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Psychological mechanisms underpinning change in intolerance of uncertainty across anxiety-related disorders: New insights for translational research

Jayne Morriss *

School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK

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ABSTRACT

Intolerance of uncertainty (IU), the tendency to find uncertainty negative, is a fundamental transdiagnostic dimension across anxiety-related disorders. Over the past two decades, there has been an increase in both clinical and experimental research on the role of IU in the maintenance and treatment of anxiety-related disorders. However, there has been a lack of integration of research findings from a mechanistic perspective, which has slowed progress in translational research. This review seeks to fill this gap by synthesising the clinical (e.g. randomised controlled trials) and experimental (e.g. lab-based) literature on the psychological mechanisms that drive change in IU across anxiety-related disorders. The review highlighted that: (1) cognitive restructuring, supported by mechanisms such as cognitive appraisal, modify IU-related cognitions, (2) behavioural exposures, supported by mechanisms such as inhibitory learning, alter IU-related cognitions and physiological arousal, and (3) mindfulness techniques underpinned by mechanisms such as attentional monitoring, decentering, and acceptance, change IU-related cognitions. Across the different therapeutic techniques reviewed, there was a lack of evidence for how different mechanisms change IU-related emotions and behaviours. Directions for further research include directly comparing the effectiveness of different mechanisms that produce change in IU across anxiety disorders and other mental health disorders, and examining the specificity of change in IU over other anxious traits. Overall, the findings provide a foundation for future translational research efforts to build upon maximising existing treatment interventions and/or to develop novel treatment interventions to target dispositional IU and situational uncertainty-related distress in anxiety-related disorders and beyond.

Uncertainty signals salience because it suggests that there may be more than one possible outcome, which consequently leads to competing predictions about what might happen (Morriss et al., 2019). Such conflict presents a clear challenge for any biological organism (Gray and McNaughton, 2000). Prior research has established that across species, the default response to uncertainty is anxiety and stress (Brosschot et al., 2016; Freeston and Komes, 2023; Hirsh et al., 2012; Peters et al., 2017), even in the absence of potentially threatening outcomes (Morriss et al., 2022). Excessive exposure to uncertainty, either based on an individuals' perceptions (e.g. individual differences in personality or temperament) (Gentes and Ruscio, 2011; McEvoy et al., 2019) or from the environment (e.g. prejudice, natural disasters, pandemics) (Afifi et al., 2012; Freeston et al., 2020; Massazza et al., 2023; Palumbo and Manna, 2020; Ricciardelli et al., 2022), increases the risk of mental health conditions, including anxiety, mood and stress disorders.

Given the impact of uncertainty-related distress on mental health, there has been an increase of research examining how individual differences in the tendency to experience uncertainty-related distress (intolerance of uncertainty) can be modified through evidence-based therapeutic interventions (Einstein, 2014; Shihata et al., 2016). This research has been conducted both within experimental (Morriss al., 2020a; Oglesby et al., 2017), and clinical settings (McEvoy and Erceg-Hurn, 2016; Miller and McGuire, 2023; Wilson et al., 2023). While the conceptualisation and operationalisation of intolerance of uncertainty is relatively standardised across clinical and experimental fields, there has been a lack of integration of research findings across these two fields, at least from a mechanistic perspective, which is hindering the progress of translational research. Thus far it is not entirely clear which psychological mechanisms that support evidence-based therapeutic

* Correspondence to: School of Psychology, University of Southampton, B44 University Rd, Southampton SO17 1PS, UK.
E-mail address: j.morriss@soton.ac.uk.

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interventions are modifying uncertainty-related distress. This review aims to address this gap in our understanding by synthesising the clinical and experimental literature on uncertainty-related distress in anxiety-related disorders. Ultimately, this review will provide a starting point for future translational research efforts that will build upon maximising existing treatment interventions and/or developing novel treatment interventions to target uncertainty-related distress in anxiety-related disorders.

For this narrative review, the author utilised their subject matter expertise and conducted a literature search to identify peer-reviewed publications about the topic of intolerance of uncertainty in humans, with a particular focus on clinical and experimental intervention studies. Online data bases such as PubMed and Google Scholar were used to identify relevant studies that were published during the last 20 years. Key words in the search were used to capture the central construct of interest ('intolerance of uncertainty'), clinical populations of interest ('anxiety disorders'), evidence-based treatments ('CBT'; 'cognitive restructuring'; 'exposure'; 'mindfulness'; 'relaxation'), and psychological mechanisms underpinning evidence-based treatments ('interpretation bias'; 'threat extinction'; 'emotion regulation'). The following inclusion criteria were used: (1) empirical studies and reviews published in the English language, (2) use of a validated questionnaire scale for assessing intolerance of uncertainty, and (3) statistical analysis examining the impact of experimental / therapeutic intervention in changing intolerance of uncertainty.

