</i>	1.06	0.64	0.96	0.52	0.73	0.38	9.06***
Denial	0.89	0.82	0.80	0.70	0.17	0.34	31.08***
Venting	1.18	0.81	1.10	0.68	1.31	0.70	1.32
Behavioral Disengagement	0.92	0.82	0.76	0.78	0.33	0.54	15.50***
Self-Blame	1.23	0.93	1.18	0.86	1.07	0.68	0.90
<i>Adaptive Coping Style</i>	1.74	0.56	2.00	0.50	2.16	0.50	13.64***
Active	1.88	0.72	2.17	0.74	2.39	0.59	11.63***
Planning	1.68	0.79	2.08	0.76	2.24	0.66	11.74***
Acceptance	1.79	0.75	1.86	0.77	2.04	0.67	2.47 [†]
Positive Reframing	1.60	0.73	1.89	0.73	1.99	0.70	6.24**
<i>Supportive Coping Style</i>	1.59	0.77	1.98	0.72	1.79	0.71	4.03**
Instrumental Support	1.60	0.81	1.99	0.77	1.89	0.80	4.04**
Emotional Support	1.57	0.84	1.97	0.81	1.69	0.81	3.25**

[†]*p* = .06. ***p* < .01. ****p* < .001.

Follow-up analyses revealed that first-episode patients used less adaptive coping styles than healthy comparison subjects, $t(1, 162) = 1.10, p < .001$, Cohen's $d = .81$, and chronic schizophrenia patients, $t(1, 115) = 1.36, p = .01$, Cohen's $d = .49$, who were intermediate between the two groups. The difference between chronic patients and healthy individuals was at the trend level of statistical significance, $t(1, 133) = 1.76, p = .08$, Cohen's $d = .33$.

First-episode schizophrenia patients also used less supportive coping styles relative to chronic schizophrenia patients, $t(1, 115) = 1.10, p < .01$, Cohen's $d = .52$, and to a lesser degree, healthy comparison subjects $t(1, 162) = 1.74, p = .08$, Cohen's $d = .27$. In contrast, chronic schizophrenia patients and healthy individuals did not differ in supportive coping.

However, both the first-episode and chronic patient groups relied more on maladaptive coping relative to healthy comparison subjects, $t(1, 162) = 4.14, p < .001$, Cohen's $d = .65$, and

$t(1, 133) = 3.01, p < .01$, Cohen's $d = .55$, respectively. There were no significant group differences in maladaptive coping styles as a function of phase of illness.

Coping styles as a moderator of stress-symptom relationships in schizophrenia

patients. In contrast to maladaptive and supportive coping styles, adaptive coping tended to moderate the relationship between interpersonal chronic stress and positive symptoms in schizophrenia patients experiencing their first-episode of illness, R^2 change = .05, $F(1, 59) = 3.49, p = .06$ (see Table 12).

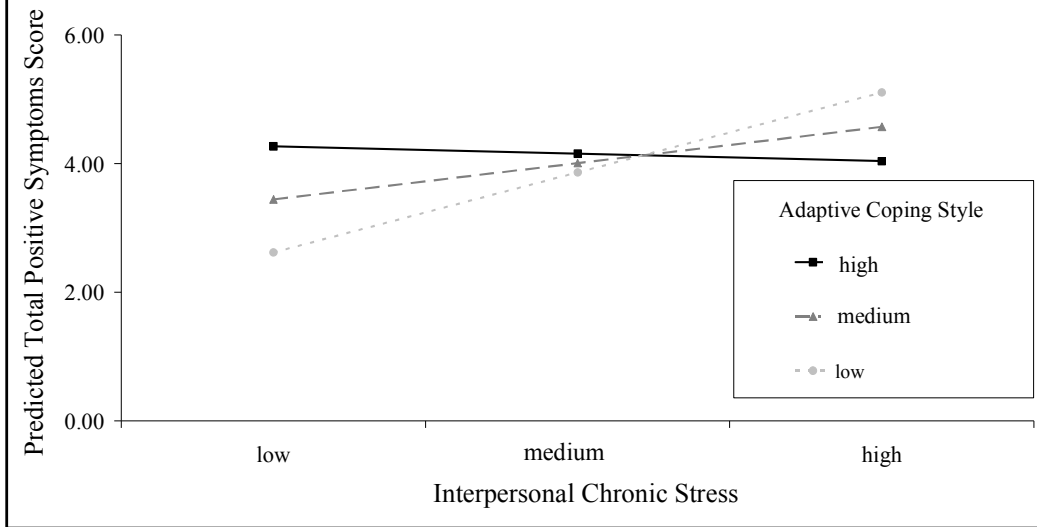
Table 12. Hierarchical Linear Regression Model of Adaptive Coping Style Moderating the Relationships between Interpersonal Chronic Stress and Positive Symptoms in First-episode Schizophrenia Patients ($n = 49$)

Variable	Total Positive Symptoms Score			Positive Formal Thought Disorder subscale		
	<i>B</i>	<i>SE B</i>	<i>B</i>	<i>B</i>	<i>SE B</i>	<i>B</i>
<i>Step 1</i>						
Gender	-2.31	0.96	-0.30*	-0.17	0.27	-.08
<i>Step 2</i>						
Interpersonal Chronic Stress	0.99	0.46	0.80*	0.40	0.13	1.12**
Adaptive Coping	5.20	2.79	0.92	2.25	0.80	1.29**
<i>Step 3</i>						
Interpersonal Chronic Stress x Adaptive Coping	-0.45	.24	-1.10 [†]	-0.22	0.07	-1.86**
R^2		0.16			0.18	

[†] $p = .06$. * $p < .05$. ** $p < .01$.

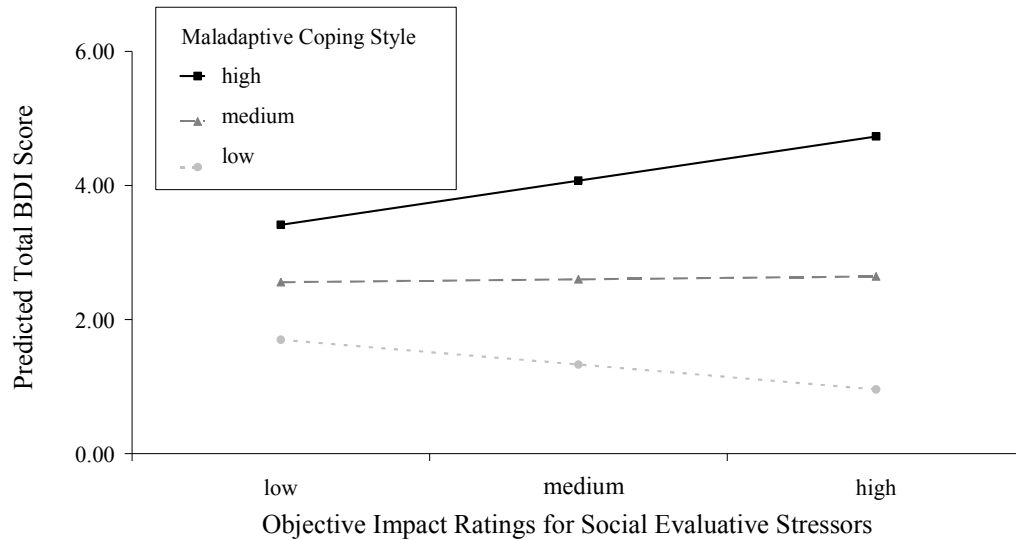
First-episode patients who relied on fewer adaptive coping styles displayed the strongest association between the interpersonal domains of chronic stress and positive symptoms, $t(1, 59) = 2.21, p = .03$, whereas a similar relationship was not detected in patients who utilized adaptive coping styles more frequently (see Figure 4).

