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Psychophysiology of the Stress Response and the Hierarchical Structure of Emotional Disorders

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ABSTRACT

Physiological stress reactivity is closely linked to emotional disorders like depression and anxiety and is believed to play a causal role in their development. Similar patterns of exaggerated reactivity across a wide range of emotional disorders indicate that physiological hyperreactivity to stress may be a multifinal, or shared, risk factor for these disorders. However, current literature examines stress reactivity in only one or two disorders at a time and is based off categorical classification systems that assume mental disorders to be discrete entities. Recent research into the observed distribution of symptoms of mental illness contests this assumption and proposes that some mental disorders have shared developmental factors that can be revealed through dimensional models of psychopathology. One dimensional model of mental disorders, the Hierarchical Taxonomy of Psychopathology, addresses this limitation by placing symptoms of internalizing disorders within a dimensional, hierarchically arranged model. The current study utilized this hierarchical model to investigate the relationship between physiological reactions to a laboratory stressor and symptoms of emotional disorders. In a sample of 201 college students, we used latent variable modeling techniques to parse symptoms of emotional disorders into their common (higher-order) and unique (lower-order) features, then examined the strength of the relationship between physiological stress reactivity and common versus unique elements. We hypothesized that common features of emotional disorders would be more strongly related to stress reactivity than any of the unique features. Our results suggested that neither common nor unique features were significantly related to physiological stress reactivity. This finding contradicts previous investigations that found evidence for exaggerated physiological responses in individuals with emotional disorders. Our study improves upon previous research by examining the full range of symptoms of emotional disorders, and our conclusion suggests that the relevance of physiological response in emotional disorders should be critically examined, particularly in light of the limitations of traditional classification systems.

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Chapter 1
Introduction

Significant life stress is highly prevalent in emotional disorders, with over 80% of individuals who meet criteria for depression in community samples having experienced a recent acute or chronic stressor (Brown & Harris, 1989). Individuals diagnosed with anxiety and depression are more than twice as likely to have experienced a major adverse life event at any point in their lives (Shrout et al., 1989) and are between 2 and 6 times more likely to have experienced such events within 6 months of the onset of disorder (Asselmann, Wittchen, Lieb, Höfler, & Beesdo-Baum, 2015; Kendler, Karkowski, & Prescott, 1999; Mazure, 1998). Epidemiological studies of the impact of childhood adversities such as neglect and abuse have found that these experiences account for nearly 30% of individual differences in risk for psychological disorders across 21 countries (Kessler et al., 2010). Findings like these suggest a robust and significant association between emotional disorders and stressful life events.

Predominant theories of the developmental course of emotional disorders implicate stressful life events as a causal factor that both precipitates disorders and maintains symptomology. Stressful life events prospectively predict the onset of affective disorders (Kim, Conger, Elder, & Lorenz, 2003; Slopen et al., 2010) and subsequent stressful life events which may aggravate symptoms (Kendler & Gardner, 2016; Technow, Hazel, Abela, & Hankin, 2015). Although genetic vulnerabilities for psychopathology are likely involved in the relationship between early adversity and psychopathology (Klengel at el., 2013), evidence suggests

that the experience of adversity does play a causal role in the development of emotional disorders, conferring risk beyond that explained by genetics. Studies of twins who are matched on family environment but have divergent early experiences support this claim. In cases where one twin has reported an acute stressor and the other has not, research finds that twins reporting sexual abuse and other stressful life events are at far greater risk for subsequent emotional disorders than the twins who do not, even if those events are independent, or unrelated to the individual's own behavior (Kendler et al., 1999, 2000). The way in which an individual reacts to stress is thought to be a crucial mechanism linking stressful events to psychopathology. Stressful life events during childhood seem to interact with genetic predispositions towards maladaptive stress response, increasing the risk for the development of emotional disorders by deleteriously altering cognitive and neurobiological responses to subsequent stress (Heim, Newport, Mletzo, Miller, & Nemeroff, 2008; Wichers et al., 2012).

Biological mechanisms of stress response

Given the central role of stress response in etiological theories of emotional disorders, understanding individual differences in stress reactivity has been one focus of clinical research. Severity of stress response is determined by multiple systems. Cognitive reactions to stressful events involve the appraisal of the event and the psychological strategies engaged to modulate emotional reactions, while biological processes affect the function of major organs and the production of hormones. These two broad classes of response are linked in that

psychological appraisal of stressors can reduce or exacerbate biological stress response. For this reason, biological processes are integrated into psychological studies of stress.

The autonomic nervous system (ANS) is one of the most heavily studied response symptoms associated with acute stress. The ANS regulates major organs including the heart, lungs, and gastrointestinal system and serves to maintain homeostasis, or equilibrium, in response to environmental input (Tsigos & Chrousos, 2002). The ANS is composed of two branches: the parasympathetic and the sympathetic. Under threat, the sympathetic branch of the ANS potentiates the so-called “fight or flight” response, which aims to enhance attention to the danger at hand and ready the organism to defend itself by accelerating cardiovascular function and respiration. The parasympathetic branch is generally deceleratory, acting in opposition to the sympathetic response to return bodily systems to their resting state. Although stress response is ultimately a function of the interaction of these two branches over time, sympathetic activation is predominant during reactions to acute stress (Bouscein, 2012).

One of the most widely used measures of sympathetic nervous system (SNS) activity is electrodermal activity (EDA; Duffy, 1972). EDA is a general term referring to dynamic changes in the electrical characteristics of human skin, primarily due to the activity of sweat glands. This measure is popular in psychological research because EDA is thought to be determined solely by the

activity of the SNS, unlike other indicators of ANS response such as heart rate or cortisol response which may also reflect activity of the parasympathetic branch (Dawson, Schell, & Filion, 2007). EDA is generally quantified as either tonic skin conductance level (SCL), the general state of conductivity of the skin, or phasic skin conductance responses (SCRs), abrupt “spikes” in conductance in reaction to some discrete stimulus or event.