The article is divided into the following sections. First, the review will provide a brief overview on individual differences in intolerance of uncertainty. Second, the review will be divided into sections that cover different evidence-based therapeutic techniques. In each of these subsections, a brief overview of the evidence-based therapeutic technique will be provided, then the relevant underlying psychological mechanisms will be outlined, and the clinical (e.g. evidence-based therapeutic interventions) and basic (e.g. lab-based interventions) research findings on intolerance of uncertainty in anxiety-related disorders will be synthesised. In these subsections, the effect sizes from meta-analytic reviews may be discussed. All reported effect sizes will be taken directly from the original peer-reviewed sources and thus reported effect size metrics may vary. Lastly, the review will summarise the common gaps across the literature and outline directions for future research.

1. Intolerance of uncertainty

Individual differences in intolerance of uncertainty (IU) refers to the degree to which a person interprets or reacts negatively to uncertain situations (Birrell et al., 2011; Carleton, 2016a, 2016b). Based on a modern definition by Carleton (2016b, p. 31), IU is described as a "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." In hierarchical personality models like the Big Three and Big Five (Kotov et al., 2010), IU is considered a fundamental lower-order construct underlying the higher-order construct of negative affectivity (also known as neuroticism) (Carleton, 2016a, 2016b). Importantly, IU is distinct from other lower-order constructs associated with negative affectivity, such as anxiety sensitivity, the need for closure, or ambiguity tolerance (Carleton et al., 2007b; Rosen et al., 2014).

IU is commonly measured using self-reported questionnaires such as the 27-item (Freeston et al., 1994) or shortened 12-item (Carleton et al., 2007a) Intolerance of Uncertainty Scale. The original 27-item Intolerance of Uncertainty Scale was developed to examine the role of IU in generalised anxiety disorder (Freeston et al., 1994). However, recent research has demonstrated that IU is transdiagnostic. For example, several large-scale meta-analyses have shown that self-reported IU is higher in populations with anxiety, mood, stress, eating and schizophrenia spectrum related disorders (Gentes and Ruscio, 2011; McEvoy et al., 2019; Morriss et al., 2024). Indeed, empirical research has demonstrated that IU accounts for larger factor loadings compared to other lower-order constructs associated with negative affectivity in hierarchical structures of personality dimensions in those with anxiety and mood disorders (Hong and Cheung, 2015; Paulus et al., 2015). In particular, several studies have highlighted how IU mediates: (1) worry or repetitive negative thinking and anxiety symptoms, and (2) rumination and depression symptoms (Huang et al., 2019; McEvoy and Mahoney, 2012, 2013; Yook et al., 2010).

Recently, experimental psychology and affective neuroscience research has been moving towards characterising the behavioral, psychophysiological, and neural markers of IU (Morriss et al., 2023; Tanovic et al., 2018). In response to everyday scenarios with uncertainty, individuals with higher levels of IU report perceiving there to be greater threat (Pepperdine et al., 2018) and feeling less safe (Cupid et al., 2021). In addition, in these type of situations, higher IU is associated with experiencing more negative emotions (such as anxiety, anger, and sadness) and fewer positive emotions (such as excitement and happiness) (Morriss et al., 2023). Under uncertain threat and to some extent uncertain reward, individuals with higher self-reported IU display attentional biases (Morriss and McSorley, 2019; Morriss et al., 2017), greater physiological arousal (e.g., skin conductance, corrugator supercilii activity, orbicularis oculi activity), and increased activation in brain regions associated with processing salience such as the amygdala, insula, and ventromedial prefrontal cortex (Carsten et al., 2022; Correa et al., 2022; Gorka et al., 2016; Morriss et al., 2020b; Morriss et al., 2015; Morriss et al., 2021a). To reduce uncertainty, individuals with higher IU are more likely to engage in safety-seeking behaviours such as behavioural avoidance (Flores et al., 2018, 2020), cognitive avoidance (Sahib et al., 2023), information gathering (Bartoszek et al., 2022), and checking (Jacoby et al., 2016; Jacoby et al., 2017; Wake et al., 2022).