Figure 4. Moderating influence of adaptive coping style on the relationship between interpersonal chronic stress and positive symptoms in first-episode schizophrenia patients ($n = 49$). This stress-symptom association was only significant for patients who reported lower levels of adaptive coping styles.



Coping styles as a moderator of stress-symptom relationships in healthy comparison subjects. For healthy individuals, only maladaptive coping style significantly moderated the relationship between social evaluative episodic stress and depressive symptoms, R^2 change = .08, $F(1, 39) = 5.5, p = .02$. As displayed in Figure 5, there was a strong positive association between social evaluative stress and depressive symptoms for healthy individuals who engaged more often in maladaptive coping, $t(1, 38) = 2.39, p = .02$, but not for individuals who used this coping style on a less frequent basis.

Figure 5. Moderating influence of maladaptive coping style on the relationship between episodic social evaluative stress and depressive symptoms in healthy comparison subjects ($n = 42$). This stress-symptom association was only significant for healthy individuals who reported high levels of maladaptive coping styles.



Early Life Adversity

Group differences in early life adversity. As indicated in Table 13, patients with schizophrenia reported poorer quality relationships with their fathers. They also tended to have worse quality maternal relationships and more parental loss relative to healthy individuals. The groups did not differ, however, in the proportion of individuals who experienced physical or sexual abuse.

Table 13. *Group Differences in Early Life Adversity*

	Schizophrenia Patients (<i>n</i> = 125)			Healthy Individuals (<i>n</i> = 95)			<i>F</i> or χ^2	Cohen's <i>d</i>
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>		
Maternal Relationship	105	1.49	0.45	89	1.38	0.43	3.41	0.27 [†]
Paternal Relationship	100	1.77	0.54	86	1.57	0.49	6.95	0.39*
		<i>n</i>			<i>n</i>			
Parental Loss (Yes/No)	105	62/43		89	41/48		3.26 [†]	
Physical Abuse (Yes/No)	86	20/66		80	13/67		1.28	
Sexual Abuse (Yes/No)	105	12/93		89	10/79		0.02	

[†]*p* = .06. **p* < .05.

Early life adversity as a moderator of stress-symptom relationships in schizophrenia

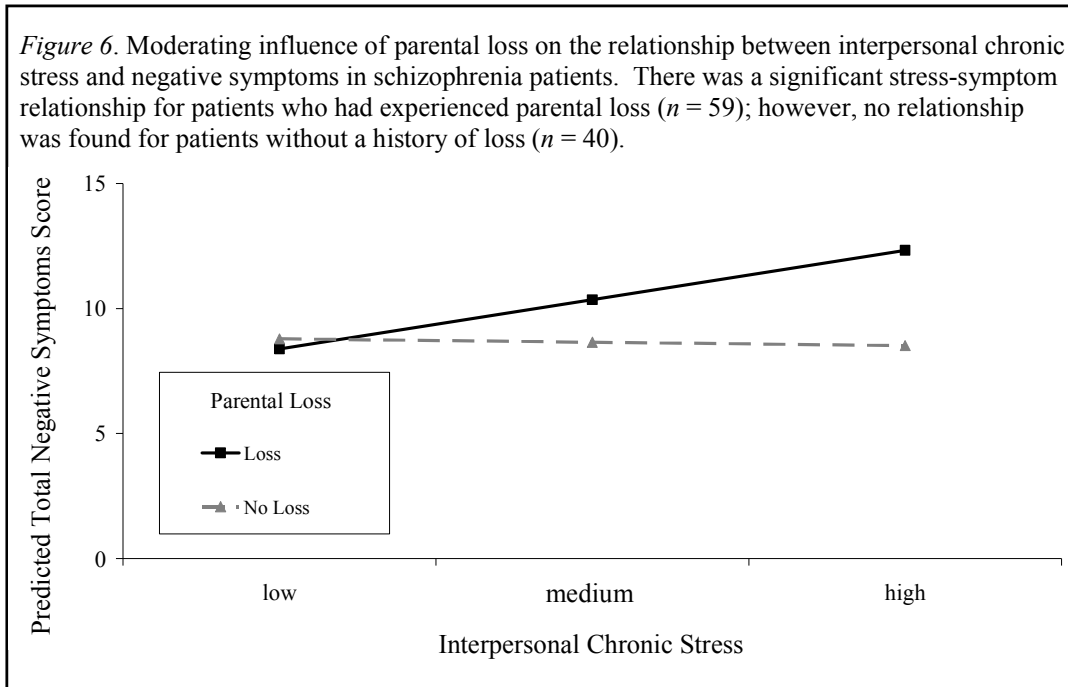
patients. Within the schizophrenia patient group, parental loss moderated the relationship between interpersonal chronic stress and negative symptoms, R^2 change = .04, $F(1, 96) = 4.71$, $p = .03$ (see Table 14).

Table 14. *Hierarchical Linear Regression Model of Parental Loss Moderating the Relationships between Interpersonal Chronic Stress and Negative Symptoms in Schizophrenia Patients (*n* = 99)*

Variable	Total Negative Symptoms Score			Anhedonia/Asociality subscale		
	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β
<i>Step 1</i>						
Gender	-1.39	1.00	-0.13	-0.45	0.28	-0.15
<i>Step 2</i>						
Interpersonal Chronic Stress	-0.04	0.32	-0.02	-0.02	0.09	-0.04
Parental Loss	-7.55	4.42	-0.77	-2.67	1.23	-0.98
<i>Step 3</i>						
Interpersonal Chronic Stress x Parental Loss	0.82	0.38	1.00*	0.25	0.11	1.11*
R^2		0.17			0.17	

***p* < .01.

As Figure 6 indicates, there was a strong association between interpersonal chronic stress and negative symptoms but only among patients who experienced parental loss ($\beta = .42, t(56) = 3.52, p < .01$).



In addition, the quality of the maternal relationship moderated the association between social evaluative episodic stress and negative symptoms in patients, R^2 change = .07, $F(1, 47) = 5.20, p = .02$ (see Table 15).

