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Neurobiology of Intolerance of Uncertainty: A Systematic Review.

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Abstract

Intolerance of uncertainty (IU) has been identified as a key component of several psychiatric disorders; however, the neural mechanisms underlying IU remains unclear. Determining the role and neural predictors of IU in the pathophysiology of various anxiety disorders may better explain the high rate of comorbidity across these conditions, which may result in more effective and precise treatment for individual patients. Thus, this paper aims to present an up to date, comprehensive, and consolidated review of the neurobiology underlying IU. For this systematic review, we searched the PubMed database for studies published between database inception and February 2025. Studies published in peer-reviewed journals examining mechanisms of brain regions associated with intolerance of uncertainty were included. Results showed that clinical and non-clinical populations with higher IU directly correspond with alterations in regional brain activity compared to populations with lower IU. In general, limbic brain regions appeared to be hyperactive, while the prefrontal cortical regions were more often reported to be hypoactive among those with high IU. Differentiating and understanding the neural structures responsible for elevated IU is crucial in order to develop and assess the effectiveness of personalized treatment options targeting trans-diagnostic features underlying a range of psychiatric disorders

Keywords: Psychiatric Disorders; Neural Mechanisms; Brain Regions; Brain Activity; Transdiagnostic Factors; Anxiety; Treatment.

Introduction

Anxiety disorders are amongst the most prevalent psychiatric disorders, occurring in 7.3% of the global population and affecting 33.7% of people throughout their lifetime [1]. Anxiety disorders are typically underrecognized, resulting in delays in treatment, increased health care costs, social and physical impairments, and high disease burden [1]. Additionally, high level of comorbidities between anxiety disorders and other psychiatric and medical disorders results in elevated psychosocial impairment, misdiagnosis, poor treatment, substance abuse/use, and reduced quality of life [2,3].

Intolerance of uncertainty (IU) is defined as "an individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and is sustained by the associated perception of uncertainty" [4]. Recent research has suggested that IU is a transdiagnostic feature across many psychiatric disorders and is present in both clinical and sub-clinical populations [5,6]. Additionally, IU has been shown to contribute to the development and maintenance of a range of anxiety disorders and lead to worse treatment outcomes in patients [7]. Although

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IU is a key component of many psychiatric disorders, the underlying neural basis and exact nature of how IU emerges remains unclear.

Determining the neural predictors of IU may provide insight into the etiology, diagnosis, and high frequency of co-occurrence across psychiatric disorders [8]. Developing targeted transdiagnostic interventions for individuals suffering from various disorders and high levels of IU are promising for establishing parameters for personalized therapy. Pharmacological and psychotherapeutic treatments that could accurately target neural structures underlying IU and are uniquely adapted to fit the needs of individual patients could enhance and optimize results of therapy. Thus, despite recent advances in the literature, there is a need for a comprehensive understanding of IU as a construct. As such, this paper seeks to present an up to date, comprehensive, and consolidated review of the neurobiology underlying IU.

Methods

To identify studies that are relevant to this systematic review, a literature search was conducted on PubMed on February 2025. The keywords used in the search include: (Prefrontal cortex)) OR (ventromedial prefrontal cortex)) OR (dorsolateral prefrontal cortex)) OR (amygdala)) OR (central nervous system)) OR (hypothalamus)) OR (hypothalamic pituitary axis)) OR (HPA axis)) AND (Intolerance of Uncertainty).

The inclusion criteria for the studies were 1) Studies written in the English language, 2) Articles published in peer-reviewed journals, 3) Studies in human participants, 4) Studies examining IU, and 5) Studies exploring the neural basis of IU. The search drew 63 studies, which was narrowed down to 27 studies. The exclusion criteria for the studies were 1) Studies written in a non-English language, 2) Articles that were not peer-reviewed, 3) Studies in non-human participants, and 4) Articles that did not present data on brain regions involved in IU.

Three reviewers worked independently to determine which studies to include using Rayyan, a web-based tool created to aid researchers in screening studies for systematic reviews [9]. After the included studies that were compatible with the inclusion/exclusion criteria were selected, the reviewers collected data from each report. A figure and a table were used to tabulate and visually display the results of the studies presented in this review. Limitations of this review include that the review was not registered, and the protocol was not prepared ahead of time.

Results

Several brain regions have been implicated in the processing of anticipatory and uncertain stimuli, including the anterior cingulate cortex (ACC), insula, amygdala, and various subdivisions of the prefrontal cortex (PFC) — ventromedial prefrontal cortex (vmPFC), medial prefrontal cortex (mPFC), posterior frontal-medial cortex (PFMC), dorsolateral prefrontal cortex (dlPFC), right superior temporal sulcus (r-STS), and the right orbitofrontal cortex (r-OFC)

