



Psychophysiological Markers of Fear and Anxiety

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Abstract

Purpose of Review The purpose of this paper is to provide a current review of the recent literature (2015–2018) on psychophysiological markers of fear and anxiety.

Recent Finding Relative to healthy controls, fear-based disorders are characterised by heightened physiological reactivity to circumscribe threat salient stimuli, whereas anxiety-related disorders are associated with a more blunted pattern of physiological reactivity.

Summary Fear and anxiety disorders are marked by abnormal patterns of physiological reactivity, characterised by hyper- and hypo-reactivity in response to stimuli varying in threat salience.

Keywords Fear · Anxiety · Psychophysiology · Markers

Introduction

Individual differences in psychophysiological measures serve as markers of maladaptive responses to salient internal and external events and can contribute to the development and expression of fear and anxiety. Anxiety disorders are the most prevalent group of mental disorders, affecting 14.4% of adults, and 6.9% of 4–17 years olds [1, 2]. Fear and anxiety are expressed through symptoms including threat-based cognitions, aberrant physiological reactivity, heightened negative emotion and avoidance behaviour. *Fear* is a primitive but vital response to imminent danger (whether real or perceived) consisting of physiological and psychological characteristics that assist the individual to respond to situational demands (i.e. fight, flight, freeze). The response is typically circumscribed and intense. *Anxiety* refers to worry, apprehension and nervousness about a situation in which the outcome may be uncertain, and in contrast to fear, the response can be broad, diffuse and of less intensity.

The purpose of this paper is to provide an up-to-date review of the literature on psychophysiological markers of fear and

anxiety, which broadly refer to physiological markers of psychological processes that characterise the expression of fear and anxiety disorders, or the risk of their development. We synthesise the literature over the past 4 years (2015–2018) on psychophysiological reactivity in fear and anxiety disorders, although we refer to seminal research that pre-dates this review period when describing the measures of psychophysiological markers and linking current research with prior findings. Following a review of commonly used psychophysiological measures, we provide a conceptual model of differential psychophysiological responsivity in fear and anxiety disorders as a function of stimulus threat salience (Fig. 1) followed by a review of the recent evidence that supports this approach.

Common Psychophysiological Measures

The autonomic nervous system (ANS) plays a central role in fear and anxiety, regulating unconscious bodily functions such as heart rate, respiration and digestion, and is comprised of two principal branches: the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Defensive responding to threat occurs through opposing patterns of activation of the two nervous systems and marked by excitation of the SNS and inhibition of the PNS, manifesting physiologically through ‘fight or flight’ responses such as increased heart rate, respiration and blood flow [3]. The SNS and PNS may also be activated together or co-deactivated, as

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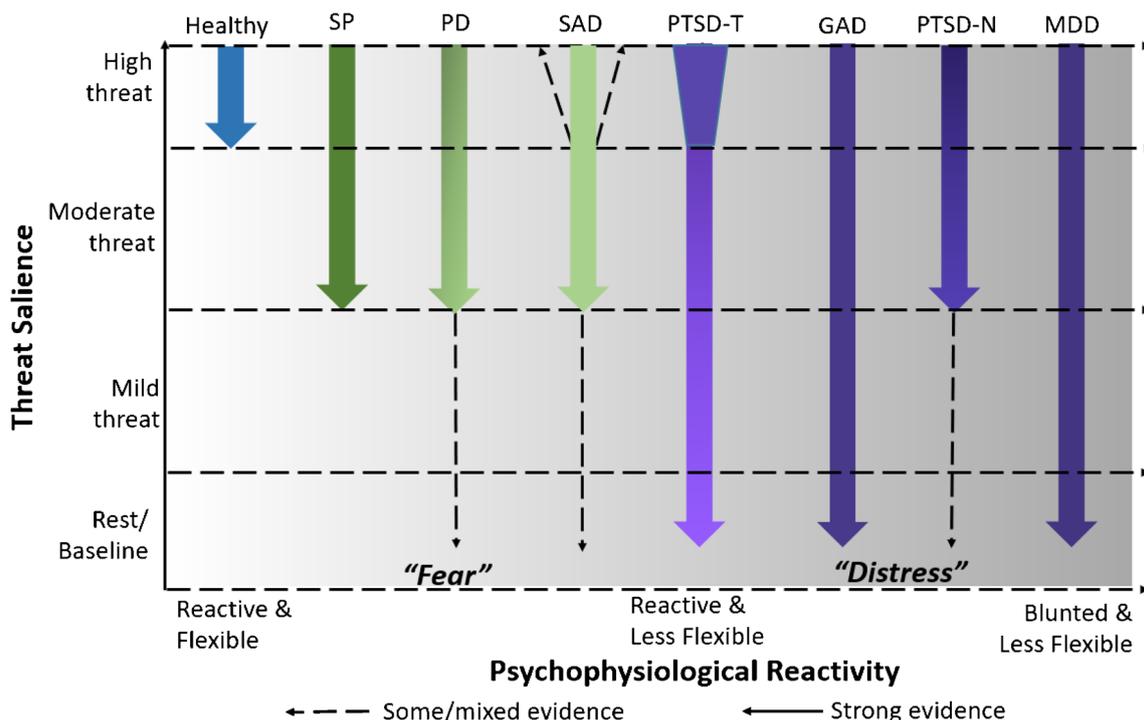