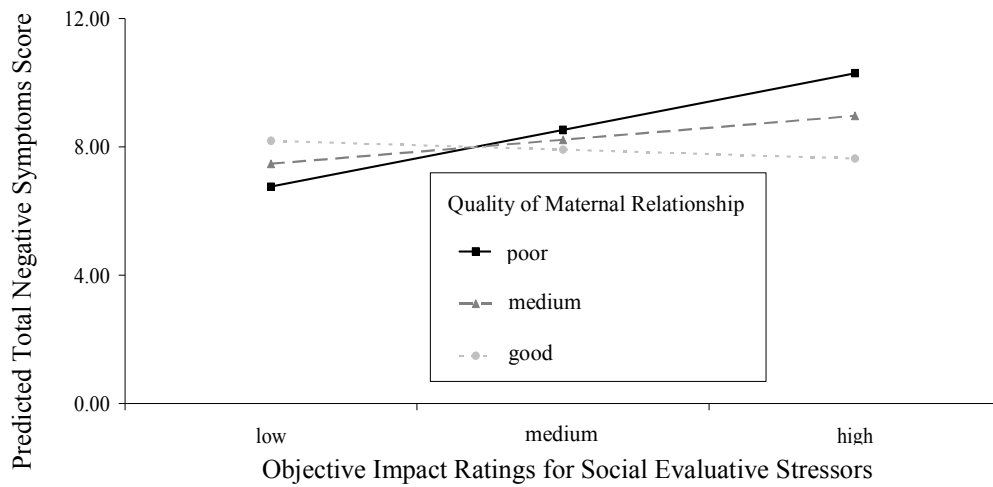
Table 15. Hierarchical Linear Regression Model of Maternal Relationship Quality Moderating the Relationships between Objective Impact Ratings for Social Evaluative Stressors and Negative Symptoms in Schizophrenia Patients ($n = 51$)

Variable	Total Negative Symptoms Score			Apathy/Avolition subscale		
	<i>B</i>	<i>SE B</i>	β	<i>B</i>	<i>SE B</i>	β
<i>Step 1</i>						
Gender	-2.73	0.99	-0.33	-0.86	0.31	-0.34
<i>Step 2</i>						
SET objective impact ratings	-1.21	0.86	-0.58	-0.43	0.27	-0.66
Maternal Relationship	-3.57	2.32	-0.45	-0.86	0.72	-0.35
<i>Step 3</i>						
SET objective ratings x Maternal Relationship	1.10	0.48	1.23*	0.35	0.15	1.24*
R^2		0.34			0.33	

* $p < .05$.

Follow-up tests revealed that negative symptoms were associated with greater social evaluative episodic stress if patients experienced poor relationships with their mothers before the age of 15, $t(1, 47) = 3.33, p < .01$ (see Figure 7).

Figure 7. Moderating influence of maternal relationship quality on the association between objective impact ratings for social evaluative stressors and negative symptoms in schizophrenia patients ($n = 51$). A significant stress-symptom relationship was only observed for the patients who had poor quality relationships with their mothers.



Early life adversity as a moderator of stress-symptom relationships in healthy

comparison subjects. In contrast to schizophrenia patients, early life adversity did not moderate stress-symptom relationships in healthy individuals.

Catechol-O-methyltransferase Val¹⁵⁸Met (COMT) Polymorphism

Group differences in COMT. As indicated in Table 16, patients with schizophrenia and healthy individuals did not differ in their distribution of COMT allelic frequencies $\chi^2(2, N = 144) = 1.44, p = .49$. Furthermore, the proportion of the three COMT genotypes did not differ according to ethnicity, $\chi^2(8, N = 141) = 2.14, p = .52$ or gender, $\chi^2(2, N = 141) = .28, p = .87$ within the entire sample or when analyses were conducted separately for the patient and healthy comparison groups (all p 's > .20).

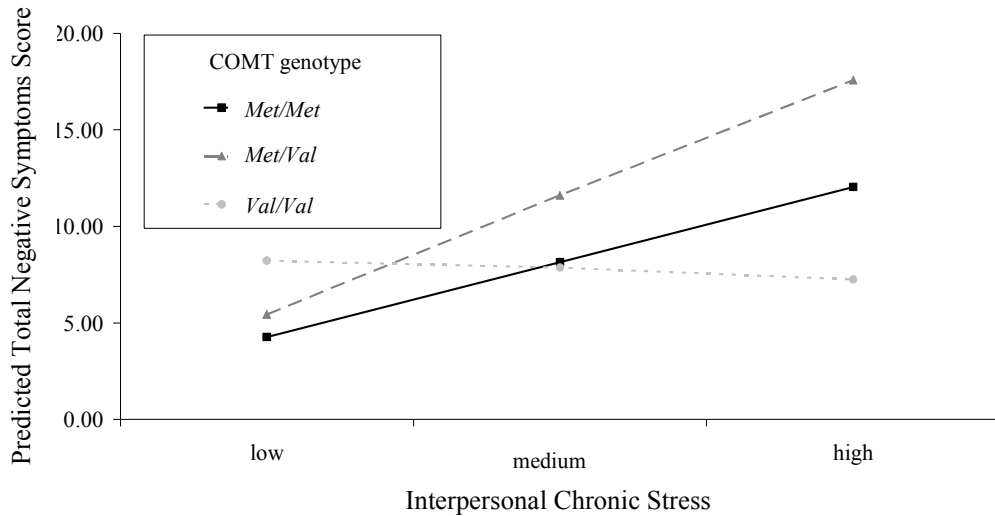
Table 16. Group Differences in COMT Genotype Distribution

	Schizophrenia Patients (<i>n</i> = 79)	Healthy Individuals (<i>n</i> = 65)	χ^2
	<i>n</i>	<i>n</i>	
COMT Genotype			1.44
Met/Met	11	10	
Met/Val	43	29	
Val/Val	25	26	

COMT as a moderator of stress-symptom relationships in schizophrenia patients.

Within the schizophrenia patient group, COMT significantly moderated the relationship between interpersonal chronic stress and negative symptoms, R^2 change = .08, $F(2, 62) = 5.20, p = .03$, such that interpersonal chronic stress significantly predicted negative symptoms but only for individuals homozygous for the *Met* allele ($\beta = .51, t(6) = 2.45, p = .04$) and for the *Met/Val* group ($\beta = .47, t(30) = 3.13, p < .01$). There was no significant stress-symptom association for individuals with the *Val/Val* genotype (see Figure 8).

Figure 8. Moderating influence of COMT on the relationship between interpersonal chronic stress and negative symptoms in schizophrenia patients. There were significant stress-symptom relationships for patients with the *Met/Met* genotype ($n = 10$) as well as the heterozygote patient group ($n = 37$); however, there was no relationship for patients with the *Val/Val* genotype ($n = 27$).



Follow-up analyses revealed that this stress-symptom relationship was primarily driven by the Affective Flattening subscale for patients with the *Met/Met* genotype and by the Affective Flattening, Alogia, and Anhedonia/Asociality subscales for the heterozygote patient group.

