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STRESS REACTIVITY IN BORDERLINE PERSONALITY DISORDER

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Lori Nicole Scott

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The dissertation of Lori Nicole Scott was reviewed and approved* by the following:

Kenneth N. Levy
Associate Professor of Psychology
Dissertation Advisor
Chair of Committee

Aaron L. Pincus
Professor of Psychology

Reginald B. Adams
Assistant Professor of Psychology

Douglas A. Granger
Professor of Biobehavioral Health and Human Development and Family Studies

Melvin M. Mark
Professor of Psychology
Head of the Department of Psychology

*Signatures are on file in the Graduate School

ABSTRACT

Emotional dysregulation is seen by many clinicians and researchers as a core feature of borderline personality disorder (BPD). However, studies of emotional reactivity among individuals with BPD have yielded mixed findings, leaving uncertainty regarding the nature of emotional dysregulation in BPD. The current study examined neuroendocrine, autonomic, and subjective emotional reactivity in response to a social stress paradigm (the Trier Social Stress Test; Kirschbaum, Pirke, & Hellhammer, 1993) in 33 women with BPD as compared to two psychologically healthy comparison groups: 27 women who scored similarly to the BPD group on measures of trait negative affect and impulsivity (temperamentally-matched controls (TMCs)); and 30 women who scored in the average range on these traits (non-temperamentally-matched controls (NTMCs)). Repeated saliva samples were taken at eight time points and assayed for salivary cortisol and alpha-amylase (sAA). In addition, subjective stress response and changes in negative affect were measured through self-report instruments. It was hypothesized that the BPD group, in comparison to both control groups, would demonstrate greater cortisol, sAA, and subjective negative affective reactivity and impaired recovery to baseline levels after stress.

Contrary to the hypotheses, the results suggested neuroendocrine and autonomic *hyporeactivity* accompanied by high general negative affectivity in those with BPD. Specifically, the BPD group demonstrated attenuated cortisol and sAA reactivity to the stressor as compared to both comparison groups. Although the BPD group reported more negative affect overall across the experiment than both comparison groups, there was

only a marginally significant difference between the NTMC and BPD groups in post-stress negative affect when controlling for pre-stress negative affect. In addition, both the BPD and TMC groups reported experiencing the procedure as more stressful than the NTMC group. BPD patients who reported higher levels of childhood trauma tended to have higher baseline sAA, less sAA reactivity, and a trend toward higher overall sAA output, in comparison to both healthy controls and BPD patients who reported less severe childhood trauma.

These results add to the emerging body of literature suggesting extreme negative affectivity, but not necessarily hyperreactivity, of emotional responses in those with BPD. Moreover, the attenuated cortisol and sAA reactivity in the BPD group suggests dysregulation of the stress response system in these patients that manifests in hyporeactivity, rather than hyperreactivity, at the level of glucocorticoid and central noradrenergic output in response to stress. The differences between the BPD and TMC groups in most indices of emotional response suggest that trait negative affect and impulsivity cannot fully explain extreme negative affectivity or neuroendocrine abnormalities in patients with BPD.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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Chapter 1

INTRODUCTION

Significance

The primary aim of the present study is to examine neuroendocrine, autonomic, and subjective emotional reactivity to a social stressor in individuals with borderline personality disorder (BPD). According to the current *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. [*DSM-IV-TR*]; American Psychiatric Association [APA], 2000), BPD is characterized by a pervasive, longstanding, and inflexible pattern of instability in affect, behavior, self-image, and interpersonal relationships that begins by early adulthood. BPD is estimated to occur in 1 to 6 percent of the general population (Grant et al., 2008; Lenzenweger, Lane, Loranger, & Kessler, 2007; Samuels, Eaton, Bienvenu, Brown, Costa, & Nestadt, 2002; Taylor & Reeves, 2007; Torgersen, Kringlen, & Cramer, 2001). The disorder is even more common in clinical populations, with estimated prevalence rates of 9 to 23 percent in psychiatric outpatients (Alnaes & Torgersen, 1988; Korzekwa, Dell, Links, Thabane, & Webb, 2008; Oldham, Skodol, Kellman, & Hyler, 1995; Zimmerman & Mattia, 1999; Zimmerman, Rothschild, & Chelminski, 2005) and up to 44 percent in psychiatric inpatients (Grilo et al., 1998; Marinangeli et al., 2000). Individuals with BPD demonstrate profound impairment in general functioning (Skodol, Gunderson, McGlashan et al., 2002; Widiger & Weissman, 1991), marked impulsivity (e.g., Kruedelbach, McCormick, Schulz, & Grueneich, 1993;

Links, Heslegrave, & van Reekum, 1999; Russ, Shearin, Clarkin, Harrison, & Hull, 1993; Zanarini, 1993), and high levels of anger and hostility (Gardner, Leibenluft, O'Leary, & Cowdry, 1991; Kernberg, 1984; Raine, 1993). In addition, BPD patients are at increased risk for self-injurious and suicidal behaviors (Black, Blum, Pfohl, & Hale, 2004; Soloff, Lis, Kelly, Cornelius, & Ulrich, 1994) with an estimated suicide completion rate of up to 10 percent (McGlashan, 1986; Oldham et al., 2001). Thus, BPD is a highly prevalent, painful, and debilitating disorder, and represents a serious clinical and public health concern (Skodol, Gunderson, Pfohl, et al., 2002).

In addition, BPD is a highly complex clinical problem that poses considerable challenges in its diagnosis and treatment. According to the *DSM-IV-TR* (APA, 2000), the diagnosis of BPD is made based on meeting at least five of nine symptom criteria, including affective instability, frantic efforts to avoid abandonment, chaotic interpersonal relationships, identity disturbance, intense and inappropriate anger, impulsive self-destructive behaviors, chronic feelings of emptiness, repeated suicide attempts or self-injury, and stress-induced transient paranoia or dissociation. These diagnostic guidelines result in 151 potential ways of meeting the BPD diagnosis (Skodol, Gunderson, Pfohl et al., 2002); consequentially, there is considerable heterogeneity in the presentation of patients with this disorder. Further complicating matters, approximately 85 percent of BPD patients meet the diagnostic criteria for at least one comorbid psychiatric disorder (Lenzenweger et al., 2007), often demonstrating a pattern of complex comorbidity (Zanarini et al., 1998) characterized by the co-occurrence of both internalizing and externalizing disorders. Although BPD often co-occurs with various other Axis I and II disorders, it is more commonly diagnosed than any other Axis II personality disorder

(Widiger & Trull, 1993), and it often negatively affects the course and prognosis of Axis I disorders (Skodol, Gunderson, Pfohl, et al., 2002).

Moreover, those with BPD tend to have more functional impairment than individuals with other personality disorders who do not also have BPD (Hueston, Mainous, & Schilling, 1996; Nakao et al., 1992). BPD patients also have the highest rates of healthcare service use among patients with personality disorders (Hueston et al., 1996). Individuals with BPD are frequent users of both medical and mental health services (Bagge, Stepp, & Trull, 2005; Bender et al., 2001, 2006; Bongar, Peterson, Golann, & Hardiman, 1990; Clarke, Hafner, & Holme, 1995; Sansone, Songer, & Miller, 2005; Sansone, Wiederman, & Sansone, 1998; Skodol, Buckley, & Charles, 1983; Zanarini, Frankenburg, Khera, & Bleichmar, 2001) and have high incidence of chronic health problems (El-Gabalawy , Katz , & Sareen, 2010; Frankenburg & Zanarini, 2004). For example, although BPD patients made up only one percent of the patient population seen in a psychiatric emergency room, they accounted for 12 percent of all general emergency room visits (Bongar et al., 1990) and 20 percent of psychiatric hospitalizations (Zanarini et al., 2001). Early mortality rates from illness-related complications or suicide among those with BPD can exceed 18 percent (Paris, 2002).

Evidence suggests that emotional dysregulation is one of the most prominent, problematic, and enduring features of BPD (Conklin, Bradley, & Westen, 2006; Glenn & Klonsky, 2009; Gunderson & Phillips, 1991; Linehan, 1993, 1995; McGlashan et al., 2005; Siever, Torgersen, Gunderson, Livesley, & Kendler, 2002; Tragesser, Solhan, Schwartz-Mette, & Trull, 2007). The definition of emotional dysregulation often applied to BPD is that of heightened emotional reactivity and impaired recovery (Linehan, 1993,

1995). For individuals with this disorder, subtle and benign events in the environment can evoke intense emotional responses, which may rapidly spiral into functionally debilitating and life-threatening behaviors such as angry outbursts, self-injury, and suicide attempts (Klonsky, 2007, 2009). In addition, chronic and repeated emotional stress can have detrimental effects for cognitive functioning, general health, and longevity.

Unfortunately, despite a rapidly growing literature of empirical studies that have examined emotional responses in BPD, the concomitants and mechanisms of emotional dysregulation in BPD patients are not yet well understood. Although numerous studies have demonstrated that BPD patients tend to report high levels of subjective negative affect (Conklin et al., 2006; Cowdry, Gardner, O'Leary, Leibenluft, & Rubinow, 1991; Ebner, Linehan, & Bohus, 2004; Ebner-Priemer et al., 2007, 2008; Henry et al., 2001; Herpertz et al., 1997; Jacob et al., 2009; Koenigsberg et al., 2002; Kuo & Linehan, 2010; Levine, Marziali, & Hood, 1997; Marissen, Meuleman, & Franken, 2010; Sinha & Watson, 1997; Stein, 1996; Stiglmayr et al., 2005; Tolpin, Gunthert, Cohen, & O'Neil 2004; Yen, Zlotnick, & Costello, 2002), the biological correlates of emotional dysregulation in terms of physiological responding remain ambiguous (Rosenthal et al., 2008; Zimmerman & Choi-Kain, 2009).

In addition, the psychological substrates of emotional dysregulation in BPD are still poorly understood. Several theorists (Cloninger, Svrakic, & Przybeck, 1993; Depue & Lenzenweger, 2001; Gurvits, Koenigsberg, & Siever, 2000; Henry et al., 2001; Herpertz et al., 1997; Linehan, 1993; Paris, 2000; Siever & Davis, 1991; Silk, 2000; Svrakic, Svrakic, & Cloninger, 1996; Trull, Sher, Minks-Brown, Durbin, & Burr, 2000;

Trull, 2001; Widiger & Costa, 2002) argue that emotional reactivity in BPD results, at least in part, from a temperamental and/or trait disposition characterized by high levels of trait negative affect (i.e., anger, anxiety, and depression; Watson & Clark, 1992) and impulsivity. However, the role of temperament has not yet been examined in experimental studies of emotional reactivity among those with BPD. It remains unclear whether emotional dysregulation in BPD represents an extreme variant of normal-range temperamental dimensions of negative affect and impulsivity.

In the effort to validate and maximize the effectiveness of current models of treatment that emphasize emotional dysregulation as a core feature of the disorder (e.g., Linehan, 1993, 1995), it is important to examine the biological and psychological concomitants of emotional dysregulation in those with BPD. Describing the characteristic phenomenological and physiological responses of BPD patients to a realistic and socially relevant stressor may help to reveal the psychological and biological mechanisms of extreme emotional reactions in patients with BPD. This understanding would inform clinical theories of BPD and may lead to the identification of preventative strategies and the development of more efficacious psychosocial and pharmacological treatments that specifically target these processes. Moreover, the examination of emotional reactivity in healthy individuals who are high in trait negative affect and impulsivity, as compared to reactivity in BPD patients, would contribute to our understanding of temperamental disposition as a putative underlying mechanism of emotional dysregulation in BPD.

Emotional Dysregulation in Borderline Personality Disorder

Linehan's (1993, 1995) biosocial theory of BPD proposes that *biological vulnerability* (i.e., high sensitivity to emotional stimuli, high emotional intensity, and difficulty modulating affect and returning to baseline moods after stressful situations) is a core component of emotional dysregulation in BPD. According to this theory, patients with BPD demonstrate emotional hyperreactivity at both phenomenological and biological levels. Other theorists (e.g., Kernberg, 1984, Depue & Lenzenweger, 2001) have also emphasized emotional dysregulation as a central aspect of BPD that is at least partially biologically determined.

Although there is ample evidence that BPD patients experience phenomenological emotional dysregulation, the evidence for biological hyperreactivity is more ambiguous (Rosenthal et al., 2008). Numerous studies suggest that BPD patients tend to report intense negative affective experiences and difficulty modulating negative affective states (Conklin et al., 2006; Ebner et al., 2004; Henry et al., 2001; Levine, Marziali, & Hood, 1997; Marissen et al., 2010; Sinha & Watson, 1997; Stiglmayr et al., 2005; Yen et al., 2002). In addition, patients with BPD tend to report excessive mood instability (Cowdry et al., 1991; Ebner-Priemer et al., 2007; Stein, 1996; Tolpin et al., 2004) with rapid alterations in moods (Ebner-Priemer et al., 2007; Herpertz et al., 1997; Koenigsberg et al., 2002) as well as enhanced and prolonged stress responses (Ebner-Priemer et al., 2007) and anger responses (Jacob et al., 2008). There is also evidence that BPD patients experience more distress in their daily lives than healthy controls, and more emotional reactivity in response to daily life stress compared to patients with psychotic disorders

and healthy controls (Glaser, Van Os, Mengelers, & Myin-Germeys, 2008). Moreover, studies have shown that BPD features are associated with increased interpersonal stress (Daley, Hammen, Davila, Burge, 1998; Trull, 1995) and that BPD patients report intense affective responses to interpersonally relevant stimuli (Herpertz et al., 1997).

Despite these findings suggesting subjective emotional dysregulation in BPD, some recent studies have demonstrated that BPD patients report heightened negative emotions but not heightened reactivity, or change, in subjective negative affect in response to distressing situations. For example, in response to a standard mood induction task, Jacob et al. (2009) found that BPD patients reported more negative emotion overall but did not differ from either healthy controls or patients with major depressive disorder in their increase or decrease of emotions. Similarly, Kuo and Linehan (2010) found that women with BPD reported more baseline negative emotion than healthy controls, but there were no differences between groups in subjective negative emotional reactivity to a mood induction task. Moreover, the BPD patients did not differ from patients with social anxiety disorder in self-reported negative emotions. Herpertz, Kunert, Schwenger, and Sass (1999) also found no evidence of heightened self-reported arousal in BPD patients in response to negatively valenced slides, although the BPD patients evaluated pleasant slides as significantly less pleasant, as compared to healthy controls.

Hence, although there is evidence from multiple studies that BPD patients experience intense negative affect, the evidence for hyperreactivity of negative affect is less clear. In addition, although BPD patients may tend to *report* emotional dysregulation, self-report measures are susceptible to bias and do not provide information regarding the biological aspects underlying these experiences. The evidence for

biological vulnerability to emotional dysregulation in BPD from studies of physiological reactivity to environmental stressors is limited and fraught with inconsistencies in results.

In support of the notion that emotional dysregulation in BPD is accompanied by biological vulnerability, there is strong evidence from structural and functional neuroimaging studies of central nervous system correlates of emotional dysregulation in patients with BPD (de la Fuente et al., 1997; Driessen et al., 2000; Hoerst et al., 2010; Irle, Lange, & Sachsse, 2005; Johnson, Hurley, Benkelfat, Herpertz, & Taber, 2003; Juengling et al., 2003; Lis, Greenfield, Henry, Guilé, & Dougherty, 2007; Rusch et al., 2003; Schmahl, Vermetten, Elzinga, & Bremner, 2003; Silbersweig et al., 2007; Soloff, Meltzer, Greer, Constantine, & Kelly, 2000; Soloff et al., 2003; Tebartz van Elst et al., 2001, 2003; Zetzsche et al., 2006). These studies have generally shown abnormalities in frontolimbic circuitry that suggest difficulties in modulating emotional arousal, processing emotional stimuli, and inhibiting behavioral responses (see Brendel, Stern, & Silbersweig, 2005 and Lis et al., 2007 for reviews). Many of these abnormalities have been observed in emotionally evocative or interpersonally relevant contexts; for example, abnormal activation has been observed in prefrontal and anterior cingulate cortex areas in response to abandonment (Schmahl, Elzinga, et al., 2003) and trauma (Schmahl, Vermetten, Elzinga, & Bremner, 2004) scripts, and amygdala hyperreactivity has been observed in response to socially relevant stimuli (Donegan et al., 2003; Herpertz et al., 2001).

There is also evidence using event-related potential technology of enhanced elaborative processing and stronger reactivity to negative emotional stimuli in BPD patients as compared to healthy controls (Marissen et al., 2010). Accordingly,

neurocognitive studies suggest that BPD patients have difficulty suppressing negative emotional material (e.g., Arntz, Appels, & Sieswerda, 2000; Domes et al., 2006; Sieswerda, Arntz, Mertens, & Vertommen, 2007). In a review of neuroimaging studies with BPD patients, Lis et al. (2007) proposed that BPD patients demonstrate difficulties controlling emotional thought with rational thought, contributing to emotional dysregulation and hyperreactivity.

Based on these observed neural correlates of emotional hyperreactivity, the intuitive hypothesis emerges that BPD patients may also demonstrate dysregulation of the stress response system, as assessed by autonomic and hypothalamic-pituitary-adrenal axis functioning. However, support for the biological vulnerability hypothesis from measures of the stress response system in patients with BPD has been equivocal (Rosenthal et al., 2008; Zimmerman & Choi-Kain, 2009), with results seeming as heterogeneous and complex as the disorder. These studies will be reviewed below after a brief introduction to the mammalian stress response system.

The Stress Response System

The mammalian stress response consists of two primary physiological components: the rapid activation of the autonomic nervous system (ANS)/sympathetic-adrenomedullary (SAM) system and the relatively slower activation of the hypothalamic-pituitary-adrenal (HPA) axis. Upon onset of a stressful or emotionally evocative event, the sympathetic division of the SAM is first activated, resulting in the rapid release of catecholamines, including norepinephrine from the locus coeruleus and epinephrine from

the adrenal medulla, as part of the body's "fight or flight" response (Cannon, 1914). Catecholamines trigger second-messenger cascades in postsynaptic target tissues within seconds after secretion (McEwen, 1995).

Minutes later, the HPA axis is activated by sympathetic nervous system (SNS) input, triggering the release of corticotrophin releasing hormone (CRH) from the hypothalamus. CRF travels through the blood to the anterior pituitary, which then releases adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH then signals the adrenal cortex to produce and release glucocorticoids, including cortisol. Cortisol is normally secreted at a rate of about 10mg daily in humans, but cortisol levels can increase at least 10-fold in response to stressful experiences (Schimmer & Parker, 1996). Cortisol levels tend to reach their peak approximately 20 to 30 minutes after the onset of an acute stressor (Kirschbaum & Hellhammer, 1989). In an inhibitory feedback loop, the presence of peak levels of cortisol signals the hypothalamus to stop releasing CRH, which in turn, suppresses ACTH levels and the subsequent release of more glucocorticoids (Posener, Schildkraut, Williams, & Schatzberg, 1997). Cortisol typically returns to near-baseline levels approximately 40 to 60 minutes after the conclusion of the stressful event (Seeman, Singer, Wilkinson, & McEwen, 2001; Young & Nolen-Hoeksema, 2001). Cortisol levels in a typical individual vacillate within the course of a day (diurnal variation) in a normal range, with the highest levels occurring in the early morning and lower levels in the evening (Kirschbaum & Hellhammer, 1989).

The stress response system is designed to protect the body in response to internal or external stress. The catecholamines released during SNS activation serve to activate behavior and mediate arousal and orientation to the environment; they also mediate

attention and learning, and can enhance encoding of emotionally laden information from stressful situations (for a review, see McEwen & Sapolksy, 1995). The cortisol that is released during HPA axis activation is involved in a number of vital bodily functions, including the modulation of immune functioning, central nervous system activity, glucose production, fat metabolism, and vascular responsiveness (Baxter, Frohman, & Felig, 1995). Short-term cortisol circulation in response to stress facilitates the breakdown of carbohydrates and proteins in order to increase the supply of glucose and oxygen to skeletal muscles, the heart, and the brain. In addition, cortisol suppresses reproductive, immune, and digestive functioning in order to conserve energy, promotes analgesia, and activates the peripheral autonomic nervous system. Through the negative feedback mechanism of the HPA axis, cortisol circulation also aids in restoring bodily homeostasis after periods of stress by suppressing further release of stress hormones. Thus, cortisol plays a central role in the moderation of the effects of stressful situations on behavior, mood, health, and the development of stress-related diseases (Meaney, Aitken, van Berkel, Bhatnagar, & Sapolsky, 1988; Breier, 1989).

Dysregulation of the Stress Response System

Both genetic variation and environmental experience play important roles in the calibration of the stress response system, which is especially malleable in early life (for review, see Boyce & Ellis, 2005). Evidence suggests that chronic stress and early trauma can alter the functioning of the stress response system, causing either abnormally high or low cortisol levels, abnormal cortisol suppression response to the presence of circulating

glucocorticoids, and/or abnormally high or low circulating levels of catecholamines (e.g., Negrao, Deuster, Gold, Singh, & Chrousos, 2000; Seeman et al., 2001). Dysregulation of the stress response system from repeated and chronic activation has wide-spread deleterious effects on general health and cognitive functioning. Several bodily tissues and functions can be destroyed or damaged due to over-exposure to glucocorticoids and catecholamines (for reviews, see Chrousos & Gold, 1992; King & Hegadoren, 2002; McEwen, 2004; McEwen & Sapolksy, 1995; Tsigos & Chrousos, 2002). The body's effort to accommodate to chronic physiological activation from prolonged stress places a demand on the organism, which is referenced in the literature as *allostatic load* (McEwen, 1998). Alterations in the functioning of the stress response system represent manifestations of allostatic load.

Dysregulated cortisol levels have been detected in connection with several psychiatric difficulties, including anxiety disorders (e.g., Hubert & deJong-Meyer, 1992; Yehuda, 1998, 2006), major depressive disorder (Burke, Davis, Otte, & Mohr, 2005), eating disorders (e.g., Piran, Kennedy, Garfinkel, & Owens, 1985), and schizotypal personality disorder (Weinstein, Diforio, Schiffman, Walker, & Bonsall, 1999), as well as in individuals who experienced early trauma (Heim et al., 2000; Rinne et al., 2002; Yehuda, 1998). Likewise, dysregulated ANS activity has been associated with a number of psychological disorders and personality traits, including neuroticism and anxiety (Dienstbier, 1989), as well as psychopathy and aggression (Lorber, 2004). Increased noradrenergic activity has been linked to irritable, aggressive, or defensive behavior (Levine, Litto, & Jacobs, 1990) and sensation-seeking (Dickerson, Hinchy, & Falve, 1987; Roy, Adinoff, & Linnoila, 1988). Evidence also suggests that increased

noradrenergic activity is associated with irritability and aggression in personality disordered populations (Coccaro et al., 1991).