Fig. 1 Threat salient model of psychophysiological reactivity in fear and anxiety. SP, specific phobia; PD, panic disorder (with or without agoraphobia); SAD, social anxiety disorder; PTSD-T, post-traumatic

stress disorder-trauma; PTSD-N, post-traumatic stress disorder-neglect; GAD, generalised anxiety disorder; MDD, major depressive disorder

co-activation may aid in limiting adverse effects of high SNS activity, whereas recent research suggests withdrawal of PNS without ensuing SNS activation may occur as a response to challenge to conserve metabolic resources [3–5].

As psychophysiological markers indexing fear- and anxiety-related differences in ANS function have been among the most commonly used in the literature, we focus our review on fear-potentiated startle (FPS), heart rate (HR), heart rate variability (HRV), respiratory sinus arrhythmia (RSA) and skin conductance response (SCR). We also review the literature on eye movements and pupillometry as well as facial EMG to index visual attention allocation and information processing¹ and studies examining cortisol, which provides an index of hypothalamic-pituitary-adrenal (HPA) axis reactivity.

Measures Assessing Psychophysiological Reactivity to Stressors

Skin conductance response (SCR) is a measurement of changes in sweat gland activity (controlled by the SNS) that produces an increase in the electrical conductivity of the skin [8]. SCRs usually reflects the conscious expectancy of a possible negative outcome, but can also index an unconscious emotional process, thereby serving as an objective, non-

voluntary indicator of anticipation and arousal [8]. Relative to controls, larger SCRs index elevated physiological arousal whereas smaller SCRs are reflective of blunted physiological reactivity.

Fear-potentiated startle (FPS) is measured by recording the contraction of the orbicularis oculi muscle beneath the eye, which is involved in the contraction of the eyelid in response to an intense startle-eliciting stimulus [9]. FPS provides an index of human defensive responding to salient negative stimuli, with larger amplitudes indicating stronger defensive reactions whereas attenuated responding reflects reduced environmental reactivity.

Pupillometry—pupillary changes are commonly linked to light changes, but have also been linked with the SNS, suggesting that pupil dilation is influenced by emotional arousal [10, 11]. Pupil dilation is typically assessed during picture viewing, listening to sounds or in anticipation of threat of shock. Greater pupil dilation is an index of the stress response.

Cortisol is a steroid hormone produced in the adrenal gland that has many functions but in particular is involved in the fight or flight response to potential threats; it is essential for an adequate response to threat [12]. Cortisol levels are typically assessed via salivary samples taken before and after stress-inducing tasks. Adaptive responses to stress are characterised by a relatively rapid cortisol increase followed by a progressive decline. Flatter reactivity and recovery is a maladaptive response often called blunted reactivity [13].

¹ We have not investigated neural psychological measures, such as event-related potentials (ERP) or fMRI, although there is substantial research in these areas, it is out of the scope of this article (see [6, 7] for reviews).

Salivary alpha-amylase (sAA) is a new biomarker of ANS activity to complement existing measures such as HR [12]. Increased levels of sAA from baseline to exposure to a stressor are adaptive stress response, reflecting reactive ANS functioning. Both high and low levels of sAA in response to acute stress and at rest in comparison with healthy controls reflect over- and under-active patterns of ANS activity [13].