COMT as a moderator of stress-symptom relationships in healthy comparison

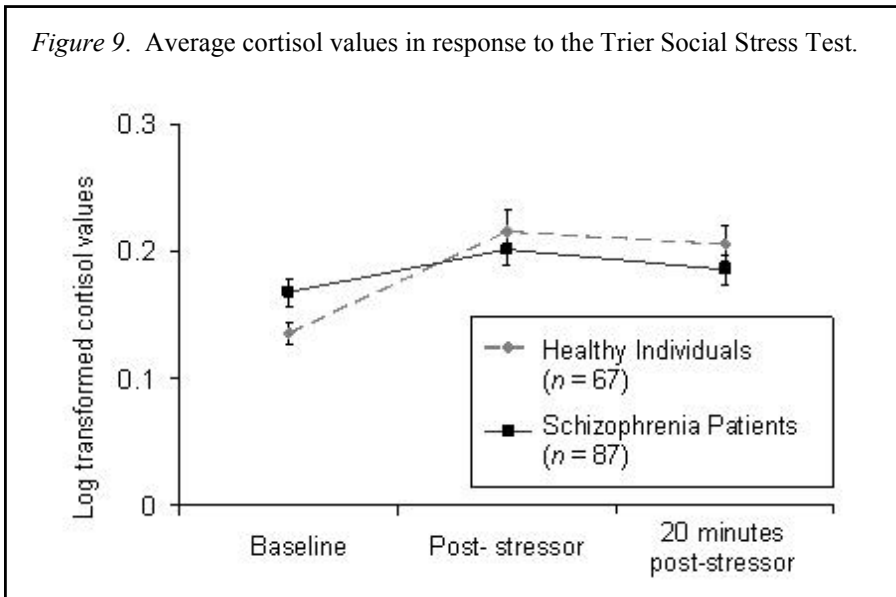
subjects. For healthy individuals, COMT was not a significant moderator of the relationship between life stress and depressive symptoms.

Study 3 Analyses: Biological Mechanisms Underlying Stress-Symptom Relationships

Because age, gender, body mass index, sleep, nicotine and caffeine use, phase of menstrual cycle, and oral contraceptive use were not found to be statistically related to the cortisol response, these variables were not included as covariates in the following analyses.

Group differences in stress reactivity to the psychosocial stressor. As indicated in Figure 9, schizophrenia patients displayed an elevated but flat cortisol response relative to healthy individuals. In comparing the two groups on AUC_i, a measure that reflects cortisol reactivity, schizophrenia patients demonstrated reduced cortisol responses to the psychosocial stressor ($M = 1.30, SD = 3.57$) relative to their healthy counterparts ($M = 2.84, SD = 4.52$), $F(1, 157) = 5.77, p < .02$, Cohen's $d = .38$. When using a measure of total cortisol output (i.e., AUC_g), schizophrenia patients ($M = 11.91, SD = 6.61$) and healthy individuals ($M = 10.81, SD = 5.37$) did not differ in the magnitude of their response.

Figure 9. Average cortisol values in response to the Trier Social Stress Test.



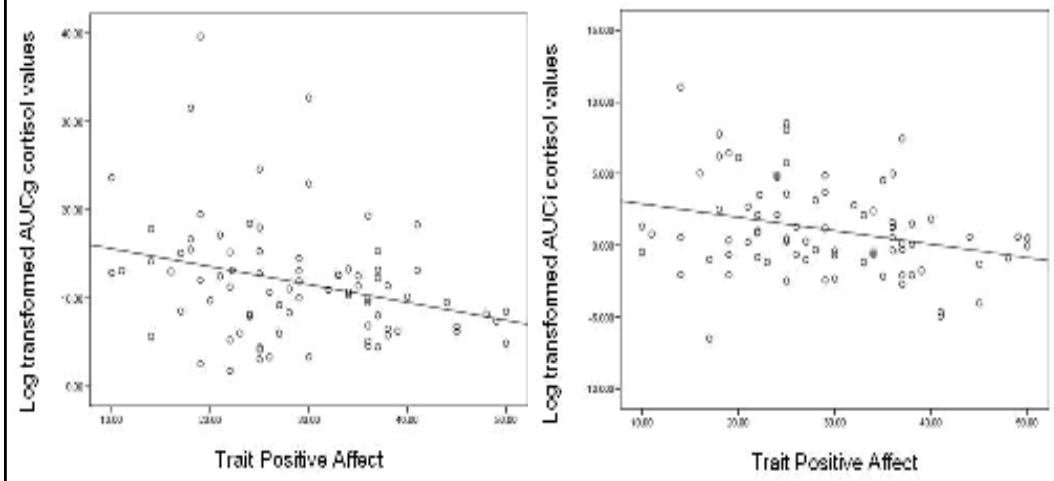
As indicated in Table 17, both groups demonstrated a significant increase in state anxiety following the stressor, $F(1, 169) = 59.91, p < .001$. However, this effect was moderated by a significant interaction, such that the magnitude of the response was greater in healthy individuals relative to patients with schizophrenia, $F(1, 169) = 6.90, p < .01$.

Table 17. *Baseline and Post-Stressor State Anxiety Levels.*

	Schizophrenia Patients (<i>n</i> = 94)		Healthy Individuals (<i>n</i> = 87)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Baseline State Anxiety	37.87	10.68	30.30	7.48
Post-Stressor State Anxiety	41.82	11.75	38.31	10.77

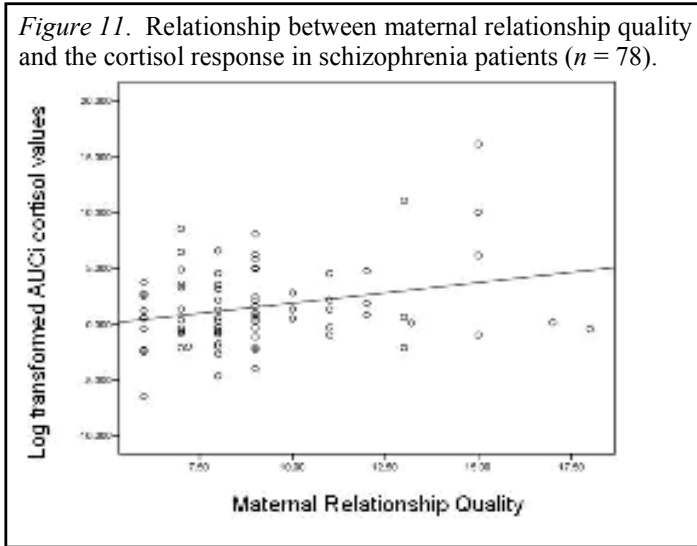
Relationship between trait affect, coping styles, early life adversity, and COMT and the cortisol response in schizophrenia patients. Similar to the findings from Study 2 where trait positive affect moderated stress-symptom relationships in schizophrenia, this variable was also associated with cortisol reactivity, such that there was an inverse relationship between trait positive affect and the cortisol AUCg measure, $r(79) = -.28, p = .01$ as well as the AUCi cortisol measure, $r(79) = -.29, p < .01$ (see Figure 10).

Figure 10. Relationships between trait positive affect and the cortisol response in schizophrenia patients (*n* = 80).



