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Focus Article

The role of intolerance of uncertainty in current and remitted internalizing and externalizing psychopathology

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ABSTRACT

Intolerance of uncertainty (IU) is a putative key, transdiagnostic factor in internalizing psychopathologies. However, it is unclear if elevated levels of IU, as measured by the Intolerance of Uncertainty Scale, short form (IUS-12) and its subscales (prospective and inhibitory IU), persist into remission of internalizing psychopathologies (or particular types of internalizing psychopathologies; e.g., fear vs. distress-misery disorders). It is also unknown if IU is specifically characteristic of internalizing (vs. externalizing) psychopathology and whether this relationship is independent of neuroticism/negative affectivity (N/NA). A large community sample (n = 517) completed a diagnostic interview and self-report measures of IU and N/NA. Results indicated that, independent of N/NA, IU was elevated in current fear and distress/misery disorders, but not externalizing disorders. Individuals with remitted fear disorders also displayed significantly elevated levels of IU in comparison to healthy controls after adjusting for levels of N/NA. In terms of subscales, elevated levels of inhibitory IU, and not prospective IU, demonstrated more reliable relationships with internalizing psychopathologies. In summary, IU was more consistently related to fear disorders, demonstrated incremental validity over and above the effects of N/NA, and may be a key, transdiagnostic mechanism in fear disorders.

1. Introduction

Psychopathologies involving anxiety and depression (i.e. internalizing psychopathologies; Kendler, Prescott, Myers, & Neale, 2003; Krueger, Caspi, Moffitt, & Silva, 1998; Vollebergh et al., 2001) are serious, prevalent, and costly public health burdens. Internalizing psychopathologies are among the top 10 leading disabilities in the United States and carry an economic burden of hundreds of billions of dollars (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014; Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015). Identifying underlying etiological mechanisms of internalizing psychopathologies could reduce this burden by providing novel clinical targets for early identification and preventative treatments. The personality trait, intolerance of uncertainty (IU), may be an important etiological mechanism of internalizing psychopathology (Carleton, 2016a, 2016b).

Carleton (2016a, p. 31)Carleton, 2016aCarleton (2016a, p. 31) recently defined IU as "an individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty" and argued that individuals high in IU experience fear in response to such absence of information (see also Carleton, Norton, & Asmundson, 2007; Freeston, Rheaume, Letarte, Dugas, & Ladouceur, 1994). Early research on IU focused on its role in the maintenance of generalized anxiety disorder (GAD; Dugas, Gagnon, Ladouceur, & Freeston, 1998). More recent evidence has shown that IU, as measured by the Intolerance of Uncertainty Scale and its short form (IUS and IUS-12; Carleton, Norton et al., 2007; Freeston et al., 1994), is not specific to GAD and may relate to anxiety-related disorders more broadly. In fact, scores on the IUS have been found to be positively associated with symptoms of obsessive-compulsive disorder (OCD; Holaway, Heimberg, & Coles, 2006; Tolin, Abramowitz, Brigidi, & Foa, 2003) Panic Disorder (Carleton, Fetzner, Hackl, & McEvoy, 2013, 2014), social anxiety disorder (SAD; Boelen & Reijntjes, 2009; Carleton, Collimore, & Asmundson, 2010; Whiting et al., 2014), and posttraumatic stress disorder (PTSD; Bardeen, Fergus, & Wu, 2013; Fetzner, Horswill, Boelen, & Carleton, 2013). IUS scores are also positively correlated with symptoms of major depressive disorder (MDD; Yook, Kim, Suh, & Lee, 2010) at rates comparable to that of other internalizing disorders (Carleton et al., 2012; Gentes & Ruscio, 2011), even when controlling for neuroticism or negative affectivity (N/NA; McEvoy & Mahoney, 2011, 2012). However, it should be noted that not all studies have found an association between IU and depression after accounting for other internalizing symptoms (Jensen, Cohen, Mennin, Fresco, & Heimberg, 2016; Khawaja & McMahon, 2011). Therefore, IU, as measured by the

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IUS, not only relates to anxiety disorders, but may be a transdiagnostic trait within internalizing psychopathologies in general.

IU appears to play a particularly important and central role among factors contributing to the etiology and maintenance of internalizing psychopathologies and is generally considered to be a vulnerability factor for internalizing psychopathologies. A meta-analysis of cognitive vulnerabilities related to anxiety or depression showed that IU accounted for the most variance among a wide range of cognitive vulnerabilities (Hong & Cheung, 2015). However, it is unclear whether elevated levels of IU in current internalizing psychopathology (Carleton et al., 2010, 2012; Holaway et al., 2006; Nelson, Shankman, & Proudfit, 2014; Nelson, Liu, Sarapas, & Shankman, 2016; Tolin et al., 2003; Whiting et al., 2014) persist into remission, a key criteria for markers of vulnerability (Zubin & Spring, 1977). In their classic study, Zubin and Spring (1977) proposed that a vulnerability marker should exist (a) before, (b) during, and (c) after an episode of psychopathology and (d) that the vulnerability marker must also be familial (i.e., correlated within families). The presence of the trait before the onset of psychopathology ensures that elevation of the trait is not merely a "scar" or byproduct of psychopathology caused by the onset of psychopathology (elevations in the trait did not lead to the onset of psychopathology). The vulnerability marker must also be present during an acute period or episode of psychopathology to ensure that the marker is, in fact, related to the disorder or disorders of interest. The marker's presence after an episode of psychopathology further demonstrates that the vulnerability marker is an enduring and stable trait and not just a characteristic of those with acute symptoms of the disorder. Lastly, establishing that a vulnerability marker is familial suggests that the trait is endogenous and perhaps heritable. Elevated levels of IU in individuals with a past, and not current, history of psychopathology (i.e., the disorder is in remission) would demonstrate that high IU is an enduring and stable trait, although IU could also represent a "scar" of psychopathology (Lewinsohn, Steinmetz, Larson, & Franklin, 1981). Moreover, the elevation of IU in remission from internalizing psychopathologies would provide strong preliminary evidence towards examining whether IU is a premorbid and familial vulnerability factor.