For decades, psychophysiological research has explicated the link between electrodermal response and cognition and emotion. A large portion of this work has examined EDA correlates of fear by presenting participants with naturally aversive stimuli, like loud noises or electric shocks. The typical response to these stimuli is increased frequency or magnitude of SCRs and heightened SCL (Dawson, Schell, & Filion, 2007). In situations where participants are aware of when the stimulus will come, such as if the experimenter provides a clock counting down to the onset of the stimulus, SCL reaches its highest peak just prior to onset, reflecting the psychological anticipation of the stimulus (Bouscein, 2012). Similarly, in fear conditioning paradigms where some neutral stimulus (e.g., a geometric shape) is paired with an aversive stimulus (e.g., electric shock) repeatedly, EDA will spike in response to the previously neutral stimulus even after the aversive stimulus is removed. This research on normative stress response has provided a foundation for the study of stress response in psychopathology.

Physiological stress reactivity in emotional disorders

Psychological stress reactions have long been incorporated into developmental theories of emotional disorders, such as Beck's classic model of depression (Beck, 1987), which posits that depressed individuals exacerbate emotional reactions to negative events by exaggerating their negative impact, or the theory that panic disorder is maintained when individuals are overly sensitive to somatic symptoms of anxiety and catastrophize these sensations, leading to uncontrollable panic and further fear of bodily sensations (Barlow & Craske, 1988). Indeed, biases towards exaggerated negative appraisal of stressors have been demonstrated to prospectively predict symptoms across the full range of emotional disorders (e.g., Conway, Starr, Espejo, Brennan, & Hammen, 2016). Research has shown that such maladaptive information-processing styles are associated with dysregulated physiological responses to unpleasant events (Gaab, Rohleder, Nater, & Ehlert, 2005; Schlotz, Hammerfald, Ehlert, & Gaab, 2011), spurring a complimentary line of research that has investigated physiological stress reactions in emotional disorders.

Physiological stress reactivity has perhaps been most comprehensively studied in the anxiety disorders. Individuals with a range of disorders, including generalized anxiety disorder, panic disorder, social and specific phobias, and posttraumatic stress disorder, tend to display maladaptive biological reactions to stressors. Specifically, these individuals demonstrate exaggerated and prolonged SNS activity in response to stress, coupled with attenuated parasympathetic nervous system activity; the initial response to stress is greater in magnitude and

longer in duration, and the return to homeostasis is slowed. This pattern is evidenced through heightened EDA and restricted heart rate variability and respiratory sinus arrhythmia, markers of parasympathetic nervous system activity (e.g. Craske et al., 2009; Pêgo, Sousa, Almeida, & Sousa, 2010). This pattern of SNS hyperactivity holds true not only for stressors, but also for baseline physiological activity under nonthreatening conditions (Blechert, Grossman, Laitman, & Wilhelm, 2007; Monk et al., 2001). Further, increased reactivity has been shown to predict or maintain later symptoms of anxiety and mood disorders (Morris, Rao, & Garber, 2012; Nelemans et al., 2017).

Aberrant biological reactions to stress are also evident in depression, although the body of literature linking EDA to depression is relatively small and inconsistent. Some researchers find attenuated EDA reactivity in depression (Bonnet & Naveteur, 2004; Donat & McCullough, 1983; Miquel, Fuentes, Garcia-Merita, & Rojo, 1999), some find heightened activity (Lin, Lin, Lin, & Huang, 2011; Sanders & Abaied, 2015), and others find variation in responses as a function of specific symptoms or subtypes of depression (Thorell, Kjellman, & D'Elia, 1987; Williams, Iacono, & Remick, 1985). Cortisol reactivity in depression has been studied more extensively and has been shown to be abnormal in depressed individuals. Initial heightened cortisol reactions to stressors are adaptive to some extent, but depression has been consistently associated with abnormally high cortisol values in the absence of threat (Burke, Davis, Otte, & Mohr, 2005; Knorr, Vinberg, Kessing, & Wetterslev, 2010; Pariante & Lightman,

2008); one meta-analysis estimates that 60-73% of depressed individuals demonstrate higher basal cortisol levels than non-depressed controls (Stetler & Miller, 2011). Biological response in the presence of threat is less consistent. Some researchers find that depressed individuals show attenuated cortisol and skin conductance reactivity compared to controls and anxiety disorders (Benning & Oumesiane, 2016; Pruneti, Lento, Fante, Carrozzo, & Fontana, 2010; Thorell et al., 2013), while others find a pattern of hyperreactive response and impaired recovery similar to that of anxiety disorders (Grillon, Franco-Chaves, Mateus, Ionescu, & Zarate, 2013; Morris et al., 2012).

In sum, abnormalities in physiological responses to stressors have been demonstrated in major depressive disorder (Grillon, Ameli, Goddard, Woods, & Davis, 1994), generalized anxiety disorder (Lieberman, Gorka, Shankman, & Phan, 2017), social anxiety disorder (Yoon & Joormann, 2012), panic disorder (Gorka, Liu, Saraspas, & Shankman, 2015), and posttraumatic stress disorder (Metzger, Orr, Berry, Ahern, Lasko, & Pitman, 1999). There is reason to believe that this feature is common across these disorders because abnormal stress reactivity is a multifinal risk factor for emotional disorders. Muiltifinality is a process where a characteristic, event, or environment confers increased risk for multiple forms of psychopathology (Cicchetti & Rogosch, 1996); for example, childhood adversity is strongly but nonspecifically predictive of psychological disorders. Those who experience childhood adversity are far more likely to develop psychopathology than those who do not, but this effect is true of all

forms of psychopathology, not a specific disorder (Afifi, Brownridge, Cos, & Sareen, 2006; McLaughlin, Conron, Koenen, & Gilman, 2010). Similarly, abnormal stress responses are evident across emotional disorders, but do not seem to reliably discriminate between disorders. This commonality may be expected, as mood and anxiety disorders are highly comorbid (Brown et al., 2001; Kessler, Chiu, Demler, & Walters, 2005) and emerging evidence suggests that they may share latent liabilities (Kreuger & Markon, 2006) and neurobiological features (Jenkins et al, 2016; Oathes, Patenaude, Schatzberg, & Etkin, 2015). It is currently difficult to discern the extent to which abnormal physiological reactivity is shared among emotional disorders, however, because most of the research in this area attempts to find physiological links to a single disorder, or a small set of disorders, at a time. Recent evidence suggests that searching for disorder-specific effects in this way may be suboptimal for psychopathology research, creating disparate literatures and masking shared etiologic pathways. Instead, investigations into the latent structure of common mental disorders have provided a dimensional and transdiagnostic framework that can further our understanding of multifinal risk factors.