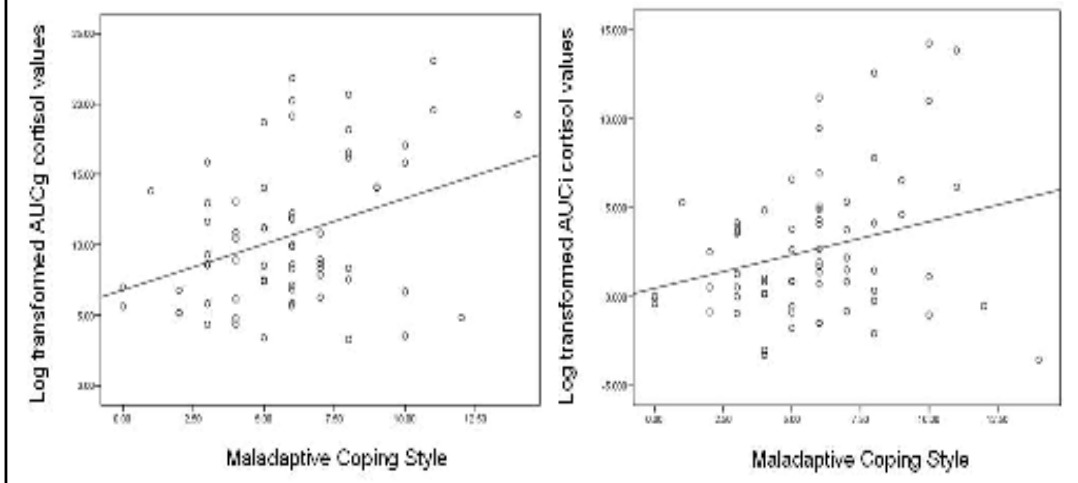
Further paralleling Study 2's findings where stress-symptom associations were significantly influenced by patients' relationships with their mothers, maternal relationship quality was positively associated with the AUCi cortisol measure within the schizophrenia patient group, $r(79) = .22, p < .01$ (see Figure 11). However, cortisol was not related to any of the other patient characteristic variables.

Figure 11. Relationship between maternal relationship quality and the cortisol response in schizophrenia patients ($n = 78$).



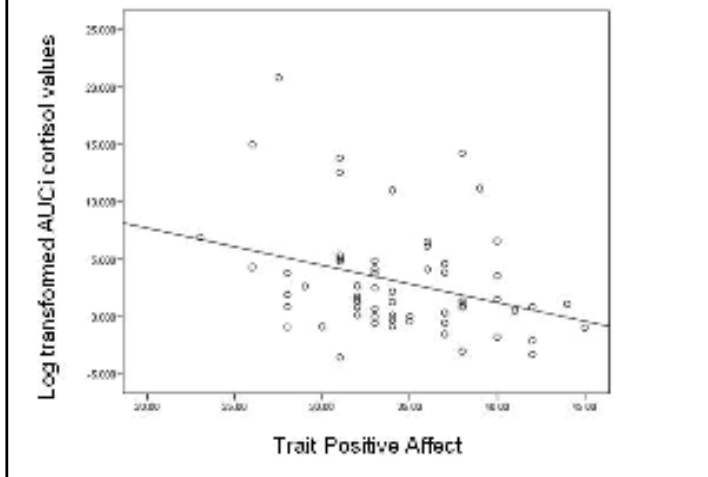
Relationship between trait affect, coping styles, early life adversity, and COMT and the cortisol response in healthy comparison subjects. A similar pattern of findings also emerged for healthy individuals, whereby maladaptive coping styles influenced stress-symptom associations in Study 2 as well as cortisol reactivity to the psychosocial stressor. Specifically, there were significant positive associations between maladaptive coping styles with the AUCi measure, $r(66) = .27, p < .03$ and the AUCg cortisol measure, $r(66) = .36, p < .01$ (see Figure 12).

Figure 12. Relationships between maladaptive coping style and the cortisol response in healthy individuals ($n = 66$).



Trait positive affect also moderated stress-symptom relationships among healthy individuals and was inversely correlated with the AUCi cortisol measure, $r(59) = -.26, p < .05$ (see Figure 13). No other relationships emerged between cortisol, coping styles, early life adversity, and the COMT polymorphism.

Figure 13. Relationship between trait positive affect and the cortisol response in healthy individuals ($n = 59$).



Discussion

Results from the present set of studies demonstrated that stress-symptom relationships among patients with schizophrenia are determined to a considerable degree by specific stressor and individual characteristics. Notably, the characteristics that appear to increase patients' susceptibility to stress-induced symptom exacerbation have been strongly associated with heightened reactivity of the cortisol response, which has been implicated in the pathophysiology of schizophrenia (Walker & Diforio, 1997; Walker, Mittal, & Tessner, 2008). Furthermore, by integrating this behavioral data with a laboratory measure of cortisol reactivity, the findings indicated that cortisol may indeed underlie the relationship between episodic stress and clinical symptoms in schizophrenia.

Stressor Attributes

The present data highlighted the importance of specifying the nature of the stressor when examining stress-symptom relationships in schizophrenia. Consistent with study hypotheses, impact ratings for episodic stressors characterized by social evaluation as well as the combined influence of social evaluative threat and uncontrollability were most strongly associated with positive and negative symptoms among schizophrenia patients. As predicted, there were also stronger relationships between interpersonal chronic stress and positive and negative symptoms in patients relative to the non-interpersonal domains of chronic stress. These findings parallel prior literature suggesting that environments characterized by hostility and criticism are associated with more severe symptomatology in schizophrenia (Butzlaff & Hooley, 1998; Ertugrul & Ulug, 2004; Janssen, Hanssen, & Bak, 2003; Ritsher & Phelan, 2004). The consistency of these findings across studies suggests that the experience of social evaluative

stress is a key factor to consider when trying to identify schizophrenia patients who may be at heightened risk for relapse.

Although both episodic and chronic social evaluative stress were strong predictors of positive and negative symptoms in schizophrenia, patients reported experiencing more social evaluation relative to healthy individuals only in relation to chronic stress. Given the high rate of stigma experienced by individuals with schizophrenia (Torrey, 1995), the lack of group differences in the experience of episodic social evaluative stressors was somewhat unexpected. However, assuming that individuals with schizophrenia experience stigma on an ongoing basis, this phenomenon may not have been fully captured by the episodic stress measure used in the present study and instead, may have been reflected as chronic stress.

Social evaluative stress, as predicted, was also strongly related to depressive symptoms in the healthy comparison group. This finding parallels previous work showing that depressive episodes are best predicted by stressful life events that leave individuals feeling devalued in relation to others (Kendler et al., 2003; Pruessner, Hellhammer, Pruessner, & Lupien, 2003). Social evaluative stress was not related to depressive symptoms in schizophrenia patients, however, suggesting that this stressor category may utilize a variety of pathways to influence distinct symptom clusters within different populations.

In contrast to past research (e.g., Brown & Birley, 1968; Norman & Malla, 1994; 2001; Ventura et al., 1989; 2000), the present study did not find associations between life stress and symptoms when examining episodic stressors according to their magnitude or date of occurrence. However, for the dependent life event category, in which the individual contributed to the stressor's occurrence, there were strong associations between impact ratings and depressive symptoms in both schizophrenia patients and healthy comparison subjects. These

findings are consistent with prior work indicating that dependent life events lead to increases in depressive symptoms through the pathway of reduced self-efficacy (Maciejewski, Prigerson, & Mazure, 2000).