Few studies have examined IU in remission. Treatment studies have found that psychotherapy can reduce the severity of IU in those with GAD, OCD, SAD, and Panic Disorder (Boswell, Thompson-Hollands, Farchione, & Barlow, 2013; Dugas & Ladouceur, 2000; Ladouceur et al., 2000), but have not evaluated whether those in remission still report elevated levels of IU in comparison to those without a history of an internalizing psychopathology.

When examining whether IU is elevated in current and remitted internalizing psychopathology it is also important to examine these relationships while controlling for trait N/NA. N/NA reflects individual differences in negative emotional responding (e.g. anxiety, irritability, sadness, anger, etc.) as well as instability in such responses (Kendler, Neale, Kessler, Heath, & Eaves, 1993; Lahey, 2009). N/NA is also elevated in internalizing psychopathology and may be a vulnerability factor as well (Farmer et al., 2002; Griffith et al., 2010; Kendler et al., 1993; Lahey, 2009; Ormel, Oldehinkel, & Vollebergh, 2004). Additionally, the high correlation between IU and N/NA as well as the conceptual overlap between the two constructs bring into question the independence and specificity of these possible etiological mechanisms (McEvoy & Mahoney, 2012; Sexton, Norton, Walker, & Norton, 2003).

The elevation of IU in both current and remitted internalizing psychopathology may also differ across different aspects of IU. While results have been mixed, factor analytic, latent class analysis, and factor mixture modeling studies have demonstrated that IU is made up of two separate, but related factors - prospective IU and inhibitory IU (Boelen & Lenferink, 2018; Carleton, Norton et al., 2007; Hale et al., 2016; McEvoy & Mahoney, 2011; Oglesby, Allan, Short, Raines, & Schmidt, 2017; Shihata, McEvoy, & Mullan, 2018). Prospective IU is characterized by future-oriented cognitive and emotional distress to uncertainty whereas inhibitory IU is described as behavioral inhibition in response to uncertainty. These subfactors of IU are correlated with each other and have also been shown to have discriminant validity such that prospective IU is associated with symptoms of GAD and OCD whereas inhibitory IU is related to symptoms of SAD, Panic Disorder, and MDD (Carleton et al., 2010; McEvoy & Mahoney, 2011, 2012). It is therefore possible that internalizing psychopathologies may more closely relate to certain subfactors of IU more than others.

In addition to the heterogeneity within IU, internalizing psychopathologies are also heterogeneous. Factor analytic studies have demonstrated that internalizing psychopathologies bifurcate into two distinct, but related, subfactors (Kendler et al., 2003; Krueger, 1999; Slade & Watson, 2006; Vollebergh et al., 2001; Watson, 2005). The first subfactor of disorders is characterized by fear (e.g., specific phobia, SAD, Panic Disorder) and the second is typified by distress and misery (e.g. MDD, GAD). Prospective and inhibitory IU may show different relationships with fear disorders as compared to distress/misery disorders.

It is also possible that IU may not be specific to internalizing psychopathologies and could be characteristic of a wider range of psychopathologies than previously thought. Kraemer, Mcleish, and Bryan (2015) examined the relationship between self-reported alcohol use motives and IU in a college sample and found that those who endorsed drinking-to-cope as well as drinking-to-conform reported greater levels of IU above and beyond the effects of gender, smoking status, marijuana use status, alcohol consumption, negative affectivity, and anxiety sensitivity. Thus, those high in IU may be more motivated to drink to avoid distress and social rejection, which could subsequently lead to greater alcohol use. Psychophysiological research has also provided further evidence that IU may not be specific to internalizing psychopathologies. Alcohol dependence (which is typically characterized as an externalizing, not internalizing, disorder; (Kendler et al., 2003; Krueger et al., 1998; Vollebergh et al., 2001)) has been shown to be related to increased startle to uncertain threat (Gorka & Shankman, 2017; Gorka, Nelson, & Shankman, 2013; Gorka, Lieberman, Phan, & Shankman, 2016). Moreover, startle potentiation to *uncertain*, but not predictable, threat is positively correlated with a family history of alcohol use disorder (AUD; Gorka, Hee et al., 2016). The increased reactivity to uncertain threat evidenced in individuals with AUD may be a behavioral correlate of IU (Nelson et al., 2016). If so, IU may also play a key role in AUD – and perhaps other externalizing psychopathologies as well.

Therefore, the aims of the current study are to assess whether IU is (1) elevated in current internalizing psychopathology and (2) elevated in remitted internalizing psychopathology. In order to examine whether IU is a separate etiological mechanism from N/NA, analyses will control for individuals' levels of N/NA. It is hypothesized that IU will be elevated in current and remitted internalizing psychopathology given its putative role as a vulnerability factor. Additional exploratory analyses will examine whether 1) N/NA is elevated in current and remitted internalizing psychopathology when adjusting for individuals' levels of IU, 2) prospective and inhibitory IU are elevated in current and remitted fear disorders and/or distress/misery disorders and 3) IU is specific to internalizing psychopathologies or if IU is also a key factor in externalizing psychopathologies such as AUD.

2. Material and methods

2.1. Participants

A total of 517 participants were drawn from a NIMH-funded family study (see Gorka, Hee et al., 2016; Katz, Hee, Hooker, & Shankman, 2017 for additional details). Participants were nested within 274 families and included 243 sibling pairs. Advertisements (fliers, internet postings, etc.) were used to recruit participants from the community and from mental health clinics. Participants were 18 to 30 years old ($M = 22.39$, $SD = 3.17$) with a wide range of psychopathologies, as well as healthy controls (see Table 1 for participant demographics and clinical

Table 1
Participant Demographics.