Figure 1. Regional Brain Activity in Individuals with High IU

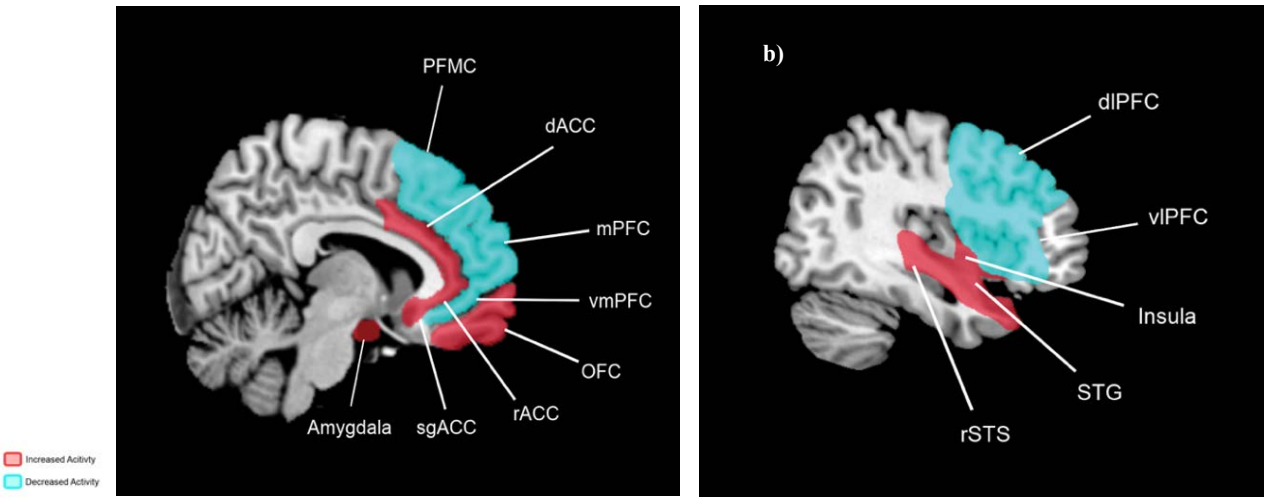

Figure 1: (a) Medial view of the brain; (b) Lateral view of the brain. The regions highlighted in red have been found to be hyperactivated in individuals with high IU. The areas in blue appear hypoactivated in individuals with high IU.

Note. PFMC = posterior frontal-medial cortex, dACC = dorsal anterior cingulate cortex, mPFC = medial prefrontal cortex, vmPFC = ventromedial prefrontal cortex, OFC = orbitofrontal cortex, rACC = rostral anterior cingulate cortex, sgACC = subgenual anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, vlPFC = ventrolateral prefrontal cortex, STG = superior temporal gyrus, and rSTS = right superior temporal sulcus.

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Table 1. This table summarizes the findings presented in this review, investigating specific brain regional activity in both non-clinical and clinical populations in the presence of high IU.

Brain Regions	Non-clinical Population	Clinical Population
ACC	High IU = decreased dACC	High IU + GAD = increased sgACC
		High IU + AN = increased dACC
		BPD = increased dACC
Insula	High IU = increased AIC High inhibitory IU = increased AIC High prohibitory IU = decreased AIC	High IU + anxiety = increased AIC
		High IU + GAD/SAD/MDD = increased AIC
		High IU + BPD = decreased right mid insula
		High IU + CD = increased IC
Amygdala	High IU = increased amygdala High IU = increased right amygdal	High IU + GAD/SAD/MDD = increased amygdala
		High IU + OCD = decreased left amygdala grey matter volume
PFC	High IU = increased mPFC High IU = increased dmrPFC High IU = decreased dlPFC High IU = decreased PFMC	High IU + IED = decreased vlPFC
FC PFC/ Limbic Regions	High IU = decreased vACC/vmPFC & amygdala coupling	High IU + GAD = decreased PFC & amygdala coupling
rSTS/ STG	Low IU = increased rSTS	High IU + anxiety disorders = increased STG
OFC	High IU = increased r-OFC	High IU + OCD = increased OFC

Note. ACC = anterior cingulate cortex, dACC = dorsal anterior cingulate cortex, sgACC = subgenual anterior cingulate cortex, AIC = anterior insular cortex, mPFC = medial prefrontal cortex, dmrPFC = dorsomedial rostral PFC, vmPFC = ventromedial prefrontal cortex, PFMC = posterior frontal-medial cortex, dlPFC = dorsolateral prefrontal cortex, vlPFC = ventrolateral prefrontal cortex, rSTS = right superior temporal sulcus, STG = superior temporal gyrus, r-OFC = right orbitofrontal cortex, OFC = orbitofrontal cortex, GAD = generalized anxiety disorder, AN = anorexia nervosa, BPD = borderline personality disorder, SAD = social anxiety disorder, MDD = major depressive disorder, CD = crohn's disease, OCD = obsessive-compulsive disorder, and IED = intermittent explosive disorder.

[10,11, Table 1]. Therefore, uncertainty and IU could be understood in terms of the linked processes between the prefrontal cortex and the areas of the limbic system [12-14]. The results of this review are organized by neuroanatomical brain regions involved in IU. Each brain region section is split into findings from articles investigating the neurobiology of IU in non-clinical and clinical populations.

The Anterior Cingulate Cortex (ACC)

The ACC is comprised of functionally distinct subregions that reside ventral, rostral, and dorsal to the corpus callosum and play important roles in emotional, cognitive, and motor processing and regulation [15,16]. Ventral and rostral regions of the ACC are often associated with modulating various aspects of reward processing, emotion, and cognitive control [14,17,18]. The dorsal regions of the ACC are associated with cognition, working memory, decision making, and top-down regulation [19,20], as well as inhibiting anxiety [21-23, Table 1].

Non-clinical population

In situations of uncertainty, activity in regions of the ACC has been found to be linearly correlated with the level of uncertainty, typically greater uncertainty was suggested to correspond with increased ACC activity [13,24,25]. Specifically, activity in the ventral ACC (vACC) and dorsal ACC (dACC) appeared to increase in response to uncertain situations [13,25]. Thus, individuals from a non-clinical population may display increased ACC activity in the response to uncertainty as these regions typically function to limit anxiety through top-down regulation of the amygdala and monitor attention, anticipation, and other uncertainty-related cognitive processes [26,27].

Individuals from a non-clinical population with high levels of IU have been shown to display less activation in areas of the ACC compared to individuals with low IU [24]. Neuroimaging research performed by Aberg, Toren, and Paz (2022) highlights that high levels of trait anxiety and elevated IU were usually correlated with lower activation of the dACC in non-clinical individuals compared to those with lower IU. This may suggest that reduced activity in the dACC could result in decreased top-down regulation of the amygdala which may reflect dysfunctional cognitive control of emotions and elevated anxiety associated with exposure to uncertainty in these individuals with high IU [24,28, Table 1].

