ARTICLE IN PRESS

Clinical Psychology Review xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Clinical Psychology Review

journal homepage: www.elsevier.com/locate/clinpsychrev

Review

Intolerance of uncertainty: Neural and psychophysiological correlates of the perception of uncertainty as threatening

Ema Tanovic*, Dylan G. Gee, Jutta Joormann

Department of Psychology, Yale University, 2 Hillhouse Ave., New Haven, CT 06511, USA

HIGHLIGHTS

- Neural and physiological correlates of intolerance of uncertainty (IU) are reviewed.
- IU is associated with greater anterior insula and amygdala activity to uncertainty.
- IU is associated with altered event-related potentials to rewards and errors.
- Findings regarding IU and the startle reflex to uncertain threat are mixed.
- IU is associated with deficiencies in safety learning indexed by skin conductance.

ABSTRACT

Intolerance of uncertainty (IU) reflects the perception of uncertainty as threatening, regardless of the true probability of threat. IU is elevated in various forms of psychopathology, uniquely associated with anxiety and depression symptoms after controlling for related constructs, and prospectively predicts symptoms. Given the ubiquity of uncertainty in daily life and the clinical implications of IU, recent work has begun to investigate the neural and psychophysiological correlates of IU. This review summarizes the existing literature and integrates findings within a mechanistic neural model of responding to uncertainty. IU is associated with heightened reactivity to uncertainty reflected in greater activity of the anterior insula and amygdala, alterations in neural responses to rewards and errors evident in event-related potentials, a mixed pattern of startle responses to uncertain threat, and deficiencies in safety learning indexed by startle and skin conductance responding. These findings provide evidence of disruptions in several domains of responding to uncertainty, threat, and reward associated with IU that may confer risk for the development of psychopathology. Significant attention is devoted to recommendations for future research, including consideration of the complex interplay of IU with emotion regulation, cognitive control, and reward processing.

Uncertainty is an ever-present feature of everyday life. Some uncertain situations can be distressing—"Will I get the job?"—while others are more tolerable—"Will there be traffic on the way to work?" In addition to varying across situations, the extent to which uncertainty is distressing varies across individuals. Intolerance of uncertainty (IU) is a trait that reflects negative beliefs about uncertainty (Dugas & Robichaud, 2007) and that has recently been defined as "an individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty" (Carleton, 2016a, p. 31). Higher levels of IU are associated with internalizing psychopathology, including generalized anxiety disorder (GAD), obsessive compulsive disorder, social anxiety disorder, panic disorder, depression, and eating disorders (Brown et al., 2017; McEvoy & Mahoney, 2012). Across disorders, uncertainty is thought to provoke anticipatory anxiety and to result in behaviors that are maladaptive attempts to reduce uncertainty, such as worry, reassurance seeking, checking, and hypervigilance (Barlow, 2004; Krohne, 1993). In addition to being elevated across disorders, IU confers risk for the development of anxiety symptoms and predicts poorer outcomes following treatment (Keefer et al., 2016; Oglesby, Boffa, Short, Raines, & Schmidt, 2016). In light of these clinical implications, as well as the ubiquity of uncertainty in daily life, understanding the predictors and effects of IU and how it is maintained may be important for preventing, understanding, and treating internalizing psychopathology.

Studies examining IU have begun to investigate physiological

* Corresponding author.
E-mail address: ema.tanovic@yale.edu (E. Tanovic).

https://doi.org/10.1016/j.cpr.2018.01.001
Received 26 July 2017; Received in revised form 5 January 2018; Accepted 5 January 2018
0272-7358/

Please cite this article as: Tanovic, E., Clinical Psychology Review (2018), https://doi.org/10.1016/j.cpr.2018.01.001

correlates of this trait through the use of neural and psychophysiological measures, such as functional magnetic resonance imaging (fMRI) and startle reflex paradigms. Strengths of such measures include their ability to elucidate the biological bases of IU and to offer a window into emotional and cognitive processing that is relatively objective, building on information yielded by self-report. Focus on neural and psychophysiological measures is in line with recent proposals that IU reflects a fundamental, evolutionarily supported fear of the unknown that has inherent biological bases (Carleton, 2016b; Shihata et al., 2016). The current review integrates findings from multiple neural and psychophysiological methods and situates those findings in the context of a recent mechanistic model of neural responding to uncertainty. The Uncertainty and Anticipation Model of Anxiety (UAMA), proposed by Grupe and Nitschke (2013), highlights various components of responses to uncertainty that perpetuate anxiety and outlines possible neural circuits involved in each component. The primary aim of this review is to examine how individual differences in IU are related to physiological indicators of responses to uncertainty, identified in the UAMA, that are associated with increased risk for anxiety. Although the UAMA focuses most on anxiety disorders, the processes implicated in the UAMA may contribute to pathological anxiety transdiagnostically (Carleton, 2016a). Thus, this review increases understanding of the potential mechanisms underlying the link between IU and elevated risk for internalizing psychopathology and identifies needs for future research.

The review first briefly describes the construct of IU and its assessment. Next, a summary of the aforementioned UAMA model (Grupe & Nitschke, 2013) is provided, followed by a comprehensive review of the literature of studies examining a measure of trait IU in conjunction with psychophysiology or neuroimaging, organized by method (Table 1). Specifically, studies examining the fear-potentiated startle reflex, skin conductance responses (SCR), heart rate and heart rate variability (HRV), electroencephalography (EEG), event-related potentials (ERPs), structural magnetic resonance imaging (MRI), and functional magnetic resonance imaging (fMRI) are included (Table 2). Each review section is followed by a summary that integrates the findings with the existing model and provides considerations for future research. Finally, we highlight what is known, remaining questions, and the potential implications of research on the neural and psychophysiological correlates of IU.

1. Intolerance of uncertainty and its measurement

The measurement of IU and its associations with related traits and clinical symptoms are briefly reviewed (for a more comprehensive review, see Carleton, 2016a). IU is most frequently measured using the Intolerance of Uncertainty Scale (IUS). The IUS is a 27-item self-report measure that assesses dislike of and responses to uncertainty (Freeston, Rhéaume, Letarte, Dugas, & Ladouceur, 1994). Findings on its factor structure have been mixed (Sexton & Dugas, 2009; Buhr & Dugas, 2002; Norton, 2005), which led Carleton, Norton, and Asmundson (2007) to develop a shortened version of the IUS (IUS-12) that yielded a stable two-factor structure. The two factors of the IUS-12 are prospective IU, which refers to desire for predictability and active seeking of certainty, and inhibitory IU, which refers to paralysis of cognition and action in the face of uncertainty (Carleton, 2012). Prospective IU is thought to reflect the cognitive aspects of IU and is more closely associated with GAD and obsessive compulsive disorder, whereas inhibitory IU is thought to reflect the behavioral aspects of IU and is more closely associated with social anxiety disorder, panic disorder, and depression (Carleton, 2012; McEvoy & Mahoney, 2012). There are several other measures of IU, including the Uncertainty Response Scale (Greco & Roger, 2001) and the Intolerance of Uncertainty Index (Gosselin et al., 2008); however, the long and short forms of the IUS are the most commonly used measures in the existing literature. The current literature search was not specifically restricted based on IU measure; nevertheless, only studies using the long or short form of the IUS were included.

IU is thought to be trait-like and stable over time (Buhr & Dugas, 2002; Carleton, 2012; Mahoney & McEvoy, 2012), although additional longitudinal research is needed to clarify its stability across the lifespan. Recent evidence has suggested that IU reflects a fundamental fear of the unknown that is present in normative samples but that is associated with clinically significant anxiety for some individuals (Carleton, 2012, 2016a). IU was originally conceptualized as a key factor contributing to worry in GAD (Freeston et al., 1994). In particular, it was theorized that worry arises as an attempt to control the unknown, and that the urge to worry may stem from aversion to uncertainty (Dugas, Buhr, & Ladouceur, 2004). IU and worry do appear to be closely linked—the two are moderately correlated (e.g., $r = 0.58$ without correction for attenuation; Norton, 2005), and individuals high in IU report worrying more when anxious than do those low in IU (Buhr & Dugas, 2009; Carleton, 2012). However, IU is not uniquely related to GAD or worry. IU is elevated in obsessive-compulsive disorder (Tolin, Abramowitz, Brigidi, & Foa, 2003), panic disorder (Carleton et al., 2014), social anxiety disorder (Carleton, Collimore, & Asmundson, 2010), and depression (McEvoy & Mahoney, 2011).

Higher IU is associated with various cognitive, affective, and behavioral factors that characterize internalizing psychopathology. IU has been associated with greater engagement in rumination (i.e., repetitive negative, passive thought about past events; Liao & Wei, 2011), higher levels of post-event processing (i.e., repetitive negative thought about social situations; Shiktani, Antony, Cassin, & Kuo, 2016), elevated levels of anxiety sensitivity (i.e., fear of the consequences associated with anxiety-related sensations; Carleton, Norton, et al. (2007) and Carleton, Sharpe, et al. (2007)), and increased checking behavior (Tolin et al., 2003). Additionally, IU has been found to prospectively predict stress throughout the semester in students (Bardeen, Fergus, & Orcutt, 2016). Thus, IU appears to be concurrently and prospectively related to factors associated with the onset and maintenance of internalizing psychopathology.

In addition to being related to known risk factors for psychopathology, IU is associated with anxiety and depression even when controlling for related constructs (Hong & Cheung, 2015; Hong & Lee, 2015). The relation of IU with anxiety and depression symptoms is independent of traits like neuroticism, anxiety sensitivity, and negative affect (Boelen, & Reijntjes 2009; Carleton et al., 2010; McEvoy & Mahoney, 2012). As well, IU has been shown to prospectively predict post-traumatic stress symptoms following trauma exposure, above and

Table 1
Summary of neural regions involved in the UAMA.

Process	Regions
Inflated estimates of threat cost and probability	Dorsomedial PFC, OFC, rostral cingulate cortex, anterior insula, and ventral striatum
Hypervigilance and increased attention to threat	Amygdala, basal forebrain
Deficient safety learning	Ventromedial PFC, amygdala
Behavioral and cognitive avoidance	Amygdala, OFC, dorsolateral PFC, striatum, anterior midcingulate cortex, and anterior insula
Heightened reactivity to threat uncertainty	Amygdala, bed nucleus of the stria terminalis, hypothalamus, pons, periaqueductal gray, and other midbrain and brainstem structures

PFC = prefrontal cortex, OFC = orbitofrontal cortex.

Table 2
Summary of reviewed studies.