Measurement of the Stress Response through Salivary Biomarkers

HPA axis functioning is most commonly assessed through measures of cortisol. Because cortisol is a lipophilic steroid with low molecular weight, it can enter cells by passive diffusion, making it possible to detect cortisol in all bodily fluids. Cortisol is most frequently measured in blood, urine, or saliva. Until recent decades, blood plasma (serum) cortisol was typically preferred over saliva, in part because of the belief that salivary cortisol levels might not accurately reflect serum cortisol levels (Kirschbaum & Hellhammer, 1989, 1994). In addition, changes in cortisol levels are detectable in the blood before they are reflected in saliva, and cortisol is present in higher concentrations in blood than it is in saliva. However, there are many disadvantages to serum cortisol, including the potential for cortisol reactivity in response to venipuncture. In addition, immediately following secretion into the bloodstream, about 90% of cortisol is bound to corticosteroid-binding globulin (CBG) and albumin, leaving only 5 to 10% of serum cortisol that is biologically “active” or “free” (Kirschbaum & Hellhammer, 1989).

On the other hand, because cortisol makes its way into saliva from the bloodstream via passive diffusion through the acinar cells lining the salivary glands, salivary cortisol is not bound by protein molecules, which means that the cortisol found in saliva is a more valid measurement of biologically active or "free" cortisol levels (Kirschbaum & Hellhammer, 1989, 1994). Furthermore, ultrasensitive assays for

salivary cortisol are now available (Maniga & Golinsky, 2001), and salivary cortisol measurement has been shown to be highly reliable, with most researchers demonstrating correlation coefficients of $r \geq .90$ between salivary and plasma free cortisol (Kirschbaum & Hellhammer, 1989, 1994). Studies have also shown that the time lag between peak serum cortisol levels and peak salivary cortisol levels is minimal. Other advantages of salivary cortisol include its noninvasiveness and simplicity. Multiple repeated saliva samples can be obtained in a short period of time and with difficult populations, such as small children. Salivary cortisol can also be collected any time and does not have to be obtained exclusively in the laboratory or with the help of highly trained personnel. Moreover, salivary cortisol levels are unaffected by salivary flow rate and remain stable at room temperature, through transport between labs, and over repeated freezing and thawing cycles (Granger et al., 2006). For these reasons, salivary cortisol is increasingly becoming the preferred method of HPA axis assessment.

Until recently, non-invasive methods of assessing ANS activation have been lacking. However, researchers have recently discovered that salivary alpha-amylase (sAA), an enzyme that is released from the salivary glands under conditions of both physiological and psychological stress, may be a marker for noradrenergic activity from activation of the SNS in response to stress. Numerous studies (e.g., Bosch et al., 1996; Bosch, de Geus, Veerman, Hoogstraten, & Amerongen, 2003; Chatterton, Vogelsong, Lu, Ellman, & Hudgens, 1996; Chatterton, Vogelsong, Lu, & Hudgens, 1997; El-Sheikh, Erath, Buckhalt, Granger, & Mize, 2008; Gordis, Granger, Susman, & Trickett, 2006, 2008; Granger et al., 2006; Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009; Kivlighan & Granger, 2006; Nater et al., 2005, 2006; Skosnik, Chatterton, Swisher, &

Park, 2000) have demonstrated increased sAA levels in response to stress. In addition, positive correlations have been observed between sAA concentrations and baseline plasma norepinephrine levels (Chatterton et al., 1996), stress-evoked change in norepinephrine levels (Chatterton et al., 1997), and sympathetic tone based on cardiovascular measures (Nater et al., 2006). Furthermore, the degree of sAA reactivity in response to emotionally arousing stimuli has been shown to predict the strength of long-term memory for those stimuli (Segal & Cahill, 2009). This is strong support for the link between sAA levels and SNS activity because catecholamines released during SNS arousal can enhance memory for emotionally laden information (McEwen & Sapolksy, 1995). Studies have also demonstrated that stress-related increases in sAA can be inhibited by beta-adrenergic receptor blockers (Speirs, Herring, Cooper, Hardy, & Hind, 1974; van Stegeren, Rohleder, Everaerd, & Wolf, 2006) and stimulated by beta-adrenergic agonists without increasing salivary flow (Gallacher & Peterson, 1983). Moreover, sAA response patterns to a variety of stressors closely correspond to the response patterns of the SNS. Specifically, sAA response patterns tend to show a rapid rise immediately upon introduction of a stressor followed by a rapid decline, as opposed to the slower peak and recovery that is seen in salivary cortisol responses.

Although the above findings strengthen the association between sAA and SNS activity, there is still some uncertainty regarding the specific relationship between sAA and social-stress-related changes in peripheral catecholamines (Nater et al., 2005, 2006; Nater & Rohleder, 2009; Rohleder, Nater, Wolf, Ehlert, & Kirschbaum, 2004). Based on a recent review of the literature, Nater and Rohleder (2009) concluded that sAA secretion appears to be largely determined by sympathetic/parasympathetic activity, with inputs

from both alpha-adrenergic and the beta-adrenergic mechanisms. Recent research also suggests that beta-adrenergic mechanisms from SNS activation are the main contributors to sAA secretion, suggesting that sAA may reflect central (as opposed to peripheral) noradrenergic activity (Ehlert, Erni, Hebisch, & Nater, 2006; Nater & Rohleder, 2009; Rohleder & Nater, 2009). Further, studies have shown that although sAA increases with stress, it does not correlate with stress-related cortisol levels, suggesting that sAA is independent from HPA axis functioning and measures a different aspect of the stress response system that is not redundant with the HPA axis (Chatterton et al., 1996; Granger et al., 2006; Nater et al., 2006).

Dysregulation of the Stress Response System in Patients with BPD

Several theorists have proposed that affective instability, impulsive aggression, and hyperreactivity to environmental cues in BPD could be mediated through hyperresponsiveness of the noradrenergic system (Figueroa & Silk, 1997; Siever & Davis, 1991; Skodol, Siever, et al., 2002). There is also evidence that HPA axis hyperactivity may underlie monoaminergic abnormalities that are often associated with depression and suicidal behaviors (Dinan, 1996; Lopez, Vazquez, Chalmers, & Watson, 1997), which are commonly seen in BPD patients. Furthermore, a plethora of evidence suggests that the physiological stress response system is acutely sensitive to social events (Dickerson & Kemeny, 2004; Flinn & England, 1995), making individuals who tend to be particularly reactive in response to social perturbation especially susceptible to chronic physiological arousal and hyperresponsiveness of the stress response system.

Moreover, a hyperreactive stress response system may underlie many of the chronic health problems, neurocognitive impairments, and central nervous system abnormalities that have been observed in BPD patients (e.g., Driessen et al., 2000; Frankenburg & Zanarini, 2004; Irle et al., 2005; Paris, 2002; Ruocco, 2005; Schmahl, Elzinga, et al., 2003; Tebartz van Elst et al., 2003). Overexposure to stress hormones is associated with cardiovascular disease, chronic high blood pressure, suppressed immune system functioning, fatigue, gastrointestinal disease, muscle and bone atrophy, diabetes, and obesity (Juster, McEwen, & Lupien, 2010), which parallel many of the chronic health problems observed in BPD patients (El-Gabalawy et al., 2010; Frankenburg & Zanarini, 2004; Paris, 2002).

Additionally, excessive exposure to stress hormones is associated with neuronal damage and volume loss in the hippocampus (e.g., Sapolsky, 1996), as well as impaired learning, memory, and cognitive processing (e.g., Het, Ramlow, & Wolf, 2005; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Wolkowitz, Reuss, & Weingartner, 1990). Accordingly, several studies have demonstrated reduced hippocampal volumes (Driessen et al., 2000; Irle et al., 2005; Schmahl, Elzinga, et al., 2003; Tebartz van Elst et al., 2003), decreased baseline left hippocampal metabolism (Juengling et al., 2003), and deficits in cognitive capacities (see Ruocco, 2005 for a review) among BPD patients in comparison to healthy controls. Therefore, the functioning of the stress response system in patients with BPD can have important implications for understanding general functioning, health, and mortality for this patient population.

HPA Axis Dysregulation in BPD

Most studies of HPA axis functioning with BPD samples have used neuroendocrine challenge tests, with relatively fewer studies examining basal cortisol or cortisol response to environmental stressors. The most commonly used neuroendocrine challenge test in studies with BPD samples is the dexamethasone suppression test (DST), which involves administration dexamethasone (DEX), a synthetic glucocorticoid that normally suppresses cortisol levels through the HPA axis negative feedback system. Several studies have reported high rates of cortisol nonsuppression in response to the DST in BPD patients (Baxter, Edell, Gerner, Fairbanks, & Gwirtsman, 1984; Beeber, Kline, Pies, & Manring, 1984; Carroll et al., 1981; Kontaxakis et al., 1987; Krishnan, Davidson, Rayasam, & Shope, 1984; Lieb et al., 2004; Reus, 1982; Rinne et al., 2002; Silk, Lohr, & Cornell, 1985; Sternbach, Fleming, Extein Pottash, & Gold, 1983; Val, Gaviria, Lahmeyer, Prasad, & Weiler, 1985), which suggests hyposensitivity of the glucocorticoid negative feedback receptors and a consequential failure to effectively modulate circulating cortisol levels. The nonsuppression of cortisol in response to DEX in BPD patients parallels findings with depressed patient samples, who also typically demonstrate nonsuppression of cortisol in the DST (Burke et al., 2005; Gillespie & Nemeroff, 2005). In a review of DST studies with BPD patients, Zimmerman & Choi-Kain (2009) acknowledged that high rates of mood disorder comorbidity and the lack of assessment for mood disorders in many early DST studies with BPD samples make it difficult to separate nonsuppression that is due to BPD from nonsuppression that is attributable to comorbid depression. However, the rates of nonsuppression in BPD

samples without comorbid major depression tend to be approximately equal to or less than the rates of nonsuppression in non-BPD depressed patients (Zimmerman & Choi-Kain, 2009).

Another neuroendocrine challenge test that has been used with BPD samples is the combined DEX/CRH test, which involves an oral dose of DEX followed by intravenous administration the next day of CRH. The DEX/CRH test is reported to be more sensitive than the DST for detecting subtle HPA axis disturbance (Holsboer & Barden, 1996). Rinne et al. (2002) reported that BPD patients with severe childhood abuse demonstrated enhanced ACTH and cortisol response to the DEX/CRH challenge as compared to both BPD patients without childhood abuse and controls, but the BPD patients with comorbid post-traumatic stress disorder (PTSD) had lower ACTH response to DEX/CRH compared to BPD patients without PTSD. This finding suggests that childhood abuse and PTSD may have differential effects on the HPA axis in patients with BPD. Specifically, in patients with BPD, childhood abuse appears to be associated with "CRH overdrive" and hyposensitivity of glucocorticoid receptors, resulting in higher cortisol levels; on the other hand, PTSD appears to be associated with hypersensitivity of glucocorticoid receptors, resulting in strong negative feedback inhibition and lower cortisol levels. A later study (Rinne et al., 2003) demonstrated that fluvoxamine, a selective serotonin reuptake inhibitor, reduced ACTH and cortisol responses to DEX/CRH in female BPD patients, especially in those with histories of childhood abuse.

Yet another neuroendocrine challenge test that does not directly involve cortisol but is relevant for HPA axis functioning involves administration of thyrotropin-releasing hormone (TRH). Administration of TRH normally signals the pituitary gland to release

thyroid-stimulating hormone (TSH). TRH and TSH are products of the hypothalamic-pituitary thyroid (HPT) axis, and the HPA axis has a direct influence over the HPT axis. In the TRH test, a normal response is a rapid but short-lived rise in TSH levels, suggesting normal HPA axis functioning. Individuals with HPA axis dysregulation can show blunted, delayed, or absent TSH responses to TRH administration. Some studies using the TRH challenge test (Garbutt, Lossen, Tipermas, & Prange, 1983; Sternbach et al., 1983) have demonstrated that BPD patients tend to show the abnormal reaction of blunted TSH levels following TRH administration, further suggesting dysregulation of the HPA axis in BPD.

On the other hand, a number of studies have not found abnormal responses to neuroendocrine challenge tests in BPD samples (de la Fuente, Bobes, Vizuete & Mendlewicz, 2002; de la Fuente & Mendlewicz, 1996; Kavoussi, Coccaro, Klar, & Lesser, 1993; Korzekwa, Steiner, Links, & Eppel, 1991; Lahmeyer et al., 1988; Nathan, Soloff, George, Peters, & McCarthy, 1986; Siever et al., 1986). For example, Lange et al. (2005) found no difference in cortisol suppression in response to dexamethasone between BPD patients and controls, but these findings are difficult to interpret due to small sample sizes and the potential effects of comorbid PTSD. Rinne et al. (2002) only found enhanced ACTH and cortisol response to DEX-CRH in those BPD patients with histories of childhood abuse, and not in those with BPD and without childhood abuse. Carrasco et al. (2003) actually found higher cortisol suppression in response to a low-dose version of the DST among BPD patients in comparison to patients with other personality disorders, a result that is usually found among PTSD samples (see de Kloet et al., 2006, for a review). A later study (Carrasco et al., 2007) also demonstrated higher

cortisol suppression in a low-dose DST among BPD patients without comorbid PTSD, as compared to healthy controls. Some of the variation in DST results with BPD samples might be due to differences in the dosage of DEX; i.e., low-doses of DEX are often a more sensitive test for the detection of hypersuppression than higher doses of DEX.

Basal cortisol refers to cortisol levels that are not stimulated by endogenous substances or environmental stress. Studies that evaluate basal cortisol seek to determine individual differences in cortisol levels at particular times of day or in typical patterns of cortisol production across the entire day. In the latter case, researchers might examine individual differences in the amplitude or the slope of the diurnal rhythm of cortisol secretion across a 12 or 24-hour period. Studies using such methods with BPD patients are few in number, but generally suggest high basal cortisol levels in BPD. In a small sample of unmedicated female patients with comorbid BPD and major depressive disorder (MDD), Kahl et al. (2006) demonstrated high resting cortisol levels and an elevated ratio between cortisol and the endogenous steroid dehydroepiandrosterone (DHEA) as compared to healthy female participants. DHEA has antiglucocorticoid properties and may act as a buffer against the deleterious effects of cortisol (Blauer, Poth, Rogers, & Bernton, 1991); therefore, an elevated cortisol-DHEA ratio suggests HPA axis hyperreactivity and vulnerability to the potentially negative consequences of hypercortisolism. These results are difficult to interpret, however, given that the patients with BPD also had comorbid MDD. Nevertheless, in a somewhat larger sample of unmedicated female BPD patients *without* comorbid MDD, Lieb et al. (2004) reported higher total cortisol release in response to awakening and higher total daily cortisol levels in the BPD patients as compared to healthy controls.

Basal cortisol levels in BPD patients may vary depending on sample characteristics such as gender, comorbid PTSD, and childhood abuse history. For instance, Southwick et al. (2003) reported that male combat veterans with both BPD and PTSD had *lower* mean 24-hour urinary cortisol levels than those with PTSD and no diagnosis of BPD. On the other hand, Jogems-Kosterman, Knijff, Kusters, and van Hoof (2007) measured diurnal salivary cortisol levels in the morning and evening hours in a sample of female BPD patients compared to healthy controls, and reported that overall cortisol levels were only higher in those BPD patients with comorbid PTSD *and* a history childhood abuse. Nonetheless, the authors did find an elevated cortisol-DHEA ratio among the entire BPD sample compared to healthy controls, suggesting vulnerability to hypercortisolism in female BPD patients that is independent of PTSD and abuse. In addition, the BPD patients' cortisol decreased less throughout the day compared to the controls, further indicating potential hypercortisolism in BPD.

Only three published studies to date have investigated cortisol reactivity in BPD samples in response to realistic environmental stressors (Nater et al., 2010; Simeon, Knutelska, Smith, Baker, & Hollander, 2007; Walter et al., 2008). The first of these studies (Simeon et al., 2007) was with a small sample of 13 medication-free BPD outpatients who were recruited from the community through newspaper advertisements. Participants were subjected to a standardized stress procedure involving a speech and oral arithmetic task in front of observers (the Trier Social Stress Test (TSST); Kirschbaum, Pirke, & Hellhammer, 1993). The authors found no difference in cortisol reactivity between the whole BPD group and the healthy comparisons, but individuals with BPD *and* severe dissociation demonstrated significantly higher peak cortisol reactivity in

response to psychosocial stress relative to a low-dissociation BPD group and the healthy comparison group.

Simeon et al.'s (2007) finding of the relationship between dissociation in BPD and heightened cortisol reactivity is unexpected in light of evidence that dissociation may mitigate emotional responsiveness (e.g., Ebner-Priemer et al., 2005), but these results suggest the importance of measuring dissociation in studies of affective dysregulation in BPD patients. Perhaps BPD patients who dissociate are more severely disturbed than those who do not; on the other hand, perhaps BPD patients who are more emotionally reactive have more need to employ dissociation as an emotion-regulation strategy. Nonetheless, the results from this study may be limited in ecological validity, given that the BPD patients were not clinically referred and were medication-free, which may indicate an atypical study group that does not generalize to the BPD patients actually seen in clinical practice. Further, all participants were admitted to a hospital for over 24 hours in order to participate in the experiment, which introduces a non-naturalistic study environment and conditions. Other limitations to these findings include the small sample size, measurement of stress reactivity during the morning hours (when baseline cortisol levels tend to be higher), and use of venipuncture to measure cortisol (which can be invasive and may elicit an artificial stress response).

Walter et al. (2008) examined salivary cortisol reactivity in a small sample of female BPD patients in response to a conflict discussion with participants' mothers. In this study, the BPD group had elevated cortisol levels, as compared to a healthy control group, but only during the recovery period after the interpersonal stressor. The groups did not differ in baseline or immediate post-stress cortisol levels. Walter et al. interpreted

these results to suggest delayed HPA axis reactivity and impaired stress recovery in BPD. Although this study is limited by the small sample size and the measurement of cortisol at only three time points, its strengths include the use of clinically referred patients, saliva sampling rather than venipuncture, and a realistic and personally relevant stressor. However, the control group did not demonstrate an increase in cortisol at all following the stressor, which raises questions regarding the effectiveness of the conflict discussion for eliciting a stress response. It is possible that the BPD group's elevated cortisol levels during the recovery period were not related to the interpersonal stressor itself, but may have been the result of some unrelated process.

Extraordinarily different results were reported in a recent study by Nater et al. (2010), who examined salivary cortisol and sAA reactivity in response to a social stress (the TSST) in 15 medication-free women with BPD who were recruited via internet advertisement as compared to 17 healthy controls. The results demonstrated *lower* cortisol and sAA levels at baseline and *attenuated* cortisol and sAA response to stress in the BPD group as compared to the control group, even though the BPD group rated the procedure as more threatening than did controls. The BPD group also rated themselves as less able to cope with the stressor, but there were no differences between groups in general subjective stress response or plasma ACTH and catecholamine levels. Interestingly, the BPD sample demonstrated an elevated ACTH/cortisol ratio. Given that ACTH signals the adrenal cortex to release cortisol, an elevated ACTH/cortisol ratio suggests the potential for adrenal hyporesponsiveness to ACTH, which may result from prolonged or excessive activation of the HPA axis.

Nater et al.'s (2010) study is significant, as it is the first to report attenuated cortisol reactivity in response to a social stress situation among BPD patients. Nonetheless, these findings were limited by the small sample size and the non-clinically referred patient sample (i.e., recruited via internet advertisement). Additionally, although those with current MDD were excluded, one-third of the BPD sample had a comorbid diagnosis of PTSD. The small sample precluded meaningful examination of the influence of PTSD on these results. As acknowledged by the authors, replication of these findings with larger samples is necessary before drawing firm conclusions regarding patterns of neuroendocrine reactivity in patients with BPD.

Autonomic Dysregulation in BPD

Most studies of ANS responding in BPD samples have assessed sympathetic reactivity through methods such as skin conductance response (SCR), heart rate, blood pressure, startle response, adrenergic receptor activity, circulating norepinephrine levels, and more recently, sAA. As with studies of HPA axis functioning in BPD samples, the findings from these studies are also quite varied. Several studies suggest sympathetic hyperarousal in BPD patients (DeVegvar, Siever, & Trestman,1998; Ebner-Priemer et al., 2005, 2008; Hazlett et al., 2007; Kozel, 2001; Lobbestael & Arntz, 2010; Southwick, Yehuda, Giller, & Perry, 1990a, 1990b; Yehuda, Southwick, Perry, & Giller, 1994). For instance, Kozel (2001) found greater SCR in response to affectively valenced pictorial slides among individuals with BPD compared to nonclinical controls. Further, BPD patients who experienced childhood abuse at earlier ages tended to show higher

autonomic responses. Additionally, in response to an abuse-related film, Lobbestael & Arntz (2010) found greater increases in self-reported negative affect and in SCR in a BPD group as compared to non-patient controls and patients with antisocial personality disorder. Moreover, Ebner-Priemer et al. (2005) found that unmedicated female BPD patients showed larger startle response compared to healthy controls. Hazlett et al. (2007) also found larger startle response in a mixed-gender BPD sample as compared to healthy controls, although the BPD patients in this study reported lower emotional arousal on self-report questionnaires.

Recently, investigators have begun to examine vagal control over visceral responses in patients with BPD using respiratory sinus arrhythmia (RSA), a measure of parasympathetic functioning. Austin, Riniolo, and Porges (2007) measured RSA and heart period in BPD patients and healthy controls in response to film clips of varying emotional content. Although no group differences in RSA or heart period were observed at baseline, the BPD group showed a trajectory of decreasing RSA and heart period during the experiment while the healthy control group showed a trajectory of increasing RSA and heart period. The correlation between RSA and heart period was only significant in the control group, indicating a relative lack of vagal control over the heart in the BPD group. These results suggest dysfunction of parasympathetic limb of the ANS in BPD patients, characterized by withdrawal of vagal control over arousal. However, the BPD patients in this study were free of comorbid diagnoses, which is unusual given the high rates of comorbidity in BPD patient samples (Lenzenweger et al., 2007; Zanarini et al., 1998). Therefore, these findings may not generalize to BPD patients seen in clinical practice.

