Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Psychiatry Research: Neuroimaging 319 (2022) 111414

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Neural and Self-report Measures of Sensitivity to Uncertainty as Predictors of COVID-Related Negative Affect

Kia J. Khorrami [a,b], Charles A. Manzler [a,b], Kayla A. Kreutzer [a,b], Stephanie M. Gorka [a,b,*]

[a] Department of Psychiatry and Behavioral Health, The Ohio State University Wexner Medical Center, 370W. 9th Avenue, Columbus, OH 43210 USA
[b] Institute for Behavioral Medicine Research, The Ohio State University, 460 Medical Center Drive, Columbus, OH 43210 USA

ARTICLE INFO

Keywords:
COVID-19 pandemic
Intolerance of uncertainty
Anterior insula
fMRI

ABSTRACT

The COVID-19 pandemic has been a period of unprecedented uncertainty. Research indicates individuals differ in their response to uncertainty and these differences are mediated by anterior insula (aINS) function. Those most sensitive to uncertainty are likely vulnerable to negative affect in the context of the pandemic. The current study was designed to directly test this question using both neural and self-reported measures of sensitivity to uncertainty. Fifty-nine volunteers completed a task designed to probe neural response to anticipation of predictable (P-) and unpredictable (U-) threat-of-electric-shock during functional magnetic resonance imaging and a self-report measure of intolerance of uncertainty (IU). Approximately two years later, during the peak of the pandemic, participants reported their emotional reactions to the COVID-19 crisis. Multilevel mixed models revealed that greater aINS activation to U-threat and greater self-reported IU were independent predictors of increased COVID-related negative affect. These findings were significant when adjusting for biological sex and depression and anxiety symptom severity. The results add to a growing literature demonstrating that individual differences in response to uncertainty have a robust impact on mood and functioning. Results also highlight that individuals highly sensitive to uncertainty may be at increased risk for poor mental health during the ongoing pandemic.

1. Introduction

The COVID-19 pandemic has been a period of unprecedented uncertainty. From uncertainty surrounding health outcomes and restrictions on socialization to disruption in almost all aspects of day-to-day life, the pandemic has functioned as an ever-present uncertain threat for many individuals. Research during past public health emergencies indicates that poor mental health outcomes are associated with these kinds of events. Increases in suicidality, anxiety, depression, and post-traumatic stress disorder (PTSD) have been documented during and after the SARS epidemic in Hong Kong and the Ebola outbreak in Sierra Leone (Cheung et al., 2008; ; Secor et al., 2020). The psychological effects of COVID-19 were investigated in China, demonstrating an increase in symptoms of anxiety and depression in the context of the pandemic (Li et al., 2020). The novelty of COVID-19, changing information and guidelines throughout the pandemic, and potential hospitalization and mortality of the disease represent an unprecedented, real-world uncertain threat.

Research indicates that individuals differ in how they respond to uncertainty, particularly uncertain threats, or stressors (U-threat). U-threat is defined as threat that is unpredictable in its timing, intensity, frequency, and/or duration. U-threat elicits a generalized feeling of apprehension and hypervigilance that is not associated with a clearly identifiable source, referred to as anticipatory anxiety (Barlow, 2000; Davis, 1998; Jackson et al., 2015). U-threat is in contrast with predictable threat (P-threat), which is signaled by a discrete cue and elicits a phasic fear response to an identifiable stimulus that is time-locked to the threat (Barlow, 2000; Davis et al., 2010). Human and animal studies have shown that U-threat and P-threat produce distinguishable aversive states that are pharmacologically distinct (Grillon et al., 2006) and mediated by overlapping, but separable, neural circuits (Alvarez et al., 2011; Davis, 2006). Although U-threat is universally aversive as it diminishes our ability to prepare for future events, research has shown that there are some individuals who are particularly sensitive to U-threat and display maladaptive cognitive and behavioral responses in the face of uncertainty (Carleton, 2012).

Individual differences in sensitivity to uncertainty can be measured in several ways, and these methods tend to have moderate convergence

* Corresponding author at: Department of Psychiatry and Behavioral Health, The Ohio State University, 460 Medical Center Drive, Columbus, OH 43210
E-mail address: Stephanie.Gorka@osumc.edu (S.M. Gorka).

https://doi.org/10.1016/j.pscychresns.2021.111414
Received 19 September 2021; Received in revised form 11 November 2021; Accepted 22 November 2021
Available online 23 November 2021

(Ferry and Nelson, 2021; Gorka et al., 2014; Shankman et al., 2014; Simmons et al., 2008). One method includes self-report, which asks participants to rate their subjective tolerance of uncertainty. Another measure involves directly exposing participants to uncertain stressors and measuring objective reactivity using psychophysiology and/or neuroimaging methods. Along these lines, Grillon and colleagues developed the widely used No-Predictable-Unpredictable threat paradigm (Schmitz and Grillon, 2012). The task includes three within-subjects conditions: no threat (N; no aversive stimulus), predictable threat (P; aversive stimulus signaled by a predictable cue), and unpredictable threat (U; aversive stimulus at random) (Schmitz and Grillon, 2012). Studies using the No-Predictable-Unpredictable (NPU) paradigm have traditionally used startle eyeblink potentiation as a behavioral index of aversive responding. These studies have shown that exaggerated behavioral reactivity to U-threat, but not P-threat, characterizes numerous anxiety disorders including panic disorder, social anxiety disorder, specific phobia, and PTSD (Gorka et al., 2013; S.M. Gorka et al., 2017; Grillon et al., 2009). In addition, magnitude of reactivity to U-threat correlates with severity of anxiety symptoms (S.M. Gorka et al., 2017) and family history of anxiety psychopathology (Nelson et al., 2013). Using a similar paradigm, it has also been shown that magnitude of behavioral reactivity longitudinally predicts PTSD symptom severity in a cohort of trauma-exposed police officers (Pole et al., 2009).

