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

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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

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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

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.