Measures of Psychophysiological Variability

Heart rate variability (HRV) indexes the variation in the time interval between heartbeats, reflecting fluctuation in autonomic nervous system influence on the heart. As this is a measure of the variation in ANS influence, both withdrawal and over-activity of the ANS may reduce HRV. Time-domain and frequency-domain measures have been employed to evaluate HRV, and although different measures of HRV may reflect different physiological processes, most typically index PNS influence [14]. Respiratory sinus arrhythmia (RSA) indexes HRV associated with respiration, and has at times been used interchangeably with high-frequency HRV (HF-HRV), as both measures index cardiac vagal control (CVC).² In contrast to other HRV parameters, interpretation of HRV in the low-frequency band (0.04–0.15 Hz) is controversial; depending on the recording measures, LF-HRV may index vagal, sympathetic or baroreflex mechanisms [14]. Thus, we use ‘HRV’ to refer to HF-HRV (0.15–0.4 Hz). Higher HRV is associated with higher emotional well-being, with lower HRV indexing heightened and less flexible physiological arousal and difficulty ‘bouncing back’ following stressors [15, 16].

Allocation of Visual Attention to Salient Stimuli

Eye tracking—this measure provides an index of rapid and sustained patterns of visual attention to salient environmental stimuli. We incorporate findings from eye-tracking studies given that psychophysiological reactivity is likely to be influenced by the stimuli to which anxious individuals attend to both automatically (bottom-up stimulus processing) and strategically (top-down control). Typical eye tracking measures include initial fixation and gaze points, distribution of gaze points, areas of interest, time to the first fixation, dwell time, fixation sequences and fixation duration.

Psychophysiological Reactivity and Threat Salience in Fear and Anxiety Disorders

Recent structural models and empirical studies have begun to identify distinct response patterns that differentiate fear disorders (social anxiety disorder, specific phobia, panic disorder,

agoraphobia, obsessive-compulsive disorder³) from distress disorders (generalised anxiety disorder, post-traumatic stress disorder, major depressive disorder) [17••, 18, 19, 20••]. Influential research [21] has suggested that fear and distress disorders may be differentiated based on physiological reactivity to stressors, with fear disorders characterised by heightened physiological reactivity, whereas distress disorders may be marked by blunted physiological responding. In addition, previous research, see reference [22], has found that some anxiety disorders are marked by less physiological variability, suggestive of elevated arousal and autonomic inflexibility to environmental demands. Thus, fear and anxiety disorders may be differentiated from healthy controls and from each other by physiological inflexibility and accentuated and attenuated physiological reactivity to stressors.

Recent conceptual models based on empirical research highlight differences in adaptive reactivity as a function of the degree of stimulus threat salience and the extent to which such reactivity is more widespread in fear and anxiety disorders (see reference [20••] for a review). In Fig. 1, we provide a visual representation of the evidence for psychophysiological reactivity in the anxiety disorders relative to healthy controls. Threat salience refers to stimulus threat intensity within the context of experimental manipulation, with ‘low’ threat salient stressors referring to reactivity at baseline/rest and in response to safe stimuli (e.g. neutral images). ‘Mild’ threat salient stressors refer to non-specific challenges such as puzzles, arithmetic and other cognitive challenges. ‘Moderate’ threat salient-stressors include neutral stimuli paired with mildly aversive stimuli (i.e. CS+) such as electric shocks, threat-related imagery, worry induction procedures and viewing distressing images. ‘High’ threat salient stressors include tasks that involve direct stress provocation, such as the Trier social stress test, VR-augmented exposure and direct, in vivo exposure [23].

Conceptualised in terms of threat salience and in accord with prior research (e.g. [24]), Fig. 1 illustrates that psychophysiological reactivity to high threat salient stimuli is characteristic of all individuals for safety and survival purposes (upper row; high threat) see reference [20••]. In contrast, and as reviewed below, elevated psychophysiological reactivity extends to moderate threat salient stimuli in fear disorders (with less evidence regarding reactivity to mild threat stimuli and baseline/rest conditions) (green panels). Such findings are consistent with the intense yet circumscribed nature of fears. However, psychophysiological responding becomes progressively more widespread, blunted and less variable in anxiety-based disorders, particularly when they are comorbid with depressive disorders (purple panels). We highlight that there

² For a more detailed review of the definitions and interpretations of various HRV parameters, see [14]

³ We do not review the evidence for OCD as it is no longer considered an anxiety disorder in the DSM-5, and empirical evidence has been mixed regarding whether it is a fear or distress disorder.

may be differences in psychophysiological reactivity among individuals with PTSD due to the high threat of harm exposure (PTSD-T) versus neglect/deprivation (PTSD-N) [25]. The former may be characterised by greater psychophysiological reactivity following high threat salient experiences and the latter by blunted and less variable responding, reflective of reduced responding due to deprivation and neglect. Next, we briefly review the evidence on each disorder.