Clinical population

Many studies have explored the importance of the ACC in IU within different clinical populations, including patients with GAD and OCD [18]. Hiser, Schneider, and Koenigs

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(2021) demonstrated that a subgroup of patients with GAD experienced greater activation of the ACC in response to uncertainty compared to healthy controls. Krain and colleagues (2008) also found that increased activity in the ventral and rostral regions of the ACC, including the subgenual ACC (sgACC), was positively correlated with IU and anxiety symptoms. These findings indicate that increased ACC neural activity may reflect high IU when individuals with anxiety disorders have to make decisions under greater uncertainty [29,30]. Increased activation of ventral and rostral regions of the ACC may be seen as related to elevated neural activity in the amygdala and other limbic regions, in association with a greater affective response to uncertain situations and increasing anxiety and distress related to uncertainty [30]. Furthermore, elevated ventral and rostral ACC activity may be understood as activating reward associated processes, leading to increased avoidance behaviour in order to reduce distress during uncertainty [12,30-32].

Additionally, Geisler and colleagues (2017) found that patients with anorexia nervosa display increased dACC activity and greater dACC-amygdala coupling after receiving negative feedback during a decision-making task, which may correlate with perfectionism and IU. One role of the dACC is to monitor performance through adjustments in cognitive control. Therefore, increased activation of the dACC and elevated dACC-amygdala coupling may reflect high IU and a greater desire for control during negative feedback in patients with anorexia nervosa [33]. In essence, this might reflect that individuals with anorexia nervosa are more distressed by uncertainty and negative feedback compared to healthy controls, which may result in increased cognitive control, behavioral changes, and activation of top-down regulation of the amygdala by the dACC, allowing these individuals to limit and extinguish distress due to uncertainty [33,34].

Olsavsky, Shott, DeGuzman, and Frank (2019) preformed a study in patients with anorexia nervosa and found that following a taste learning reward task, patients with anorexia nervosa and low IU exhibited elevated ACC activity compare to individuals with bulimia nervosa and healthy controls. Research by Zhao and colleagues (2023) also showed that patients with OCD present with reduced dACC activity during high uncertainty compared to low uncertainty. Furthermore, Mortensen and colleagues (2016) revealed that patients with borderline personality disorder display increased dACC activity compared to healthy controls during an uncertainty task, which may be associated with reduced IU. The negatively correlated relationship between IU and ACC activity in response to high uncertainty may be explained by the activation of higher order cognitive brain regions, including areas of the prefrontal cortex, during uncertainty in these patients instead of increased ACC activity. Previous research suggests that increased cognitive control and activation of conflict-oriented cognitive circuitry may occur in patients with anorexia nervosa, which facilitates these patients to experience an increased sense of control during uncertain situations that appear difficult to tolerate [35,36].

Overall, multiple studies have identified the critical role of the ACC in IU and have shown that IU is a production of altered ACC activity. There appears to be a differential response to uncertainty that is associated with elevated ACC activity in individuals from clinical populations compared to healthy controls.

The Insula

The insula is located within the lateral sulcus and plays an important role in the process of interoception, which is the subjective evaluation of how emotionally salient environmental information could impact an individual's internal state [37]. In short, this means that the insula facilitates the understanding of experiences of sensations. Specifically, the anterior insular cortex (AIC) has been shown to be involved in the processing of unpredictable aversive stimuli [11, Figure 1].

Non-clinical population

In previous studies, non-clinical subjects demonstrated greater activation of the AIC during tasks that were involved in the anticipation of unpredictably negative stimuli compared to those with predictable aversive stimuli [14, 25,38]. Simmons, Matthews, Paulus, and Stein (2008) suggested that IU was positively correlated with AIC activity, particularly in situations where stimuli were unpredictable and difficult to classify. Furthermore, research has suggested that the AIC is responsible for mediating the relationship between IU and subsequent behavioral responses, as it transmits signals to other regions of the brain to direct attention and initiate a behavioral response [14]. Consistent with these results, individuals from a non-clinical population with higher IU have demonstrated greater activation of the insula compared to those with low IU during situations of perceived ambiguity [38,39]. Perhaps this suggests a role of the AIC in decreasing uncertainty by providing information in relation to unique sensations perceived [Table 1].

Previous research by DeSerisy and colleagues (2020) assessed the connections between inhibitory IU, prospective IU, and the overall intrinsic functional connectivity (iFC) of the AIC in a group of non-clinical youth participants. Inhibitory IU, which refers specifically to the inhibition of behaviors in response to current, existing uncertainty, was correlated with increased iFC between the AIC and right inferior and middle frontal gyri during a resting state functional MRI. These regions have been implicated in top-down regulation by the PFC, which includes behavioral and emotional regulation that controls attention, monitors irregularities, and interprets emotionally salient information [40]. Increased top-down regulation facilitated by increased

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iFC between these areas may be associated with higher levels of inhibitory IU which could potentially lead to a situation in which an individual is unable to make a decision or to redirect their attention towards positive coping strategies [40, Table 1].

Additionally, youth with higher prospective IU, which refers to higher levels of anticipation and apprehensive anxiety about the future, showed a decrease in iFC between the AIC and dACC during fMRI [40]. This data suggests that individuals with higher prospective IU typically struggle to direct their attention away from any real or perceived future-oriented and/or abstract threats and would be less likely to be able to engage in situations that require spontaneous decision-making when exposed to ambiguous stimuli [40]. However, further studies are required to fully appreciate and understand the unique associations between the sub-types of IU with AIC network connectivity [Table 1].

