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Linking Dimensional Models of Internalizing Psychopathology to Neurobiological Systems: Affect-Modulated Startle as an Indicator of Fear and Distress Disorders and Affiliated Traits

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Abstract

Integrative hierarchical models have sought to account for the extensive comorbidity between various internalizing disorders in terms of broad individual difference factors these disorders share. However, such models have been developed largely on the basis of self-report and diagnostic symptom data. Toward the goal of linking such models to neurobiological systems, we review studies that have employed variants of the affect-modulated startle paradigm to investigate emotional processing in internalizing disorders as well as personality constructs known to be associated with these disorders. Specifically, we focus on four parameters of startle reactivity: fear-potentiated startle, inhibition of startle in the context of pleasant stimuli, context-potentiated startle, and general startle reactivity. On the basis of available data, we argue that these varying effects index differing neurobiological processes related to mood and anxiety disorders that are interpretable from the standpoint of dimensional models of the internalizing spectrum. Further, we contend that these empirical findings can feed back into and help reshape conceptualizations of internalizing disorders in ways that make them more amenable to neurobiological analysis.

Keywords

Startle blink; internalizing disorders; neurobiology of internalizing disorders

Linking Dimensional Models of Internalizing Psychopathology to Neurobiological Systems: Affect-Modulated Startle as an Indicator of Fear and Distress Disorders and Affiliated Traits

In the two decades that have passed since the finding of affect-modulated startle was initially reported in humans (Vrana, Spence, & Lang, 1988), an extensive literature has developed on the use of this measure for investigating affective individual differences in relation to psychopathology (cf. Grillon & Baas, 2003; Cook, 1999; Patrick & Bernat, 2006). In particular, startle reflex modulation has been examined in relation to traits associated with fear, neuroticism, and negative affectivity, and in relation to disorders involving an excess of emotional reactivity (e.g., phobias, panic, post-traumatic stress, and depression) as well as those

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involving putative emotional deficits (e.g., psychopathy, schizophrenia). This line of research is important because much is known about the neurobiological substrates of startle modulation effects. Alongside this work, systematic efforts have been devoted during the past 20 years to the development of integrative dimensional models of psychopathology (e.g., Clark & Watson, 1991; Kendler, Prescott, Myers, & Neale, 2003; Krueger, 1999; Krueger, Markon, Patrick, Benning, & Kramer, 2007; Mineka, Watson, & Clark, 1998; Watson, 2005) that incorporate the well-known phenomenon of diagnostic co-morbidity and provide a framework for understanding common as well as distinctive factors contributing to varying interrelated disorders. However, these models have been constructed largely on the basis of diagnostic and self-report data, and linkages to findings on neurobiology have been speculative for the most part. Our aim in the current paper is to review what is known about variations in affect-modulated startle in relation to anxiety and mood ("internalizing") disorders, and affiliated trait constructs, with the aim of linking this work to existing dimensional models of internalizing psychopathology. A comprehensive review of this kind is important for advancing our understanding of the neurobiological foundations of internalizing disorders and traits, and providing insights into how conceptualizations of psychopathologic syndromes can be refined to make them more amenable to neurobiological analysis (cf. Hyman, 2007).

Focus of the Current Review

Psychological disorders involving mood and anxiety symptoms exhibit systematic co-occurrence (comorbidity) that has been interpreted as reflecting core emotional processes these disorders have in common — broadly subsumed under the rubric of "negative affectivity" (NA; Clark & Watson, 1991; Mineka et al., 1998; Watson, 2005). The internalizing disorders, so-called since they are thought to represent problematic thoughts and/or behaviors directed towards the self or a tendency to *internalize* psychological distress, are a family of disorders in which high levels of fear, anxiousness, and misery are observed (cf. Krueger, 1999). They include several of the anxiety disorders along with major depressive disorder and dysthymia, as described within the Diagnostic and Statistical Manual for Mental Disorders (*DSM-IV-TR*, 2000).

Personality traits in the domain of negative affectivity (NA) have been conceptualized as general substrates for varying forms of internalizing psychopathology (Clark & Watson, 1999). Several influential theories, including Tellegen's three-factor model of personality (Tellegen, 1985), Clark and Watson's (1991) tripartite model of anxiety and depression, and Gray's (1981) neurobiological theory of motivation, have sought to account for the comorbidity of these disorders in terms of common personality traits that contribute to each. From a neurobiological standpoint, one major construct of interest in this regard has been sensitivity of the brain's defensive motivational system—which can be viewed as a core substrate for individual differences in negative affectivity (e.g., Patrick & Bernat, 2006; Rosen & Schulkin, 1998). The current paper focuses on human research to date that has employed the startle blink reflex as a measure of defense system activation to investigate individual differences in emotional reactivity associated with internalizing psychopathology and affiliated personality constructs.[1]

Previous integrative reviews dealing with the topic of internalizing disorders (e.g., Clark & Watson, 1991; Mineka et al., 1998) have focused primarily on phenotypic aspects of these disorders—including patterns of diagnostic comorbidity among them and overlapping associations they exhibit with particular personality traits. In contrast, the current paper focuses

[1]Grillon and Baas (2003) previously reviewed findings from affect-startle studies of internalizing psychopathology conducted up to 2002. In addition to updating coverage of mood and anxiety disorder studies, the current review covers findings from startle studies of trait constructs affiliated with internalizing disorders, and advances a conceptual framework within which existing work in these areas can be integrated and guide future research.

on the biological mechanisms implicated in these disorders—in particular, reactivity of the brain's defensive motivational system as indexed by potentiation of the startle probe reflex—rather than focusing exclusively on psychometric or diagnostic constructs (personality traits, DSM disorders). Our major aims in this review are to: (1) integrate findings from existing published studies of internalizing syndromes employing startle probe methodology, and (2) link these findings to current conceptualizations of the structure of internalizing disorders and affiliated trait constructs. As discussed in further detail below, we opted for an integrative, descriptive approach here rather than a quantitative, meta-analytic approach in order to highlight and discuss marked variations in sample characteristics and methodology that will need to be considered in further research.

Our review opens with a synopsis of studies of startle modulation effects in relation to varying anxiety and mood disorders, followed by a survey of such effects in relation to trait constructs associated with these disorders. A brief analysis of startle modulation findings for the syndrome of psychopathy is also provided. Given substantial evidence for affective (in particular, fear) deficits in psychopathy, a survey of findings in this area in conjunction with those for phobic disorders provides evidence for continuity of effects on emotion-modulated startle across a broad dispositional fear continuum. The review concludes with a discussion of startle research findings in relation to integrative hierarchical conceptualizations of internalizing psychopathology.

Internalizing Psychopathology and Affiliated Trait Dispositions: Empirical-Conceptual Background

Analyses of patterns of comorbidity among the various internalizing disorders have revealed that their interrelations can be accounted for by an overarching factor that subsumes two distinct, but correlated dimensions – one encompassing “fear” syndromes, and the other “anxious-misery” syndromes (cf. Krueger, 1999). High levels of fearfulness in relation to specific stimuli characterize the first dimension, around which disorders such as simple phobias, social phobia, and panic disorder can be organized. The other dimension is marked by more pervasive negative activation and high levels of dysphoria (“anxiousness and misery” [Krueger, 1999], or “distress” [Watson, 2005]), and encompasses major depressive disorder, dysthymia and generalized anxiety disorder (see also Kendler et al., 2003). More recent research (e.g., Cox, Clara, & Enns, 2002) has also located post-traumatic stress disorder (PTSD) within this latter cluster of internalizing disorders.

Other theories have sought to account for the observed comorbidity among these disorders and the distinctive features of each in terms of shared versus unique personality traits that are implicated in them. For example, in Clark and Watson's (1991) tripartite model, high negative affect (NA), defined as enhanced proneness to negative states including anxiousness, irritability, and stress reactivity, serves as a general distress factor that is present in both anxiety and mood disorders. Each type of disorder, additionally, has components that are specific to it – anxiety disorders entail physiological hyperarousal, while low positive affect (PA) or anhedonia (defined as a reduced capacity to experience pleasurable activation or enjoyment in life), is considered specific to depression. Similarly, Tellegen's (1985) three-factor model of personality posits high negative emotionality (NEM) as a common dispositional factor involved in depression and anxiety disorders, and low positive emotionality (PEM) as playing a specific role in depression. Another related conceptualization is Gray's (1981) notion of the Behavioral Inhibition System (BIS), which is postulated to inhibit movement towards goals in the face of cues signaling punishment and/or possible danger. According to Gray, individuals with a hypoactive BIS system show low levels of trait anxiety whereas those possessing an oversensitive BIS system exhibit high levels of anxiety, fear, frustration, and sadness, predisposing them toward anxiety disorders and depression. In addition, Gray hypothesized

the existence of a Behavioral Activation System (BAS) that is sensitive to signals of reward, nonpunishment, and avoidance of harm, and accounts for positive states such as joy and hope. From the standpoint of Gray's model, hypoactivity of the BAS can be viewed as a distinctive substrate for depression.

While there are similarities among the personality constructs identified as relevant by each theory, they nonetheless differ enough that direct comparisons between studies that utilize different personality measures may not always be possible. This complexity is compounded further by variations in experimental parameters such as the type of emotion-eliciting stimuli used in the study (pictures, imaginal stimuli, shock, etc.), subject exclusionary criteria (e.g., comorbid psychopathology such as other anxiety disorders/depression/psychotic disorders), assessment strategy (e.g., groups with or without psychopathology as determined by DSM criteria, extreme groups on Fear Survey Schedule or Beck Depression Inventory, etc.), and other potential confounding variables such as medication use. Additionally, differences in statistical methodology (e.g., correlational analyses which accommodate information about degree of psychopathology vs. t-tests which focus on discrete group differences) and definition of operational variables (e.g., “baseline” startle response operationalized as reactivity during neutral pictures in some studies, and as reactivity during intertrial intervals in others) complicate matters even further. Such marked discrepancies necessitate a qualitative review of studies in this area rather than a quantitative one.

Task Paradigms for Assessing Affect-Modulated Startle

The startle blink reflex is a basic protective (defensive) reaction that occurs when an individual encounters an abrupt, intense stimulus. Research has shown the startle blink reflex to be a versatile measure that can be evoked by a variety of stimuli and that is sensitive to (modulated by) both emotional and attentional influences.

In studies examining variations in emotion-modulated startle, participants are typically exposed to intermittent stimuli that are emotionally evocative, and during periods of exposure, the blink response to an intervening auditory probe stimulus is measured. For example, in the frequently used affective picture-startle paradigm subjects are presented with photographic images depicting a range of emotional objects or scenes such as babies, animals, insects, buildings, kitchen utensils, guns, physical injury, sickness, etc. Abrupt acoustic probes (e.g., 50 ms, 95-110 dB broadband noise bursts with immediate rise time) are delivered intermittently during picture-viewing intervals, and eyeblink reactions to the probe stimuli are measured using electomyographic sensors (for guidelines on processing eyeblink response data, see Blumenthal, Cuthbert, Filion, Hackley, Lipp, & van Boxtel, 2005). The blink reflex has been found to be reliably modulated by the affective valence of the foreground picture stimulus, with healthy control participants generally exhibiting enhanced (potentiated) magnitude of blink response during unpleasant pictures in comparison to neutral, and attenuated (inhibited) reactivity during pleasant scenes relative to neutral (cf. Lang, Bradley, & Cuthbert, 1990; Vrana et al., 1988).

Lang et al. (1990) advanced a motivational priming hypothesis to account for this bidirectional impact of foreground emotional valence on the startle reflex. According to this model, aversive and pleasurable affective scenes lead to activation of defensive and appetitive motivational states, respectively, in the viewer (e.g., Greenwald, Cook, & Lang, 1989; Lang, Greenwald, Bradley, & Hamm, 1993). Since the startle reflex is inherently a defensive (protective) response, it demonstrates augmentation when the viewer is in a pre-existing defensive motivational state (i.e., arising from exposure to an aversive foreground). In contrast, pleasant foreground stimuli instigate an appetitive (approach) state that is inconsistent with the defensive startle reflex, leading to inhibition of the probe-elicited blink response. On average,

startle responses elicited during processing of neutral foregrounds (i.e., outside the context of appetitive or defensive mobilization) fall in between these two extremes.

A variant of the affect startle modulation paradigm is the affective-imagery procedure in which startle probe stimuli are delivered during periods in which participants imagine pleasant, unpleasant, and neutral scenes. Notably, studies using this procedure have generally demonstrated the largest magnitude of startle reactivity during unpleasant scenes, followed by pleasant scenes and then by neutral (e.g., Witvliet & Vrana, 1995; Miller, Patrick, & Levenston, 2002)—indicating general enhancement of startle reactivity for emotionally arousing scenes (regardless of valence) versus low-arousal neutral scenes. This pattern of results has been interpreted as reflecting concurrent, contrasting effects of depth of imaginal engagement and defensive vs. appetitive activation on startle reactivity within this context (Miller et al., 2002).[2]

Yet another variant of the affect-modulated startle paradigm entails delivery of startle probe stimuli during exposure to conditioned aversive stimuli. This procedure has been used especially in studies investigating post-traumatic stress disorder (PTSD). Studies of this kind usually include an initial habituation phase in which participants are exposed to simple non-affective visual cues (e.g., colored lights) that are paired predictably or unpredictably with an aversive stimulus, leading to cue conditioning (e.g, Morgan, Grillon, Southwick, Davis, & Charney, 1995; Jovanovic, Norrholm, Fennell, et al., 2009). Startle reactivity is then measured in subsequent phases, during periods in which conditioned stimuli are either present or absent. An alternative to this paradigm involves assessing reactivity to startle probes alone (e.g., Shalev, Orr, Peri, Schreiber, & Pitman, 1992; Orr, Lasko, Shalev, & Pitman, 1995), or reactivity to probes under instructed threat of shock (e.g., Pole, Neylan, Best, Orr, & Marmar, 2003; Grillon, Morgan, Davis, & Southwick, 1998b), or in conditions of darkness (e.g., Grillon, Morgan, Davis, & Southwick, 1998a), with the idea that such manipulations are sufficiently potent to evoke defensive reactivity on their own, without any prior conditioning. These latter procedures (e.g., context-potentiated startle, reactivity to probes alone) differ from picture viewing or imaginal processing paradigms in that startle modulation is examined for aversive cuing alone in relation to non-affective (neutral) cuing.

However, despite notable differences as mentioned, a common feature of these varying task paradigms is that each includes measurement of changes in startle blink reactivity as a function of induced motivational states. Because of its utility as an index of negative affective reactivity in particular, startle reflex modulation has been employed in numerous studies of internalizing disorders and affiliated personality traits. Some studies have also examined deviations in positive emotional reactivity within picture-viewing and imagery paradigms, particularly in relation to depression.

Given the variety of startle modulation effects to be discussed in this review, some clarification of terminology is called for to minimize confusion and permit comparisons of modulatory patterns across differing studies. In the following pages, “general startle reactivity” refers to average startle reactivity in the absence of or without regard to foreground stimulus manipulations, if present. The term thus encompasses blink reactivity in probe-alone paradigms, startle reactivity during inter-trial intervals of a task procedure, and mean reactivity across all trial conditions within a particular study. (The expression “baseline startle reactivity” has also been commonly used in the literature. Although the term implies reactivity in the absence of an explicit task manipulation, this expression has in fact been applied to conditions of various other types in the literature—including reactivity during inter-trial intervals, reactivity to neutral foreground stimuli, and reactivity in non-threatening contexts. We have

[2]For a thorough review of studies investigating anxiety disorders that used this paradigm, see Lang and McTeague (2009).

opted for the term "general startle reactivity" because it more aptly encompasses these varying operationalizations.) The term "valence-modulated startle effect" (also referred to as "linear startle effect") refers to the normative pattern of startle blink modulation observed across stimulus valence conditions (unpleasant > neutral > pleasant) in picture viewing paradigms. "Emotion-modulated startle" refers to the increase (potentiation) or decrease (inhibition) in the magnitude of blink startle during viewing of an affective foreground relative to a neutral comparison condition. "Context-potentiated startle" refers to the increase in startle reactivity in stressful contexts in an experiment (e.g., attachment of shock electrodes suggesting that shocks may occur later in the experiment, but are not imminent) as compared to a more neutral condition within the same experiment.

Neurobiology of the Defensive Motivational System and Processes Indexed by Startle Modulation

As mentioned earlier, the startle response is considered a basic defensive reflex that functions as a behavioral interrupt to direct attention to the stimulus that caused the startle response (Graham, 1979). Though it was initially theorized that the blink reflex indexed an arousal-engagement dimension (i.e., the more arousing and engaging the foreground stimulus, the greater the *inhibition* of startle to a probe in a differing stimulus modality), research on affective valence and startle modulation led to a revision of this perspective. Lang, Bradley, and Cuthbert (1997) postulated a cascade of defensive responses that occurs in mammals upon exposure to an explicit aversive stimulus. According to this theory, differing physiological systems respond in a progressive manner as the level of defensive activation increases with increasing imminence of danger. At lower levels of activation, evident during initial stages of an encounter with a potential threat, the startle reflex first decreases as a function of early attentional processing of threat cues. Then, as the threat becomes clearer and more imminent and activation of the defensive system increases, the magnitude of the startle response increases as well.