First author, year	Sample type	Sample size (*N*)	IUS version	Measure	Primary finding regarding trait IU
Gorka et al., 2016	Healthy adults	37	IUS-27	fMRI	Prospective IU is positively correlated with anterior insula activation during uncertain reward.
Krain et al., 2008	Adolescents with social anxiety disorder and HC adolescents	16; 13	IUS-27	fMRI	IU is positively correlated with ACC and amygdala activity in anxious adolescents high in IU during an uncertain decision making task.
Krain et al., 2006	Healthy adults and adolescents	12; 12	IUS-27	fMRI	IU is positively correlated with ACC activity in adolescents, but not adults, during an uncertain decision making task.
McFadden et al., 2014	Women with anorexia nervosa, recovered from anorexia nervosa, and HCs	20; 24; 24	IUS-27	fMRI	IU is positively correlated with default mode network and sensory motor network activity.
Morriss et al., 2015	Unselected community members	22	IUS-27	fMRI, SCR	Early in fear extinction, high IU individuals have higher SCRs to both threat and safety cues, as well as greater right amygdala activity in response to safety. Later in extinction, high IU individuals have greater SCRs and right amygdala and vmPFC activity to threat versus safety cues.
Oathes et al., 2015	Patients with GAD and HCs	50; 39	IUS-27	fMRI	IU is positively correlated with bilateral anterior insula activity when anticipating uncertainty in patients with GAD.
Schienle et al., 2010	Healthy women	30	IUS-27	fMRI	IU was positively correlated with amygdala activity and negatively correlated with PFMC, ACC, and dlPFC activity under uncertainty.
Shankman et al., 2014	Unselected community members	19	IUS-12	fMRI	Inhibitory IU is positively correlated with right anterior insula activity when anticipating temporally unpredictable images.
Simmons et al., 2008	Unselected undergraduates	14	IUS-27	fMRI	IU is positively correlated with bilateral insula activity during affective ambiguity.
Somerville et al., 2013	Healthy community members	61	IUS-27	fMRI	IU is positively correlated with sustained right insula activity and transient amygdala response to negative pictures.
Hilbert et al., 2015	Patients with GAD and HCs	19; 24	IUS-12	MRI	IU is positively correlated with gray matter volume in the right superior temple pole.
Kim et al., 2017	Unselected undergraduates	61	IUS-27	MRI	IU is positively correlated with gray matter volume in the striatum, particularly the putamen.
Nelson et al., 2014	Patients with MDD only, PD only, comorbid PD and MDD, and HCs	40; 28; 58; 65	IUS-12	EEG	IU mediates the relation between MDD and reduced frontal EEG asymmetry during reward anticipation.
Jackson et al., 2016	Unselected undergraduates	64	IUS-27	ERP	Inhibitory IU is associated with attenuation of the ERN, whereas prospective IU is associated with enhancement of the ERN.
Nelson et al., 2016	Unselected undergraduates	64	IUS-12	ERP	Inhibitory IU is associated with attenuation of the RewP, whereas prospective IU is associated with enhancement of the RewP.
Nelson et al., 2015	Unselected undergraduates	48	IUS-12	ERP	Prospective IU is associated with attenuation of the LPP to fear and generalization stimuli in a fear conditioning paradigm.
Thibodeau et al., 2013	Unselected community members	40	IUS-12	Heart rate, SCR	IU is not correlated with heart rate or SCRs.
Deschenes et al., 2016	Unselected undergraduates	76	IUS-27	HRV	IU is associated with greater decreases in high frequency HRV during worry.
Ottaviani et al., 2014	High worriers and HCs	31; 36	IUS-27	HRV	IU is correlated with a higher ratio between low and high frequency HRV in high worriers.
Dunsmoor et al., 2015	Unselected community members	47	IUS-27	SCR	IU is positively correlated with spontaneous recovery of SCRs during extinction.
Kirschner et al., 2016	High and low worriers	23; 23	IUS-12	SCR	IU is not correlated with SCRs when passively viewing pictures.
Morriss, Christakou, et al., 2016	Unselected undergraduates	38	IUS-27	SCR	High IU individuals have high SCRs to both threat and safety cues early in fear extinction. Later in extinction, high IU individuals have greater SCRs to threat versus safety cues.
Morriss, Macdonald, et al., 2016	Unselected undergraduates	54	IUS-27	SCR	High IU individuals have higher SCRs to both threat and safety cues during fear acquisition than do those low in IU. In extinction, high IU individuals have greater SCRs to threat versus safety cues.
Chamberlain et al., 2013	Adolescents with autism and HCs	18; 21	IUS-12	Startle reflex	IU predicts decreased startle responses to uncertain threat in a regression model including generalized anxiety and behavioral rigidity.
Chin et al., 2016	Unselected undergraduates	45	IUS-27	Startle reflex	IU is positively correlated with startle magnitude under a 50%, but not 75%, chance of threat.
Gorka et al., 2014	Patients with PDr only, MDD only, comorbid PD and MDD, and HCs	22; 30; 52; 68	IUS-12	Startle reflex	At high, but not low, levels of IU, panic disorder is associated with greater startle magnitude under safety.
Lieberman et al., 2016	Patients with PD and HCs	71; 71	IUS-12	Startle reflex	At high, but not low, levels of IU, panic disorder is associated with greater startle magnitude under safety. This relation is mediated by cognitive flexibility.
Nelson & Shankman, 2011	Unselected undergraduates	69	IUS-12	Startle reflex	Inhibitory IU is negatively correlated with startle magnitude under uncertain threat.

MRI = magnetic resonance imaging; fMRI = functional magnetic resonance imaging; EEG = electroencephalography; ERP = event-related potential; SCR = skin conductance response; HRV = heart rate variability; IU = intolerance of uncertainty; IUS = Intolerance of Uncertainty Scale; OFC = orbitofrontal cortex; dlPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; ERN = error-related negativity; RewP = reward positivity; LPP = late positive potential; SPN = stimulus-preceding negativity; MDD = major depressive disorder; PD = panic disorder; GAD = generalized anxiety disorder; HC = healthy control.

beyond anxiety sensitivity and negative affect (Oglesby et al., 2016). Overall, IU appears to have an important and unique role in several forms of internalizing psychopathology.

2. Uncertainty and Anticipation Model of Anxiety

As reviewed above, IU has been associated with risk for various forms of internalizing psychopathology, but the mechanisms by which IU may increase risk are unclear. A recent synthesis of contemporary models of uncertainty proposed that IU reflects the inability to endure anxiety that arises in the face of uncertainty and confers risk for a range of psychopathology (Carleton, 2016a). Difficulty enduring uncertainty and its associated anxiety is proposed to reflect an inherent, biologically based mechanism (Carleton, 2016a), in line with the UAMA, which posits that disruptions in the neural circuitry underlying responding to uncertainty go awry, result in anxiety, and confer risk for psychopathology (Grupe & Nitschke, 2013). Proposed by Grupe and Nitschke (2013), the UAMA identifies five processes that relate to how excessive anxiety arises in the face of uncertainty: (1) Estimates of the cost and probability of uncertain threat are inflated; (2) individuals experience hypervigilance in uncertain situations and exhibit increased attention to potential threat; (3) the ability to resolve uncertainty and learn that situations are in fact safe is deficient; (4) individuals engage in behavioral and cognitive avoidance in uncertain situations that have the potential to be threatening; and (5) reactivity to uncertain threat is heightened. Each process is thought to underlie adaptive responding to threat that goes awry in uncertain situations and confers risk for the experience of anxiety (Grupe & Nitschke, 2013). These psychological processes are thought to dynamically interact. For example, inflated estimates regarding how costly and probable an uncertain threat is increase the vigilance and attention to information about potential threat (Grupe & Nitschke, 2013). According to the model, even when threat is absent and the context indicates safety, the ability to inhibit anxious responding is disrupted. Together, inflated estimates of threat and deficient safety learning contribute to avoidance in uncertain situations, at both the cognitive and behavioral levels, which reinforces anxiety (Grupe & Nitschke, 2013). These factors all increase reactivity to uncertainty, in turn leading to further avoidance. Examining how alterations in some or all of these five interconnected processes may be associated with IU is essential for increasing our understanding of how IU may confer risk for clinical levels of anxiety and thereby internalizing disorders. The UAMA outlines the proposed neural correlates of each component (for a brief summary, see Table 1), making this model especially relevant when integrating the psychophysiological and neural literature on IU.

Inflated estimates of the probability of threat are thought to result from disruptions in parts of the dorsomedial prefrontal cortex, which is associated with probability assessment (Grupe & Nitschke, 2013). In addition to probability, the model also highlights *inflated estimates of the cost of threat*, which may reflect disruptions in the orbitofrontal cortex and related circuitry, such as the ventral striatum and anterior insula, associated with calculating the expected value and cost of a future event. Disruptions in prediction error signaling, generated by midbrain dopaminergic neurons, are also thought to contribute to inflated estimates of both the probability and cost of threat by preventing the appropriate adjustment of expectancies when aversive events that were expected do not occur (Grupe & Nitschke, 2013).

Hypervigilance arises from hyperactivity of the basolateral amygdala in response to and in anticipation of threat, which contributes to difficulty in correctly associating environmental cues with aversive outcomes, such that ambiguous material is more readily associated with threat (Grupe & Nitschke, 2013). Disruptions in the central nucleus of the amygdala, which is involved in attentional gating, further contribute to *increased attention to stimuli that are perceived as threatening*.

Impairments in accurately identifying what is or is not threatening are further manifested in *deficient safety learning*, through which individuals have difficulty discriminating threatening stimuli versus those that denote safety (Grupe & Nitschke, 2013). The UAMA model posits that difficulty discriminating between threat and safety is reflected in hyperactivity of the amygdala and altered connectivity of the amygdala with the ventromedial prefrontal cortex (vmPFC), which is thought to be involved in responding to safety by downregulating the amygdala.

Avoidance, both behaviorally and cognitively, of uncertainty may also result from alterations in the amygdala and its interactions with regions involved in action selection, such as the orbitofrontal cortex, lateral prefrontal cortex, ventral and dorsal striatum, and anterior midcingulate cortex (Grupe & Nitschke, 2013). Heightened expectations of fear, reflected in the anterior insula, may also contribute to avoidance by causing the individual to think the event will be highly aversive and is thus important to avoid (Grupe & Nitschke, 2013).

Expectations of fear and related activation of the anterior insula are also thought to promote *heightened responding to uncertain threat*, manifested as anticipatory anxiety and reflected in sustained activation of the bed nucleus of the stria terminalis (BNST) to uncertain threat (Grupe & Nitschke, 2013). Exposure to uncertainty also results in activation of the amygdala, although the amygdala (particularly the medial portion of the central nucleus) is thought to reflect phasic responses to relatively certain threat rather than sustained responding to uncertainty. In turn, the UAMA model posits that activation of both the BNST and amygdala mobilizes defensive responding that is mediated by areas such as the hypothalamus and pons. Individuals who experience these exaggerated responses to uncertain threat may be less able to exert control over their anxiety due to disruptions in the connectivity of the anterior midcingulate cortex, which helps guide action in the face of uncertainty, with regions such as the amygdala, anterior insula, and dorsolateral prefrontal cortex (Grupe & Nitschke, 2013). Overall, disruptions in these five domains are thought to dynamically interact and lead to clinical anxiety. The UAMA parallels recent proposals that suggest individuals who are high in IU have difficulty enduring and effectively responding to uncertainty and subsequently experience elevated levels of anxiety in uncertain situations (Carleton, 2016a,b).

3. Intolerance of uncertainty and MRI/fMRI

Neuroimaging has provided insight into the structure and function of brain regions implicated in responding to uncertainty and how they are disrupted in individuals with high IU. A variety of structural (MRI) and functional (fMRI) imaging paradigms have been used to delineate how altered interactions between regions, including those highlighted in the UAMA, contribute to the processing of uncertainty.

Altered function of the anterior insula has been consistently linked with IU across fMRI paradigms involving uncertain threat and even reward. When contrasting anticipation of unpredictable negative images with predictable negative images, Shankman et al. (2014) found that the unpredictable images were associated with greater right anterior insula activation. The degree of activation was positively correlated with inhibitory, but not prospective, IU (Shankman et al., 2014). These results are similar to those of Somerville et al. (2013), who examined responses to sustained and transient uncertain threat in the form of negative pictures and found that total IU score was positively correlated with both sustained activity in the right insula and transient activity in the amygdala under uncertainty. A positive correlation between IU and bilateral insula activity was also found in the context of ambiguity in a paradigm that used ambiguous emotional faces (Simmons, Matthews, Paulus, & Stein, 2008). Oathes, Hilt, and Nitschke (2015) also used a picture-viewing paradigm and found that IU was positively correlated with bilateral anterior insula activation to uncertainty; however, the results were specific to patients with GAD and were not observed in healthy controls. The finding that activity of the anterior insula is associated with IU also extends to the appetitive domain of uncertainty. Gorka, Nelson, Phan, and Shankman (2016) showed that prospective IU is positively correlated with increased bilateral anterior insula activation during uncertain reward. Together, these results highlight that anterior insula function, which is implicated in the assessment and anticipation of uncertainty (Grupe & Nitschke, 2013), is central to understanding the neural correlates of IU.

