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The uncertainty of errors: Intolerance of uncertainty is associated with error-related brain activity

Felicia Jackson*, Brady D. Nelson, Greg Hajcak

Department of Psychology, Stony Brook University, Stony Brook, NY, United States

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ABSTRACT

Errors are unpredictable events that have the potential to cause harm. The error-related negativity (ERN) is the electrophysiological index of errors and has been posited to reflect sensitivity to threat. Intolerance of uncertainty (IU) is the tendency to perceive uncertain events as threatening. In the present study, 61 participants completed a self-report measure of IU and a flanker task designed to elicit the ERN. Results indicated that IU subscales were associated with the ERN in opposite directions. Cognitive distress in the face of uncertainty (Prospective IU) was associated with a larger ERN and slower reaction time. Inhibition in response to uncertainty (Inhibitory IU) was associated with a smaller ERN and faster reaction time. This study suggests that sensitivity to the uncertainty of errors contributes to the magnitude of the ERN. Furthermore, these findings highlight the importance of considering the heterogeneity of anxiety phenotypes in relation to measures of threat sensitivity.

1. Introduction

The predictability of threat is an important feature that impacts the ability to avoid or mitigate undesirable consequences (Grupe & Nitschke, 2013). Indeed, the anticipation of unpredictable, relative to predictable, threat has been shown to elicit greater self-reported anxiety (Nelson & Shankman, 2011), startle response (Grillon, Baas, Lissek, Smith, & Milstein, 2004), and insula activation (Shankman et al., 2014). Task-irrelevant unpredictability has also been shown to increase amygdala activation and attentional bias to threat (Herry et al., 2007). These findings support a growing literature suggesting that unpredictability can potentiate negative valence system activation.

To date, most research has examined the impact of unpredictability on emotional responses while anticipating exogenous threat (e.g., noises, pictures, shocks). In contrast, few studies have examined whether unpredictability is also important for the processing of endogenous threat. For example, errors are a form of endogenous threat that interrupt behavior in unpredictable ways, and therefore can place an individual in danger (Hajcak, 2012; Weinberg et al., in press). Indeed, error commission is followed by a cascade of defense system activation, including increased negative affect (Spunt, Lieberman, Cohen, & Eisenberger, 2012), startle response (Hajcak & Foti, 2008), skin conductance response (Hajcak, McDonald, & Simons, 2004), and amygdala activation (Pourtois et al., 2010).

An electrophysiological index of errors is the error-related negativity (ERN), a negative deflection in the event-related potential (ERP) that occurs approximately 50 ms after the commission of an error (see Gehring, Liu, Orr, & Carp, 2012 for review). The ERN is larger in individuals with generalized anxiety disorder (GAD; Weinberg, Olvet, & Hajcak, 2010; Weinberg, Kotov & Proudfit, 2014), obsessive–compulsive disorder (OCD; Hajcak, Franklin, Foa & Simons, 2008), checking behaviors (Weinberg et al., in press; Weinberg et al., 2014), and pathological worry (Moser, Moran, Schroder, Donnellan, & Yeung, 2013). Moreover, the ERN has been shown to be enhanced when errors are perceived as more motivationally salient, such as when errors are punished with an aversive loud sound (Riesel, Weinberg, Endrass, Kathmann, & Hajcak, 2012) or monetary loss (Hajcak, Moser, Yeung, & Simons, 2005), and when individuals with social anxiety are socially evaluated (Barker, Troller-Renfree, Pine, & Fox, 2015). The ERN is also enhanced in individuals with a familial history (i.e., risk) of OCD (Riesel, Endrass, Kaufmann, & Kathmann, 2011), and has been shown to prospectively predict the onset of new anxiety disorders (Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, 2015). Together, these findings support the ERN as a potential transdiagnostic index of sensitivity to threat and risk for psychopathology (Proudfit, Inzlicht, & Mennin, 2013). However, given the inherent unpredictability of errors, the elevated defensive responding observed across anxiety disorders may reflect a heightened sensitivity to unpredictability (Proudfit et al., 2013).