The increase in startle that occurs during exposure to an explicit aversive cue has a known neurobiological basis. Upon presentation of an acoustic startle probe, an obligatory reflex circuit is activated in which stimulus input is transmitted from the cochlear root neurons to the nucleus reticularis pontis caudalis (nRPC), which in turn activates motor neurons to instigate the startle response. However, this circuit also receives input from secondary neural pathways that can alter (modulate) the basic startle reflex. Research with rodents has revealed two distinct systems, both associated with the amygdala, that modulate the startle response as a function of negative emotional states (see Davis and colleagues, 1997, 1998). One of these is a short-term (phasic) fear system, associated with the central nucleus of the amygdala (CeA), which is responsive to explicit threat cues. Fear-potentiated startle is mediated by this system (i.e., by a pathway from the CeA to the nRPC). The other system, a tonic negative arousal system, is associated with the extended amygdala—in particular, the bed nucleus of the stria terminalis (BNST). This BNST system mediates persisting increases in startle reactivity associated with longer-lasting emotional stressors. While acknowledging some interrelationship between the two systems (e.g., intense or repeated activation of the amygdala by stressful events may lead to longer-term activation of the BNST via processes such as kindling; cf. Rosen & Schulkin, 1998), Davis and colleagues posited that these systems play differing roles in fear and anxiety states—with the amygdala more important for cue-specific fear, and the BNST more important for nonspecific anxiety. In humans, phasic enhancement of startle during aversive cuing (i.e., fear-potentiated startle) has been interpreted as reflecting activation of the central amygdala (Lang et al., 1990), whereas tonic enhancement of startle associated with a stressful context (i.e., context-potentiated startle) has been interpreted as reflecting activity in the BNST (Grillon & Davis, 1997). On the other hand, startle inhibition during exposure to pleasant stimuli is thought to be mediated by the nucleus accumbens (NAC). For example, Koch, Schmid, and Schnitzler (1996) demonstrated that the NAC plays a crucial role in reducing fear-potentiated

startle in the presence of a conditioned reward stimulus in rats. However, the precise mechanism by which the NAC accomplishes this in conjunction with the neural circuitry for fear-potentiated startle remains to be determined.

In summary, attempts to map out the neurobiology of the acoustic startle reflex have shown that it is a variegated system involving interconnections among several different brain structures. An obligatory startle reflex, regardless of foreground stimulus valence, is instigated by the basic brainstem circuit upon exposure to an intense abrupt noise or other rapid-onset stimulus. Fear-potentiated startle is mediated by connections from structures such as the CeA and BNST to the nRPC node of the brainstem circuit, with the former more associated with phasic fear response and the latter with tonic anxiety response. Startle responses to pleasant stimuli appear to be moderated additionally by input from the NAC. While the basic structures involved in this circuit are clear, further research is required to understand the interplay of these various structures in producing startle response modulation, in particular startle inhibition during processing of pleasurable foreground stimuli.

Startle Reflex Modulation and Internalizing Psychopathology

Startle modulation has been frequently used to study internalizing disorders and affiliated personality traits. A recent review by Grillon and Baas (2003) provided a broad summary of the use of the startle reflex in studying various forms of psychopathology including internalizing and externalizing disorders, psychotic disorders, and personality pathology. The objective of this prior review was to summarize findings for differing startle modulation effects in relation to varying specific disorders. The central aim of the current review is different from this. Beyond providing an updated survey of findings in this area, our goal is to integrate startle findings for varying diagnostic syndromes and affiliated individual difference constructs into a hierarchical-dimensional framework (cf. Watson, 2005), in order to facilitate understanding of prior research findings and guide future research in these interrelated domains.

While several variants of the startle paradigm have been used to study internalizing psychopathology, theoretical considerations have informed the use of certain procedures with particular disorders. For example, the picture-viewing startle task has been used most frequently in studies of phobic disorders and dispositional fearfulness (see Tables 1 and 3). Because phobias by definition are characterized by extreme levels of fear (i.e., defense-system activation) to specific environmental stimuli considered aversive, phobic subjects would be expected to show heightened startle potentiation—reflecting enhanced activation of the phasic fear (amygdala) system–during exposure to such stimuli. As discussed in detail below, this hypothesis has received substantial support across many published studies to date.

However, in the disorder of PTSD, for which exaggerated startle serves as a specific diagnostic criterion, studies have tended to focus on reactivity to startle probes alone without any other foreground stimuli (e.g., Shalev et al., 1992; Orr and colleagues, 1995, 2003). Related work by Grillon and colleagues has posited that this enhancement of startle in PTSD is dependent on the presence of an aversive context, and these researchers have investigated startle reactivity in experimental situations that are manipulated to be stressful or unpleasant in some manner, compared with a neutral experimental context (e.g., Grillon et al., 1998b; Grillon & Morgan, 1999). Startle studies of depression, on the other hand, have predominantly employed affect-modulated startle paradigms, since theoretical accounts of depression emphasize both a deficiency in positive affect and an excess of negative affect (e.g., Allen, Trinder, & Brennan, 1999; Dichter, Tomarken, Shelton, & Sutton, 2004).

Differing hypotheses can be advanced regarding deviations in startle modulation in individuals with internalizing disorders of these types. One possibility is that individuals with disorders such as PTSD or major depression may show enhanced startle potentiation during viewing of

threatening scenes, as is the case for phobic disorders. On the other hand, if increased fear-potentiated startle reflects an augmentation of cue-specific fear that is unique to phobic/fear disorders, a different pattern of results might be expected for the anxious-misery syndromes. Given that disorders of this type are marked by high levels of free-floating anxiety, enhanced general startle reactivity or increased startle reactivity in relation to aversive or unfamiliar situations (i.e., enhanced context potentiation) might be expected. Alternatively, if anxiety levels are abnormally high and persistent across time, the startle response to abrupt probe stimuli might be generally diminished. The basis for this prediction comes from Seligman's conceptualization of learned helplessness (1975), in which repeated exposure to unavoidable negative stimulation leads to a general lack of behavioral reactivity, even when avenues of escape subsequently become available. Yet another possibility is that the lack of positive affectivity apparent in disorders of this type might be associated in particular with a lack of normal inhibition of startle during viewing of pleasurable stimuli—either alone, or in conjunction with enhanced aversive startle potentiation or general sensitization of startle reactivity.

With these considerations in mind, this review seeks to highlight consistent patterns of findings in studies to date that have examined startle modulation effects in samples of individuals selected for the presence of internalizing disorders or personality traits affiliated with these disorders.

Phobic disorders—Phobias are characterized by clinically significant anxiety evoked by specific feared stimuli (e.g., snakes, spiders, social situations). Since the mechanism of the fear-potentiated startle effect is most directly relevant to cue-specific fear disorders, early studies focused on startle potentiation during aversive cuing in subjects with specific phobias. As reviewed by Grillon and Baas (2003), early studies in this area (Vrana, Constantine, & Westman, 1992; de Jong et al., 1991, 1996) attempted to utilize the blink reflex as an indicator of treatment success by assessing it pre- and post-intervention in subjects with specific phobia. Results were in the predicted direction, with phobic subjects showing reduced fear-potentiated startle during viewing of fear-relevant stimuli after completion of treatment sessions, suggesting that the blink reflex could indeed be used as an outcome measures. Hamm and colleagues (Hamm, Cuthbert, Globisch, & Vaitl, 1997; Globisch, Hamm, Esteves, & Ohman, 1999) compared startle reactivity during picture viewing in phobic subjects and non-phobic controls. Findings from these two studies indicated that phobic subjects showed greater startle potentiation during processing of phobic scenes, as compared to non-phobic controls. These results provide further support for the hypothesis that phobic subjects exhibit greater levels of defensive reactivity than controls during exposure aversive stimuli.

A more recent study by McTeague, Lang, Laplante, Cuthbert, Strauss, and Bradley (2009) investigated aversive startle potentiation in treatment-seeking patients diagnosed with social phobia compared with healthy controls. The authors used an imagery paradigm in which subjects visualized neutral and fearful scenes, with startle probes presented at unpredictable points during image processing. Scripts for fear scenes consisted of standardized scenarios involving social threat and non-social threat along with personalized scenes based on subjects' own worst fears. The social phobic group was subdivided into a *circumscribed* subgroup, for whom social anxiety was limited to performance contexts alone, and a *generalized* subgroup, for whom fear of social situations were more pervasive. Compared with the circumscribed subgroup, the generalized subgroup showed greater comorbidity with mood-related (depressive) disorders, indicating a larger component of distress or generalized negative affectivity (cf. Watson, 2005) in this subgroup.

Findings from the imagery assessment indicated startle potentiation for fearful scenes relative to neutral scenes in healthy controls as well as socially phobic individuals; however, general

startle reactivity across all imagery scenes (regardless of content) was greater for patients than controls. Healthy controls showed potentiation only during imagery of personalized fear and non-social threat scenes relative to neutral scenes. In contrast, patients demonstrated significant startle potentiation for social threat scenes (standard as well as personalized). This effect was driven by the generalized social phobic group, rather than the circumscribed social phobic group, suggesting pervasive defensive reactivity across all aversive scenarios. However, this finding of pervasive potentiation was limited to generalized social phobic patients *without* comorbid depression. Subjects who met criteria for depression as well as social phobia demonstrated potentiation of startle only for personalized fear scenes (i.e., not for standard social threat or non-threat scenes), suggesting that the presence of depression may operate to blunt defensive mobilization to threat cues except when the threat is potent/imminent (see section on depression, below).

While the aforementioned studies have all found evidence of heightened startle potentiation for individuals with phobic fear disorders, two additional studies that did not do so. One of these (de Jong, Arntz, & Merckelbach, 1993) contrasted startle reactivity in phobic subjects exposed to unpleasant-fearful, pleasant, and neutral conditions (a live spider, appetizing food, and a block of wood, respectively) in pre- and post-treatment assessments. Although blink responses for the spider condition decreased significantly from the pre- to the post-treatment assessment, phobic subjects did not show the expected pattern of valence-modulated startle in either the pre-treatment or immediate post-treatment assessment. In another study that failed to show fear-potentiated startle in phobic subjects (Merckelbach, de Jong, Leeuw, & van den Hout, 1995), spider phobics and healthy controls were presented with backwardly masked phobic stimuli (spider scenes) along with non-phobic scenes (i.e., pictures of flowers, mushrooms, and snakes), with probes delivered after offset of the masking stimulus. It is unclear as to why these authors did not find any differences between groups.

In summary, with the exception of the two studies discussed above, research to date has generally demonstrated greater fear-potentiated startle among phobic subjects, in comparison to controls. Additionally, one study (McTeague et al., 2009) reported blunted defensive reactivity as indexed by startle potentiation to standardized (i.e., non-personally relevant) threat scenes in patients with generalized social phobia and depression.

Panic disorder with or without agoraphobia—Recurrent unexpected panic attacks causing significant clinical impairment are the defining characteristic of panic disorder. These may or may not co-occur with agoraphobia, which entails anxiety about situations from which escape is difficult. Analyses of interrelations among DSM disorders, as determined by structured clinical interviews, (e.g., Krueger, 1999; Cox et al., 2002) have indicated that panic disorder coheres more closely with the phobic disorders than with depression or PTSD. This is somewhat unexpected, as a diagnosis of panic disorder requires at least two *uncued* or unexpected panic attacks not tied to any specific stimulus—a phenomenon that appears more indicative of nonspecific anxiety (as seen in the “distress” disorders) than cue-specific fear. On the whole, as described below, findings from startle modulation studies are more consistent with the notion of panic disorder as a “distress” syndrome—although evidence from at least one study suggests that there may be a subgroup of panic patients who respond more like phobic individuals.

Melzig, Weike, Zimmermann, and Hamm (2007) examined startle response potentiation in subjects with panic disorder compared to diagnosis-free controls in two different aversive conditions – threat of shock, and darkness. The experiment consisted of an adaptation or habituation phase followed by a dark/light phase in which startle probes, but no shocks, were delivered. This was followed by a dark/light phase that included periods entailing threat of shock interspersed with safe (no shock) periods. No group differences in general startle

reactivity were evident during the adaptation phase, dark/light condition, or dark/light+safe/shock condition, nor did groups differ in degree of startle potentiation during dark versus light or shock versus safe conditions. However, when patients with panic disorder were subdivided into those with comorbid depression and those without, those with comorbid depression failed to show significant startle potentiation during threat versus safe periods, whereas panic patients without depression did show significant potentiation. Indeed, panic patients without depression showed a trend toward even stronger threat versus safe potentiation than control subjects. In addition to McTeague et al.'s (2009) study, these findings provide further evidence that the presence of comorbid depression mitigates against robust cue-specific startle potentiation.

Another study by Cuthbert, Lang, Strauss, Drobes, Patrick, and Bradley (2003) compared general startle reactivity during inter-trial intervals (ITI), and potentiation during aversive imagery relative to ITI trials, in treatment-seeking patients diagnosed with varying anxiety disorders (specific phobia, social phobia, and panic disorder with agoraphobia) as well as healthy controls. Participants imagined scripted neutral, and standardized and personalized fearful scenes. Startle potentiation was defined as mean blink reactivity for the fear versus neutral imagery conditions. Across all groups, significant startle potentiation was observed for fearful imagery scenes as a whole. However, for personal fear scenes, significant startle potentiation was observed in patients with specific and social phobia and in controls, but *not* in patients with panic disorder. Instead, panic patients showed a trend (approaching significance) toward larger general startle reactivity (measured as startle reactivity during ITI) relative to controls and patients diagnosed with either specific phobia or social phobia. These results provide evidence of deficient cue-specific startle potentiation coupled with enhanced general startle reactivity in patients with panic disorder.

In a follow-up to this study, Lang, McTeague, and Cuthbert (2007) used a similar imagery paradigm to examine startle reactivity in patients diagnosed with specific phobia, social phobia, panic disorder with agoraphobia, and/or generalized anxiety disorder, and a no-disorder control group. Specific phobics showed the greatest startle potentiation during imagery of fearful scenes relative to startle during inter-trial intervals, followed by those with social phobia, panic disorder with agoraphobia, and generalized anxiety disorder. Additionally, scores on a measure of trait anxiousness (akin to NA, or general distress; Watson, 2005; Watson & Tellegen, 1985) showed an inverse relationship with fear-potentiated startle, such that subjects with the highest levels of trait anxiousness showed the smallest degree of startle potentiation for personal fear scenes. These results again suggest that panic disorder in patient samples is more similar to generalized anxiety disorder and depression than to the phobic disorders. These data also indicate that reductions in fear-potentiated startle may be characteristic of the anxious-misery subgroup of internalizing disorders.

Grillon, Lissek, Rabin, McDowell, Dvir, and Pine (2008) conducted a study examining startle reactivity in patients with panic disorder (screened to exclude individuals with comorbid depression) and control subjects. Startle probes were delivered during three conditions – a "neutral" condition in which visual cues were presented without accompanying aversive stimuli, a predictable aversive condition in which the occurrence of the aversive stimuli were signaled by distinctive visual cues (i.e., cues different from those in the other two conditions), and an unpredictable aversive condition that included non-contingent visual cues. Startle probes were delivered both during cue presentation periods and during intertrial intervals in each condition. While all subjects demonstrated startle potentiation during predictable and unpredictable conditions relative to the neutral condition, panic patients alone showed a significant increase in startle reactivity to intertrial interval probes occurring *within the unpredictable aversive condition* relative to the neutral condition. The authors interpreted this as evidence that non-specific (contextual) fear associated with unpredictability of aversive events represents a key component in panic disorder.

An earlier study by the same authors (Grillon, Ameli, Goddard, Woods, & Davis, 1994) examined startle reflex potentiation in patients diagnosed with panic disorder in a threat of shock paradigm. However, the results of this study are somewhat unclear as the primary finding was that younger patients with panic disorder (< 40 years old), compared to age-matched controls, showed larger startle response magnitudes across probes delivered during the threat periods, while older subjects did not. The authors hypothesized that this could have been an effect of age, or that older patients could have developed some sort of immunity, as manifested by relatively normal startle reactivity. They interpreted the increased startle in younger patients as indicating an effect of global context in the experimental phase of the study, such that a stressful context led to generally augmented startle among panic disorder patients.