The amygdala has long been hypothesized to play a key role in responding to uncertainty (e.g., Pearce & Hall, 1980), and the association between the amygdala and IU has also been investigated. Consistent with Somerville et al.'s (2013) results, Schienle, Köchel, Ebner, Reishofer, and Schäfer (2010) have shown that, in adult women, IU is associated with increased amygdala activity when anticipating uncertain pictures. By contrast, the authors found that IU was negatively correlated with activity of the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex, and posterior frontomedial cortex under uncertainty. This pattern of results may reflect enhanced reactivity to uncertainty, coupled with weaker top-down emotion regulation, among individuals high in IU.

The association between the amygdala and IU has also been investigated using fear conditioning paradigms. During early extinction, individuals low in IU showed greater SCRs and greater activity in the right amygdala to cues that previously signaled threat compared to those that signaled safety (Morriss, Christakou, & van Reekum, 2015). In contrast, individuals high in IU showed greater right amygdala activity in response to safety compared to threat cues, though they did not exhibit differential SCRs (Morriss et al., 2015). These results suggest that individuals high in IU have difficulty discriminating between threat and safety early in extinction and that their responses to threat may generalize to stimuli that denote safety. During later extinction, individuals low in IU showed comparable SCRs and amygdala activity in response to both threat and safety. In contrast, individuals high in IU showed greater SCRs and right amygdala activity in response to threat versus safety cues, as well as greater activity of the vmPFC (Morriss et al., 2015). These results suggest that high IU individuals continue to express fear to previously learned threat stimuli, despite the absence of threat; the authors suggest that difficulty inhibiting fear expression may be reflected in elevated amygdala and vmPFC activity and result from reduced flexibility of amygdala-vmPFC circuitry.

Research focusing on neural networks, rather than isolated regions, is particularly promising in further understanding IU. In women who have recovered from anorexia nervosa, higher IU has been associated with lower default mode and sensory motor network activity (McFadden, Tregellas, Shott, & Frank, 2014). Associations between IU and default mode or sensory motor network activity were not observed in currently anorexic or healthy control women (McFadden et al., 2014). These findings may reflect a trait vulnerability to anorexia that is then altered by changes that accompany the disorder, including food restriction and further increased IU scores.

Initial findings in adolescents, among whom internalizing psychopathology is particularly prevalent (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), lend a developmental perspective on the neural correlates of IU. Krain et al. (2008) compared responses to maximal uncertainty versus lower levels of uncertainty in a reward task and found that IU was positively correlated with activity in the right and left amygdala, medial frontal gyrus, and ACC in adolescents. Among adolescents with GAD and/or social anxiety disorder, those higher in IU had greater activity in posterior and temporal regions, including the precentral gyrus, posterior cingulate, parietal cortex, and middle temporal gyrus (Krain et al., 2008). Using the same reward paradigm, Krain et al. (2006) found that IU was associated with greater increases in ACC activity that co-occurred with increases in uncertainty in adolescents, but not in adults. These results suggest that the association between IU and ACC activity in particular may differ throughout development, specifically around the transition from adolescence to adulthood. The authors propose that adults develop compensatory neural responses such that activity of the ACC, although enhanced by uncertainty in a task, is not related to trait IU, whereas adolescents high in IU may experience greater conflict as reflected in ACC activity when making uncertain decisions.

While the majority of neuroimaging studies of IU have focused on functional tasks, a structural MRI study by Hilbert et al. (2015) found that IU is positively correlated with gray matter volume in the right superior temporal pole. Alterations in the structure of the temporal gyri have been found in patients with GAD, and the temporal poles in particular are involved in emotion processing (Hilbert et al., 2015; Moon, Kim, & Jeong, 2014; Olson, Plotzker, & Ezzyat, 2007). Increased gray matter volume in the temporal poles region may be associated with enhanced emotion processing in individuals higher in IU, but further research using fMRI will be necessary to better understand the function of the temporal poles in relation to IU. Additionally, Hilbert et al. (2015) found that IU and gray matter volume in the striatum were positively correlated. Although the correlation did not survive a conservative correction for multiple comparisons, recent findings from Kim et al. (2017) have also documented a positive correlation between gray matter volume in the striatum—particularly the putamen—and IU. Given that the striatum is involved in encoding how predictable and expected outcomes are, the authors suggest that higher striatal volume associated with IU may reflect a neuroanatomical correlate of heightened desire for predictability (Kim et al., 2017).

3.1. Summary

Evidence from fMRI studies suggests that IU is associated with activity of the anterior insula, particularly under conditions of uncertain threat or reward. These results are consistent with the UAMA, which highlights the association of the anterior insula with inflated estimates of the cost and probability of threat, heightened reactivity to uncertainty, avoidance, and maladaptive control. Elevated amygdala activation in response to uncertainty also appears to be associated with IU, consistent with the notion of heightened responding to uncertainty highlighted in the UAMA. However, none of the three studies that showed a correlation between IU scores and amygdala activation (Krain et al., 2008; Schienle et al., 2010; Somerville et al., 2013) found an association between IU and BNST activation—a key part of the UAMA. Although BNST activation was not correlated with IU, Somerville et al. (2013) did find greater BNST activation to unpredictable (relative to predictable) images.

There are several possible explanations for the lack of findings showing an association between IU and the BNST despite findings linking the amygdala and IU. The amygdala has long been highlighted in models of learning in the context of uncertainty (e.g., Pearce & Hall, 1980; Rescorla & Wagner, 1972) and responds to uncertain stimuli, such as surprised faces (Kim et al., 2004). The results showing that trait IU is associated with amygdala activation to uncertain stimuli are consistent with this broad literature. Despite involvement of the amygdala in processing uncertainty (e.g., Kim et al., 2004), the UAMA does not emphasize the amygdala as a key part of heightened responding to uncertain threat (Grupe & Nitschke, 2013). Instead, Grupe and Nitschke (2013) posit that activation of the amygdala (particularly the medial portion of the central nucleus) occurs in a phasic manner in response to threat that is relatively imminent and certain. Conversely, the model suggests that activity of the BNST reflects sustained responding to uncertainty. Recent work, including reformulations of influential early models (Davis, Walker, Miles, & Grillon, 2010), has suggested that both the amygdala and BNST are involved in phasic and sustained responding to uncertainty (Shackman & Fox, 2016). Thus, the UAMA may benefit from greater attention to the role of the amygdala in responding to threat uncertainty, especially in light of findings that trait IU is associated with greater amygdala activity in response to uncertainty.

It is possible that the task paradigms used in studies finding a correlation between IU and amygdala activity did not elicit sustained responding. Krain et al. (2008) had anticipation periods that ranged from

2 to 6 s, while Schienle et al. (2010) had 6-second-long anticipation periods. In both paradigms, the task switched between uncertainty and certainty randomly for every trial. Detecting BNST activation may be aided by using designs that have longer anticipation periods and require less frequent switching. In addition, the type of aversive stimulus used may be important—negative pictures and uncertain decision-making tasks elicit BNST activation more weakly than more noxious stimuli like electric shocks (e.g., Somerville, Whalen, & Kelley, 2010).

Finally, technological limitations may also partially account for the lack of BNST activation in studies of IU. The BNST is an anatomically small subcortical region that may be difficult to image at the spatial resolution afforded by 3 Tesla magnetic field strengths (Lebow & Chen, 2016). Recent advances in fMRI technology have allowed for higher magnetic field strengths (i.e., 7 Tesla) that allow for greatly improved spatial resolution. Although studies using 3 Tesla and even 1.5 Tesla MRI scanners (e.g., Straube, Mentzel, & Miltner, 2007) have found BNST activation, research using higher magnetic field strengths may help elucidate the relation of the BNST with responses to uncertainty, as well as trait IU.

Evidence from Krain et al.'s (2006; 2008) studies suggests that the ACC might also be critically involved in IU. The authors found that adolescents, but not adults, who were higher in IU showed greater ACC activation to uncertainty during a decision-making task (Krain et al., 2006). The differential relationship in adults is consistent with Schienle et al.'s (2010) study showing an opposite pattern (i.e., a negative correlation between IU and ACC activation) in adults. The UAMA does not offer specific predictions about the ACC; instead, the UAMA is focused on the subgenual ACC, which is considered as part of a large region, the vmPFC, involved in safety learning. The vmPFC downregulates amygdala activity, consistent with findings that show that vmPFC activation is associated with reduced anxiety (e.g., Grupe & Nitschke, 2013; Nitschke et al., 2009). However, other studies have found that the vmPFC is associated with increased anxiety (e.g., Grupe & Nitschke, 2013; Hayes, LaBar, Petty, McCarthy, & Morey, 2009). Such findings are consistent with Morriss et al.'s (2015) finding that greater vmPFC activity is associated with higher IU. Some researchers have posited that posterior parts of the vmPFC, as well as the dorsal ACC, are associated with the expression of fear, while more anterior regions are associated with safety learning and fear extinction (Milad et al., 2009; Myers-Schulz & Koenigs, 2012; Phelps, Delgado, Nearing, & LeDoux, 2004). Additional research is needed to clarify the role of the ACC and vmPFC in responding to uncertainty, as well as developmental changes in how this circuitry responds to uncertainty.

Understanding the neural correlates of IU will further depend on examining connectivity between regions, in addition to examining activation of regions in isolation. For example, connectivity between the amygdala and vmPFC may be important for understanding the relation between IU and deficient safety learning; it may be that individuals higher in IU have diminished connectivity between the amygdala and vmPFC, regardless of the correlations between IU and activity in either region alone. While Morriss et al. (2015) found that activity of both the right amygdala and the vmPFC is positively correlated with IU in late extinction, they did not examine connectivity between the two regions, which would be helpful to understand functional interactions within this circuit. The findings on networks reviewed above, such as the negative correlation between IU and default mode network activity in recovered anorexic women (McFadden et al., 2014), have thus far only been found in this specific population. Future research examining broader networks such as the default mode network in healthy individuals and those with anxiety will be helpful to more generally understand these effects with regard to IU. Moreover, future fMRI studies examining prospective and inhibitory IU separately (e.g., Jackson, Nelson, & Hajcak, 2016) will also be essential for understanding the neural correlates of IU.

4. Intolerance of uncertainty and EEG/ERPs

Electroencephalography (EEG) and event-related potentials (ERPs) have the temporal resolution to allow for the examination of different stages of responses to uncertainty. Three ERP components have been studied in relation to IU and are discussed below. The error-related negativity (ERN) is elicited when mistakes are made, is thought to reflect endogenous threat, and may relate to estimates of the cost of threat in the UAMA (Weinberg et al., 2016). The late positive potential (LPP) has been suggested to reflect arousal and may relate to heightened attention and responses to uncertainty in the UAMA (Hajcak, Weinberg, MacNamara, & Foti, 2011). Finally, the reward positivity (RewP) reflects the evaluation of outcomes as rewarding and may be related to neural responses to the receipt of rewards (Proudfit, 2015); however, it is not yet clear how reward processing relates to IU, so RewP results may suggest a new direction for the model. Frontal EEG asymmetry has also been examined in relation to IU. Frontal EEG asymmetry represents the ratio between left and right frontal activity; greater left versus right asymmetry is thought to reflect approach motivation, while right versus left asymmetry is thought to reflect withdrawal (Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Examining frontal EEG asymmetry in a reward paradigm may provide further support for the importance of considering reward processing in understanding responses to uncertainty.