Another study of RSA in BPD patients produced results that were contrary to those reported by Austin et al (2007). In a recently published article, Kuo and Linehan (2010) reported no differences between women with BPD, women with social anxiety disorder (SAD), and healthy controls in RSA, SCR, or self-reported emotion in response to a standard mood induction task. However, Kuo and colleagues did find lower baseline RSA in the BPD group relative to both the SAD and healthy control groups, as well as higher baseline SCR and self-reported negative emotion in the BPD relative to the healthy control group only. These results can be interpreted to suggest vulnerability to emotional dysregulation in women with BPD characterized by high baseline arousal but not by heightened reactivity. However, the higher baseline negative emotion and SCR may not be specific to BPD, as the patient samples did not differ on these indices.

There is also some evidence for noradrenergic system dysregulation in BPD patients from studies of adrenergic receptor functioning. For example, a few studies (Southwick et al., 1990a, 1990b; Yehuda et al., 1994) have found decreased platelet alpha2 adrenergic receptor binding in patients with BPD, which may reflect downregulation of these receptors due to neuronal overexposure to catecholamines. As a measure of postsynaptic adrenergic activity, some researchers have examined growth hormone (GH) levels in response to clonidine (an alpha2 adrenergic agonist), because GH is secreted in response to alpha2 adrenergic receptor stimulation. DeVegvar et al. (1998) found increased GH response to cholinergic challenge in BPD patients. In addition, Coccaro et al. (1991) showed that in a sample of male personality disorder patients (25% of whom had a diagnosis of BPD), GH levels in response to clonidine challenge were positively correlated with self-reported irritability.

Only three published studies (Nater et al., 2010; Simeon et al., 2007; Weinberg, Klonsky, & Hajcak, 2009) have examined ANS reactivity among BPD patients in response to environmental stressors. In the aforementioned study by Simeon et al. (2007), peripheral (i.e., plasma) norepinephrine levels were measured at baseline and after social stress in a small sample of BPD patients in comparison to healthy controls. The authors found no differences between the patients and the controls in either basal or stress-induced norepinephrine levels. The lack of significant group differences in catecholamine reactivity in this study could have been due to the small sample size. However, they found that dissociation severity was significantly positively correlated with peak norepinephrine stress reactivity. In addition, even though the difference between high-dissociation-BPD patients and healthy controls did not reach statistical significance, the mean differences suggest a moderate effect size (f = .53), with BPD patients who were high in dissociation showing higher catecholaminergic reactivity in response to stress.

Nater et al. (2010) also found no difference between a small BPD sample and healthy controls in peripheral catecholamine response to the TSST. However, Nater and colleagues reported attenuated sAA reactivity in the BPD patients as compared to healthy controls, which could potentially reflect reduced central noradrenergic activity in those with BPD. Given the interplay between the HPA axis and ANS in stress reactivity, the authors tentatively hypothesized that reduced central noradrenergic activity could at least partially explain the attenuated cortisol reactivity that was also observed in this BPD sample. Nonetheless, as acknowledged by the authors, replication of these results with

larger samples is necessary, and the potential influence of comorbid PTSD on these results could not be ruled out.

Using a social stress paradigm similar to the TSST (involving a mental arithmetic task without the public speech component), Weinberg et al. (2009) investigated both sympathetic and parasympathetic responses of BPD patients in comparison to healthy controls. The results suggested ANS hyperreactivity in the BPD group. Specifically, the BPD patients showed a higher cardiac sympathetic index (CSI) and lower RSA (reflecting withdrawal of parasympathetic control over arousal) during the stress task relative to healthy controls. In addition, examination of trajectories of change indicated that the BPD patients' sympathetic arousal increased during the course of the stressor (as evidenced by increasing CSI), whereas, the control participants' sympathetic arousal decreased during as the stressor progressed. The BPD patients also reported the stress task to be more frustrating than did controls.

The above studies have assessed emotional responding under laboratory conditions, but some researchers have begun to monitor psychophysiological indices of emotion during normal daily life conditions. Ebner et al. (2004) demonstrated through 24-hour psychophysiological monitoring that BPD patients had higher heart rate and high-frequency heart-rate variability compared to non-BPD patients. Further, Ebner-Priemer et al. (2008) found more reported distress and elevated heart rates under 24-hour daily life conditions among BPD patients in comparison to healthy controls.

Several studies have failed to find evidence of autonomic hyperarousal in BPD patients in comparison to healthy controls (Herpertz et al., 1999, 2000; Herpertz & Koetting, 2005; Kuo & Linehan, 2010; Schmahl, Elzinga, et al., 2004; Simeon et al.,

2007). Some of these studies have been limited by small sample sizes. For example, Schmahl, Elzinga, et al. (2004) found a nonsignificant trend of greater SCR in response to abandonment scripts in a small sample of BPD patients, but the sample size might not have afforded sufficient power to detect significant results.

Some studies have reported evidence for physiological *hyporeactivity* in BPD patients as measured by SCR in response to standardized pictorial slides of varying emotional content (Herpertz et al., 1999, 2000). However, an interesting finding in these studies was that instead of demonstrating the normal accelerated heart rate response to positive emotional stimuli, the BPD group showed deceleration of heart rate in response to positive stimuli, along with less pleasant self-reported evaluations of pleasant slides (as compared to healthy controls). These studies did not find differences between the BPD and control groups in startle response or heart rate. Possibly, the negative emotional stimuli used in these studies may not have been relevant to the interpersonal concerns, such as abandonment, which are characteristic of BPD. In addition, the hyporeactivity observed in the BPD patients could have been the result of dissociation, which may have mitigated autonomic responses (Herpertz et al., 2002). According to the cortolimbic disconnection model of dissociation proposed by Sierra and Berrios (1998), the medial prefrontal cortex has an inhibitory effect on processing in the amygdala during dissociation, leading to a dampening of autonomic and emotional response. Accordingly, Ebner-Priemer et al. (2005) reported attenuated startle responses in BPD patients with dissociative features. On the other hand, Simeon et al. (2007) found that dissociation severity was related to higher peak norepinephrine stress reactivity among BPD patients.

It is therefore unclear how dissociation may impact physiological indices of emotional responding in BPD patients.

Limitations of Previous Studies

Due to the highly varied results from previous studies, the biological concomitants of emotional arousal in BPD patients in response to a realistic social stressor are still poorly understood. Conclusions from several previous studies are limited by the potential irrelevance of the experimental stimuli for borderline pathology, invasive sampling methods, and small sample sizes. In addition, several studies have used exclusionary criteria that may have resulted in nonrepresentative study groups. Although studies with medication-free BPD groups provide internal validity by controlling for the influence of medications on emotional responding, such samples may not be generalizable to BPD patients who are seen in actual clinical practice. Thus, evidence from such studies should be supplemented by evidence from more naturalistic samples.

It is likely that the considerable heterogeneity in BPD may explain discrepancies in results between previous studies. Differential symptom patterns, as well as features such as trauma exposure, dissociative tendencies, and comorbid conditions such as PTSD and MDD, are probable sources of variance in both HPA axis and ANS reactivity among those with BPD. For example, as far as HPA axis functioning, MDD has most often been associated with higher baseline cortisol, blunted cortisol reactivity in response to stress, impaired recovery to baseline cortisol levels after stress, and nonsuppression of cortisol

after administration of dexamethasone (Burke et al., 2005; Gillespie & Nemeroff, 2005). Conversely, PTSD has often been shown to be associated with lower cortisol levels and hypersuppression in response to dexamethasone and increased cortisol levels both in anticipation of and during cognitive stressors (see de Kloet et al., 2006, for a review).

Furthermore, it is unclear how childhood trauma, independent from PTSD, may influence neuroendocrine reactivity in BPD patients. Some studies suggest that a history of childhood abuse may be associated with hyperresponsiveness of the HPA axis in BPD patients (e.g., Jogems-Kosterman et al., 2007; Rinne et al., 2002; Soloff, George, & Nathan, 1982). However, studies with other clinical and non-clinical populations show mixed effects of childhood trauma, with some studies suggesting that childhood trauma is associated with greater reactivity (e.g., Heim et al., 2000, 2002; Heim, Meinlschmidt, & Nemeroff, 2003) and others suggesting that childhood trauma is associated with attenuated reactivity (e.g., Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Carpenter et al., 2007, 2009). It is possible that the type and characteristics of the early trauma (e.g., age, chronicity, etc.), the clinical and/or demographic characteristics of the samples, and genetic variation (i.e., predisposition to reactivity) might explain these differential effects of childhood trauma on neuroendocrine reactivity in BPD patients.

Thus, although limited, some evidence suggests that BPD patients with histories of early trauma, MDD, and/or dissociative tendencies may tend to demonstrate hyperreactivity and impaired recovery of the HPA axis; whereas, those with comorbid PTSD may demonstrate the opposite pattern, i.e., hyporeactivity and enhanced sensitivity of glucocorticoid receptors (see Zimmerman & Choi-Kain, 2009 for a review). However,

these are merely tentative hypotheses to be further evaluated in large, diverse, and clinically representative study samples.

Furthermore, most previous studies of HPA axis functioning in BPD have measured either unstimulated (basal) cortisol levels or HPA axis response to pharmacological challenge, neither of which captures the rising phase of cortisol reactivity in response to stress. As observed by Yehuda (2006), the various components of the HPA axis are differentially mediated; therefore, findings from basal cortisol and pharmacological challenge studies are not necessarily informative regarding HPA axis reactivity in response to psychosocial stress. For example, pharmacological challenge studies do not directly take into account the interface between mind and body in the stress response because they do not employ a psychologically activating stimulus that is relevant to real-life situations. The few studies (Nater et al., 2010; Simeon et al., 2007; Walter et al., 2008) that have examined patterns of cortisol reactivity in response to a realistic and socially relevant stressor among individuals with BPD had small samples, leading to difficulties interpreting their results.

The evidence regarding ANS reactivity to a realistic social stressor among BPD patients is similarly ambiguous. Most prior studies of ANS reactivity in BPD patients have measured momentary peripheral physiological responses to aversive *stimuli* rather than responses to active engagement in an aversive *task* that involves social interaction. Most previous studies have also used methods that required either psychophysiological equipment or venipuncture, which may elicit responses that are unrelated to the actual experimental procedures or stimuli. Few studies to date have noninvasively examined the full temporal trajectory of sympathetic reactivity and recovery in response to active

engagement in a realistic social stressor in a clinically representative group of patients with BPD. Those that have done so have yielded contradictory results, and only one study (Nater et al., 2010) thus far (with small samples) has examined sAA response to a realistic social stressor among BPD patients. Thus, further study is warranted to clarify the characteristic pattern of ANS reactivity to stress in BPD patients, particularly with noninvasive approaches that can capture the full range of the stress response over an extended period of time of active engagement in an interpersonally relevant task.

Aims and Hypotheses of the Present Study

Given the demonstrated propensity toward emotional reactivity observed among individuals with BPD, as well as the harmful consequences of an overactive stress response system for general health and functioning, it is important to determine the underlying biological and psychological characteristics and mechanisms of emotional dysregulation in BPD. Once these mechanisms are clearly identified, treatments can be developed that directly target these underlying processes. The primary aim of the current study is to identify the characteristic patterns of HPA axis reactivity, ANS arousal, and subjective emotional reactivity in response to a social stressor (the TSST; Kirschbaum et al., 1993) among treatment-seeking BPD patients as compared to two healthy comparison groups: 1) a temperamentally matched control (TMC) group who scores similarly to BPD patients on trait measures of negative affect and impulsivity; and 2) a non-temperamentally-matched control (NTMC) group who scores in the average range on these measures. Salivary cortisol was measured to assess HPA axis response and sAA

was measured as a marker of ANS activity. Subjective emotional reactivity was assessed through self-report measures. The long-term goal of this research is to elucidate the biological markers and psychological mechanisms involved in emotional reactivity in BPD, and to facilitate the translation of these findings into the development and validation of efficacious treatments for BPD.

In accordance with Linehan's (1993, 1995) theory of biological vulnerability to emotional dysregulation in BPD, and consistent with studies suggesting heightened emotional reactivity in BPD (e.g., Ebner-Priemer et al., 2005, 2008; Hazlett et al., 2007; Lobbestael & Arntz, 2010; Walter et al., 2008; Weinberg et al., 2009; for review, see Wingenfeld, Spitzer, Rullkötter, & Löwe, 2010), the central hypothesis for the proposed research is that in response to a social stress, patients with BPD, as compared to both TMC and NTMC groups, will show HPA axis and ANS hyperreactivity and impaired recovery, as well as higher levels of subjective stress and negative emotional reactivity. Specific aims and hypotheses include:

Aim 1: Test the hypothesis of HPA axis hyperreactivity and impaired recovery in response to social stress in BPD. It is predicted that in response to social stress, the BPD group, as compared to TMC and NTMC groups, will show more total salivary cortisol output, more increase in cortisol levels, and impaired recovery in returning to baseline cortisol levels.

Aim 2: Test the hypothesis of ANS hyperreactivity and impaired recovery in response to social stress in BPD. It is predicted that in response to social stress, the BPD group, as compared to TMC and NTMC control groups, will show more total sAA

output, more increase in sAA levels, and impaired recovery in returning to baseline sAA levels.

Aim 3: To test the hypothesis of greater subjective stress and negative emotional reactivity in response to social stress in BPD. It is predicted that the BPD group, as compared to TMC and NTMC control groups, will report higher overall levels of negative affect and greater increase in state negative affect in response to social stress. In addition, it is predicted that the BPD group, in comparison to both control groups, will report experiencing the procedure as more stressful.

Choice of Temperamentally Matched Comparison Group

Several authors have described BPD as an extreme variant of normal personality or temperament, with affective dysregulation in BPD stemming from high levels of negative affect and impulsivity (Cloninger et al., 1993; Depue & Lenzenweger, 2001; Gurvits et al., 2000; Paris, 2000; Svrakic et al., 1996; Trull, 2001; Trull et al., 2000; Widiger & Costa, 2002). Consistent with this conceptualization, several studies have demonstrated a positive correlation between BPD symptom scores and inventory measures reflecting trait negative affect and impulsivity or disinhibition (e.g., Ball, Tennen, Poling, Kranzler, & Rounsaville, 1997; Scott, Levy, & Pincus, 2009; Svrakic, Whitehead, Przybeck, & Cloninger, 1993; Trull, 1992, 2001; Trull, Widiger, Lynam, & Costa, 2003; Wiggins & Pincus, 1989). Although negative affect is associated with nearly every personality disorder, the co-occurrence of negative affect and impulsivity appear relatively specific to BPD compared to other personality disorders (Widiger,

Trull, Clarkin, Sanderson, & Costa, 2002). A predisposition to negative emotions and disinhibition may increase vulnerability to heightened subjective and physiological reactivity in stressful situations.

However, trait negative affect and impulsivity can also be elevated in nonpathological populations that do not demonstrate the same behavioral and functional abnormalities as do BPD patients (Levy et al., 2005; Posner et al., 2002, 2003). In addition, several studies have shown that personality traits, such as neuroticism or trait negative affect, are not strong predictors of physiological (i.e., neuroendocrine) reactivity in adults in response to a novel psychological stressor (e.g., Arnetz & Fjellner, 1986; Blood et al., 1994; Kirschbaum, Bartussek, & Strasburger, 1992; van Eck, Berkhof, Nicolson, & Sulon, 1996), and the association between temperament and neuroendocrine reactivity in children is moderated by social cognitive variables such as attachment to caregivers (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996).

Nonetheless, the role of these temperamental characteristics for explaining emotional dysregulation in BPD has not been explored in previous studies. Rather than simply comparing BPD patients to healthy controls in studies of emotional dysregulation, a control group that is high in trait negative affect and impulsivity is a relevant comparison group for examining temperamental characteristics as potential mechanisms of emotional dysregulation in BPD. If the hypothesized differences between the BPD and TMC group are observed in indices of stress reactivity, then the inference can be made that an exaggeration of normal-range personality traits does not account for affective dysregulation among patients with BPD. On the other hand, if differences are

not observed between the BPD and TMC groups, but these groups differ in the hypothesized direction from the NTMC group, then it can be inferred that affective dysregulation in BPD appears to result from the core temperamental characteristics underlying the disorder. Further, it can then be inferred that BPD patients are no more reactive, in terms of subjective negative affect, HPA axis reactivity, or ANS arousal, than healthy individuals who tend to experience high levels of negative emotions and impulsiveness. Thus, in either direction, the results will be informative regarding trait-level negative affect and impulsivity as putative underlying mechanisms of emotional dysregulation in BPD.

Chapter 2

METHODS

Participants

Participants included 90 women between the ages of 18 and 48, divided into three groups: (1) 33 clinically-referred women diagnosed with BPD; (2) 27 psychologically healthy women who were matched to the BPD group in trait negative affect and impulsivity (temperamentally matched control (TMC) group); and (3) 30 psychologically healthy women who scored in the average range on measures of trait negative affect and impulsivity (non-temperamentally matched control (NTMC) group). Because of the demonstrated effects of age (Gotthardt et al., 1995; Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004) and sex (Kirschbaum et al., 1999; Kirschbaum, Pruessner, et al., 1995; Kudielka et al., 2004), and the evidence that BPD is more commonly diagnosed in women than men (APA, 2000; Skodol & Bender, 2003), participation in this study was limited to women between the ages of 18 and 50. This research was approved by the Pennsylvania State University (PSU) Office for Research Protections and the PSU Psychological Clinic.

Participant Recruitment

Female patients with prominent BPD features were recruited from the PSU Psychological Clinic based on clinician referrals or patient self-referrals in response to advertisements in patient waiting areas. Psychologically healthy female comparison participants were identified through two mechanisms: 1) online screening of introductory psychology students at PSU; and 2) online screening of community residents responding to flyers and web-based advertisements. Online screening measures included scales to assess trait negative affect and impulsivity (i.e., Revised NEO Personality Inventory (NEO-PI-R; Costa & McCrae, 1992) facet scales for Angry Hostility, Anxiety, Depression, and Impulsivity). NTMC participants were identified whose scores on these measures were within one standard deviation of the total screening sample's mean scores on the trait measures. TMC participants were selected who scored within one standard deviation from the BPD sample's mean scores. Participants received their choice of either payment of $10 per hour of participation or course credits (one credit per hour) toward their introductory psychology research participation requirements.

Exclusion Criteria

In order to obtain an ecologically valid sample of BPD patients, to avoid interfering in their treatment, and to generate research results that are generalizable to BPD patients that are commonly seen in clinical practice, psychiatric comorbidity and medication use were permitted in our BPD sample. In addition, even though hormonal contraceptives may alter endocrine system response (Kirschbaum et al., 1999;

Kirschbaum, Pirke, Hellhammer,1995; Rohleder, Wolf, Piel, & Kirschabaum, 2003), we included participants who were taking them because females between the ages of 18 and 50 are often taking hormonal contraceptives and excluding these participants may have lead to a biased and small sample. Medication use and psychiatric comorbidity were carefully assessed and documented for later analyses.

Exclusion criteria for the patient group included diagnoses of schizophrenia, schizophreniform and schizoaffective disorders, delusional disorder, Bipolar I disorder, delirium, dementia, amnestic disorders, and other cognitive disorders. Exclusion criteria for the two control groups included any current *DSM-IV* Axis I or II diagnoses, including probable Axis II diagnoses. In order to ensure that the BPD and comparison groups were distinct, TMC and NTMC participants who engaged in suicidal or self-injurious behaviors or who met more than three *DSM-IV* criteria for BPD as assessed by structured interview were also excluded. All comparison participants were assessed with the trait measures again during their first laboratory visit, and any participants with inconsistent scores (i.e., an average difference across the trait scales of more than 10 points, or one T-score standard deviation, between scores on the two administrations of the trait scales) were excluded in order to ensure the validity of the temperamentally matched and non-matched groups. Other exclusion criteria that applied to all participants included endocrinological disease (except for diabetes and thyroid disorders, which were common in our samples), heart disease, and pregnancy within the last six months, and current lactation.

A total of 52 patient participants were initially recruited and began the study, 8 of whom withdrew or failed to complete the study procedures. After diagnostic assessment,

11 patient participants were excluded (9 who did not meet criteria for BPD and 2 with possible psychotic disorders). A total of 112 comparison participants were recruited for participation, 30 of whom withdrew or failed to complete the study, and 25 of whom were excluded (15 who met criteria for an Axis I or II disorder, 3 who engaged in self-injurious behaviors, and 7 with inconsistent scores on the two administrations of the trait measures). Clinical referrals were made for those participants who were not currently receiving psychological treatment but whose assessment results suggested possible psychological difficulties or diagnoses.

Participant Demographics and Clinical Characteristics

The final groups consisted of a total of 90 participants (BPD $n = 33$; TMC $n = 27$; NTMC $n = 30$). Demographics for the three groups, as well as descriptive statistics and group comparisons for the trait measures, are provided in **Table 1**. The BPD group was older, on average, than both control groups, but the two control groups did not differ significantly from each other in age (see **Table 1**). The BPD group was also marginally different from both comparison groups in ethnicity (Hispanic/Latina versus Non-Hispanic/Latina) at a trend level ($p = .054$), as none of the BPD participants identified themselves as Hispanic or Latina. The BPD group was significantly more likely to have been divorced or separated as compared to the control groups, but this may have been at least partially due to age differences between the groups. The three groups did not differ in education, racial distribution (White/Caucasian versus non-White), or employment status (employed versus unemployed). Income level could not be examined due to large

amounts of missing data on this variable, as several participants did not complete that portion of the questionnaire.

Both the BPD and TMC groups were significantly higher than the NTMC group in each of the four trait negative affect and impulsivity scales, suggesting successful differentiation of the TMC group from the NTMC group (see **Table 1**). In addition, the TMC group did not differ significantly from the BPD group in trait Angry Hostility or Impulsivity, indicating successful matching on these trait variables. However, the TMC group was significantly lower than the BPD group in trait Anxiety and Depression. Nonetheless, the TMC group was still significantly higher than the NTMC group on these traits, suggesting partial matching to the BPD group and successful differentiation from the NTMC group on these variables.