Although an increased number of episodic life events has been observed previously to predict clinical symptoms in schizophrenia (e.g., Brown & Birley, 1968; Nuechterlein et al., 1994; Ventura et al., 1989), the impact associated with a stressor was found to be a stronger predictor of clinical symptoms in the present study. It is possible that the absence of findings when using number of life events as a predictor of stress-symptom relationships was a result of reduced variability in this measure as compared to impact ratings. Nonetheless, the importance of impact ratings compared to number of stressors is consistent with the transactional model of stress and coping, in which appraisals and the potential impact of stressful events are important predictors of future health and functioning (Delongis et al., 1982; Folkman & Lazarus, 1985; Lazarus & Folkman, 1984). It is also noteworthy that clinical symptoms were predicted by both the participant's self-reported impact ratings as well as the objective impact ratings determined by a team of raters. Thus, the present findings do not appear to be the result of "effort after meaning effects," whereby participants may bias their report of stressful life events in an attempt to explain recent increases in symptomatology (Paykel, 1978).

Thus, the overall findings from this study demonstrate that specific stressor attributes, notably social evaluative stress, are important determinants of stress-symptom relationships in schizophrenia patients and healthy individuals. One interpretation of these data is that social evaluative stress is most closely linked with the biological pathways underlying positive, negative, and depressive symptoms. This is based on available data indicating that acute and chronic threats of social evaluation preferentially elicit increased cortisol reactivity (Dickerson &

Kemeny, 2004; Miller, Chen, & Zhou, 2007), which may then mediate stress-symptom relationships in schizophrenia (Walker & Diforio, 1997; Walker, Mittal, & Tessner, 2008) and are associated with depressive symptoms in healthy individuals (Pruessner et al., 2003). Future research investigating the psychobiological pathways underlying the strong association between social evaluative stress and clinical symptoms is warranted.

In addition, these results have important implications for the development of interventions involving stress management. Given prior work indicating that interventions focused on reducing hostility and criticism in the family environment can lead to dramatic decreases in relapse rates among patients with schizophrenia (Hogarty et al., 1991; McFarlane et al., 1995), future treatment would likely benefit from additional interventions centered around reducing patients' exposure and sensitivity to social evaluative stress. In particular, interventions might incorporate strategies that help patients cope more effectively with social evaluative stress, ultimately reducing the negative impact associated with these stressors. Initial research in this area is promising and also indicates that programs aimed at reducing stigma have the potential to enhance self-esteem and treatment adherence (Fung, Tsang, & Cheung, 2011).

Individual Characteristics

Consistent with the study's hypotheses, schizophrenia patients reported higher levels of trait negative affect and lower levels of trait positive affect relative to healthy individuals (Horan et al., 2008). Furthermore, schizophrenia patients and healthy comparison subjects who were lower on trait positive affect displayed greater levels of negative and depressive symptoms, respectively, following the experience of social evaluative episodic stress. These findings may be interpreted through the broaden-and-build theory of positive emotions (Fredrickson, 1998), which states that positive emotions can buffer against the deleterious effects of life stress by

broadening cognitive and behavioral flexibility in stressful situations (Burns et al., 2008; Folkman, 2008; Fredrickson & Joiner, 2002). This interpretation concurs with available evidence indicating that greater positive affect is associated with lower subjective stress during a psychosocial stressor task, perceptions that the task is less difficult and that the individual has greater control, and better overall performance on the task (Bostock et al., 2011). Furthermore, past research has suggested that the diminished emotional expressivity and engagement displayed by individuals with low trait positive affect could create uncomfortable social interactions for others, ultimately leading to more social rejection or criticism (Horan, 2008). Thus, it appears that lower levels of trait positive affect can lead to greater threat appraisals as well as increased exposure to social evaluative stress, which can result in greater cortisol reactivity and elevated negative symptoms (Dickerson & Kemeny, 2004; Miller, Chen, & Zhou, 2007; Walker & Diforio, 1997; Walker, Mittal, & Tessner, 2008).

Contrary to hypotheses, trait negative affect did not moderate stress-symptom relationships in schizophrenia patients. This is somewhat surprising given prior work indicating that higher levels of negative affect increase stress sensitivity in schizophrenia (Horan & Blanchard, 2003) as well as cortisol reactivity in healthy individuals (Habra et al., 2003; Polk et al., 2005). This lack of an effect may have been due to the present study's lower trait negative affect scores and reduced variability, thus making it more difficult to detect significant associations.

As predicted, first-episode schizophrenia patients endorsed significantly fewer adaptive and supportive coping styles relative to healthy comparison subjects. Chronic schizophrenia patients, however, only differed marginally from the healthy normal comparison subjects in their overall use of adaptive coping styles. One possible explanation for this pattern of findings is that,

unlike patients in the chronic phase of illness, the recent diagnosis of schizophrenia among first-episode patients may limit their cognitive, emotional, and social resources, and their overall ability to adequately cope with life stress. In support of this interpretation, reductions in self-confidence, self-efficacy, attention, as well as the perceived availability of psychological support from friends and family have been associated with lower use of adaptive and approach-oriented coping behaviors in schizophrenia (Hultman et al., 1997; Macdonald et al., 1998; Ventura et al., 2004). In contrast, chronic schizophrenia patients have been contending with their illness for at least five years, and therefore may have had more time to obtain access to treatment resources and thereby develop more effective coping styles. Indeed, prior research has shown that chronic schizophrenia patients engage in more coping styles relative to individuals experiencing an earlier phase of the illness (Thurm & Haefner, 1987).

As hypothesized, both first-episode and chronic schizophrenia patients reported using more maladaptive coping styles relative to healthy normal comparison subjects. Because coping styles have been characterized as the psychological component of stress processing (e.g., Jansen et al., 1998), schizophrenia patients' reliance on maladaptive coping styles suggests that their ability to psychologically perceive and respond effectively to life stressors may be impaired. Consistent with this interpretation, coping through denial has been related to impaired insight in schizophrenia patients (Moore et al., 1999). Furthermore, patients' tendency to rely on more passive and avoidant coping styles might also be the result of greater levels of anxiety and negative symptoms (Lysaker et al., 2005).

Further supporting the study's predictions, adaptive coping style moderated the degree to which interpersonal chronic stress was associated with elevated clinical symptoms in schizophrenia. Specifically, among first-episode patients who used less adaptive coping styles,

there were strong positive associations between interpersonal chronic stress and positive symptoms. Somewhat unexpectedly, no effects were found for patients in the chronic phase of illness, which may have been the result of decreased variance and lower positive symptom scores in this patient group relative to first-episode patients.

The moderating influence of adaptive coping styles on stress-symptom relationships in first-episode schizophrenia patients is consistent with prior work showing that adaptive coping lessens the impact of stressful life events and lowers the risk of relapse among younger schizophrenia patients (Pallanti et al., 1997). Although the pathways underlying this finding were not directly studied in the present study, prior work suggests that adaptive coping styles can reduce stress appraisals to psychosocial stress, resulting in decreased cortisol reactivity (Arnetz et al., 1991; Bohnen et al., 1991; O'Donnell et al., 2008) and fewer positive symptoms (Walker & Diforio, 1997; Walker, Mittal, & Tessner, 2008).