Research using ERPs and frontal EEG asymmetry suggests that IU may relate to alterations in reward processing. Nelson, Shankman, and Proudfit (2014) examined the relation of IU with frontal EEG asymmetry when anticipating uncertain rewards across patients with major depressive disorder (MDD) only, patients with panic disorder only, patients with both disorders, and healthy controls. Greater IU was associated with reduced frontal EEG asymmetry in the overall sample, and the relation between MDD and reduced frontal EEG asymmetry was mediated by IU. These results suggest that IU is associated with diminished anticipation of uncertain rewards and may explain the association between MDD and reduced frontal EEG asymmetry, at least in the context of uncertain rewards. When examining IU and reward processing using ERPs, Nelson, Kessel, Jackson, and Hajcak (2016) found that higher inhibitory IU was associated with smaller responses to receiving rewards as indexed by the RewP, whereas higher prospective IU was associated with a larger RewP. The authors examined the RewP in a gambling task in the contexts of predictable tone sequences and unpredictable tone sequences. The RewP was diminished in the unpredictable context, but the associations between the IU subscales and the RewP persisted across both contexts. These results suggest that uncertainty may interfere with neural responses to rewards, but that in both predictable and unpredictable contexts, trait IU is associated with reward responses. More specifically, inhibitory and prospective IU appear to have opposite relations with reward responses.

Similarly, work by Jackson et al. (2016) has shown that error processing has differential relations with inhibitory and prospective IU. Inhibitory IU is associated with a smaller ERN in response to errors in a flanker task, whereas prospective IU is associated with a larger ERN. The authors suggest that inhibitory IU and the associated diminishment of the ERN reflect avoidance and inhibition in the face of uncertainty, while prospective IU and the associated enhancement of the ERN reflect action in the face of uncertainty.

Within a fear conditioning paradigm, Nelson, Weinberg, Pawluk, Gawlowska, and Proudfit (2015) investigated ERPs in response to conditioned stimuli and perceptually similar (generalized) stimuli. The authors compared the LPP across these two classes of stimuli to examine whether the LPP is enhanced for stimuli to which fear might generalize due to their perceptual similarity to the conditioned stimulus. The LPP was larger for conditioned stimuli than for generalized stimuli. Interestingly, prospective IU was associated with diminished LPP amplitudes to both conditioned and generalized stimuli. Given that the LPP is thought to index sustained attention and arousal, these results suggest that individuals high in prospective IU may engage in cognitive avoidance in the face of stimuli that signal threat or that are uncertain.

4.1. Summary

Using both EEG and ERPs, IU has been shown to be associated with alterations in reward processing in uncertain contexts. Higher total IUS scores are associated with reduced anticipation, while inhibitory IU is associated with blunted responses to reward receipt and prospective IU with enhanced responses to reward receipt (Nelson et al., 2014, 2016). These findings raise interesting questions about the nature of reward processing alterations in relation to IU, which have begun to be explored in behavioral studies as well (e.g., Carleton et al., 2016; Luhmann, Ishida, & Hajcak, 2011; Tanovic, Hajcak, & Joormann, in press). Exploring the relation between IU and responding to rewards is especially important given that IU is elevated among individuals who also have deficits in reward processing, such as those with MDD (Liao & Wei, 2011; McEvoy & Mahoney, 2012). However, most recent psychophysiology and neuroimaging work, as well as the UAMA, has focused on threat processing. Future work should consider how responding to uncertainty, both at the state and trait levels, impacts the processing of rewards. To that end, task paradigms examining ERPs in response to uncertain reward feedback may be particularly informative (for an example, see Hirsh & Inzlicht, 2008).

IU is also associated with responding to errors, which can be conceptualized as a source of endogenous threat that is uncertain—the participant is unsure of whether or not he/she will make an error. Specifically, inhibitory IU is associated with diminished responses to errors, and prospective IU with enhanced responses. The relation between prospective IU and ERN enhancement may reflect the overestimation of the cost of threat that is a component of the UAMA. Errors that are more costly elicit larger ERNs (Potts, 2011). Thus, if individuals high in prospective IU perceive errors, which are uncertain and threatening, as more costly, the heightened perceived cost could be reflected in ERN enhancement.

The relation between the ERN and inhibitory IU found by Jackson et al. (2016) may reflect avoidance of the threat and uncertainty associated with errors. This notion would be consistent with the UAMA, which highlights both behavioral and cognitive avoidance in the face of uncertainty. Other work by Nelson et al. (2015) examining the LPP may appear inconsistent, given that diminished LPP amplitudes were associated with prospective, not inhibitory, IU. However, the ERN and LPP paradigms differ in an important way: the former required a motor response, while the latter required passive viewing. Inhibitory IU, which has been conceptualized as reflecting a behavioral manifestation of IU, may be associated with avoidance when one is required to act (i.e., behavioral avoidance), whereas prospective IU, which has been conceptualized as reflecting a cognitive manifestation of IU, may be associated with avoidance when one is simply supposed to pay attention (i.e., cognitive avoidance; Carleton, 2012). Future work examining IU and forms of avoidance, perhaps in a single paradigm that varies the type of response required, would help to disentangle the association between the ERN and IU.

5. Intolerance of uncertainty and the startle reflex

The startle reflex is a measure of defensive responding that is thought to reflect fear or anxiety in response to a conditioned stimulus (Davis, 2006; Lang, 1995). Both the amygdala and BNST are involved in the generation of the startle reflex (Davis, 2006), and the startle reflex may be an index of heightened reactivity to uncertainty that is central to the UAMA (Grupe & Nitschke, 2013). The startle response is typically measured by recording electromyogram (EMG) activity of the eye muscles responsible for blinking, the orbicularis oculi. A common paradigm used to elicit startle responses is the Neutral-Predictable-Unpredictable (NPU) threat test, where startle is measured in three conditions: a neutral condition, where participants are safe from receiving an electric shock or some other noxious stimulus; a predictable threat condition, where participants are shocked at predictable times that are always signaled by a cue; and an unpredictable threat condition, where participants are shocked at unpredictable times (Schmitz & Grillon, 2012). The startle reflex is measured in response to startle probes, such as bursts of white noise, that are administered during each condition (Schmitz & Grillon, 2012).

In the face of maximal uncertainty of a threat (i.e., a 50% chance of receiving an electric shock), higher levels of IU were associated with a heightened startle reflex in unselected undergraduates (Chin, Nelson, Jackson, & Hajcak, 2016). Interestingly, the relation between IU and the startle reflex was not evident for less uncertain threat; Chin et al. (2016) found that when there was a 75% chance of electric shock, there was no relation between IU and the startle reflex. Their findings suggest that IU may be associated with exaggerated startle responses only in the most uncertain situations, despite the fact that these situations may be less objectively threatening than some situations characterized by greater certainty.

In a similar sample of unselected undergraduates, Nelson and Shankman (2011) found that IU was associated with startle responses only in the face of uncertain threat, not certain threat or safety. Contrary to the authors' hypotheses, individuals higher in IU had smaller startle responses, a finding that was driven by inhibitory IU. The relation between the IUS total score and startle responding was mediated by perceived control over anxiety-related events, such that higher IU led to lower perceived control, which was associated with smaller startle responding. These results suggest that inhibitory IU may be associated with decreased perceptions of control over anxiety-inducing events, which is associated with diminished defensive responding to uncertain threat. Chamberlain et al. (2013) also found that IU is associated with diminished startle responses to uncertain threat in adolescents with autism, over and above effects of generalized anxiety and behavioral rigidity. The authors suggest that diminished startle responsiveness might reflect diminished physiological flexibility.

At high levels of IU, panic disorder is associated with greater startle responses under conditions of safety compared to healthy controls (Gorka, Lieberman, Nelson, Sarapas, & Shankman, 2014). While panic disorder is associated with greater startle responses to safety, uncertain threat, and certain threat (Shankman et al., 2013), only in the context of safety is there an interaction with IU. A follow-up study showed that the relation between IU and the startle response to safety is mediated by cognitive flexibility, which was hypothesized to be relevant because conditions in the NPU task switch between safety and threat (Lieberman, Gorka, Sarapas, & Shankman, 2016). Taken together, these results suggest that IU is associated with exaggerated defensive responding to safety in patients with panic disorder, which may result from deficits in cognitive flexibility.

5.1. Summary

Findings regarding the relation between startle responses and uncertain threat are mixed. While Chin et al. (2016) found that greater IU was associated with greater startle responses to uncertain threat, Nelson and Shankman (2011) and Chamberlain et al. (2013) found that greater IU was associated with diminished responses. It is possible that the discrepancy stems from differences in inhibitory and prospective IU. Diminished startle responses appear to be associated with inhibitory IU, perhaps by way of a mechanism involving perceived control. Although Chin et al. (2016) did not report analyses considering the two subscales individually, it may be that their results are driven by prospective IU and involve a different mechanism that enhances defensive responding. For example, prospective IU, which reflects active seeking of certainty, could be associated with greater BNST activation to uncertainty, which may result in greater startle responses. Regardless of whether there is specificity to a particular subscale, Chin et al.'s (2016) findings are consistent with the notion of heightened reactivity to uncertainty, as proposed by the UAMA.

In individuals high in IU, panic disorder appears to be associated with impaired discriminate responding to safety (Gorka et al., 2014; Lieberman et al., 2016). The relation between IU and the startle response to safety is mediated by cognitive flexibility, suggesting that the ability to dynamically adapt responses to changes in the environment may be an important factor in understanding safety signal responding (Lieberman et al., 2016). These findings are consistent with the emphasis on deficient safety learning in the UAMA, which highlights lack of discriminate responding to safety signals as reflected in altered amygdala and vmPFC function. This work also extends the UAMA to consider how components of executive function may relate to safety learning.

Future research should consider the role of perceived control in mediating the association between IU and defensive responding. Uncertainty may elicit different types of responses based on the degree of control the individual perceives, both over the situation and one's own responses. Nelson and Shankman (2011) assessed “perceived control over anxiety-related events” using the Anxiety Control Questionnaire (Rapee, Craske, Brown, & Barlow, 1996), which examines control over a situation and one's own responses. It may be fruitful to disentangle whether one of these components in particular is associated with responding to uncertainty. For example, IU may be associated with greater defensive responding in those who feel that they should have control over their situation (but do not) and with diminished defensive responding in those who feel that they are able to control their anxiety. Integrating perceived control could be a useful extension of the UAMA, which highlights difficulties in controlling responses to uncertainty but does not specifically consider perceptions of control over uncertain situations and one's responses to them.

In general, assessment of perceptions in paradigms like the NPU is important to investigate whether individuals high in IU have different initial evaluations of levels and controllability of uncertainty, in addition to different responses over time. Investigating the relation between perceptions of uncertainty and IU could be done by simply using self-report or by incorporating measures that are sensitive to perceptions of probability, such as ERP components like the P3. Such work would also clarify whether overestimating the cost and probability of threat, as highlighted in the UAMA, is related to IU. Finally, the mixed findings regarding IU and the startle reflex in unselected samples highlight the value of considering inhibitory and prospective IU individually in future work.

6. Intolerance of uncertainty and the skin conductance response

The SCR refers to electrodermal activity that occurs in response to a given stimulus (Critchley, Elliott, Mathias, & Dolan, 2000). Changes in skin conductance are thought to reflect changes in emotional arousal, although the measure does not appear to be sensitive to valence (Davis, 2006). The neurobiological mechanisms underlying SCRs is thought to involve the orbitofrontal cortex, anterior insula, lingual gyrus, fusiform gyrus, and cerebellum (Critchley et al., 2000), as well as projections from the central nucleus of the amygdala to the hypothalamus (Davis, 1992). SCRs may be related to the component of the UAMA that focuses on heightened responses to uncertainty, which involves activity of the BNST, amygdala, and anterior insula in the face of uncertain threat. Activity in the BNST and amygdala in particular may mobilize defensive responding via connections with the hypothalamus, periaqueductal gray, and other midbrain and brainstem structures (Grupe & Nitschke, 2013).

The SCR can be examined in various types of paradigms, ranging from passive viewing tasks to fear conditioning studies. A typical fear conditioning paradigm involves a neutral stimulus (e.g., a shape presented on the screen) and an unconditioned stimulus (e.g., an electric shock), which produces an unconditioned response (e.g., anxiety and an increase in skin conductance). The neutral and unconditioned stimuli are repeatedly associated, usually by being presented together, and the neutral stimulus becomes a conditioned stimulus that elicits the same response (e.g., anxiety and an increase in skin conductance) as the unconditioned stimulus, even when presented alone (Delgado, Olsson, & Phelps, 2006).