Table 1. Demographic and trait characteristics for each group

	BPD (n = 33)		TMC (n = 27)		NTMC (n = 30)		
	M	*SD*	*M*	*SD*	*M*	*SD*	Test Statistic (*df*)
Age	30.42_a	7.64	23.74_b	7.51	22.70_b	7.59	$F(2,87) = 9.64$**
Education (yrs)	14.00	1.54	13.78	2.38	13.53	2.21	$F(2, 73.21) = 0.39$
NEO-PI-R scales							
Angry Hostility	68.28_a	10.29	63.26_a	10.28	46.93_b	6.85	$F(2,86)=44.15$**
Anxiety	64.94_a	7.07	57.93_b	9.57	47.83_c	6.90	$F(2,86) = 36.93$**
Depression	70.34_a	6.94	60.41_b	8.75	44.47_c	5.99	$F(2,86) = 99.76$**
Impulsivity	62.13_a	11.00	58.59_a	6.84	43.47_b	6.25	$F(2,71.75)=43.80$**
Race	*n*	%	*n*	%	*n*	%	
White	28	84.8	22	81.5	24	80.0	$\chi^2(2) = 0.27$ [d]
Black	2	6.1	1	3.7	4	13.3	
Asian	1	3.0	2	7.4	0	0	
Other	2	6.1	2	7.4	2	6.7	
Ethnicity							
Hispanic/Latina	0	0	4	14.8	5	16.7	$\chi^2(2) = 5.84$†
Marital Status							
Single	20	60.6	22	81.5	26	86.7	$\chi^2(4) = 10.06$*
Divorced	8	24.2	1	3.7	1	3.3	
Married	5	15.2	4	14.8	3	10.0	
Employed	17	51.5	20	74.1	18	60.0	$\chi^2(2) = 3.20$

†$p < .10$. * $p < .05$. **$p < .001$. [d] White/Caucasian versus non-White.

Notes: Degrees of freedom with decimal places denote Brown-Forsythe Robust Test of Equality of Means (correcting for inhomogeneity of variance). The BPD group sample size was $n = 32$ for NEO-PI-R scales due to one BPD participant who did not complete those measures. Row means with different subscripts are significantly different from each other at $p < .05$ or less using Bonferroni-corrected (or Tamhane's T2 in the case of inhomogeneity of variance) post-hoc tests.

Past and current Axis I diagnoses for each group are presented in **Table 2**, and comorbid Axis II diagnoses for the BPD group are presented in **Table 3**. Although past Axis I diagnoses were permitted in the control groups, none of the NTMC or TMC participants met criteria for any current Axis I diagnoses or current or past Axis II diagnoses.

Descriptive statistics for personality disorder dimensional scores resulting from diagnostic interviews are provided in **Table 4**, and the percentage of participants in each group who fully met each individual BPD criterion is provided in **Table 5**. The high average BPD dimensional score (M = 13.22, SD = 2.39; possible range = 0-16) and high rates of suicidal and parasuicidal behaviors (68.8%) in the BPD group demonstrate the extreme severity of impairment in the patient sample. Interestingly, 100% of the patients met the affective instability criterion, although this was not required for inclusion in the study.

Table 2. Frequencies of past and current Axis I diagnoses in each group

	BPD (n = 33)		TMC (n = 27)		NTMC (n = 30)	
Axis I Diagnosis	Past	Current	Past	Current	Past	Current
Adjustment Disorder	0	0	2	0	1	0
Anorexia	1	0	1	0	0	0
Anxiety Disorder NOS	0	2	0	0	0	0
Bulimia	0	1	0	0	0	0
Dysthymia	1	2	0	0	0	0
Eating Disorder NOS	4	1	0	0	1	0
Generalized Anxiety Disorder	1	3	1	0	0	0
Major Depressive Disorder	11	5	2	0	0	0
Panic Disorder	1	2	0	0	0	0
Panic Disorder w/Agoraphobia	2	1	0	0	0	0
Post-Traumatic Stress Disorder	7	1	0	0	0	0
Social Phobia	0	3	0	0	0	0
Somatoform Disorder	0	4	0	0	0	0
Substance Abuse	13	3	2	0	2	0
Substance Dependence	8	4	1	0	0	0

Note: Only diagnoses with past or current frequencies > 0 in the full sample are listed.

Table 3. Frequencies and percentages of the BPD group (n = 33) with definite or probable non-BPD personality disorder diagnoses

Personality Disorder	Definite		Probable	
	n	%	*n*	%
Avoidant	4	12.1	6	18.2
Histrionic	4	12.1	1	3.0
Narcissistic	3	9.1	1	3.0
Obsessive Compulsive	2	6.1	1	3.0
Paranoid	2	6.1	2	6.1

Notes: Definite and probable diagnoses were determined based on results from the International Personality Disorder Examination (IPDE; Loranger, 1999). None of the NTMC or TMC participants met criteria for definite or probable personality disorder diagnoses. Only diagnoses with frequencies > 0 are listed.

Table 4. Descriptive statistics for personality disorder dimensional scores in each group

	BPD (n = 33)		TMC (n = 27)		NTMC (n = 30)	
Personality disorder	*M*	*SD*	*M*	*SD*	*M*	*SD*
Paranoid	3.69	3.19	0.33	0.78	0.03	0.18
Schizoid	0.69	1.09	0.11	0.42	0.03	0.18
Schizotypal	2.00	1.46	0.11	0.32	0.00	0.00
Antisocial	5.78	3.47	0.67	1.30	0.13	0.43
Borderline	13.22	2.39	1.19	1.67	0.27	0.69
Histrionic	4.78	3.81	0.30	0.54	0.37	0.89
Narcissistic	3.91	4.85	0.19	0.62	0.23	0.57
Avoidant	4.09	4.02	0.59	1.37	0.00	0.00
Obsessive Compulsive	3.47	3.65	0.56	1.16	0.30	0.75

Notes: Dimensional scores were based on results from the International Personality Disorder Examination (IPDE; Loranger, 1999).

Table 5. Percentage of participants in each group who met each borderline personality disorder (BPD) criterion

BPD criterion	% of BPD (n = 33)	% of TMC (n = 27)	% of NTMC (n = 30)
Frantic efforts to avoid abandonment	31.3	0	0
Unstable interpersonal relationships	75.0	3.7	3.3
Identity disturbance	71.9	3.7	0
Impulsivity	81.3	3.7	3.3
Suicidal or self-injurious behavior	68.8	0	0
Affective instability	100.0	18.5	3.3
Chronic Emptiness	59.4	3.7	0
Intense anger	43.8	3.7	6.7

Notes: Criterion scores were based on results from the International Personality Disorder Examination (IPDE; Loranger, 1999).

Measures

The study was conducted in two parts, which were administered on separate days: Part 1 consisted of a thorough diagnostic assessment, and Part 2 consisted of the laboratory stress procedure.

Part 1: Assessment Measures

Demographics Questionnaire. A demographics questionnaire was constructed by the author to assess factors such as age, race, ethnicity, marital status, education, and employment status.

Revised NEO Personality Inventory (NEO-PI-R; Costa & McCrae, 1992) facet scales. Thirty-two items from the NEO-PI-R were administered during initial online screening for comparison participants and during participants' first visit to the laboratory in order to assess trait negative affect and impulsivity. The NEO-PI-R is a highly reliable and valid measure of stable personality traits that are believed to be distributed in the general population. The items corresponding to the Angry Hostility, Anxiety, Depression, and Impulsivity facet scales (8 items per scale) were administered in this study. Each item is rated on a five-point scale (0 = *strongly disagree*, 4 = *strongly agree*). In accordance with the NEO-PI-R manual, items corresponding to each facet scale were summed and then converted into T-scores. Each of the scales demonstrated high internal consistency in the present study sample as measured by Cronbach's alpha (Depression $\alpha = .92$; Angry Hostility $\alpha = .88$; Anxiety $\alpha = .85$; Impulsivity $\alpha = .84$).

Childhood Trauma Questionnaire – Short Form (CTQ-SF; Bernstein et al., 2003). The CTQ-SF is a 28-item self-report inventory that yields scale scores for five types of childhood trauma, including Physical Abuse (PA), Sexual Abuse (SA), Emotional Abuse (EA), Physical Neglect (PN), and Emotional Neglect (EN). Five items assess each of the trauma scales. Three additional items comprise a Denial scale that was designed to detect false negative trauma reporting. Items were rated on a five-point scale (1 = *never true*, 5 = *very often true*). Items corresponding to each trauma scale were summed to yield continuous scale scores with acceptable levels of internal consistency (PA $\alpha = .81$; SA $\alpha = .96$; EA $\alpha = .93$; PN $\alpha = .79$; EN $\alpha = .93$). Previous studies have demonstrated that the CTQ-SF has good criterion validity in both clinical and community samples, high convergent reliability with therapist assessments of abuse histories, and good sensitivity

and specificity for classification of maltreated individuals (Bernstein & Fink, 1998; Bernstein et al., 2003).

Structured Clinical Interview for DSM-IV, Clinician Version (SCID-I-CV; First, Gibbon, Spitzer, & Williams, 1997). The SCID-I-CV is a well-validated semi-structured clinical interview for diagnosing *DSM-IV* Axis I disorders in persons 18 years of age or older. The SCID-I-CV includes sections for the assessment of mood, psychotic, substance-related, anxiety, somatoform, eating, and adjustment disorders.

International Personality Disorder Examination (IPDE; Loranger, 1999). The IPDE is a semi-structured interview for diagnosing *DSM-IV* personality disorders consisting of 99 items arranged in six categories. Each item assesses part or all of a *DSM-IV* personality disorder criterion and is rated on a three-point scale (0 = *absent or normal*, 1 = *exaggerated or accentuated*, 2 = *meets criteria or pathological*). The IPDE generates both probable and definite categorical diagnoses for each of the *DSM-IV* personality disorder diagnoses, as well as dimensional scores for each diagnosis. The IPDE has good interrater reliability and temporal stability, and is known to be a relatively conservative instrument for assessing personality disorders that results in very few false-positive diagnoses. Only participants who met criteria for a definite diagnosis of BPD were included in the BPD group for the current study.

Part 2: Stress Procedure Measures

Health Form. The Health Form was administered one hour prior to the stress procedure in order to assess activities and events that may influence cortisol and sAA

levels, such as any recent stressors, participants' food and beverage intake, physical activity, medications taken, alcohol or drug usage, smoking, caffeine intake, recent dental hygiene activity, sleep-wake patterns, and menstrual cycle phase.

Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS was administered three times (approximately 45 minutes prior to the onset of the stressor, 15 minutes after onset of the stressor, and 55 minutes after the onset of the stressor) to assess changes in subjective affective experiences in response to the stress procedure. The PANAS consists of words that describe different emotions, and participants were asked to rate the extent to which they were experiencing each emotion at the present moment. Each item is rated on a five-point scale (1 = *very slightly*, 5 = *extremely*). The original PANAS consists of two 10-item subscales, one for state positive affect (PANAS-PA) and the other for state negative affect (PANAS-NA). Two additional items, "happy" and "unhappy", were added to the PANAS for the current study. Each subscale was calculated based on the sum of the 11 items corresponding to the scale. Both scales demonstrated high internal consistency across the three administrations of the PANAS in the current study sample (PANAS-PA α = .90 to .91; PANAS-NA α = .81 to .87).

Subjective Stress Perception Rating Form (SSPRS). The SSPRS was administered immediately following the stressor. The SSPRS was created by the author and contained six items designed to assess the participants' subjective perception of the stress procedure as: 1) difficult, 2) stressful, 3) uncontrollable, 4) threatening, 5) hostile, and 6) evaluative. Items were rated on a nine-point scale (1 = *not at all*, 9 = *very much*). Inter-item correlations and exploratory factor analysis of these items suggested that they

comprised one robust factor. Hence, a continuous scale score reflecting S*ubjective Stress Response* (SSR) was calculated based on the mean of these six items. The internal consistency of this scale was high (α = .82).

Dissociation Tension Scale (DSS; Stiglmayr, Shapiro, Steglitz, Limberger, & Bohus, 2001; Stiglmayr, Braakmann, Haaf, Steiglitz, & Bohus, 2003). The DSS is a 19-item self-report measure of present-state dissociative experiences consisting of items that assess somatic as well as psychological dissociation. This instrument was administered immediately after the stress procedure in order to assess present-state dissociative experiences during the procedure. The DSS items are dissociative experiences that were derived from the Dissociative Experience Scale (Bernstein & Putnam, 1986) and the Somatoform Dissociation Questionnaire (SDQ-20; Nijenhuis, Spinhoven, Van Dyck, & Van Der Hart, 1996). Participants were asked to rate the intensity with which they experienced each item during the course of the stress procedure using a Likert scale from 0 to 9. Scores for the somatic and psychological dissociation scales were calculated based on the mean of items corresponding to each scale. These scales were highly correlated in our sample (r = .85), and evidence suggests little support for the differentiation between somatic and psychological dissociation in the DSS scores of BPD patients (Stiglmayr et al., 2001). Therefore, the mean of all items was calculated to arrive at a single DSS total score, which had excellent internal consistency (α = .92). The internal consistency and construct validity of the DSS has been demonstrated in both clinical and nonclinical samples (Stiglmayr et al., 2010). According to Stiglmayr et al. (2001), a score of 2.7 or greater on the DSS (in a possible range from 0 to 9) suggests severe dissociative features.

Procedures

All potential participants were administered a brief telephone screen to assess for health factors that are known to affect HPA axis and ANS reactivity, including somatic disease, pregnancy, and lactation. Participants who met inclusion criteria based on the phone screen were invited to come into the laboratory for a series of questionnaires and diagnostic interviews (Part 1 of the current study).

Part 1: Assessment Procedures

Participants were administered a packet of questionnaires (Demographics, NEO-PI-R scales, and CTQ) and two diagnostic interviews (SCID-I-CV and IPDE). All diagnostic interviews were conducted by advanced clinical psychology graduate students who were trained in diagnostic interviewing and were blind to participants' group membership. The research team met on a weekly basis to review interview data, and the longitudinal, expert, all-data (LEAD) standard (Pilkonis, Heape, Ruddy, & Serrao, 1991) was employed in order to obtain the most accurate diagnoses possible. This method involves using all available data, including participants' treatment notes, diagnoses, length of treatment, and other information contained in their clinical files, to obtain an accurate diagnosis.

All diagnostic interviews were videotaped, and a randomly selected sample of 21 participant interviews (approximately 20% from each group, i.e., 7 from the NTMC group, 6 from the TMC group, and 8 from the BPD group) were scored by an independent rater who was blind to the participants' group membership. Diagnoses from

both the interviewer and independent raters were used to calculate interrater reliability Kappas (κ) for diagnoses with frequencies of 5% or more. Kappas ranged from κ = .64 to κ = 1.0 for Axis I diagnoses, and from κ = .71 to κ = 1.0 for Axis II diagnoses (κ = .88 for BPD diagnosis). Intraclass correlation coefficients were .94 for number of BPD criteria met and .98 for BPD dimensional scores. Participants who met inclusion criteria based on diagnostic interviews were invited to return to the laboratory on another day to participate in a "mock job interview" (Part 2 of the current study).

Part 2: Stress Procedures

The Trier Social Stress Test

The Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) is a widely used psychosocial stress procedure that involves a public speaking and a cognitive (verbal arithmetic) task in front of a small group of research confederates who act as "judges". The TSST was chosen because it contains both uncontrollable and social-evaluative elements, which are associated with the largest and most reliable increases in HPA axis and ANS arousal without involving any degree of physical exertion or pain (Dickerson & Kemeny, 2004). In addition, because the research confederates do not offer any feedback, encouragement, or facial expressions, the TSST involves an ambiguous social interaction that can trigger the interpersonally related emotional dysregulation that is often observed in those with BPD. The TSST officially begins when participants are shown the judges and asked to prepare a speech, and it ends

when participants complete the verbal arithmetic task. Hence, the TSST takes a total of 15 minutes from beginning to end.

Participants were run individually through the TSST procedure during the mid to late afternoon when cortisol levels are lowest (Kirschbaum & Hellhammer, 1994) to reduce variability in baseline measures and to enhance sympathetic and hormonal responses to laboratory stress. Because there is evidence of increased HPA-axis reactivity and reduced glucocorticoid receptor sensitivity in the midluteal phase of the menstrual cycle (Altemus et al., 1997; Kanaley, Boileau, Bahr, Misner, & Nelson, 1992) and increased resting levels of catecholamines in the luteal phase (Altemus et al., 1997), every effort was made to schedule participants or the TSST during the follicular phase (i.e., during the first two weeks) of the menstrual cycle whenever possible. The number of days since the start of the last menstrual period was documented for later analysis.

In order to minimize other factors that may influence the measurement of salivary biomarkers, participants were asked at the time of scheduling to follow these instructions: 1) no alcohol for 24 hours; 2) no medications or drugs for 6 hours, except for any regular medications prescribed to be taken daily; 3) no caffeine, tobacco, rigorous exercise, tooth brushing/flossing, or dental work for at least 2 hours; 4) no food or beverages other than water for at least 1 hour; 5) no dairy or citrus foods or beverages (including drink crystals) for at least 30 minutes prior to the appointment; and 6) remain awake for at least four hours prior to their appointment. These instructions were given to participants both verbally and in writing at the time of scheduling, and each participant received a reminder call from the project coordinator on the day prior to their appointment to remind them of the instructions. Participants completed the Health Form after arriving for their

appointment to assess compliance with these instructions, as well as any recent stressors. Those who were not compliant or who were experiencing stressful circumstances were rescheduled to complete the study at another time. Student participants were not scheduled during midterm or final exam periods unless an individual participant indicated that she had no examinations or evaluations (e.g., term papers due) during these periods.

Upon arrival at the laboratory for their TSST appointment, the participant was greeted by the study coordinator. The coordinator informed the participate that she would be asked to engage in a mock job interview that would be videotaped, and that saliva samples would be taken to monitor her hormone levels before, during, and after the interview. After providing written consent, the participant was asked to rinse her mouth with water. The participant was then asked to complete the Health Form, which was promptly reviewed by the research coordinator for compliance with instructions. At least 10 minutes after rinsing their mouth, the participant provided the first saliva sample and completed the first administration of the PANAS. The participant was then asked to sit quietly in a comfortable chair and read light magazines that were provided in the laboratory room for a period of 30 minutes. Thirty minutes after the first sample, the second saliva sample was taken.

Next, the coordinator escorted the participant into another room where three "judges" (research confederates) that the participant had never met were seated at a long table. The judges wore white laboratory coats, and two video cameras were clearly visible. The participant was asked to pretend that she was invited to interview for her ideal job. She was asked to prepare a five-minute speech explaining to the committee (i.e., the "judges") why she would be the best candidate for that job. Participants were

informed that their performance was to be videotaped and rated by the judges for logical coherence, poise, and expressiveness. Then, the participant was escorted back into the other room where she had rested previously, and was given five minutes to prepare her speech. Although participants were allowed to use pen and paper to prepare, they were told that they would not be allowed to use their notes during the speech.

After the five-minute preparation period, the participant was asked to provide the third saliva sample, and was then escorted back to the room with the judges. The coordinator turned on the videotape recorder and asked the participant to begin her speech. No encouragement or reassurance was given, and the judges appeared expressionless. If the participant stopped talking, she was asked by one of the judges to continue until the five minutes were finished. Next, the coordinator asked the participant to complete a five-minute serial subtraction task (i.e., to count aloud backwards in increments of 13 starting at 1,022). If the participant miscalculated, she was instructed by one of the judges to start again at 1,022. The coordinator then escorted the participant out of the room after the 5 minutes had elapsed.

For the next 40 minutes, the participant was asked to sit quietly, provide periodic saliva samples, and complete self-report measures. The fourth saliva sample was taken and the second PANAS, the DSS, and the SSPRS were administered immediately following the TSST. After the participant finished completing self-report measures, she was asked to sit quietly and read light magazines. Participants were asked for saliva samples every 10 minutes until the eighth sample was taken. After the eighth saliva sample, the third and final PANAS was administered.

Finally, the study coordinator thoroughly debriefed the participant regarding the purposes of the stress procedure. To ensure the safety and comfort of participants, an advanced clinical psychology graduate student or licensed clinical psychologist from the research team met with any participant who appeared emotionally disturbed prior to dismissing the participant from the laboratory.

Saliva Sampling

When providing saliva samples, participants were instructed to move their mouth in a chewing motion and to imagine they were eating their favorite food in order to generate saliva. A total of eight saliva samples were collected from each participant via the passive drool method (by spitting through a straw into a plastic vial) over the course of the TSST: (1) 35 minutes prior to starting the TSST; (2) 5 minutes prior to starting the TSST; (3) immediately after speech preparation, prior to starting the speech portion of the TSST; (4) immediately following completion of the TSST; (5 to 8) each occurring ten minutes after the last sample. The saliva-sampling schedule is illustrated in **Figure 1**, with the TSST starting when participants are shown the experimental setup (the judges) and asked to prepare a speech, and ending with the conclusion of the verbal arithmetic task.

Figure 1

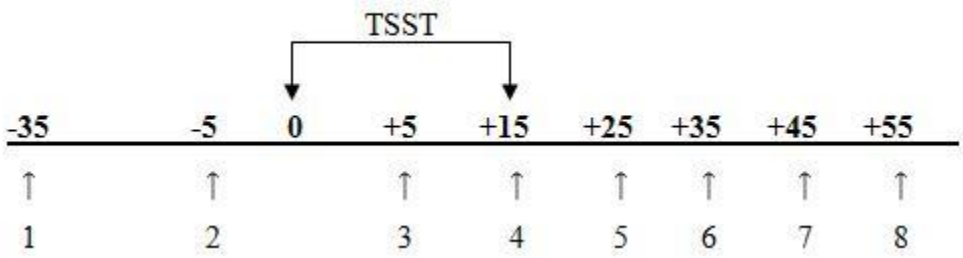

Figure 1. Saliva-sampling schedule

Each arrow below the line represents a saliva sample. Numbers below the arrows are sample numbers. Numbers at the top indicate minutes pre and post-TSST.

Saliva Storage and Salivary Assays

Because blood in saliva has been shown to affect the detection of biomarkers in saliva, samples were visibly inspected upon collection by the study coordinator for potential blood contamination. None of the samples were visibly contaminated with blood. Each sample was immediately stored at -20 degrees Celsius upon collection. Frozen samples were later transported to the Pennsylvania State University endocrinology laboratory (Salimetrics) where they were stored at -80 degrees Celsius until assay.

Assays for all samples were conducted at Salimetrics in State College, PA using 96-well microtiter plates with precision multichannel pipettes, an optical density reader, and technically trained laboratory personnel. On the day of assay, samples were centrifuged at 3000rpm for 15 minutes to remove mucins. In order to minimize error

variance caused by intraassay imprecision, samples from each individual participant were analyzed on the same plate.

Samples were assayed for salivary cortisol using an expanded-range, high-sensitivity salivary cortisol enzyme immunoassay (Salimetrics, State College, PA), which has a range of sensitivity from .003 to 1.8 µg/dl and average intra- and inter-assay coefficients of variation of less than 5% and 10%, respectively. Salivary cortisol detected with this method has been demonstrated to be highly correlated with serum cortisol (r = .91). The test uses a minimal test volume of saliva (25 µl) for singlet determinations. Cortisol assays were run in duplicate for the purposes of quality control, and the average of the duplicates for each sample were used in the analyses.