	Mean	Standard Deviation
Age	22.39	3.17
Global Assessment of Functioning Symptom Severity	72.65	13.70
Global Assessment of Functioning Impairment	74.80	13.07
Total IU	27.99	9.28
Prospective IU	18.27	5.78
Inhibitory IU	9.72	4.18
N/NA	0.97	0.43

	Percent of Sample
Gender (% Female)	63.62%
Race/Ethnicity (%White)	42.35%
Currently Taking Psychiatric Medication	9.74%
Education (% graduated from a 4-year college)	18.53%

Psychopathology Status	Current	Remitted
Fear Disorders	24.95%	16.05%
Social Anxiety Disorder	10.25%	9.28%
Obsessive-Compulsive Disorder	3.68%	2.71%
Panic Disorder	2.32%	5.61%
Post-traumatic Stress Disorder	1.16%	5.80%
Specific Phobia	14.51%	5.80%
Distress/Misery Disorders	7.93%	29.98%
Major Depressive Disorder	4.64%	29.40%
Generalized Anxiety Disorder	4.26%	6.00%
Externalizing Disorders	9.67%	27.47%
Alcohol Use Disorder	5.42%	23.40%
Substance Use Disorder	5.61%	15.09%
No lifetime history of any psychopathology	33.46%	

characteristics). A Research Domain Criteria (RDoC) approach was taken to participant recruitment such that recruitment screening was agnostic to Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic categories (beyond the exclusion criteria listed below). However, participants with severe internalizing psychopathology were oversampled to ensure that the sample was clinically relevant. Specifically, the Depression, Anxiety, and Stress Scale (DASS; Lovibond & Lovibond, 1995) was administered during the initial phone screen to ensure that the severity of internalizing symptomology within the sample was normally distributed, but that participants also had higher average symptoms (M = 10.35, SD = 10.07) than the general population (M = 8.3, SD = 9.83; Crawford, Cayley, Lovibond, Wilson, & Hartley, 2011).

Inclusion criteria specified that participants had at least one full biological sibling that was also willing to participate in the study. Exclusion criteria included personal or family history of psychosis or mania at the time of the interview (given that psychosis and mania have been shown to be separable from internalizing and externalizing disorders; Caspi et al., 2014; Kotov et al., 2011; Krueger et al., 1998; Markon, 2010), inability to read or write in English, history of serious head trauma, and left-handedness (to protect against confounds with the neurophysiological data collected for the main aims of the larger study).

2.2. Measures

2.2.1. The intolerance of uncertainty scale, short form (IUS-12)

The IUS-12 (Carleton, Norton et al., 2007) is a 12-item self-report scale that assesses reactions to uncertainty or ambiguity. The IUS-12 has demonstrated better psychometric properties than the original 27-item Intolerance of Uncertainty Scale (Carleton, Norton et al., 2007; Freeston et al., 1994). Factor analysis has shown that the IUS-12 consists of two subscales: prospective and inhibitory IU. The prospective IU subscale consists of 7 items (e.g., “One should always look ahead so as to avoid surprises”) and the inhibitory IU subscale consists of 5 items (e.g., “The smallest doubt can stop me from acting”). Items are measured by a 5-point Likert scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me). The total (α = .90), prospective (α = .84), and inhibitory (α = .86) IU scales demonstrated high internal consistency in the present sample.

2.2.2. Structured clinical interview for diagnostic and statistical manual of mental disorders 5 (SCID)

The SCID (First, Williams, Karg, & Spitzer, 2015) is a semi-structured clinical interview used to assess whether an individual meets criteria for any diagnoses as defined by the fifth edition of the DSM. The following modules were administered in the current study: MDD, AUD, Substance Use Disorder (SUD), PTSD, Panic Disorder, Agoraphobia, SAD, Specific Phobia, OCD, GAD, Anorexia, Bulimia, Binge Eating Disorder, and the bipolar and psychotic screening modules. Doctoral students and bachelor’s level research assistants were trained to criterion on the SCID and were supervised by a licensed clinical psychologist. Interrater agreement was in the fair to substantial ranges for lifetime diagnoses (k’s = .46–.87) and in the fair to moderate ranges for current diagnoses (k’s = .54–.74) with the exception of lifetime (k = .18) and current (k = .29) social anxiety disorder diagnoses with interrater agreement in the slight range (Shankman et al., 2018; Shrout, 1998).

2.2.3. The personality inventory for DSM-5 (PID-5)

The Negative Affect domain of the PID-5 (Krueger, Derringer, Markon, Watson, & Skodol, 2012) was used to assess N/NA. The PID-5 was designed to assess the personality traits of the alternative model of personality disorders in DSM-5 and is a 220-item self-report scale that measures five broad pathological personality domains (Negative Affect, Detachment, Antagonism, Disinhibition, and Psychoticism) and 25 underlying facets of these domains. Each item on the PID-5 is rated on a 4-point Likert scale ranging from 0 (very false or often false) to 3 (very true or often true). The Negative Affect domain has been shown to be strongly correlated with Neuroticism (Watson, Stasik, Ro, & Clark, 2013). Three facets or subscales comprise the Negative Affect domain: Emotional Lability (e.g. “My emotions are unpredictable”), Anxiousness (e.g. “I worry about almost everything”), and Separation Insecurity (e.g. “I’d rather be in a bad relationship than be alone”). Cronbach’s alpha for the PID-5 Negative Affect domain in the present study was .94.

2.3. Statistical analyses

As current psychiatric medication status (yes vs. no), N/NA, gender, and age have all been shown to be related to internalizing psychopathology status or severity (Clark, Watson, & Mineka, 1994; Fournier et al., 2010; Griffith et al., 2010; Kessler et al., 2005, 2007), the associations between these variables and the dependent variables (total, prospective, and inhibitory IU scores) were examined. Variables found to be associated with dependent measures were included as covariates in analyses where appropriate. Hierarchical linear mixed models were conducted to assess the study aims as the sample consists of individuals that are nested within families. The family-level intercept was entered as a random effect for all analyses. Diagnostic status (i.e., current and remitted) and any relevant covariate were entered as fixed effects. Total, prospective, and inhibitory IU scores, as well as N/NA scores, were entered as dependent variables in separate models. All analyses were conducted in version 3.4.3 of R and by utilizing version 1.1–13 of the lme4 package and version 2.0–33 of the lmerTest package (Bates, Mächler, Bolker, & Walker, 2014; Kuznetsova, Brockhoff, & Christensen, 2017; R Core Team, 2017).