2. Evidence-based techniques that modify IU

Cognitive-behavioural therapy (CBT) is a widely used first line treatment for anxiety-related disorders (Beck, 1979). CBT includes several different therapeutic components such as cognitive restructuring and behavioural exposure. Newer treatment interventions such as the Unified Protocol (UP) have extended traditional CBT to target transdiagnostic processes related to emotion regulation (Ellard et al., 2010). In addition to CBT to UP, other evidence-based therapeutic techniques such as mindfulness (Blanck et al., 2018) and relaxation (Kim and Kim, 2018) may also be used to treat anxiety-related disorders.

Current research suggests that entire CBT (McEvoy and Erceg-Hurn, 2016), UP (Khakpoor et al., 2019), mindfulness protocols (Alimehdi et al., 2016), and components of CBT (e.g. behavioural, cognitive) and relaxation, compared to passive controls, are effective in treating IU in anxiety-related disorders (for meta-analyses see, Miller and McGuire, 2023; Näsling et al., 2024). However, a recent meta-analysis by Näsling et al. (2024) observed that psychotherapies compared to active controls resulted in no significant effect of treatment on IU. Caution is warranted for this finding, as the comparison was conducted across only four studies.

With regards to how change in IU impacts other symptoms, two meta-analyses of psychotherapies revealed that larger treatment effects on IU are associated with significant reductions in symptom severity across anxiety-related disorders (number of studies = 28, Miller and McGuire, 2023) and generalised anxiety disorder (number of studies = 26, Wilson et al., 2023). Interestingly, CBT protocols that specifically target IU (Dugas and Ladouceur, 2000; Dugas et al., 2022; Mofrad et al., 2020; Wahlund et al., 2020), compared to traditional CBT protocols have also been found to be more effective in reducing IU and worry in generalized anxiety disorder (for meta-analysis see Wilson et al., 2023).

Several moderators of treatment effects on IU have been identified. Firstly, across evidence-based psychological therapies, effects for reducing IU are larger for patients with comorbid anxiety and depression, compared to mixed presentation of anxiety disorders, and

generalised anxiety disorder only (Miller and McGuire, 2023). Secondly, across evidence-based psychological therapies, effects for reducing IU are larger for those in longer treatment protocols (Miller and McGuire, 2023; but see Wilson et al., 2023) and individual therapy (Wilson et al., 2023). Lastly, no significant moderating effects on IU have been observed for concurrent serotonin reuptake inhibitor use or demographic factors such as age, gender, and biological sex (Miller and McGuire, 2023; Wilson et al., 2023).

While these advances have propelled the field forward, there remain questions as to how different therapeutic techniques that form part of CBT, UP, mindfulness, and relaxation precisely change IU. Isolating each therapeutic technique (Adams et al., 2015) in relation to IU may provide further insights into the psychological mechanisms that change IU, which can inform the development and optimisation of treatments that target IU in anxiety-related disorders. To address this gap, in each section below there is a brief overview of the relevant evidence-based therapeutic technique, the purported underlying psychological mechanisms of change, and the clinical (e.g. randomised controlled trials) and basic (e.g. lab-based studies) evidence as to whether these different therapeutic techniques and underlying mechanisms alter IU. Lastly, a synthesis of the clinical and basic evidence is provided.

Please see Fig. 1 to visualise the linkage between the different psychotherapy techniques, underlying mechanisms, and common lab-based tasks to capture change in mechanisms.

3. Cognitive Restructuring

Cognitive restructuring is a core component of CBT (Kaczkurkin and Foa, 2022) and the UP (Ellard et al., 2010). Cognitive restructuring aims to train the client to access alternative interpretations of events, in order to counter and reduce automatic negative interpretations that contribute to anxiety (Clark, 2013). Initially, the therapist helps the client discover and become aware of their negative interpretations that contribute to anxiety symptoms. Next, the therapist encourages the client to challenge their negative interpretations via verbal intervention strategies. For instance, the therapist may ask the client to gather evidence for and against the justification of a negative interpretation about an anxiety-provoking situation (e.g. I don't know whether something bad will happen), as well as to generate alternative interpretations (e.g. maybe something interesting will happen). Cognitive restructuring techniques primarily target thoughts, with the purpose of creating change that filters down to other facets associated with anxiety (e.g. emotions, physiological arousal, and safety-seeking behaviours).