* Corresponding author at: Psychology Department, Stony Brook University, Stony Brook, NY 11794-2500, United States. Fax: +1 631 632 7876.
E-mail address: felicia.jackson@stonybrook.edu (F. Jackson).

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Intolerance of uncertainty (IU) is the tendency to perceive, interpret, and respond to ambiguous or uncertain events as threatening (Dugas, Schwartz, & Francis, 2004). IU was originally conceptualized as a cognitive trait that contributed to increased worry and the development of GAD (Dugas, Gosselin & Ladouceur, 2001; Dugas, Buhr & Ladouceur, 2004; Gentes & Ruscio, 2011). However, recent conceptualizations have characterized IU as a transdiagnostic factor of emotional disorders (Boswell, Thompson-Hollands, Farchione, & Barlow, 2013; Mahoney & McEvoy, 2012). IU consists of two related (but distinct) factors—Prospective IU and Inhibitory IU (Carleton, Norton, & Asmundson, 2007; Fergus, 2013; McEvoy & Mahoney, 2011). Prospective IU measures anxiety, cognitive distress, and the urge to act in the face of uncertainty. High Prospective IU has been particularly associated with pathological worry and checking behaviors (McEvoy & Mahoney, 2011, 2012), GAD (McEvoy & Mahoney, 2012), and OCD (McEvoy & Mahoney, 2012). Inhibitory IU measures avoidance, inhibition of action, and paralysis when faced with uncertainty. Inhibitory IU has been particularly associated with social anxiety (Carleton, Collimore, & Asmundson, 2010; Whiting et al., 2014), panic disorder with agoraphobia (Carleton et al., 2014), post-traumatic stress disorder (PTSD; Fetzner, Horswill, Boelen, & Carleton, 2013) and depression (Carleton et al., 2010; McEvoy & Mahoney, 2011).

Research has indicated that total IU (Somerville et al., 2013) and the IU subscales are differentially associated with neural and psychophysiological indicators of sensitivity to unpredictability. For example, Prospective and Inhibitory IU have been associated with an enhanced and attenuated, respectively, startle reflex in anticipation of unpredictable (but not predictable) threat (Nelson, Liu, Sarapas, & Shankman, under review; Nelson & Shankman, 2011). Furthermore, Nelson, Kessel, Jackson, & Hajcak, (in press) recently demonstrated that Prospective and Inhibitory IU were also associated with enhanced and attenuated, respectively, ERP response to reward (i.e., the reward positivity; RewP). This pattern of findings suggests that Prospective IU may be associated with an enhanced psychophysiological response to motivationally-salient stimuli, while Inhibitory IU is associated with an attenuated response—particularly when there is an element of unpredictability. However, to date no study has examined the association between IU and the ERN.

The present study examined the relationship between individual differences in IU and error-related brain activity. Specifically, 61 participants completed the Intolerance of Uncertainty Scale (IUS; Freeston, Rhéaume, Letarte, Dugas, & Ladouceur, 1994) and a flanker task designed to elicit the ERN. As previously mentioned, several anxiety disorders (e.g., GAD, OCD) have been associated with both an enhanced ERN (Hajcak et al., 2008; Weinberg et al., 2010) and greater IU (Dugas, Buhr et al., 2004; Tolin, Abramowitz, Brigidi, & Foa, 2003). Furthermore, Prospective and Inhibitory IU have been associated with an enhanced and attenuated, respectively, startle response in anticipation of unpredictable threat (Nelson and Shankman, 2011; Nelson et al., under review). Therefore, we hypothesized that Prospective IU and Inhibitory IU would be associated with an enhanced and attenuated ERN, respectively.

2. Methods

2.1. Participants

The sample included 64 undergraduates who participated for course credit. Participants were college-aged ($M = 19.90$, $SD = 2.47$), 57.4% female, and ethnically/racially diverse, including 29.5% Caucasian, 13.1% Black, 14.8% Latino, 34.4% Asian, and 8.2% 'Other'. Exclusion criteria were an inability to read or write English or history of a neurological disorder. Informed consent was obtained prior to participation and the research protocol was approved by the Stony Brook University Institutional Review Board.