It is also noteworthy that adaptive coping styles moderated the relationship between interpersonal chronic stress and clinical symptoms, but had no impact on the episodic stress-symptom relationships. A meta-analysis has found similar effects, such that adaptive coping styles (i.e., active coping, positive reframing, problem solving) were associated with psychological outcomes for chronic stressors, but not for acute stressors (Penley, 2002). One interpretation of these findings is that schizophrenia patients may take more time to marshal and implement their adaptive coping resources. Thus, under conditions of chronic stress, schizophrenia patients who tend to rely more on adaptive coping styles would have sufficient time to positively reframe and problem solve around the stressor, thereby reducing their stress reactivity. For episodic stress, however, the patient group's delay in marshalling adaptive coping

resources may obscure any positive benefits of adaptive coping styles on episodic stress-symptom relationships.

Although maladaptive coping did not influence stress-symptom relationships in schizophrenia patients, this coping style did moderate the relationship between social evaluative episodic stress and depressive symptoms in the healthy comparison subject group. The negative impact of maladaptive coping on episodic stress-symptom relationships is consistent with results of a meta-analysis, demonstrating that maladaptive coping styles (i.e., self-blame and escape-avoidance) are significantly associated with psychological outcomes for acute stressors but not for chronic stressors (Penley et al., 2002).

As expected, schizophrenia patients experienced poorer quality maternal and paternal relationships and more parental loss relative to healthy individuals. However, there were no group differences in the frequency of sexual or physical abuse, which may have been due to the low incidence of abuse reported in the present study. Thus, future studies with larger sample sizes will help to clarify these results.

Consistent with the study's predictions, greater early life adversity moderated stress-symptom relationships in schizophrenia. For schizophrenia patients who experienced parental loss, interpersonal chronic stress was found to be strongly associated with negative symptoms. Positive associations between social evaluative episodic stressors and negative symptoms were also observed in schizophrenia patients with poor quality relationships with their mothers. There are a variety of psychobiological pathways by which early life adversity can lead to symptom exacerbation following life stress in schizophrenia. Several studies have found that early life adversity can produce disturbances within the dopamine system, which is dysregulated in schizophrenia patients (Lewis et al., 1990; Kehoe, Shoemaker, Arons, Triano, & Suresh, 1998;

Cabib et al., 2002; Pruessner, Champagne, Meaney, & Dagher, 2004). Early life experience can also influence cortisol reactivity through epigenetic regulation of the hippocampal glucocorticoid receptor gene. More specifically, the epigenetic changes associated with low levels of maternal care can lead to a reduced capability to shut off the cortisol response in adulthood (McGowan et al., 2009; Weaver et al., 2004). Taylor and colleagues (2006) have also reported that offspring from family environments characterized by harsh parenting show signs of greater amygdala activation to emotional stimuli as well as a significantly positive relationship between right ventrolateral prefrontal cortex and amygdala activation. This pattern of findings suggests that these individuals over-react to and demonstrate an inability to regulate their responses to emotional stimuli, which can result in heightened cortisol reactivity via amygdala innervations of the hypothalamic nuclei (Frankel et al., 1978; Ghashghaei & Barbas, 2002; Herman et al., 2003; Risold et al., 1997; Saphier & Feldman, 1986). Lastly, prior work has shown that poor parental care creates deficits in an individual's ability to interact with others in an effective manner as well as cope successfully with social evaluative stress throughout the life span (Repetti et al., 2002; Taylor et al., 2004).

It is also important to highlight that it was the influence of the maternal relationship, not the paternal relationship, which influenced stress vulnerability in schizophrenia. This maternal specific effect may have been due to the fact that many schizophrenia patients in the present sample did not have contact with a paternal figure during their childhood. Prior research has also shown that social aspects of the early environment, especially maternal care, are closely linked to epigenetic regulation, which may in turn influence biological reactivity in adulthood (McGowan et al., 2009; Taylor, Way, & Seeman, 2011; Weaver et al., 2004).

In support of the study's hypotheses, increased stress sensitivity was only found in schizophrenia patients who were carriers of the *Met* allele of the COMT polymorphism. In particular, these individuals displayed greater negative symptoms following interpersonal chronic stress. COMT, however, did not moderate stress-symptom relationships in healthy individuals. These findings are consistent with the Warrior/Worrier model of COMT (Stein et al., 2006), which suggests that the *Val* allele is a risk factor for cognitive dysfunction but a protective factor in stressful situations (warrior) while the *Met* allele reflects enhanced performance on cognitive tasks but results in exaggerated reactivity to aversive stimuli (worrier). Although the mechanisms underlying this stress-sensitivity of *Met* allele carriers are not entirely clear, there is evidence to suggest that the functioning of the pre-frontal cortex (PFC) is involved. According to the inverted U-shaped dose response curve described earlier, schizophrenia patients who are *Met* allele carriers likely experience decreased prefrontal efficiency under challenging tasks (Mattay et al., 2003), which can lead to increased amygdala and cortisol reactivity (Herman et al., 2003), and ultimately increases in negative symptoms (Walker & Diforio, 1997; Walker, Mittal, & Tessner, 2008). Consistent with this biological interpretation, there is behavioral evidence showing that the emotional information processing biases displayed by individuals who are carriers of the *Met* allele can lead to behaviors characteristic of negative symptoms, including a lack of interest in the external world, decreased goal-directed behavior, and flattened affect (Bilder et al., 2004; Costas et al., 2011).

The U-shaped curve model of PFC functioning also provides a framework for evaluating how the *Met* allele might lead to increases in negative symptoms following the experience of chronic but not episodic stress. In particular, an episodic stressor may not have produced enough DA release to shift the *Met* allele's placement away from the optimal peak of the curve, thereby

resulting in reduced prefrontal efficiency. However, the experience of interpersonal stress on a chronic basis may have produced enough DA release to lead to information processing biases and ultimately symptom exacerbation.

Taken together, these findings demonstrate that trait affect, coping styles, early life adversity, and genetic factors are important to consider when differentiating which patients may be more vulnerable to stress-induced relapse. Moreover, the results suggest that tailoring interventions to individual patient characteristics may be particularly helpful in reducing symptom exacerbation in schizophrenia. Prior work indicates that individualized interventions targeted at helping schizophrenia patients develop specific coping strategies to more effectively confront and manage stressors can be very effective (Hogarty, 2002). Furthermore, there is growing evidence to suggest that interventions that elicit positive emotions, including Mindfulness exercises, decrease relapse rates in schizophrenia patients (Bach & Hayes, 2002; Bach, Hayes, & Gallop, 2012).