Psychological Mechanism. Change in thought patterns is the fundamental principle supporting cognitive restructuring success (Beck, 1979). Essentially, maladaptive thought patterns are believed to be modified over time by exploring and evaluating these thoughts and engaging with different points of view, making way for alternative thought patterns. This process is known as a cognitive reappraisal (Clark, 2022), which is considered a key emotion regulation strategy (Gross, 2002). Engaging in cognitive reappraisal activates multiple subcortical and prefrontal regions in the brain (Buhle et al., 2014; Kohn et al., 2014; Lee and Siegle, 2012)

Clinical Research Findings. Findings from a recent meta-analysis (Miller and McGuire, 2023) demonstrates that cognitive-based interventions ($n = 11$) and cognitive bias modification interventions ($n = 2$), compared to active (pharmacological) or waitlist control, reduce self-reported intolerance of uncertainty and associated symptoms across anxiety- and mood-related disorders. In this meta-analysis, cognitive-based interventions produced descriptively larger effect sizes for IU-related change ($g = 0.95$), compared to behavioural and relaxation interventions, although these differences were not significant. Furthermore, findings from an emotion regulation therapy study in individuals with generalised anxiety disorder found that skill training in cognitive reappraisal strategies, compared to active control (attention training), reduced IU over the course of treatment (Clayton et al., 2023).

Experimental Research Findings. As noted previously, IU is associated with biased cognitions related to uncertainty, threat, and safety (Cupid et al., 2021; Pepperdine et al., 2018). A handful of experimental studies in community samples have examined whether IU can be changed

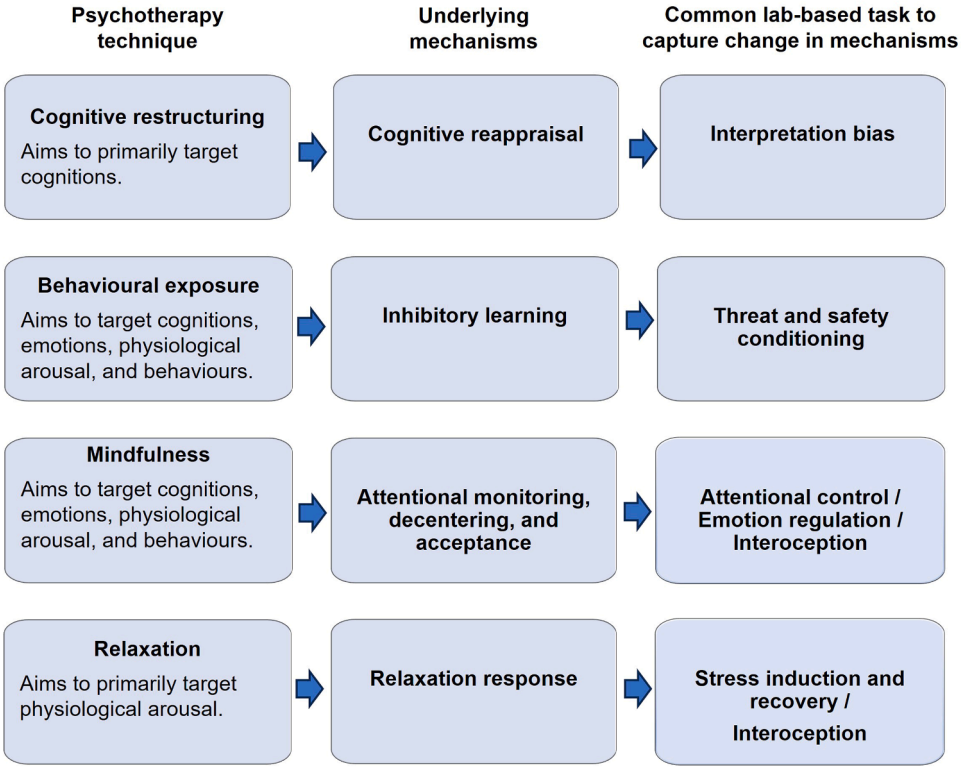

Fig. 1. Linkage between psychotherapy techniques, underlying mechanisms, and common lab-based tasks to capture change in mechanisms.

through cognitive bias modification training (Li et al., 2021; Oglesby et al., 2017; Tör-Çabuk and Koç, 2024). In these studies, an interpretation bias task was used, where participants were asked to identify whether two phrases were related or not. In the control group, participants receive no feedback based on their choices, whereas in the intervention group, participants receive feedback as to whether they are correct or not (e.g. incorrect if they link an ambiguous phrase with a negative phrase). All three studies found that the intervention reduced interpretation bias scores from pre to post test (1 week or 4 weeks) (Li et al., 2021; Oglesby et al., 2017; Tör-Çabuk and Koç, 2024). Additionally, two out of the three studies reported that the intervention reduced intolerance of uncertainty scores from pre to post test (1 week) and at a 1 month follow up (Li et al., 2021; Oglesby et al., 2017). Lastly, two of the studies performed mediation analyses to further understand the relationship between change in IU, interpretation bias scores, and intervention type / anxiety symptoms. The study by Li et al. (2021) demonstrated that change in IU scores mediated interpretation bias and anxiety. The study by Oglesby et al. (2017) reported that change in interpretation bias scores mediated the intervention type and IU scores. This mediation was specific to IU, compared to general negative affect.