2.2. Measures

2.2.1. Intolerance of uncertainty scale

The IUS (Freeston et al., 1994) is a 27-item self-report measure that assesses the degree to which individuals find uncertainty to be distressing and undesirable. Items are rated on a five-point Likert scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me), with higher scores indicating greater IU. The present study utilized the psychometrically improved 12-item version of the IUS (Carleton et al., 2007), which includes two factor-analytically derived subscales of Prospective IU (7-items) and Inhibitory IU (5-items). Cronbach's alpha values for the IUS and its subscales in the current sample are shown in Table 1.

2.3. Flanker task

Participants completed a flanker task using Presentation software (Neurobehavioral Systems Inc., Albany, CA). On each trial, five horizontally aligned white arrowheads were presented for 200 ms. Participants indicated the direction of the central arrowhead with their right hand by clicking the left or right mouse button.[1] Half of the trials were compatible (e.g., ««< or »»>) and half were incompatible (e.g., «>« or »<»); trial type was randomly determined. A variable inter-trial interval of 600–1000 ms followed the response. Participants completed a practice block containing 20 trials and the actual task consisted of 11 blocks of 30 trials (330 total trials).

2.4. EEG recording and processing

Continuous EEG was recorded using an elastic cap with 34 electrode sites placed according to the 10/20 system. Electrooculogram was recorded using four additional facial electrodes: three electrodes were placed around the right eye (one above, one below, and one on the outer canthus) and one electrode was placed on the outer canthus of the left eye. All electrodes were sintered Ag/AgCl electrodes. Data were recorded using the Active Two BioSemi system (BioSemi, Amsterdam, Netherlands). EEG was digitized with a sampling rate of 1024 Hz using a low-pass fifth order sinc filter with a half-power cutoff of 204.8 Hz. A common mode sense active electrode producing a monopolar (non-differential) channel was the recording reference.

EEG data were analyzed using Brain Vision Analyzer (Brain Products, Gilching, Germany). Data were referenced offline to the average of left and right mastoids, band-pass filtered from .1 to 30 Hz, and corrected for eye movement artifacts (Gratton, Coles, & Donchin, 1983). Response-locked epochs of 1500 ms were extracted, including a 500 ms pre-response interval. The 500–300 ms pre-response interval was used as the baseline (Weinberg et al., 2010). Epochs containing a voltage greater than 50 μV between sample points, a voltage difference of 175 μV within a 400 ms segment, or a maximum voltage difference of less than .50 μV within 100 ms intervals were automatically rejected. Tri-

[1] All participants completed the Flanker task with their right hand; therefore, left-handed individuals used their non-dominant hand to key in responses during the task. In order to examine the possible impact of handedness on study results, we conducted additional analyses that excluded participants who were left-handed ($n = 6$), leaving a sample of 55 right-handed individuals for analysis. All results remained significant when the left-handed participants were excluded from analyses (all $ps < .05$).

Table 1
Descriptive statistics and correlations for the intolerance of uncertainty scale and flanker task RT and ERPs.

	1	2	3	4	5	6	7
Intolerance of uncertainty scale							
Prospective IU	–	.75***	.97***	.05	−.01	.07	−.03
Inhibitory IU		–	.90***	−.16	−.21	.14	.19
Total IU			–	−.03	-.10	.10	.05
Flanker task RT and ERPs							
Correct RT (ms)				–	.79***	−.34**	−.21
Error RT (ms)					–	−.33**	−.15
CRN (μV)						–	.34**
ERN (μV)							–
M	17.49	9.75	27.25	401.22	321.52	6.83	.81
SD	6.51	3.73	9.63	57.64	33.22	5.29	5.74
Cronbach's α	.90	.79	.92	–	–	–	–

Note. CRN—correct response negativity; ERN—error-related negativity; ERP—event-related potential; IU—intolerance of uncertainty; *M*—mean, ms—milliseconds; *SD*—standard deviation; RT—reaction time.
** $p < .01$.
*** $p < .001$.

als with response times below 200 ms and above 1000 ms were excluded (Weinberg et al., 2014).

Response-locked ERPs were averaged separately for the neural response to correct responses (i.e., the correct response negativity; CRN) and errors (i.e., the ERN). ERPs were quantified as the mean amplitude from 0 to 100 ms post response pooled across fronto-central electrode sites Fz, FCz, FC1, FC2, and Cz, where the ERN was maximal.