More recently, researchers have adapted the NPU paradigm for use during functional magnetic resonance imaging (fMRI) to probe the neural correlates of sensitivity to U-threat. Research suggests that the insula (INS) and the dorsal anterior cingulate cortex (dACC) are highly connected and function in a larger, frontolimbic salience network in the brain (Grupe and Nitschke, 2013; Uddin, 2015). This network influences behavior by scanning environmental stimuli for emotionally salient information and analyzing threats and outcomes. The anterior portion of the insula (aINS) is a key part of the circuit that is involved in anticipation of aversive events (Carlson et al., 2011; Sarinopoulos et al., 2010). More specifically, studies suggest that the aINS mediates response to uncertainty and subjective experiences of stress and anticipatory anxiety (Craig, 2009, 2011; Grupe and Nitschke, 2013). Thus, individual differences in aINS activation during U-threat contribute to anticipatory anxiety, feelings of distress, and negative affect. Exaggerated aINS reactivity to threat has also been observed in individuals with internalizing psychopathology including social anxiety disorder, panic disorder, and specific phobia (Klumpp et al., 2012; Radoman et al., 2019).

Previous research has demonstrated that public health crises increase the risk for negative affect and mood disturbance (Cheung et al., 2008; Jalloh et al., 2015; Secor et al., 2020). It is therefore likely that the COVID-19 pandemic has had a negative impact on mental health for many individuals, which is corroborated by emerging research (Hamza Shuja et al., 2020; Kumar and Nayar, 2021; Li et al., 2020). The global scale and sustained impacts of the COVID-19 pandemic present an unprecedented, real-world U-threat with far-reaching impacts. Our lab, and others, have established that individual differences in reactivity to U-threat contributes to anxiety psychopathology and risk for mental health problems (Gorka et al., 2013; S.M. Gorka et al., 2017; Grillon et al., 2009). We therefore theorize that those highly sensitive to uncertainty may have difficulty coping during the pandemic and that individuals with exaggerated sensitivity to uncertainty may represent an at-risk group for poor mental health outcomes during the COVID-19 pandemic. Others have also proposed that individuals who are more sensitive to uncertainty may experience greater distress in the context of the COVID-19 pandemic (Freeston et al., 2020).

The aim of the current study was to investigate the relationships between neural reactivity to U-threat, self-reported intolerance of uncertainty (IU), and subsequent COVID-related negative affect at the height of the pandemic. We utilized an existing, pre-COVID cohort of healthy young adults, aged 17–19, to directly investigate our hypotheses. Participants completed a task designed to probe neural response to anticipation of U-threat and P-threat during fMRI between 2017 and 2019. Baseline assessments of mood symptoms and self-reported intolerance of uncertainty were also collected at that time. During the peak of the COVID-19 pandemic, participants completed a self-report measure assessing emotional reactions to the COVID-19 crisis. We hypothesized that both self-reported IU and aINS reactivity to U-threat would be positively associated with COVID-related negative affect.

2. Methods

2.1. Participants and procedure

Participants were drawn from a larger longitudinal study investigating associations between reactivity to U-threat and changes in psychopathology over time in young adults. Participants were recruited via advertisements posted in the Chicago community and nearby college campuses. Participants were enrolled before the COVID-19 pandemic between July 2017 and July 2019 and were followed for 1-year via clinical assessments every 3-months. Inclusion criteria for the larger study included self-reported lifetime consumption of >1 but <100 standard alcoholic drinks, affiliation with risky peers, and access to alcohol if desired. These criteria were selected to ensure the sample was at high-risk for alcohol abuse, due to the aims of the larger project. Participants were also required to be between the ages of 17 and 19. Demographic characteristics of the sample are listed in Table 1. Exclusion criteria included any major medical or neurological illness, active suicidal ideation, psychosis, deafness, traumatic brain injury, psychotropic medication use within the past four months, smoking 5 cigarettes or more per day, lifetime history of alcohol use disorder or substance use disorder (AUD/SUD), contraindications for fMRI (e.g., ferrous metal in body), pregnancy or trying to become pregnant, positive urine drug screen for illicit substances (including tetrahydrocannabinol, cocaine, amphetamine, morphine, phencyclidine, barbiturates, benzodiazepines, 3,4-methylenedioxymethamphetamine, oxycodone, and buprenorphine) or positive breathalyzer test for alcohol. Psychopathology was assessed via the Structured Clinical Interview for DSM-5 Disorders (First et al., 2015), in-person, by trained assessors, and supervised by a clinical psychologist.

The study occurred at the University of Illinois at Chicago and was approved by the University Institutional Review Board. Participants provided written informed consent. The first study visit involved a battery of self-report questionnaires and the Structured Clinical Interview for DSM-5 (SCID-V). During the second study visit (2 to 7-days later), participants completed an fMRI scan including the NPU-threat task. Participants were instructed to abstain from drugs and alcohol at least 24-hours prior to the lab assessments, which was verified via breath

Table 1
Participant demographics and characteristics.