Fear Disorders

Specific Phobia Specific phobia is defined by intense fear or anxiety in the presence of a specific object or situation which typically occurs immediately and disproportionately to the actual danger posed by the feared stimulus [26]. The ‘threat’ which defines specific phobia is circumscribed and of high intensity.

Two studies assessed measures of autonomic reactivity in response to phobia-specific imagery. Wannemueller et al. [27] assessed HR and FPS in response to dental phobia-specific picture stimuli (moderate threat salience), finding adults with dental phobia exhibited greater HR acceleration (reactivity) to the phobia-related stimuli compared to controls; however, both groups displayed the same startle potentiation. Sanchez-Navarro et al. [28] assessed HR and SCR in response to neutral- and phobia-specific images (moderate threat salience), comparing adults with a snake phobia, blood-injection-injury (BII) phobia and adults without phobia disorders. The BII phobia group exhibited greater SCRs to blood-related images compared to other images and the snake phobia group showed greater SCRs to both snake- and blood-related images than neutral images. Only the snake phobia group exhibited HR acceleration, and this was in response to snake-specific images only. These results suggest that different phobias may be marked by distinct patterns of psychophysiological reactivity; animal phobias may be characterised by more generalised reactivity to moderate threat-related stimuli whereas BII may be more circumscribed to phobia-specific threat cues.

Two recent studies assessed virtual reality (VR) exposure, and one study evaluated in vivo exposure. Employing a VR height simulation (high threat salience), Diemer et al. [29] compared height phobic and healthy adults’ HR, SCR, and salivary cortisol responses, finding that both groups exhibited the same increase in SCR during height exposure but neither group experienced a change in cortisol response. Both groups exhibited the same pattern of HR increase during exposure, which only differed during the most phobia-related event (i.e. looking downwards during the simulation), when the phobic sample recorded a significantly higher HR (phobia-specific threat salience), suggestive of elevated physiological arousal to disorder-specific cues only. Notzon et al. [30] found that

both spider phobic and healthy adults exhibited an increase in SCRs and HR from baseline to exposure in the VR spider situation, with changes in SCR and HR significantly greater for the spider phobic participants (phobia-specific threat salience), however, there were no group differences during VR spider exposure (high threat salience). In contrast, Schumacher et al. [31] did not find group differences in phobic adults’ salivary cortisol and sAA responses between two in vivo exposure conditions (flooding vs. graduated exposure), as neither group recorded changes in sAA and cortisol levels from baseline to exposure. Taken together, results suggest a common fear response in all adults during actual exposure to high threat salient stimuli, marked by increased autonomic activity, but greater reactivity in phobic individuals when transitioning from baseline to exposure to their phobia-relevant cue. Also, HR and SCR may be more sensitive than cortisol and sAA to these phobia-related differences.

Panic Disorder Panic disorder (PD) refers to recurrent unexpected panic attacks, chronic anticipation of future panic attacks and behavioural avoidance in an attempt to avoid further episodes [26]. Agoraphobia is characterised by fear and/or avoidance of situations where it might be difficult to escape or get help in the event of panic-related symptoms [26]. Although the DSM-5 specifies PD and agoraphobia are two separate anxiety disorders, studies have employed mixed samples with either PD or PD with agoraphobia, and so both disorders are discussed together.

Two studies evaluated HRV at baseline and in response to a mental arithmetic task (mild threat salience), with Kotianova et al. [32] reporting no differences in HRV during baseline or in response to the stressor, whereas Choi et al. [33] found no differences in baseline HRV group differences but lower HRV in PD compared with controls during the mental arithmetic task. Moreover, Katz et al. [34] found that during an electrodermal shock threat sensitivity task (moderate threat salience), adults with PD demonstrated greater FPS compared to healthy controls. Similarly, Cooper et al. [35] evaluated FPS during fear conditioning (moderate threat salience), finding that participants with PD demonstrated impaired discrimination between the CS+ paired with an unpleasant US and CS- compared to controls.