2.5. Data analysis

Three participants were excluded from analyses due to poor quality EEG data ($n = 2$) or outlier ERP values ($n = 1$), leaving a final sample of 61. To examine the difference between the CRN and ERN, we conducted a repeated measures analysis of variance (ANOVA) with response (correct vs. error) as the within-subjects factor. To examine the association between IU and behavioral performance and ERP responses, we conducted two linear regressions with (1) Total IU as the independent variable and (2) Prospective and Inhibitory IU as simultaneous independent variables. Separate linear regressions were conducted for flanker task behavior (i.e., error reaction time, correct reaction time, number of errors) and ERPs as the dependent variable.

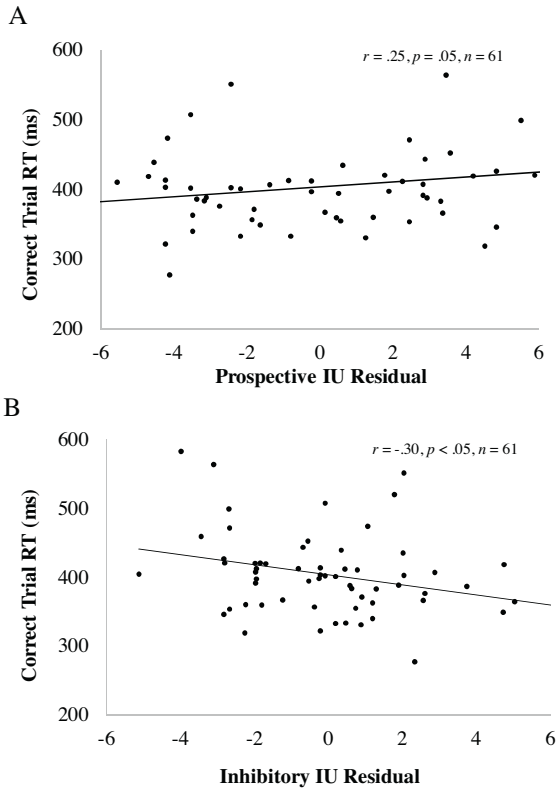

Fig. 1. Scatterplots depicting the association between reaction time on correct trials and Prospective IU (panel 1A) and Inhibitory IU (panel 1B) residuals. IU = intolerance of uncertainty; ms = milliseconds; RT = reaction time.

3. Results

3.1. Behavioral performance

Table 1 displays descriptive statistics and correlations for the IUS and flanker task behavioral performance. As expected, reaction time for errors and correct responses differed, $F(1, 60) = 273.96$, $p < .001$, $\eta_p^2 = .82$, such that participants responded significantly faster on error relative to correct trials. For the IU analyses, Total IU was not associated with reaction time for correct or error responses ($ps > .45$). However, greater Prospective IU associated with slower reaction time for correct responses; this effect was trending toward significance for error responses. Alternatively, greater Inhibitory IU was associated with faster reaction time for correct and error responses (see Table 2 and Fig. 1).[2] There were no associations between any IU measure and task accuracy ($ps > .13$).

[2] In order to examine a possible association between post-error slowing and IU, we conducted additional analyses on the association of post-error and post-correct reaction times with total IU and IU subscale scores. Consistent with the results observed in primary reaction time analyses, post-correct and post-error reaction times were associated with Prospective and Inhibitory IU in opposite directions. Specifically, higher Prospective IU was associated with slower post-correct ($p < .05$) and post-error reaction times ($p < .07$) while greater Inhibitory IU was associated with faster reaction times following correct and error responses ($ps < .05$).

Table 2
Linear regressions with IUS subscales as the independent variables and flanker task RT and ERPs as the dependent variables.

	Correct RT			Error RT		
	F	R^2	β	*F*	R^2	β
	2.96	.09		2.90	.09	
Prospective IU			.40*			.33†
Inhibitory IU			−.46*			−.46*
	CRN			ERN		
	F	R^2	β	*F*	R^2	β
	.67	.02		3.19	.10	
Prospective IU			−.09			−.39*
Inhibitory IU			.20			.48*

Note. CRN—correct response negativity; ERN—error-related negativity; IU—intolerance of uncertainty; RT—reaction time.
† $p < .10$.
* $p < .05$.