Samples were assayed for salivary α-amylase using a kinetic reaction assay (Salimetrics, State College, PA) with average inter- and intra-assay coefficients of less than 8%. The assay uses 10 µL of saliva diluted with 90 µL of α-amylase diluent. This method utilizes a chromagenic substrate, 2-chloro-*p*-nitrophenol, linked to maltotriose. The enzymatic action of salivary α-amylase on this substrate yields 2-chloro-*p*-nitrophenol, which can be spectrophotometrically measured at 405 nm. The amount of α-amylase in the sample is directly proportional to the increase in absorbance at 405 nm over a 2-minute period. The lower limit of sensitivity of the assay method is governed by the change in absorbance (e.g., a change in absorbance of less than .01 will not result in a reliable value).

Planned Statistical Analysis

Analyses were conducted using PASW 18 (SPSS Inc., Chicago, IL). All analyses were two-tailed with significance set at $p < .05$. Data were tested for normality of distributions and homogeneity of variance by means of the Kolmogorov-Smirnov and Levene's test before statistical procedures were applied. Brown-Forsythe *F* values are reported (as reflected in degrees of freedom with decimal values) for data that violated the homogeneity of variance assumption. For repeated measures analyses, Mauchly's Test of Sphericity was examined. When assumptions of sphericity were violated, the Greenhouse-Geisser correction was applied, as reflected in degrees of freedom with decimal values. Bonferroni corrections were applied where required for multiple comparisons, except in the case of inhomogeneity of variance, in which case the Tamhane's T2 test (a conservative pairwise comparison test that does not assume homogeneity of variances) is reported.

The primary aims of the study were accomplished as follows:

Aims 1 and 2. To test the hypotheses of greater hyperreactivity and impaired recovery in HPA axis and ANS responses to social stress in the BPD group, two different data analytic procedures were performed. First, in order to simultaneously examine within and between-participant change trajectories in cortisol and sAA, as well as between-group differences in cortisol and sAA at each individual timepoint, 8x3 mixed model ANOVAs were conducted with time as the repeated measure (with 8 occasions of measurement) and group as the between-participants measure. For both cortisol and sAA, the hypothesized results were: 1) main effects of time, reflecting within-participants change in biomarkers over time; 2) main effects of group, reflecting higher overall

biomarker output in the BPD group relative to both comparison groups; and 3) time × group interactions, reflecting more increase in biomarkers during the stress procedure and less decrease in biomarkers during the recovery period in the BPD group relative to both comparison groups.

Given the limitations of repeated measures ANOVA in the current study design (particularly the uneven intervals between biomarker measures), a second data analytic strategy was employed in which three different forms of area under the response curve (AUC) were calculated for both cortisol and sAA using the trapezoid formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). AUC formulas incorporate information regarding both baseline and reactivity within one score, which simplifies the statistical analyses when the number of repeated measurements is high, corrects for differences in time intervals between measurements, and limits the amount of statistical comparisons between groups to minimize the chance of Type I errors (Pruessner et al., 2003). AUC values can also be calculated in the case that one or more biomarker measures are missing. One-way ANOVAs were conducted to assess group differences in each of the AUC indices. The three types of AUC formulas that were used are:

1) AUC-ground (AUC_G; Pruessner et al., 2003) gives an index of total biomarker output, independent from changes over time. The formula for AUC_G calculates the total area under the curve of all measurements, taking into account the differences between the single biomarker measurements and the distance of these measures from the ground, or zero. It was hypothesized that AUC_G would be higher for the BPD group than both comparison groups, suggesting higher total biomarker output among BPD patients.

2) AUC-increase (AUC_I; Pruessner et al., 2003) emphasizes sensitivity of the biological system and changes over time rather than total biomarker output. The formula for AUC_I ignores the distance of measures from zero, and is identical to that for AUC_G except that it omits the area between ground (or zero) and the first (baseline) measure for all time points. In the case that the repeated measurements show a stronger decrease than increase over time (for instance, if biomarker levels for some individuals fall well below baseline levels during the measurement period), the AUC_I formula can lead to negative values. In this case, Pruessner et al. (2003) recommend retaining the negative values and regarding them as indices of decrease, rather than increase. Thus, AUC_I can not only provide information regarding strength of increase in biomarker level, but can also provide information regarding overall sensitivity of the stress response system and strength of decrease (or recovery). Moreover, AUC_I has been shown to be significantly correlated with measures of patterns or rates of change over time, such as reactivity and slope (Fekedulegn et al., 2007). It was hypothesized that AUC_I would be higher for the BPD group than both comparison groups, suggesting higher biomarker system sensitivity (i.e., hyperreactivity) among the BPD patients.

3) AUC-recovery (AUC_R; Nierop et al., 2006) provides an index of biomarker system recovery (return to baseline) after the conclusion of a stressor, with higher values reflecting more decrease in biomarkers during the recovery period following the stressor. It is calculated by taking the area under the curve from the highest level (peak of reactivity according to visual inspection of response curves, i.e., measure 5 of cortisol and measure 4 of sAA) to the last recovery time point, corrected by the last measurement. It was predicted that AUC_R would be lower for the BPD group than both comparison

groups, suggesting impaired biomarker system recovery (i.e., slower return to baseline) among BPD patients. However, it should be noted that recovery can only occur when there is reactivity; hence, this measure should be interpreted in the context of the results for AUC_I and inspection of response curves.

Aim 3. To test the hypothesis of greater subjective stress and negative emotional reactivity in response to social stress in BPD, two analyses were conducted:

1) A 3x3 mixed model ANOVA was conducted for state negative affect (as measured by the PANAS) with time as the repeated measure and group as the between-participants measure. Hypothesized results were: a) main effect of time, reflecting within-participants change in negative affect over time; b) main effect of group, reflecting higher overall negative affect in the BPD group relative to both comparison groups, and c) time × group interaction, reflecting more increase in negative affect over time in the BPD group relative to both comparison groups.

2) A one-way ANOVA was conducted for Subjective Stress Response scores, which were calculated based on the SSPRS measure. It was hypothesized that the BPD group would have higher scores on this scale than both comparison groups, reflecting more subjective stress in response to the procedure.

Power Analysis

The power to detect effects with the total sample size of 90 participants was determined by power analysis using G*Power 3.0 (Faul, Erdfelder, Lang, & Buchner, 2007), in which alpha was set at .05 with beta equal to .20, yielding .80 probability of

rejecting the null hypothesis. With 90 participants, medium to large effect sizes should be detectable. Specifically, the approximate effect sizes for each type of analysis that should be detectable are:

(1) for one-way ANOVA, $f \geq .33$ ($\eta^2 = .10$);

(2) in mixed-model repeated measures ANOVA with 8 measures (assuming correlation between repeated measures of $r = .50$), $f \geq .10$ ($\eta^2 = .01$) for within-subjects effects, $f \geq .25$ ($\eta^2 = .06$) for between-subjects effects, and $f \geq .11$($\eta^2 = .01$) for within-between interactions;

(3) in mixed-model repeated measures ANOVA with 3 measures (assuming correlation between repeated measures of $r = .50$), $f \geq .13$ ($\eta^2 = .02$) for within-subjects effects, $f \geq .27$ ($\eta^2 = .07$) for between-subjects effects, and $f \geq .15$ ($\eta^2 = .02$) for within-between interactions;

(4) for multiple regression (omnibus with one predictor or R^2 increase with up to four predictors), $f^2 \geq .09$; and

(5) for correlations, $r \geq .29$.

Chapter 3

RESULTS

Preliminary Analyses and Data Preparation

Outliers

Univariate outliers were definied by ±3 *SD* from the group means on dependent measures. There were five participants with one or more cortisol values that were greater than 3 *SD* above the mean (BPD *n* = 2; TMC *n* = 2; NTMC *n* = 1) and five participants with one or more sAA values that were greater than 3 *SD* above the mean (BPD *n* = 3; TMC *n* = 1; NTMC *n* = 1). Three participants (one from each group) had values greater than 3 *SD* above the group mean on the third PANAS-NA measure. Following previous studies (e.g., Edwards, Hucklebridge, Clow, & Evans, 2003; Eiden, Veira, & Granger, 2009; Haley, Weinberg, & Grunau, 2006; Harmon, Towe-Goodman, Fortunato, & Granger, 2008; Schuetze, Lopez, Granger, & Eiden, 2008), these values were winsorized according to Tukey's (1977) method (i.e., replaced with values exactly 3 *SD* from the mean; see also Dixon, 1960; Tabachnick & Fidel, 2007). There were no differences in any of the results when participants with winsorized values were included or not included in the data set. Therefore, results are reported for analyses including participants with winsorized values.

Missing Data

Due to insufficient sample volumes or excessive viscosity of some of the saliva samples, four participants were missing one of their cortisol values (BPD *n* = 3; NTMC *n* = 1) and four participants were missing one of their sAA values (BPD *n* = 3; NTMC *n* = 1). AUC formulas can still be calculated with missing data points by adjusting the formulas to account for missing values and the time intervals between the missing data points. Hence, for those participants who were missing cortisol or sAA values, the AUC formulas were adjusted in this manner, resulting in no missing AUC values. However, repeated measures analyses require no missing values on any data point. For repeated measures analyses, missing values for cortisol and sAA were replaced with the mean of adjacent measures for a given individual. When participants were missing the first or last measure, the values were replaced with the value of the adjacent measure. This strategy was preferred over replacement with group means because individuals within groups varied greatly in their response trajectories. One participant in the BPD group was missing her last PANAS measure due to experimenter error. This value was replaced with the BPD group mean for that measure. Results for repeated measures analyses were the same whether participants with missing values were excluded or included with their replaced missing values.

Normality of Distributions

As recommended by Tabachnick and Fidel (2007), variables that were substantially skewed were subjected to natural log transformation, and variables that were moderately skewed were subjected to square root transformation prior to analysis. Raw cortisol and sAA values were square root-transformated prior to analyses to correct for moderate skew. Although salivary cortisol data are typically log-transformed, the square root transformation was more successful in reducing skewness in the current study data.

AUC variables were calculated based on raw biomarker values. sAA AUC_G values were square root transformed to correct moderate skew. Cortisol AUC_R, sAA AUC_I, and Negative affect (PANAS-NA) values were natural log-transformed prior to analysis to correct substantial skew in these variables. For ease of interpretation and comparison to other studies, descriptive statistics are reported for raw data values unless otherwise indicated.

Time Intervals between Measurements

One-way ANOVAs were conducted in order to examine differences between groups in time intervals (minutes) in between saliva samples. Groups were significantly different only in the time interval between the second and third samples, but Tamhane's T2 pairwise comparisons demonstrated only marginally significant differences ($ps < .10$) between the NTMC and TMC groups and between the NTMC and BPD groups in this time interval, with the NTMC group tending to have a shorter interval between these two measures. Although AUC values were calculated with time intervals between measures

already taken into account, it is possible that this variability between groups could influence repeated measures analyses of biomarker data. However, when this time interval was entered as a covariate in the repeated measures analyses for cortisol and sAA, it was not a significant covariate in the models, and did not influence the results. In addition, this time interval was not significantly correlated with the second or third biomarker measures. Therefore, results are reported without controlling for this variable.

Self-Report Measures of Positive Affect, Dissociation, and Childhood Trauma

Descriptive statistics and group comparisons for self-reported positive affect (average across all three PANAS administrations), dissociation, and childhood trauma are provided in **Table 6**. The groups did not differ in dissociation (DSS) or positive affect (PANAS-PA) scores, but group differences were significant for each of the childhood trauma (CTQ) scales. The BPD group reported significantly more trauma than both the NTMC and TMC groups on each of the CTQ scales. Furthermore, the TMC group reported significantly more Emotional Abuse, Emotional Neglect, and total trauma (sum of all trauma scales) than the NTMC group.

Table 6. Descriptive statistics and group comparisons for self-report measures of dissociation, positive affect, and childhood trauma

	BPD (n = 33)$_d$		TM (n = 27)		NTM (n = 30)		
Scale	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F* value (*df*)
DSS	1.24	1.30	1.01	1.37	0.68	0.93	F (2, 86) = 1.69
PANAS-PA	22.18	7.21	24.27	6.71	25.11	7.96	F (2, 87) = 1.34
CTQ EA	16.00_a	6.20	8.63_b	4.12	6.10_c	1.71	F (2, 60.51) = 43.77*
CTQ PA	9.30_a	4.75	5.96_b	1.53	5.63_b	1.10	F (2, 43.02) = 15.49*
CTQ SA	10.30_a	7.17	5.96_b	2.90	5.47_b	1.80	F (2, 47.63) = 11.00*
CTQ EN	14.55_a	5.21	9.37_b	4.70	6.67_c	2.02	F (2, 66.99) = 28.63*
CTQ PN	9.06_a	4.37	6.26_b	1.68	5.40_b	0.97	F (2, 45.57) = 15.76*
CTQ-Total	59.21_a	21.84	36.19_b	11.72	29.27_c	5.19	F (2, 53.82) = 37.35*

* $p < .001$. $_d$ The BPD group sample size was n = 32 for the DSS due to one BPD participant who did not complete this measure.

Notes: DSS = Dissociation Tension Scale; Pos Affect = Positive Affect (averaged across three administrations of the PANAS); CTQ = Childhood Trauma Questionnaire, EA = Emotional Abuse, PA = Physical Abuse, SA = Sexual Abuse, EN = Emotional Neglect, PN = Physical Neglect, CTQ-Total = sum of all five CTQ trauma scales. Row means with different subscripts are significantly different from each other at $p < .05$ or less using Tamhane's T2 post-hoc comparisons.

Health and Lifestyle Factors

Medications

Medication and hormonal birth control use are documented in **Table 7**. As expected, most of the BPD patients (approximately 73 percent) were on at least one psychotropic medication, whereas, medication use was rare in the control groups. There

was no difference between the three groups in the percentage of participants who were taking hormonal contraceptives, $\chi^2(2) = 0.22$, $p = .90$.

Table 7. Medication use (frequencies) in each group

	BPD (n = 33)	TMC (n = 27)	NTMC (n = 30)
Antibiotic	0	1	0
Anticonvulsant	9	0	0
Anti-diabetic medication	2	0	0
Antihistamine	0	0	2
Asthma medication (non-steroid/stimulant)	1	0	0
Asthma medication (steroid/stimulant)	2	0	0
Atypical antipsychotic	10	0	0
Antihypertensive agent (non-beta-blocker)	1	0	0
Beta-blocker	1	0	0
Estrogen replacement	1	0	0
Hormonal contraceptives	14	11	14
Lithium	1	0	0
Muscle relaxant	3	0	0
Non-steroidal anti-inflammatory	2	1	1
Norepinephrine-dopamine reuptake inhibitor	11	0	0
Proton pump inhibitor	0	0	2
Sedative (e.g., benzodiazepine, barbiturate)	10	0	0
Selective serotonin reuptake inhibitor	13	1	0
Serotonin-norepinephrine reuptake inhibitor	3	0	0
Stimulant (e.g., adrenergic agonist)	5	0	0
Typical Antipsychotic (e.g., Thorazine)	1	0	0
Thyroid medication	2	0	0
Trazodone	2	0	0
Tricyclic antidepressant	0	0	1

The direction and size of all effects were similar whether participants who were taking any single class of medication were included in the samples or not; therefore, all participants were included in the reported results. Nonetheless, in order to further explore the influence of medications on emotional reactivity dimensionally, the procedures developed by Granger and colleagues (Granger, Hibel, Fortunato, & Kapelewski, 2009) for coding the likely influence of medications on cortisol activity were applied to the current study sample. This procedure results in a dimensional score for each participant, which serves as an index of the total likely influence of all medications on salivary cortisol for a given participant, taking into account the various pathways by which different medications can affect salivary cortisol levels. These pathways include direct effects on the HPA axis, indirect effects on other physiological systems that are networked with the HPA axis, moderation or mediation of cortisol secretion by changing the subjective experience of the stressor, effects on the availability or composition of saliva, and cross-reactions with antibodies that are used to detect salivary cortisol by immunoassay. The more pathways that a given medication could potentially influence, the greater the estimated total effect of the medication on a given participant's cortisol levels. No such system has been created for sAA activity; however, given the interconnections between the HPA axis and the ANS, the same codes were applied to analyses for sAA. The means for estimated total influence of medications in each group are presented in **Table 8**. As expected given their clinical status, the estimated influence of medications was significantly higher in the BPD group as compared to both comparison groups.

Menstrual Cycle

Also presented in **Table 8** are the means and standard deviations in each group for the number of days since the beginning of each participant's last menstrual cycle, the time of day at which participants were run through the TSST, and the number of hours participants were awake prior to the start of the TSST. Menstrual cycle data were missing for three participants who did not have regular menstrual cycles, including one TMC participant with an intrauterine device and two BPD participants with partial hysterectomies. These three participants were included in the reported results because the findings did not differ when they were excluded from when they were included in the analyses. Among those participants with regular menstrual cycles, there was no significant difference between groups in the number of days since the beginning of their last menstrual cycle.

Time of Day and Hours Since Awakening

There was no significant difference between groups in the time of day when participants began the TSST (to the nearest hour in military time; see **Table 8**). Groups differed in the number of hours they had been awake before the TSST based on the Brown-Forsythe *F* test, but Tamhane's T2 pairwise post-hoc tests showed no significant or trend-level differences between any two groups (all *p*s > .10).

Table 8. Descriptive statistics and one-way ANOVA results for medications, menstrual cycle, time of day, and sleep patterns that could potentially influence biomarker levels

	BPD (n = 33)		TMC (n = 27)		NTMC (n = 30)		
	M	*SD*	*M*	*SD*	*M*	*SD*	*F* value (*df*)
Med. influence	0.17_a	0.12	0.02_b	0.07	0.07_b	0.09	$F(2, 75.56) = 19.16$**
Menstrual cycle	8.16	4.28	8.42	3.35	7.03	4.73	$F(2, 84) = 0.90_c$
Time of day	15.67	1.38	15.63	0.97	15.27	1.11	$F(2,87) = 1.06$
Hrs since awakening	8.35	2.45	7.19	1.73	7.23	1.77	$F(2,82.79) = 3.38$*

* $p < .05$. ** $p < .001$. $_c$ Degrees of freedom differ due to missing data for participants whose menstrual cycles are irregular or absent.

Notes: Degrees of freedom with decimal values correspond to Brown-Forsythe *F* values for variables that violated the homogeneity of variance assumption. Row means with different subscripts are different ($p \leq .001$) based on Tamhane's T2 pairwise comparisons. Med. influence = estimated influence of medications on cortisol per Granger et al. (2009); Menstrual cycle = number of days since beginning of last menstrual cycle; Time of day = time of TSST rounded to the nearest hour, military time; Hrs since awakening = number of hours between awakening and beginning of TSST.

Correlations between Dependent Variables and Potential Covariates

Associations between dependent measures and possible confounding dimensional variables were examined via Pearson product-moment correlations (see **Appendix**). Based on the correlations observed between cortisol and age, medications, hours since awakening, and education level, these variables were explored as potential covariates in all cortisol analyses. Additionally, age and medications were explored as potential covariates in sAA analyses. Age, education, and average positive affect were also explored as potential covariates in the analysis of subjective negative affect (as measured

by the PANAS). Only those variables that remained at least marginally significant in the models were retained in the final reported analyses. As recommended for repeated-measures ANCOVA (e.g., Annaz, Karmiloff-Smith, Johnson, & Thomas, 2009), because the within-participants main effects of time are independent of the effects of between-participants covariates (i.e., factors that covary between participants such as age, medications, education level, etc.), repeated measures analyses were first conducted excluding the covariate in order to examine pure within-participants main effects. Thus, pure within-participants main effects were reported excluding covariates, and between-participants effects and interactions were reported including covariates.

Although trait negative affect and impulsivity were related to many of the dependent variables, these factors were at least partially controlled by the inclusion of the TMC group. Even though the TMC and BPD groups differed in trait anxiety and depression, the TMC group also differed from the NTMC group in these traits. Therefore, if trait anxiety or depression influenced results, differences should be expected between the TMC and NTMC groups. In addition, these trait measures, as well as trauma, dissociation, and personality disorder dimensional scales, were related to BPD severity and were not randomly distributed across groups. Several authors (e.g., Cochran, 1957; Maxwell & Delaney, 1990; Miller & Chapman, 2001; Porter & Raudenbush, 1987) have noted problems with using pre-existing group differences that overlap with nonrandom group membership as covariates in ANCOVA. This becomes particularly problematic when one considers factors that are common in BPD samples but have low base-rates in nonpsychiatric samples, such as dissociation, childhood trauma, and concurrent psychiatric disorders and symptomatology. These variables may be

important predictors of the dependent variables in the current study, but are inherently tied to group membership and are not randomly distributed across the groups. Given these considerations, the influence of such factors were further examined through supplemental analyses.

Results of Primary Analyses

Salivary Cortisol

From among the potential covariates explored for cortisol (age, medications, hours since awakening, and years of education), only hours since awakening emerged as a significant covariate, and only for repeated measures analysis of cortisol and analysis of total cortisol output (AUC_G).

Cortisol response trajectories in each group are illustrated in **Figure 2**. Repeated measures ANOVA for square-root transformed cortisol values across the eight time points revealed a significant main effect of time, F (2.03, 176.20) = 24.58, $p < .001$, $\eta^2 = .20$, indicating change in cortisol levels during the course of the experiment. Participants' cortisol levels significantly decreased during the pre-stress resting period from the first to the third measures (-35 min to -5 min, $p < .01$), increased during the 25 minutes following the TSST (+5 min to +25 min, ps $< .001$), and then decreased during the recovery period (+35 min to +45 min, $p < .001$).

After controlling for hours since awakening, there was no significant main effect of group for cortisol levels, F (2, 86) = 0.17, $p = .85$, $\eta^2 = .004$. However, there was a significant time × group interaction, F (4.01, 172.35) = 4.12, $p = .003$, $\eta^2 = .08$.

Polynomial contrasts for the interaction demonstrated a significant linear effect, F (2, 86) = 6.99, p = .002, η^2 = .14. One-way ANCOVA for the linear polynomial change term (controlling for hours since awakening) with Bonferroni-corrected post-hoc tests demonstrated that the BPD group showed less linear change in cortisol over time compared to both the TMC (p = .003) and NTMC (p = .01) groups, but the NTMC and TMC groups did not differ in linear change. Hence, the BPD group showed less increase in cortisol than both comparison groups in response to the stress task.