Two studies evaluated autonomic reactivity to the TSST (high threat salience), finding no differences between adults with PD and healthy controls in HRV [36], HR and sAA [37]. These results may reflect that the TSST is stressful for all individuals and may not be sensitive to PD-specific perturbations in reactivity. However, there were no differences observed between the two groups in HRV in response to the dexamethasone–corticotropin-releasing hormone DEX-CRH test, which elicits uncomfortable hormonal stress and thus provides an interoceptive stressor, which may be more relevant to PD, but may also be generally unpleasant for all

individuals, i.e. high threat salient [38]. In contrast, two other TSST studies (high threat salience) evaluated cortisol response, finding no differences in cortisol levels at baseline between adults with and without PD, whereas after exposure to the TSST, adults with PD exhibited blunted cortisol responding in comparison to controls [38, 39]. This finding has been observed in previous studies [40, 41], and together may indicate that psychophysiological reactivity in response to mild through high non-PD-specific threat stimuli does not differentiate individuals with and without PD. Difficulty ‘bouncing back’ after stress in PD and whether this predicts agoraphobia onset warrants further research.

Social Anxiety Disorder SAD is characterised by fear, anxiety and/or avoidance of social situations and events which involve the potential for real or perceived negative evaluation by other people [26]. The ‘threat’ which elicits fear in SAD is a negative evaluation by others, and this threat may be either circumscribed to performance-related social situations or generalised to multiple social situations.

Physiological reactivity in SAD appears to vary in response to the experimental paradigm, with one of five studies reporting blunted physiological reactivity in comparison to healthy controls, two studies reporting a mixed pattern of reactivity and two studies reporting no differences between participant groups. Alkozei et al. [42••] evaluated HR and HRV at baseline and in response to a difficult puzzle (mild threat salience) and a speech (high threat salience), comparing children aged (7–12) with SAD against matched controls, finding no differences in either HR and HRV at baseline or in response to either stressor. Similarly, Myllyneva et al. [43] compared a sample of adolescents with SAD against matched controls, evaluating SCRs in response to looking at a person’s face (mild threat salience) who was either looking directly at the participant (direct eye contact), looking at the participant from an angle (indirect eye contact) or presenting with eyes closed, with results indicating no differences between the two groups.

Three studies reported altered physiological reactivity in SAD in response to disorder-specific and higher threat salient stressors. Keil et al. [44] evaluated 10–13-year-old children’s pupillary reactivity and eye contact processing in response to happy, angry and neutral faces (moderate threat salience), finding that children with SAD demonstrated a hypervigilant–avoidant pattern of eye contact, exhibiting a faster fixation on the eye region of faces and then quickly directing attention away from the eye region. Moreover, social anxiety severity was correlated with blunted pupil dilation in response to faces and shorter first fixations, indicating greater symptom severity may be associated with attentional disengagement with anxiety-provoking social settings [31]. Ketay et al. [45] evaluated adult’s salivary cortisol response to two stressors—a high disclosure conversation (moderate threat salience) versus a low disclosure conversation with a same-sex

stranger (mild threat salience)—finding that although in the low-disclosure condition, both groups demonstrated a similar pattern of cortisol decline over time; in the high-disclosure condition, participants with elevated social anxiety demonstrated a weaker decline in cortisol than participants with low social anxiety, suggesting sustained stress during the high disclosure interaction. Finally, Garcia-Rubio et al. [46] found that adults with SAD exhibited lower HRV at rest and in response to the TSST (high threat salience) suggestive of increased and less flexible autonomic arousal prior to and during a highly salient stressor, although there were no group differences in sAA.

Taken together, SAD may be characterised by elevated psychophysiological reactivity during baseline, as indexed by HRV (more research is required), and during moderate and possibly high social-specific threatening situations, as indexed by eye gaze, pupil dilation and cortisol levels. However, findings of an absence of differences in HRV in children with and without SAD are novel and suggest more flexible physiological responding in youth with SAD which may become less variable with development.