Similarly, a recent study by Radoman and Gorka (2022) measured levels of brain activity in younger adults during a reward anticipation task using functional magnetic resonance imaging (fMRI). The results of this study demonstrated that when the reward was unpredictable, individuals with higher levels of IU had greater functional connectivity between the right AIC and the dACC [41]. The enhancement of connectivity between these two regions in individuals with high IU suggests that this type of sudden intrinsic activation is related to an overgeneralization of all forms of uncertain stimuli being perceived as aversive [Table 1]. A study conducted by Wu et al. (2024) demonstrated homogenous findings such that higher generalizations of positive and negative anticipatory reward cues were found in participants with high IU compared to individuals with low IU, accompanied by increased activation of the right AIC. Thus, the overgeneralization of uncertain stimuli, in addition to the observed atypical activation of the insula, may be involved in high IU and potentially increase an individual's vulnerability of developing psychiatric conditions, particularly anxiety disorders [42].

Clinical population

IU has been suggested to be mediated by abnormal activity in the AIC in patients with various anxiety disorders [43]. The insular cortex plays a crucial role in integrating salient multimodal information, including sensation and cognitive-affective stimuli, in order to form conscious interoception [44]. Hiser and colleagues (2021) proposed that in the context of uncertainty, higher levels of AIC activation occurs, which may reflect that patients with anxiety disorders experience greater IU compared to non-clinical individuals. Research by Oathes, Hilt, and Nitschke (2015) suggested that patients with pre-existing diagnoses of GAD, SAD, and/or MDD may display altered AIC activity and IU depending on the variation in the serotonin transporter gene. In fact, LA/LA homozygotes of the serotonin transporter gene displayed increased AIC activity compared to S/LG patients, which correlated with elevated IU. This indicates that activity of the AIC may be associated with the level of IU in individuals with clinical anxiety disorders in relation to serotonin reuptake and levels of serotonin in the synapse [45, Table 1].

Additionally, Mortensen et al. (2016) showed that a reduction in right mid insula brain activity may correspond with reduced tolerance of uncertainty (i.e., higher IU) and enhanced impulsivity in patients with borderline personality disorder. The right mid insula forms connections with regions of the prefrontal cortex and is involved in integrating cognitive, emotional, and higher-order sensory information. This implies that reduced activity in the right mid insula would lead to an increase in IU during uncertainty. Research by Zhao and colleagues (2023) also indicate that patients with OCD show decreased AIC activity during high uncertainty, supporting the idea that individuals with a range of psychopathologies associated with IU display dysfunctional insula activity [Table 1].

Furthermore, even in the absence of phenomenologically defined DSM disorders, high IU can occur in patients with inflammatory conditions, such as Crohn's disease (CD), due to the frequent risk of relapse episodes. Rubio et al. (2016) showed that during events of uncertainty, patients with CD experienced stronger activation of the insular cortex, which was found to positively correlate with both trait-anxiety and IU. This suggests that increased activation of the insular cortex directly relates to anxiety associated with the fear of recurring CD episodes and IU, even in the absence of a DSM anxiety disorder [46, Table 1].

The Amygdala

The amygdala is located in the temporal lobe and is comprised of many distinct interconnected nuclei [47, Figure 1]. This structure is part of the limbic system and plays an important role in decision making, fear acquisition, associative learning, and adapting to behaviors and changes in the environment [48,49]. The formation and processing of fearful and reward stimuli occurs in the amygdala which are then sent to various regions, including the hypothalamus, midbrain, and medulla [50]. Additionally, the amygdala is involved in processing the salience of stimuli, where uncertain or novel stimuli tend to correspond with greater amygdala activity due to uncertain situations being potentially more arousing or threatening than certain events [51].

Non-clinical population

Studies with non-clinical individuals show that there is a positive correlation between IU and activation of the amygdala in threatening situations of ambiguity, such that individuals with higher baseline levels of IU have increased amygdala activity [24,48]. This indicates that people with

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high IU at baseline typically perceive uncertain situations as more threatening, as opposed to neutral or safe [24, Table 1].

Morriss, Christakou, and van Reekum (2015) examined the relationship between fear extinction and IU and found that individuals with high IU showed greater fear towards a learned visual threat and a neutral safety cue. More specifically, individuals with high IU displayed increased activation of the right amygdala when exposed to both threat and safety cues [48]. During early extinction, elevated activation of the right amygdala in response to perceived safety cues relative to threat cues suggested that individuals with high IU were more likely to generalize fear. In late extinction, individuals with high IU showed increased activation of the right amygdala in response to threat cues relative to safety cues, which was indicative of the maintenance of the fear response to learned threat cues [48]. In contrast, during the extinction phase, individuals with low IU had lower levels of activation in the right amygdala for safety versus threat cues, later followed by reduced right amygdala activity to threat versus safety cues [48]. This progression demonstrates the accurate discrimination between threat and safety cues, and the eventual extinction of the fear response to learned threat cues [48, Table 1].

However, another study by Morriss, Bell, Biagi, Johnstone, and van Reekum (2021) explored the relationship between IU and brain region response during cue-signaled uncertainty of a threat and found that the level of IU did not directly impact activation in the amygdala or insula during threat versus safety cues. It was hypothesized that this inconsistency of results with previous reports may be attributable to the fact that there was only one main source of uncertainty in the study, namely the outcome uncertainty in response to a threat, as opposed to several sources of uncertainty across other studies [52]. Nonetheless, one might in the broadest terms, suggest the possibility that overactivity of the right amygdala is associated with significant uncertainty fears [Table 1].