Two studies in student samples with OCD symptoms have examined whether obsessive beliefs related to perfectionism and uncertainty can be altered through cognitive bias modification training (Black and Grisham, 2016; Wong et al., 2021). In these studies, the interpretation bias task presented participants with trials that included scenarios and follow up phrases to disambiguate the scenario or not. At the end of each trial, participants were asked to complete a comprehension question to reinforce positive interpretations or an unrelated question to maintain interpretation bias. Alongside, these measures, participants also completed other tasks related to checking behaviour. In both studies, the intervention relative to control condition reduced interpretation bias scores, and obsessive beliefs related to perfectionism and uncertainty at one week follow up. However, there was little evidence for change in checking behaviours following the interventions.

Synthesis. In sum, the findings from clinical and experimental research suggest that cognitive reappraisal is a fundamental psychological mechanism that alters IU-related cognitions. There is strong evidence that both the cognitive-based therapies in clinical settings and cognitive bias modification techniques in the lab change self-reported IU scores, which serve as a proxy of IU-related cognitions. The lab-based studies suggested that change in IU is related to change in interpretation bias task scores. However, it is yet to be established as to whether the relationship between change in IU and change in interpretation bias scores is bidirectional. This is likely given that interpretation bias scores reflect IU-related cognitions in action.

From the clinical and experimental research there was less evidence on how cognitive appraisal changes IU-related arousal, behaviours, and emotions. Although, the studies in clinic related to cognitive-behavioural interventions have shown that IU is associated with change in a variety of self-reported somatic and emotional symptoms related to anxiety and mood, and in one of the lab-based studies IU mediated change in anxiety symptoms.

4. Behavioural exposure

Behavioural exposure is a fundamental component of CBT (Kaczkurkin and Foa, 2022). Behavioural exposure aims to train the client to learn that anxiety-provoking situations (e.g. particular places, bodily sensations, thoughts) are manageable, without the need for over engaging in safety-seeking behaviours (e.g. avoidance, checking) (Abramowitz et al., 2019). First, the therapist and client typically work to identify a hierarchy of anxiety-provoking situations. For example, for someone suffering with social anxiety disorder, number five on the list may be speaking to a stranger, while number one on the list may be speaking to a group of strangers. Second, with the guidance of the therapist, the client attempts to move through the hierarchy either via imagination or in vivo, gradually exposing themselves to the anxiety-provoking situation(s), while resisting the use of safety-seeking behaviours such as avoidance (e.g. not engaging in conversation) and checking (e.g. seeking information about strangers on social media). Thus, behavioural exposures can address and target multiple facets of anxiety (e.g. cognitions, emotions, physiological arousal, and behaviours).

Psychological Mechanism. Inhibitory learning is postulated to be the central principle that carries exposure success (Craske et al., 2014). Through inhibitory learning, the original threatening cues or contexts are not 'unlearned' or 'erased', but rather new safety information related to these stimuli and contexts is learned, which competes for expression. The reduction in defensive responding to these stimuli over time is known as threat extinction learning. Successful threat extinction can be observed across all facets of anxiety e.g. changes in cognitions, emotions, physiological arousal, and engagement of safety seeking behaviours such as avoidance and checking (Jacoby and Abramowitz, 2016; Lonsdorf et al., 2017; Pittig et al., 2018).

The process of threat extinction is broadly supported by brain regions that form part of the default mode and salience networks. More specifically, modern neuroimaging evidence in humans has implicated that threat extinction involves the following key brain regions: dorsal anterior cingulate cortex, insula, ventromedial prefrontal cortex, hippocampus, and amygdala (Fullana et al., 2018; but see Morriss et al., 2018 for further discussion of the amygdala).

Clinical Research Findings. A recent meta-analysis by Miller and McGuire (2023) found that behavioural interventions using primarily exposure therapy techniques ($n = 11$), compared to active (neutral condition, placebo pill or pharmacological intervention) or waitlist control, reduced self-reported intolerance of uncertainty across anxiety- and mood-related disorders, with a medium effect size ($g = 0.54$). More specifically, one behavioural therapy study using written exposure demonstrated how change in IU was associated with change in worry symptoms (Goldman et al., 2007). Furthermore, a behavioural therapy designed to target IU led to change in several self-reported cognitive, somatic, and emotional symptoms of anxiety and depression (Dugas et al., 2022).