In summary, studies conducted in this area generally suggest that patients with panic disorder appear to be a diverse group with regard to startle reactivity. Findings from one study (Melzig et al., 2007) indicate that there may be a specific subgroup of panic patients (i.e., those without comorbid depression) who show enhanced cue-specific fear—akin to patients with specific phobias. Additionally, this study along with others, suggests that patients with panic disorder and agoraphobia, or comorbid panic and depression, show limited startle potentiation for aversive stimuli. In other words, panic disorder appears to have characteristics that are similar to both the fear disorders and to the anxious-misery disorders, suggesting that it may not necessarily be best classified as a fear disorder alone.

Post-traumatic stress disorder—The DSM-IV-TR defines PTSD as "the reexperiencing of an extremely traumatic event accompanied by symptoms of increased arousal and by avoidance of stimuli associated with the trauma." Given that one of the diagnostic criteria for this disorder is an exaggerated startle response, the startle blink reflex is an obvious candidate for study in individuals with PTSD. Indeed, a vast literature exists on physiological reactivity in PTSD in general, and startle reactivity in particular. Based on this extant research base, three separate reviews (Metzger, Orr, Berry, Ahern, Lasko, & Pitman, 1999; Grillon & Baas, 2003; Pole, 2007) have concluded that there is evidence for the presence of enhanced startle reactivity in subjects diagnosed with PTSD. Additionally, Grillon and Baas (2003) noted that this effect was particularly evident in a stressful or aversive context (e.g., an experimental situation, being exposed to shocks, etc.). Given these comprehensive pre-existing reviews, we provide a brief summary of the various studies in this field and their principal findings, and discuss how these findings fit within the conceptual framework of the current review.

Following the line of reasoning that exaggerated startle is a diagnostic symptom of PTSD, a number of investigators have examined startle blink reactivity in PTSD to probes presented alone, in the absence of other concurrent stimuli. Several studies of this type have reported evidence of increased startle reactivity in subjects with PTSD as compared to control subjects (Butler, Braff, Rausch, Jenkins, Sprock, & Geyer, 1990; Shalev et al., 1992; Morgan, Grillon, Southwick, Nagy, Davis, Krystal, et al., 1995; Morgan et al., 1995; Orr et al., 1995; Morgan, Grillon, Southwick, Davis, & Charney, 1996; Morgan, Grillon, Lubin, & Southwick, 1997; Shalev, Peri, Orr, Bonne, & Pitman, 1997; Grillon et al., 1998a; Ladwig et al., 2002; Cuthbert et al., 2003). However, in direct contrast to this, several others have found no evidence of increased blink reactivity in subjects with PTSD (Ross, Ball, Cohen, Silver, Morrison, & Dinges, 1989; Grillon, Morgan, Southwick, Davis, & Charney, 1996; Orr, Lasko, Metzger, & Pitman, 1997; Orr, Solomon, Peri, Pitman, & Shalev, 1997; Metzger et al., 1999; Orr et al., 2003; Karl, Malta, Alexander, & Blanchard, 2004; Guthrie & Bryant, 2005; Carson, Metzger, Lasko, Paulus, Morse, Pitman, & Orr, 2007; Jovanovic, Norrholm, Sakoman, Esterajher, & Kozarić-Kovačić, 2009).

In a conceptual reinterpretation of these findings, Grillon and Baas (2003) proposed that the increased startle response observed in PTSD occurs as a function of the presence of a stressful

or aversive experimental context. They posited that without this aversive priming, PTSD might not be associated with increased startle reactivity. Empirical support for this viewpoint derives from experiments that have induced stressful experimental contexts by methods such as creating unpredictable conditions where cues signal the possible delivery of aversive stimuli (Grillon, Pine, Lissek, Rabin, & Vythilingam, in press), attaching shock electrodes to subjects while mentioning that shocks would not delivered until later (Grillon et al., 1998b; Pole et al., 2003), and assessing startle reactivity in two separate, but identical sessions where mild electric shocks were administered in the first session (Grillon & Morgan, 1999). Findings from these studies have generally indicated that participants with PTSD show increased startle reactivity during the stressful phases of these experiments, but not in the non-stressful phases. Along these lines, Pole, Neylan, Otte, Henn-Hasse, Metzler, and Marmar (2009) reported that startle reactivity during stressful versus neutral contexts in police officers without psychopathology prospectively predicted PTSD symptom severity one year later following exposure to trauma.

Relatedly, another line of research (Shalev, Peri, Brandes, Freedman, Orr, & Pitman, 2000; Griffin, 2008) has investigated differences in startle reactivity *after* trauma exposure. Shalev et al. (2000) demonstrated that there were no differences in general startle reactivity between individuals with and without PTSD (diagnosed at 4 months after trauma) at 1 week post-trauma. However, at 1- and 4-month post-trauma, subjects with PTSD took longer to habituate to startle probes. Similarly, Griffin (2008) showed that at 1-month post-trauma assessment, there were no differences in startle reactivity between subjects with and without PTSD. However, at the 6-month followup, those diagnosed with PTSD had larger startle responses; this effect was due to increased startle blink reactivity for the PTSD group between the two assessments. The Shalev et al. (2000) and Griffin (2008) studies appear to suggest that abnormalities in startle reactivity develop after trauma exposure, in contrast with Pole et al.'s (2009) findings. It must be noted, however, that neither of the former studies included pre-trauma startle assessments. Thus, definitive conclusions cannot be drawn regarding the development of abnormal startle reactivity following trauma exposure.

Another explanation for unusual startle reactivity in PTSD was suggested by Miller and Litz's (2004) study, which examined startle reactivity during affective picture viewing in veterans diagnosed with PTSD according to DSM-IV criteria relative to non-PTSD control veterans. This study included an interesting manipulation in which veterans were exposed to a non-trauma related stressor (threat of shock) followed by a trauma-related stressor (combat-related photographs presented with war-related sounds). At pre-test, and immediately following each of the two-stressor manipulations, subjects completed a standard picture-startle assessment that included varied pleasant and unpleasant scenes. Modulation scores for affective stimuli (trauma- and non-trauma related) were calculated in relation to startle during inter-trial intervals (ITI). Subjects in both groups showed enhanced blink reactivity during unpleasant compared with pleasant scenes, and reduced blink reactivity during both pleasant and unpleasant scenes relative to ITI. Similar results were observed during both the pre-shock and post-shock startle assessments. However, for the startle assessment following the trauma-related stressor, controls showed no significant difference in startle reactivity for pleasant versus unpleasant stimuli (with reactions for both affective contents reduced in comparison to ITI trials), whereas veterans with PTSD showed significantly enhanced blink response during unpleasant pictures relative to either ITI trials *or* pleasant picture trials. Thus, results indicated that subjects with PTSD acted like phobic subjects from previous studies once they had been primed by presentations of trauma-specific stimuli. The implication is that exposure to relevant aversive cues is required to precipitate increased startle reactivity in PTSD.

Cuthbert et al. (2003) attempted to explain elevated startle in PTSD from a slightly different standpoint by comparing patients with PTSD against healthy controls and subjects with other anxiety disorders including specific phobias, social phobia, and panic disorder with

agoraphobia. Similar to patients with panic disorder, those with PTSD *did not* show significant blink potentiation for their specific fear scenes relative to standard neutral scenes. Likewise, as mentioned earlier, patients with PTSD also tended to display enhanced general startle reactivity (measured as startle reactivity during ITI), relative to control participants and patients diagnosed with either specific phobia or social phobia. The authors interpreted these findings in the context of elevated negative affectivity (as defined by scores on questionnaire measures of anxiety symptoms, fear and anxiety related scales, depressive symptoms, and comorbid diagnoses of depression). They noted that controls, and patients with specific phobia or social phobia, were comparatively low in negative affectivity compared with panic disorder or PTSD patients. Interestingly, the latter two groups also showed the least startle potentiation during personal fear scenes. The authors posited that while a certain amount of negative affectivity predisposes subjects with phobias to increased cue-specific fear reactivity (i.e., fear-potentiated startle), being extremely high on negative affectivity appears to be associated with limited cue-specific fear reactivity. Of note, this pattern of results, together with the finding of higher general startle reactivity for panic disorder and PTSD patients, is consistent with the results of studies of panic disorder patients discussed earlier. These data again suggest that patients with panic disorder may be more similar to patients with PTSD in terms of physiological reactivity than they are to specific phobic patients.

Complicating this explanation, however, are studies that have found no differences in fear-potentiated startle between subjects with and without PTSD, but only differences in context-potentiated startle (Grillon & Morgan, 1999; Grillon et al., in press) or a lack of fear inhibition to safety cues (Grillon & Morgan, 1999; Jovanovic, Norrholm, Fennell et al., 2009). Jovanovic, Norrholm, Fennell, et al. (2009) reported an additional intriguing result, showing that the lack of fear inhibition during safety cues was specifically related to the re-experiencing and avoidance symptoms of PTSD, and not to the hyperarousal symptoms—suggesting that the various symptom dimensions of PTSD are differentially associated with startle reactivity. Additionally, as one further twist in this complex literature, two studies have reported an opposite pattern of *decreased* startle reactivity in participants with PTSD (Ornitz & Pynoos, 1989; Medina, Mejia, Schell, Dawson, & Margolin, 2001).

In summary, there have been numerous studies using varying types of experimental paradigms that have investigated startle blink responding in PTSD. While several interesting explanations have been proposed for the range of results reported in these studies, the reasons for differences in findings across studies is not readily apparent. Though it is difficult to draw strong conclusions at this point, as per our review of the studies in this field and prior meta-analytic reviews by Metzger et al. (1999) and Pole (2007), the general trend of results suggests that PTSD is associated with exaggerated startle reactivity. However, it is unclear whether this increased reactivity occurs primarily in aversive contexts, as Grillon and colleagues have suggested, or whether it occurs pervasively across contexts. Results for fear-potentiated startle (i.e., augmentation in relation to specific fear-relevant cues) appear even more mixed, with some studies showing no difference in startle reactivity for fear-relevant versus neutral conditions in individuals with PTSD, and others showing enhanced fear-potentiation in PTSD patients subsequent to an aversive priming manipulation (e.g., exposure to trauma-related cues).

Some of these divergences in findings may reflect procedural differences across studies. For example, it is unclear whether startle reactivity under threat of shock is equivalent to blink reactivity while imagining an aversive scene. It can be argued that though context-conditioning experiments attempt to differentiate between fear-potentiated startle and context-potentiated startle, studies of this type do not lend themselves readily to such differential analysis insofar as context-conditioning paradigms focus on assessment of startle reactivity during the *anticipation* aversive stimulus events, either cued or uncued. In contrast, affect-imagery and

affect-startle paradigms do not rely on conditioning or anticipation effects, but rather assess startle reactivity directly in the presence of the aversive stimulus—making them more suitable for assessing fear-potentiated startle.

Conversely, it could be debated whether affect-imagery and affect-picture studies of patient samples have assessed general startle reactivity adequately. Some studies of this type studies (e.g., Cuthbert et al., 2003; Miller & Litz, 2004, Lang et al., 2007) have included presentation of startle probes during inter-trial intervals, while others (e.g., Allen et al., 1999; Kumari et al., 2001) have examined differences in mean startle reactivity across all foreground stimulus trials between patient and control groups. While it could be assumed that startle reactivity to probes occurring within intertrial intervals or across stimulus trials overall taps something akin to reactivity to probes alone (i.e., in the absence of any foreground stimulus), this assumption has not been systematically evaluated and thus should be considered provisional and in need of verification.

Another source of discrepancies in results could be the presence of comorbid diagnoses. As can be seen in Table 2, subject samples in the different PTSD studies varied widely with regard to the comorbid disorders they experienced. However, not all studies assessed and/or attempted to control for comorbid disorders. Of those that did do so (in most cases for depression or panic disorder), all reported that results were unaffected by the presence of additional disorders. However, further systematic research on this issue is required before firm conclusions can be drawn. An additional source of variation arises from the fact that although most studies have utilized categorical diagnoses of PTSD as the criterion measure of psychopathology, some have examined startle reactivity in relation to PTSD *symptom severity*. In this regard, Cox et al. (2002) noted that PTSD as a diagnostic entity includes criteria that overlap with distress disorders (e.g., diminished interest, emotional numbing, etc.) as well as criteria that overlap with fear disorders (e.g., avoidance, physiological reactivity). Thus, participants in studies that employing diagnostic cutoffs requiring a threshold of several PTSD criteria to be satisfied may differ from participants in studies that used symptom severity as a criterion, leading to samples that vary significantly with respect to levels of anxiety and depression. Some preliminary evidence for this hypothesis is provided by studies such as that of Jovanovic, Norrholm, Fennell, et al. (2009), which reported differing patterns of startle reactivity in relation to varying PTSD symptom dimensions.

In summary, the basis for discrepancies in results across PTSD studies remains uncertain due to a variety of methodological factors. In the future, to gain a more comprehensive understanding of how general startle reactivity, context-potentiated startle, and fear-potentiated startle operate in PTSD, further studies of the kind undertaken by Cuthbert et al. (2003) are needed in which common task paradigms are used to assess startle reactivity across multiple internalizing disorders including PTSD. Of value would be studies of this kind using the probe-alone and conditioning or context-potentiated startle paradigms used in the PTSD literature, and studies using the affect-picture startle paradigms that have been used more often with phobias. Such studies would help resolve discrepancies in results across studies employing varying task paradigms and ultimately, answer the questions at the heart of the current discussion – how best to define, measure, and distinguish constructs of “fear” and “anxiety”, and the role that each plays in internalizing forms of psychopathology.

Mood disorders—The diagnostic criteria for a major depressive episode specify at least two weeks of depressed mood or a loss of interest as essential symptoms of the disorder, with several other ancillary features. Despite the systematic comorbidity evident between depression and anxiety disorders, the key affective processes implicated in the two are theorized to be different. Anxiety disorders entail heightened negative emotional reactivity in particular, whereas major depressive disorder is thought to additionally involve attenuated reactivity to

pleasant stimuli (Clark & Watson, 1991; Tellegen, 1985). Accordingly, some research has been undertaken to address the hypothesis that individuals with depression might exhibit lesser inhibition of startle during processing of pleasurable stimuli relative to neutral stimuli, along with heightened potentiation of startle for unpleasant stimuli.

Allen et al. (1999) examined the relationship between diagnoses/symptoms of depression and startle blink modulation in an affective picture paradigm. Their results indicated that depressed subjects showed smaller general startle reactivity across stimulus conditions, as compared to nondepressed controls. Additionally, patients exhibiting *severe* depression demonstrated significant startle *potentiation* during pleasant pictures compared with either neutral or unpleasant pictures. In contrast, the mild and moderately depressed groups showed a normal valence-modulated pattern of startle reactivity, analogous to controls. Dichter et al. (2004) demonstrated similar results in a separate sample of depressed patients.

Another study by Forbes, Miller, Cohn, Fox, and Kovacs (2005) sought to clarify whether there was a difference between the startle blink reactivity of patients with either childhood onset unipolar depression or bipolar disorder, relative to controls with no history of psychopathology. All subjects showed startle potentiation during viewing of unpleasant pictures as compared to pleasant pictures. However, follow-up comparisons with neutral pictures revealed that in the bipolar disorder and control groups, this modulation reflected mainly potentiation for unpleasant scenes in relation to neutral scenes. In contrast, subjects with major depressive disorder showed significant inhibition of blink responses during pleasant scenes as compared to neutral, and nonsignificant potentiation for unpleasant versus neutral scenes. Additionally, those with a history of repeated depressive episodes in their lifetime showed no significant modulation of the startle response, either for pleasant or for unpleasant pictures. The presence of a comorbid anxiety disorder did not appear to moderate startle response patterns. Hence, findings consistent with prior research were evident when subjects with multiple depressive episodes were considered. This implies that a greater number of prior depressive episodes are indicative of greater severity depressive symptomatology and/or with greater anhedonia.

In another study, Kaviani, Gray, Checkley, Raven, Wilson, and Kumari (2004) compared startle reactivity to pleasant, neutral, and unpleasant film clips in depressed and non-depressed subjects. Depressed patients were subdivided into high and low depressed groups and high and low anhedonia groups on the basis of scores on inventories of physical anhedonia. Controls and subjects in the low depressed group showed the expected valence-modulation pattern of startle reactivity across film valence categories, whereas subjects in the high-depressed group did not. When depressed patients were divided into low and high anhedonia subgroups, the flat modulation pattern was found to be characteristic of the high anhedonia subgroup in particular; the low anhedonia group showed blink reflex modulation similar to controls. Thus, consistent with previous research, the findings of this study indicate that patients exhibiting prominent anhedonia and/or depressive symptoms demonstrate a lack of valence modulation of the startle reflex.