Externalizing psychopathology was defined as the diagnoses of AUD or SUD. Distress/Misery disorders were defined as GAD or MDD. Fear disorders were defined as Panic Disorder, Agoraphobia, SAD, OCD,

PTSD,[1] or specific phobia. The comparison group for all analyses consisted of individuals with no lifetime history of the disorder being examined (e.g., no lifetime diagnoses of a fear disorder for the fear disorder analyses, etc). The SCID only assessed current and lifetime diagnostic status. Consistent with the definition of remission used in other studies (Bandelow, Baldwin, Dolberg, Andersen, & Stein, 2006; Springer, Levy, & Tolin, 2018), remission was defined as having met criteria for a DSM-5 diagnosis within the individual's lifetime, but not meeting criteria for the DSM-5 diagnosis at the time of, or during the month prior to, the interview (e.g. lifetime history of MDD and no current MDD). Individuals with remitted psychopathology were excluded from the current psychopathology analyses and those with current psychopathology were excluded from the remitted psychopathology analyses. For example, those with a diagnosis of current internalizing psychopathology were compared to individuals with no lifetime history of internalizing psychopathology which meant that those diagnosed with remitted internalizing psychopathology were not included in this particular set of analyses.

3. Results

3.1. Identification of covariates

Table 2 displays results for zero-order correlations between total IU, prospective IU, inhibitory IU, and N/NA as well as standardized beta estimates for the associations between each of these variables and current and remitted psychopathology. Individuals that were currently taking psychiatric medications ($\beta = 5.292$, $p < .001$) and were high in N/NA ($\beta = 0.631$, $p < .001$) displayed elevated total IU scores. Age ($\beta = .742$, $p = .080$) and gender ($\beta = -.914$, $p = .296$) did not have significant effects on levels of total IU. Regarding the IU subscales, individuals that were currently taking psychiatric medications ($\beta = 2.920$, $p < .001$) and were high in N/NA ($\beta = 0.557$, $p < .001$) showed higher levels of prospective IU, but age ($\beta = .432$, $p = .103$) and gender ($\beta = -.454$, $p = .403$) did not relate to prospective IU. For inhibitory IU, individuals that were currently taking psychiatric medications ($\beta = 2.380$, $p < .001$) and were high in N/NA ($\beta = .632$, $p < .001$) demonstrated elevated levels of inhibitory IU, but age ($\beta = .315$, $p = .099$) and gender ($\beta = -.454$, $p = .249$) had no effect on levels of inhibitory IU. Consequently, psychiatric medication status and N/NA were entered as covariates for all models[2].

3.2. Current psychopathology

Tables 3 and 5 display results for models examining the association between current psychopathology and IU.

[1] Data is mixed as to which factor of internalizing disorders PTSD and OCD best load on to or whether PTSD and OCD are separate from internalizing disorders (Forbes et al., 2011; Kotov et al., 2015; Raines et al., 2015; Slade & Watson, 2006). PTSD was included as a fear disorder because Forbes et al. (2011) found that the majority of PTSD criteria were shown to best fit onto the fear subfactor while only one criterion, termed dysphoria, loaded onto the distress/misery subfactor. OCD was included as a fear disorder because while the best fit of OCD may vary by differing symptom presentations (Naragon-Gainey, Prenoveau, Brown, & Zinbarg, 2016; Raines et al., 2015), it has been shown to covary with other fear disorders (Naragon-Gainey et al., 2016). It is important to note, however, that the pattern of results largely remained the same when OCD and PTSD were analyzed differently.

[2] Anxiety sensitivity has previously been found to be highly associated with intolerance of uncertainty and internalizing psychopathology (Boelen & Reijntjes, 2009; Carleton et al., 2010; Carleton, Sharpe, & Asmundson, 2007). In the current sample, total Anxiety Sensitivity Index-3 (Taylor et al., 2007) and IUS-12 scores were also found to be highly correlated ($\beta = .617$, $p < .001$). However, despite this high correlation, when total Anxiety Sensitivity Index-3 scores, as well as N/NA and psychiatric medication status, were entered into the models as covariates, the pattern of results reported in Sections 3.2 and 3.3 below remained the same (see Supplemental Tables 1 and 2).

Table 2
Zero-Order Correlations and Standardized Beta Estimates.

	Total IU	Prospective IU	Inhibitory IU	N/NA
Correlations				
Total IU	1.00***	–	–	–
Prospective IU	0.95***	1.00***	–	–
Inhibitory IU	0.90***	0.73***	1.00***	–
N/NA	0.63***	0.55***	0.63***	1.00***
β				
Current Fear	0.76***	0.67***	0.77***	0.84***
Current Distress/Misery	1.34***	1.13***	1.42***	1.43***
Current Externalizing	0.18	0.03	0.38*	0.51***
Remitted Fear	0.44***	0.34**	0.50***	0.51***
Remitted Distress/Misery	0.42***	0.34***	0.48***	0.65***
Remitted Externalizing	0.24*	0.20	0.25*	0.32**

* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 3
Main Effects of Current Internalizing Diagnostic Status on IU Levels.

Diagnosis	Total	Prospective	Inhibitory
Current Fear (n = 129)	0.252**	0.211*	0.279**
Current Distress/Misery (n = 41)	0.486**	0.331*	0.486**

* $p < .05$. ** $p < .01$. *** $p < .001$.