Evidence from SCR studies suggests that individuals with high IU have poorer fear extinction. Dunsmoor, Campese, Ceceli, LeDoux, and Phelps (2015) found that higher IU was associated with greater spontaneous recovery of the SCR during an extinction retention test that occurred 24 h after the initial conditioning and extinction. In other words, their findings suggest that higher IU is associated with diminished extinction of fear responses, even after the threat is removed for an extended period of time. Interestingly, in a novelty-facilitated extinction condition in which the threat was replaced with a novel, non-threatening stimulus (instead of basic omission of threat), IU was not related to SCRs (Dunsmoor et al., 2015). The authors suggest that the introduction of a novel stimulus reduces uncertainty and thus may decrease defensive responding in those high in IU.

Similarly, (Morriss et al. (2016) found evidence of weaker fear extinction among individuals with higher IU. Specifically, the authors found that individuals low in IU showed greater SCRs to cues that previously signaled threat compared to those that signaled safety early in extinction. Later in extinction, individuals low in IU showed comparable SCRs to both threat and safety cues, suggesting that they had learned that neither cue is threatening. Conversely, individuals high in IU showed elevated SCRs to both threat and safety cues early in extinction, suggesting that their response to threat may have been generalized even to stimuli that indicated safety. Later in extinction, individuals high in IU showed greater SCRs to threat cues compared to safety cues. These results suggest that individuals with elevated IU have difficulty discriminating between threat and safety cues early in extinction and show continued defensive responding to former threat cues later in extinction, despite the total absence of threat. Similar patterns of results have been found in other studies using fear conditioning paradigms (Morriss et al., 2015; Morriss, Macdonald, & van Reekum, 2016). As well, evidence of heightened and indiscriminate responding to threat and safety has also been found during fear acquisition, where high IU participants show elevated SCRs to both threat and safety cues compared to those low in IU (Morriss, Macdonald, et al., 2016).

By contrast, other studies have failed to find significant associations between IU and SCRs. During a keyboard typing task in which participants were asked to type a passage as quickly and accurately as possible, there was no relation between IU and SCRs (Thibodeau, Carleton, Gomez-Perez, & Asmundson, 2013). In a picture viewing task that featured safe, dangerous, and uncertain pictures, IU was not correlated with SCRs when anticipating the pictures (Kirschner, Hilbert, Hoyer, Lueken, & Beesdo-Baum, 2016).

6.1. Summary

IU appears to be associated with deficient safety learning, as evidenced by elevated defensive responding indexed by SCR among individuals high in IU during conditions that were no longer threatening (Dunsmoor et al., 2015; Morriss et al., 2015; Morriss, Christakou, & van Reekum, 2016). This elevated SCR was evident even 24 h after an initial laboratory conditioning session (Dunsmoor et al., 2015), suggesting that inability to respond appropriately to once-threatening stimuli may persist long after the threat is removed. High IU individuals also had difficulty discriminating between safe and threatening stimuli early in extinction (Morriss et al., 2015; Morriss, Christakou, et al., 2016). This pattern of responding might reflect hypervigilance in situations that are new and uncertain, like the beginning of an extinction period. Difficulty discriminately responding to safe and threatening stimuli is also evidence of disruptions in safety learning, which is further supported by the fact that high IU individuals continued to exhibit elevated SCRs to stimuli that formerly signaled threat in the late extinction period (Morriss et al., 2015; Morriss, Christakou, et al., 2016). The finding that there is no relation between IU and SCRs when extinction is facilitated by the introduction of a novel stimulus suggests that reducing the uncertainty that may be inherent in extinction could aid safety learning for those high in IU (Dunsmoor et al., 2015). These results are consistent with the UAMA and may reflect disruptions in the basolateral amygdala, as well as its connections with the vmPFC, which are thought to be involved in effective safety learning.

Thus far IU and SCR have not been linked in paradigms that do not involve fear conditioning. Based on the null finding in the typing paradigm used by Thibodeau et al. (2013), it is possible that IU is not related to defensive responding when attempting to perform a stressful task. Although the authors hypothesize that IU may be related to typing performance because individuals high in IU would be more concerned with ensuring the accuracy of their keystrokes, it is unclear whether this type of paradigm elicits processing that is directly related to uncertainty. Thus, IU may be related to defensive responding but only during tasks in which uncertainty is more salient. Overall, Thibodeau et al.'s (2013) approach highlights the importance of considering how exaggerated responses to uncertainty impact behavior. The UAMA focuses on the distressing consequences of these responses and difficulties controlling them, but it may be fruitful to consider the extent to which exaggerated responses to uncertainty interfere with performance on both related and unrelated tasks.

In another null finding, Kirschner et al. (2016) found that SCRs were not related to IU when anticipating safe, dangerous, or uncertain pictures. It may be that the pictures the authors used did not denote uncertainty explicitly enough to detect IU-related differences, or that they were not aversive enough. Future work should use explicit and aversive stimuli, such as varying probabilities of electric shock (e.g., Ring & Kaernbach, 2015), to examine whether there is an association between IU and physiological arousal in the face of uncertainty, as measured by SCRs. This work also highlights an interesting question about responses to uncertainty, which is the extent to which the stimulus that is uncertain must be aversive to provoke anxiety versus the extent to which uncertainty itself is sufficiently aversive. The UAMA highlights the importance of hypervigilance and heightened attention to what is perceived as threatening, but it may be fruitful to better understand the mechanisms by which uncertain stimuli are evaluated and categorized as threatening. Evaluation and categorization of uncertain stimuli could be investigated using multiple methods, including eye tracking, ERPs, and behavioral paradigms.

7. Intolerance of uncertainty and heart rate

Heart rate is thought to be a coarse measure of arousal and is defined simply as the number of heart beats per minute (Berntson et al., 1997). HRV refers to variations in the time between heart beats and is regulated by both sympathetic and parasympathetic function (Berntson et al., 1997). High frequency HRV is primarily regulated by the parasympathetic nervous system through the vagus nerve and is thought to be an index of vagal tone (Berntson et al., 1997). As such, greater high frequency HRV is thought to reflect greater flexibility of parasympathetic responding to various contexts. Both heart rate and HRV can be measured in various paradigms, including at rest, in response to emotional stimuli, and when performing a task.

HRV is thought to be mediated by connections between cortical and subcortical systems that include the PFC, cingulate cortex, insula, amygdala, and brainstem with visceromotor and neuroendocrine systems that are involved in regulating physiological and affective responses (Deschenes, Dugas, & Gouin, 2016; Thayer & Lane, 2000). Recent work has suggested that HRV is particularly relevant to the regulation of the threat response in uncertain situations (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). In terms of the UAMA, diminished HRV may reflect disruptions in safety learning that result in diminished flexibility in contexts that may be safe; heightened responses to uncertainty that result in sustained BNST activity; and difficulty appropriately and flexibly regulating responses to uncertainty as reflected in anterior midcingulate cortex disruptions. For example, in an unselected sample of undergraduates, Deschenes et al. (2016) found that higher IU was associated with lower high frequency HRV in tasks in which participants were asked to worry in both a structured and unstructured manner. Lower high frequency HRV suggests diminished flexibility of parasympathetic responding during worry in individuals high in IU.

IU-related alteration of HRV has also been found in a sample of high worriers (Ottaviani et al., 2014). Specifically, greater IU was associated with a higher *ratio* of low to high frequency HRV while participants were induced to worry. The authors suggest that the ratio between low and high frequency HRV may reflect sympathetic activity, but they acknowledge that this is not a clear conclusion due to research showing that low frequency HRV may not reflect sympathetic activation (Ottaviani et al., 2014; Reyes del Paso et al., 2013). They interpret their results to mean that, in individuals who chronically worry, worry becomes a maladaptive emotion regulation strategy that increases arousal instead of decreasing it. However, their findings are difficult to interpret given the lack of clarity regarding what the ratio between low and high frequency HRV reflects. In the typing performance task described above, Thibodeau et al. (2013) found no relation between IU scores and heart rate. The authors did not examine HRV.

7.1. Summary

Overall, the research on heart rate and HRV in relation to IU is limited. Deschenes et al. (2016) found that IU was associated with lower high frequency HRV during worry, consistent with the notion of diminished flexibility of responding. However, Ottaviani et al. (2014) did not find the same pattern of results—in their sample, IU was not related to high frequency HRV in either high or low worriers. Additional research investigating the association between high frequency HRV and IU is needed. While diminished flexibility related to IU (Deschenes et al., 2016) is certainly consistent with several parts of the UAMA (e.g., impairments in safety learning, exaggerated responding to uncertainty, and diminished control over responses), additional studies investigating the relation between IU and HRV in various contexts are necessary. The existing findings highlight the importance of considering the type of task that participants are engaged in when HRV is measured. Neither the work of Deschenes et al. (2016) nor Ottaviani et al. (2014) found results for non-worry conditions (such as at rest or during reappraisal or distraction). Thus, it may be important to incorporate various conditions, including worry, into future work. The approach of considering high and low worriers (e.g., Ottaviani et al., 2014) also highlights the value of considering the role of both state and trait variables.

8. Conclusions

Examination of the neural and psychophysiological correlates of IU is a burgeoning field. Associations with IU have been observed across various measures, including fMRI, MRI, ERP, EEG, startle reflex, skin conductance, and HRV (see Table 1). Overall, the pattern of findings regarding IU and physiological responses is largely consistent with predictions by the UAMA (Grupe & Nitschke, 2013), with some exceptions. Critically, inhibitory and prospective IU (the two subscales of the IUS) may have differential relationships with neural and psychophysiological measures. The overall pattern of results from each method is synthesized briefly below in the context of the UAMA, with greater emphasis on results shown in more than one study.

The relation between IU and *inflated estimates of the probability and cost of threat*, highlighted in the UAMA, has not been thoroughly investigated. However, research examining the ERN suggests that prospective IU may be associated with heightened perceptions of errors, which are uncertain and threatening, as costly. Studies using task paradigms that are focused on examining perceptions of threat and measuring IU are necessary to elucidate how IU relates to estimates of the probability and cost of threat, as highlighted in the UAMA.

IU appears to be related to the *hypervigilance* component of the UAMA, although results are mixed. Numerous findings show that IU is correlated with activity of the amygdala, which is thought to mediate hypervigilance by contributing to the association of ambiguity with threat (Grupe & Nitschke, 2013). The startle reflex, which is often described as a physiological manifestation of hypervigilance (e.g., Conoscenti, Vine, Papa, & Litz, 2009), has been associated with IU in both directions. Thus, further work is necessary to determine whether prospective and inhibitory IU have opposing relations with magnitude of the startle reflex. Contrary to the notion of hypervigilance, prospective IU has been associated with blunted arousal or allocation of attention to threat-related stimuli as reflected in the LPP.

Several studies show that IU is associated with *deficient safety learning*. Individuals higher in IU show elevated SCRs and amygdala activity in the context of safety than do those lower in IU. Particularly among patients with panic disorder, high IU is associated with indiscriminate responding to safety signals compared to cues indicating threat, and this relation appears to be mediated by deficits in cognitive flexibility. Further research, particularly examining connectivity between regions, is necessary to clarify whether deficits in safety learning may be related to the association between IU and activity of the vmPFC or ventral ACC.

Evidence for *avoidance at both the cognitive and behavioral levels* in relation to IU is limited. Inhibitory IU has been associated with blunting of the ERN, which has been argued to reflect avoidance of the uncertain nature of mistakes. Similarly, prospective IU has been associated with blunting of the LPP, a measure of arousal and attention, in response to fear stimuli, which may reflect cognitive avoidance. Importantly, IU has been reliably associated with increased activity of the anterior insula, which is thought to reflect heightened expectations of fear. The UAMA suggests that heightened expectations of fear lead to increased avoidance, but no direct evidence of this link in the context of IU exists.