Also pertinent to the issue of startle modulation in depressed patients are findings from Cuthbert et al.'s (2003) imagery-startle study, which included a comparison of blink modulation effects for subgroups of anxiety disorder patients with and without comorbid depression. Although both subgroups showed comparable startle potentiation for fearful scenes in relation to neutral, the patients with comorbid depression showed significantly larger blink magnitude during ITI trials than patients without depression. However, Lang et al.'s (2007) follow-up investigation reported somewhat different results. In order to evaluate the influence of depression on fear-potentiated startle, these investigators subdivided fearful patients (diagnosed with either specific or social phobia) and anxious patients (diagnosed with either panic disorder or agoraphobia) into subgroups consisting of those with and without comorbid depression. As

noted earlier, fearful patients as a whole showed significantly greater potentiation of startle during fearful versus neutral imagery than anxious patients. However, within each of these two groups, patients with comorbid depression showed lesser fear-potentiation than patients without depression. This result provides further evidence of a blunting of emotion-modulated startle in individuals with depression, and suggests that this dampening effect of depression on startle modulation may operate independently of the facilitatory effect of fearfulness.

In summary, findings to date generally indicate that depressed individuals show diminished startle modulation effects for both pleasant and unpleasant stimuli, especially as the severity of depressive symptoms increases. A study by Allen et al. (1999) reported increased startle potentiation during pleasant picture viewing in a subgroup of patients with severe levels of depression, but this finding has not been precisely replicated in subsequent studies. In addition, one study by Cuthbert et al. (2003) reported evidence of increased general startle reactivity in depressed patients, in terms of enhanced blink reactivity to noise probes occurring during inter-trial intervals. The reason for differences in results across these varying studies is unclear at this point, with further research needed to systematically evaluate the impact of potential moderating variables (e.g., inpatient versus outpatient samples, etc.).

Other anxiety disorders—Limited research has been conducted to date on other anxiety-related disorders using the affect-startle paradigm. A search of the literature revealed only five such studies, two of which examined startle modulation effects in individuals with obsessive-compulsive disorder (OCD) and three examining startle reactivity in individuals with generalized anxiety disorder (GAD). OCD is marked by anxiety-provoking obsessions, in some cases accompanied by compulsive behaviors that help to neutralize the obsessions. The nature of negative affect in OCD is similar in many cases to that of phobias to the extent that it is evoked by specific stimuli in the environment. However, OCD can also be conceptualized as entailing more pervasive anxiety, since obsessions and compulsions in OCD may generalize to multiple stimuli (e.g., checking doors, locks, stoves, or ruminative thoughts, etc.) and not just one specific stimulus. In this regard, OCD could be more related to the anxious-misery cluster of disorders. To date, based on statistical modeling research, it is unclear whether OCD belongs more to the fear or distress disorders (Slade & Watson, 2006). Likewise, the nature of startle reactivity in OCD remains an open question.

Among the few studies examining this topic, Kumari, Kaviani, Raven, Gray, and Checkley (2001) investigated startle reactivity to unpleasant, pleasant, and neutral film clips in inpatients diagnosed with OCD relative to healthy controls. While patient and control groups each showed valence-modulated startle reactivity across the three types of clips, the OCD group showed increased general startle reactivity as compared to controls. A subsequent study by Buhlman, Wilhelm, Deckersbach, Rauch, Pitman, and Orr (2007) compared startle reactivity in controls and subjects with OCD, recruited from an outpatient OCD clinic. Participants were presented with 15 auditory startle probes unaccompanied by any affective foreground stimuli. A trend toward higher mean startle reactivity was found in subjects with OCD as compared to controls, but this effect did not achieve statistical significance. Although weak, these results are nonetheless consistent with those of Kumari et al. (2001) in suggesting that general startle reactivity is elevated in patients with OCD. Overall, startle findings imply that OCD might be more similar to distress disorders than anxiety disorders. However, given the lack of research in this area, this is a highly tentative conclusion.

Similar to OCD, generalized anxiety disorder (GAD) has received limited attention in startle studies to date. The core feature of GAD, as defined by the DSM-IV-TR, is “at least 6 months of persistent and excessive anxiety and worry.” Structural analyses of internalizing disorders have revealed that GAD falls within the anxious-misery subgroup (cf. Krueger, 1999). Relatedly, Mineka et al. (1998) concluded that GAD and depression were closely related in

terms of genetic transmission. Based on this prior work, and in line with findings for other anxious-misery disorders, it could be hypothesized that subjects with GAD would exhibit heightened general startle reactivity, and possibly decreased fear-potentiated startle. However, evidence for this hypothesis appears to be mixed.

As reviewed earlier, in Lang et al.'s (2007) imagery-startle study involving a sample of subjects diagnosed with specific or social phobia, panic disorder with agoraphobia, or GAD, it was the GAD group in particular that showed the weakest fear-potentiated startle. In another study, Ray et al. (2009) exposed subjects with GAD to startle probes during an initial probe-alone period, and in tasks entailing attentional and arousal manipulations. These investigators reported that subjects with GAD showed greater general startle reactivity across the experiment as a whole as compared to controls. However, contrary to these findings, Grillon et al. (in press) demonstrated that startle reactivity in subjects with GAD did not differ from that of controls when tested during conditions involving predictable and unpredictable aversive stimuli. The reasons for this divergence in findings are unclear. One possible, though highly speculative, explanation could be that the subjects with GAD in Grillon et al.'s (in press) study lacked the high level of pervasive distress characteristic of GAD patients in Lang et al.'s (2007) study. As noted in Table 1, at least half of all subjects in the latter study had comorbid depression, whereas the GAD sample in the former study showed less comorbid psychopathology and were more similar to subjects diagnosed with phobias alone. However, Ray et al.'s (2009) study did not report on comorbid conditions in their sample. Given this inconsistency in findings, no firm conclusions can be drawn regarding startle reactivity in GAD on the basis of these three experiments.

Summary and integration—The studies reviewed in this major section indicate that subjects with specific phobias show increased startle reactivity in the presence of their feared stimuli. However, results for other anxiety disorders, such as PTSD and panic disorder, suggest that general startle reactivity (i.e., magnitude of blink response across stimulus conditions, or in the absence of any foreground stimulus) appears to be elevated, whereas fear-potentiated startle if affected, appears diminished. Studies of startle reactivity in major depressive disorder, on the other hand, suggest a lack of startle modulation for both pleasant and unpleasant stimuli. In addition to studies described in the foregoing subsections, three family studies by Grillon and colleagues (Grillon, Dierker, & Merikangas, 1997, 1998; Grillon, Warner, Hill, Merikangas, Bruder, Tenke, et al., 2005) provide further indirect support for the hypothesis that startle reactivity is elevated in subjects with anxiety disorders. Specifically, data from these studies consistently indicate that even children of subjects with anxiety disorders (including panic disorder with/without agoraphobia, generalized anxiety disorder and/or social phobia), with or without comorbid major depressive disorder, tend to show greater general startle reactivity as compared to children of control subjects.

This pattern of results (enhanced cue-specific startle potentiation for phobic disorders; decreased fear-potentiated startle and/or heightened general startle reactivity for major depression, PTSD, panic disorder when accompanied by depression, and OCD) appears consistent despite varying methodological discrepancies among studies including differing criteria used to assess for internalizing psychopathology (see Tables 1 and 2), and differences in task procedures used to manipulate affective states (e.g., exposure to live phobic stimuli, imaginal scenes, affective picture stimuli, shock threat, exposure to darkness).

Further, while some studies have assessed for the presence of comorbid DSM disorders, many have not, and others have excluded subjects based on comorbidity for certain disorders such as depression or drug abuse. Considering available evidence indicating high levels of comorbidity among several of the internalizing disorders, and the notion that greater comorbidity is indicative of a greater severity of psychopathology, failing to assess for

comorbid conditions or systematically excluding participants with "extraneous" disorders can lead to loss of valuable information regarding sample characteristics, and/or to sampling bias. Yet another factor to consider in comparing findings across studies has to do with variations in how "general" startle reactivity is defined (e.g., reactivity to probes during ITI vs. probes during other affective stimuli), and what comparison condition is used to assess startle modulation effects (e.g., modulation during stimulus processing relative to ITI; modulation during affective as opposed to neutral stimulus processing; modulation following treatment compared with before treatment). Such factors can be crucial when attempting to compare findings across studies.

Startle Modulation and Personality Traits Associated with Internalizing Disorders

A number of different personality traits have been linked to internalizing disorders. The most prominent of these are broad trait constructs such as negative affect, neuroticism, and negative emotionality. In addition, narrower facets of these traits such as fearfulness and anxiety or distress have received attention based on theoretical notions of particular disorders. For example, phobic disorders have been discussed in relation to fearfulness (see Cook et al., 1991, 1992), whereas disorders of the anxious-misery type have been conceptualized more in relation to anxiety, negative affect, or generalized distress (e.g., Mineka et al., 1998). Other constructs of relevance to internalizing disorders include positive affect or positive emotionality, the lack of which has been discussed as a specific feature of major depressive disorder (e.g., Clark & Watson, 1991), and sensation seeking, which intersects with the construct of fearlessness (see Tellegen, in press) and also that of impulsiveness (e.g., Zuckerman, 1979).

Dispositional fearfulness—The trait that has been studied most extensively in relation to startle reflex modulation, in varying incarnations, is fearfulness. The earliest work of this kind was by Cook and colleagues. These investigators defined fearfulness in terms of overall scores on the Fear Survey Schedule (FSS; Arrindell, Emmelkamp, & van der Ende, 1984), an inventory of specific fears on which respondents rate the degree of fear experienced in relation to various objects and situations. As noted by Grillon and Baas (2003), Cook and colleagues (Cook, Hawk, Davis, & Stevenson, 1991; Cook, Davis, Hawk, Spence, & Gautier, 1992), reported that subjects with high scores on the FSS exhibited greater fear-potentiated startle than subjects with low scores, while exposed to aversive stimuli (aversive imagery scenes vs. pleasant scenes in the first study, and aversive slides relative to neutral slides in the second study). Similarly, in a study by Grillon, Ameli, Foot, and Davis (1993), subjects with higher scores on the state portion of the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), which the authors equated to fearfulness, showed greater fear-potentiated startle, but not general startle, in a threat of shock paradigm, as compared to subjects with lower scores. Trait anxiety, however, was not linked to differences in either fear-potentiated or general startle responses.

In another line of work, Corr and colleagues investigated startle modulation during affective picture viewing in relation to scores on the Harm Avoidance (HA) scale of the Tridimensional Personality Questionnaire (TPQ; Cloninger, 1987). This subscale of the TPQ indexes fearfulness in terms of reported inclinations to avoid unfamiliarity, danger, and risk. Consistent with the findings of Cook et al. (1991, 1992), Corr et al. (1995, 1997) reported that subjects above the median in scores on the HA scale showed significant startle blink potentiation during viewing of unpleasant pictures compared with neutral pictures, whereas subjects low in HA failed to show this effect.

While most research on fearfulness and startle modulation has utilized adults as subjects, one study reported evidence of a similar relationship in infants. Schmidt and Fox (1998) first

assessed fearfulness at the age of 4 months in terms of positive versus negative expressive behavior in response to novel auditory and visual stimuli. Subsequently, at 9 months of age, infants classified earlier as fearful (negative response to novelty) or nonfearful (positive response to novelty) were compared in their levels of startle reactivity under two conditions: alone with mother and stranger approach. Infants in the fearful group displayed significantly greater blink reactivity than infants in the positive group only during the stranger approach test. However, the groups did not differ in startle reactivity when along with their mothers, indicating that differential startle reactivity was associated specifically with the presence of a fear-eliciting event.

To summarize, the foregoing studies provide compelling evidence that individuals high in dispositional fear show increased startle potentiation during exposure to discrete aversive stimuli or events, relative to individuals low in dispositional fear.

Traits related to anxiety and depression—Studies that have examined differences in startle modulation effects for individuals differing in traits related to anxiety or dysphoria form a more heterogeneous group, as they have used a diversity of measures to assess for anxiety and depressive tendencies. In one study, Wilson, Kumari, Gray, and Corr (2000) reported on the relationship between the trait of neuroticism and startle reactivity during viewing of fearful and disgusting film clips. Subjects were selected from the general population and divided into high versus low neuroticism groups on the basis of scores on the Neuroticism scale of the Eysenck Personality Questionnaire (EPQ; Eysenck, Eysenck, & Barrett, 1985). Subjects low in neuroticism showed greater blink reactivity during the disgusting clips than during the fearful clips, whereas subjects high in neuroticism showed comparable levels of reactivity during clips of the two types. The authors interpreted these results as indicating that subjects high on neuroticism are more watchful or cautious in situations that are perceived as fearful or threatening.

A similar study by the same authors (Kaviani et al., 2004) compared startle reactivity during viewing of unpleasant, pleasant, and neutral film clips in depressed and non-depressed subjects. Depressed subjects in this study were subdivided into low and high anxiety groups based on their scores on the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Both depressed groups showed patterns of valence-related startle modulation similar to controls. However, the high-anxious depressed group demonstrated elevated general startle reactivity relative to both the low-anxious depressed and control groups. The findings of this study parallel those of studies described earlier involving clinical patients with panic disorder, PTSD, and mild to moderate depression, in which enhanced general startle reactivity has been reported in conjunction with normal affective modulation.

Verona, Patrick, and Lang (2002) investigated the impact of the broad trait of negative emotionality (NEM) on the blink reflex in the context of a study investigating affective priming of aggressive behavior. Participants consisted of male undergraduates scoring in the highest and lowest 20th percentile on the NEM factor of the MPQ (Tellegen, in press). They were exposed to threat periods involving intermittent air blasts directed toward the larynx, and safe phases involving no aversive air blasts. Auditory probes were delivered at varying points during periods of each type (threat, safe) to assess startle reactivity. Startle reflex *potentiation* was defined as the increase in blink magnitude occurring during threat periods compared with safe periods. Startle *sensitization* was quantified as change in magnitude of blink reactivity during the testing session compared with reactivity during a pre-test startle session. The data indicated that although high and low NEM participants did not differ in startle potentiation during threat versus safe periods, high NEM participants demonstrated heightened startle sensitization during the test session as a whole compared with low NEM participants. The findings of this

study are consistent with the idea that traits related to general anxiousness and depression are associated with differences in general startle reactivity, rather than fear-potentiation.

Another study by Larson, Nitschke, and Davidson (2007) examined startle reflex modulation in participant groups pre-selected to be distinctively high on traits of anxious arousal (proneness to panic-like symptoms), anxious apprehension (future-oriented worry), or anhedonia (deficient responsiveness to pleasurable events) in relation to a control group low on all of these traits. Startle reactivity was measured during presentation of pleasant, neutral, and unpleasant pictures. The anxious arousal, anhedonic, and control groups all showed evidence of potentiated startle during viewing of unpleasant pictures relative to neutral pictures. In contrast, the anxious apprehension group showed no such effect. This result is similar to findings in Cuthbert et al.'s (2003) study, where subjects with the greatest negative affect demonstrated least fear-potentiated startle. On the other hand, the anxious apprehension group showed normal inhibition of startle (i.e., equivalent to that of controls) during viewing of pleasant versus neutral pictures, whereas the anhedonia and anxious arousal groups (relative to controls) showed weaker inhibition of startle during pleasant picture viewing. In fact, both these groups demonstrated *larger* blink reactivity for pleasant as compared to neutral stimuli, although this effect achieved statistical significance only for the anxious arousal group. While results in the anhedonia group are readily interpretable in that they are similar to effects reported for depressed subjects, those for the anxious arousal group are more puzzling. With regard to psychopathology, this latter group was most similar to those diagnosed with panic disorder. However, there are no comparable findings in the panic disorder literature; as such, the interpretation of these results is unclear at this point. Perhaps, those high on anxious arousal are prone to being startled easily by the presentation of any novel stimulus – whether positive or negative.

In other work, Hawk and Kowmas (2003) examined variations in affect-modulated startle in relation to dispositional defensive and appetitive reactivity as indexed by Carver and White's (1994) Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS) scales. The BIS-BAS systems are postulated to index inhibition and activation of movement towards goals, respectively (Gray, 1975), with the BIS showing positive associations with measures of negative affect and temperament, and the BAS showing positive relation with measures of positive affect and temperament (Carver & White, 1994). Subjects in this study were selected from the lowest and highest quartiles based on their BIS/BAS scale scores, leading to four groups: low BIS-low BAS, low BIS-high BAS, high BIS-low BAS, and high BIS-high BAS. Participants underwent a picture-startle assessment in which pleasant, neutral and unpleasant pictures served as stimuli. High and low BIS groups did not differ in degree of startle potentiation for unpleasant pictures relative to neutral pictures—but in neither case was significant potentiation observed for unpleasant scenes. The authors posited that the absence of aversive potentiation in either group, and the lack of any low- versus high-BIS group difference in this effect, could have been due to the nature of aversive stimuli used. Specifically, unpleasant scenes consisted mainly of depictions of physical injury and vicarious attack rather than depictions of direct threat to the viewer (e.g., aimed weapons, attackers), which tend to be maximally effective in eliciting defensive startle potentiation (e.g., Bernat, Patrick, Benning, & Tellegen, 2006; Levenston, Patrick, Bradley, & Lang, 2000). In contrast with this null effect for unpleasant scenes, low- and high-BIS subjects in this study differed in blink *inhibition* during viewing of pleasant scenes relative to neutral, with high-BIS subjects showing significant inhibition and low-BIS participants showing no such effect. However, the authors did not propose an explanation for this BIS group difference. With regard to BAS score groupings, high-BAS participants showed the expected pattern of valence-modulated startle reactivity whereas low-BAS participants did not. These findings are consistent with theories positing an under-reactive BAS in depressive disorders, and also with studies described earlier

that have reported diminished startle modulation for both pleasant and unpleasant stimuli relative to neutral in clinically depressed patients.