Distress Disorders

Generalised Anxiety Disorder GAD is characterised by persistent and excessive worry centred on multiple domains of an affected individual’s life, which is perceived as difficult to control and significantly impairs functioning [26]. As the ‘threat’ which defines GAD is related to multiple feared events and outcomes, and threat frequently manifests cognitively rather than physically, threat salience is typically low yet chronic, and thus can be conceptualised as a generalised, as opposed to circumscribed, threat.

Evidence for altered baseline patterns of autonomic reactivity in GAD is mixed. Of the four studies evaluating resting HRV in adults with GAD, one study found lower resting HRV in GAD compared to healthy controls after an fMRI brain scan, which may suggest difficulty ‘bouncing back’ after mild threat salient events [47]. Shinba et al. [48] found a higher HRV in adults with GAD relative to controls during baseline but no differences between the two groups during or after a mild cognitive stressor (random number generation task). In contrast, Seeley et al. [49] and Levine et al. [50] found no differences between adults with GAD and healthy controls on baseline measures but observed that participants with GAD had lower HRV than healthy controls during exposure to fear-eliciting film clips and a personalised worry induction and worry imagery induction respectively (moderate threat salience). Similarly, Cooper et al. [35•] evaluated FPS in response to a fear conditioning procedure (moderate threat salience), finding that participants with GAD demonstrated impaired discrimination between CS+ paired with an unpleasant

US and CS− compared to controls, and this persisted during a second training period. Thus, GAD was associated with more persistent elevations in defensive responding to moderate (CS+) and mild threats (CS−).

One study evaluated HRV in response to an explicit threat. Kircanski et al. [51•] evaluated HRV in response to a modified, three-phase version of TSST (i.e. TSST anticipation, TSST exposure, TSST recovery—high threat salience) finding that healthy controls demonstrated a sharp decrease in HRV from anticipation to exposure to the TSST followed by a sharp increase in HRV immediately afterwards, reflective of flexible withdrawal of vagal control in response to environmental demands. Adults with GAD, MDD and comorbid GAD-MDD each presented with the same pattern of blunted reactivity, involving weaker fluctuations in HRV during and after TSST exposure, which may be associated with decreased ability to cope with stressors, and impairment in the stress-recovery response. Together, findings suggest that GAD is characterised by broad-based psychophysiological impairment characterised by sympathetic reactivity in anticipation of, and during, moderate threat salient conditions and parasympathetic inhibition during and after high threat salient challenges, which also characterises, and may contribute to comorbidity with, MDD.

Post-Traumatic Stress Disorder Post-traumatic stress disorder (PTSD) is acquired in response to direct or indirect exposure to actual or threatened harm and is defined by intrusion symptoms, avoidance, abnormal arousal and negative cognition and mood [26]. Thus, the ‘threat’ which defines PTSD is the traumatic event itself.

Recent research indicates that physiological measures recorded at rest point to a pattern of blunted responding in PD, whilst threat-related reactivity is more variable. Pan et al. [52••] conducted a meta-analysis of 22 studies evaluating basal salivary cortisol in PTSD patients, finding a trend for lower salivary cortisol in patients with PTSD compared to controls. Similarly, a recent meta-analysis by Campbell et al. [53] of 50 studies found lower resting HRV in participants with PTSD, with no significant differences in the magnitude of this relationship between the type of trauma experienced (i.e. combat, interpersonal, mixed). Supporting these findings, Jenness et al. [54] evaluated HRV during a fear conditioning and extinction paradigm in youths aged 6–18 with a history of child abuse, finding that lower resting HRV was associated with greater PTSD symptoms. Park et al. [55] evaluated HRV at rest, finding that Korean combat veterans with PTSD recorded lower HRV compared to combat veterans without PTSD. Supporting this finding, Dennis et al. [56] found participants diagnosed with PTSD demonstrated lower HRV compared to controls at baseline and after acute momentary distress, suggestive of greater autonomic inflexibility.