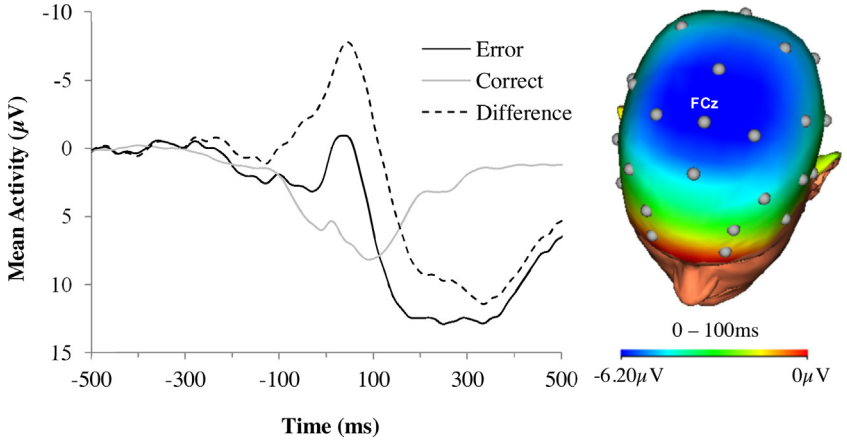

Fig. 2. Flanker task ERP waveforms for frontocentral electrodes (Fz, FCz, FC1, FC2, Cz) and 3D-rendered topographical map. The difference waveform represents error minus correct trials. The topographical map displays the mean activity between 0 and 100 ms after response for error minus correct trials (i.e., ΔERN). ERP = event-related potential; ERN = error-related negativity; ms = milliseconds.

3.2. ERPs

Table 1 also displays descriptive statistics and correlations for the IUS and flanker task ERPs. Fig. 2 displays the response-locked waveforms and 3-D rendered topographical map of the ERN scalp distribution. As expected, the ERN was significantly more negative than the CRN, $F(1, 60) = 54.59$, $p < .001$, $\eta_p^2 = .48$. For the IU analyses, Total IU was not associated with the CRN or ERN ($ps > .44$). However, Prospective IU and Inhibitory IU demonstrated the opposite relationship with the ERN. Specifically, greater Prospective IU was associated with an enhanced ERN, and greater Inhibitory IU was associated an attenuated ERN (see Table 2 and Fig. 3).[3] There were no associations between any IU measure and the CRN.

4. Discussion

The present study is the first to demonstrate a relationship between IU and the ERN. Specifically, Prospective IU was associated with a larger (i.e., more negative) ERN, while Inhibitory IU was associated with a smaller (i.e., less negative) ERN; there was no relationship between IU and the CRN. Furthermore, Prospective IU was related to slower reaction time on correct and error responses, while Inhibitory IU was associated with faster reaction times. We have previously conceptualized errors as a form of endogenous, uncertain threat (Proudfit et al., 2013; Weinberg et al., in press). Consistent with this theory, the present findings suggest that—in addition to other factors such as motivational salience and threat sensitivity—sensitivity to uncertainty may contribute to variation in the ERN.

The current findings are consistent with an extant literature demonstrating a relationship between anxiety disorders and both IU and the ERN. For example, McEvoy and Mahoney (2012) found that Prospective IU mediated the relationship between neuroticism and GAD and OCD—disorders that have also been associated with an enhanced ERN (Gehring, Himle, & Nisenson, 2000; Weinberg et al., 2010, 2014). Therefore, it is possible that the association between Prospective IU and an enhanced ERN reflects the increased motivational salience and urge to act in response to uncertain threat. In turn, this enhanced signal may reinforce performance of maladaptive behaviors characteristic of GAD and OCD, such as checking, reassurance seeking, and worrying (Weinberg et al., 2014; Weinberg et al., in press).