Descriptive statistics for untransformed AUC values for both cortisol and sAA are presented in **Table 9**. One-way ANOVAs for each of the three cortisol AUCs demonstrated no group differences in overall cortisol output (AUC_G) with hours since awakening entered as a covariate, F (2, 86) = 0.02, p = .98, η^2 < .001, or in log-transformed cortisol recovery (AUC_R), F (2, 71.72) = 0.70, p = .52, η^2 = .01. However, consistent with the results of the repeated measures analysis, groups differed in amount of cortisol increase (AUC_I), F (2, 87) = 6.55, p = .002, η^2 = .13. Bonferroni-corrected post-hoc comparisons demonstrated that the BPD group showed significantly less increase in cortisol as compared to both the TMC (p = .007) and NTMC (p = .009) groups, but the TMC and NTMC groups did not differ from each other in the amount of cortisol increase.

Figure 2

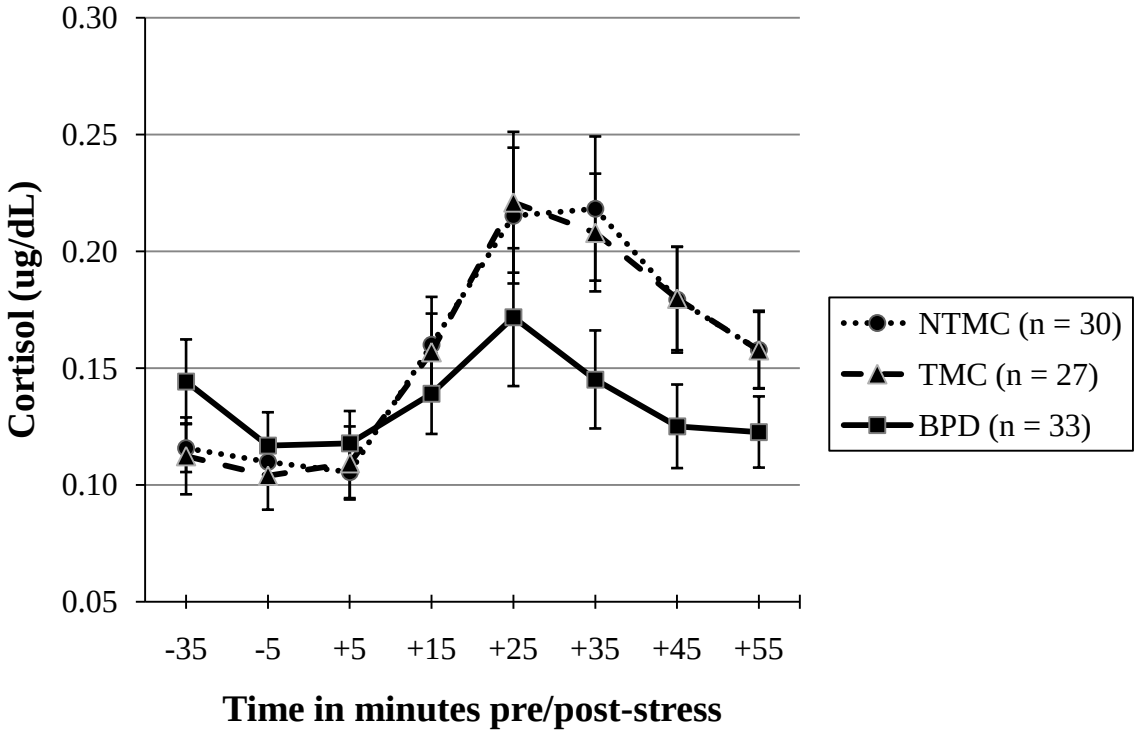

Figure 2. Mean cortisol levels during the Trier Social Stress Test in each group
Note: Error bars represent standard error (*SE*) from the mean.

Salivary Alpha-Amylase (sAA)

sAA response trajectories in each group are illustrated graphically in **Figure 3**. Medications emerged as a significant covariate for overall sAA output (sAA AUC_G), and was therefore entered as a covariate for sAA AUC_G analysis. There were no other significant covariates for sAA.

Repeated measures ANOVA for square-root transformed sAA values across the eight time points revealed a significant main effect of time, F (4.85, 422.26) = 48.33, p < .001, η^2 = .35, indicating change in sAA levels during the course of the experiment. Participants' sAA levels showed a rapid increase with introduction of the stress task (-5 min to +5 min, p < .05; +5 min to +15 min, p < .001), and then significantly decreased during the recovery period following the stress task (+15 min to +45 min, ps < .01).

The main effect of group for sAA was not significant, F (2, 87) = 0.54, p = .59, η^2 = .01. However, there was a significant time × group interaction effect, F (9.71, 422.26) = 2.07, p = .03, η^2 = .03. Polynomial contrasts for the interaction demonstrated significant differences between groups in both quadratic change, F (2, 87) = 3.54, p = .03, η^2 = .08, and cubic change, F (2, 87) = 3.55, p = .03, η^2 = .08. The NTMC group demonstrated significantly more quadratic change (increase and then decrease in sAA) in comparison to the BPD group, p = .03. In addition, the TMC group demonstrated more cubic change (increase, decrease, and then another small increase) in comparison to the BPD group, p = .03. Polynomial change trends in each group are illustrated graphically in **Figure 4**. As shown in the graphs, the BPD group tends to have higher sAA levels at baseline and to show an overall decrease in sAA across the stress procedure; whereas, the NTMC and TMC groups start with lower sAA levels prior to stress and then show reactivity (increase) and recovery (decrease) in sAA levels in response to stress.

One-way ANOVAs on AUCs of sAA response demonstrated no group differences in overall sAA output (square-root transformed AUC_G with medications entered as a covariate), F (2, 86) = 0.38, p = .69, η^2 = .01, or in sAA recovery (AUC_R), F (2, 87) = 1.40, p = .25, η^2 = .03. However, consistent with the results of the repeated measures

analysis, groups differed in the amount of sAA increase (log-transformed AUC_I), F (2, 87) = 4.91, p = .01, η^2 = .10. Bonferroni-corrected post-hoc comparisons demonstrated that the BPD group showed significantly less increase in sAA as compared to the TMC group (p = .01), and less increase in sAA than the NTMC group at only a trend level (p = .08). TMC and NTMC groups did not differ from each other in sAA increase.

Figure 3

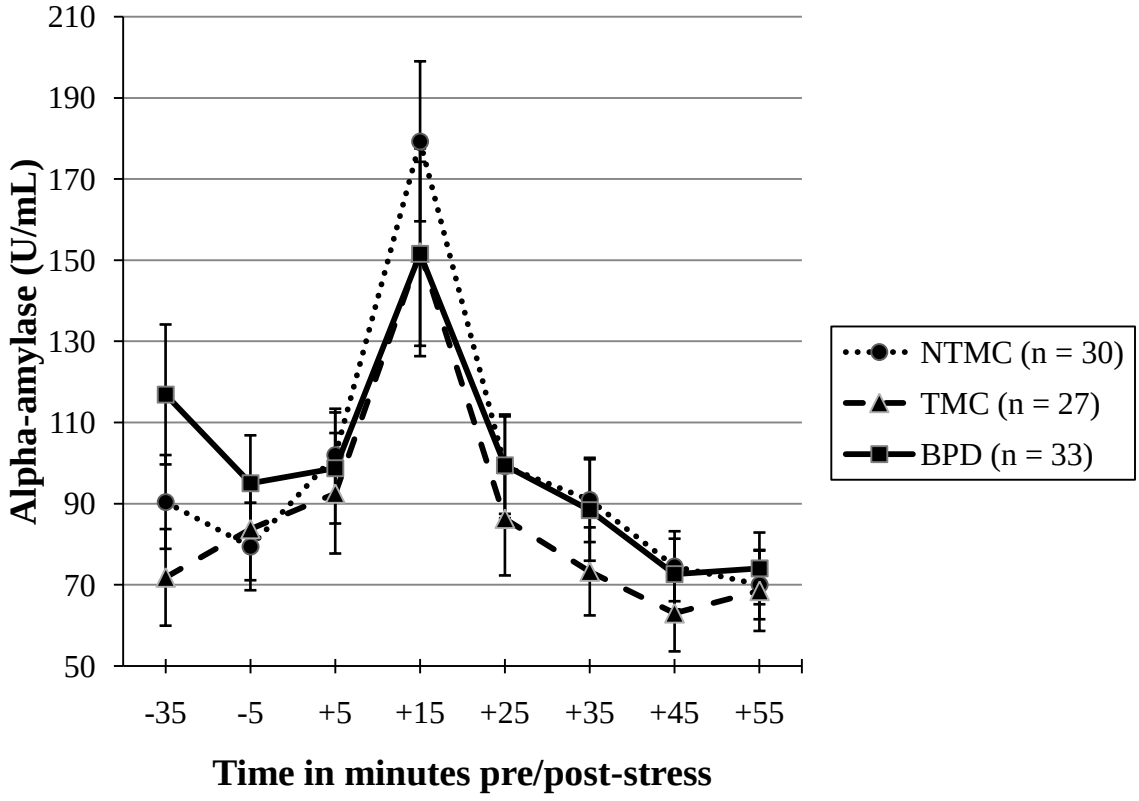

Figure 3. Mean sAA levels during the Trier Social Stress Test in each group

Note: Error bars represent standard error (*SE*) from the mean.

Figure 4

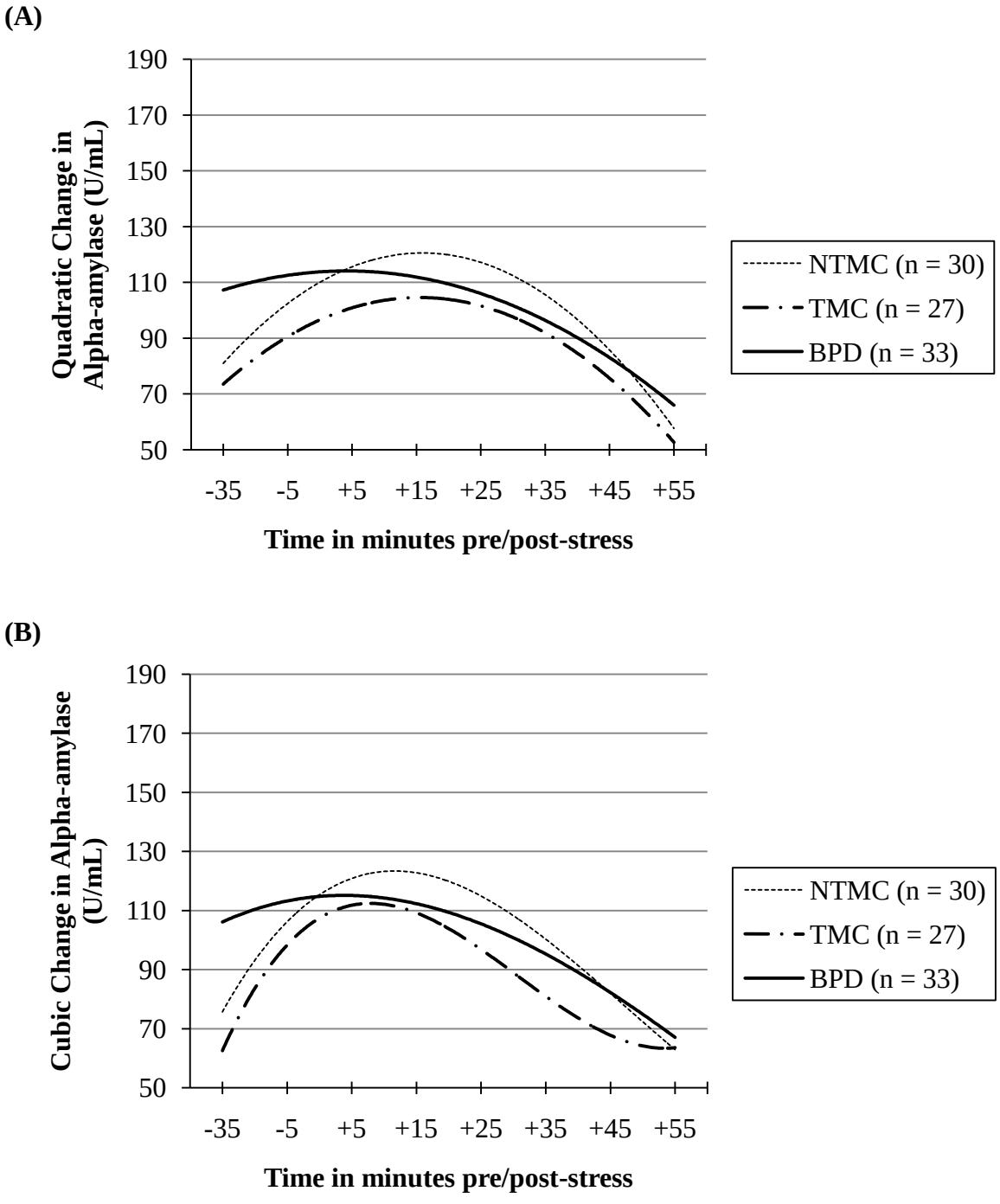

Figure 4. Quadratic (A) and cubic (B) trend lines for sAA response during the Trier Social Stress Test in each group

Subjective Negative Affect

Both within- and between-groups change in negative affect was examined by conducting a 3x3 mixed model ANOVA for log-transformed PANAS-NA scores on three occasions of measurement. From among the potential covariates for negative affect (i.e., age, education, and average positive affect), only education level emerged as a significant covariate. Therefore, education was retained as a covariate in the PANAS-NA analysis. Subjective negative affect in each group during the stress procedure is illustrated graphically in **Figure 5**; descriptive statistics for negative affect are presented in **Table 9**.

The initial mixed model ANOVA for PANAS-NA without any covariates revealed a significant main effect of time, F (1.74, 151.36) = 88.50, $p < .001$, $\eta_p^2 = .50$, with a strong quadratic effect, F (1, 87) = 173.77, $p < .001$, $\eta^2 = .67$, suggesting a large increase in negative affect immediately following the stressor ($p < .001$) and a decrease in negative affect over the post-stress recovery period ($p < .001$). After controlling for years of education, there was a significant main effect of group, F (2, 86) = 10.12, $p < .001$, $\eta^2 = .19$. Bonferroni-corrected post-hoc comparisons demonstrated that the BPD group reported significantly more negative affect (collapsed across time) than both the TMC ($p = .04$) and NTMC ($p < .001$) groups, and the TMC and NTMC groups did not differ in average negative affect. However, there was no significant time × group interaction effect, F (3.50, 150.29) = 1.13, $p = .34$, $\eta^2 = .03$, suggesting no differences between groups in change in negative affect across time.

The assessment of subjective negative affective reactivity in populations that are already high in negative affect at baseline may be limited by ceiling effects of measures. Those who start with lower levels of negative emotion at baseline have more room to

increase with the introduction of stress than do those who start at higher levels. Therefore, as an additional test of group differences in subjective negative affective reactivity, a univariate ANCOVA was conducted to determine if groups differed in immediate post-stress negative affect levels after controlling for baseline negative affect as a covariate. The results demonstrated a marginally significant group difference, F (2, 86) = 3.04, p = .05, η^2 = .07, with the BPD group showing more increase in subjective negative affect than the NTMC group, $p < .05$, but the TMC group did not differ significantly from either the BPD or NTMC group, ps > .05.

Figure 5

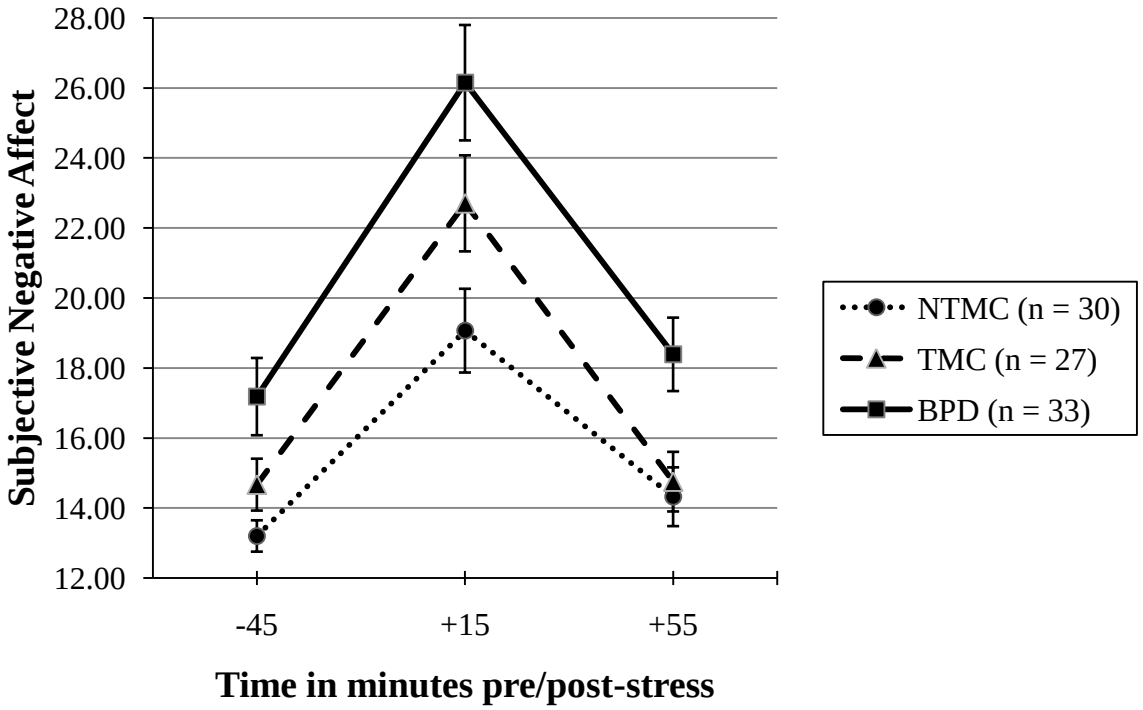

Figure 5. Subjective negative affect in each group, as measured by the Positive and Negative Affect Schedule (PANAS), during the Trier Social Stress Test

Subjective Stress Response

A one-way ANOVA for Subjective Stress Response (SSR) scores (see Table 10 for descriptive statistics) demonstrated that groups differed in their subjective stress response to the TSST, F (2, 87) = 10.11, $p < .001$, $\eta^2 = .19$. Bonferroni-corrected post-hoc tests showed that the NTMC group rated the TSST as significantly less stressful than both the TMC ($p < .001$) and BPD ($p = .001$) groups, but the BPD and TMC groups did not differ in their subjective stress response.

Table 9. Descriptive statistics for cortisol and salivary alpha-amylase (sAA) area under the curve (AUC) values, subjective negative affect (PANAS-NA), and subjective stress response in each group

	BPD (n = 33)		TMC (n = 27)		NTMC (n = 30)	
	M	*SD*	*M*	*SD*	*M*	*SD*
Cortisol AUC_G	12.96	8.92	13.96	7.76	13.76	7.39
Cortisol AUC_I	-0.92	4.86	3.34	5.23	3.13	5.66
Cortisol AUC_R	0.50	0.97	1.04	1.49	1.10	2.36
sAA AUC_G	9798.98	6850.04	8326.89	6367.78	9086.57	5249.05
sAA AUC_I	-1605.74	5229.22	1551.10	1955.42	800.06	2738.98
sAA AUC_R	803.07	1284.88	594.01	892.11	1104.70	1230.54
PANAS-NA T1	17.18	6.34	14.67	3.85	13.20	2.46
PANAS-NA T2	26.15	9.47	22.70	7.13	19.07	6.55
PANAS-NA T3	18.39	6.03	14.75	4.43	14.32	4.60
Subjective Stress Response	6.38	1.57	6.65	1.51	4.97	1.55

Notes: AUC_G = Area under the curve with respect to ground; AUC_I = Area under the curve with respect to increase; AUC_R= Area under the curve with respect to recovery; sAA = Salivary alpha-amaylse; PANAS-NA = Positive and Negative Affect Schedule, negative affect scale (T1 = Time 1 (pre-stress); T2 = Time 2 (immediately post-stress); T3 = Time 3 (post-recovery)).

Supplemental Analyses: Examination of the Influence of Age, Trait Anxiety and Depression, Comorbidity, Trauma, and Dissociation on Results

Group Differences in Age

The BPD group was significantly older than both comparison groups, and older participants tended to have lower cortisol and sAA responses (see Appendix). This raises the possibility that the blunted cortisol and sAA reactivity in the BPD group as compared to both the NTMC and TMC groups could be explained by age. To explore this possibility, a set of focused supplemental analyses for cortisol and sAA reactivity measures (AUC_I values) were conducted to determine if the results remained the same when a smaller group of BPD patients was compared to an age-matched healthy comparison group.

Participants from the full sample (N = 90) were selected who were between the ages of 20 and 40 years old. Because the NTMC and TMC groups were not significantly different in cortisol or sAA reactivity, one comparison group with a combination of NTMC and TMC participants was used to maximize statistical power. This resulted in a group of 27 comparison participants (comprised of 13 NTMC and 14 TMC participants; M_{age} = 27.44, SD = 7.26) and 27 BPD participants (M_{age} = 27.89, SD = 5.84). The two groups did not differ from each other in age, t (52) = 0.25, p = .81, d = .07.

Independent samples t-tests were conducted in order to compare the BPD subsample and the age-matched comparison groups on cortisol and sAA AUC_I values. The results were consistent with the previously reported results, with medium to very large effect sizes. Specifically, the BPD group had significantly less cortisol increase (cortisol AUC_I), t (52) = 2.99, p = .004, d = .83, and less sAA increase (sAA AUC_I), t (52) = 2.03, p = .05, d = .57, as compared to the age-matched healthy comparison group. Thus, despite the negative correlation between age and biomarker reactivity, the attenuated biomarker reactivity of the BPD group does not appear to be due to age differences between groups.

Trait Anxiety and Depression

Because the TMC and BPD groups were not completely matched in trait Anxiety and Depression according to their NEO-PI-R facet scale scores (the TMC group was significantly higher than the NTMC group, but lower than the BPD group, on these traits), this leaves uncertainty as to whether trait Anxiety and Depression could explain differences between the TMC and BPD groups. Therefore, a small group of TMC participants were identified who did not differ from the BPD group in any of the trait measures.[1] These two groups (BPD, n = 12; TMC, n = 12) were then compared on

[1] To create a trait-matched group, the Anxiety and Depression scales were first summed to yield one scale score because these scales were highly correlated in the current study sample (r = .85). Then, TMC participants were identified with scores within one standard deviation from the BPD group's mean on this composite Depression-Anxiety scale (12 TMC participants were identified who met this criterion). Next, the same number of BPD participants were selected who were matched on this composite scale to the selected TMC participants (± 2 points). This process resulted in a TMC group (n = 12) that did not differ from the subgroup of 12 BPD patients on any of the trait measures (Angry Hostility, p = .77, d = .13; Anxiety, p = .71, d = .16; Depression, p = .87, d = .07; and Impulsivity, p = .41, d = .36).

biomarker AUC levels, average negative affect across the stress procedure, and Subjective Stress Response scores. Effect sizes of *t*-test results were examined rather than *p*-values due to the small sample sizes.