Experimental Research Findings. Threat conditioning experiments have demonstrated that higher IU in community samples is specifically associated with disrupted threat extinction learning and retention, indexed by continued physiological responding to cues that no longer signal threat (Morriss et al., 2021b; Morriss, Zuj, et al., 2021). Importantly, several studies have shown that threat extinction retention can be promoted in individuals with high IU by pairing a novel stimulus with the safety cues (e.g. a tone) (Dunsmoor et al., 2015; Lucas et al., 2018; Wake et al., 2021) or by including more safety cue trials (Morriss et al., 2020a) during the threat extinction training phase. In these studies, IU-related change in threat extinction has been observed via physiological metrics (i.e. skin conductance), but not self-reported metrics related to cognitions (i.e. threat / safety expectancy) and emotional states (i.e. feelings of anxiety).

Synthesis. These findings from the clinical and experimental literature suggest that inhibitory learning is an important psychological mechanism that can modify IU-related cognitions, physiological arousal, and emotional states. The behavioural therapies conducted in clinical settings pointed to change in self-reported IU scores, a proxy of IU-related cognitions. Additionally, one behavioural therapy study showed how change in IU was associated with change in worry, a key cognitive symptom of anxiety. Furthermore, a behaviour therapy that was specifically designed to target IU led to change in several self-reported markers of cognitive, somatic, and emotional aspects of anxiety.

The threat conditioning experiments from the lab demonstrated that heightened IU-related physiological arousal during threat extinction learning can be mitigated by presenting new safety information or more safety information that violates expectations about existing threat-safety

contingencies.

From the clinical and experimental research no studies explicitly examined the extent to which inhibitory learning brings about change in IU-related behaviours such as avoidance.

5. Mindfulness

Mindfulness aims to train the client to notice their internal experiences in the present moment and to engage in curiosity, openness, and acceptance of these experiences, rather than to suppress or actively change these experiences through safety-seeking behaviours (Bishop et al., 2004). In programmes such as Mindfulness-based Stress Reduction (Williams and Penman, 2012), clients perform experiential exercises such as bringing their attention to the present moment through mindfulness meditation and Hatha yoga. Additionally, other programmes such as Mindfulness-based Cognitive Therapy (Teasdale et al., 2000) encourage clients to practise decentering from negative self-bias. Therefore, mindfulness can address and target multiple facets of anxiety (e.g. cognitions, emotions, physiological arousal, and behaviours).

Psychological Mechanism. Key psychological mechanisms underscoring mindfulness include attentional monitoring of present sensory and perceptual experiences, viewing these experiences as objective events via decentering, and acceptance of these experiences regardless of their valence (Lindsay and Creswell, 2017; Teasdale et al., 2000). Attentional monitoring is likely reliant on selective and executive control brain networks (Lindsay and Creswell, 2017), as well as brain regions associated with interoception such as the insula (Treves et al., 2019). Decentering and acceptance are emotion regulation strategies that are supported by the default mode and salience networks in the brain (Rahrig et al., 2022).

Clinical Research Findings. In Miller and McGuire's (2023) meta-analysis, a variety of different mindfulness-based interventions ($n = 5$), compared to active (CBT or neutral condition) or waitlist control were observed to reduce self-reported intolerance of uncertainty across anxiety- and mood-related disorders, with a large effect size ($g = 0.98$). Similar results for mindfulness-based interventions and IU have also been observed in single studies on populations with generalisaed anxiety disorder (Alimehdi et al., 2016; Beheshtian et al., 2020) and obsessive compulsive disorder (Asli Azad et al., 2019; Saberizadeh and Zarehneyestanak, 2024). Moreover, findings from an emotion regulation therapy study in individuals with generalised anxiety disorder found that skill training in decentering strategies, compared to active control (attention training), reduced IU over the course of treatment (Clayton et al., 2023).

Experimental Research Findings. Two experiments in student samples have examined the impact of mindfulness interventions on IU and associated symptoms (Moser et al., 2024; Papenfuss et al., 2022). One study used an intervention with audio-instructed mindfulness meditation exercises that were practiced in the baseline session and outside the lab for twelve days. In this study, the mindfulness intervention, compared to an active neutral control, reduced IU. Moreover, change in IU mediated change in social anxiety and worry symptoms, but not panic, phobia, or obsessive-compulsive disorder symptoms. Another study, however, that used a self-guided wellness programme of 8 weeks found no specific change in IU across the mindfulness intervention versus behavioural activation intervention, and IU was not found to mediate or moderate change in anxiety symptoms for the mindfulness intervention.