Demographics and clinical characteristics	Mean (SD) or% ($N = 59$)
Age (years)	18.5 (0.6)
Sex (% Female)	78%
Ethnicity (% Hispanic)	39%
Race	
White	50.8%
Black	3.4%
Asian	20.3%
American Indian or Alaskan Native	3.4%
Biracial, other or unknown	22.1%
Lifetime COVID-19 Diagnosis	13.8%
Baseline IDAS Depression	39.6 (11.3)
Baseline IDAS Anxiety	8.7 (2.9)
Baseline Intolerance of Uncertainty Scale Total	28.9 (9.3)
Lifetime History of Internalizing Disorder	48.3%

Note. IDAS = Inventory of Depression and Anxiety Symptoms.

alcohol and urine screens. All participants were monetarily compensated for their time.

During the peak of the Coronavirus Pandemic in the United States, in the Fall of 2020, The Young Adult Coronavirus Impact Survey was sent to all participants enrolled in the study (i.e., active participants and study completers). The survey was distributed online and participants were monetarily compensated for completing the form. The survey was sent to a total of 118 individuals and 63 (53%) completed the optional COVID-19 measure. Individuals who completed the measure did not differ from those who did not complete the measure on age ($p = 0.48$), sex ($p = 0.07$), race (ps > 0.19), or severity of baseline depression ($p = 0.42$) or anxiety symptoms ($p = 0.97$) (scale information described below). Of those 63 respondents, 59 had good quality imaging task data resulting in a final sample of 59 subjects.

2.2. Self-report assessments

Self-reported depression and anxiety symptomology was assessed via the Inventory of Depression and Anxiety Symptoms (IDAS-II) (Watson et al., 2012). The IDAS-II measures symptomology of several disorders, including depression and anxiety disorders, via subscales and a total score. There are 99 questions, listed as statements with a 5-point Likert scale with 1 indicating that they not having felt or experienced the statement at all and 5 indicating that they have felt or experienced the statement to an extreme degree. Internal reliability of the IDAS-II subscales at each wave were good to excellent ($\alpha = 0.85 – 0.90$).

Self-reported intolerance of uncertainty was assessed via the short version of the Intolerance of Uncertainty Scale (IUS-12) (Carleton et al., 2007). The IUS-12 measures an individual's emotional and behavioral responses to uncertainty. The scale is comprised of first-person statements with a 5-point Likert scale with 1 indicating the statement to be not at all characteristic of the respondent and 5 indicating that the statement is entirely characteristic of the respondent. The IUS-12 produces a total score ranging from 12 to 60 with higher scores indicating greater intolerance of uncertainty. In the present sample, internal reliability of IUS-12 total was good ($\alpha = 0.88$).

2.2.1. The young-adult coronavirus impact survey

To assess for COVID-related negative affect, participants were sent the Young-Adult Coronavirus Impact Survey in the Fall of 2020, approximately two years after enrollment. The measure was developed by our lab to match the characteristics of our young adult cohort. The measure included selected items from the CoRonavIruS Health Impact Survey (CRISIS) (Merikangas et al., 2020) and original The Epidemic – Pandemic Impacts Inventory (EPII) (Grasso et al., 2020). Notably, the EPII is part of the National Institute of Health (NIH) Disaster Research Response Repository of COVID-19 Research Tools. Our adapted measure included 69-questions capturing background information about medical conditions, living situations, education/work impacts, COVID-19 exposure, and pandemic impact. A series of questions specifically asking about negative affect were included. Our selected affect items aligned with the CRISIS 'emotions' subsection. Participants were asked "During the past month, on average, to what extent have you felt": 1) worried or anxious, 2) sad, 3) fatigued or tired, 4) irritable or easily angered, and 5) lonely. Responses were made on a 5-point Likert-scale (1 – 5; 'not at all' to 'extremely') and averaged across individual items to create a composite negative affect measure. The five negative affect items demonstrated adequate internal reliability ($\alpha = 0.78$).

Participants were monetarily compensated for completing this follow-up survey.

2.3. fMRI threat task

The fMRI threat task and laboratory procedures described here have been used previously by our group (Gorka et al., 2020; Radoman et al., 2021). During the task, participants were administered brief, mild electrical shocks to their left foot at a level that they described as 'highly annoying but not painful' (between 1 and 5 mA). The electrodes were placed on the left foot to minimize movement during the task and to limit potential scan artifacts. This level of shock was reached via a work-up procedure before the start of the actual task. Ideographic shock levels were used to ensure equality in perceived shock aversiveness (Rollman and Harris, 1987). The shock stimuli lasted 400 ms and were delivered using a Biopac MP150 with an STM100C module (Biopac Systems, Inc., Goleta, CA) connected to a 200 V maximum stimulus isolation unit (STMISOC, Biopac System, Inc., Goleta, CA). Task stimuli were administered using Presentation software package (Neurobehavioral Systems, Inc., Albany, CA).

To examine the neural correlates of temporally unpredictable threat, we used a modified version of the original NPU-threat task developed by Grillon and colleagues (Schmitz and Grillon, 2012). Participants experienced three, within-subject conditions: no shock (N), predictable shock (P) and unpredictable shock (U). A numeric countdown was displayed during each condition ranging between 3 and 8 s, jittered ($M = 5$ s). Text displayed at the bottom of the monitor indicated the current condition. During N trials, no shocks were delivered and the text read 'No Shock'. During P trials, participants received a shock only when the countdown reached '1′ and the text read 'Shock at 1′. During U trials, participants received a shock at random, regardless of the countdown and the text read 'Shock at Anytime'. Following each countdown, individuals saw a fixation cross for 5–7 s, jittered (M = 6 s). N, P and U countdowns were presented in blocks of 6, and each condition/block was administered in a randomized order (counterbalanced) 6 times over the course of two runs. Participants received 10 electric shocks during P and 10 electric shocks during U, during each run. The rate of 'Shock at 1′ during the P condition was 60%, consistent with the NPU version used by Grillon and colleagues (Schmitz and Grillon, 2012).