Clinical population

The amygdala has been implicated in various affective disorders due to its influence on social-emotional processing and is suggested to be an essential structure involved in IU. In association, variations in the serotonin transporter gene, SLC6A4, have been found in patients with GAD, MDD, and SAD and can directly influence amygdala activity and the level of IU in individual patients. Specifically, Oathes and colleagues (2015) revealed that those with the S/LG allele for the serotonin transporter gene display less amygdala activity compared to LA/LA homozygotes. Greater amygdala activity found in LA/LA patients positively correlated with IU, conceivably due to reduced transporter expression, and as such, led to elevated stress responses [45, Table 1].

Additionally, Nakamae and colleagues (2012) examined the correlation between whole brain gray matter volume and OCD-related dysfunctional beliefs using a voxelwise analysis. Results suggest that left amygdala grey matter volume may be negatively correlated with dysfunctional beliefs, such as threat overestimation, IU, and enhanced control of thoughts. Therefore, alterations in both amygdala structure and activity have been introduced to play a potential role underlying IU in individuals with anxiety disorders [53, Table 1].

Areas of the Prefrontal Cortex (PFC)

The prefrontal cortex (PFC) plays an important role in cognitive control and is comprised of multiple interconnected neocortical areas that receive inputs from nearly all sensory, motor, and subcortical regions [54]. Areas of the PFC are responsible for guiding thoughts, behaviors, and feelings using fundamental executive functions including attention regulation, impulse control, working memory, and planning [55]. The medial prefrontal cortex (mPFC) modulates several cognitive functions including attention and inhibitory control and is involved in the regulation of threat and safety-signals [29,52,56]. The ventrolateral prefrontal cortex (vlPFC) receives visual, motivational, and emotional information for decision making and goal-directed behavior [57]. The dorsolateral prefrontal cortex (dlPFC) is part of the executive control network and plays a critical role in decision-making and behavioral response regulation [41, Figure 1].

Non-clinical population

Research by Morriss and colleagues (2021) examined brain region activation in female adults during a task in which the participants received a cue to signal the probability of being unexpectedly exposed to a low-level electric shock, between 1mA and 10mA, to the index and middle finger. There was an association between higher IU and increased activation in the mPFC when participants were given uncertain threat cues compared to safe cues [52]. Similarly, high IU correlated with increased activation in the dorsomedial rostral PFC (dmrPFC)– a region of the brain that is also implicated in threat appraisal. The mPFC and dmrPFC are implicated in models of uncertainty and anticipation as these regions are suggested to play a role in threat estimation, uncertainty, and safety signaling. These findings may indicate that individuals highly distressed by uncertainty consciously attempt to estimate the level of threat during the cue period, which is reflected through increased mPFC and dmrPFC activity [52, Table 1].

The dlPFC is associated with emotion regulation strategies such as reappraisal and mechanisms implicated in lowering uncertainty and may thereby be activated by ambiguous situations. However, individuals with high IU tended to show less activation in the dlPFC in anticipation of aversive stimuli [24,25]. This may suggest that non-clinical individuals with low IU recruit areas such as the dlPFC during uncertain

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situations in order to regulate emotions using cognitive strategies. Conceivably, those with high IU experience alterations in emotional control due to reduced activity in the dlPFC [24]. Similarly, in the context of uncertain situations, there was an inverse relationship between levels of IU and activation in the posterior frontal-medial cortex (PFMC)—individuals high in IU showed less activation in the PFMC [24]. The PFMC is implicated in predicting the context of uncertainty and activity in this area may reflect the engagement of cognitive coping strategies and actions to prepare for uncertainty signals [24]. Therefore, these findings support that elevated IU may be associated with a lack of emotional regulation, cognitive coping, and preparatory actions due to reduced activity in the PFMC. Perhaps, the lack of activation in the PFMC could be reflective of the inability to think, act, or process during uncertain situations, thereby inhibiting the ability to reduce distress and lower the uncertainty of the situation in individuals who struggle with IU [24, Table 1].

Previous research by Radoman and Gorka (2022) revealed that there is a positive association between levels of IU and functional connectivity between the dlPFC and AIC. More specifically, in a reward task paradigm, fMRI showed that young adults with higher IU had increased functional connectivity between the dlPFC and AIC when the reward was uncertain [41]. Such results could indicate that enhanced activation in the AIC leads to an overcompensation by the executive control network to manage the subjective aversiveness to uncertainty [41]. Also given the AIC's role in providing context to sensation, it could act to provide input as to whether the potentially uncertain stimuli are happening as expected thereby decreasing uncertainty and facilitating top-down regulation of the amygdala [Table 1].

Clinical population

Abnormal activation of the vlPFC has been a suggested mechanism underlying IU and aggressive behavior in individuals with a diagnosis of intermittent explosive disorder (IED). The primary role of the vlPFC is to regulate social pain and predict reductions in social distress or physiological arousal in the presence of situations of social exclusion [59]. Gorka and colleagues (2018) demonstrated that hypoactivation of the vlPFC is associated with increased levels of IU and trait aggression in patients with IED following social exclusion. Patients with high baseline IU tend to find ambiguity distressing in social situations, which can lead to an increase in aggressive behavior. This too may suggest that top-down inhibitory control is destabilized or disrupted in individuals with IED and high IU and may point to decreased vlPFC activity playing an important role in both IU and aggression [59, Table 1].

Functional Connectivity Between the PFC and Limbic Regions

Regions of the PFC and the limbic system are highly interconnected and are involved in cognitive and emotional processing and regulation [60]. Functional connections between the PFC and limbic regions of the brain have also been associated with decision-making under uncertain conditions in non-clinical individuals and patients with anxiety disorders. Additionally, projections from the PFC are suggested to initiate top-down control over activity in the areas of the limbic system [61, Table 1].