In a related study, Caseras, Fullana, Riba, Barbanoj, Aluja, and Torrubia (2006) investigated relations between affect startle modulation and individual differences in BIS reactivity as assessed by the Sensitivity to Punishment Scale (SPS; Torrubia, Avila, Molto, & Caseras, 2001). Subjects in this study consisted of individuals scoring one standard deviation above or below the mean for a larger screening pool administered the SPS. A picture-startle paradigm was used that included pleasant, neutral, and unpleasant scenes, with unpleasant scenes consisting of two types: a blood-disgust category, and a fear category consisting of "scenes of accidents and interpersonal violence." Subjects in both the low- and high-BIS groups showed startle potentiation for blood-disgust pictures compared with pleasant pictures, and inhibition of startle for pleasant pictures compared with neutral pictures. However, only subjects in the high BIS group showed significant potentiation of startle for fear pictures compared with pleasant pictures; the low BIS group showed no such effect. The two groups did not differ in general startle reactivity across stimulus conditions. The authors concluded from these findings that high BIS reactivity as indexed by elevated scores on the SPS is associated with heightened sensitivity of the amygdala to fear- and stress-inducing situations specifically. The discrepancy in results for high versus low BIS groups in this study compared with those reported by Hawk and Kowmas (2003) could reflect differences in the item content of scales used for subject selection in the two studies. In particular, the items of the SPS can be interpreted as reflecting sensitivity to discrete aversive events and situations more so, whereas the items of the Carver and White (1994) scale reflect generalized negative affect (distress) more so. Alternatively, perhaps stimulus specifity may play a role in these differences. Whereas Caseras et al. (2006) specifically attempted to distinguish scenes that were directly threatening to the viewer from those that depicted injuries to others, Hawk and Kowmas (2003) did not do so. It is conceivable that follow-up analyses of data by stimulus subsets in the latter study may have yielded differences between high- and low-BIS groups.

In contrast with results for the aforementioned studies, two studies employing variants of the picture-startle paradigm found no effect of anxiety-related personality traits on emotion-modulated startle. A study by Nitschke et al. (2002) examined the relationship between scores on a measure of anxious apprehension and modulation of the startle reflex during *anticipation* of affective pictures. Picture presentations were immediately preceded by a distinct warning cue (plus sign, minus sign, or circle) designating the valence of the upcoming picture, and startle probes were presented intermittently during warning cue periods. Anxious apprehension was measured using the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990). Participants as a whole showed a pattern of enhanced startle magnitude during both aversive and pleasant *warning periods* relative to neutral warning periods. Low and high anxious apprehension groups did not differ in this modulatory pattern, nor did groups differ in general startle reactivity (across cuing conditions). While the absence of group differences in modulatory effects may seem at odds with findings of other picture-startle studies already described, it is important to note that the observed pattern of enhanced startle for pleasant as well as unpleasant pictures (versus neutral) in this study indicates a modulatory effect of *arousal* during affective anticipation (cf. Witvliet & Vrana, 1995), as opposed to the valence-modulated startle pattern commonly observed during picture viewing.

Another study by Smith, Bradley, and Lang (2005) examined modulation of startle reactivity across time during blocked presentations of pleasant, neutral, or unpleasant pictures in an unselected undergraduate sample. Results for the sample as a whole indicated that within unpleasant picture blocks alone, startle magnitude increased across successive picture presentations. Subjects in this study completed the State-Trait Anxiety Inventory (STAI) prior to the picture-startle task. No impact of state or trait anxiety was evident for either the

aforementioned unpleasant block effect, or general startle reactivity across stimulus conditions. As with the effects reported by Nitschke et al. (2002), modulatory effects in this study may reflect substantially different mechanisms than effects in the standard picture-startle task, and thus, null effects for anxiety measures in this study are difficult to interpret in relation to findings from other work reviewed here.

Psychopathy and affiliated traits—At the other extreme of the internalizing spectrum, several investigators (e.g., Fowles, 1980; Hare, 1965; Lykken, 1995; Patrick, 1994) have posited that the classic syndrome of psychopathy (cf. Cleckley, 1976) entails a specific deficit in defensive (fear) reactivity. In particular, empirical data indicate that the core affective-interpersonal features of psychopathy—reflecting shallow affectivity, lack of remorse or empathy, and an insouciant, manipulative social style—are associated with reduced fear reactivity in laboratory task paradigms. In the dominant clinical diagnostic instrument for assessing psychopathy, the Psychopathy Checklist – Revised (PCL-R; Hare, 2003), the first factor (Factor 1) indexes the affective-interpersonal component of the disorder. In the best-validated self-report measure of psychopathy, the Psychopathic Personality Inventory (PPI; Lilienfeld & Andrews, 1996), it is again the first factor (PPI-I; reflecting traits of stress immunity, social potency, and fearlessness) that indexes this affective-interpersonal component (Benning, Patrick, Hicks, Blonigen, & Krueger, 2003; Blonigen, Hicks, Patrick, Krueger, Iacono, & McGue, 2005). Scores on both PCL-R Factor 1 and PPI-I show negative associations with trait measures of fear and negative affectivity (Hicks & Patrick, 2006; Patrick, 1994; Benning, Patrick, & Iacono, 2005), and positive associations with measures of interpersonal dominance (Harpur, Hare, & Hakstian, 1989; Verona, Patrick, & Joiner, 2001; Benning et al., 2003). PPI-I also shows positive correlations with sensation seeking (in particular, its thrill-adventure seeking facet; Benning et al., 2005).

Studies employing the affective-picture paradigm have consistently shown that elevations on the first factor of each of these instruments predict an absence of startle potentiation during viewing of unpleasant pictures relative to neutral pictures (e.g., Patrick, Bradley, & Lang, 1993; Vanman, Mejia, Dawson, Schell, & Raine, 2003; Benning et al., 2005; for a review, see Patrick & Bernat, in press). High scores on this factor of psychopathy also predict diminished startle reflex potentiation during anticipation of a physical stressor (Patrick, 1994). Data from studies of psychopathy in childhood and adolescence also point to deficient fear reactivity in young individuals exhibiting high levels of callous-unemotional traits—the counterpart to Factor 1 in youth (Frick & White, 2008; Marsh, Finger, Mitchell, Reid, Sims, Kosson, et al., 2008).

Similar results have been reported for personality traits associated with psychopathy, such as sensation seeking—a construct that reflects inclinations to attain stimulation through pursuit of novelty or risk (Zuckerman, 1979). While the construct of sensation seeking differs markedly from the construct of dispositional fear (Hicks & Patrick, 2006; Vaidyanathan, Patrick, & Bernat, 2009; Zuckerman, 1979), the facet of sensation seeking that entails tolerance for danger represents an intersection between the two (Kramer, Patrick, Bayevsky, & Krueger, 2009). This facet is indexed by the Thrill and Adventure Seeking subscale of Zuckerman's (1979) well-known Sensation Seeking Scale. There is evidence that scores on this component of sensation seeking, in parallel with scores on the affective-interpersonal factor of psychopathy, are associated with diminished fear reactivity as indexed by aversive startle potentiation (Benning et al., 2005).

In an initial study, Lissek and Powers (2003) examined variations in picture-startle modulation as a function of scores on the Sensation Seeking Scale (SSS-V; Zuckerman, 1994) and the State-Trait Anxiety Inventory (STAI). Subjects were selected on the basis of their overall scores on the SSS, and their scores on the Thrill and Adventure Seeking subscale (SSS-TAS) in

particular—posited by Zuckerman (1979) to reflect proneness to negative activation in the face of physical danger. Consistent with this, SSS-TAS scores have been shown to predict differences in reactivity to threatening stimuli in prior work (Franken, Gibson, & Rowland, 1992). The task procedure used by Lissek and Powers (2003) was a standard affective-picture task. Unpleasant pictures were limited to depictions of aimed weapons and attacking animals in order to aversive maximize potentiation effects. Subjects with high scores on the SSS as a whole and its SSS-TAS subscale showed negligible potentiation of startle for threatening pictures relative to neutral pictures, whereas subjects low in sensation seeking showed highly significant potentiation. No group difference in blink modulation was evident for pleasant pictures in relation to neutral. Notably, the high and low SSS/SSS-TAS groups did not differ in STAI scores, indicating that effects on aversive startle potentiation were unrelated to general negative affectivity/anxiousness. Parallel results were obtained in a follow-up study (Lissek, Baas, Pine, Orme, Dvir, Rosenberger, & Grillon, 2005) that examined startle reflex potentiation during anticipation of predictable and unpredictable aversive noise stimuli.

Summary and integration—Available data indicate that the core affective-interpersonal features of psychopathy are associated with a lack of startle reflex potentiation during aversive picture viewing that reflects an underlying weakness in defensive (fear) reactivity. This result for psychopathy appears opposite to the finding of enhanced startle potentiation in individuals scoring high on fear-relevant personality measures such as the FSS and the Harm Avoidance scale of the TPQ. These reciprocal effects point to the possibility that fear-potentiated startle may function as a physiological indicator of a broad bipolar dispositional continuum of fear/fearlessness. In support of this, a recent structural modeling investigation by Kramer et al. (2009) reported evidence of a coherent dimension (labeled Trait Fear) underlying varying self-report inventories of fear and psychopathy/fearlessness. Positive indicators of this trait fear dimension included the FSS, the subscales of the TPQ Harm Avoidance Scale, and the Fearfulness subscale of the EAS Temperament Inventory (Buss & Plomin, 1984); negative indicators included the three subscales of PPI Factor 1 and the Thrill-Adventure Seeking subscale of the SSS. As described in the final “Implications” section below, a recently published follow-up study (Vaidyanathan, Patrick, & Bernat, 2009) demonstrated a positive monotonic relationship between scores on the broad trait fear dimension reflecting the intersection of these differing scales and magnitude of fear-potentiated startle during affective picture viewing.

In contrast with these effects for measures of dispositional fear and fearlessness, scales indexing general distress/neuroticism and anhedonia do not show reliable associations with affect-modulated startle. Instead, higher scores on measures of this type tend to be associated with heightened general startle reactivity (i.e., across varying stimulus conditions) or tonic elevations in reactivity within contexts of uncertainty or threat. As discussed further below, these differing results for fear- versus distress-related traits parallel findings for fear versus distress disorders. In turn, both sets of findings can be referenced to neuroscientific data that point to distinctive brain systems underlying phasic fear and tonic anxiety. It must however be noted that only a few of the studies discussed in the foregoing section have assessed for both psychopathology and personality traits in relation to startle reactivity within the same participant sample. As reviewed in earlier sections, since the presence of comorbid psychopathology such as depression or PTSD can affect various parameters of startle reactivity, future studies that focus on characterizing subjects in a sample in terms of a broader array of diagnostic and trait variables will prove most beneficial in advancing understanding of the interplay of these various measures.

Implications and Directions for Future Research

This review of findings from studies using the affect-modulated startle paradigm was undertaken with the overarching aim of illustrating how research on the structure of psychopathologic syndromes and research on the neurobiological correlates of such disorders (and personality constructs with which they are affiliated) can inform one another. In this concluding section, we discuss findings reviewed in the foregoing sections in relation to three specific points tied to this overarching aim. First, we consider how hierarchical-dimensional models of psychopathology derived from symptom data and of affiliated personality constructs derived from self-report data can be valuable in interpreting findings from neurobiological studies of particular mental disorders. Second, we consider how findings from neurobiological studies and psychopathology can feed back into conceptualizations of mental disorders and their interrelations. Finally, emerging from these considerations, we discuss a targeted approach to research that can serve as a vehicle for systematically tightening linkages between structural models of psychopathology and neurobiologically based dimensions of human variation.

Interpreting Findings from Affect-Startle Studies of Internalizing Disorders in Relation to Hierarchical-Dimensional Models

As a whole, the findings of published research on startle reactivity in relation to anxiety and mood disorders and affliliated traits exhibit a pattern that parallels the structural organization of internalizing psychopathology. Disorders marked by cue-specific fear (specific and social phobia) tend to be associated with one parameter of startle reactivity (potentiation of startle during exposure to aversive stimuli) whereas disorders marked by diffuse negative affectivity or distress tend to be associated with others (heightened general reactivity or increased context-potentiated startle, and possibly, decreased fear-potentiated startle). Trait variables reflecting fear/fearlessness and general negative affectivity or neuroticism likewise appear to be associated with differing parameters of startle reactivity. Tables 1, 2, and 3, list the various studies covered in this review and provide key information for each study including the type of startle paradigm used, sample characteristics, diagnostic measures that were utilized, comorbid conditions (where available), medication use (if noted), and chief results. For ease of reading, we have endeavored to organize these tables in parallel with the text as much as possible. Table 1 focuses on studies investigating startle reactivity in all internalizing disorders with the exception of PTSD. This latter disorder is covered separately in Table 2 due to the large number of studies on this topic. Table 3 summarizes studies that examined startle reactivity in relation to personality traits and psychopathic personality. In the following section, we summarize results from these various studies and consider the conceptual distinction between cue-specific fear reactivity and diffuse distress as individual difference variables—followed by a discussion of their differential neurobiological underpinnings.

Trait fear and fearlessness: phobic disorders and psychopathy—Our review of the literature indicates that subjects with phobic disorders exhibit an augmented fear-potentiated startle response during exposure to aversive stimuli, compared with controls. Conversely, decreased fear-potentiated startle has been found to be characteristic of psychopathic subjects, especially those exhibiting high levels of the core affective-interpersonal features of the disorder (cf. Patrick, 1994; Patrick et al., 1993). Studies investigating relations between affect-modulated startle and personality traits such as fearfulness and sensation-seeking have yielded congruent findings. This pattern of results, evident in both the personality and psychopathology domains, suggests that the magnitude of fear-potentiated startle systematically covaries with individual differences in dispositional fear and fearlessness, reflecting heightened or deficient fear reactivity, respectively, in response to discrete aversive cues.

Such findings point to the existence of a bipolar dimension of fear/fearlessness, spanning the domains of phobic disorders and psychopathy, that is associated with variations in fear-potentiated startle. A recent study by Vaidyanathan et al. (2009) directly evaluated this hypothesis by investigating the relationship between an omnibus psychometric dimension of fear/fearlessness labeled *Trait Fear* and startle reflex modulation in an undergraduate sample. Trait Fear scores were calculated as scores on the first component from a principal components analysis of differing scale measures of fearlessness and fearfulness, most of which have previously been linked to variations in fear-potentiated startle. Scale measures included the FSS, TPQ-Harm Avoidance Subscale, PPI-Stress Immunity, PPI-Fearlessness, PPI-Social Potency, and SSS-Thrill and Adventure Seeking Scale, along with the Fearfulness scale of the EAS Temperament Inventory (Buss & Plomin, 1984). Analyses revealed a robust linear association between Trait Fear scores and degree of startle reflex potentiation during viewing of aversive pictures—in particular, pictures depicting scenes of direct threat or attack that most reliably potentiate the startle reflex (Bradley et al., 2001; Levenston et al., 2000). These findings provide direct empirical support for the idea that fear-potentiated startle represents a physiological indicator of dispositional differences in reactivity of the brain's basic defensive (fear) system—with fear and fearlessness scales serving as indicators of this dispositional dimension in the domain of self-report.

Variations in reactivity of the brain's defensive motivational system in turn have been posited to underlie vulnerability to internalizing disorders in both the adult and child literatures. For example, Buss and Plomin (1984) theorized that fear was one of the earliest facets of negative emotionality to emerge among infants. Likewise, Kagan (1994) hypothesized that timidity in novel situations in children was a risk factor for future anxiety-related problems. Adult counterparts of such theories have postulated that a broad trait continuum of negative affectivity underlies vulnerability to internalizing disorders in general, with low positive affect as a specific substrate for depressive disorders (Clark & Watson, 1991; Mineka et al., 1998). Watson (2005) expanded on this conceptualization by identifying anxious *hyperarousal* as a specific characteristic of the fear disorders. Relatedly, Sellbom, Ben-Porath, and Bagby (2008) reported high levels of *negative activation* to be more characteristic of fear disorders than distress disorders. At the other end of the dispositional fear continuum, studies by Hicks and Patrick (2006) and Blonigen et al. (2005) have established that individuals scoring high on the affective-interpersonal features of psychopathy show immunity to internalizing disorders. Given that fear-potentiated startle is closely tied to this dimension of fear reactivity, such research implies that this physiological response measure might prove effective as a marker of underlying biological vulnerability to internalizing psychopathology.