2.4. fMRI data collection and processing

fMRI was performed on a 3.0 Tesla GE MR 750 scanner (General Electric Healthcare; Waukesha, WI) using an 8-channel phased-array radio frequency head coil. A standard T2-sensitive gradient-echo echo-planar imaging sequence was used (2 s repetition time (TR); 22.2 ms echo time (TE); 90° flip; 64 × 64 matrix; 22 cm FOV; 44 axial slices; 3.44 × 3.44 × 3.0 mm voxels; 308 vol per run). Structural scans were obtained with a 3D BRAVO pulse sequences with the following parameters: flip angle 13°, inversion time 450 ms, field of view 22 × 22 cm, matrix size 256 × 256, slice thickness 1 mm and 182 axial slices of the whole brain. Statistical Parametric Mapping software (SPM12, Wellcome Department of Imaging Neuroscience, London, UK) was used to perform conventional preprocessing steps. Images were spatially realigned to correct for head motion, slice-time corrected (44 slices, TR = 2, TA = 2, slice order: ascending interleaved, reference slice 21), spatially normalized to Montreal Neuro- logical Institute (MNI) space using the participants' T1 structural image (default settings), resampled to 2 mm^3 voxels and smoothed with an 8 mm^3 kernel to minimize noise and residual differences in gyral anatomy. The general linear model was applied to the time series, convolved with the canonical hemodynamic response function and with a 128 s high-pass filter. Condition effects for U, P and N anticipation were separately estimated at each voxel for each subject. For each condition, only the countdowns prior to the shock, or prior to trial termination in instances where there was no shock, were modeled. Importantly, number of data points (i.e. TRs/repetition times) was the same across the three conditions (N, P and U). Movement parameters obtained during realignment were included in the model as regressors-of-no-interest to account for motion-related effects on blood-oxygen-level-dependent (BOLD).

In line with our study aims, we created individual contrast maps for unpredictable threat (U-threat) > No-threat for each person during first-level analysis. These contrast maps were then entered into a second-level one-way analysis of variance (ANOVA) in order to examine the main

effects of U-threat across all participants.

Radoman et al., 2021 demonstrated that the fMRI threat task robustly activates the aINS. In the current subsample, we confirmed that the left (MNI peak [−34, 22, 6]; $Z = 5.50$) and right (MNI peak [36, 26, 2]; $Z = 6.55$) aINS was significantly activated during U-threat > No-threat across all subjects using a whole brain one sample *t*-test (FWE-corrected, $p < 0.05$).

Therefore, for the aims of the current study, we extracted BOLD activation parameter estimates (arbitrary units [a.u.]) from left and right anatomical aINS masks applied to the U-threat > No-threat contrast for each subject. The left and right aINS masks were defined by the AAL atlas and the mask extractions were averaged to reflect bilateral aINS activation to U-threat.

2.5. Data analysis plan

We first ran a series of descriptive Pearson's correlations to examine associations between study variables. To test our hypothesis, we ran a flexible multilevel mixed model with COVID-19 related negative affect as the dependent variable. Biological sex, confirmed or suspected positive COVID-19 diagnosis (yes/no), time (in months) between study baseline and COVID-19 follow-up, and report of receiving mental health treatment (yes/no) were all included as fixed covariates given their potential impact on negative affect. IDAS depression and IDAS anxiety scores from each data collection wave (i.e., baseline, 3 months, 6 months, 9 months, and 12 months) were included as time-varying covariates. Baseline IUS scores and aINS activation to U-threat were entered as simultaneous predictors. The model used restricted maximum likelihood (REML) estimation and an unstructured covariance matrix. Continuous variables were grand-mean centered and dichotomous variables were effects coded.

3. Results

3.1. Descriptives

On average, the COVID-related questionnaire was completed 23.9 ± 7.0 months (range: 14.5 to 38.5 months) following baseline data collection. A total of 10.2% of participants reported they received a positive COVID-19 diagnosis at some point since the start of the pandemic. An additional 3.4% reported they likely had COVID-19 but were never officially diagnosed. With regard to psychopathology, 48% of the sample had a lifetime mood or anxiety disorder. During the COVID-related assessment, 17% of participants were currently receiving mental health treatment and an additional 6.8% were pursuing treatment but had not yet enrolled.

At baseline, greater IUS total scores were associated with greater IDAS anxiety ($r = 0.55$, $p < 0.01$) and IDAS depression ($r = 0.56$, $p < 0.01$). There was no association between IUS total scores and aINS activation during U-threat ($r = 0.17$, $p = 0.20$). There was also no association between aINS activation to U-threat and IDAS anxiety ($r = 0.16$, $p = 0.20$) or IDAS depression ($r = 0.13$, $p = 0.32$).

3.2. Longitudinal analyses

Results from the multilevel mixed model are included in Table 2. With regard to covariates, there was a main effect of biological sex revealing that females reported higher levels of COVID-related negative affect than males. There was also a main effect of receiving mental health treatment such that individuals who reported reciving services had higher levels of COVID-related negative affect. The main effects of pre-COVID depression and anxiety symptom severity were not significant.

Our primary variables of interest were IUS total scores and aINS activation to U-threat. The model indicated that both individual differences factors were significant predictors. That is, greater baseline IUS total scores were associated with greater COVID-related negative affect. In addition, greater aINS activation to U-threat was associated with greater COVID-related negative affect.