3.2.1. Fear disorders

After adjusting for N/NA and psychiatric medication status, individuals with a current fear disorder exhibited significantly higher levels of total ($\beta = .252$, $p = .004$), prospective ($\beta = .211$, $p = .028$), and inhibitory ($\beta = .279$, $p = .001$) IU in comparison to those with no lifetime history of fear disorders.

3.2.2. Distress/Misery disorders

Similar to fear disorders, after adjusting for N/NA and psychiatric medication status, levels of total ($\beta = .486$, $p = .001$), prospective ($\beta = .331$, $p = .041$), and inhibitory ($\beta = 0.486$, $p = .001$) IU were significantly elevated in those with a current distress/misery disorder as compared to those with no lifetime history of distress/misery disorders.

3.2.3. Externalizing psychopathology

Individuals currently experiencing an externalizing psychopathology *did not* show significantly elevated levels of total ($\beta = -0.163$, $p = .165$) or inhibitory ($\beta = .034$, $p = .772$) IU compared to those with no lifetime history of externalizing psychopathology after adjusting for N/NA and psychiatric medication status. In contrast, those with a current externalizing disorder exhibited significantly *lower* levels of prospective IU than those with no lifetime history of externalizing psychopathology ($\beta = -.287$, $p = .022$).

3.3. Remitted psychopathology

Tables 4 and 5 display results for models examining the association between remitted psychopathology and IU.

3.3.1. Fear disorders

After adjusting for N/NA and psychiatric medication status, individuals in remission from a fear disorder displayed significantly elevated levels of inhibitory IU ($\beta = .265$, $p = .006$) relative to those with no lifetime history of fear disorders. No differences were found for prospective ($\beta = .094$, $p = .374$ and total IU ($\beta = .179$, $p = .069$).

3.3.2. Distress/Misery disorders

Unlike fear disorders, no significant differences were found between

Table 4
Main Effects of Remitted Internalizing Diagnostic Status on IU Levels.

Diagnosis	Total	Prospective	Inhibitory
Remitted Fear (n = 83)	0.179	0.094	0.265**
Remitted Distress/Misery (n = 155)	0.043	−0.010	0.112

*$p < .05$. **$p < .01$. ***$p < .001$.

Table 5
Main Effects of Externalizing Diagnostic Status on IU Levels.

Diagnosis	Total	Prospective	Inhibitory
Current Externalizing (n = 50)	−0.163	−0.287*	0.034
Remitted Externalizing (n = 142)	0.024	0.011	0.043

*$p < .05$. **$p < .01$. ***$p < .001$.

those with remitted distress/misery disorders and those with no lifetime history of distress/misery disorders on levels of total (β = .043, p = .597), prospective (β = −.010, p = .913), and inhibitory (β = .112, p = .150) IU, suggesting specificity of the effects to fear disorders.

3.3.3. Externalizing psychopathology

Further demonstrating specificity to fear disorders, individuals in remission from an externalizing psychopathology did not significantly differ on levels of total (β = .024, p = .766), prospective (β = .011, p = .897), and inhibitory (β = .043, p = .596) IU from those with no lifetime history of externalizing psychopathology.

3.4. Specificity of IU within internalizing psychopathology

Exploratory analyses were conducted to further investigate the relative strength of the associations between IU, fear disorders, and distress/misery disorders. Both fear and distress/misery disorder status were entered in as simultaneous fixed effect predictors to assess the strength of IU's association with one subfactor of internalizing psychopathology's relative to IU's association with the other subfactor of internalizing psychopathology. Table 6 displays results for models examining the relative strength of associations between IU and internalizing psychopathologies.

3.4.1. Fear disorders

After adjusting for current distress/misery disorder status, N/NA and psychiatric medication status, individuals meeting criteria for a current fear disorder continued to display elevated levels of total (β = .292, p = .012), prospective (β = .267, p = .037), and inhibitory (β = .283, p = .011) IU, as compared to those with no lifetime history of fear disorders. However, no differences were found in remitted fear disorders on levels of total (β = .111, p = .265), prospective (β = .064, p = .557), and inhibitory (β = .159, p = .091) IU.

3.4.2. Distress/Misery disorders

After adjusting for current fear disorder status, N/NA, and psychiatric medication status, individuals meeting criteria for a current distress/misery disorder again displayed elevated levels of inhibitory IU (β = .358, p = .028), but no longer significantly differed from those with no lifetime history of distress/misery disorders on levels of total (β = .255, p = .132) and prospective (β = .148, p = .427) IU. Individuals with remitted distress/misery disorders continued to not differ from those with no lifetime history of distress/misery disorders on levels of total (β = .030, p = .754), prospective (β = −0.022, p = .833), and inhibitory (β = .099, p = .281) IU.

Table 6
Main Effects of Internalizing Diagnostic Status on IU Levels Adjusting for the Main Effects of the Other Internalizing Subfactor.

Diagnosis	Total	Prospective	Inhibitory
Current Fear (n = 129)	0.292*	0.267*	0.283*
Current Distress/Misery (n = 41)	0.255	0.148	0.358*
Remitted Fear (n = 83)	0.111	0.064	0.159
Remitted Distress/Misery (n = 155)	0.030	−0.022	.099

*$p < .05$. **$p < .01$. ***$p < .001$.

3.5. Relation between psychopathology and N/NA

As IU largely demonstrated specificity to fear but not distress-misery or externalizing disorders, parallel analyses to the ones above (3.2 Current Psychopathology and 3.3 Remitted Psychopathology) were conducted to evaluate whether N/NA demonstrates similar specificity independent of IU. N/NA served as the dependent variable for these analyses (see supplemental Tables 3 and 4). Interestingly, after adjusting for levels of total IU, N/NA was found to be significantly elevated in both current and remitted fear and distress/misery disorders and current, but not remitted, externalizing disorders as compared to those with no lifetime history of fear, distress/misery, and externalizing disorders, respectively.