A hierarchical framework for clinical research

The prevailing systems of classification of mental disorders conceptualize disorders as discrete entities with separate etiologies. However, several decades ago psychopathology researchers began to question the validity of categorical diagnostic systems. This was in part due to the recognition of substantial

psychiatric comorbidity, or the simultaneous presence of two or more distinct disorders in a single individual. Psychiatric comorbidity is rampant, occurring far more often than would be expected if mental illnesses were truly independent of one another (Krueger & Markon, 2006). A more likely interpretation is that traditional classification systems are flawed, and comorbidity is an artifact of drawing divisions that are not true to how psychiatric illness actually presents. Current diagnostic boundaries are rationally derived; symptoms are grouped into diagnoses based on clinical judgement. Recent work has sought to improve the classification of mental disorders through empirically-driven methods that honor the observed distribution of symptoms.

Evidence suggests that the boundaries drawn by categorical classification systems are to some extent arbitrary. One major finding of research that examines the structure of psychopathology is that symptoms of common mental illnesses are distributed continuously throughout the population (Haslam, Holland, & Kuppens, 2012; Widiger & Samuel, 2005). Current classification systems do not account for this continuity and specify diagnostic thresholds that are counterintuitive. Under these systems, an individual who displays three of six symptoms of anxiety would be diagnosed as having generalized anxiety disorder, whereas an individual who displays only two symptoms would not, even if the latter individual were more severely impaired. Categorical classifications that ignore the dimensionality of psychopathology obscure important clinical information, such as gradations of severity within diagnoses or similarities

between cases that barely reach the diagnostic threshold and those that barely miss it. The dimensional distribution of psychopathology blurs lines not only between healthy and disordered individuals, but also between categories of disorders. Factor analytic studies suggest that traditionally-defined disorders share a common structure where observed symptoms covary due to latent traits which cut across traditional diagnostic boundaries (Forbush & Watson, 2013). Again, categorical classifications that separate clusters of symptoms into discrete disorders fail to recognize commonalities between disorders, masking shared core traits that could provide valuable clinical information. For these reasons clinical researchers have migrated toward dimensional models of psychopathology. One such model, known as the Hierarchical Taxonomy of Psychopathology (HiTOP; for a review, see Kotov et al., 2017), organizes the available knowledge of the underlying structure of psychopathology into a dimensional and hierarchical system that can better guide clinical research.

The hallmark of the HiTOP model is its hierarchical structure. Latent dimensions of psychopathology can be organized according to level of specificity, with dimensions consisting of specific symptoms at the bottom of a hierarchy and very broad, generalized dimensions at the top. Five levels of the HiTOP hierarchy have been identified (see Figure 1). At the bottom, singular symptoms that are strongly correlated with each other cluster into symptom components, the most specific level of the hierarchy. For example, losing interest in enjoyable activities and feeling unmotivated are symptoms that cooccur very frequently and

compose a symptom component that is labeled anhedonia. Symptom components that are highly correlated compose syndromes; anhedonia, dysphoria, and appetite disturbance cluster into a syndrome resembling depression. Syndromes that share many core features cluster into subfactors, such as the distress subfactor that encompasses syndromes resembling depression, post-traumatic stress disorder, and generalized anxiety disorder. Overarching spectra account for similarities among subfactors, such as the internalizing spectrum. This spectrum is composed of distress and fear subfactors and subsumes a range of traditionally-defined disorders, including mood and anxiety disorders and eating pathology. Finally, spectra converge on a highly general trait known as the “p factor” that represents features shared amongst all forms of psychopathology, analogous to the “g factor” of general intelligence.

The higher-order dimensions of the HiTOP model are well-studied and have been shown to be temporally stable and highly reliable, replicating across age groups, genders, clinical and non-clinical populations, specific assessment instruments, and measurement modalities (Eaton et al., 2013; Eaton, Krueger, & Oltmanns, 2011; Fergusson, Horwood, & Boden, 2006; Krueger, Chentsova-Dutton, Markon, Goldberg, & Ormel, 2003; Sellbom, 2016). As confidence in the reliability of this statistical model has grown, researchers have begun to demonstrate its utility as a guide for research. This model allows one to parse traditionally-defined disorders into disorder-specific variance, or features that

pertain only to a narrow band of symptoms, and transdiagnostic variance, features that are common across multiple forms of psychopathology. We can then ask whether the more specific or more general features of psychopathology are most relevant to the question at hand by comparing the predictive ability of disorder-specific factors to that of transdiagnostic factors. For example, we may find that the efficacy of exposure therapy is highly related to standing on the fear subfactor, but less so to the more general internalizing spectrum, which encompasses fear-based disorders as well as disorders that are better characterized by distress.

Researchers have begun to identify instances in which general dimensions of psychopathology are more effective predictors than disorder-specific dimensions. In longitudinal studies, transdiagnostic factors outperform disorder-specific variance in predicting psychopathology; one study found this to be the case 97% of the time, even when disorder-specific factors at Wave 1 were predicting the same specific disorder at Wave 2 (Kim & Eaton, 2015). It has been found that early childhood adversity, a robust correlate of psychopathology later in life, predicts standing on the latent spectra but not specific disorders (Conway, Raposa, Hammen, & Brennan, 2018; Vachon et al., 2015). Transdiagnostic factors are also more predictive than specific disorders of clinically-relevant outcomes, such as domains of function in personality pathology (Wright et al., 2016), suicidality and treatment-seeking (Sunderland & Slade, 2015), and impairment associated with anxiety and depression (Markon, 2010).