McEvoy and Mahoney (2012) further reported that Inhibitory IU mediated the relationship between neuroticism and depression, panic disorder with agoraphobia, and social anxiety—disorders characterized by avoidance, inhibited behavior, and, in the case of depression, a decreased ERN (Ladouceur et al., 2012; Weinberg et al., 2014). Moreover, Inhibitory IU has been uniquely associated with avoidance behaviors in panic disorder (Carleton et al., 2014),

[3] In order to examine the association of IU with conscious error recognition, we conducted supplementary analyses with the error positivity (Pe). The Pe is a positive going slow wave that is observed approximately 200–400 ms following the commission of an error. Results indicated that neither Total, Inhibitory, nor Prospective IU were associated with the Pe ($ps > .55$), suggesting IU was uniquely associated with the ERN.

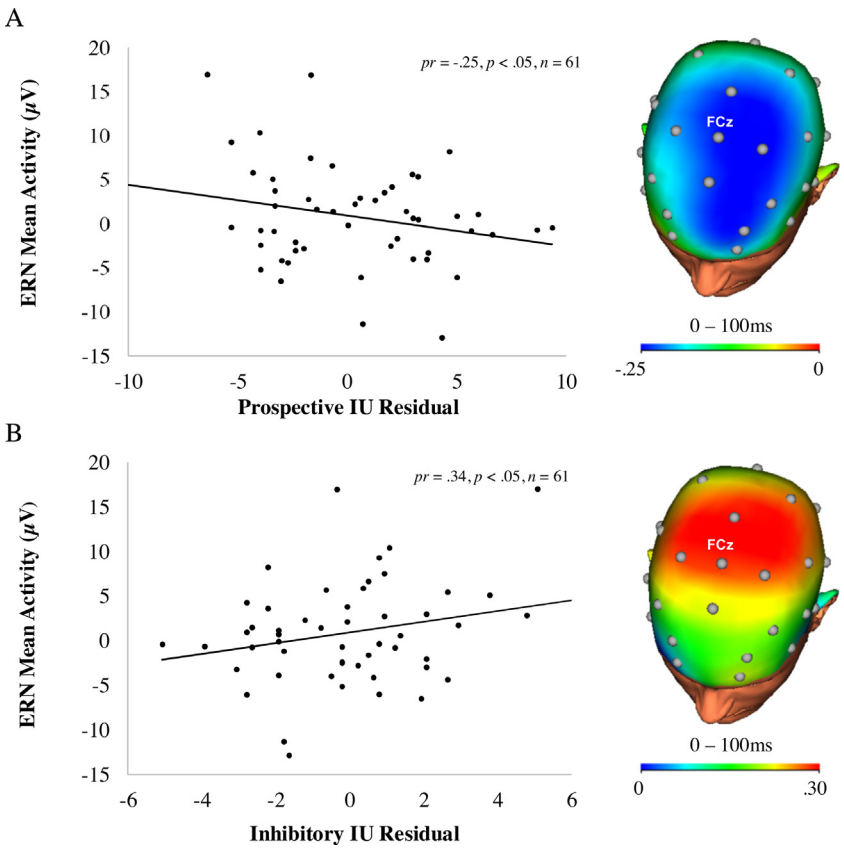

Fig. 3. Scatterplots and partial correlation coefficient topographical maps depicting the association between the ERN and Prospective IU (panel 3A) and Inhibitory IU (panel 3B) residuals. The topographical maps depict that the correlation between IU and the ERN was strongest where the ERN was maximal (i.e., frontocentral electrodes). The ERN for the scatterplots was pooled at Fz, FCz, FC1, FC2, and Cz, where it was maximal. ERN = error-related negativity; IU = intolerance of uncertainty.

and a reduced physiological response to both reward (Nelson et al., in press) and threat (Nelson & Shankman, 2011; Nelson et al., under review). Thus, it is possible that the association between Inhibitory IU and an attenuated ERN is related to avoidance or inhibition in response to uncertain threat. Together, these findings suggest Prospective IU is associated with enhanced neural signals that motivate action and Inhibitory IU is associated with reduced neural signals that facilitate avoidance and/or inhibition. Furthermore, these findings highlight the importance of examining more specific phenotypes in relation to neural systems that contribute to the heterogeneity in anxiety phenomenology. For example, examining the relation of neural measures with Prospective and Inhibitory IU better elucidates underlying substrates, relative to the more general total IU score or broad heterogeneous diagnostic groups (see Shackman et al., 2013 for further discussion).