Non-clinical population

A previous study by Sommerville et al. (2013) explored the emotional function of a unique network comprised of a single region in the ventral ACC (vACC) which borders on the ventromedial prefrontal cortex (vmPFC) and is in communication with the amygdala. In conditions of greater unpredictability, individuals with higher IU showed reduced capacity for recruitment of the vACC region bordering on the vmPFC (vACC/vmPFC) [62]. Furthermore, the results demonstrated an inverse relationship of activation between the vACC/vmPFC and amygdala, such that the sustained hypo-recruitment of the vACC/vmPFC was directly associated with greater amygdala activation in response to potential threat cues [62]. Therefore, in individuals with high IU, the amygdala was increasingly more responsive and involved in emotional regulation, which correlates with a simultaneous lack of activation in the prefrontal region, reflecting reduced top-down regulation of the amygdala by the PFC [62]. Thus, it is suggested that the reduced engagement of the region of the vACC adjacent to the vmPFC could reflect that individuals with high levels of IU are impaired in their ability to notice safety cues when faced with unpredictable situations [62, Figure 1]. Further to this point, greater activation of the amygdala may result in reduced sensitivity to the type of cues, which may lead to a biased interpretation of uncertain situations as being threatening, thereby resulting in a persistent anxiety response [10, Table 1].

Clinical population

Prior studies have shown that reduced PFC-amygdala functional connectivity appears to be intimately correlated with IU in patients with GAD, suggesting a potential neural mechanism that underlies GAD psychopathology. Specifically, Assaf and colleagues (2018) showed that abnormally weaker PFC-amygdala functional connectivity may be indicative of a lack of regulation and specifically a lack of inhibition of emotional responses by the PFC, resulting in stronger reactivity by the amygdala during uncertainty [63]. This anomalous connectivity may explain the associated anxiety comorbidities in a variety of illnesses including attention deficit hyperactivity disorder (ADHD)

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[64-66], depression [67], and bipolar mood disorder [68]. Furthermore, Li and colleagues (2020) have shown that patients with GAD demonstrate less top-down connections and more bottom-up connections than healthy controls during neutral, negative, and positive conditions, revealing that these patients have significantly abnormal PFC-limbic network responses. A lack of top-down control in these patients may suggest inadequate cognitive control by the PFC over emotional reactivity that usually occurs in limbic areas of the brain. Increased bottom-up connections may be reflective of an overly-responsive limbic system and hypo-functional inhibiting PFC, resulting in an overgeneralization of fear thoughts and responses during non-threatening stimuli and increased IU in patients with GAD [69, Table 1].

The Right Superior Temporal Sulcus (r-STS)/ The Superior Temporal Gyrus (STG)

The right superior temporal sulcus (r-STS) is activated when processing different types of external stimuli including motion, faces, language, and theory of mind [70]. The superior temporal gyrus (STG) is associated with language and auditory processing and has also been suggested to play a critical role in social cognition [71, Figure 1].

Non-clinical population

Cristaldi and colleagues (2022) examined resting state brain activity during an affective prediction task paradigm and found that individuals with high levels of IU, when compared to individuals with low IU, had greater activation of the r-STS when exposed to stimuli that did not reflect their predicted outcome. This increased activation was only observed during the generation stage, the time period when the brain creates an expectation about an outcome. The r-STS is critically involved in extracting social-affective information from different stimuli, which indicates that elevated activity in this area may result in lower efficiency in processing and extracting information [70]. Thus, these results highlight that increased activation of the r-STS may impact the modulation of emotional information, suggesting that individuals with high levels of IU are unable to accurately extract information and as a result are typically hypervigilant of their environment and have greater levels of salience to emotional stimuli. Furthermore, the r-STS is highly connected to regions of the limbic system, including the amygdala and insula, that are associated with high levels of IU. In essence, the r-STS also influences activity in other brain regions through top-down regulation, emphasizing its role in IU [70].

Clinical population

Research indicates that the STG may be involved in the development of IU in individuals with various clinical anxiety disorders. The STG in humans plays a critical role in the selection and extraction of meaningful linguistic information from speech input [72]. Hiser and colleagues (2021) revealed that patients with anxiety experience elevated neural activity in the STG region in response to uncertainty. Therefore, it can be hypothesized that higher levels of uncertainty and IU may be positively correlated with an increase in STG activity in patients with anxiety disorders, giving greater insight into the understanding of the neurobiological mechanisms underlying IU [29, Table 1].

The Orbitofrontal Cortex (OFC)

The orbitofrontal cortex (OFC) is a critical brain region implicated in reward processing and punishment [73]. In fact, the OFC has been shown to be involved in motivational, emotional, and social behavior, as it plays an important role in learning and modulating reward, punishment, and emotional behavior [74]. Additionally, this area of the brain is included in the network responsible for decision-making, response-selection, and cognitive control of behavior, such as inhibitory control [75, Figure 1].

Non-clinical population

Similar to the findings associated with the r-STS, individuals with high levels of IU had significantly greater activation in the r-OFC during resting state, compared to individuals with low IU [70]. The right orbitofrontal cortex (r-OFC) is responsible for processing visual information and integrating sensory information, providing individuals with a more complete understanding of incoming stimuli, which might be understood as contributing to the lowering of uncertainty. The significantly increased activity in the r-OFC was only observed during the prediction updating stage, a stage in which expectations are modified based on observed outcomes [70]. Therefore, the r-OFC is hyperactive in individuals with high IU when they are updating predictions as a result of their expectations of the stimulus being inaccurate [70]. Perhaps this excessive activation of the r-OFC causes hyperarousal and abnormally heightened emotional processing in uncertain situations, indicating that individuals with high IU may experience elevated physiological reactions towards uncertainty, partly due to increased r-OFC activity [70, Table 1].