The upper levels of the hierarchical structure help to explain multifinal risk factors. For example, the finding that early adversity is more strongly linked to higher-order spectra than disorder-specific factors suggests that the deleterious effects of adversity operate through transdiagnostic pathways that may result in many forms of psychopathology (Conway et al., 2018; Vachon et al., 2015). This suggests that this risk factor likely causally affects the features that are shared by most pathologies, such as emotion dysregulation or executive dysfunction, rather than directly causing specific symptoms, like compulsive behaviors or substance abuse. In addition to providing hints to causal relations, the HiTOP model helps to streamline etiologic research. Given the strong link between higher-order dimensions and early adversity, attempts to link early adversity to specific lower-level components of psychopathology would be inefficient; we would expect to find the same relationship between adversity and each specific component because adversity influences a higher-order trait that subsumes these components. Rather than demonstrating the relevance of a biological trait or environmental influence to multiple categorical disorders, we can determine whether a given risk factor confers widespread risk for generalized pathology or affects only a narrow band of symptomology. The current study sought to use the HiTOP model in this way to investigate stress reactivity as a multifinal factor in the development of emotional disorders.

The current study

Previous research has linked physiological stress hyperreactivity to many mood and anxiety disorders, suggesting that stress reactivity may be a transdiagnostic risk factor that relates to a range of emotional disorders but is not specific to any disorder. However, current research has limited ability to evaluate this claim because prior work has assessed stress reactivity in only one or two categorically-defined disorders. The purpose of the current study was to investigate the utility of higher-order internalizing dimensions in predicting physiological stress response in comparison to specific symptom components of internalizing disorders. We monitored EDA in sample of high-risk young adults as they completed a laboratory stressor. Internalizing pathology was assessed with a comprehensive dimensional measure that allowed us to parse symptom variance into general and specific components across the entire range of internalizing symptoms. We hypothesized that general dimensions of internalizing disorders would be more robustly linked to physiological indices of stress reactivity than any specific symptom component.

Chapter 2
Methods

Participants

Our sample consisted of 201 undergraduate freshmen who were screened over two semesters (n = 158, spring 2017; n = 43, fall 2017) at a southeastern university using the Neuroticism subscale of the Big Five Inventory (BFI-44; John & Srivastava, 1999). The study was advertised to freshmen across campus

through flyers, business cards, social media posts, and classroom announcements. Interested students took the initial screening survey, which consisted of basic demographic information and the Neuroticism subscale of the BFI-44. Neuroticism scores from this survey were used to overselect for individuals who scored above 27 on this scale; this cutoff indicates the upper tertile of normal populations (Srivastava, John, Gosling, & Potter, 2003). Participants who scored above this cutoff (high-N) and below (low-N) were invited via email to the laboratory session at a 2:1 rate. A total of 1040 freshmen completed the screening survey over the two semesters; 632 were contacted. Of those participants contacted, 281 completed the laboratory session. The present sample consisted of 201 participants; 3 participants from spring 2017 and 77 participants from fall 2017 were dropped due to incomplete data at the time of analysis. The final sample was composed of 69.2% high-N participants. This sample was 75.1% female (22.9% male, 2.0% neither male nor female), 75.6% white (15.9% Asian American/Asian, 6.5% African American/Black, 0.5% Native Hawaiian, 0.5% Middle Eastern, 0.5% other race or ethnicity).

Measures

The Inventory of Depression and Anxiety Symptoms–II (IDAS-II; Watson et al., 2012) is a 99-item self-report measure of symptoms of internalizing psychopathology. The IDAS-II is a dimensional measure, comprised of 18 non-overlapping subscales that assess symptom components of internalizing disorders, such as mania, anhedonia, panic, and social anxiety. Respondents

report on symptoms experienced over the past two weeks using a 5-point scale ranging from “not at all” to “extremely”. This scale has been extensively validated in patient, adult, and student samples and has shown good to excellent internal consistency (α = .72-.92; Watson & O’Hara, 2017). This scale has also demonstrated good convergent and divergent validity with relevant personality traits (e.g., the dysphoria subscale is strongly positively correlated with trait neuroticism and moderately negatively correlated with trait conscientiousness; Watson et al., 2012) and with clinical interview measures of internalizing pathology (Dornbach-Bender et al., 2017). Reliability estimates in our sample ranged from .70-.90 for the subscales.

The short-form of the Positive and Negative Affect Schedule (PANAS-SF; Thompson, 2007) is a 10-item measure of positive and negative affect. For this study, participants were asked to report on the extent to which they endorsed 10 internal states (five positive states, such as “inspired”, and five negative, such as “nervous”) at the present moment. Responses were rated on a 5-point scale ranging from “very slightly/not at all” to “extremely”. This is a widely used measure of change in affect before and after a stressor.

Electrodermal activity was recorded by Biopac MP150 hardware running AcqKnowledge 4.0 software. The bioamplifier (GSR100C) was set to direct current, sensitivity of sensitivity of 5 μohm/V with a 1.0-Hz low-pass filter. Ag-AgCL electrodes (BIOPAC EL507) were applied to the distal phalanx of the index and middle fingers of the non-dominant hand using isotonic paste (BIOPAC Gel

101). Participants didn't consume caffeine, alcohol, or non-necessary ADHD and anxiety medication nor did they engage in strenuous physical activity three hours prior to the study session to avoid influencing EDA. To reduce movement, the index and middle fingers were taped together and Velcro straps were placed around the wrist to stabilize the electrode leads. Participants sat at a desk during the recording and Velcro straps were also affixed over the participants' hands to secure them to desk and reduce hand movement. Electrodermal activity was recorded continuously throughout a behavioral task, detailed below. Events representing the onset of each period were manually recorded in Acqknowledge during the laboratory session by experimenters.

The raw EDA signal was resampled at 62.5 samples/second using linear interpolation and smoothed at a factor of 63. A low-pass filter fixed at 1Hz was applied. Artifacts were identified by creating a new waveform representing the absolute difference between the smoothed and filtered waveform from the raw waveform and marking any discrepancies using a simple peak detection method. Discrepancies were manually removed from the data.

Procedures

Participants underwent a modified version of the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993). This behavioral task consisted of four phases: a 3-minute baseline period, a 4-minute preparatory period, a 4-minute speech, and a 3-minute recovery period (see Figure 2).