Generalized negative affect and anhedonia in distress disorders—In contrast with individuals exhibiting specific or social phobia, subjects diagnosed with PTSD or panic disorder demonstrate heightened startle reactivity under conditions of prolonged stress or uncertainty, and in some studies, enhanced general startle reactivity, relative to controls. On the other hand, compared with controls, individuals diagnosed with depression show deficits in startle modulation during processing of both pleasant and unpleasant stimuli, with severely depressed patients in some research showing atypical potentiation of startle during pleasant relative to neutral stimuli. Findings from studies examining these parameters of startle in relation to personality constructs indexing general negative affectivity or depression have generally yielded parallel results.

This pattern of results for distress disorders becomes readily interpretable when viewed through the lens of Krueger's (1999) and Watson's (2005) research on hierarchical models of internalizing psychopathology. In particular, startle findings for these disorders suggest that whereas high levels of general anxiousness or NA are associated with diffuse activation of the brain's defensive system, not tied to particular cues, states of demoralization or anhedonia are

associated with decreased modulatory effects for both pleasant and aversive cues. The transition from this exaggerated general startle reactivity pattern to apparent blunting of both positive and negative emotional reactivity could be interpreted as reflecting the phenomenon of learned helplessness (Seligman, 1975). Specifically, the constant worry and hypervigilance experienced by anxious individuals may in time lead to the hopelessness seen in depression, which may manifest as decreased emotional responsiveness (i.e., valence-modulated startle in this case) to any stimulus, whether positive or negative. As a whole, startle research findings in the current review are congruent with this perspective in showing enhanced general or context-potentiated blink reactivity in disorders of this type, along with decreased fear-potentiated startle, as greater negative affectivity or severity of depression is observed (e.g., Cuthbert et al., 2003; Lang et al.; 2007, Forbes et al., 2005; Grillon et al., in press). Along similar lines, Mineka et al. (1998) reported evidence that depression tends to be preceded by anxiety, and that disorders such as PTSD, OCD, and panic disorder with agoraphobia, that entail more chronic negative affect and feelings of helplessness, show greater comorbidity with depression.

How Knowledge of Underlying Neurobiological Systems can Inform Structural Models of Psychopathology

While patterns of results for parameters such as aversive potentiation and general startle reactivity are broadly consistent with the notion of distinct subgroups of fear versus distress disorders within the internalizing spectrum, some notable divergences in results are evident for particular disorders within one or the other subgroup. For example, panic disorder and OCD fall within the category of fear disorders according to models based on diagnostic data (e.g., Krueger, 1999; Watson, 2005), but startle research on these disorders has generally yielded a pattern of results more characteristic of distress disorders (i.e., enhanced general startle reactivity but not aversive potentiation). In this section, we discuss how patterns of startle results for fear versus distress disorders can be interpreted in relation to what is known about brain systems underlying differing parameters of startle reactivity. We then discuss how discrepant findings for particular disorders can help to inspire refinements in the conceptualization and positioning of these disorders within structural models.

Linking findings of startle studies of internalizing psychopathology to underlying brain systems—

Diverging relations of phobic disorders and distress disorders with differing parameters of startle reactivity can be interpreted in terms of what is known about subdivisions of the brain's defensive motivational system. Davis and colleagues (1997, 1998) presented evidence for the existence of two distinct neural systems contributing to effects of negative emotional activation on startle – one based in the central nucleus of the amygdala (CeA) and the other in the bed nucleus of the stria terminalis (BNST) – with the first of these more important for fear-potentiated startle, and the latter more important for general or context-potentiated startle reactivity. These investigators posited that these systems play differing roles in fear and anxiety states – with the CeA more important for cue-specific fear, and the BNST more important for non-specific anxiety states.

Considering this evidence from basic neuroscience studies in conjunction with aforementioned results from startle studies of internalizing disorders, it would appear that the CeA subsystem is more important for deviations in reactivity evident in the “fear” disorders, whereas the BNST is more important for deviations observed in the “anxious-misery” disorders, including PTSD and depression (Grillon, 2008). Interestingly, at the very highest levels of distress and dysphoria seen in depression, modulatory pathways for aversive startle potentiation (originating from the CeA) and inhibition of startle by pleasant stimuli (arising from the nucleus accumbens; Koch et al., 1996) appear to be inhibited or suppressed. One possibility is that the BNST subsystem may play a role in this—as evidenced by research demonstrating deficient modulation of startle

during affective cuing in patients with depression, despite generally enhanced general startle reactivity (cf. Cuthbert et al. 2003). However, as other studies (e.g., Allen et al., 1999; Dichter et al., 2004; Forbes et al., 2005, etc.) have not yielded evidence of this increased general reactivity in depression, further research is required to elucidate conditions under which this effect is manifested.

An additional point to note when considering the neurobiology of the startle reflex is that, somewhat surprisingly, medication use did not appear to moderate startle reactivity in many of the studies covered in this review (see Tables 1, 2, and 3). Admittedly, not all studies assessed for medication use, and of those that did, only some attempted to control for effects of medication in some systematic way (e.g., excluding subjects on medication, comparing startle reactivity in medicated versus unmedicated subjects, etc.). However, out of this latter pool of studies, contrary to expectations, most authors reported that medication use did not affect results in any way. These results are similar to those found in Pole's (2007) meta-analysis of PTSD studies, where medication did not moderate psychophysiological effects. It also stands in direct contrast with prior pharmacological studies that have reported effects of anxiolytic medication effects on both fear-potentiated startle and general startle (e.g., Grillon, Levenson, & Pine, 2004; Patrick, Berthot, & Moore, 1996;Quednow, Kuhn, Stelzenmuelle, Hoenig, Maier, & Wagner, 2004). Again, it must be borne in mind that these results are based on a somewhat a biased sample of studies. Nonetheless, if these results prove to hold up in future studies, this could imply that psychopathological states exert greater effects on an individual than medications do.

Implications for the structure of internalizing psychopathology—The findings of the current review have important implications for hierarchical conceptualizations of anxiety and mood disorders. Whereas models based on symptom data have consistently identified specific and social phobias as cohering together in one subgroup, and depression and GAD as cohering closely together in another, these models are less clear as to where other disorders such as OCD or PTSD fall (Watson, 2005). Additionally, while panic disorder has been shown to associate closer with fear disorders than distress disorders, startle research with panic disorder patients has generally yielded results more similar to findings for distress disorders. The unexpected startle results for these disorders, coupled with reports of subtypes exhibiting differing startle response patterns (e.g., Melzig et al., 2007), point to a need to conceptualize these disorders in alternative terms in order to achieve closer convergence with neurobiological data. The following three subsections consider how panic disorder, OCD, and PTSD might be reconceptualized along these lines.

I. Panic disorder—A crucial question emerging out of the current review is why panic disorder, which has been classified as a fear disorder in hierarchical models of internalizing psychopathology, demonstrates a pattern of startle response findings more characteristic of the distress disorders than the fear disorders. Part of the answer may lie in systematic differences between individuals diagnosed with panic in community samples that have served as the basis for structural modeling studies compared with clinic patient samples on which startle research studies have focused. Structural modeling studies that have included panic disorder with the fear disorders have all used large-scale epidemiological samples (Krueger, 1999; Vollebergh, Iedema, Bijl, de Graaf, Smit, & Ormel, 2005; Slade & Watson, 2006), while studies reporting enhanced startle reactivity in participants diagnosed with panic disorder employed patient populations alone (e.g, Melzig et al., 2007; Cuthbert et al., 2003; Lang et al. 2007; Grillon et al., 2008).

Given these differences in sample composition, one possible explanation for variations in results across physiological studies and structural modeling studies of panic disorder might be that cases of “pure” panic disorder (i.e., without accompanying depression, dysphoria, or GAD)

are more common in the general population than in treatment-seeking clinic samples. For example, in Krueger's (1999) study, out of a sample of 8098, only a small subset of participants (N = 251) were seeing mental health professionals at the time of the survey were considered clinical cases. Consistent with the hypothesis that clinical cases of panic disorder patients tend to exhibit greater comorbidity, within the smaller clinical sample of this study, a two-factor model specifying broad internalizing and externalizing factors, with no division of internalizing into fear and anxious-misery subfactors, emerged as the best-fitting model—indicating greater overlap between fear- and distress-related disorders in individuals who seek treatment as a function of more severe and pervasive internalizing problems. This is in contrast to the three-factor model that specifies a distinction between the fear and anxious-misery syndromes for the full sample.

These data point to a need to distinguish diagnostically between cases of “pure” panic disorder akin to phobic disorders and more severe cases of panic that intersect with distress syndromes. A recent study by Melzig et al. (2007) provided evidence that this distinction is biologically meaningful. In this study, subjects diagnosed with both panic disorder *and* comorbid depression (i.e., those exhibiting the “distress” variant of panic) showed *reduced* potentiation of startle during exposure to aversive stimuli relative to controls, whereas panic patients without comorbid depression (i.e., those exhibiting the “fear” variant of panic) disorder showed *increased* potentiation relative to controls. As noted below in relation to PTSD, a crucial issue to consider in differentiating fear versus distress variants of conditions like panic disorder is the issue of severity of emergent neurobiological dysregulation. In this regard, for example, Rosen and Schulkin (1998) posited that high levels of generalized distress (“pathological anxiety”) reflect an underlying biological vulnerability (e.g., high dispositional fear; low capacity for positive affect) in conjunction with exposure to intense or prolonged environmental stressors that promulgate sensitization and poorly regulated functioning of brain systems.

II. OCD—A second disorder that has eluded classification in hierarchical models is OCD. While Watson (2005) reported some tentative evidence that OCD is more associated with disorders in the fear subgroup, findings from other research (Sellbom et al., 2008; Watson, de Graaf, Nolen, & Vollebergh, 2005) indicate that OCD is not distinctively associated with either fear or distress disorders. Further, findings from two published studies that have examined affect-startle modulation in relation to OCD show enhanced general startle reactivity for OCD patients relative to controls, without significant differences in affective modulation—paralleling results for distress disorders. Notably, however, participants in one of these studies (Kumari et al., 2001) were recruited from a psychiatric inpatient facility, and those in the other (Buhlman et al., 2007) exhibited varying comorbid disorders in conjunction with OCD. Hence, as discussed for panic disorder, it is conceivable that participants in each of these studies consisted of OCD with pervasive internalizing psychopathology, entailing sensitization of broader affective circuitry in the brain and attendant dysregulation.

III. PTSD—Another disorder that poses a challenge for hierarchical classification systems is PTSD. As a whole, data from startle research studies of PTSD indicate effects more similar to those for general distress disorders than for fear disorders or major depressive disorder. Indeed, three prior summaries of research in this area (Metzger et al., 1999; Grillon and Baas, 2003; Pole, 2007) have concluded that PTSD is associated with generally exaggerated startle reactivity. However, in contrast with studies of phobic disorders that have for the most part employed the affective-picture startle paradigm, research on PTSD has generally focused on startle reactivity in other contexts—e.g., aversive cues (e.g., Grillon et al., 1998b; Jovanovic, Norrholm, Fennell, et al., 2009), or conditions of darkness (e.g., Grillon et al., 1998a), or exposure to noise probes alone (e.g., Shalev et al., 1992, 1997; Orr et al., 1995). It is unclear whether the affective states evoked by these differing task procedures are comparable. For

example, the state of heightened defensive reactivity elicited by an aversive picture (cf. Lang, Bradley, & Cuthbert, 1990) may differ meaningfully from 'fear' states evoked by threat of shock or mental imagery of feared situations. Hence, results from startle studies of PTSD may not be directly comparable to findings from startle studies of other internalizing disorders. To address this issue, it will be important in future research to systematically evaluate general reactivity differences and modulatory effects on startle for disorders such as PTSD in varying task contexts, including shock threat, picture viewing, and image processing.

A further important point with regard to the classification of PTSD is that the criteria for PTSD include symptoms such as strong emotional reactivity to and avoidance of specific feared situations that are characteristic of fear disorders, along with symptoms such as general hypervigilance and emotional numbing that are more characteristic of distress disorders (Cox et al., 2002; Watson, 2005). However, as noted by Watson (2005), PTSD showed relatively weak convergence with the other distress disorders (i.e., PTSD symptoms loaded only .39 on the distress subfactor of internalizing, compared with loadings of .64 to .83 for other disorders such as GAD and major depression) in this study. As a means of reconciling these contrasting findings, and accommodating the diversity and heterogeneity of diagnostic criteria for this disorder, Watson (2005) proposed a theoretical bifurcation of PTSD into fear and distress variants. There is some preliminary evidence suggesting that such subtyping may prove useful. Specifically, Jovanovic, Norrholm, Fennell, et al. (2009) demonstrated that subjects with PTSD, in contrast with controls, showed a lack of fear inhibition even under safe conditions; this effect, however, was related only to the re-experiencing and avoidance symptoms of PTSD, and *not* the hyperarousal symptoms. Thus, as discussed in relation to panic disorder and OCD, subtyping PTSD along these lines is likely to be helpful in clarifying its relations with neurobiological systems/measures.

Distinguishing between underlying vulnerability and manifest pathology—A crucial issue to consider in conceptualizing anxiety and mood disorders in dimensional terms, and establishing linkages between dimensional models of this kind and underlying neurobiological systems/processes, is the distinction between underlying vulnerability and manifest disturbance. With regard to this issue, Rosen and Schulkin (1998) formulated a model of the etiology of PTSD in which above average levels of fear responsiveness can give rise to pathological anxiety conditions through the moderating impact of intense or recurrent stressors. The mechanism for this progression is sensitization of the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST) subsystems through repeated stimulation, leading to hyperexcitability (dysregulated responsivity) of these subsystems. This neural hyperexcitability is manifested clinically in the form of symptoms like hypervigilance and pervasive distress that characterize pathological anxiety conditions such as PTSD.

From this perspective, individual differences in dispositional fear constitute an underlying *vulnerability* factor for internalizing psychopathology. However, this vulnerability does not necessarily lead to pathological anxiety/distress unless the at-risk individual is exposed to intense or recurrent traumatic events that sensitize the extended defensive system and cause it to respond in a dysregulated fashion. Following from Rosen and Schulkin (1998) and recent empirical work by Vaidyanathan et al. (2009), we propose that variations in fear-potentiated startle index a continuum of *normal-range* defensive reactivity, from low to high, that in turn reflects varying degrees of vulnerability to pathology arising from stress exposure. Further, we hypothesize that the transition from enhanced potentiation of startle in relation to discrete aversive cues to pervasive enhancement of the startle response across cuing contexts is symptomatic of a shift from a normatively functioning defensive system to a dysregulated defensive system.

Internalizing disorders of varying types can be seen as falling at differing points along the range from normative responsiveness of the defensive system to pathological dysregulation of this system (cf. Lang, 1988). For example, specific phobias can be viewed as falling near the point of transition between normative responsiveness and pathological sensitization of fear circuits. The targets for these phobias consist of stimuli that most people find at least somewhat aversive (e.g., snakes, spiders, blood/injury, heights, enclosed places), and individuals with phobias show exaggerated fear (enhanced startle potentiation) to these discrete stimuli. Similarly, some amount of social anxiety is normative, and social phobia represents an accentuation of this normal fear in relation to performance situations. In contrast, disorders like GAD and major depression entail symptoms such as pervasive anxiousness, worry, and dysphoria that are not tied to specific eliciting stimuli. The symptom profile of these disorders fits with the concept of broad defense-system sensitization posited by Rosen and Schulkin (1998)—with depression in its most severe form entailing a shift from hyperexcitability to an inhibitory physiologic mode (Cuthbert et al., 2003; Seligman, 1975). As noted in preceding subsections, recent empirical findings point to distinct variants of panic, OCD, and PTSD. One of the variants in each case can be conceptualized as a less pathologic, cue-modulated ("fear") variant, and the other as a more pathologic, dysregulated ("distress") variant.

From this perspective, some neurophysiological measures are likely to be informative as indicators of *dispositional vulnerability* (i.e., reflecting normative variations in the functioning of basic brain systems) whereas others are likely to be informative as indicators of emergent *pathology* (i.e., reflecting dysregulated responding of basic brain systems). The current review highlights the possibility that differing parameters of the startle reflex response (fear potentiation, general startle reactivity or context potentiation) might be distinctly informative in these ways. Systematic prospective research (e.g., Karl et al., 2004; Guthrie & Bryant, 2005; Pole et al., 2009) would be required to effectively evaluate this possibility. Our review also highlights how findings for these differing parameters of startle can feed back into conceptualizations of the structure of internalizing disorders. The final section below discusses a more general research strategy for improving linkages between constructs in the realms of psychopathology and neurobiology.