Table 2
Multilevel mixed model examining predictors of COVID-related negative affect.

Variable	b	SE	T	p-value
Intercept	2.17	0.46	4.66	<0.001
Sex	1.05	0.28	3.76	<0.001
Positive COVID-19	0.38	0.34	1.11	0.272
Time between Assessments	−0.01	0.02	−0.66	0.511
Receiving Mental Health Treatment	0.69	0.29	2.42	0.019
IUS Total Score	0.03	0.01	3.01	0.004
aINS Activation	0.32	0.14	2.35	0.024
Time-Varying Covariates				
IDAS Depression	0.01	<0.01	0.60	0.540
IDAS Anxiety	<0.01	<0.01	0.04	0.970

Note. IUS = Intolerance of Uncertainty Scale; aINS = anterior insula; IDAS = Inventory of Depression and Anxiety Symptoms.

4. Discussion

The present study investigated whether pre-COVID individual differences in sensitivity to uncertainty predicted COVID-19 related negative affect during the peak of the pandemic approximately two years later. Consistent with our hypothesis, we found that both self-reported IU and bilateral aINS reactivity to U-threat were independent predictors of COVID-related negative affect. This relationship was observed when adjusting for several important baseline covariates including biological sex and severity of depression and anxiety symptoms. There was no association between self-report IU and bilateral aINS reactivity to U-threat. Together, these findings indicate that individual differences in the way people tolerate and respond to uncertainty play a role in coping with the inherent stress of the ongoing public health crisis.

Our results revealed that aINS reactivity to U-threat was a significant predictor of subsequent COVID-related negative affect. As has been demonstrated in previous research, the aINS is a key region of the brain involved in the anticipation of uncertainty. The aINS integrates salient internal and external information to generate anticipatory, affective responses to potential future events (Craig, 2009, 2011; Grupe and Nitschke, 2013; Tanovic et al., 2018; Shankman et al., 2014). Exaggerated aINS reactivity to threat characterizes several anxiety disorders and correlates with severity of negative affect (Gorka et al., 2013; S.M. Gorka et al., 2017; Grillon et al., 2009). It is therefore well-established that aINS function contributes to mood and psychopathology. The present findings importantly extend this literature by demonstrating that aINS reactivity not only contributes to acute negative affectivity but also longitudinally predicts change in negative affect in the context of a real-world U-threat. Thus, pre-COVID individual differences in brain response to U-threat influenced real-world affective response to U-threat. This finding highlights the potential role of aINS function in mental health outcomes. It also converges with numerous studies across diagnoses and syndromes pointing to the role of the aINS in psychiatric functioning (Blanc et al., 2014; Engelmann et al., 2017; Klumpp et al., 2012; Moran et al., 2013). Indeed, aINS inhibition has been noted as a promising intervention and prevention target for addiction and anxiety (Downar et al., 2016; Ibrahim et al., 2019).

Our results also revealed that self-reported IU was a significant predictor of subsequent COVID-related negative affect. IU characterizes numerous disorders and is correlated with internalizing symptomology (Gentes and Ruscio, 2011; McEvoy and Mahoney, 2011). Research has shown that IU is fairly stable over time, though it can be modified with treatment (Birrell et al., 2011; Mahoney and McEvoy, 2012). IU has also been shown to longitudinally predict mental health outcomes (Boelen, 2019; Cai et al., 2020; Oglesby et al., 2016). Our findings add to the existing body of literature by confirming that IU is correlated with

baseline depression and anxiety. Furthermore, the present study demonstrated that IU longitudinally predicts change in negative affect in response to real world uncertainty. Pre-COVID individual differences in self-reported IU influenced real-world affective response to uncertainty. These findings taken together indicate multiple potential intervention targets. In addition to potential aINS inhibition, behavioral strategies aimed at enhancing an individuals' ability to tolerate uncertainty could prove helpful in the context of the COVID-19 pandemic. A novel behavioral intervention targeting the improvement of tolerance of uncertainty for the treatment of generalized anxiety disorder (GAD) currently exists (Hebert and Dugas, 2019), though this could be expanded and potentially applies to a broader treatment group.

We found that both self-reported IU and aINS reactivity during U-threat at baseline prospectively predicted of COVID-related negative affect approximately two years later. There was no association between IUS scores and aINS reactivity. There are a few potential explanations of both measures being significant, yet independent predictors of COVID-related negative affect. The NPU paradigm that assesses aINS reactivity to U-threat is objective as it involves the anticipation of mild electric shock. The task is specific to external threat. In contrast, IUS total scores are self-reported and therefore subjective. The questionnaire is not specific to external threat and encompasses broader intolerance of uncertainty. Thus, although the two measures are designed to capture a similar core construct, the differences in methods contributes to inherent divergence. As a result, there have been somewhat inconsistent results across previous studies with regard to the correlation between self-reported IU and psychophysiological reactivity during uncertain threat (Morriss, 2019; Bennett et al., 2018).

These findings should be reviewed in the context of several limitations that may inform future research. First, due to the timing of the COVID-19 pandemic, the Young-Adult Coronavirus Impact Survey was created by our lab and used for the first time in this study. We used published questionnaires and adapted them to our sample, though this measure has not been validated due to its first-time use. Second, many subjects were sent the optional COVID questionnaire following their completion of the original study. Accordingly, only 53% of subjects submitted the completed form. Although subjects who did and did not fill out the form did not differ in demographics or anxiety and depression symptom severity, there may have been untested differences between groups that influenced results. Third, related to the point above, the overall sample size was modest. Despite the sample size we were able to detect significant results though the findings still require replication, especially as the pandemic has continued. It will also be informative for future studies to examine additional factors (or moderators) that may impact the link between sensitivity to uncertainty and COVID-related negative affect, such as preexisting anxiety psychopathology. Lastly, our aINS findings are based on a very specific threat paradigm that distinctly manipulated the timing of mild electric shock. Other versions of the NPU paradigm have used varying threat types (e.g., aversive noise or pictures) and manipulations of threat predictability (e.g., probability, intensity, location). It is presently unclear whether the current findings are specific to temporal manipulation of electric shock and thus future studies would benefit by exploring the role of aINS function more broadly.