Participants completed the PANAS-SF immediately prior to the 3-minute baseline period. Experimenters then read scripted instructions telling participants that they would be giving a short speech, acting as if they were interviewing for their “dream job”. Further, they were led to believe that the speech would be videotaped and later judged by their peers with respect to speech quality and presenter intelligence and charisma. During the 4-minute preparatory period, participants were allowed to take notes (to plan the speech), which the experimenter removed without warning immediately prior to turning on the video camera. Participants then completed the 4-minute, video-recorded speech. To make the task more challenging, the experimenter faced the presenter and maintained an impassive facial expression—even when there were signs that the presenter was foundering—during the recording (see Frisch, Häusser, & Mojzisch, 2015, for the rationale behind experimenter behavior during this task). If participants paused for more than 5 seconds or concluded the presentation prior to the 4-minute limit, the experimenter prompted him or her to resume until time was up. Throughout the task, experimenters followed a script and refrained from answering questions, saying only “I can’t answer any questions” or “Your four minutes aren’t up yet, please continue”. Immediately following the speech and after the camera was turned off by the experimenter, participants completed a second PANAS-SF. Participants were then asked to rest motionless during a 3-minute recovery period. The original TSST has been shown to be a highly effective elicitor of stress responses in many populations (see Allen et al., 2017, for a review) and modifications such as those made here have also been

successfully implemented by other research groups (e.g., Hamilton & Alloy, 2017; Portnoy et al., 2015; Walter, Fernandez, Snelling, & Barkus, 2018). A depiction of one participant's EDA response throughout the stages of the task is shown in Figure 3.

All participants who completed the screening survey were entered into a raffle for a $50 gift card; participants who were invited to the laboratory session were compensated $25. During the experimental session, participants gave informed consent and completed a battery of questionnaires (not reported on here) prior to the laboratory stressor. Experimenters debriefed all participants immediately following the recovery period, assuring them the recorded videos would be deleted and not shown to peers. This study was approved by the William and Mary Protection of Human Subjects Committee (PHSC-2017-12-30-12582).

Data Analysis

All analyses were conducted using Mplus version 8 software with the robust maximum likelihood estimator (MLR). Mplus input files are available on OSF. For measurement and structural models, we evaluated model fit according to the comparative fit index (CFI), Tucker Lewis index (TLI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). Following conventions, we interpreted CFI and TLI values close to .90 and above, RMSEA values less than .08, and SRMR values less than or equal to .08 as indicating acceptable fit (Brown & Cudeck, 1992; Hu & Bentler, 1999). Chi-

square values were also examined, but not emphasized due to sensitivity to even minor perturbations in model fit in large samples (Andrich, Sheridan, & Luo, 2009). In addition to chi-squared values, we evaluated change in Bayesian information criterion (BIC) values (Raftery, 1993; Schwarz, 1978). There are no absolute guidelines for interpreting BIC values, but lower BIC values indicate better fit (Markon & Kreuger, 2004).

Electrodermal reactivity to the speech task was computed by subtracting the mean skin conductance level at baseline from the mean skin conductance level during the speech.

Measurement model comparison. We empirically compared two CFA models of the IDAS-II that are based on previous findings. The first was a unidimensional model wherein all subscales load onto a single latent factor representing internalizing problems. This structure was the best fit to the IDAS-I (Watson et al., 2007) and subsequent evidence suggests it may explain the majority of the common variance in the IDAS-II (up to 79%; Watson & O'Hara, 2017). However, with the addition of eight new subscales to the IDAS-II, several EFA studies have favored a three-factor structure (Nelson, O'Hara, & Watson, 2017; Watson et al., 2012). Our second CFA model estimated a three-factor solution, which consists of "Obsessions/Fear", "Distress", and "Positive Mood" dimensions. We based our three factor CFA solution off previously published EFA results (see Table 1, Watson et al., 2012), assigning each subscale to the factor on which it had the highest loading (and constraining subscale loadings on

the other factors to 0). We carried forward the better-fitting model (i.e., 1 factor vs 3 factor) to subsequent analyses.

Multiple indicator, multiple cause (MIMIC) model. To test for unique relationships between lower-order symptom components and EDA after controlling for the higher-order dimension(s) of internalizing problems, we used a technique based in MIMIC modeling. Our MIMIC model involved three components: the factor(s) that represent the higher-order internalizing dimension(s), the IDAS-II subscales (i.e., factor indicators), and EDA as an exogenous covariate (i.e., correlate of the latent variables). The strategy we used to test for the "indirect" effects of the exogenous variables on factor indicators was developed by Woods and colleagues (2009) and was originally used to detect differential item functioning. This strategy involves three basic steps. First, a measurement model of internalizing problems is specified. Next, a structural model where the latent variable(s) is (are) regressed on EDA is estimated. This model implies an indirect relationship between EDA and lower-order symptoms because the predictive effect of EDA flows entirely through the internalizing factor(s). Finally, we estimate the direct effects of EDA on each indicator by regressing the symptom dimensions (i.e., residual components of each IDAS-II subscale) on EDA directly, while controlling for the internalizing factor(s). Significant direct effects of EDA on the symptom dimensions indicate a unique relationship of physiological reactivity with lower-order symptom dimensions, over and above the higher-order factors.

Following Woods et al. (2009), to test for significant direct effects we first identified a set of “anchor” items, or subscales which do not exhibit significant direct associations with EDA and which are used to identify later models. This was accomplished by fitting 18 separate models (i.e., one per subscale) where the direct paths of all but one subscale to the exogenous variables were constrained to zero. Subscales which do not exhibit significant direct effects with the exogenous variables were allocated to an “anchor” set and all other subscales became part of a “study” set to be examined further.

Next, we tested the significance of the direct effects on our “study” subscales (i.e., those that had the potential to have direct associations with EDA) by comparing a series of nested models using likelihood ratio difference tests. A full model wherein the direct effects of EDA on all the “study set” subscales are modeled was compared to a model where the direct effect on one particular “study set” subscale at a time was constrained to zero. For example, if the Lassitude subscale had been allocated to the “study” set in the previous step, we compared a model where the direct effect on all study set subscales, including Lassitude, was estimated to a nested model where the direct effects on all studied subscales except Lassitude were estimated. If the difference between the full and constrained model was significant, this indicates that the subscale constrained to zero had a unique relation to the exogenous variable. This comparison was repeated for each subscale in the “study” set, and Bonferroni adjustments were made to the p-values. Because likelihood ratio difference

testing can be overly sensitive with large sample sizes (Andrich, Sheridan, & Luo, 2009), we also evaluated changes in BIC to assess differences in fit between full and constrained models.