Tightening Linkages Between Phenotypic Conceptualizations of Psychopathology and Underlying Neurobiological Systems: A Systematic Methodological Strategy

Prominent researchers in the mental health field have called for conceptions of mental disorders to be informed by neurobiological data, rather than clinical judgments alone (e.g., Hyman, 2007; Insel & Scolnick, 2006). The current review, which integrates findings from the psychophysiological literature with recent hierarchical conceptualizations of anxiety and mood disorders, represents a valuable step in this direction. Though not all studies fit perfectly in the framework that we have advocated, our review broadly suggests that differing parameters of startle reactivity are indicative of distinct neurobiological processes with differing relevance to fear versus distress subfactors of internalizing psychopathology. However, future work is clearly needed to clarify this line of research (e.g., startle reactivity to threat of shock in subjects with phobias, or alternatively, affect-modulated startle paradigms in subjects with PTSD). Furthermore, given the sheer volume of literature on internalizing disorders and practical constraints of space, we focused on one psychophysiological measure in particular in the current review. Integrating these findings with other psychophysiological measures from other reviews such as those by Pole (2007), Heller and Nitschke (1998), Olvet and Hajcak (2008), and Whalen, Shin, Somerville, McLean, and Kim (2002), will be crucial in gaining a systemic understanding of pathophysiology of internalizing problems. Likewise, additional reviews are also needed that summarize findings for other established physiological response measures in relation to families of externalizing, and psychotic disorders. Reviews of this kind will be

important for identifying candidate indicators of underlying vulnerability and manifest expression of disorders of these kinds.

Beyond this, we advocate a research focus on *neurobehavioral trait* constructs – i.e., traits that have both biological and behavioral referents – as opposed to exclusive reliance on traditional conceptualizations of mental disorders that are solely informed by clinical judgment or self-report. For example, a key point arising from the current review is the existence of distinct, albeit correlated constructs of cue-specific defensive reactivity (fear) and dysregulated defensive activation (distress). Further research is required to distinguish these phenomena from one another, both phenotypically and neurobiologically. As an example of this, recent published work on the dimensional construct of Trait Fear (Vaidyanathan et al., 2009) provides a phenotypic operationalization of individual differences in cue-specific defensive reactivity. Specifically, the self-report dimension of *Trait Fear* represents a *psychometric* operationalization of the neurobehavioral construct of fear that covaries with an established physiological indicator of fear (i.e., aversive potentiation of the startle reflex). In turn, the physiological indicator (startle potentiation) provides a candidate marker of vulnerability to internalizing psychopathology. Future research could focus on similar neurobehavioral operationalizations of trait anxiety, more akin to the general negative activation or distress that is prominent in several of the internalizing disorders (Watson, 2005). Systematic analysis of relations among various physiological indicators obtained from such analyses will contribute to understanding of neurobiological systems/processes underlying the phenotypic constructs to which these indicators are tied (Patrick & Bernat, in press).

Using this methodological approach, findings from psychometric and neurobiological domains can directly inform one another, and thereby enhance convergence and intersection between these two domains. This line of scientific inquiry is particularly advantageous in that it accommodates the phenomenon of diagnostic comorbidity among mental health disorders, clarifies our understanding of the biological processes involved in psychopathology, and is able to efficiently incorporate findings from psychometric and neurobiological domains in a unified framework. Such a strategy is likely to advance scientific efforts to understand, ameliorate, and prevent mental health problems.

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Table 1

Summary of studies examining affect-modulated startle reactivity in various internalizing disorders except PTSD.

Category	Study	Experimental Paradigm	Diagnostic Instrument	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
Phobias	Vrana et al. (1992)	Startle during imagery; pre- and post-treatment assessments	DSM-IIIR	2 SP	None noted	A	Reduced FPS after treatment
	de Jong et al. (1991)	Startle during live exposure; pre- and post-treatment assessments	Spider Questionnaire	41 SP	None noted	A	Reduced FPS after treatment
	de Jong et al. (1996)	Startle during live exposure; pre- and post-treatment assessments	DSM-IV	20 SP	None noted	A	Reduced FPS after treatment
	Hamm et al. (1997)	Affective-picture startle paradigm	Snake, Spider, and Mutilation Questionnaire	48 SP 16 controls	None noted	A	FPS for phobic scenes: SP > Controls
	Globisch et al. (1999)	Affective-picture startle paradigm	Snake and Spider Questionnaire	38 SP; 48 controls	None noted	A	FPS for phobic scenes: SP > Controls
	McTeague et al. (2009)	Startle during imagery	ADIS-IV	75 SO; 75 controls	25 circumscribed SO; 50 generalized SO; 27 generalized SO with mood disorder; 4 circumscribed SO with mood disorder	D	- General startle reactivity greater for all patients than controls - Generalized SO group showed potentiation across all scenes - However, generalized SO and MD showed potentiation only for personalized fear scenes - Medication use had no effect on results
	de Jong et al. (1993)	Startle during live exposure; pre- and post-treatment assessments	Spider Questionnaire	37 SP	None noted	A	SP did not show valence-modulated startle
	Merckelbach et al. (1995)	Startle during backward-masked 30 ms slides	DSM-IIIR	17 SP; 12 controls	None noted	A	No differences in FPS between groups
Panic Disorder with or without Agoraphobia	Melzig et al. (2007)	Startle under adaptation, threat of shock, darkness and safe conditions	ADIS-IV	26 outpatients with PD; 22 controls	17 AGO; 11 MD; 3 SP; 1 SO; 1 somatoform	D	- PD with MD did not show threat-potentiated startle while PD alone did - Trend toward greater startle in PD alone than controls ($p = .08$) - PD using SSRIs showed greater startle during adaptation than all other subjects
	Cuthbert et al. (2003)	Startle during imagery	ADIS-R	28 SP; 30 SO; 26 PD w/ AGO; 22 PTSD; 24 controls; 3 past BP	26% SO; 17% SP; 27% GAD; comorbid mood disorder (MD or DYS) lowest for SP (11%) and highest for PD (42%) and PTSD (55%)	D	- Startle potentiation in SP, SO and controls, but not in PD - PD trend toward larger general startle (startle during inter-trial intervals) than SP, SO and controls

Category	Study	Experimental Paradigm	Diagnostic Instrument	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
							- Medication use had no effect on results
	Lang et al. (2007)	Startle during imagery	ADIS-IV	30 SP; 36 SO; 27 PD w/ AGO; 26 GAD; 40 controls	52% MD	D	- FPS: SP > SO > PD w/ AGO > GAD - Trait anxiety inversely related to FPS - Medication use had no effect on results
	Grillon et al. (2008)	Startle during anticipation of aversive stimuli	SCID-I	24 PD; 24 controls	5 SO; MD excluded	B	PD patients showed greater startle reactivity to intertrial interval probes in unpredictable aversive condition than neutral condition; Controls showed no such effect
	Grillon et al. (1994)	Startle during threat of shock	ADIS-R	34 PD; 49 controls	5 PD w/o AGO; 26 PD w/ AGO; 1 SO; 2 GAD	A	Younger patients (< 40 y.o.) with PD showed larger startle during threat periods; Older patients did not
Depression	Allen et al. (1999)	Affect-picture startle	SCID-R	14 inpatient with current MD; 14 nondepressed	Details not noted though article mentions subjects had other diagnoses	C	- General startle reactivity for MD less than controls - Severely MD subjects showed startle potentiation during pleasant pictures
	Dichter et al. (2004)	Affect-picture startle; assessed effect of Bupropion on startle	DSM-IV and Hamilton Rating Scale for Depression	14 outpatient MD; 16 nondepressed	3 with some anxiety disorder	D	- Valence-modulated startle absent in MD - Medication use had no effect on results
	Forbes et al. (2005)	Affect-picture startle	A variety of instruments using DSM-III, DSM-III-R, or DSM-IV criteria	38 MD; 38 BP; both groups had childhood-onset depression; 60 controls	68.4% (76.3% MD) with lifetime history of anxiety disorder, and 12.3% (5.6% MD) with ASPD	D	- MD showed blink inhibition during pleasant scenes relative to neutral, and no potentiation for unpleasant versus neutral scenes - Lack of startle modulation associated with history of repeated depressive episodes - Medication use had no effect on results
	Kaviani et al. (2004)	Affect-movie clips startle	DSM-IV	22 inpatients with MD; 22 controls	None noted	C	- Controls and low MD showed valence-modulated startle; high MD did not - Effect related to anhedonia scores
	Cuthbert et al. (2003)	Startle during imagery	ADIS-R	28 SP; 30 SO; 26 PD w/ AGO; 22	26% SO; 17% SP; 27% GAD; comorbid mood disorder (MD or DYS)	D	- No differences in FPS for subjects with and without comorbid MD

Category	Study	Experimental Paradigm	Diagnostic Instrument	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
				PTSD; 24 controls	lowest for SP (11%) and highest for PD (42%) and PTSD (55%)		- However, greater general startle (startle during inter-trial intervals) for comorbid MD than without - Medication use had no effect on results
	Lang et al. (2007)	Startle during imagery	ADIS-IV	30 SP; 36 SO; 27 PD w/ AGO; 26 GAD; 40 controls	52% MD	D	- FPS in those with comorbid MD less than those without comorbid MD - Medication use had no effect on results
Other anxiety disorders	Kumari et al. (2001)	Affect-movie clips startle	DSM-IV	10 inpatient OCD; 10 controls	None noted	C	Increased general startle reactivity in OCD
	Buhlman et al. (2007)	Startle probe alone	SCID	20 outpatient OCD; 21 controls	4 SO; 3 body dysmorphic disorder; 2 MD; 2 DYS; 2 SP; 1 GAD; 1 PD w/ AGO; 1 trichotillomania	D	- Trend toward higher general startle reactivity in OCD ($p = .07$) - Unmedicated participants did *not* differ from controls
	Lang et al. (2007)	Startle during imagery	ADIS-IV	30 SP; 36 SO; 27 PD w/ AGO; 26 GAD; 40 controls	52% MD	D	- FPS: SP > SO > PD w/ AGO > GAD - Trait anxiety inversely related to FPS - Medication use had no effect on results
	Ray et al. (2009)	Startle probes during probes alone, tasks engaging ANS and attention, and relaxation and rumination/worry periods	ADIS-IV	9 GAD; 9 controls	None noted	B	GAD showing greater general startle than controls across entire task except for probe alone period at beginning of task
	Grillon et al. (in press)	Startle during anticipation of aversive stimuli	SCID and for PTSD patients, CAPS	16 PTSD; 18 GAD; 34 controls	PTSD patients: 4 current MD; 2 past MD; 2 past SA GAD patients: 3 SO; 1 current MD; 1 past SA; 1 SP	B	- No differences in FPS among groups PTSD patients: -Context-potentiated startle during unpredictable periods > predictable > neutral Controls and GAD: -Context-potentiated startle during predictable periods > unpredictable & > neutral

Note:

Under Diagnostic Instruments: ADIS-IV = Anxiety Disorder Interview Schedule for DSM-IV; ADIS-R = Anxiety Disorders Interview Schedule–Revised; SCID = Structured Clinical Interview for DSM-IV axis I disorders; SCID-R = Structured Clinical Interview for DSM-III-R

Under Comorbid Diagnosis: AA = Alcohol Abuse/Dependence; AGO = Agoraphobia; ASPD = Antisocial Personality Disorder; BP = Bipolar Disorder; DYS = Dysthymia = DYS; GAD = Generalized Anxiety Disorder; MD = Major depression; OCD = Obsessive Compulsive Disorder; PD = Panic Disorder; PTSD = Post-traumatic stress disorder; SA = Substance Abuse/Dependence; SO = Social Phobia; SP = Specific Phobia

Under Key Result(s): FPS = Fear-Potentiated Startle

Medication usage varied widely and included multiple classes of drugs such as anti-anxiety, antidepressant, and neuroleptic medication. For the sake of simplicity, we treated all classes of drugs the same and collapsed them into a generic medication category. Additionally, some studies also noted subjects stopping medication use for some arbitrary period prior to the experiment (e.g., 2 weeks, 4 weeks, etc.). In such cases, we elected to classify these subjects as “medication-free” for the purposes of that particular study.

* Medication use was classified as follows:

A = None noted

B = Medication-free

C = Medication use specified, but effect of medication not assessed

D = Medication use specified and effect of medication assessed

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Table 2

Summary of studies examining affect-modulated startle reactivity in PTSD.

Category	Study	Experimental Paradigm	Diagnostic Instrument	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
Studies investigating general startle	Butler et al. (1990)	Startle probe alone	DSM-IIIR	13 PTSD; 12 combat controls	No comorbid diagnosis	A	Higher startle in PTSD for 95 and 100 dB probes, but not other probes
	Shalev et al. (1992)	Startle probe alone	SCID-R	14 PTSD; 14 other anxiety disorders (7 PD; 3 GAD; 4 OCD); 15 subjects with trauma exposure, but no psychopathology; 19 with no trauma exposure or psychopathology	PTSD: 2 AA; 1 MD	C	Trend toward larger general startle in PTSD
	Morgan, Grillon, Southwick, Nagy, et al. (1995)	Startle probe alone	SCID-R	18 PTSD; 11 combat controls	5 past and current PD; 15 past MD	B	- General startle greater in PTSD - No difference in results due to PD diagnosis
	Orr et al. (1995)	Startle probe alone	SCID-R	37 PTSD; 19 combat controls	PTSD: 1 BP II; 14 MD; 7 DYS; 1 psychotic disorder not otherwise specified; 6 AA; 7 SA; 6 PD w/o AGO; 7 SO; 2 SP; 3 OCD; 2 GAD; 6 borderline personality; 2 ASPD Combat controls: 1 MD; 2 DYS; 2 AA; 1 PD w/ o AGO; 2 SO; 1 GAD; 1 borderline personality	D	- General startle greater in PTSD than combat controls - No differences due to comorbid disorder - Medication use had no effect on results
	Morgan et al. (1996)	Startle probe alone	SCID-R	10 PTSD; 7 combat controls; 15 civilian controls	2 AA	B	- General startle greater in PTSD than civilian and combat controls - Civilian and combat controls not different from each other
	Morgan et al. (1997)	Startle probe alone	SCID-R	13 PTSD; 16 controls	6 PD w/o AGO; 11 MD	B	- General startle greater in PTSD group greater than controls for left eye, but not right eye - This effect more driven by recent-PTSD group and not long-standing PTSD group - No difference in results due to comorbid PD or MD
	Shalev et al. (1997)	Startle probe alone	SCID-R	Patients referred for trauma-related distress: 30 with PTSD; 28 without PTSD	PTSD: 12 MD; 4 PD; 1 dissociative disorder Without PTSD: 18 past PTSD; 5 MD; 2 adjustment disorder	B	General startle greater in PTSD than non PTSD

Category	Study	Experimental Paradigm	Diagnostic Instrument	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
	Ladwig et al. (2002)	Startle probe alone	Diagnostic checklist recommended by World Health Organization	11 PTSD; 19 controls; all subjects had peritraumatic dissociation	None noted	A	General startle greater in PTSD than controls
	Ross et al. (1989)	Startle probe alone	DSM-IIIR	9 PTSD; 9 controls	4 MD; 3 GAD; 2 DYS; 2 ASPD	B	No differences between groups
	Grillon et al. (1996)	Startle probe alone	SCID-R	19 PTSD; 10 combat controls; 16 civilian controls	MD and OCD exclusionary criteria; 4 PD; 10 AA	B	No differences among groups
	Orr, Lasko, et al. (1997)	Non-startling probes alone	SCID-R	20 PTSD; 19 combat controls	None noted, apart from past AA or SA	B	No differences between groups
	Orr, Solomon, et al. (1997)	Startle probe alone	SCID-R	19 current PTSD; 74 combat controls	PTSD: 5 GAD; 6 current MD Combat controls: 2 GAD; 2 current MD	C	No differences between groups
	Metzger et al. (1999)	Startle probe alone	SCID-R	57 women with history of child sexual abuse: 21 current PTSD; 23 lifetime, but not current PTSD; 13 never PTSD	Current PTSD: 2 BP; 5 MD; 5 DYS; 5 PD; 3 AGO; 7 SO; 8 SP; 3 GAD; 1 somatoform; 3 eating disorder; 1 SA Lifetime PTSD: 1 MD; 1 DYS; 1 PD; 1 SP; 2 eating disorder Never PTSD: 1 PD; 1 SO; 1 SP; 2 SA; 1 AA	D	- No differences among groups - Medication use had no effect on results
	Orr et al. (2003)	Startle probe alone	CAPS	MZ twins discordant for combat exposure and PTS: 50 PTSD; 53 control twin	Comorbidity noted, though details not provided	C	No differences between groups
	Karl et al. (2004)	Startle probe alone with neutral, startle and trauma-related sounds; pre- and post-treatment assessment	CAPS	17 motor vehicle accident survivors - 10 PTSD; 3 subsyndrome; 4 non PTSD - Subjects randomly assigned to treatment or control waitlist	None noted	A	- No differences among groups at pre-treatment - No differences between startle and trauma-related sounds in groups - Decreased general startle in treatment group as compared to waitlist controls
	Guthrie and Bryant (2005)	Startle probe alone; EMG activity assessed pre- and post-trauma	CAPS	35 trauma-exposed firefighters; 36 non-trauma exposed controls	None noted	B	- No differences between groups - In both groups, mean pre-trauma startle activity predictive of mean post-trauma startle activity