Clinical population

Recently, the role of the OFC in IU has been examined primarily within patients with OCD. The OFC is a brain region usually involved in adaptive and flexible behaviors and is an important area for initiating changing behavior in the presence of unexpected outcomes [76]. During a decision-making task, Rotge and colleagues (2015) showed that increased IU is associated with the level of activity in the OFC and the amount of checking behaviors in both patients with OCD and individuals from a non-clinical population. In healthy controls, a greater number of errors in decision-making tasks led to an increased number of checking behaviors; however, patients with OCD cannot easily adapt to context-

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related issues. Additionally, an increased number of checking behaviors reduced OFC activity in healthy controls but not in patients with OCD, suggesting that these patients experience reduced cognitive flexibility and problems with responses to the context of behaviors. Therefore, hyperactivity of the OFC in patients with OCD could lead to difficulties interrupting perceived uncertain signals, resulting in intrusive distressing thoughts and inappropriately enhanced checking behaviors associated with IU [77, Table 1].

Discussion

Figure 1 and Table 1 presented above, summarizes the reported findings. The results discussed in this review emphasize that individuals in clinical and non-clinical populations with higher IU consistently display distinct alterations in brain activity compared to individuals with low IU. High IU in both non-clinical individuals and psychiatric patients was associated with greater activation of brain regions including the ACC, insula, amygdala, OFC, rSTS, mPFC, and STG. In contrast, a reduction in activation of specific brain regions in the PFC, including the vlPFC, vmPFC, and the dlPFC, was observed in individuals with high IU [Figure 1]. Thus, studies performed within non-clinical and clinical populations have revealed distinct neurobiological differences in those with high IU, thereby highlighting regions of the brain that are potential targets for more effective treatment interventions and advancing our understanding of the neurobiological mechanisms underlying IU. Furthermore, considering IU as a potential treatment target may elucidate the importance of targeting underlying psychological presentation of brain functions as opposed to clusters of symptoms. This approach could potentially lead to better outcomes and symptomatic recovery [78].

The findings of this review support the notion that IU is a common construct across various psychopathology. In addition, the results have identified associations between IU and neural activity and connectivity even in sub-clinical populations, which include non-clinical individuals with high levels of IU. In general, there is a pattern of hyperactivation in limbic regions contrasted with overall hypoactivation in the prefrontal cortex. This pattern is seen in both clinical and non-clinical populations with high IU and might be reflective of poor top-down regulation in individuals that are overwhelmed or distressed by uncertainty. An appreciation of IU as a transdiagnostic factor provides greater insight into the common physiological mechanisms that underlie various clinical disorders. Furthermore, identifying IU as a transdiagnostic factor allows for targeted prevention and focused treatment approaches that may translate and generalize to multiple disorders.

This paper provides an up-to-date synopsis regarding the underlying psycho-biological mechanisms of IU in both non-clinical and clinical populations. We have highlighted the clinical importance of IU and the value of conceptualizing psychological characteristics transdiagnostically. Examining the construct of IU across various clinical populations rather than solely investigating IU in individual disorders has a number of potential advantages. For instance, a deeper understanding of the neural basis of anxiety-related features, including IU, could provide an opportunity for the development of newer and novel targets for the treatment of various clinical anxiety disorders [29,30]. Stimulating specific targeted neuronal substrates in order to facilitate alterations in pathological baseline activity, such as those observed in individuals with high IU, could provide dramatic benefits and alleviation of symptoms [79]. Neurofeedback is another technique which could be a novel treatment approach that allows individuals with high IU to effectively normalize their brain activity in specific cerebral regions including the ACC, insula, and amygdala [80]. Future studies which directly target regions involved in IU utilizing either neurostimulation or neurofeedback in addition to psychotherapy may inspire the development of individualized therapies and personalized medicine, ultimately optimizing better treatment for patients with anxiety disorders [45,63].

Furthermore, research shows that IU may influence the activity in brain regions that are involved in cognitive processes related to estimation or appraisal of situations of threat, personal safety, and uncertainty. These cognitive patterns could be targeted in therapies including cognitive behavioral therapy (CBT) [52,81]. CBT usually conceptualizes psychopathology in terms of patterns of dysfunctional thinking that influence mood and behavior. CBT is effective at treating cognitive distortions, such as mis- interpreting neutral events as negative [82]. This approach is applicable to the overestimation of threat and fear generalization that is often seen in individuals with high IU. Current CBT approaches might be adapted to directly target IU; however, further investigation and timely alteration of CBT protocols to directly target the construct of IU, including focused psychoeducation and the use of exposure, seem warranted. In contrast to the typical pharmacological treatments for anxiety disorders, such as selective serotonin reuptake inhibitors (SSRIs), CBT targeting IU was found to improve many symptoms of GAD, including excessive worry and IU, and displayed greater benefits compared to the group prescribed SSRIs only [83]. Therefore, CBT focusing on targeting IU has been shown to be beneficial in patients with GAD, which could translate into potential benefits for other psychiatric populations, although more studies are required to examine this approach [84].

There is an abundance of evidence suggesting that cognitive retraining strategies can effectively reduce anxiety symptoms [85]. It is well documented that individuals with anxiety disorders experience a heightened attentional bias

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for threat and that training these individuals to reduce their attention on perceived threats and attend to non-threat stimuli can alter attention mechanisms [86]. Studies using various cognitive retraining strategies, such as reducing negative emotion towards tasks and altering attention towards threat, reveal that these techniques can increase activation of the dlPFC, vlPFC, right PFC and ACC, and lead to reduced activity in the amygdala [87]. Since the results of this review have indicated that individuals with high IU demonstrate increased amygdala activity and decreased dlPFC and vlPFC activity, decreasing amygdala and increasing PFC activity through cognitive retraining may be an effective approach to consider with cognitive therapy. Ultimately, there may be utility in altering regional brain activity in individuals with elevated IU as adapting these cognitive therapeutic approaches may be effective in lowering IU and alleviating anxiety symptoms.