Synthesis. The reported clinical and experimental findings above indicate that mindfulness-based mechanisms such as attention monitoring, acceptance, and decentering may play a role in modifying IU-related cognitions. Because each of these mindfulness-based mechanisms were not tested separately, it is difficult to establish which mechanisms specifically change IU.

The majority of the clinical and experimental findings from the mindfulness literature pointed to change in self-reported IU scores, a proxy of IU-related cognitions. However, there was limited use of other measures to capture anxiety-related phenomena in this literature. Thus, the extent to which mindfulness-based mechanisms change IU-related arousal, emotions, or behaviours remains unknown.

6. Relaxation

Relaxation techniques may be used in tandem with mindfulness techniques (Luberto et al., 2020) and/or CBT (Kim and Newman, 2019; Newman et al., 2018). Relaxation techniques such as breathing exercises (Meuret et al., 2003) allow the client to deescalate physical symptoms associated with anxiety to a more manageable level (Esch et al., 2003; Manzoni et al., 2008). Therapists may train clients how to use relaxation techniques when faced with anxiety, particularly when experiencing heightened physical symptoms (e.g. chest tightness). Relaxation techniques primarily target physiological arousal. Interestingly, however, recent evidence suggests that relaxation techniques such as breathing exercises may also be beneficial for inadvertently targeting other facets of anxiety-related pathology as well (e.g. by 'staying in the moment', clients may be able to accept distressing thoughts and emotions, and more readily engage with relevant behaviours) (Blanck et al., 2018).

Psychological Mechanism. Under states of distress or challenge, the stress response is engaged through the sympathetic nervous system (e.g. increased heart rate) (Russell and Lightman, 2019) and under states of rest, the relaxation response is engaged through the parasympathetic nervous system (e.g. decreased heart rate) (Benson, 1983). The human body dynamically switches between stress and relaxation responses. However, prolonged engagement of the stress response is associated with an increased risk of physical and mental health ailments, including anxiety-related disorders (Russell and Lightman, 2019). Thus, the logic behind using relaxation techniques is to increase engagement with the relaxation response, in order to offset the stress response.

Clinical Research Findings. Within Miller and McGuire's (2023) meta-analysis of the effects of evidence-based therapies on IU, only one study used relaxation techniques (i.e. progressive muscle relation). This relaxation intervention, compared to waitlist control significantly reduced self-reported intolerance of uncertainty in a community sample with elevated worry symptoms ($g = 0.78$).

Experimental Research Findings. There is ample evidence that higher IU is associated with heightened physiological arousal under uncertain conditions (Morriss et al., 2023a; Tanovic et al., 2018). However, no studies were identified to have examined how relaxation techniques alter IU-related physiological arousal and associated anxiety symptoms.

Synthesis. Given the limited clinical and experimental findings above, it is difficult to establish how relaxation mechanisms modify IU. The usage of relaxation seems to change self-reported IU scores, which measures IU-related cognitions. However, this effect is yet to be replicated.

7. Summary

The review highlighted that cognitive restructuring, supported by mechanisms such as cognitive appraisal, can modify IU-related cognitions. Furthermore, behavioural exposures, supported by mechanisms such as inhibitory learning, can modify IU-related cognitions and physiological arousal. In addition, the review demonstrated that mindfulness techniques underpinned by mechanisms such as attentional monitoring, decentering, and acceptance, can alter IU-related cognitions. Moreover, there was some evidence that relaxation techniques and associated mechanisms can change IU-related cognitions. Interestingly, across the different therapeutic techniques, there was a lack of evidence for how different mechanisms change: (1) IU-related emotions other than anxiety/mood, and (2) IU-related behaviours such as avoidance and information gathering.

8. Directions for future research

There are numerous opportunities for future translational research to explore how different psychological mechanisms drive changes in IU and associated symptoms within evidence-based treatments for anxiety-related disorders.