4. Discussion

Intolerance of uncertainty may be a key, transdiagnostic, factor in internalizing psychopathologies. It is unknown whether IU continues to be elevated in remission from internalizing psychopathologies and if IU does so independently of N/NA. It is also unclear whether IU is characteristic of fear and/or distress/misery disorders or if IU is even specific to internalizing psychopathologies (vs. externalizing psychopathologies). Results indicated that total, prospective, and inhibitory IU scores were elevated in individuals with current fear disorders, even when adjusting for levels of N/NA and current distress/misery disorder status. Levels of inhibitory IU continued to be elevated into remission of fear disorders when adjusting for levels of N/NA, but did not reach significance when also adjusting for remitted distress/misery disorder status. Consequently, IU was shown to be more consistently related to current fear disorders as levels of IU were not significantly elevated in current externalizing disorders and only inhibitory IU was elevated in those with a current distress/misery disorder when adjusting for N/NA and current fear disorder status. In contrast to the results for IU, N/NA was not found to be specific to internalizing psychopathology. N/NA continued to be significantly elevated in fear, distress/misery, and externalizing psychopathologies during remission suggesting that N/NA may be characteristic of externalizing psychopathologies in addition to internalizing psychopathologies.

In terms of which specific aspects of IU were related to internalizing psychopathology, after controlling for N/NA, inhibitory IU was elevated in remitted fear disorders while no differences in levels of prospective IU were found in remission of fear or distress/misery disorders. Only inhibitory IU scores were elevated across both current fear and distress/misery disorders when adjusting for N/NA as well as distress/misery and fear disorder status, respectively. Thus, the role of inhibitory IU in psychopathology was stronger than that of prospective IU and therefore may be more likely to play a significant role in internalizing psychopathology.

There are several reasons that the relation between IU and current fear disorders was more consistent, than the relation between IU and current distress/misery disorders. On the one hand, the inconsistent relationship between IU and current distress/misery disorders might be surprising as initial research on IU largely focused on its role in GAD (Dugas et al., 1998), a distress-misery disorder. It is possible that the small sample size of individuals with remitted GAD (n = 31) did not provide enough power to detect potentially elevated scores on all subscales of the IUS-12 in those with current distress/misery disorders. On the other hand, as N/NA greatly overlaps with the symptoms of

distress/misery disorders (Ormel et al., 2013), N/NA may explain similar variance in IU as distress/misery disorders status. Therefore, all aspects of IU may still have a strong relationship with distress/misery disorders, but no variance was left for distress/misery disorder status to explain in our findings once the effects of N/NA were accounted for.

In remission, fear disorders also initially appeared to have a stronger relationship with IU than distress/misery disorders as, when adjusting for levels of N/NA, inhibitory IU scores were elevated in remitted fear disorders whereas no aspects of IU were elevated in remitted distress/misery disorders. It is possible that psychotherapy (or another treatment) was successful in reducing levels of IU to that of healthy controls in those with remitted distress/misery disorders. In treatments specifically targeting IU, reductions in IU have been found to be associated with reductions in symptoms of anxiety and depression, such as worry and rumination, (Boswell et al., 2013; Dugas & Ladouceur, 2000; Ladouceur et al., 2000). As worry and rumination are prominent characteristics of distress/misery disorders, the lack of elevated levels of IU in individuals with remitted distress/misery disorders may reflect successful outcomes of psychotherapy rather than a weaker association with IU. While 60.65% of those with remitted distress/misery disorders sought treatment for emotional or psychiatric problems in their past, it is unclear what type of treatment the participants were receiving. Future studies should investigate whether, in participants with distress/misery disorders, psychotherapies targeting IU reduce levels of IU to that of healthy controls.

It is important to note that individuals with remitted fear disorders no longer displayed elevated levels of IU after adjusting for remitted distress/misery disorder status and N/NA. Comorbid remitted distress/misery disorders likely drove the increased levels of IU in remitted fear disorders in models that only adjusted for N/NA. There are several explanations for this finding. First, comorbidity between anxiety and depressive disorders has been shown to be positively associated with illness severity (Bernstein, 1991; Kessler et al., 2003; Lamers et al., 2011) and 42.17% of the remitted fear disorder group also had a remitted distress/misery disorder while only 22.58% of the remitted distress/misery group also had a remitted fear disorder. The higher rates of comorbidity in the remitted fear disorders group suggests that the remitted fear disorders group may have been more severe, which could have accounted for their increased levels of IU. However, the *current* fear disorder group displayed lower rates of comorbidity (19.38%) than the current distress/misery group (60.98%) and, despite the potential for being less severe than those with a current distress/misery disorder, still showed more robust relationships with IU. Second, the inconsistency in findings for remitted fear disorders may also be due to the discrepancies in sample size. Only 48 individuals in the remitted fear disorders group did not also have a remitted distress/misery disorder whereas 120 individuals in the remitted distress/misery group did not also have a remitted fear disorder. Thus, the analyses adjusting for comorbidity may not have been properly powered to detect elevated IU in remitted fear disorders as compared to remitted distress/misery disorders.