In conclusion, our study reveals preliminary evidence demonstrating that individuals differences in aINS reactivity to U-threat and self-reported IU are associated with subsequent COVID-related negative affect. Individuals with baseline sensitivity to uncertainty may therefore be vulnerable to the sustained emotional impact of COVID-19. As the pandemic continues, it will be important to identify those most vulnerable for poor mental health outcomes and mechanisms that may contribute to chronic negative affect.

Declaration of competing Interest

The authors declare no conflict of interest.

Acknowledgements

Research reported in this publication was supported by the National Institute on Alcohol Abuse And Alcoholism of the National Institutes of Health under Award Number K23AA025111 (PI: Gorka). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

Alvarez, R.P., Chen, G., Bodurka, J., Kaplan, R., Grillon, C., 2011. Phasic and sustained fear in humans elicits distinct patterns of brain activity. Neuroimage 55 (1), 389–400. https://doi.org/10.1016/j.neuroimage.2010.11.057.

Barlow, D.H., 2000. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. Am. Psychol. 55 (11), 1247. https://doi.org/10.1037/0003-066X.55.11.1247.

Bennett, K.P., Dickmann, J.S., Larson, C.L., 2018. If or when? Uncertainty's role in anxious anticipation. Psychophysiology 55 (7), e13066 https://doi.org/10.1111/psyp.13066.

Birrell, J., Meares, K., Wilkinson, A., Freeston, M., 2011. Toward a definition of intolerance of uncertainty: a review of factor analytical studies of the Intolerance of Uncertainty Scale. Clin. Psychol. Rev. 31 (7), 1198–1208. https://doi.org/10.1016/j.cpr.2011.07.009.

Blanc, F., Noblet, V., Philippi, N., Cretin, B., Foucher, J., Armspach, J.P., 2014. Right anterior insula: core region of hallucinations in cognitive neurodegenerative diseases. PLoS ONE 9 (12), e114774. https://doi.org/10.1371/journal.pone.0114774.

Boelen, P.A., 2019. Intolerance of uncertainty predicts analogue posttraumatic stress following adverse life events. Anxiety, Stress, Coping 32 (5), 498–504. https://doi.org/10.1080/10615806.2019.1623881.

Cai, R.Y., Uljarević, M., Leekam, S.R., 2020. Predicting mental health and psychological wellbeing in mothers of children with autism spectrum disorder: roles of intolerance of uncertainty and coping. Autism Res. 13 (10), 1797–1801. https://doi.org/10.1002/aur.2341.

Carleton, R.N., 2012. The intolerance of uncertainty construct in the context of anxiety disorders: theoretical and practical perspectives. Expert Rev. Neurother. 12 (8), 937–947. https://doi.org/10.1586/ern.12.82.

Carleton, R.N., Norton, M.A.P.J., Asmundson, G.J.G., 2007. Fearing the unknown: a short version of the Intolerance of Uncertainty Scale. J. Anxiety Disord. 21 (1), 105–117. https://doi.org/10.1016/j.janxdis.2006.03.014.

Carlson, J.M., Greenberg, T., Rubin, D., Mujica-Parodi, L.R., 2011. Feeling anxious: anticipatory amygdalo-insular response predicts the feeling of anxious anticipation. Soc. Cogn. Affect. Neurosci. 6 (1), 74–81. https://doi.org/10.1093/scan/nsq017.

Cheung, Y.T., Chau, P.H., Yip, P.S., 2008. A revisit on older adults suicides and severe acute respiratory syndrome (SARS) epidemic in Hong Kong. Int. J. Geriatr. Psychiatry 23 (12), 1231–1238. https://doi.org/10.1002/gps.2056.

Craig, A.D., Craig, A.D., 2009. How do you feel–now? The anterior insula and human awareness. Nature Rev. Neurosci. 10 (1) https://doi.org/10.1038/nrn2555.

Craig, A.D., 2011. Significance of the insula for the evolution of human awareness of feelings from the body. Ann. N. Y. Acad. Sci. 1225 (1), 72–82. https://doi.org/10.1111/j.1749-6632.2011.05990.x.

Davis, M., 1998. Are different parts of the extended amygdala involved in fear versus anxiety? Biol. Psychiatry 44 (12), 1239–1247. https://doi.org/10.1016/S0006-3223(98)00288-1.

Davis, M., 2006. Neural systems involved in fear and anxiety measured with fear-potentiated startle. Am. Psychol. 741 (8), 61. https://doi.org/10.1037/0003-066X.61.8.741.

Davis, M., Walker, D.L., Miles, L., Grillon, C., 2010. Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety. Neuropsychopharmacology 35 (1), 105–135. https://doi.org/10.1038/npp.2009.109.

Downar, J., Blumberger, D.M., Daskalakis, Z.J., 2016. The neural crossroads of psychiatric illness: an emerging target for brain stimulation. Trends Cogn. Sci. (Regul. Ed.) 20 (2), 107–120. https://doi.org/10.1016/j.tics.2015.10.007.