Both IU and the ERN have previously been associated with cognitive aspects of anxiety (e.g., worry; Buhr & Dugas, 2009; Dugas et al., 2001; Moser et al., 2013). However, it is unclear if the current association between IU and the ERN was due to shared variance with worry or a unique association between the two constructs. Interestingly, recent research has indicated that the enhanced ERN in GAD and OCD is better accounted for by checking behaviors than trait worry (Weinberg et al., 2014). Moreover, in one study depressed individuals who reported high levels of worry did not exhibit an enhanced ERN (Weinberg et al., 2014). Although worry has been associated with the ERN, IU may be a broader factor that contributes to variation in the ERN across multiple anxiety disorders. It is important to highlight that the present study did not measure worry, and future research should simultaneously examine IU, worry, and the ERN to further elucidate these relationships.

The IU subscales also demonstrated opposing relationships with reaction time during the flanker task. On correct and error trials, Prospective IU was associated with slower responding, while Inhibitory IU was associated with faster responding. The slower reaction time observed in Prospective IU may reflect greater attention to performance and more planful responding in an attempt to reduce the likelihood of an uncertain event (i.e., error). Indeed, the ERN is posited to signal the need for cognitive control (Cavanagh & Shackman, 2015), thus, a large ERN is associated with increased performance monitoring and slowed reaction time. Alternatively, the reduced ERN in Inhibitory IU (i.e., reduced signal for cognitive control), may further reduce compensatory behavior adjustment (i.e., increased RT) and performance monitoring, resulting in more sustained, rapid responses throughout the task.

Cognitive models of error processing suggest that a large ERN—although potentially maladaptive at clinical levels—should signal the need for cognitive control, and thereby should be associated with improved task performance (Holroyd & Coles, 2002); likewise a smaller ERN should be associated with poorer task performance. However, the current results are not consistent with these expectations. Individuals higher in Prospective IU—despite having an enhanced ERN and slowed reaction time—performed the task with equivalent accuracy to their high Inhibitory IU counterparts. Thus, when taking into consideration speed-accuracy trade off, Prospective IU individuals performed the task worse, or less efficiently than those high in Inhibitory IU. This inefficiency of task performance is consistent with the maladaptive behaviors that are associated with Prospective IU (e.g., checking, reassurance seeking, and worrying). After a certain threshold, increasing these behaviors, or the neural signal that motivates them, is no longer beneficial and in fact may contribute to inefficiencies and functional

impairments. Future research should examine possible interactions between Prospective IU, task performance and the ERN, and how they may relate to the performance of maladaptive behaviors.

The present study was, however, limited to a cross-sectional sample of undergraduates, thereby limiting the generalizability of these findings. Future studies should explore the association between IU and the ERN in clinical populations to investigate the possible role of IU as a moderator of the link between the ERN and psychopathology. Additionally, the R^2 values were relatively low, suggesting that IU explained a relatively small portion of ERN magnitude and reaction time. It is important to note, however, that this pattern is neither uncommon nor unexpected given that there is no shared method variance among target variables (i.e. self-report measures vs. behavioral responding vs. psychophysiological measures).

In sum, the current study examined the association between IU and error-related brain activity. Specifically, Prospective IU was associated with an enhanced ERN, while Inhibitory IU was associated with an attenuated ERN. These findings suggest heterogeneity in the association between the ERN and various anxiety phenotypes (e.g., Prospective IU and Inhibitory IU). Furthermore, although these findings are from a sample of unselected undergraduates (and therefore do not directly reflect clinical level symptomatology), the current results demonstrate that the ERN is related to anxiety phenotypes, and thereby support the ERN as a possible transdiagnostic index of sensitivity to uncertain threat (Proudfit et al., 2013). These findings suggest interesting avenues of future investigation in clinical populations that could further edify the role of IU and the ERN as indices of sensitivity to uncertainty, and their role in the etiology and maintenance of anxiety phenomenology.

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