Based on the presented results, it is also possible that IU does not play as significant of a role in connoting vulnerability for distress/misery disorders as it does in fear disorders. A recent conceptualization of IU argued that IU indexes a higher order, fundamental, "fear of the unknown" (Carleton, 2016a, 2016b) that is characterized as "an individual's propensity to experience fear caused by the perceived absence of information at any level of consciousness or point of processing" (Carleton, 2016a, p. 39Carleton, 2016aCarleton, 2016a, p. 39). Accordingly, high levels of IU may more closely reflect the specific fear responses exhibited in fear disorders as opposed to the fear or distress responses associated with distress/misery disorders. Fear disorders are characterized by fear in response to concrete, situational, and disorder-specific stimuli (e.g., fear of negative social evaluation in SAD, fear of physiological arousal in Panic disorder) rather than the continual 'free-floating' distress and anxious-misery that cuts across situations exhibited in both GAD and MDD as well as the fear of a broad range of stimuli in GAD. IU may only be a vulnerability factor for the fear responses to concrete and inconsistently present stimuli in fear disorders as opposed to the continuous and cross-situational fear and anxious-misery experienced in GAD and MDD. Mechanisms other than IU, such as the broader construct of N/NA, may be more important vulnerability factors for distress/misery disorders. The recent conceptualization of IU as the fear of the unknown focuses on a fear response, but this does not mean that anxious-misery and distress do not play significant roles in fear of the unknown. In fact, the present results for current fear and distress/misery disorders provide further evidence that IU may be a key maintaining factor in both fear and distress/misery disorders. The present findings of more consistent associations between IU and fear, rather than distress/misery, disorders provide further evidence that IU may indeed represent a fear of the unknown and, consequently, play a larger role in connoting vulnerability for psychopathologies characterized by fear.

Interestingly, the results for externalizing psychopathology further demonstrated IU's more robust relationship with fear disorders. IU was not shown to be characteristic of externalizing psychopathologies as IU was not significantly elevated in current or remitted externalizing psychopathology. In fact, individuals with a current externalizing psychopathology exhibited significantly *lower* levels of prospective IU compared to those with no lifetime history of externalizing psychopathology. As prospective IU reflects future-oriented cognitions, it is possible that low levels of IU may be pathological and could reflect the impulsivity evidenced in externalizing psychopathologies (Verdejo-García, Lawrence, & Clark, 2008). However, the presence of decreased levels of prospective IU in current externalizing psychopathology requires replication as such low levels were not displayed in individuals with remitted externalizing psychopathologies and findings have been mixed as to whether the prospective IU subscale is psychometrically valid (Boelen & Lenferink, 2018; Carleton, Norton et al., 2007; Hale et al., 2016; McEvoy & Mahoney, 2011; Oglesby et al., 2017; Shihata et al., 2018).

The lack of positive and significant associations between IU and externalizing psychopathology are inconsistent with prior research on alcohol use and important correlates of IU (Kraemer et al., 2015; McEvoy, Carleton, Correa, Shankman, & Shihata, 2019). For example, prior research has shown a positive association between IU and drinking to cope and drinking to conform. Several psychophysiological studies have also shown that individuals with externalizing disorders display a heightened startle reactivity to unpredictable threat (Gorka & Shankman, 2017; Gorka et al., 2013, 2016) and this biomarker may be an endophenotype of alcohol use disorders (Gorka & Shankman, 2017). There are several reasons that the present results differ from prior studies. First, it is possible that individuals who are high in IU are more likely to drink for coping and conformity reasons when they do drink but are not more likely to drink overall. Second, the discrepancy may be due to an underreporting bias of IU on the IUS-12 scale in those with externalizing psychopathology (Johnson & Fendrich, 2005; Morral, McCaffrey, & Iguchi, 2000), especially since the IUS-12 was developed with internalizing psychopathology in mind. For example, individuals with externalizing psychopathology may be more susceptible to social desirability (Johnson & Fendrich, 2005; Kypri et al., 2016), which could result in underreporting. Alternatively, the descriptions of IU in the IUS-12 may differ from how IU is exhibited in externalizing psychopathologies. Such differences could also result in reduced IU even if those with externalizing psychopathologies do indeed experience high levels of IU. Lastly, it is also possible that heightened reactivity to unpredictable threat may only be a psychophysiological correlate of IU during threatening contexts and not during uncertainty in general.

In the current study, not all aspects of IU were significantly associated with psychopathology. Results indicated that levels of inhibitory IU (which is characterized by behavioral inhibition), and not prospective IU (which is typified by future-oriented cognitive and

emotional distress) were significantly elevated in remitted fear disorders when only adjusting for levels of N/NA. It is possible that inhibitory IU displayed a more consistent relationship with fear disorders because the items on the inhibitory IU scale (e.g., "I must get away from all uncertain situations.") are more similar to the avoidance evidenced in fear disorders than the worry and rumination characteristic of distress/misery disorders. However, the items on the prospective IU scale (e.g., "One should always look ahead so as to avoid surprises") should be similar to future-oriented worry and rumination in distress/misery disorders, yet prospective IU was not found to be elevated in distress/misery disorders. The more robust relationship found between inhibitory IU and fear disorders is consistent with prior findings suggesting that inhibitory, and not prospective, IU is specific to symptoms of Social Anxiety Disorder, which is categorized as a fear disorder (Carleton et al., 2010; Mahoney & Mcevoy, 2012; McEvoy & Mahoney, 2011, 2012). In contrast, findings have been mixed regarding the unique associations of prospective IU with internalizing psychopathologies (Mahoney & Mcevoy, 2012; McEvoy & Mahoney, 2011, 2012). Recent studies have even called into question the psychometric properties of the prospective IU scale. Including prospective IU in a model with total IU does not improve the fit and prospective IU has also failed to explain unique variance in certain psychopathologies over and above the total IUS-12 score (Hale et al., 2016; Shihata et al., 2018). The lack of consistency in the associations between the prospective IU subscale and internalizing psychopathology evidenced in prior studies, as well as the present null findings, may suggest that prospective IU is not informative for understanding internalizing psychopathologies, especially as compared to total IUS-12 scores. Newer measures of IU are needed to capture and test whether there are multiple facets of IU and how such facets may relate to internalizing psychopathologies as defined by DSM-5.