1. In prior research there has been a lack of comparison between different active interventions. For instance, more studies compare interventions against waitlist control, than against other active interventions. To better understand which psychological mechanisms are most effective in modifying IU, further research is needed to directly compare the effectiveness of various interventions that are underpinned by different psychological mechanisms (e.g. cognitive reappraisal versus inhibitory learning).
2. Both clinical and experimental research should focus their efforts on isolating different components of interventions and comparing them. For example, in mindfulness interventions, it would be beneficial to compare the components related to decentering versus acceptance, in order to determine whether these psychological mechanisms produce similar change upon IU or not.
3. Some components from different interventions overlap and therefore it would be helpful to further tease these apart. For instance, UP, mindfulness, and relaxation protocols likely engage psychological mechanisms related to interoception (Ellard et al., 2010; Luberto et al., 2020). While the link between IU and interoception has been purported to exist (Freeston & Komes, 2023), there has been a lack of clinical and experimental research on this topic.
4. There is emerging evidence that other components of psychotherapies such as psychoeducation (Hebert and Dugas, 2019; Shapiro et al., 2023), and psychopharmacological interventions related to serotonin (Kanen et al., 2021; Zemestani et al., 2021; Zemestani et al., 2022) may change IU and associated symptoms. Further research on alternative psychological therapies and newline psychopharmacological treatments is required to understand how mechanisms underpinning these different treatments alter IU.
5. Several studies have begun to investigate whether digital health interventions can target IU (Bouchard et al., 2022; Goonesekera and Donkin, 2022; Hedman et al., 2013). While in the early stages of development, there is some evidence that CBT via videoconferencing (Bouchard et al., 2022) and self-help modules on an internet platform (Hedman et al., 2013) can reduce IU in populations with clinical anxiety. Future research should examine the extent to which digital health interventions versus traditional face to face therapy changes IU, given the that such mediums of therapy may be useful for the general population, those with milder symptoms, and/or for those who cannot access in person therapy (Patel et al., 2020).
6. The literature so far has primarily focused on IU in individuals with anxiety and mood disorders and adult community samples. However, recent studies suggest that IU is transdiagnostic across stress, eating, and schizophrenia spectrum disorders (McEvoy et al., 2019; Morriss et al., 2024). Moreover, there is evidence that IU is relevant for populations that are developing (Osmanağaoğlu et al., 2018), ageing (Koscinski et al., 2024), and living with long term physical health conditions (Gibson et al., 2023). Furthermore, experiences of uncertainty-related distress are common in neurodivergent populations (Boulter et al., 2014). Therefore, it is important to examine whether the IU-related psychological mechanisms of change and respective evidence-based treatments highlighted here, also have utility for other populations.
7. It is essential to examine the specificity of change in IU and how these changes lead to alterations in secondary measures (e.g. self-reported symptoms, lab-based tasks and measures of physiology and behaviours). For example, previous research on aerobic exercise interventions have shown that these interventions successfully change anxiety sensitivity scores, but not IU scores (LeBouthillier and Asmundson, 2015; Mason and Asmundson, 2018). Conducting this type of 'specificity' research will allow us to clarify how IU compares to other lower- and higher-order transdiagnostic dimensions (e.g. neuroticism, anxiety sensitivity) (Morriss, 2023), providing valuable insights into which psychological mechanisms target IU in evidence-based treatments.
8. Currently, research on alleviating uncertainty-related distress has primarily focused on an individual perspective. However, there is ample evidence to suggest that situational uncertainty-related distress from systemic factors (e.g. discrimination, poverty) and environmental events (e.g. pandemics, natural disasters) (Afifi et al., 2012; Freeston et al., 2020; Massazza et al., 2023; Palumbo and Manna, 2020; Ricciardelli et al., 2022) cause significant risk for mental health. Interventions based on advocacy and empowerment (Reading and Rubin, 2011), and broader systemic policy changes at the meso (Onyeador et al., 2021) and macro levels are needed to alleviate these types of situational uncertainty-related distress.

Conclusion

To conclude, the review highlighted that: (1) cognitive restructuring, supported by mechanisms such as cognitive appraisal, modifies IU-related cognitions, (2) behavioural exposures, supported by mechanisms such as inhibitory learning alters IU-related cognitions and physiological arousal, and (3) mindfulness techniques underpinned by mechanisms such as attentional monitoring, decentering, and acceptance, change IU-related cognitions. However, across the therapeutic techniques reviewed, there was a gap in evidence regarding how different mechanisms influence IU-related emotions and behaviours. Future research should focus on directly comparing the effectiveness of various mechanisms that are responsible for changing IU across anxiety and other mental health disorders, as well as exploring the specificity of changes in IU compared to other anxious traits. Excitingly, these findings provide a foundation for future translational research efforts to build upon maximising existing treatment interventions and/or developing novel treatment interventions to target dispositional IU and situational uncertainty-related distress in anxiety-related disorders and beyond.

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