Biological Mechanisms

In assessing cortisol reactivity, schizophrenia patients were found to demonstrate an elevated and flattened cortisol response to the psychosocial stressor as compared to the healthy comparison group. This flattened cortisol response in schizophrenia patients may be characteristic of allostatic load (McEwen, 1998), or it may have been the result of a biological ceiling effect, given that patients were significantly elevated in their baseline cortisol levels. Alternatively, there is data to suggest that patients' reduced cortisol reactivity immediately after a psychosocial stressor may be the result of a delayed cortisol response (Brenner et al., 2009). Because the present study did not monitor cortisol continuously throughout the post-exposure period, it is possible that schizophrenia patients' peak cortisol responses may have been missed.

However, when examining the Area Under the Curve with respect to ground measure of cortisol, which is an indicator of total cortisol output, schizophrenia patients did not differ from healthy individuals.

As hypothesized, the individual characteristics of poor quality maternal relationships and low trait positive affect were related to greater cortisol responses to a laboratory psychosocial stressor characterized by social evaluation in the schizophrenia patient group. Low trait positive affect as well as greater reliance on maladaptive coping styles were also associated with greater cortisol reactivity among healthy individuals, paralleling prior research (Arnetz et al., 1991; Rosenberger et al., 2004). However, adaptive coping, parental loss, and the *Met* allele of COMT were not found to be related to cortisol reactivity in the current investigation.

When integrating these cortisol results with the behavioral data from the previous study, an interesting pattern of findings emerges. Specifically, the individual characteristics that moderated the relationship between *episodic* social evaluative stress and clinical symptoms (i.e., low trait positive affect, poor quality maternal relationships, and greater use of maladaptive coping styles) were also associated with increased cortisol reactivity to a laboratory psychosocial stressor. Thus, it appears that cortisol may underlie *episodic* stress-symptom relationships in schizophrenia patients and healthy individuals. In contrast, the patient characteristics that moderated the associations between interpersonal *chronic* stress and clinical symptoms (i.e., greater use of adaptive coping styles, more parental loss, *Met* allele of COMT) were not related to cortisol reactivity in the present study.

The disparate findings between episodic and chronic social evaluative stress may be attributable to the type of laboratory stressor and cortisol measures that were used in the present study. In particular, given that the TSST (Kirschbaum et al., 2003), is an acute psychosocial

stressor, the cortisol response evoked by this task would be very similar to cortisol reactivity following a real life episodic life stressor. Thus, if specific individual characteristics do indeed influence *episodic* stress-symptom relationships through increased cortisol reactivity, these effects in cortisol would likely be observed through the laboratory stressor design used in the present investigation. However, *chronic* interpersonal stress may lead to symptom exacerbation through multiple instances of cortisol dysregulation, including a general flattening of the diurnal cortisol rhythm, an exaggerated cortisol response following a stressful event, and delayed recovery of the cortisol response (McEwen, 1998; Pruessner, Hellhammer, & Lupien, 2003). In turn, the use of cortisol measures that only captured the peak response to the TSST may have prevented important effects from being detected. Thus, reliance on a variety of cortisol measures (e.g., diurnal rhythm, cortisol reactivity and recovery) in future research may reveal that individual characteristics (e.g., adaptive coping, parental loss, and the *Met* allele) that influence chronic-stress symptom relationships are also related to the cortisol response.

An absence of associations between parental loss and the *Met* allele with cortisol reactivity may have also occurred because the influence of these characteristics depends on other variations in COMT or early life adversity. For example, prior work has shown that COMT interacts with other genes in the dopamine system to influence the cortisol response (Alexander et al, 2011). Moreover, studies have reported that parental loss is only associated with cortisol dysregulation if parenting by the surviving parent or caregiver is poor (Luecken, 2000).

Limitations

In order to maximize sample size and increase statistical power, first-episode and chronic schizophrenia patients were collapsed to form a single group. Although the two groups did not significantly differ in symptomatology or in their responses to most dependent measures,

significant disparities emerged for age, duration of illness and utilization of adaptive and supportive coping styles. The present investigation attempted to address these differences statistically; however, the possibility remains that collapsing the patient groups may have precluded detection of important associations between some of the psychosocial, clinical, and physiological variables. Because the patients participating in this study were clinically stable and relatively low in symptoms, they also cannot be considered entirely representative of the general schizophrenia population.

In addition, this investigation was cross-sectional and correlational in design, and thus, did not allow for examination of causality among variables. Although the present findings suggest that trait positive affect, early life adversity, and maladaptive coping styles are associated with increased cortisol responses, these relationships may be bidirectional. It is also possible that patients with elevated baseline clinical symptoms are more reactive to stress, both behaviorally and biologically, and also may be more likely to report greater levels of psychosocial adversity. Although follow-up analyses controlling for baseline clinical symptoms in a subset of schizophrenia patients indicated that the main findings did not change, future studies controlling for baseline symptom levels in the entire sample, including in healthy individuals, may be warranted. Furthermore, the cortisol and life stress data were collected at a different time point than the symptom measurements which relied upon a retrospective analysis of the preceding three months. Other psychosocial variables included in this study were similarly derived from retrospective reports as well as self-reported questionnaires on a single occasion, which may represent less reliable measures of these constructs. The estimates of prevalence of early life adversity as well as the scores for the psychosocial variables were comparable to prior research, however, even though this study did not corroborate the participants' reports through

observational data or third party reporters. The current investigation also used interview measures of life stress as well as early life adversity to help reduce subjective response biases. Nonetheless, to reduce recall bias, memory distortion, or any influence of the current mood state on measures of trait affect, future research would benefit from using longitudinal designs and more observational measures to further clarify stress-symptom relationships and the mediating role of cortisol in schizophrenia.

Conclusions and Future Directions

Notwithstanding these limitations, the present results provide important insights regarding the nature of stress reactivity in schizophrenia. By integrating behavioral and biological levels of analysis, the current results revealed that social evaluative stress is associated with clinical symptoms in schizophrenia patients as well as depressive symptoms in healthy individuals. Furthermore, greater psychosocial vulnerability, including low levels of trait positive affect, reduced use of adaptive coping styles, more early life adversity, as well as the *Met* allele of the COMT polymorphism, appear to place individuals at greater risk for increased symptom levels following the experience of social evaluative stress. Consistent with the neural-diathesis stress model of schizophrenia (Walker & Diforio, 1997; Walker, Mittal, & Tessner, 2008), these results support the theory that cortisol is likely one of the biological pathways underlying episodic stress-symptom relationships in schizophrenia.

Given that specific stressor and individual characteristics help explain the considerable variability in stress-symptom relationships across individuals with schizophrenia, future research would benefit from additional analyses within this broader domain. Other characteristics that have been found to influence the cortisol response include social support (e.g., Eisenberger et al., 2007) personality traits (e.g., Pruessner et al., 1998; Savic et al., 2011), and other genetic

variations in the dopamine system (e.g., Armbruster et al., 2009). Research with a larger sample would also provide greater opportunities to examine interactions between the different patient characteristics and their influence on stress-symptom relationships. In addition, work clarifying the mechanistic role of cortisol using naturalistic stressors in addition to laboratory stressors is an important direction for future research. Together, these results can provide important information for the development of future interventions with schizophrenia patients that are aimed at resolving stress in the lives of individuals with this chronic and highly debilitating condition.

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