In terms of physiological reactivity to threats, two studies reported hyper-reactive physiological responding, one study reported similar reactivity to matched controls and one study reported under-reactivity. Hinrichs et al. [57] evaluated SCRs before and during a standard trauma-related interview (moderate threat salience), finding that adults with PTSD recorded significantly higher SCRs than trauma-exposed adults without PTSD, and higher SCR during the interview was associated with greater PTSD symptoms score. Similarly, van’t Wout et al. [58] found veterans with PTSD demonstrated elevated SCRs during combat-related VR events (high threat salience) compared to veterans without PTSD, and SCR was marginally correlated with the severity of hyperarousal symptoms. Kirsch et al. [59] evaluated effects of idiographic trauma scripts on facial EMG and indices of autonomic reactivity (HR, SCR and HRV) in trauma-exposed and non-exposed children and adolescents (moderate threat salience), finding that, unlike adults with trauma-focused PTSD, groups did not differ on autonomic reactivity, but children with PTSD demonstrated elevated facial EMG activity, suggestive of elevated trauma-related information processing. Finally, Quevedo et al. [60•] evaluated effects of early neglect on startle reflex in adopted youths aged 12–13, finding that whilst non-adopted youths demonstrated a heightened startle reflex in response to threatening compared to neutral images (moderate threat salience), youths with a history of neglect exhibited smaller startle responses to threat compared to neutral images, with severity of neglect associated with greater degree of blunted startle potentiation. These preliminary findings suggest that threat of harm exposure may be associated with broad-based parasympathetic impairment at rest and in anticipation of threats, as well as increased sympathetic reactivity to threat salient events. In contrast, neglect exposure may be characterised by broad-based psychophysiological blunting and warrants further research [25].

Overlap with MDD

Major depressive disorder (MDD) is marked by pervasive feelings of significantly lowered mood and/or loss of interest or pleasure in almost all activities, with these symptoms enduring for at least 2 weeks [26]. Although not an anxiety disorder, MDD is highly comorbid with anxiety disorders, and therefore MDD may exhibit a similar pattern of psychophysiological responding as, or influence psychophysiological reactivity in, comorbid anxiety disorders.

Recent reviews consistently report lowered HRV in depressed individuals in comparison to controls, both at rest and in response to stressors, in adults [61], children and adolescents [62]. Similarly, Shinba et al. [48] found lowered HRV at rest and during a random number generation task (mild threat salience) in participants with MDD compared to GAD and healthy controls (reviewed above), highlighting that MDD is characterised

by more generalised blunted autonomic reactivity than GAD. Yancey et al. [63] evaluated FPS in response to threat and mutilation pictures (moderate threat salience) in adults with fear disorders (i.e. specific phobia, SAD, PD or agoraphobia), with and without comorbid MDD. Of the adults without comorbid MDD, the fear disorder group exhibited enhanced FPS in comparison to adults without fear disorders, consistent with previous research [21]. However, among adults with comorbid MDD, adults with fear disorders exhibited attenuated FPS compared to those without fear disorders. Results were the same when analysed as a function of broad distress conditions (i.e., GAD, dysthymia, MDD) rather than MDD alone. These results suggest that comorbid MDD/distress disorders attenuate psychophysiological reactivity to moderate threat salient stressors in those with fear disorders. Similarly, Dekel et al. [64] recorded salivary cortisol in trauma survivors before and after a standardised trauma interview (moderate threat salience), finding that adults with comorbid PTSD and MDD exhibited decreased cortisol following trauma recollection, whereas the PTSD only group recorded an increase in cortisol. Taken together, findings suggest that MDD may exacerbate a more restricted profile of autonomic blunting in those with distress disorders and attenuate autonomic reactivity in those with fear disorders, leading to a generalised profile of blunted psychophysiological responding.

Temporal Relationship Between Psychophysiological Markers and Fear and Anxiety

Much of this review has focused on psychophysiological markers of fear and anxiety disorders evaluated at rest, or before and after exposure to stressors administered within a time-limited experimental procedure. Although these studies report fluctuations in psychophysiological responding as a function of threat salience and fear versus distress disorders, experimental studies preclude the ability to determine the long-term temporal relationship between psychophysiological markers and anxiety; specifically, whether these psychophysiological markers precede diagnoses as an innate disposition ('trait' markers) is correlated with current anxiety symptoms ('state' markers), or whether there is a causal relationship between anxiety and altered psychophysiological responding. Recent studies employing treatment designs (such as RCTs) and evaluate psychophysiological markers of fear and anxiety such as cardiac parameters (HR, HRV), cortisol and FPS provide some evidence for a causal, bidirectional relationship between anxiety symptoms and psychophysiological responding.