All analyses with the trait-matched groups demonstrated similar effect sizes to those reported in the primary analyses, including less cortisol increase (cortisol AUC_I, d = 1.27) and sAA increase (sAA AUC_I, d = 0.64) and more average subjective negative affect across time (d = 1.27) in the BPD group as compared to the TMC group. In addition, consistent with the results from the larger BPD and TMC groups, this smaller BPD group did not differ from the fully-matched TMC group in subjective stress in response to the TSST, d = .18. Hence, it does not appear that trait negative affect and impulsivity can explain the blunted cortisol and sAA reactivity and high levels of subjective negative affect in the BPD group as compared to healthy controls; however, trait negative affect and impulsivity may explain higher subjective stress response, as the BPD and TMC groups did not differ on this variable.

Psychiatric Comorbidity

In order to explore the influence of different types of comorbid psychopathology on the results, all primary analyses were re-run with each of the following groups of participants excluded from analyses (one group excluded at a time): those with current MDD, past MDD, current mood disorders of any kind, past mood disorders of any kind, current PTSD, past PTSD, current anxiety disorders of any kind, current substance dependence, and probable or definite diagnoses for each of the non-BPD personality

disorders. For each set of analyses, all of the results were in the same direction and of similar magnitude of effect size to those reported in the full sample, suggesting that the results cannot be explained by any one particular type of comorbid psychiatric condition within the BPD sample.

Additionally, simple bivariate correlations were examined within the BPD group (n = 33) for the relationships between the number of comorbid non-BPD psychiatric diagnoses (both Axis I and II disorders) and the dependent variables on which significant group differences were found (i.e., biomarker AUC_I values, average negative affect, and subjective stress response scores); all correlations were nonsignificant and negligible in effect size. Thus, the number of non-BPD psychiatric diagnoses does not appear to explain these results. However, the possibility that severity of impairment or comorbid conditions other than BPD could influence biomarker and subjective reactivity in BPD patients cannot be fully discarded without a psychiatric comparison group.

Childhood Trauma

Most of the five childhood trauma scales were related to lower biomarker reactivity (see Appendix), and childhood trauma has been shown in a number of studies to influence stress hormone reactivity (e.g., Heim et al., 2000, 2001, 2002, 2003; Carpenter et al., 2007, 2009). Therefore, the influence of childhood trauma on biomarker reactivity was further examined.

Because the CTQ Total trauma score (sum of all five CTQ trauma scales) was highly correlated with each of the CTQ trauma subscales ($rs \geq .75$), and exploratory

factor analysis of the five CTQ subscales indicated a one-factor solution, the total CTQ trauma score (CTQ-Total) was used as a continuous index of childhood trauma. The BPD group was split into high-trauma (n = 17) and low-trauma (n = 16) groups based on the median of CTQ-Total within the BPD sample (median = 58). The NTMC and TMC groups were combined into one healthy comparison group (n = 57). The comparison group was not split according to trauma due to lack of sufficient variability and low endorsement of trauma within the control groups (see Table 6). The cortisol and sAA response trajectories for the high-trauma BPD, low-trauma BPD, and comparison groups are illustrated in Figures 6 and 7. It should be noted, however, that trauma scores were highly correlated with BPD dimensional scores, which introduces the possibility that any observed differences between BPD patients with and without severe trauma may be due to severity of BPD features and not necessarily a direct result of experiences of trauma per se. [2]

A one-way ANOVA for cortisol AUC_I revealed significant group differences for cortisol increase, F (2, 87) = 6.72, p = .002, η^2 = .13. Bonferroni-corrected post-hoc tests demonstrated that the high- and low-trauma BPD groups were significantly lower in cortisol increase than the healthy comparison group (ps < .05), but the high- and low-trauma BPD groups did not differ from each other in cortisol increase. Hence, level of self-reported childhood trauma does not appear to moderate the attenuated cortisol

[2] In the full sample, BPD dimensional scores from the IPDE were significantly correlated with total CTQ trauma scores, r(88) = .71, p < .001; BPD dimensional scores were also correlated with total CTQ scores within the comparison sample only, r (55) = .38, p = .004, and within the BPD sample only, r (31) = .41, p = .02. In addition, the high-trauma BPD group was higher than the low-trauma BPD group in relationship instability, t(17.94) = 2.11, p < .05, and intense anger, t(19.83) = 2.45, p = .02, according to interviewer-rated BPD features from the IPDE.

response in the BPD group relative to the healthy comparisons. Figure 6 illustrates the similar patterns of cortisol response among BPD patients who reported high and low levels of childhood trauma.

Figure 6

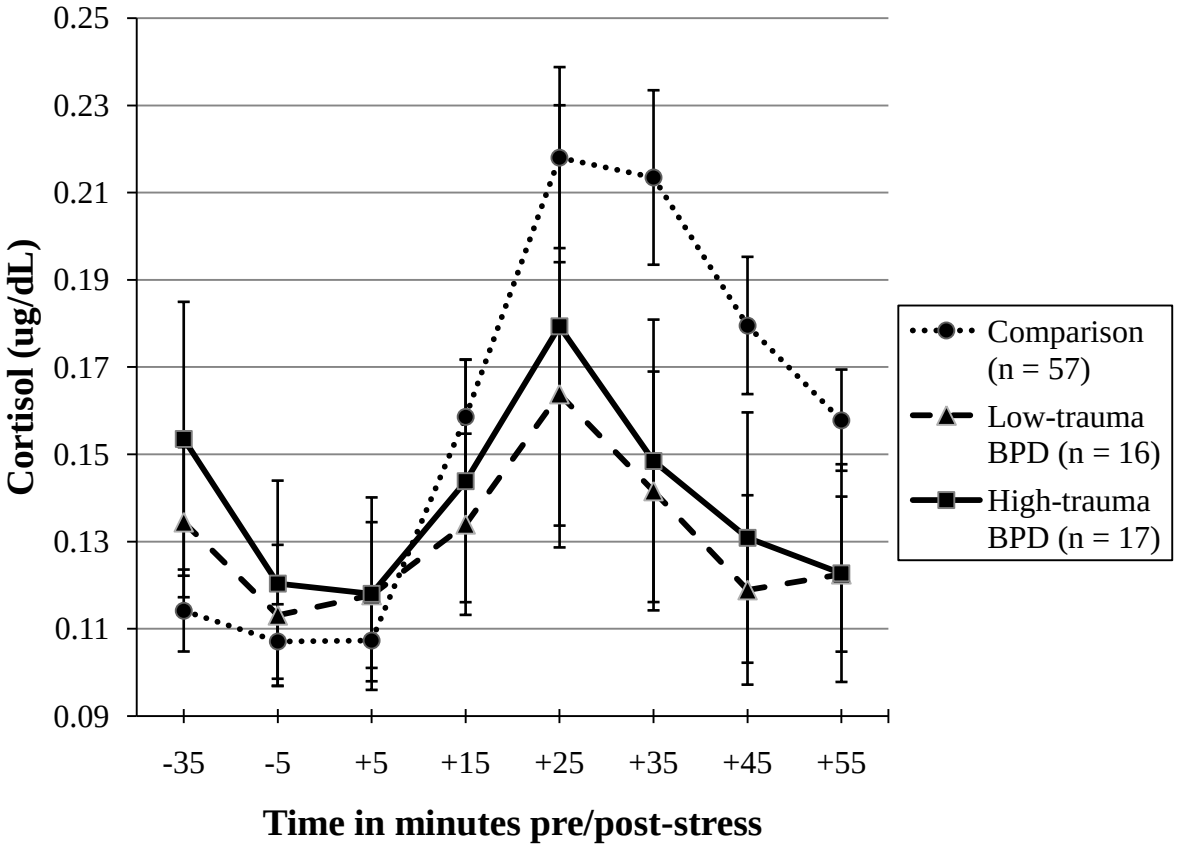

Figure 6. Mean cortisol levels during the Trier Social Stress Test in healthy comparisons and BPD patients with low- and high-trauma histories

Note: Error bars represent standard error (*SE*) from the mean.

A one-way ANOVA for sAA AUC_I also revealed significant group differences for sAA increase, F (2, 87) = 9.17, $p < .001$, $\eta^2 = .17$. For sAA, the high-trauma BPD group demonstrated significantly less sAA increase than both the healthy comparison and low-trauma BPD groups (ps < .05), and the low-trauma BPD group did not differ from

the healthy comparisons in sAA increase. As shown in Figure 7, the BPD patients with high levels of childhood trauma had higher sAA levels at the first measure relative to both of the other groups (*p*s < .05), but they appeared to show a rapid decline in sAA prior to the introduction of stress and then a robust response to the stress. In addition, there was a trend-level group difference in overall sAA output (AUC_G), F (2, 87) = 2.50, p = .09, η^2 = .05, such that high-trauma BPD patients tended to have more overall sAA output than both the low-trauma BPD patients (p = .04) and healthy controls (p = .06).

Figure 7

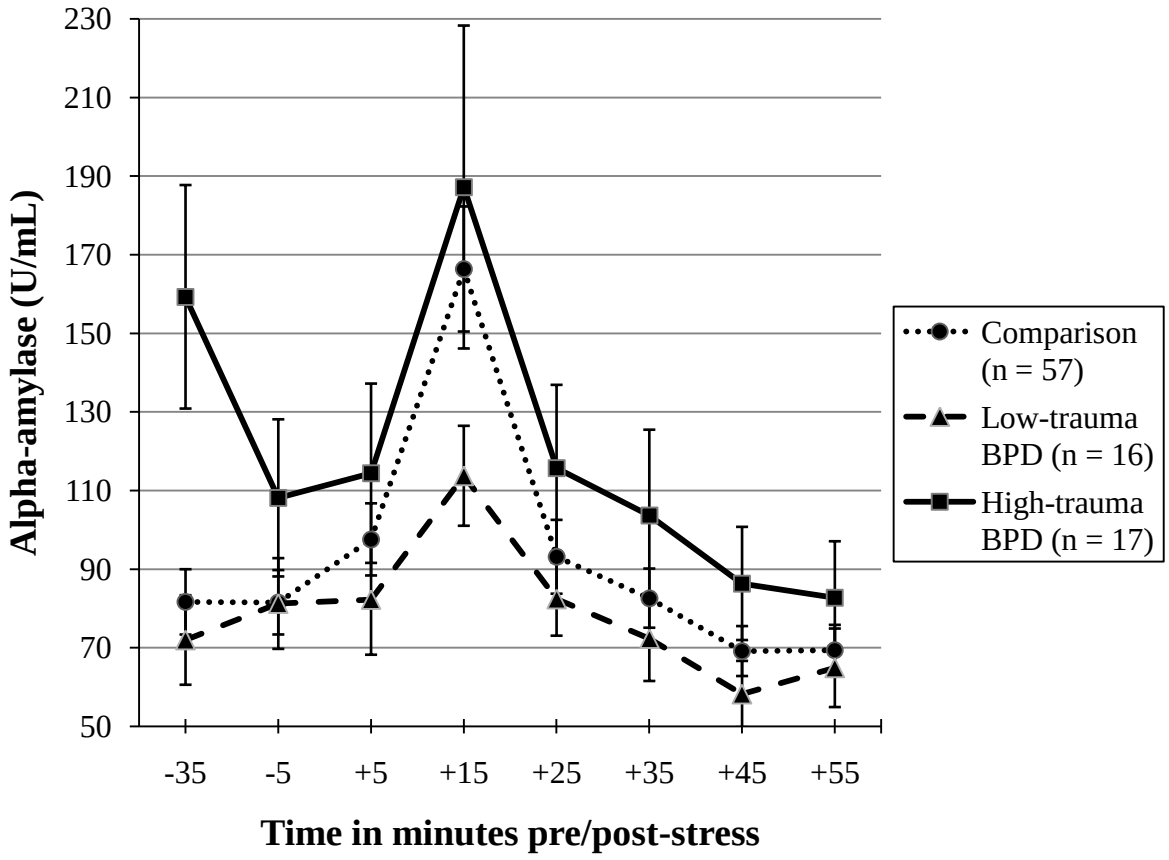

Figure 7. Mean sAA levels during the Trier Social Stress Test in healthy comparisons and BPD patients with low- and high-trauma histories

Note: Error bars represent standard error (*SE*) from the mean.

Dissociation

Dissociation during the stress procedure, as measured by the DSS, was not related to cortisol or sAA reactivity but was related to higher phenomenological reactivity (i.e., higher self-reported negative affect and subjective stress response (see Appendix)). However, the BPD group did not differ from the comparison groups in DSS scores (see Table 6). In addition, using the cut-off score of 2.7 for severe dissociative tendencies (Stiglmayr et al., 2001), there were four comparison participants and only three BPD participants who endorsed severe dissociation. Thus, the proportion of patients and comparisons who endorsed severe dissociation was approximately equal, $\chi^2(1) = 0.13$, $p = .72$. Moreover, when DSS scores were entered as a covariate in analyses for subjective negative affect and stress response, the group differences reported in the primary analyses remained similar in direction and effect size, with the BPD group endorsing more negative affect overall than both comparison groups and more subjective stress than the NTMC group. Based on these findings, it is unlikely that the group differences in phenomenological reactivity (i.e., the BPD group's higher overall self-reported negative affect and subjective stress response) can be explained by any greater tendency for dissociation within the BPD group.

Chapter 4

DISCUSSION

The current study sought to examine cortisol, sAA, and subjective emotional reactivity in response to a social stressor among women with BPD, psychology healthy women who were matched to the BPD group in trait negative affect and impulsivity (TMC group), and healthy women who were not matched to the BPD group in these traits (NTMC group). In accordance with Linehan's (1993, 1995) theory of biological vulnerability to emotional dysregulation in BPD, as well as numerous studies suggesting heightened stress reactivity in BPD (for reviews, see Wingenfeld et al., 2010; Zimmerman & Choi-Kain, 2009), it was hypothesized that the BPD group would demonstrate evidence of emotional hyperreactivity and impaired recovery in terms of higher cortisol, sAA, and subjective emotional responses to the stress induction procedure and impaired return to baseline levels after stress.

Contrary to these hypotheses, the BPD group demonstrated blunted cortisol and sAA reactivity, despite reporting higher levels of negative affect throughout the experiment, as compared to both the TMC and NTMC groups. This result is particularly striking when considering the fact that all of the BPD patients in the current sample met the BPD criterion of affective instability, although this was not a requirement for inclusion in the study. Additionally, when controlling for baseline subjective negative affect, the BPD group demonstrated marginally significant subjective hyperreactivity of negative affect in response to stress, but only in comparison to the NTMC group. Nonetheless, the BPD patients reported higher negative affect than both comparison groups when averaged across all time points, suggesting general high negative affectivity

in BPD, regardless of environmental stress. Furthermore, both the TMC and BPD groups reported more subjective stress in response to the social stressor than did the NTMC group; otherwise, the TMC group did not differ from the NTMC group in measures of reactivity. Supplemental analyses suggested that these results could not be explained by comorbid psychopathology, medication use, age differences between groups, or dissociation during the stress procedure. However, the BPD patients who reported histories of severe childhood trauma demonstrated particularly blunted ANS reactivity with high baseline sAA levels, more decrease relative to increase in sAA over the course of the stress procedure, and a trend toward higher overall sAA output.

These results generally did not support the hypothesis of heightened emotional reactivity and impaired recovery in terms of higher cortisol and sAA reactivity (i.e., change from baseline) to social stress in women with BPD. Nevertheless, these findings do suggest general intensity of negative affect as well as dysregulated HPA axis and ANS responding among women with BPD in the direction of *hyporeactivity* rather than hyperreactivity. These results are generally consistent with those reported by Nater et al. (2010), who found attenuated cortisol and sAA response to stress in a small, unmedicated BPD sample as compared to a healthy control group. In accordance with Nater et al.'s findings, the current results provide additional evidence of adrenal and central noradrenergic hyporesponsiveness to environmental stress in patients with BPD.

Moreover, the finding of attenuated sAA *reactivity* in the current study is consistent with previous studies suggesting autonomic hyporeactivity among individuals with BPD as assessed by SCR (Herpertz et al., 1999, 2000). However, the lower sAA reactivity in the BPD group may be explained by the high baseline sAA levels, especially

among the more severely impaired BPD group who reported more experiences of childhood abuse and neglect. Thus, these results suggest the potential for baseline autonomic hyperarousal in certain individuals with BPD, which obscures measures of reactivity (or change from baseline) in autonomic response. The current study's finding of higher baseline sAA among the BPD patients is consistent with results from Kuo and Linehan (2010) of higher baseline SCR and lower vagal control over visceral responses at baseline in patients with BPD. Combined with these previous findings, the current results provide further evidence of biological vulnerability to emotional dysregulation in those with BPD. Specifically, high baseline autonomic arousal combined with high baseline negative affect may predispose individuals with BPD to intense negative emotional responses, hypervigilance to threat, and the negative consequences of chronic stress for health and functioning.

Further, the trend for higher sAA output overall in the BPD patients who reported more trauma and who had more severe BPD features is consistent with other studies that suggest sympathetic hyperarousal in BPD patients (DeVegvar et al., 1998; Ebner-Priemer et al., 2005, 2008; Hazlett et al., 2007; Kozel, 2001; Lobbestael & Arntz, 2010; Southwick et al., 1990a, 1990b; Yehuda et al., 1994). In the current study, the BPD patients appear to show high baseline autonomic hyperarousal and less increase in arousal from baseline levels, as compared to both comparison groups. Thus, in patients with BPD, autonomic functioning might be better characterized by chronic hyperarousal rather than hyperreactivity, and this hyperarousal appears to be particularly strong in those who have experienced severe abuse or neglect during childhood.

In addition, the finding of general negative affectivity in the BPD patients as compared to both healthy control groups is consistent with a number of studies (e.g., Herpertz et al., 1999; Jacob et al., 2008, 2009; Kuo & Linehan, 2010) showing evidence of intense negative affect among individuals with BPD, but not necessarily hyperreactivity, in subjective negative emotional responding. The disposition to experience high levels of negative affect, even before the introduction of aversive stimuli, also suggests vulnerability to emotional dysregulation that is at least partially consistent with Linehan's (1993, 1995) theory of BPD (Kuo & Linehan, 2010). Specifically, the results of the repeated measures analysis of subjective negative affect do not support *the high reactivity* and *impaired recovery* aspects of Linehan's (1993) theory, but they do appear to support the notion of high emotional intensity in those with BPD. Hence, these results might be interpreted to provide further evidence that emotional dysregulation in those with BPD might more appropriately be characterized as intense subjective negative affectivity, rather than emotional hyperreactivity (Jacob et al., 2009). However, the univariate analysis of group differences in post-stress negative affect after controlling for baseline negative affect revealed a marginally significant group difference, with the BPD group demonstrating more increase in negative affect than the NTMC group, and the TMC and NTMC groups did not differ in their increase in negative affect. Thus, the results provide some evidence for subjective hyperreactivity in BPD that may be partially due to trait negative affect and impulsivity, but these results were relatively weak in magnitude compared to the overall high negative affectivity demonstrated across time in the BPD group relative to both healthy comparison groups.

With the inclusion of a TMC group that was matched to the BPD group in trait negative affect and impulsivity, the current results add to the extant literature by showing that these patterns of emotional responding among women with BPD cannot be fully explained by an exaggeration of normal-range personality traits. Despite being matched to the BPD group in trait negative affect and reporting similar levels of subjective stress in response to the procedure, the TMC group still reported experiencing less negative emotions overall during the experiment and showed more sensitivity in biomarker responding in comparison to the BPD group. In addition, the perception of the event as more stressful did not manifest in differential subjective negative affect or biomarker responsiveness in the TMC group relative to the NTMC group. This suggests that the perception of the event as stressful can be differentiated from the experience of state negative affect and biomarker response to social stress. Moreover, the similar levels of reactivity in the TMC and NTMC groups suggests that trait negative affect and impulsivity are not the primary mechanisms for intense negative affect and decreased reactivity of the biological stress response system in patients with BPD. Trait negative affect and impulsivity may be broadband risk factors for BPD, but these traits also occur in nonpsychiatric samples and do not necessarily lead to extreme affective dysregulation.

The differences between this study's results and those of other studies that have found evidence of HPA axis or autonomic hyperreactivity (e.g., Simeon et al., 2007; Ebner-Priemer et al., 2005; Hazlett et al., 2007; Walter et al., 2008; Weinberg et al., 2009) may be attributable, at least in part, to differences in methodology. First, the current study used noninvasive saliva sampling and did not expose participants to venipuncture or psychophysiological equipment, which might have created spurious

reactivity among patients in some previous studies. Second, the current study had the benefit of a larger sample than previous studies of neuroendocrine reactivity to environmental stressors in those with BPD (Simeon et al., 2007; Walter et al., 2008; Nater et al., 2010). With smaller samples, previous studies may not have been able to sample the full range of BPD presentations and severity, and results may have been influenced by extreme outliers in the data.

Third, different measures of HPA axis and autonomic reactivity do not necessarily measure the same physiological mechanisms. The stress response system is comprised of anatomically distinct but functionally interconnected circuits, which may become dysregulated in different ways at different levels, even within the same neurobiological system (Boyce & Ellis, 2005; Gunnar et al., 2006; Yehuda, 2006). Because the components of the stress response system are functionally integrated, sometimes acting in alliance and sometimes in opposition to each other with complex negative feedback loops, hyperreactivity at one level can manifest in hyporeactivity at another level of the system. This might explain the apparent discordance between evidence of structural and functional abnormalities in BPD patients that are consistent with emotional hyperreactivity (Brendel et al., 2005; Lis et al., 2007) and the mixed findings from peripheral measures (Rosenthal et al., 2008; Zimmerman & Choi-Kain, 2009). Therefore, biomarker reactivity should be carefully interpreted in the context of multiple sources of information, including subjective reports, behavioral data, and responses from different neurobiological circuits (Bauer, Quas, & Boyce, 2002).