We retained in the final model the associations of EDA with the higher-order internalizing factor(s) as well as any significant direct effects of EDA on lower-order symptom dimensions as identified through the process outlined above.

Chapter 3
Results

Preliminary Analyses

To confirm that the behavioral task was perceived as stressful by participants, we ran a paired samples t-test comparing negative affect before and after the speech. As expected, we found a significant increase in negative affect following the speech task $t(198) = -15.30$, $p < .0001$. Descriptive statistics and intercorrelations among the subscales of the IDAS-II and EDA are reported in Table 2.

Measurement Model

We ran a unidimensional confirmatory factor analysis where all IDAS-II subscales loaded onto a single underlying factor, followed by a three-factor CFA where subscales loaded onto underlying factors following the pattern of loadings

found in previous exploratory investigations (see Table 1). The unidimensional solution fit our data poorly (fit indices for all models are described in Table 3) and the three-factor solution failed to converge. We chose instead to use exploratory structural equation modeling for the remainder of our analyses.

We ran an exploratory factor analysis, allowing the subscales of the IDAS-II to load freely on one to four factors. Consistent with previous investigations, a three-factor solution fit best, falling just below acceptable fit. Examination of the model residuals revealed a negative residual associated with the euphoria subscale, and for subsequent models we constrained the residual for this indicator to .2, a value similar to the average residuals for the other indicators. In the constrained EFA model the first factor was composed primarily of subscales that reflect distress, such as dysphoria, lassitude, and suicidality. Well-being, euphoria, and mania loaded most strongly on the second factor and symptoms associated with obsessions, like checking, ordering, and cleaning, defined the third (see Table 4 for factor loadings). This structure is similar to that found by prior research (Nelson et al., 2018; Watson et al., 2012). The three-factor solution formed the basis of our subsequent MIMIC model.

MIMIC Model

Tests of the direct effects of each indicator on our exogenous variable revealed no significant relations between any of the IDAS-II subscales and physiological stress reactivity. The results of these tests are presented in Table 5. Because no indicators were allocated to the “study” set, no model

comparisons were evaluated. The final model therefore estimated the indirect effects of each indicator on physiological reactivity mediated by the three latent internalizing dimensions. The effects of the latent dimensions on stress reactivity were also found to be small and nonsignificant (see Table 5).

Chapter 4

Discussion

Exaggerated physiological responses to stress appear to be a common feature of emotional disorders. Current research has examined physiological stress reactivity only in relation to individual disorders, or very small groups of disorders, limiting the extent to which researchers can draw conclusions about the transdiagnostic relevance of abnormal stress responses (Sanislow, 2016). We extended prior research by assessing the full range of internalizing symptomology. Using a hierarchical model of psychopathology (Kotov et al., 2017), we evaluated the relation of physiological stress response to both general and specific components of internalizing disorders. Contrary to our hypotheses, the higher-order internalizing dimensions were not significantly associated with physiological stress reactivity. As predicted, the lower-order symptom components of internalizing disorders were also not associated with physiological stress reactivity. We expected to find that higher-order dimensions of internalizing pathology would be more strongly related to stress reactivity than lower-order components, but our findings do not support that conclusion.

The lack of association between physiological stress response and psychopathology in our sample may be due to several reasons. Prior investigations of exaggerated EDA responses in clinical populations have generally found small effect sizes. It may be that this effect is not large enough to be detected in a college population, where levels of psychopathology are generally less severe than in groups that meet diagnostic criteria for psychiatric disorders. Although overselected for elevated trait neuroticism, a series of t-tests revealed that our sample had significantly lower means[1] on 13 of the 19 IDAS-II subscales than a clinical sample (Watson et al., 2012). Internalizing pathology may have been underrepresented in our sample and limited our ability to find physiological differences. Further, we chose to characterize physiological stress reactivity as the difference between mean SCL at baseline and during the speech task. Though this is a popular way to measure EDA response, it may not be the best characterization of physiological stress response. Specifically, if high internalizing pathology is associated with overall elevated arousal, not only arousal in reaction to a stimulus, a difference score may be attenuated by high baseline levels of arousal. Future studies should continue to investigate dimensional measures of internalizing pathology in clinical populations with a variety of physiological indices.

[1] Dysphoria, $t(1107)= -6.91$, $p <.001$; Lassitude, $t(1107)= -3.71$, $p <.001$; Insomnia, $t(1107)= -9.48$, $p <.001$; Suicidality, $t(1107)= -6.94$, $p <.001$; Appetite Loss, $t(1107)= -4.02$, $p <.001$; Ill Temper, $t(1107)= -9.96$, $p <.001$; Mania, $t(1107)= -2.09$, $p <.05$; Panic, $t(1107)= -7.41$, $p <.001$; Claustrophobia, $t(1107)= -8.26$, $p <.001$; Traumatic Intrustions, $t(1107)= -9.21$, $p <.001$; Traumatic Avoidance, $t(1107)= -10.59$, $p <.001$; Cleaning, $t(1107)= -2.97$, $p <.05$

Although all of our effects were nonsignificant, we did not find that symptom components of internalizing disorders were more predictive of stress reactivity than transdiagnostic dimensions. Transdiagnostic perspectives could still help to unify a body of literature that is currently divided by diagnostic boundaries and can improve the efficiency of this work by eliminating the need to replicate an identical effect in multiple individual disorders. Beyond efficiency, the advantages of transdiagnostic factors to understand neurobiological research has been illustrated before. In one recent review, the authors sought to resolve conflicting findings from studies that related emotional disorders to startle responsivity to threat. At the spectrum level, when all emotional disorders were considered together as the full internalizing spectrum, these results were inconsistent and difficult to explain. However, the pattern of findings became interpretable when the fear and distress subfactors were examined separately (Vaidyanathan, Patrick, & Cuthbert, 2009). Because structural models of psychopathology are empirically-driven, their divisions fall along naturally occurring boundaries that are more closely tied to genetic and biological parameters (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017), likely making these models more useful and appropriate for organizing neurobiological findings.