Heightened responding to uncertain threat in relation to IU has been demonstrated. IU is associated with greater activity of the anterior insula and amygdala, both of which are thought to reflect elevated anxiety to uncertainty (Grupe & Nitschke, 2013). Contrary to predictions of the UAMA, however, existing research has not yet documented a correlation between IU and BNST activity – as discussed above, there may be numerous reasons (technological, methodological, and functional) for the lack of an association between IU and BNST activity in studies to date. Heightened responding to uncertain threat is also reflected in startle reflex, skin conductance, and HRV, but these findings are mixed.

Finally, *maladaptive control* over responses to uncertainty has received limited attention. Results showing that cognitive flexibility mediates the relation between IU and the startle reflex in response to safety in patients with panic disorder suggest that the ability to effectively modulate responding to changing contexts may be important. HRV has been conceptualized as a measure of the ability to regulate emotional responding (e.g., Holzman & Bridgett, 2017), but findings regarding the association between IU and HRV are mixed. The ERN is thought to be a signal of the need for greater cognitive control (Shackman et al., 2011), and blunting of the ERN in relation to inhibitory IU may reflect disruptions in this signaling. However, additional research examining the ability to exert control in uncertain contexts is needed to clarify the relation with IU.

Overall, the components of the UAMA that have received the most attention in relation to IU are heightened reactivity to uncertainty and deficient safety learning. However, important questions remain—for example, do inhibitory and prospective IU have opposite relationships with reactivity to uncertainty, and if so, what are the functional consequences of these opposing associations? Furthermore, other components of the UAMA have received relatively little attention, and other findings – such as the association of IU with reward processing – highlight potential extensions of the UAMA.

9. Future directions

Based on the pattern of results reviewed above, one key recommendation for future research investigating the relation between IU and physiological measures is to examine and report associations between the individual IUS subscales of prospective and inhibitory IU. If prospective and inhibitory IU have opposing associations with a given measure, as has been reported several times in the literature (Jackson et al., 2016; Nelson et al., 2015), then only examining total IUS scores may obscure these relations and lead to misleading null findings. Additionally, reporting both total and subscale scores will help refine the current conceptualization of IU. For example, identifying when associations between IU total score and a given measure of interest are driven by only one subscale of the IUS or are common to both subscales may point to important similarities or differences between the two facets of IU. Given that the factor structure of the 27-item IUS has been found to be unstable (Norton, 2005; Roma & Hope, 2016), it is also recommended that future studies use the 12-item version (IUS-12) developed by Carleton, Norton, et al. (2007) and Carleton, Sharpe, et al. (2007)).

An important issue to consider in future research on IU is how this construct is measured. The vast majority of research on IU has used the original long version of the IUS or the IUS-12. While the preponderant use of one measure allows for ease of comparison across studies, it especially highlights the importance of construct validity. The IUS and IUS-12 have demonstrated evidence of construct validity in various ways, such as the ability to predict the development of anxiety symptoms (Oglesby et al., 2016) and convergence with other traits that are conceptually related, such as the tendency to worry (Buhr & Dugas, 2009). However, because the IUS was originally developed to examine GAD in particular, concerns have been raised about whether the measure may be biased toward or overlap substantially with GAD symptoms (Carleton et al., 2010; Gosselin et al., 2008). In response to these concerns, other measures like the Intolerance of Uncertainty Index have been developed (Gosselin et al., 2008). Future work should administer multiple measures of IU to examine whether they converge in their relations with neural and psychophysiological measures.

Further investigation is needed to evaluate the construct validity of the IUS and to strengthen the measurement of IU via self-report. As the field moves forward, the literature on IU would also benefit from expanding beyond self-report measures to assess IU. Using self-report measures of IU may preclude measurement of individual differences in responding to uncertainty that occur in very early stages of information processing and may not be subject to conscious awareness. For example, theoretical work on emotion has suggested that categorizing a stimulus as "sudden, familiar, or unpredictable" is one of the first, most fundamental stages of information processing (Scherer, 2013, p. 151; for a more comprehensive discussion of the relation between Scherer's emotion theory and IU, see Carleton, 2016a). Similarly, the UAMA proposes that very early alterations in attention to uncertain threat contribute to heightened anxiety in the face of uncertainty (Grupe & Nitschke, 2013). If alterations in attention occur as early as several hundred milliseconds after the presentation of a stimulus, individual differences in such an early stage of information processing may not be reflected in self-report. This limitation of self-report measures of IU is important to consider when interpreting null findings from studies that have not found associations between self-reported IU and psychophysiological or neural measures. Going forward, developing laboratory assessments of IU using multiple methods may facilitate understanding of how difficulty with uncertainty manifests at various levels of information processing (Shihata et al., 2016). For example, assessing each aspect of the UAMA – estimates of uncertain threat, hypervigilance and attention under uncertainty, safety learning in uncertain situations, avoidance of uncertain threat, and reactivity to uncertain threat – may provide a more complete understanding of individual differences in responding to uncertainty and how they relate across levels of analysis, including self-report, behavior, cognition, and physiology.

The UAMA overall appears to be a valuable working model for organizing future research investigating the neural and psychophysiological correlates of IU. However, the existing literature points to several potential extensions of the UAMA that would continue to facilitate research on IU. Specifically, it may be important to consider the roles of (a) emotion regulation, (b) cognitive control, and (c) reward processing.

Emotion regulation is closely tied to IU, but this link remains relatively unexplored. The construct of IU was originally conceptualized in relation to worry in GAD, and scores on the IUS are highly correlated with scores on measures of worry, rumination, and post-event processing (Norton, 2005; Liao & Wei, 2011; Shiktani et al., 2016). However, it may be that IU and various measures of emotion regulation have differential relations with neural and psychophysiological responses to uncertainty. For example, worry has been conceptualized as a maladaptive emotion regulation strategy that acts as a form of avoidance and has physiologically blunting effects (Borkovec, Alcaine, & Behar, 2004). It is possible that IU is associated with physiological arousal but that these effects are not detected because IU is highly correlated with worry within the same individuals. In addition to emotion regulation strategies that are traditionally conceived as maladaptive, it is also important to investigate the relation between IU and adaptive emotion regulation. For example, it may be that individuals high in IU who tend to engage in reappraisal or distraction are less likely to experience anxiety in the face of uncertainty. Certain strategies may be more beneficial depending on levels of IU; for example, distraction in uncertain situations may be more effective for high IU individuals than reappraisal, given the fact that it is difficult to eliminate uncertainty with reappraisal. Such investigations could be used to tailor the use of particular strategies to particular individuals. Overall, assessing emotion regulation and examining interactions with IU may be a useful approach for future research.

Relatedly, the ability to exercise cognitive control in the face of uncertainty may be relevant to IU. One reason for the cascade of interrelated, maladaptive responses to uncertainty proposed in the UAMA could be that the ability to use cognitive control in the context of uncertain material is diminished, especially in those high in IU. Recent work has demonstrated that uncertain threat is associated with alterations in various domains of cognitive control, such as response inhibition (e.g., Robinson, Vytal, Cornwell, & Grillon, 2013). Cognitive control, particularly in the context of emotional material, has been conceptualized as a key mechanism of emotion regulation (Joormann & Tanovic, 2015). Thus, deficits in cognitive control could contribute to difficulties regulating anxiety in the face of uncertainty in individuals high in IU.

Much of the research investigating responses to uncertainty has focused on aversive or threatening stimuli, such as electric shocks and unpleasant pictures. Because of the nature of the stimuli, the use of threatening stimuli may be particularly effective at inducing anticipatory anxiety and thus be well-suited for examining individual differences in responses to uncertainty. However, in such studies, it remains unclear whether the stimulus needs to be aversive to elicit the observed responses or for there to be an association between physiological responding and IU. Initial evidence suggests that IU may be related to responses to uncertainty even in the context of reward. Specifically, blunting of both anticipation and receipt of rewards in uncertain contexts has been associated with IU (Nelson et al., 2014, 2016). These findings suggest that uncertainty may elicit maladaptive responding even when stimuli are not inherently aversive. As well, blunting of reward anticipation and receipt points to the potential importance of considering the relation between reward processing and IU. Diminished responses to rewards in uncertain contexts may further contribute to increased salience of threat and fuel the interpretation of uncertainty as threatening.

Research showing that IU is associated with reward processing deficits also points to the relation between IU and depression. IU is elevated in depression, as well as other forms of psychopathology (Carleton et al., 2012; Gentes & Ruscio, 2011; McEvoy & Mahoney, 2012; Miranda, Fontes, & Marroquin, 2008; Yook, Kim, Suh, & Lee, 2010). For example, IU has been examined in relation to eating disorders (Frank et al., 2012), autism (Oglesby et al., 2016), and prolonged grief (Boelen et al., 2016). IU appears to be a highly transdiagnostic construct, but the vast majority of work on the neural and psychophysiological correlates of IU has been restricted to non-clinical, depressed, or anxious samples. Future work should examine various diagnostic groups to understand the extent to which IU is associated with the same neural and psychophysiological correlates across diagnoses and how IU manifests across disorders. Understanding the neural and psychophysiological correlates of IU in samples of consisting of various diagnostic groups also has the potential to inform understanding of multifinality and divergent trajectories of symptoms across disorders (Shihata et al., 2016; Nolen-Hoeksema & Watkins, 2011).

Finally, one fruitful avenue for future research on the neural and psychophysiological correlates of IU may be the use of naturally occurring uncertain situations in place of artificial, laboratory-based ones. For example, studying changes in neural and physiological measures during particularly uncertain times of life, such as when awaiting the results of an important exam, the birth of a first child, or the outcome of a serious medical diagnosis, may be informative (e.g., Sweeny & Andrews, 2014). Changes that occur in neural and psychophysiological responding during such times may overlap or differ compared to changes that occur in response to uncertain lab-based conditions. Investigating how IU relates to measures collected during real-life uncertainty may provide a more ecologically valid understanding of the relation between and nature of trait dislike of uncertainty and responses to uncertainty.

Overall, a growing body of research has found that self-reported IU is associated with neural and psychophysiological measures that reflect heightened reactivity to uncertainty and deficient safety learning. Findings regarding the relation between IU and physiological measures of hypervigilance are mixed, and more research is needed to understand how physiological mechanisms of avoidance and threat estimation relate to IU. Furthermore, investigating the relations between IU and emotion regulation, cognitive control, and reward processing may be promising avenues for future research. Such research has the potential to elucidate the mechanisms of how IU confers risk for anxiety, depression, and other forms of psychopathology.

Role of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Contributors

Ema Tanovic and Jutta Joormann decided the scope and content of the review. Ema Tanovic conducted literature searches and wrote the first draft of the manuscript. Jutta Joormann, Dylan Gee, and Ema Tanovic contributed to writing subsequent drafts. All authors approved the final version of the manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

The authors would like to thank Dr. Tyrone Cannon for his comments on the manuscript.

References

Bardeen, J. R., Fergus, T. A., & Orcutt, H. K. (2016). Examining the specific dimensions of distress tolerance that prospectively predict perceived stress. *Cognitive Behaviour Therapy,* 1–13.

Barlow, D. H. (2004). *Anxiety and its disorders: The nature and treatment of anxiety and panic.* New York, NY: Guilford Press.

Berntson, G. G., Thomas, B. J., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., ... Van Der Molen, M. W. (1997). Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology, 34*(6), 623–648.

Boelen, P. A., & Reijntjes, A. (2009). Intolerance of uncertainty and social anxiety. *Journal of Anxiety Disorders, 23*(1), 130–135.

Boelen, P. A., Reijntjes, A., & Smid, G. E. (2016). Concurrent and prospective associations of intolerance of uncertainty with symptoms of prolonged grief, posttraumatic stress, and depression after bereavement. *Journal of Anxiety Disorders, 41*, 65–72.

Borkovec, T. D., Alcaine, O. M., & Behar, E. (2004). Avoidance theory of worry and generalized anxiety disorder. In R. G. Heimberg, C. L. Turk, & D. S. Mennin (Eds.). *Generalized anxiety disorder: Advances in research and practice* (pp. 77–108). New York, NY: Guilford Press.