Pharmacological approaches developed to treat anxiety disorders that may enhance or spare the PFC from side effects could potentially be beneficial for patients with high IU. Previous research has suggested that pharmacological treatments decrease anxiety through reducing limbic brain region activity. For instance, SSRIs have been revealed to reduce hyperactivity of limbic regions, particularly in the amygdala, and may be able to do this without inhibiting prefrontal activity [88]. Since poor top-down regulation and hypoactivity in the PFC is suggested to contribute to the neurobiological mechanism underlying high IU, pharmacotherapy that increases PFC activity while directly inhibiting activity in limbic regions may be optimal for individuals that are highly distressed by uncertainty. This may suggest a benefit in some individuals of using more prefrontally sparing, catecholamine raising medications, including Mixed Multi Modal, or higher dose SNRI antidepressants, over SSRIs which may inhibit amygdala activity, but also affect prefrontal cortical activity resulting in poorer top-down regulation of the amygdala [89-91]. Therefore, a combination of pharmacological treatments and psychotherapeutic approaches that target regions of the brain associated with high IU could be seen as more optimal treatment options for those with high IU.

Based on the results discussed in this review, future research should move forward to evaluate treatment approaches that uniquely target IU to better assess and understand how IU targeted therapy could be utilized to specifically prevent or reduce the impact of disorders associated with high IU. Thus, both psychotherapeutic and pharmacotherapeutic approaches may be beneficial in decreasing treatment resistance and enhancing the quality of life in people who are suffering with higher IU and its related disorders. It is evident from this review that there is great applicability and utility for brain imaging techniques as a marker for assessing levels of IU, thus future studies could investigate the impact of selected treatments with either pharmacological, nootropics or alternative agents on brain region activity of individuals with high IU. Finally, this review emphasizes that future research on the construct of IU as a whole should be thoroughly evaluated and targeted to optimize better evidence -based treatments and develop personalized, targeted interventions.

There are evident limitations to this review, specifically related to the sample size of the included studies. Several of the studies had small sample sizes, (from N=14 to N=171), which limits the power of the results [38,41]. In addition, some of the studies included very specific populations, for example, only female gender or only youth at risk for alcohol use [41,52]. Such samples may decrease the generalizability of our findings. Furthermore, some of the studies investigating "non-clinical" populations may not have adequately screened for past mental health history and studies examining "clinical" populations may not have accounted for comorbid psychiatric disorders. Therefore, the sample could have been more heterogeneous and the results might not be reflective of a true population. Future research should aim to build on previous findings and include larger and more diverse samples that better account for heterogeneity. Perhaps one of the most important limitations to consider is the potential that differing activity associated with higher IU may not only seem to represent the neurobiological substrate of higher IU, but also might be seen as the compensatory response to higher IU. Thus, further neurobiological investigation of IU as a targeted substrate is key to developing better understanding of its related psychopathology.

This review suggests that elevated IU within both clinical and non-clinical populations directly corresponds with changes in regional brain activity compared to populations with lower IU. Overall, limbic regions of the brain are revealed to be hyperactive and various areas of the PFC are reported to be hypoactive in individuals with high IU. Importantly, identifying and understanding the neural structures responsible for elevated IU is critical in order to develop and investigate the effectiveness of personalized treatment options targeting transdiagnostic features underlying a range of psychiatric disorders.

Conflicts of Interest

Martin Katzman reports a relationship with S.T.A.R.T Clinic for Mood and Anxiety Disorders that includes: employment and non-financial support. Martin Katzman reports a relationship with Adler Graduate Professional School that includes: employment. Martin Katzman reports a relationship with NOSM University that includes: employment. Martin Katzman reports a relationship with Lakehead University that includes: employment. Martin Katzman reports a relationship with AbbVie Inc that includes: consulting or advisory and funding grants. Martin Katzman reports a relationship with Eisai Co Ltd that includes:

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consulting or advisory and funding grants. Martin Katzman reports a relationship with Canopy that includes: consulting or advisory and funding grants. Martin Katzman reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory and funding grants. Martin Katzman reports a relationship with Otsuka Pharmaceutical Co Ltd that includes: consulting or advisory, funding grants, and travel reimbursement. Martin Katzman reports a relationship with Pfizer Inc that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Elvium/Purdue Pharma LP that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Genuine Health that includes: funding grants. Martin Katzman reports a relationship with Idorsia that includes: consulting or advisory and funding grants. Martin Katzman reports a relationship with Biotics that includes: consulting or advisory. Martin Katzman reports a relationship with Takeda Pharmaceutical Company Limited that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Eli Lilly that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Knightsbridge that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Merck that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Tilray Inc that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Taro Pharma that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Biron that includes: consulting or advisory. Martin Katzman reports a relationship with Bausch Pharma that includes: consulting or advisory. Martin Katzman reports a relationship with Fertin Pharma that includes: consulting or advisory. Martin Katzman reports a relationship with GoodCap Pharma that includes: consulting or advisory. Martin Katzman reports a relationship with Sun Pharma that includes: consulting or advisory. Martin Katzman reports a relationship with Supernus that includes: consulting or advisory. Martin Katzman reports a relationship with Lundbeck that includes: consulting or advisory, funding grants, and travel reimbursement. Martin Katzman reports a relationship with Boehringer Ingelheim that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Bristol-Myers Squibb that includes: consulting or advisory and travel reimbursement. Martin Katzman reports a relationship with Biohaven Ltd that includes: funding grants. Irvin Epstein reports a relationship with Pfizer Inc that includes: funding grants and speaking and lecture fees. Irvin Epstein reports a relationship with Janssen Pharmaceuticals Inc that includes: funding grants and speaking and lecture fees. Irvin Epstein reports a relationship with Alkermes Plc that includes: equity or stocks.

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