Accumulating evidence that shared features of disorders are highly predictive of functional impairment and clinical outcomes suggests that transdiagnostic approaches may also improve the efficiency and efficacy of

treatment. Current disorder-specific treatments are already known to have transdiagnostic benefits, likely due to shared fundamental components (Barlow, Allen, & Choate, 2004), and some research suggests that clinicians already base treatment decisions off of symptom components, not categorical diagnoses (Waszczuk et al., 2017). However, practitioners are still taught numerous therapies meant to target specific disorders. Requiring practitioners to administer multiple overlapping treatments adds to the burden associated with training clinicians and impedes the dissemination of evidence-based practices (Kazdin & Blasé, 2011). If generalized latent dimensions undergird a variety of manifest symptoms, transdiagnostic treatment protocols could be developed that target these dimensions and replace disorder-specific therapies, streamlining training and practice. Such protocols have already begun to be developed. The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders is one such therapy. This protocol targets the shared processes of internalizing pathology, like emotion dysregulation and stress reactivity, and has been shown to be as efficacious as disorder-specific protocols across a range of disorders and symptoms (Barlow et al., 2017). Research investigating transdiagnostic processes is a promising avenue for improving how evidence-based therapy is conducted and disseminated.

Limitations aside, we believe that the present work meaningfully extends previous investigations on the role of stress reactivity in internalizing problems. We found that when considering the full range of internalizing

symptoms in a nonclinical population, neither general nor specific aspects of emotional disorders were related to physiological stress responses. Replications of this study could meaningful inform etiological models of emotional disorders, many of which currently include exaggerated physiological stress response as a causal factor. Future research should continue to critically examine claims about physiological correlates of psychiatric disorders and do so using dimensional models that are empirically grounded, rather than categorically-defined diagnoses.

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Table 1. Promax loadings of the IDAS-II subscales

	Distress	Obsessions/Fear	Positive Mood
Dysphoria	**.90**	-.01	-.13
Lassitude	**.76**	-.09	-.01
Ill Temper	**.68**	.04	.01
Panic	**.68**	.16	.05
Traumatic Intrusions	**.66**	.11	-.03
Insomnia	**.61**	.01	.06
Appetite Loss	**.56**	-.04	.04
Mania	**.55**	.15	.33
Suicidality	**.52**	.15	-.13
Traumatic Avoidance	**.47**	.25	.00
Appetite Gain	**.32**	.16	.08
Cleaning	-.04	**.72**	-.01
Ordering	.03	**.69**	.10
Checking	.08	**.64**	.08
Claustrophobia	.11	**.60**	-.10
Social Anxiety	.40	**.41**	-.13
Euphoria	.16	.10	**.70**
Well-Being	-.26	-.04	**.69**

Note. Taken from Watson et al., 2012.

Table 2. Descriptive statistics and intercorrelations among the IDAS-II subscales and EDA

	M	SD	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Dysphoria	2.35	0.78	-																		
2. Lassitude	2.49	0.82	.67	-																	
3. Insomnia	2.03	0.82	.52	.47	-																
4. Suicidality	1.25	0.47	.52	.39	.40	-															
5. Appetite Loss	1.90	0.82	.48	.35	.41	.31	-														
6. Appetite Gain	2.15	0.84	.31	.31	.18	.24	.00	-													
7. Well-Being	2.98	0.74	-.45	-.36	-.25	-.42	-.20	-.05	-												
8. Ill Temper	1.56	.090	.61	.46	.45	.38	.36	.19	-.23	-											
9. Mania	2.01	0.87	.43	.31	.34	.29	.22	.29	.03	.40	-										
10. Euphoria	1.71	0.70	.09	.05	.16	.09	.22	.11	.42	.25	.54	-									
11. Panic	1.55	0.54	.66	.60	.45	.41	.37	.28	-.23	.51	.47	.25	-								
12. Social Anxiety	2.28	0.92	.67	.44	.38	.31	.28	.26	-.20	.43	.37	.11	.52	-							
13. Claustrophobia	1.36	0.67	.32	.26	.43	.20	.16	.05	-.11	.20	.31	.18	.41	.48	-						
14. Traumatic Intrusions	1.74	0.84	.51	.37	.44	.46	.30	.14	-.25	.42	.40	.15	.43	.43	.30	-					
15. Traumatic Avoidance	1.89	0.76	.34	.28	.32	.21	.26	.12	-.06	.38	.37	.31	.27	.34	.27	.57	-				
16. Checking	2.40	1.08	.30	.23	.26	.18	.11	.27	.09	.23	.49	.36	.37	.42	.36	.25	.47	-			
17. Ordering	1.92	0.90	.17	.10	.15	.03	.15	.12	.09	.12	.42	.39	.21	.25	.32	.18	.55	.67	-		
18. Cleaning	1.41	0.58	.16	.25	.15	.09	.03	.12	.04	.22	.32	.29	.24	.20	.32	.20	.31	.49	.47	-	
19. EDA Reactivity	3.70	2.16	.02	.07	-.02	-.03	-.001	-.03	-.02	.12	-.04	.09	.02	-.06	.09	-.08	-.02	-.09	.01	-.01	-

Table 3. Fit indices

	χ^2	*df*	*p*	CFI	TLI	RMSEA	SRMR	BIC
1-Factor CFA	618.95	135	.000	.626	.576	.13	.11	7480.83
2-Factor EFA	378.98	118	.000	.835	.786	.11	.06	7233.94
3-Factor EFA	280.76	102	.000	.887	.830	.09	.05	7220.58

Table 4. Loadings for the 3-Factor EFA solution

	Factor I	Factor II	Factor III
Dysphoria	**.91**	-.06	.01
Lassitude	**.74**	-.04	-.02
Ill Temper	**.68**	.21	-.09
Panic	**.71**	.18	.02
Traumatic Intrusions	**.55**	.03	.12
Insomnia	**.61**	.07	.03
Appetite Loss	**.51**	.12	-.06
Mania	.34	**.44**	.22
Suicidality	**.63**	-.03	-.07
Traumatic Avoidance	.18	.04	**.54**
Appetite Gain	**.29**	.09	.06
Cleaning	-.01	.07	**.54**
Ordering	-.21	-.01	**.95**
Checking	.02	.08	**.75**
Claustrophobia	.27	-.01	**.34**
Social Anxiety	**.59**	-.03	.21
Euphoria	-.01	**.73**	.12
Well-Being	-.56	**.61**	-.00