Paradoxically, chronic or extreme stress can manifest in either hyporeactivity or hyperreactivity of the stress response system, depending on timing of the stressor, when

and how reactivity is measured, and the characteristics of the individual being measured (Miller, Chen, & Zhou, 2007). For example, research with both animals and humans suggests that hyporeactivity of the HPA axis can occur after a long period of hyperactivation due to chronic stress (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Miller et al., 2007). Hypocortisolism may result from several different underlying mechanisms, including reduced biosynthesis or depletion of cortisol or other hormones within the HPA axis that trigger cortisol release, hypersecretion of HPA axis hormones resulting in downregulation of target receptors, enhanced negative feedback inhibition of the HPA axis, or morphological changes (Fries et al., 2005). Recent studies have also begun to implicate dysregulations in neuropeptides such as oxytocin and vasopressin in those with BPD, and neuropeptide dysregulation as been associated with lower cortisol reactivity (for a review, see Stanley & Siever, 2010). Just as hypercortisolism is associated with negative health outcomes, hypocortisolism is also associated with various health conditions and symptoms, including chronic pain, fatigue, and enhanced stress sensitivity, which are often seen in BPD patients as well as those with other stress-related disorders.

Hence, although contrary to expected manifestations of emotional hyperreactivity in terms of higher cortisol and sAA responsiveness, attenuated reactivity at the level of glucocorticoid and central noradrenergic responsiveness to acute stress can be a consequence of prolonged or excessive activation of the stress response system, especially in those who experience adversity in early life (e.g., Boyce & Ellis, 2005; Gunnar et al., 2006; Heim et al., 2000; Miller et al., 2007; Neigh, Gillespie, & Nemeroff, 2009). Accordingly, a large percentage of BPD patients report histories of trauma,

adversity, and chronic stress (e.g., Glaser et al., 2008; Yen et al., 2002; Zanarini, 1997). Such experiences may culminate in a neurobiological adaptation of the stress response system, which may be the body's effort to protect itself from the damaging effects of overexposure to catecholamines and glucocorticoids. The finding of cortisol and sAA hyporeactivity in the context of higher subjective negative affect and perceived stress among the BPD patients in the current study suggests the conclusion that the functioning of the stress response system may be compromised due to a long history of chronic activation.

Moreover, the reduced hippocampal volumes and metabolism found among BPD patients (Driessen et al., 2000; Irle et al., 2005; Juengling et al., 2003; Schmahl, Elzinga, et al., 2003; Tebartz van Elst et al., 2003) is consistent with a history of hyperreactivity and overexposure to stress hormones, which has been shown to cause hippocampal damage (e.g., Sapolsky, 1996). Furthermore, hippocampal damage and reduced hippocampal volumes are associated with hypocortisolism (Buchanan, Tranel, & Kirschbaum, 2009; Pruessner, Pruessner, Hellhammer, Pike, & Lupien, 2007). Putting this evidence together, it is plausible that earlier hyperreactivity may lead to hippocampal damage in patients with BPD; as the system adapts and downregulates after prolonged hyperactivation, hypocortisolism may develop, but the changes in hippocampal morphology and functioning remain. This hypothesis might be further explored in longitudinal research.

HPA axis and ANS hyporeactivity in patients with BPD may represent reduced sensitivity of the biological stress response system to environmental input. On the other hand, in accordance with the developmental model of adaptive phenotypic plasticity in

the stress response system proposed by Boyce and Ellis (2005), high biomarker reactivity in the healthy comparisons relative to the BPD patients may reflect heightened *biological sensitivity to context* in these individuals. Boyce and Ellis have proposed that high reactivity may have protective effects under conditions of support, and negative health effects under conditions of adversity. For children who grow up in low-stress environments, heightened reactivity may represent adaptive permeability to the influence of environmental conditions, allowing these individuals to more readily reap the rewards of their supportive environments as they grow and develop, and to respond with appropriate arousal under conditions of challenge or threat. On the other hand, high biological sensitivity in a child exposed to chronic stress, maltreatment, and/or inadequate nurturance and support would tend to have the opposite effect, imparting greater risk for negative outcomes in terms of general health and psychological functioning. Boyce and Ellis have compared the biologically sensitive individuals to orchids because their ability to thrive is closely tied to their environmental conditions; like orchids, they flourish with nurturance and care, but they deteriorate under neglectful or harsh conditions. Accordingly, studies suggest that highly reactive children from stressful environments have disproportionately high rates of morbidity and negative health outcomes, whereas, highly reactive children from low-stress and supportive environments demonstrate unusually low rates of morbidity and disease (for a review, see Boyce & Ellis, 2005).

It is possible that individuals who later develop BPD may start out as *orchid children*, with high reactivity and susceptibility to environmental input; however, with chronic environmental stress, their biological systems may eventually become

downregulated, resulting in lower than normal reactivity accompanied by heightened negative affectivity. Thus, biological hyporeactivity in adults with BPD may be a consequence of earlier hyperreactivity in the context of a stressful and nonsupportive environment, which would be an important avenue to explore in longitudinal studies. This explanation would be consistent with theories of BPD that emphasize an interaction between innate biological and early environmental factors in the etiology of the disorder (e.g., Kernberg, 1984; Linehan, 1993). Studies examing biological markers of emotional responding in adolescent samples at risk for BPD may be particularly informative in testing this hypothesis.

Importantly, the supplemental analyses demonstrated that severe childhood trauma may moderate central noradrenergic responding in BPD patients, leading to higher baseline levels and possibly higher overall noradrenergic output (although group differences in overall sAA output only reached a trend level in this study). Among the BPD patients with histories of childhood trauma, ANS hyporeactivity may be explained by heightened anticipatory ANS arousal that precluded the detection of ANS reactivity to subsequent stimulation. Visual examination of the sAA response trajectories of the BPD patients who reported high levels of childhood trauma in comparison to those who reported low levels of trauma suggests that these subgroups of BPD patients may demonstrate very different ANS response patterns, which should be further explored in larger samples.

Childhood trauma did not, on the other hand, appear to moderate BPD patients' cortisol response to stress, even though trauma was generally negatively correlated with cortisol reactivity. Cortisol reactivity was lower, relative to healthy comparisons, among

the entire BPD group. In fact, examination of the mean cortisol levels in the BPD group suggests that this group shows especially attenuated cortisol responses in the recovery stage, i.e., in the hour after the stress procedure. This pattern is suggestive of enhanced negative feedback of the HPA axis in those with BPD. Although high and low levels of self-reported childhood trauma do not appear to moderate this pattern in those with BPD, this does not necessarily mean that experiences of trauma do not play a role. Even the BPD patients who reported lower levels of childhood trauma tended to report more trauma than did healthy comparison participants. It will be important to investigate the influence of childhood trauma on emotional responding in BPD patients in comparison to groups with similar trauma histories without concurrent BPD. Additionally, childhood adversity may be an even more important predictor of biological reactivity in those with BPD than comorbid PTSD, as not everyone who experiences severe trauma will develop PTSD. The observed abnormalities in reactivity persisted when patients with current or past PTSD were excluded from the BPD sample, suggesting that PTSD may not explain blunted biomarker reactivity in BPD.

High overall central noradrenergic output accompanied by attenuated cortisol response suggests the potential for adrenal hyporesponsiveness to SNS input in the subgroup of more severely impaired and traumatized patients. In other words, these patients may show a vulnerability to autonomic hyperarousal (even under resting conditions), but their HPA axis may not be responding with normal activation to ANS arousal. In addition, higher overall sAA output in the context of lower cortisol reactivity suggests a decoupling of the ANS and HPA axis in this group of patients. Empirical evidence suggests that repeated stress may lead to asymmetry between neurobiological

systems (e.g., Bauer et al., 2002; Gordis et al., 2008). Moreover, the co-occurrence of low biomarker reactivity and high negative affectivity in the BPD group suggest asymmetry between subjective experience and physiological responses. Similar patterns of asymmetry between perceived stress and HPA axis reactivity have been shown in sexually abused women who were classified as unresolved with respect to trauma (Pierrehumbert, Torrisi, Glatz, Dimitrova, Heinrichs, & Halfon, 2009). The degree to which asymmetry between response systems may predict the course of illness and treatment outcomes in patients with BPD would be an important area of future research.

As previously mentioned, however, the BPD patients who reported severe childhood trauma also demonstrated more severe BPD features, which is consistent with other reports relating severity of childhood trauma to severity of BPD (Yen et al., 2002). This introduces the possibility that experiences of trauma may impart risk for greater severity of BPD, which in turn, may relate to higher anticipatory noradrenergic response and perhaps higher overall ANS arousal. Interestingly, the BPD patients who reported more severe childhood trauma tended to have more relational dysfunction and excessive anger than the BPD patient who reported less childhood trauma. Future studies might attempt to tease apart adverse experiences, BPD severity, and clusters of BPD symptoms to determine the underlying mechanisms of these abnormalities in stress system functioning. Furthermore, given the evidence that age of onset of abuse is inversely associated with autonomic arousal in patients with BPD (Kozel, 2001), the timing and characteristics of traumatic experiences should be documented in future studies to determine how these factors may influence differential emotional response patterns among individuals with BPD.

Contrary to findings from Simeon et al. (2007), no significant relationship was found in the current study between dissociation and biomarker reactivity. However, the groups in the current study did not differ in self-reported dissociation during the stress procedure, and severe dissociation as measured by self report was rare in the current BPD sample. The lack of relationship between dissociation and biomarker reactivity may have been obfuscated by a restricted range of dissociation in the current study samples. Given the inconsistency between these results and those of Simeon and colleagues, the role of dissociation in emotional responding of BPD patients should be further explored in future research.

Although the results of the current study are primarily descriptive in nature, they may have implications for clinical interventions with BPD patients. As suggested by Kuo and Linehan (2010), the results with regard to general negative affectivity suggest that BPD patients may benefit from interventions focused on reducing chronic and baseline negative affect, in addition to those focused on reducing emotional reactivity. The high baseline negative emotionality in patients with BPD may cause them to be more vulnerable to difficulties regulating their emotions. Interestingly, most of the patients in this study were taking psychoactive medications, but this did not seem to dampen their subjective experiences of negative emotions. Additionally, the results for biomarker and subjective reactivity are generally consistent with those from Nater et al.'s (2010) unmedicated BPD sample. These findings suggest that medications alone may not be enough to reduce negative affect and stabilize abnormal patterns of stress response system functioning in those with BPD. Although medications may be beneficial to

reduce acute symptoms, psychosocial interventions may be the best tools for improving emotion regulation in BPD.

In addition, the current results suggest that those patients with severe childhood trauma and more severe BPD features (especially chaotic interpersonal relationships and extreme anger) may be at increased risk for chronic autonomic arousal. These patients could potentially benefit from behavioral relaxation strategies and coping skills aimed at reducing physiological arousal and subjective distress. Furthermore, clinicians should be aware that hypocortisolism in patients with BPD may be a potential risk factor for chronic health conditions and physical symptoms that may require adjunctive medical treatment.

Moreover, based on evidence that children who have low cortisol reactivity to threat respond poorly to psychosocial interventions (van de Wiel, van Goozen, Matthys, Snoek, & van Engeland, 2004), it is possible that BPD patients who demonstrate neuroendocrine hyporesponsiveness may require different interventions than those who show normative or heightened reactivity. In accordance with Boyce and Ellis (2005), those who are hyporeactive may be less responsive to environmental influence, which may translate into less receptiveness to psychosocial intervention. Examining biological markers of reactivity in BPD patients during psychotherapy and the relations between these markers and psychotherapy process and outcomes may be a particularly informative line of research with direct clinical implications.

The strengths of the current study include the use of a realistic and standardized social stress procedure, the clinically referred patient sample, and the measurement of multiple response systems (i.e., HPA axis, ANS, and subjective emotional experiences)

through noninvasive sampling methods. The TSST was highly effective in eliciting a stress response in each group of participants, and the full trajectory of the stress response from baseline through recovery was assessed through multiple measurements. In addition, all participants were carefully assessed and well-characterized using structured clinical interviews for both Axis I and II disorders. All of the BPD participants met the criterion of affective instability on a structured interview for personality disorders, making this a particularly relevant group for examining emotion regulation processes. Also, the BPD patients were receiving psychological services and were representative of those seen in clinical practice in terms of severity, medication use, and comorbidity. The measurement of dissociation and trauma history allowed for the examination of these factors as potential influences on emotional reactivity in those with BPD. Moreover, sAA is a novel marker for central noradrenergic functioning, and this is only the second study to measure sAA reactivity in patients with BPD. Furthermore, this is the first study to explore emotional reactivity in BPD patients in comparison to a group of healthy individuals with high levels of trait negative affect and impulsivity.

Nonetheless, limitations of the current study included demographic differences between groups, the lack of a clinical comparison sample, the lack of dimensional measurement of PTSD or depressive symptoms, and the lack of measures of coping style or cognitive emotion regulatory processes. The BPD group was older and more likely to be divorced or separated than both comparison groups, and the potential influence of socioeconomic status on these results could not be fully assessed due to missing income data. Additionally, the low base rate of childhood trauma in the comparison groups and the significant association between trauma and BPD severity prevented the examination

of trauma as a predictor of emotional responses independent of BPD features or diagnosis. The exclusion of men, children, and the elderly from this study also limits generalizability of these findings to men with BPD or to BPD across the lifespan. Furthermore, the measure of subjective negative affect used in the current study (the PANAS) may not adequately capture subjective emotional reactivity among individuals with BPD. For example, the PANAS is limited in its ability to tap into aggression and anger, which may be more relevant to subjective reactivity in those with BPD than negative affect more generally.

It is also not clear what emotion regulatory processes the BPD patients might have used during the stress procedure, or how relevant the public speaking and oral arithmetic task was to the BPD patients. The BPD group's subjective reporting of the perceived stressfulness of the procedure suggests that they did become personally involved in the task and found it to be highly stressful. Nonetheless, the patients could have been using any number of emotion regulation strategies that served to dampen their physiological responding. For example, the BPD patients seemed to have a greater tendency to refuse engagement in the oral arithmetic task (choosing to stand silently for five minutes rather than counting backwards as instructed) or to use humor during the mock job interview, seemingly trying to evoke laughter from the panel of "judges". This anecdotal evidence is consistent with empirical evidence that individuals with BPD tend to use more avoidant regulation strategies (Bijttebier & Vertommen, 1999) and are less willing to tolerate distress in order to pursue goal-directed behavior and to approach a potentially distressing situation (Gratz, Rosenthal, Tull, Lejuez, & Gunderson, 2009). In addition, a mock job interview may not be a relevant interpersonal stressor for some

individuals with BPD who are not actively engaged in the workforce. The TSST may also fail to tap into the interpersonal and emotional regulation problems that individuals with BPD tend to experience within their intimate relationships (e.g., Critchfield, Levy, Clarkin, & Kernberg, 2008; Hill et al., 2007).

Another limitation of the current study relates to the tradeoff between external and internal validity. Specifically, the BPD group was highly medicated and heterogeneous with regard to psychiatric comorbidity and chronic health problems. Although the results remained the same in magnitude and direction when patients with diagnoses of major depression or PTSD were excluded, the degree of clinically relevant depressive or anxious symptoms could still influence patterns of emotional responding, which could not be assessed without dimensional measures of these symptoms. Additionally, although the current results remained similar in magnitude and direction when patients taking any single class of medication and when patients with any single comorbid psychiatric diagnosis were excluded, the additive effects of multiple medications and psychiatric diagnoses on emotional reactivity could potentially have influenced these results.

Moreover, the heterogeneity of the BPD patients in terms of comorbidity, although typical of BPD patient samples in the community, makes it difficult to determine the specificity of these findings to BPD. Similar patterns of blunted biomarker reactivity have been associated with a number of clinical problems (e.g., PTSD, atypical depression, chronic fatigue syndrome, chronic pain disorders, irritable bowel syndrome; see Fries et al., 2005 for a review). Hence, it is important for future studies to include a relevant clinical comparison group in order to further elucidate the patterns of biological

and subjective emotional reactivity that are specific to BPD rather than descriptive of psychopathology or chronic illness more generally.

In addition to further investigating the role of trauma, dissociation, psychiatric comorbidity, and medication use on emotional responding in patients with BPD, future studies might also examine how heterogeneity of BPD symptomatology may predict different patterns of emotional responding. The analyses in the current study are limited in that they assume homogeneity of responses within groups, an assumption that is highly unlikely to be met in reality. Individual cortisol and sAA response trajectories within groups were extremely varied in this study. Identifying subgroups of BPD patients based on their patterns of emotional responding, and then elucidating the predictors of these response patterns, may help to clarify inconsistencies in the empirical literature on emotional responding in BPD. Additionally, such work may lead to the identification of subgroups of BPD patients who may respond differentially to psychosocial and pharmacological interventions, having direct clinical value. This may be accomplished through group-based trajectory modeling procedures (Nagin, 2005), which take into account potential population heterogeneity and can be used to identify subgroups with qualitatively different response patterns (see Gunnar, Frenn, Wewerka, & Ryzin, 2009).

In summary, these findings suggest that emotional dysregulation in women with BPD is characterized by intense negative emotions and blunted HPA axis and autonomic reactivity. These patterns do not appear to be explained by trait negative affect and impulsivity, medication use, comorbid mood or anxiety disorders, or dissociation. However, the results suggest that severe childhood trauma in the BPD group may predict greater baseline autonomic arousal and higher overall central noradrenergic output. The

observed HPA axis and autonomic hyporeactivity in the BPD group could be explained by a long history of hyperactivation of the stress response system (i.e., allostatic load), resulting in down-regulation of the stress response. These results add to existing evidence that emotional dysregulation in BPD may be characterized more by intense and chronic negative affect rather than heightened reactivity from baseline or impaired recovery to baseline levels. The high baseline emotional arousal of BPD patients may leave them vulnerable to experiencing even more negative affect and less positive emotions during daily life stress. In addition, high baseline autonomic arousal and hypocortisolism may leave patients with BPD vulnerable to chronic health problems and physiological ailments. Although further research is needed to clarify these patterns and determine their clinical implications, these findings suggest that psychosocial interventions aimed at reducing baseline negative emotions, regulating general physiological arousal, and reducing daily life stress may be beneficial for stabilizing emotional dysregulation in BPD, which may potentially lead to better general health outcomes.

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Appendix

Pearson correlations between dependent measures and potential covariates in the full sample (*N* = 90)

	Cort AUC_G	Cort AUC_I	Cort AUC_R	sAA AUC_G	sAA AUC_I	sAA AUC_R	NA T1	NA T2	NA T3	SSR
Age	-.21†	-.16	-.09	.08	-.32**	.02	.05	-.05	.03	-.10
Meds	-.02	-.27*	-.14	.06	-.24*	-.06	.19†	.05	.24*	.07
Mens	.07	.01	.01	.00	-.16	-.10	.11	-.03	-.03	.04
Time	-.13	.01	-.12	-.08	-.05	-.01	-.06	-.02	.10	.04
Hrs awake	-.28**	-.11	-.14	.06	-.15	.13	-.09	-.12	-.11	-.11
Educ	-.19†	.04	.04	.06	.02	-.03	-.08	-.16	-.18†	-.16
$Angry_a$	.05	-.17	-.02	.05	-.03	-.07	.37***	.33**	.27*	.35**
$Anxiety_a$	-.08	-.28**	-.09	.07	-.16	-.22*	.41***	.40***	.34**	.30**
$Depress_a$	.03	-.27*	.01	.03	-.21*	-.11	.37***	.36**	.28**	.30**
$Impuls_a$	.06	-.17	-.02	.08	-.14	-.02	.33**	.28**	.17	.36***
DSS_a	.05	.04	.05	.04	-.06	.01	.30**	.44***	.49***	.34**
Pos Aff	.02	.00	-.03	.08	.00	.12	-.13	-.12	-.18†	-.09
CTQ EA	-.03	-.30**	-.01	.11	-.30**	.16	.11	.17	.14	.16
CTQ PA	.07	-.17	.01	-.07	-.24*	.01	.10	.16	.09	.10
CTQ SA	-.14	-.22*	-.02	.05	-.36**	-.03	-.15	.01	.01	-.06
CTQ EN	.01	-.24*	-.02	.12	.25*	.13	-.02	.16	.14	.13
CTQ PN	.07	-.23*	.01	.20†	-.20†	.13	-.01	.09	.09	.07
CTQ-T	-.02	-.29**	-.04	.10	-.33**	.10	.01	.14	.11	.10

Notes: For dependent variables that were not normally distributed, correlations were calculated using transformed values. Cort = salivary cortisol; sAA = salivary alpha-amylase; NA T1 = negative affect 45 min pre-stress; NA T2 = negative affect 10 min post-stress onset; NA T3 = negative affect 55 min post-stress onset; SPS = Subjective Stress Response; Meds = estimated influence of medications on cortisol per Granger et al. (2009); Mens = number of days since beginning of last menstrual cycle (*N* = 87 due to missing data for participants whose menstrual cycles are irregular or absent); Time = time of TSST rounded to the nearest hour, military time; Hrs awake = number of hours between awakening and beginning of TSST; Educ = Education in years; Angry = NEO-PI-R Angry Hostility facet scale; Anxiety = NEO-PI-R Anxiety facet scale; Depress = NEO-PI-R Depression facet scale; Impuls = NEO-PI-R Impulsivity facet scale; DSS = Dissociation Tension Scale; Pos Affect = positive affect (averaged across three administrations of the PANAS); CTQ = Childhood Trauma Questionnaire, EA = Emotional Abuse, PA = Physical Abuse, SA = Sexual Abuse, EN = Emotional Neglect, PN = Physical Neglect, CTQ-T = total (sum) of all five CTQ trauma scales.

[a] *N* = 89 for NEO-PI-R scales and DSS due to one BPD participant who did not complete the NEO-PI-R scales and one other BPD participant who did not complete the DSS.

† $p < .10$. * $p < .05$. ** $p < .01$. *** $p < .001$.

Vita

Lori Nicole Scott
Department of Psychiatry, Western Psychiatric Institute and Clinic
University of Pittsburgh Medical Center
3811 O'Hara Street, Pittsburgh, PA 15213
scottln2@upmc.edu; lnscot@gmail.com
(c) 814-321-8448, (o) 814-246-5844

Education

August, 2011	Ph.D. Clinical Psychology Pennsylvania State University, University Park, PA
2010-2011	Predoctoral Internship in Clinical Psychology University of Pittsburgh Medical Center
August, 2007	M.S. Clinical Psychology Pennsylvania State University, University Park, PA
May, 1998	B.F.A. Dance, Minor in Arts Administration Marymount Manhattan College, New York, NY

Selected Publications

Scott, L. N., Levy, K. N., & Granger, D. A. (2011). *Cortisol, alpha-amylase, and subjective emotional reactivity in women with borderline personality disorder.* Manuscript submitted for publication.

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