Category	Study	Experimental Paradigm	Diagnostic Instrument	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
	Carson et al. (2007)	Startle probe alone	CAPS and SCID	Nurses with Vietnam War-related PTSD: 39 current PTSD; 40 past PTSD; 49 exposed but no PTSD	Current group: 2 other BP; 16 MD; 4 DYS; 7 PD; 1 AGO; 6 SO; 5 SP; 1 OCD; 1 undifferentiated somatoform; 4 binge-eating; 2 AA Past group: 2 PD; 1 SP; 1 body dysmorphic disorder No PTSD: 2 MD; 2 DYS; 4 SP; 1 binge eating disorder	D	- No differences among groups - Medication use had no effect on results
	Jovanovic, Norrholm, Sakoman, et al. (2009)	Startle probe alone	CAPS	45 PTSD; 33 controls	Exclusionary criteria included SA or BP	A	- No differences between groups - Some evidence for impaired habituation across trials in PTSD
	Shalev et al. (2000)	Startle probe alone; EMG activity assessed 1 week, 1 month and 4 months post-trauma	CAPS and SCID-R	21 PTSD alone; 15 PTSD and MD; 16 MD alone; 166 neither PTSD nor MD	None noted except for MD	A	- No difference among groups at 1 week post-trauma - At 1- and 4-month post-trauma, PTSD took longer to habituate to startle - No difference among groups because of MD
	Griffin (2008)	Startle probe alone; EMG activity assessed 1-month and 6-months following trauma	CAPS and SCID	40 rape or trauma survivors; PTSD classification based on diagnosis at 6-month followup	At 1-month post-trauma: 26 women with PTSD symptom diagnosis; 12 PTSD symptom and MD; 1 MD only At 6-month post-trauma: 16 women with PTSD; 5 PTSD and MD; 4 MD	B	- No differences in startle at 1-month post-trauma assessment - PTSD group had larger startle at 6-month followup than non-PTSD - This was due to increase in startle for PTSD group
	Ornitz and Pynoos (1989)	Startle probe alone	DSM-III	6 PTSD; 6 controls	None noted	B	General startle in PTSD less than controls
	Medina et al. (2001)	Startle probe alone	LASC	46 women exposed to high levels of childhood corporal punishment and high levels of partner aggression	None noted	A	PTSD symptom score negatively correlated with general startle
Studies investigating context-potentiated, fear potentiated, and/or general startle	Morgan, Grillon, Southwick, Davis, et al. (1995)	Startle probes presented alone, and during anticipation of aversive stimuli and recovery phases	SCID-R	9 PTSD; 10 controls	4 PD; 5 AA	A	- Greater general startle in PTSD during probes alone and anticipation phases, but not recovery phase - Evidence regarding FPS unclear as significantly greater FPS in PTSD driven by one subject

Category	Study	Experimental Paradigm	Diagnostic Instrument	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
	Grillon et al. (1998a)	Startle probes during adaptation phase, and light and darkness conditions	SCID-R	19 PTSD; 13 combat controls; 20 civilian controls	BP and SA exclusionary criteria	B	- No differences among groups during adaptation - Startle during darkness and light conditions greater in PTSD than combat and civilian controls - No differences in context-potentiated startle (startle during darkness – light) between PTSD and combat controls - However, PTSD showed greater context-potentiated startle than civilian controls - 6 additional subjects eliminated due to being “nonresponders”
	Grillon et al. (1998b)	Startle probe in non-stressful and stressful experimental contexts; subjects tested twice; session 1 involved probe alone; session 2 involved probes under safety and threat of shock conditions	SCID-R	34 PTSD; 17 combat controls; 14 civilian controls	1 BP; 17 MD; 4 SA; 6 PD w/ AGO; 4 PD w/o AGO; 8 SO; 1 OCD; 1 antisocial behavior/borderline personality disorder	B	- No differences in session 1 (i.e., general startle) - No differences in FPS among groups in session 2 - Greater general startle in PTSD in second session - Comorbid MD did not affect results
	Grillon and Morgan (1999)	Startle in conditioning paradigm using safe and threat cues in 2 separate sessions	SCID-R	12 PTSD; 12 combat controls	1 AA; no other psychiatric disorder	B	- PTSD showed increased startle from the first session to session two in habituation and pre-conditioning phases; controls showed decreased startle for the same comparison - No differences between startle to safe and threat cues in first session in PTSD
	Pole et al. (2003)	Startle during threat of shock	SCID, CAPS, and MS-PV	55 police officers endorsing range of PTSD symptoms; 6 full PTSD	Full PTSD: MD; DYS; AA; SA; SO; SP and/or GAD Remaining subjects: SP; AA; SA	D	- Startle reactivity during threat of shock with electrodes attached, but no imminent shock (i.e., medium threat), positively related to greater PTSD symptoms - Medication use had no effect on results
	Pole et al. (2009)	Startle during threat of shock; EMG activity assessed only prior to trauma exposure	SCID and PTSDCL	138 police academy cadets; PTSD symptoms assessed after 1 year of exposure to police trauma	No mental health disorder during initial assessment	B	- No differences in resting (i.e., general) startle - After accounting for age, general psychiatric distress, and prior trauma exposure, startle reactivity during threat of shock with electrodes attached, but no imminent shock (i.e., medium threat), was a significant predictor of PTSD symptoms

Category	Study	Experimental Paradigm	Diagnostic Instrument	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
	Jovanovic, Norrholm, Fennell, et al. (2009)	Startle in conditioning paradigm using safe and threat cues	CAPS and SCID	27 PTSD - subjects divided into high and low PTSD symptom groups; 28 controls	Comorbid MD and SA present but details not noted; BP excluded	D	- No differences in FPS among groups - High symptom PTSD group did not show fear inhibition to threat cue when paired with safe cue like low symptom PTSD group and controls - This effect mostly due to re-experiencing and avoidance symptoms, but not hyperarousal symptoms - Medication use had no effect on results
	Grillon et al. (in press)	Startle during anticipation of aversive stimuli	SCID and for PTSD patients, CAPS	16 PTSD; 18 GAD; 34 controls	PTSD patients: 4 current MD; 2 past MD; 2 past SA GAD patients: 3 SO; 1 current MD; 1 past SA; 1 SP	B	- No differences in FPS (i.e., startle during cue – cue-free periods) among groups - Context-potentiated startle greater in PTSD (i.e., startle during unpredictable periods > predictable > neutral) Controls and GAD: - Context-potentiated startle during predictable periods > unpredictable & > neutral
Studies using affect-modulated startle paradigms	Cuthbert et al. (2003)	Startle during imagery	ADIS-R	28 SP; 30 SO; 26 PD w/ AGO; 22 PTSD; 24 controls	26% SO; 17% SP; 27% GAD; comorbid mood disorder (MD or DYS) lowest for SP (11%) and highest for PD (42%) and PTSD (55%)	D	- General startle (startle during inter-trial intervals) in PTSD > SP, SO, and controls - Lack of FPS (startle during imagery) in PTSD - Startle pattern similar to PD - Medication use had no effect on results
	Miller and Litz (2004)	Affect picture-startle paradigm interspersed with shock stressor and trauma stressor	CAPS	35 veterans with PTSD; 24 combat controls	None noted	C	- No differences in resting (i.e., general) startle - Startle before trauma stressor similar in all groups - However, after trauma stressor, greater startle to unpleasant pictures for PTSD group

Note:

Under Diagnostic Instruments: ADIS-R = Anxiety Disorders Interview Schedule–Revised; CAPS = Clinician Administered PTSD Scale; LASC = Los Angeles Symptom Checklist; MS-PV = Mississippi Scale – Police Version; PTSDCL = PTSD Symptom Checklist; SCID = Structured Clinical Interview for DSM-IV axis I disorders; SCID-R = Structured Clinical Interview for DSM-III-R

Under Comorbid Diagnosis: AA = Alcohol Abuse/Dependence; AGO = Agoraphobia; ASPD = Antisocial Personality Disorder; BP = Bipolar Disorder; DYS = Dysthymia = DYS; GAD = Generalized Anxiety Disorder; MD = Major depression; OCD = Obsessive Compulsive Disorder; PD = Panic Disorder; PTSD = Post-traumatic stress disorder; SA = Substance Abuse/Dependence; SO = Social Phobia; SP = Specific Phobia

Under Key Result(s): FPS = Fear-Potentiated Startle

Medication usage varied widely and included multiple classes of drugs such as anti-anxiety, antidepressant, and neuroleptic medication. For the sake of simplicity, we treated all classes of drugs the same and collapsed them into a generic medication category. Additionally, some studies also noted subjects stopping medication use for some arbitrary period prior to the experiment (e.g., 2 weeks, 4 weeks, etc.). In such cases, we elected to classify these subjects as "medication-free" for the purposes of that particular study.

* Medication use was classified as follows:

A = None noted

B = Medication-free

C = Medication use specified, but effect of medication not assessed

D = Medication use specified and effect of medication assessed

Table 3

Summary of studies examining affect-modulated startle reactivity in conjunction with personality traits affiliated with internalizing disorders.

Personality Trait	Study	Experimental Paradigm	Personality Trait Measure	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
Fearfulness	Cook et al. (1991)	Startle during imagery	FSS	32 – upper and lower third of scores; 17 high and 15 low fear	None noted	B	- Greater FPS in high scorers than low scorers
	Cook et al. (1992)	Affect-picture startle	FSS	32 – high and low scores; 17 high and 15 low fear	None noted	A	- Greater FPS in high scorers than low scorers
	Grillon et al. (1993)	Startle during threat of shock	STAI	22 unselected	None noted	A	- Greater FPS in high scorers - No difference in general startle
	Corr et al. (1995)	Affect-picture startle	TPQ	38 unselected	No psychiatric illnesses	A	Low TPQ-Harm Avoidance scorers did not show FPS
	Corr et al. (1997)	Affect-picture startle	TPQ	23 unselected	No psychiatric illnesses	A	Low TPQ-Harm Avoidance scorers did not show FPS
	Schmidt and Fox (1998)	Startle during stranger approach	Motor activity, positive and negative affect to novel auditory and visual stimuli	9 month old infants; 10 showing above average motor activity and negative affect; 6 showing above average motor activity and positive affect; 7 showing below average motor activity, positive and negative affect	None noted	A	- Greater FPS in negative group when exposed to stranger - No differences in general startle
Traits Related to Anxiety and Depression	Wilson et al. (2000)	Affect-movie clips startle – with fear- and disgust-inducing clips	EPQ	42 unselected; median split on EPQ-Neuroticism scores	None noted	A	Greater startle to disgust clips in low Neuroticism subjects; equal startle for both disgust and fear in high Neuroticism subjects
	Kaviani et al. (2004)	Affect-movie clips startle	DSM-IV and HADS	22 inpatients with MD; 22 controls	None noted	C	Greater general startle in high anxious-depressed group compared to low-anxious depressed group

Personality Trait	Study	Experimental Paradigm	Personality Trait Measure	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
	Verona et al. (2002)	Startle during Buss aggression paradigm	MPQ	48 total - 24 each in high (> 80th %ile) and low (< 20th % ile) MPQ - Negative Emotionality	None noted	A	- Greater general startle in high Negative Emotionality participants - No differences in FPS
	Larson et al. (2007)	Affect-picture startle paradigm	PSWQ and MASQ	14 anxious apprehension, 19 anhedonic depression, 10 anxious arousal, 39 controls	None noted	A	- Lack of FPS in anxious apprehension group - Weak inhibition to pleasant stimuli in anxious arousal and anhedonia groups
	Hawk and Kowmas (2003)	Affect-picture startle paradigm	BIS/BAS Scales	21 low-BIS/low-BAS, 19 low-BIS/ high-BAS, 18 high-BIS/low-BAS, and 22 high-BIS/high-BAS	None noted	A	- No differences in FPS between high- and low-BIS groups - Low-BIS did not show significant inhibition to pleasant pictures like high-BIS group - Low-BAS scores did not show valence-modulated startle
	Caseras et al. (2006)	Affect-picture startle paradigm - but had separate categories of “fear” vs. “blood-disgust” pictures	SPSRQ	24 participants high Sensitivity to Punishment group and 28 low Sensitivity to Punishment group	No psychiatric illness	A	High-BIS group showed significant potentiation for fear pictures compared to pleasant pictures; low-BIS group did not; no differences in responses to blood-disgust pictures
	Nitschke et al. (2002)	Affect-picture startle paradigm; pictures were immediately preceded by a warning sign (a plus sign, a minus sign or a circle) to indicate the valence of the following picture; startle probes were presented during warning signs	PSWQ and MASQ	12 anxious apprehension, 14 anxious arousal, 18 anhedonic depression, 12 controls	None noted	A	No differences among groups
	Smith et al. (2005)	Startle during blocks of affective pictures of the same valence category - probe at 2nd and 11th picture	STAI	37 unselected	None noted	A	No differences between groups

Personality Trait	Study	Experimental Paradigm	Personality Trait Measure	Subjects	Comorbid Diagnosis?	Medication*	Key result(s)
Psychopathy	Patrick et al. (1993)	Affect picture – startle	PCL-R	18 psychopaths; 18 mixed; 18 nonpsychopaths	None noted	A	- FPS in psychopaths less than nonpsychopaths - This effect due to psychopaths with high Factor 1 scorers
	Vanman et al. (2003)	Affect picture - startle	None	80 unselected	None noted	A	Decreased FPS in high Factor 1 scorers
	Benning et al. (2005)	Affect picture - startle	MPQ-predicted Fearless Dominance and Impulsive Antisociality scores	31 high and 31 low Fearless Dominance; 31 high and 31 low Impulsive Antisociality	Details not noted but authors report that subjects excluded if serious mental handicap present	A	Decreased FPS in high Fearless Dominance groups; no differences between Impulsive-Antisociality groups
	Patrick (1994)	Startle during anticipation of aversive stimuli	PCL-R	18 nonpsychopaths; 14 high emotional detachment, low antisocial behavior; 8 high antisocial behavior; 18 psychopaths	None noted	A	Decreased FPS during anticipation of aversive stimuli in psychopaths and detached group
Sensation seeking	Vaidyanathan et al. (2009)	Affect picture - startle	Trait Fear	88 unselected	None noted	A	Trait Fear correlated positively with FPS
	Lissek and Powers (2003)	Affect picture - startle	SSS and SSS-TAS	32 – 16 high and low scores	None noted	A	No FPS in high SSS group
	Lissek et al. (2005)	Startle during anticipation of aversive stimuli	SSS	34 – 17 high and low scores	No psychiatric illness	B	Greater FPS in low SSS group during both predictable and unpredictable aversive stimuli

Note:

Under Diagnostic Instruments: BIS/BAS Scales = Behavioral Inhibition System/Behavioral Activation System scales; EPQ = Eysenck Personality Questionnaire; FSS = Fear Survey Schedule; HADS = Hospital Anxiety and Depression Scale; MASQ = Mood and Anxiety Symptom Questionnaire; MPQ = Multidimensional Personality Questionnaire; PCL-R = Psychopathy Checklist-Revised; PSWQ = Penn State Worry Questionnaire; SPSRQ = Sensitivity to Punishment and Sensitivity to Reward Questionnaire; SSS = Sensation Seeking Scale; SSS-TAS = Sensation Seeking Scale – Thrill and Adventure Seeking subscale; STAI = State-Trait Anxiety Inventory; TPQ = Tridimensional Personality Questionnaire

Under Key Result(s): FPS = Fear-Potentiated Startle

Medication usage varied widely and included multiple classes of drugs such as anti-anxiety, antidepressant, and neuroleptic medication. For the sake of simplicity, we treated all classes of drugs the same and collapsed them into a generic medication category. Additionally, some studies also noted subjects stopping medication use for some arbitrary period prior to the experiment (e.g., 2 weeks, 4 weeks, etc.). In such cases, we elected to classify these subjects as “medication-free” for the purposes of that particular study.

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