Engelmann, J.B., Berns, G.S., Dunlop, B.W., 2017. Hyper-responsivity to losses in the anterior insula during economic choice scales with depression severity. Psychol. Med. 47 (16), 2879–2891. https://doi.org/10.1017/S0033291717001428.

Ferry, R.A., Nelson, B.D., 2021. Tactile P300 to unpredictable electric shocks: association with anxiety symptoms, intolerance of uncertainty, and neuroticism. Biol. Psychol. 162, 108094 https://doi.org/10.1016/j.biopsycho.2021.108094.

First, M.B., Williams, J.B.W., Karg, R.S., Spitzer, R.L., 2015. Structured Clinical Interview For DSM-5—Research Version (SCID-5 For DSM-5, Research version; SCID-5-RV). Arlington, VA: American Psychiatric Association, pp. 1–94.

Freeston, M., Tiplady, A., Mawn, L., Bottesi, G., Thwaites, S., 2020. Towards a model of uncertainty distress in the context of Coronavirus (COVID-19). Cogn. Behav. Ther. 13 https://doi.org/10.1017/S1754470X2000029X.

Gentes, E.L., Ruscio, A.M., 2011. A meta-analysis of the relation of intolerance of uncertainty to symptoms of generalized anxiety disorder, major depressive disorder, and obsessive–compulsive disorder. Clin. Psychol. Rev. 31 (6), 923–933. https://doi.org/10.1016/j.cpr.2011.05.001.

Gorka, S.M., Kreutzer, K.A., Petrey, K.M., Radoman, M., Phan, K.L., 2020. Behavioral and neural sensitivity to uncertain threat in individuals with alcohol use disorder:

associations with drinking behaviors and motives. Addict. Biol. 25 (3), e12774. https://doi.org/10.1111/adb.12774.
Gorka, S.M., Lieberman, L., Klumpp, H., Kinney, K.L., Kennedy, A.E., Ajilore, O., Francis, J., Duffecy, J., Craske, M.G., Nathan, J., Langenecker, S., Shankman, S.A., Phan, K.L., 2017a. Reactivity to unpredictable threat as a treatment target for fear-based anxiety disorders. Psychol. Med. 47 (14), 2450–2460. https://doi.org/10.1017/S0033291717000964.
Gorka, S.M., Lieberman, L., Nelson, B.D., Sarapas, C., Shankman, S.A., 2014. Aversive responding to safety signals in panic disorder: the moderating role of intolerance of uncertainty. J. Anxiety Disord. 28 (7), 731–736. https://doi.org/10.1016/j.janxdis.2014.06.004.
Gorka, S.M., Nelson, B.D., Shankman, S.A., 2013. Startle response to unpredictable threat in comorbid panic disorder and alcohol dependence. Drug Alcohol Depend. 132 (1–2), 216–222. https://doi.org/10.1016/j.drugalcdep.2013.02.003.
Grasso, D.J., Briggs-Gowan, M.J., Ford, J.D., Carter, A.S., 2020. The Epidemic–Pandemic Impacts Inventory (EPII). University of Connecticut School of Medicine.
Grillon, C., Baas, J.M., Pine, D.S., Lissek, S., Lawley, M., Ellis, V., Levine, J., 2006. The benzodiazepine alprazolam dissociates contextual fear from cued fear in humans as assessed by fear-potentiated startle. Biol. Psychiatry 60 (7), 760–766. https://doi.org/10.1016/j.biopsych.2005.11.027.
Grillon, C., Pine, D.S., Lissek, S., Rabin, S., Bonne, O., Vythilingam, M., 2009. Increased anxiety during anticipation of unpredictable aversive stimuli in posttraumatic stress disorder but not in generalized anxiety disorder. Biol. Psychiatry 66 (1), 47–53. https://doi.org/10.1016/j.biopsych.2008.12.028.
Grupe, D.W., Nitschke, J.B., 2013. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. Nat. Rev. Neurosci. 14 (7), 488–501. https://doi.org/10.1038/nrn3524.
Hamza Shuja, K., Aqeel, M., Jaffar, A., Ahmed, A., 2020. COVID-19 pandemic and impending global mental health implications. Psychiatr. Danub. 32 (1), 32–35. https://doi.org/10.24869/psyd.2020.32.
Hebert, E.A., Dugas, M.J., 2019. Behavioral experiments for intolerance of uncertainty: challenging the unknown in the treatment of generalized anxiety disorder. Cogn. Behav. Pract. 26 (2), 421–436. https://doi.org/10.1016/j.cbpra.2018.07.007.
Ibrahim, C., Rubin-Kahana, D.S., Pushparaj, A., Musiol, M., Blumberger, D.M., Daskalakis, Z.J., Le Foll, B., 2019. The insula: a brain stimulation target for the treatment of addiction. Front. Pharmacol. 10, 720. https://doi.org/10.3389/fphar.2019.00720.
Jackson, F., Nelson, B.D., Proudfit, G.H., 2015. In an uncertain world, errors are more aversive: evidence from the error-related negativity. Emotion 15 (1), 12. https://doi.org/10.1037/emo0000020.
Klumpp, H., Angstadt, M., Phan, K.L., 2012. Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. Biol. Psychol. 89 (1), 273–276. https://doi.org/10.1016/j.biopsycho.2011.10.010.
Kumar, A., & Nayar, K.R. (2021). COVID 19 and its mental health consequences. https://doi.org/10.1080/09638237.2020.1757052.
Li, J., Yang, Z., Qiu, H., Wang, Y., Jian, L., Ji, J., Li, K., 2020. Anxiety and depression among general population in China at the peak of the COVID-19 epidemic. World Psychiatry 19 (2), 249. https://doi.org/10.1002/wps.20758.
Mahoney, A.E., McEvoy, P.M., 2012. Changes in intolerance of uncertainty during cognitive behavior group therapy for social phobia. J. Behav. Ther. Exp. Psychiatry 43 (2), 849–854. https://doi.org/10.1016/j.jbtep.2011.12.004.
McEvoy, P.M., Mahoney, A.E., 2011. Achieving certainty about the structure of intolerance of uncertainty in a treatment-seeking sample with anxiety and depression. J. Anxiety Disord. 25 (1), 112–122. https://doi.org/10.1016/j.janxdis.2010.08.010.
Merikangas, K., Milham, M., Sringaris, A., Bromet, E., Colcombe, S., Zipunnikov, V., 2020. The CoRonavIruS Health Impact Survey (CRISIS). Adult Self-Report Baseline Form.
Moran, L.V., Tagamets, M.A., Sampath, H., O'Donnell, A., Stein, E.A., Kochunov, P., Hong, L.E., 2013. Disruption of anterior insula modulation of large-scale brain networks in schizophrenia. Biol. Psychiatry 74 (6), 467–474. https://doi.org/10.1016/j.biopsych.2013.02.029.
Morriss, J., 2019. What do I do now? Intolerance of uncertainty is associated with discrete patterns of anticipatory physiological responding to different contexts. Psychophysiology 56 (9), e13396. https://doi.org/10.1111/psyp.13396.
Nelson, B.D., McGowan, S.K., Sarapas, C., Robison-Andrew, E.J., Altman, S.E., Campbell, M.L., Shankman, S.A., 2013. Biomarkers of threat and reward sensitivity demonstrate unique associations with risk for psychopathology. J. Abnorm. Psychol. 122 (3), 662. https://doi.org/10.1037/a0033982.
Oglesby, M.E., Boffa, J.W., Short, N.A., Raines, A.M., Schmidt, N.B., 2016. Intolerance of uncertainty as a predictor of post-traumatic stress symptoms following a traumatic event. J. Anxiety Disord. 41, 82–87. https://doi.org/10.1016/j.janxdis.2016.01.005.
Pole, N., Neylan, T.C., Otte, C., Henn-Hasse, C., Metzler, T.J., Marmar, C.R., 2009. Prospective prediction of posttraumatic stress disorder symptoms using fear potentiated auditory startle responses. Biol. Psychiatry 65 (3), 235–240. https://doi.org/10.1016/j.biopsych.2008.07.015.
Radoman, M., Lieberman, L., Jimmy, J., Gorka, S.M., 2021. Shared and unique neural circuitry underlying temporally unpredictable threat and reward processing. Soc. Cogn. Affect. Neurosci. 16 (4), 370–382. https://doi.org/10.1093/scan/nsab006.
Radoman, M., Phan, K.L., Gorka, S.M., 2019. Neural correlates of predictable and unpredictable threat in internalizing psychopathology. Neurosci. Lett. 701, 193–201. https://doi.org/10.1016/j.neulet.2019.02.031.
Rollman, G.B., Harris, G., 1987. The detectability, discriminability, and perceived magnitude of painful electrical shock. Percept. Psychophys. 42, 257–268. https://doi.org/10.3758/BF03203077.
Sarinopoulos, I., Grupe, D.W., Mackiewicz, K.L., Herrington, J.D., Lor, M., Steege, E.E., Nitschke, J.B., 2010. Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala. Cereb. Cortex 20 (4), 929–940. https://doi.org/10.1093/cercor/bhp155.
Schmitz, A., Grillon, C., 2012. Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). Nat. Protoc. 7, 527–532. https://doi.org/10.1038/nprot.2012.001.
Secor, A., Macauley, R., Stan, L., Kagone, M., Sidikiba, S., Sow, S., Aronovich, D., Litvin, K., Davis, N., Alva, S., Sanderson, J., 2020. Mental health among Ebola survivors in Liberia, Sierra Leone and Guinea: results from a cross-sectional study. BMJ Open 10 (5), e035217 https://doi.org/10.1136/bmjopen-2019-035217.
Shankman, S.A., Gorka, S.M., Nelson, B.D., Fitzgerald, D.A., Phan, K.L., O'Daly, O, 2014. Anterior insula responds to temporally unpredictable aversiveness: an fMRI study. Neuroreport 25 (8), 596. https://doi.org/10.1097/WNR.0000000000000144.
Simmons, A., Matthews, S.C., Paulus, M.P., Stein, M.B., 2008. Intolerance of uncertainty correlates with insula activation during affective ambiguity. Neurosci. Lett. 430 (2), 92–97. https://doi.org/10.1016/j.neulet.2007.10.030.
Tanovic, E., Gee, D.G., Joormann, J., 2018. Intolerance of uncertainty: neural and psychophysiological correlates of the perception of uncertainty as threatening. Clin. Psychol. Rev. 60, 87–99. https://doi.org/10.1016/j.cpr.2018.01.001.
Uddin, L.Q., 2015. Salience processing and insular cortical function and dysfunction. Nat. Rev. Neurosci. 16 (1), 55–61. https://doi.org/10.1038/nrn3857.
Watson, D., O'Hara, M.W., Naragon-Gainey, K., Koffel, E., Chmielewski, M., Kotov, R., Stasik, S.M., Ruggero, C.J., 2012. Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). Assessment 19 (4), 399–420. https://doi.org/10.1177/1073191112449857.