Brown, M., Robinson, L., Campione, G. C., Wuensch, K., Hildebrandt, T., & Micali, N. (2017). Intolerance of uncertainty in eating disorders: A systematic review and meta-analysis. *European Eating Disorders Review, 25*(5), 329–343.

Buhr, K., & Dugas, M. J. (2002). The Intolerance of Uncertainty Scale: Psychometric properties of the English version. *Behaviour Research and Therapy, 40*(8), 931–945.

Buhr, K., & Dugas, M. J. (2009). The role of fear of anxiety and intolerance of uncertainty in worry: An experimental manipulation. *Behaviour Research and Therapy, 47*(3), 215–223.

Carleton, R. N. (2012). The intolerance of uncertainty construct in the context of anxiety disorders: Theoretical and practical perspectives. *Expert Review of Neurotherapeutics, 12*(8), 937–947.

Carleton, R. N. (2016a). Into the unknown: A review and synthesis of contemporary models involving uncertainty. *Journal of Anxiety Disorders, 39*, 30–43.

Carleton, R. N. (2016b). Fear of the unknown: One fear to rule them all? *Journal of Anxiety Disorders, 41*, 5–21.

Carleton, R. N., Collimore, K. C., & Asmundson, G. J. (2010). "It's not just the judgements—It's that I don't know": Intolerance of uncertainty as a predictor of social anxiety. *Journal of Anxiety Disorders, 24*(2), 189–195.

Carleton, R. N., Duranceau, S., Freeston, M. H., Boelen, P. A., McCabe, R. E., & Antony, M. M. (2014). "But it might be a heart attack": Intolerance of uncertainty and panic disorder symptoms. *Journal of Anxiety Disorders, 28*(5), 463–470.

Carleton, R. N., Duranceau, S., Shulman, E. P., Zerff, M., Gonzales, J., & Mishra, S. (2016). Self-reported intolerance of uncertainty and behavioural decisions. *Journal of Behavior Therapy and Experimental Psychiatry, 51*, 58–65.

Carleton, R. N., Mulvogue, M. K., Thibodeau, M. A., McCabe, R. E., Antony, M. M., & Asmundson, G. J. G. (2012). Increasingly certain about uncertainty: Intolerance of uncertainty across anxiety and depression. *Journal of Anxiety Disorders, 26*, 468–479.

Carleton, R. N., Norton, M. A. P. J., & Asmundson, G. J. G. (2007). Fearing the unknown: A short version of the Intolerance of Uncertainty Scale. *Journal of Anxiety Disorders, 21*(1), 105–117.

Carleton, R. N., Sharpe, D., & Asmundson, G. J. G. (2007). Anxiety sensitivity and intolerance of uncertainty: Requisites of the fundamental fears? *Behaviour Research and Therapy, 45*(10), 2307–2316.

Chamberlain, P. D., Rodgers, J., Crowley, M. J., White, S. E., Freeston, M. H., & South, M. (2013). A potentiated startle study of uncertainty and contextual anxiety in adolescents diagnosed with autism spectrum disorder. *Molecular Autism, 4*(1), 31.

Chin, B., Nelson, B. D., Jackson, F., & Hajcak, G. (2016). Intolerance of uncertainty and startle potentiation in relation to different threat reinforcement rates. *International Journal of Psychophysiology, 99*, 79–84.

Conoscenti, L. M., Vine, V., Papa, A., & Litz, B. T. (2009). Scanning for danger: Readjustment to the non-combat environment. In S. M. Freeman, B. Moore, & A. Freeman (Eds.). *Living and surviving in Harm's way: A psychological treatment handbook for pre- and post deployment of military personnel* (pp. 123–146). New York: Routledge.

Costello, E., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry, 60*(8), 837–844.

Critchley, H. D., Elliott, R., Mathias, C. J., & Dolan, R. J. (2000). Neural activity relating to generation and representation of galvanic skin conductance responses: A functional magnetic resonance imaging study. *The Journal of Neuroscience, 20*(8), 3033–3040.

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002). Depression: Perspectives from affective neuroscience. *Annual Review of Psychology, 53*(1), 545–574.

Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience, 15*(1), 353–375.

Davis, M. (2006). Neural systems involved in fear and anxiety measured with fear-potentiated startle. *American Psychologist, 61*(8), 741–756.

Davis, M., Walker, D. L., Miles, L., & Grillon, C. (2010). Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology, 35*(1), 105–135.

Delgado, M. R., Olsson, A., & Phelps, E. A. (2006). Extending animal models of fear conditioning to humans. *Biological Psychology, 73*, 39–48. http://dx.doi.org/10.1016/j.biopsycho.2006.01.006.

Deschenes, S. S., Dugas, M. J., & Gouin, J.-P. (2016). Intolerance of uncertainty, worry catastrophizing, and heart rate variability during worry-inducing tasks. *Personality and Individual Differences, 90*, 199–204.

Dugas, M. J., Buhr, K., & Ladouceur, R. (2004). The role of intolerance of uncertainty in etiology and maintenance. In R. G. Heimberg, C. L. Turk, & D. S. Mennin (Eds.). *Generalized anxiety disorder: Advances in research and practice* (pp. 143–163). New York, NY: Guilford Press.

Dugas, M. J., & Robichaud, M. (2007). *Cognitive-Behavioral treatment for generalized anxiety disorder: From science to practice.* NY, USA: Routledge.

Dunsmoor, J. E., Campese, V. D., Ceceli, A. O., LeDoux, J. E., & Phelps, E. A. (2015). Novelty-facilitated extinction: Providing a novel outcome in place of an expected threat diminishes recovery of defensive responses. *Biological Psychiatry, 78*(3), 203–209.

Frank, G. K., Roblek, T., Shott, M. E., Jappe, L. M., Rollin, M. D., Hagman, J. O., & Pryor, T. (2012). Heightened fear of uncertainty in anorexia and bulimia nervosa. *International Journal of Eating Disorders, 45*(2), 227–232.

Freeston, M. H., Rhéaume, J., Letarte, H., Dugas, M. J., & Ladouceur, R. (1994). Why do people worry? *Personality and Individual Differences, 17*(6), 791–802.

Gentes, E. L., & Ruscio, A. M. (2011). A meta-analysis of the relation of intolerance of uncertainty to symptoms of generalized anxiety disorder, major depressive disorder, and obsessive-compulsive disorder. *Clinical Psychology Review, 31*(6), 923–933.

Gorka, S. M., Lieberman, L., Nelson, B. D., Sarapas, C., & Shankman, S. A. (2014). Aversive responding to safety signals in panic disorder: The moderating role of intolerance of uncertainty. *Journal of Anxiety Disorders, 28*(7), 731–736.

Gorka, S. M., Nelson, B. D., Phan, K., & Shankman, S. A. (2016). Intolerance of uncertainty and insula activation during uncertain reward. *Cognitive, Affective, & Behavioral Neuroscience, 16*(5), 929–939.

Gosselin, P., Ladouceur, R., Evers, A., Laverdière, A., Routhier, S., & Tremblay-Picard, M. (2008). Evaluation of intolerance of uncertainty: Development and validation of a new self-report measure. *Journal of Anxiety Disorders, 22*(8), 1427–1439.

Greco, V., & Roger, D. (2001). Coping with uncertainty: The construction and validation of a new measure. *Personality and Individual Differences, 31*(4), 519–534.

Grupe, D. W., & Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: An integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience, 14*(7), 488–501.

Hajcak, G., Weinberg, A., MacNamara, A., & Foti, D. (2011). ERPs and the study of emotion. In E. Kappenman, & S. Luck (Eds.). *The Oxford handbook of event-related potential components* (pp. 441–472). New York, NY: Oxford University Press.

Hayes, J. P., LaBar, K. S., Petty, C. M., McCarthy, G., & Morey, R. A. (2009). Alterations in the neural circuitry for emotion and attention associated with posttraumatic stress symptomatology. *Psychiatry Research: Neuroimaging, 172*(1), 7–15.

Hilbert, K., Pine, D. S., Muehlhan, M., Lueken, U., Steudte-Schmiedgen, S., & Beesdo-Baum, K. (2015). Gray and white matter volume abnormalities in generalized anxiety disorder by categorical and dimensional characterization. *Psychiatry Research: Neuroimaging, 234*(3), 314–320.

Hirsh, J. B., & Inzlicht, M. (2008). The devil you know: Neuroticism predicts neural response to uncertainty. *Psychological Science, 19*(10), 962–967.

Holzman, J. B., & Bridgett, D. J. (2017). Heart rate variability indices as bio-markers of top-down self-regulatory mechanisms: A meta-analytic review. *Neuroscience & Biobehavioral Reviews, 74*, 233–255.

Hong, R. Y., & Cheung, M. W. L. (2015). The structure of cognitive vulnerabilities to depression and anxiety: Evidence for a common core etiologic process based on a meta-analytic review. *Clinical Psychological Science: A Journal of the Association for Psychological Science, 3*, 892–912.

Hong, R. Y., & Lee, S. S. (2015). Further clarifying prospective and inhibitory intolerance of uncertainty: Factorial and construct validity of test scores from the Intolerance of Uncertainty Scale. *Psychological Assessment, 27*, 605–620.

Jackson, F., Nelson, B. D., & Hajcak, G. (2016). The uncertainty of errors: Intolerance of uncertainty is associated with error-related brain activity. *Biological Psychology, 113*, 52–58.

Joormann, J., & Tanovic, E. (2015). Cognitive vulnerability to depression: Examining cognitive control and emotion regulation. *Current Opinion in Psychology, 4*, 86–92.

Keefer, A., Kreiser, N. L., Singh, V., Blakeley-Smith, A., Duncan, A., Johnson, C., ... Vasa, R. A. (2016). Intolerance of uncertainty predicts anxiety outcomes following CBT in youth with ASD. *Journal of Autism and Developmental Disorders,* 1–10.

Kim, M. J., Shin, J., Taylor, J. M., Mattek, A. M., Chavez, S. J., & Whalen, P. J. (2017). Intolerance of uncertainty predicts increased striatal volume. *Emotion, 17*(6), 895–899.

Kim, H., Somerville, L. H., Johnstone, T., Polis, S., Alexander, A. L., Shin, L. M., & Whalen, P. J. (2004). Contextual modulation of amygdala responsivity to surprised faces. *Journal of Cognitive Neuroscience, 16*, 1730–1745.

Kirschner, H., Hilbert, K., Hoyer, J., Lueken, U., & Beesdo-Baum, K. (2016). Psychophsyiological reactivity during uncertainty and ambiguity processing in high and low worriers. *Journal of Behavior Therapy and Experimental Psychiatry, 50*, 97–105.

Krain, A. L., Gotimer, K., Hefton, S., Ernst, M., Castellanos, F., Pine, D. S., & Milham, M. P. (2008). A functional magnetic resonance imaging investigation of uncertainty in adolescents with anxiety disorders. *Biological Psychiatry, 63*(6), 563–568.

Krain, A. L., Hefton, S., Pine, D. S., Ernst, M., Castellanos, F., Klein, R. G., & Milham, M. P. (2006). An fMRI examination of developmental differences in the neural correlates of uncertainty and decision-making. *Journal of Child Psychology and Psychiatry, 47*(10), 1023–1030.

Krohne, H. W. (1993). Vigilance and cognitive avoidance as concepts in coping research.

In H. W. Krohne (Ed.). *Attention and avoidance: Strategies in coping with aversiveness* (pp. 19–50). Seattle, WA: Hogrefe and Huber.

Lang, P. J. (1995). The emotion probe: Studies of motivation and attention. *American Psychologist, 50*(5), 372–385.

Lebow, M. A., & Chen, A. (2016). Overshadowed by the amygdala: The bed nucleus of the stria terminalis emerges as key to psychiatric disorders. *Molecular Psychiatry, 21*(4), 450–463.