HR parameters are the most researched markers. A recent meta-analysis by Goncalves et al. found that cognitive-behavioural therapy (CBT) was effective in reducing HR reactivity to stressors in PTSD, specific phobia and social anxiety disorder, but not in PD [65]. Wend et al.'s [66] recent large-scale RCT may clarify the relationship between HR parameters and

symptoms in PD, with results indicating lower HRV at pre-treatment was associated with increased dropout rates and residual PD symptoms at post-treatment. The inverse relationship between HRV and anxiety has also been assessed, with a recent meta-analysis by Goessl et al. [67] finding HRV biofeedback training significantly improved symptoms of stress and anxiety in both typical and clinical samples. Thus, cardiac measures such as HR and HRV are not only correlated with the current state of anxiety and may be changed through psychological therapy, but this relationship appears to be bidirectional, meaning that symptoms of anxiety may also be improved through interventions targeting HR parameters. HRV in particular may provide prognostic utility in determining who may benefit from evidence-based treatment such as exposure therapy.

Furthermore, in another study, FPS was evaluated in response to unpredictable shock before and after CBT with findings indicating that adults with fear disorders (PD or SAD; PTSD is also included in this condition) demonstrated greater startle magnitude than both healthy controls and adults with distress disorders (dysthymia, MDD or GAD) as these two groups did not differ [68]. After CBT, startle magnitude decreased only for adults with fear disorders, and a greater decrease in startle magnitude was correlated with the decrease in fear disorder-specific anxiety symptoms. A limitation of this study is that the authors did not specify type of trauma in the PTSD group (e.g. neglect vs trauma) and assigned all adults with PTSD to the fear disorder condition; however, as the number of adults with PTSD comprised of a small proportion of the sample ($n = 4$ PTSD; $N = 22$ fear disorders), findings could be interpreted that heightened FPS appears to be a specific state marker of fear disorders—and potentially PTSD—that is amenable to change with psychological treatment.

Very little research has examined the temporal relationship between cortisol and anxiety symptoms. However, a recent open-label clinical trial by Keefe et al. [69] evaluated effects of chamomile extract on cortisol and GAD symptoms, finding improved anxiety symptoms from pre- to post-treatment was correlated with increased morning cortisol and greater decreases in cortisol slope over the course of the day. Lower morning cortisol levels were associated with more severe GAD symptoms, supporting previous findings of blunted physiological reactivity in GAD. These results indicate that cortisol levels may be changed through intervention and may provide a state marker of severity in GAD and potentially other anxiety disorders.

Taken together, although recently published longitudinal studies are limited in number and constrained to a few frequently researched psychophysiological markers, results support the hypothesis that psychophysiological markers such as HRV, cortisol and FPS are mutable, reflecting a current state of fear or anxiety, as opposed to stable trait characteristics. This body of research suggests exciting possibilities for differences in psychophysiological reactivity to be amenable to treatment and warrants further investigation.

Conclusions

From this review of the recent literature, findings suggest psychophysiological reactivity in fear and anxiety disorders varies as a function of threat salience. Reactivity to high threat salient stressors is adaptive and inherent in all individuals, as it elicits essential protective reflexes needed for safety and survival (i.e. fight, flight, freeze). Anxiety disorders, by contrast, may be marked by aberrant patterns of reactivity that are blunted, heightened or inflexible, and thus result in poor ability to adapt to stressors. Supporting previous findings [21, 70••, 71], this review found that fear disorders (SP, SAD, PD) are characterised by heightened autonomic reactivity to stressors of moderate-high threat salience, whereas distress disorders (PTSD, GAD, MDD) are associated with increasingly blunted and inflexible patterns of reactivity that cuts across a wide range of situational demands. Thus, the fear and anxiety disorders form a spectrum based on psychophysiological reactivity, ranging from fear disorders (over-reactive and flexible to situational demands) to distress disorders (blunted and inflexible to situational demands). Although studies are needed to compare psychophysiological responsivity of each of these anxiety disorders within the same study, findings of common patterns of psychophysiological reactivity shared between anxiety disorders align with innovative models of psychopathology such as the Research Domain Criteria (RDoC) [70••] and the Hierarchical Taxonomy of Psychopathology (HiTOP) [17••], which emphasise the importance of dimensional criteria and transdiagnostic markers of psychopathology.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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