Table 5. Direct effects of factors and subscales on EDA

	β	SE	*p*
Factor I	.02	.26	.80
Factor II	-.04	-.49	.62
Factor III	.05	.64	.52
Dysphoria	.02	.41	.69
Lassitude	.06	1.14	.26
Ill Temper	.10	1.89	.06
Panic	.001	.02	.99
Traumatic Intrusions	-.09	-1.57	.12
Insomnia	-.03	-.58	.56
Appetite Loss	-.02	-.36	.72
Mania	-.08	-1.45	.15
Suicidality	-.05	-.86	.39
Traumatic Avoidance	-.01	-.14	.89
Appetite Gain	-.03	-.50	.62
Cleaning	.02	.24	.81
Ordering	.12	2.04	.04
Checking	-.10	-1.94	.05
Claustrophobia	.10	1.65	.10
Social Anxiety	-.07	-1.26	.21
Euphoria	.12	1.88	.06
Well-Being	-.07	-1.14	.26

Figure 1. Illustration of the Hierarchical Taxonomy of Psychopathology

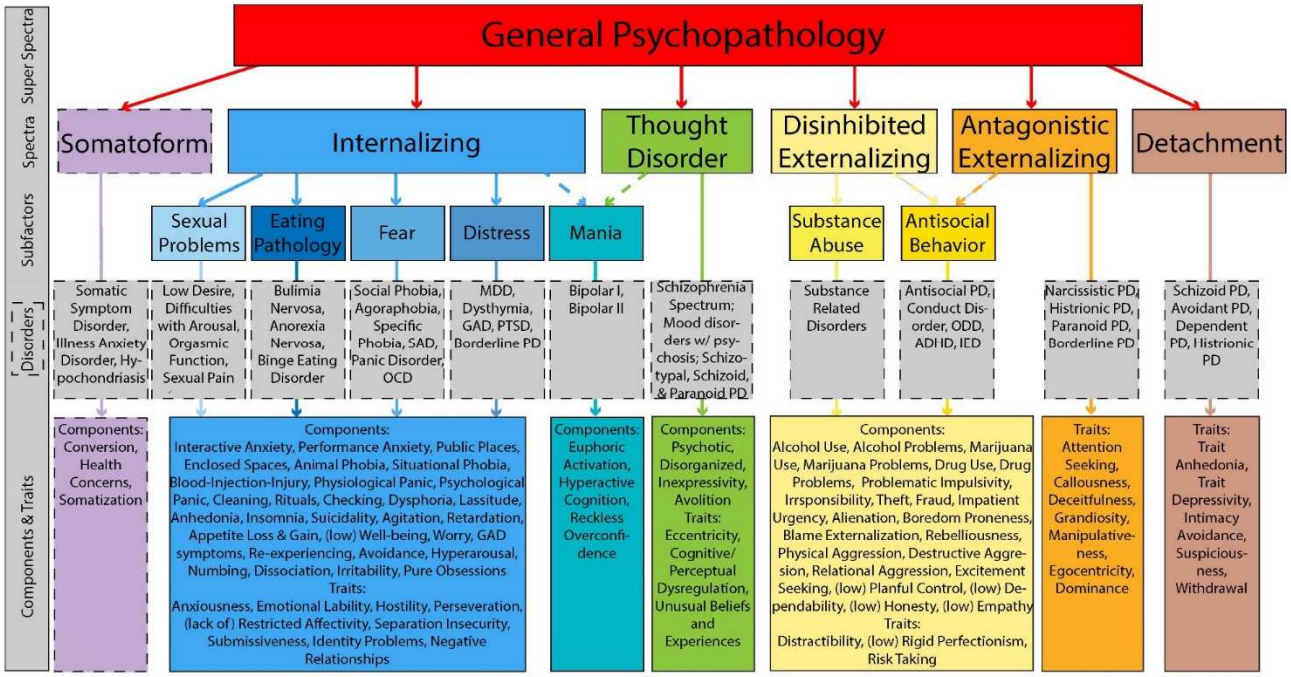

Figure 2. Timeline of the behavioral task

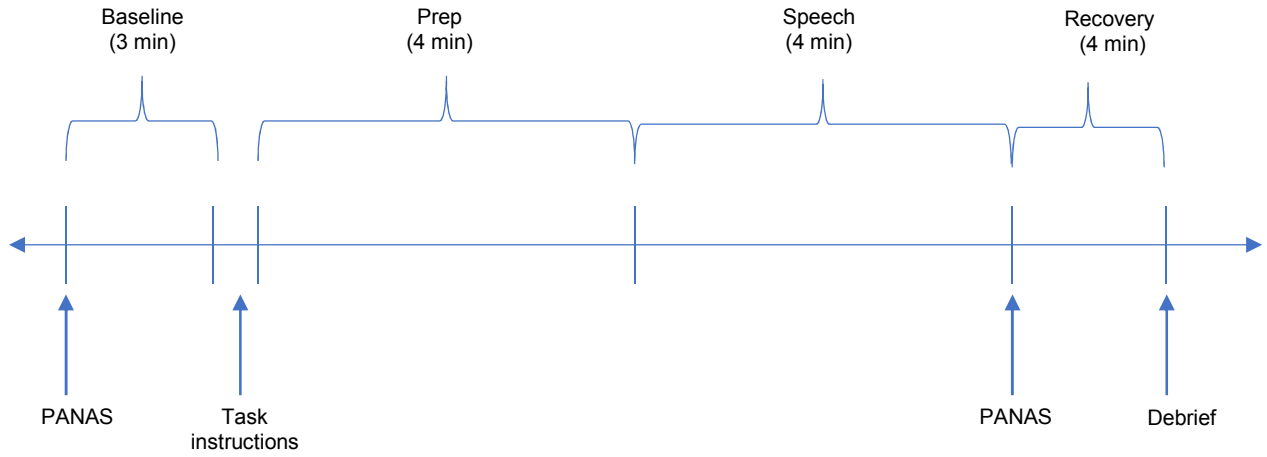

Figure 3. Illustration of a typical individual EDA response during different phases of the behavioral task.