Liao, K. Y. H., & Wei, M. (2011). Intolerance of uncertainty, depression, and anxiety: The moderating and mediating roles of rumination. *Journal of Clinical Psychology, 67*(12), 1220–1239.

Lieberman, L., Gorka, S. M., Sarapas, C., & Shankman, S. A. (2016). Cognitive flexibility mediates the relation between intolerance of uncertainty and safety signal responding in those with panic disorder. *Cognition and Emotion, 30*(8), 1495–1503.

Luhmann, C. C., Ishida, K., & Hajcak, G. (2011). Intolerance of uncertainty and decisions about delayed, probabilistic rewards. *Behavior Therapy, 42*(3), 378–386.

Mahoney, A. E. J., & McEvoy, P. M. (2012). Trait versus situation-specific intolerance of uncertainty in a clinical sample with anxiety and depressive disorders. *Cognitive Behaviour Therapy, 41*(1), 26–39.

McEvoy, P. M., & Mahoney, A. E. J. (2011). Achieving certainty about the structure of intolerance of uncertainty in a treatment-seeking sample with anxiety and depression. *Journal of Anxiety Disorders, 25*(1), 112–122.

McEvoy, P. M., & Mahoney, A. E. J. (2012). To be sure, to be sure: Intolerance of uncertainty mediates symptoms of various anxiety disorders and depression. *Behavior Therapy, 43*(3), 533–545.

McFadden, K. L., Tregellas, J. R., Shott, M. E., & Frank, G. K. (2014). Reduced salience and default mode network activity in women with anorexia nervosa. *Journal of Psychiatry & Neuroscience, 39*(3), 178–188.

Milad, M. R., Pitman, R. K., Ellis, C. B., Gold, A. L., Shin, L. M., Lasko, N. B., ... Rauch, S. L. (2009). Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biological Psychiatry, 66*(12), 1075–1082.

Miranda, R., Fontes, M., & Marroquin, B. (2008). Cognitive content-specificity in future expectancies: Role of hopelessness and intolerance of uncertainty in depression and GAD symptoms. *Behaviour Research and Therapy, 46*, 1151–1159.

Moon, C. M., Kim, G. W., & Jeong, G. W. (2014). Whole-brain gray matter volume abnormalities in patients with generalized anxiety disorder: Voxel-based morphometry. *Neuroreport, 25*(3), 184–189.

Morriss, J., Christakou, A., & van Reekum, C. M. (2015). Intolerance of uncertainty predicts fear extinction in amygdala-ventromedial prefrontal cortical circuitry. *Biology of Mood & Anxiety Disorders, 5*(4).

Morriss, J., Christakou, A., & van Reekum, C. M. (2016). Nothing is safe: Intolerance of uncertainty is associated with compromised fear extinction learning. *Biological Psychology, 121*, 187–193.

Morriss, J., Macdonald, B., & van Reekum, C. M. (2016). What is going on around here? Intolerance of uncertainty predicts threat generalization. *PLoS One, 11*(5), e0154494.

Myers-Schulz, B., & Koenigs, M. (2012). Functional anatomy of ventromedial prefrontal cortex: Implications for mood and anxiety disorders. *Molecular Psychiatry, 17*(2), 132–141.

Nelson, B. D., Kessel, E. M., Jackson, F., & Hajcak, G. (2016). The impact of an unpredictable context and intolerance of uncertainty on the electrocortical response to monetary gains and losses. *Cognitive, Affective, & Behavioral Neuroscience, 16*(1), 153–163.

Nelson, B. D., & Shankman, S. A. (2011). Does intolerance of uncertainty predict anticipatory startle responses to uncertain threat? *International Journal of Psychophysiology, 81*(2), 107–115.

Nelson, B. D., Shankman, S. A., & Proudfit, G. H. (2014). Intolerance of uncertainty mediates reduced reward anticipation in major depressive disorder. *Journal of Affective Disorders, 158*, 108–113.

Nelson, B. D., Weinberg, A., Pawluk, J., Gawlowska, M., & Proudfit, G. H. (2015). An event-related potential investigation of fear generalization and intolerance of uncertainty. *Behavior Therapy, 46*(5), 661–670.

Nitschke, J. B., Sarinopoulos, I., Oathes, D. J., Johnstone, T., Whalen, P. J., Davidson, R. J., & Kalin, N. H. (2009). Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. *American Journal of Psychiatry, 166*(3), 302–310.

Nolen-Hoeksema, S., & Watkins, E. R. (2011). A heuristic for developing transdiagnostic models of psychopathology: Explaining multifinality and divergent trajectories. *Perspectives on Psychological Science, 6*, 589–609.

Norton, P. J. (2005). A psychometric analysis of the Intolerance of Uncertainty Scale among four racial groups. *Journal of Anxiety Disorders, 19*(6), 699–707.

Oathes, D. J., Hilt, L. M., & Nitschke, J. B. (2015). Affective neural responses modulated by serotonin transporter genotype in clinical anxiety and depression. *PLoS One, 10*(2), e0115820.

Oglesby, M. E., Boffa, J. W., Short, N. A., Raines, A. M., & Schmidt, N. B. (2016). Intolerance of uncertainty as a predictor of post-traumatic stress symptoms following a traumatic event. *Journal of Anxiety Disorders, 41*, 82–87.

Olson, I. R., Plotzker, A., & Ezzyat, Y. (2007). The enigmatic temporal pole: A review of findings on social and emotional processing. *Brain, 130*(Pt 7), 1718–1731.

Ottaviani, C., Borlimi, R., Brighetti, G., Caselli, G., Favaretto, E., Giardini, I., ... Sassaroli, S. (2014). Worry as an adaptive avoidance strategy in healthy controls but not in pathological worriers. *International Journal of Psychophysiology, 93*(3), 349–355.

Pearce, J. M., & Hall, G. (1980). A model for Pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychological Review, 87*, 532–552.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron, 43*(6), 897–905.

Potts, G. F. (2011). Impact of reward and punishment motivation on behavior monitoring as indexed by the error-related negativity. *International Journal of Psychophysiology, 81*(3), 324–331.

Proudfit, G. H. (2015). The reward positivity: From basic research on reward to a biomarker for depression. *Psychophysiology, 52*(4), 449–459.

Rapee, R. M., Craske, M. G., Brown, T. A., & Barlow, D. H. (1996). Measurement of perceived control over anxiety-related events. *Behaviour Therapy, 27*, 279–293.

Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black, & W. F. Prokasy (Eds.). *Classical conditioning II: Current research and theory* (pp. 64–99). New York: Appleton-Century-Crofts.

Reyes del Paso, G. A., Langewitz, W., Mulder, L. J., Roon, A., & Duschek, S. (2013). The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. *Psychophysiology, 50*(5), 477–487.

Ring, P., & Kaernbach, C. (2015). Sensitivity towards fear of electric shock in passive threat situations. *PLoS One, 10*(3), e0120989.

Robinson, O. J., Vytal, K., Cornwell, B. R., & Grillon, C. (2013). The impact of anxiety upon cognition: Perspectives from human threat of shock studies. *Frontiers in Human Neuroscience, 7*(203).

Roma, V. G., & Hope, D. A. (2016). Are we certain about which measure of intolerance of uncertainty to use yet? *Cognitive Behavior Therapy,* 1–12.

Scherer, K. R. (2013). The nature and dynamics of relevance and valence appraisals: Theoretical advances and recent evidence. *Emotion Review, 5*(2), 150–162. http://dx.doi.org/10.1177/1754073912468166.

Schienle, A., Köchel, A., Ebner, F., Reishofer, G., & Schäfer, A. (2010). Neural correlates of intolerance of uncertainty. *Neuroscience Letters, 479*(3), 272–276.

Schmitz, A., & Grillon, C. (2012). Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). *Nature Protocols, 7*(3), 527–532.

Sexton, K. A., & Dugas, M. J. (2009). Defining distinct negative beliefs about uncertainty: Validating the factor structure of the Intolerance of Uncertainty Scale. *Psychological Assessment, 21*(2), 176–186.

Shackman, A. J., & Fox, A. S. (2016). Contributions of the central extended amygdala to fear and anxiety. *Journal of Neuroscience, 36*(31), 8050–8063.

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & &. Davidson, R. J. (2011). The integration of negative affect, pain, and cognitive control in the cingulate cortex. *Nature Reviews Neuroscience, 12*, 154–167.

Shankman, S. A., Gorka, S. M., Nelson, B. D., Fitzgerald, D. A., Phan, K., & O'Daly, O. (2014). Anterior insula responds to temporally unpredictable aversiveness: An fMRI study. *NeuroReport: For Rapid Communication of Neuroscience Research, 25*(8), 596–600.

Shankman, S. A., Nelson, B. D., Sarapas, C., Robison-Andrew, E. J., Campbell, M. L., Altman, S. E., ... Gorka, S. M. (2013). A psychophysiological investigation of threat and reward sensitivity in individuals with panic disorder and/or major depressive disorder. *Journal of Abnormal Psychology, 122*(2), 322–338.

Shihata, S., McEvoy, P., Mullan, B. A., & Carleton, R. N. (2016). Intolerance of uncertainty in emotional disorders: What uncertainties remain? *Journal of Anxiety Disorders, 41*, 115–124. http://dx.doi.org/10.1016/j.janxdis.2016.05.001.

Shiktani, B., Antony, M. M., Cassin, S. E., & Kuo, J. R. (2016). Examining the role of perfectionism and intolerance of uncertainty in postevent processing in social anxiety disorder. *Journal of Psychopathology and Behavioral Assessment, 38*(2), 297–306.

Simmons, A., Matthews, S. C., Paulus, M. P., & Stein, M. B. (2008). Intolerance of uncertainty correlates with insula activation during affective ambiguity. *Neuroscience Letters, 430*(2), 92–97.

Somerville, L. H., Wagner, D. D., Wig, G. S., Moran, J. M., Whalen, P. J., & Kelley, W. M. (2013). Interactions between transient and sustained neural signals support the generation and regulation of anxious emotion. *Cerebral Cortex, 23*(1), 49–60.

Somerville, L. H., Whalen, P. J., & Kelley, W. M. (2010). Human bed nucleus of the stria terminalis indexes hypervigilant threat monitoring. *Biological Psychiatry, 68*(5), 416–424.

Straube, T., Mentzel, H. J., & Miltner, W. H. R. (2007). Waiting for spiders: Brain activation during anticipatory anxiety in spider phobics. *NeuroImage, 37*(4), 1427–1436.

Sweeny, K., & Andrews, S. E. (2014). Mapping individual differences in the experience of a waiting period. *Journal of Personality and Social Psychology, 106*(6), 1015–1030.

Tanovic, E., Hajcak, G., & Joormann, J.. Hating waiting: Individual differences in willingness to wait in uncertainty. Journal of Experimental Psychopathology. (in press)

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews, 36*(2), 747–756.

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders, 61*(3), 201–216.

Thibodeau, M. A., Carleton, R., Gomez-Perez, L., & Asmundson, G. J. (2013). "What if I make a mistake?" Intolerance of uncertainty is associated with poor behavioral performance. *Journal of Nervous and Mental Disease, 201*(9), 760–766.

Tolin, D. F., Abramowitz, J. S., Brigidi, B. D., & Foa, E. B. (2003). Intolerance of uncertainty in obsessive-compulsive disorder. *Journal of Anxiety Disorders, 17*(2), 233–242.

Weinberg, A., Meyer, A., Hale-Rude, E., Perlman, G., Kotov, R., Klein, D. N., & Hajcak, G. (2016). Error-related negativity (ERN) and sustained threat: Conceptual framework and empirical evaluation in an adolescent sample. *Psychophysiology, 53*(3), 372–385.

Yook, K., Kim, K. H., Suh, S. Y., & Lee, K. S. (2010). Intolerance of uncertainty, worry, and rumination in major depressive disorder and generalized anxiety disorder. *Journal of Anxiety Disorders, 24*, 623–628.