Unlike the distressing future-oriented cognitions about uncertainty, reflected by prospective IU, the "freezing" response assessed by inhibitory IU may be a more informative and pathological response to uncertainty. If IU does indeed represent the larger construct of fear of the unknown (Carleton, 2016b), it is possible that inhibitory IU is more akin to pathological responses to feared stimuli which may explain inhibitory IU's more consistent relationship with fear disorders. Although speculative, the behavioral response to uncertainty assessed by inhibitory IU may also be a more biologically mediated response to uncertainty than the cognitions assessed by prospective IU. For example, inhibitory IU may more closely relate to the behavioral inhibition system, a proposed neurobiological system involved in risk assessment processes, heightened arousal, vigilance, and behavioral inhibition associated with fear and anxiety (Carleton, 2016a; Gray & McNaughton, 2003; Shankman & Klein, 2003). If inhibitory IU is indeed more biologically mediated than prospective IU, inhibitory IU may not remit (either with or without treatment) as easily and could explain the elevated levels of inhibitory, but not prospective, IU in remission of fear disorders that were present after adjusting for levels of N/NA.

As mentioned above, recent studies have also questioned the appropriateness of using the inhibitory IU subscale. Results have suggested that a more parsimonious one factor model of IU consisting of only total IU may be more appropriate for the IUS-12 (Hale et al., 2016; Shihata et al., 2018). On the other hand, the inhibitory IU subscale has been shown to (a) still explain a small proportion of reliable variance in the IUS-12, (b) be distinct from total IU (at least in some studies) (c) significantly relate to transdiagnostic symptoms and (d) characterize a valid and reliable subfactor overall (Boelen & Lenferink, 2018; Carleton, Norton et al., 2007; Hale et al., 2016; McEvoy & Mahoney, 2011; Oglesby et al., 2017; Shihata et al., 2018). While more research is needed to further assess the psychometric properties of the IUS-12 and its subfactors, the present findings suggest that inhibitory IU may play a significant role in internalizing psychopathology, and possibly more so with fear disorders.

Notably, the present findings are independent of, and cannot be explained by N/NA. N/NA is correlated with IU (McEvoy & Mahoney, 2012; Sexton et al., 2003), but is a broader trait than IU that is quite multifaceted (Ormel, Oldehinkel et al., 2004). The measure of N/NA used in the present study (PID-5) is a conglomeration of three facets of N/NA – Emotional Lability, Anxiousness, and Separation Insecurity – that assess different constructs than IU does. Measures of N/NA also often contain similar items as assessments of internalizing symptoms (Ormel et al., 2013), which increases its collinearity with internalizing psychopathology. Consequently, it is a "riskier test" (Meehl, 1978) to assess whether IU meets criteria for a vulnerability factor independent of N/NA. Despite this risk and similar to previous findings (Boelen & Reijntjes, 2009; McEvoy & Mahoney, 2011, 2012; Yook et al., 2010), results showed that IU added incremental validity over and above N/NA in its associations with internalizing psychopathologies.

IU may also provide greater specificity than N/NA in predicting certain psychopathologies. N/NA has previously been shown to play a role in all internalizing psychopathologies, substance use disorders, and has even been shown to predict the onset of psychotic psychopathologies (Clark et al., 1994; Griffith et al., 2010; Ormel et al., 2013; Ormel, Oldehinkel et al., 2004). Findings from the current study provided further evidence that N/NA is a much broader trait than IU as N/NA related to current and remitted internalizing *and* externalizing psychopathology whereas IU demonstrated specificity to internalizing psychopathology and was more consistently associated with fear disorders. Ormel, Rosmalen, and Farmer (2004) argued that N/NA is a vulnerability factor for many disorders because measures of N/NA assess for fairly stable levels of distress that therefore predict future and past levels of such distress. Assessing for levels of IU may, therefore, increase our specificity in predicting outcomes, perhaps especially for fear disorders.

The current study had several limitations which point to future directions of further research. First, the current study demonstrated that elevated levels of inhibitory IU persist into remission from fear disorders when only adjusting for N/NA, but did not evaluate whether IU longitudinally predicts the onset of psychopathology. A longitudinal high-risk design is needed to assess whether inhibitory IU predisposes individuals to developing fear disorders or if inhibitory IU reflects a "scar" or residuals effects of fear disorders. Such a longitudinal study should also further examine the specificity of IU to the internalizing psychopathology subfactors by assessing IU in those with comorbid fear and distress/misery disorders, those who only have a fear disorder, and those who only have a distress/misery disorder. Second, PTSD and OCD were included within the fear disorders subfactor, but findings have been mixed as to which subfactor of internalizing psychopathology PTSD and OCD best load on to (Forbes et al., 2011; Kotov, Perlman, Gámez, & Watson, 2015; Raines, Allan, Oglesby, Short, & Schmidt, 2015; Slade & Watson, 2006) or whether PTSD and OCD are separate from the fear vs. distress-misery dichotomy. Unfortunately, there was not enough power to tease apart these differences as the sample only included 33 individuals with a lifetime diagnosis of OCD and 36 individuals with a lifetime diagnosis of PTSD. Third, the study did not examine why high IU was related to certain internalizing psychopathologies and not others. Research is needed to determine what mechanisms link high levels of IU to specific internalizing psychopathologies (Nolen-Hoeksema & Watkins, 2011).

4.1. Conclusions

In summary, results suggested that IU may be a key transdiagnostic factor that is more consistently related to fear disorders than distress/misery disorders and is not characteristic of externalizing disorders. Additionally, results showed that inhibitory IU, and not total or prospective IU, exhibited a strong relationship with internalizing psychopathology. The relationship between IU and internalizing psychopathology cannot be explained by levels of N/NA, which is highly correlated with both psychopathology and IU. IU also demonstrated

specificity over N/NA as IU was shown to be more consistently related to fear disorders whereas, N/NA was found to be elevated in current and remitted fear, distress/misery, and externalizing disorders. While these findings provide preliminary evidence suggesting that inhibitory IU plays a key role in fear disorders, further research is needed to evaluate (a) how comorbidities affect levels of IU, (b) whether the IUS-12 and its subscales or newer measures of IU best capture the experience of IU, and (c) whether inhibitory IU is elevated in individuals before the onset of internalizing psychopathologies or if inhibitory IU is a byproduct of past experiences of internalizing psychopathology.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.janxdis.2019.01.001.

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