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Response to Uncertain Threat in Acute Trauma Survivors

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RESPONSE TO UNCERTAIN THREAT IN ACUTE TRAUMA SURVIVORS

by

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ABSTRACT

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Uncertainty is often associated with subjective distress and a potentiated anxiety response. The heightened response to uncertainty may be a central mechanism via which anxiety-, trauma-, and stressor-related disorders are developed and maintained. The current study compared the neural response to predictable and unpredictable threat in acute trauma survivors to clarify the role of the response to uncertain threat in fear circuitry and further inform the nature of the development of PTSD in the context of uncertain threat. The novel study showed that anticipating unpredictable (primarily *negative* images) relative to predictable images increased activation in a frontoparietal network and was associated with decreased acute trauma symptoms, suggesting this network may be associated with an adaptive mechanism for responding to unpredictable threat. Results also showed increased PTSD symptoms was associated with more sustained activation during unpredictable vs. predictable blocks in the insula. Additionally, those with more severe PTSD symptoms had greater response to transient relative to sustained unpredictable (vs. predictable) conditions in the superior frontal gyrus. These findings extend previous work highlighting the insula's role in sustained responsivity to unpredictability in anxiety disorders and PTSD to symptomatology in acute trauma survivors. Finally, widespread sustained activation of predominantly frontocentral and frontoparietal regions in unpredictable relative to predictable blocks was associated with increased intolerance of uncertainty.

To

my mother,

my brother,

my late father,

my cohort,

and my lab mates

– thank you for your unlimited support.

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Response to Uncertain Threat in Acute Trauma Survivors

Anxiety is one of the most common mental health problems, with anxiety disorders having a lifetime prevalence of 28.8% (Greenberg et al., 1999; Kessler, Ruscio, Shear, & Wittchen, 2009). Anxiety disorders are associated with a significant amount of psychological distress, physical distress, and many adverse life outcomes, such as marital instability, low occupational status, and reduced educational attainment (Lépine, 2002). Additionally, anxiety creates a significant economic burden, costing the United States over $42 billion annually (Greenberg et al., 1999). These individual and societal impacts of anxiety prompt a need for understanding the risks for developing anxiety- and anxiety-related disorders.

One such risk factor, acute trauma, is considered a strong predictor of future negative mental health outcomes, specifically anxiety disorders and trauma- and stress-related disorders (Isserlin, Zerach, & Solomon, 2008; Wiseman, Foster, & Curtis, 2013). Individuals suffering from acute stress disorder (ASD) experience fear-based symptoms, such as avoidance of reminders of the trauma, hyperarousal, dissociation, and re-experiencing the traumatic event (American Psychiatric Association, 2013). Nearly 70-90% of the population will experience a trauma in their lifetime (Norris, 1992; Ogle, Rubin, Berntsen, & Siegler, 2013). Roughly 19% of those individuals will develop ASD, which can be diagnosed 3 days to 1 month following exposure to a traumatic event (American Psychiatric Association, 2013). This symptomology is also predictive of posttraumatic stress disorder (PTSD), a chronic trauma-related disorder (Bryant, Harvey, Guthrie, & Moulds, 2003; Bryant, 2017; Elsesser, Sartory, & Tackenberg, 2005) that has high comorbidity with depression (Breslau, Davis, Peterson, & Schultz, 2000; Breslau, 2012; Stander, Thomsen, & Highfill-McRoy, 2014), substance use problems (Cottler, Compton, Mager, Spitznagel, & Janca, 1992; Mills, Teesson, Ross, & Peters, 2006) and anxiety

disorders (Liebschutz et al., 2007). PTSD can be diagnosed at least one-month post-trauma, and is also characterized by symptoms of re-experiencing, avoidance, negative thoughts and feelings, and hyperarousal (American Psychiatric Association, 2013).

It is clear that trauma can have an acute effect on those exposed, as in ASD, as well as a more severe, chronic effect. According to epidemiological data, 7-18% of trauma survivors develop PTSD (Breslau et al., 1998; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Moreover, a recent neuroimaging meta-analysis suggests that trauma, regardless of diagnosis, has a long-lasting effect on the functional dynamics of the brain (Stark et al., 2015). However, the acute impact of trauma on the emotion regulation and other systems of the brain are not well understood. Thus, clarifying the acute post-trauma effects may ultimately aid in identifying factors that predict risk for chronic PTSD.

Posttraumatic stress symptoms are often experienced alongside other maladaptive anxiety symptoms, such as anxious apprehension and worry (American Psychiatric Association, 2013; McTeague & Lang, 2012). Apprehension and worry are core aspects of anxiety, and are characterized by a future-oriented emotional state focused on possible unknown events (Borkovec, 1985). Anticipatory representations of uncertain events can have important downstream consequences, such as eliciting avoidance or defensive responses (McNaughton & Gray, 2000). Normally this process is adaptive, but can be disrupted in pathological anxiety for example, when this system is engaged in situations that are seemingly safe (Rosen & Schulkin, 1998). The ‘uncertainty and anticipation model of anxiety’ proposed by Grupe & Nitschke (2013) posits that a series of disrupted underlying processes related to uncertainty in anxiety disorders, such as increased hypervigilance, behavioral and cognitive avoidance, and heightened reactivity to threat uncertainty, bias individuals to use inefficient preparatory behaviors when

faced with uncertainty. Moreover, engaging these maladaptive responses to uncertainty can cause a vicious cycle to maintain anxiety. For example, being hypervigilant in an uncertain threatening environment, such as a warzone, is likely adaptive. However, remaining hypervigilant and alert in an objectively non-threatening civilian environment may be maladaptive and could perpetuate other post-traumatic symptoms, such as increased startle responsivity and avoidance of potentially threatening environments. Thus, heightened response to uncertainty may be a central mechanism via which anxiety disorders are developed and maintained (Grupe & Nitschke, 2013).

Neural Circuitry of Anxiety

The neural circuitry involved in uncertainty is mostly shared with anxiety, which is one of the factors that led Grupe and others to hypothesize that dysregulation in the circuitry instantiating the processing of uncertainty may be central to anxiety (Grupe & Nitschke, 2013; Paulus & Stein, 2006; Sarinopoulos et al., 2009; Williams et al., 2015). Grupe and Nitschke's seminal review paper on the central role of uncertainty in anxiety (2013) linked the maladaptive responsivity to uncertainty in anxious individuals to the amygdala, anterior insula, anterior mid-cingulate cortex (aMCC), bed nucleus of the stria terminalis (BNST), orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011; Davis, Walker, Miles, & Grillon, 2010; Duval, Javanbakht, & Liberzon, 2015; Grupe & Nitschke, 2013; LeDoux, 2007; Rauch, Shin, & Wright, 2003; Shankman et al., 2014; Shin & Liberzon, 2010; Walker, Miles, & Davis, 2009).

The amygdala has been well-documented as a structure that plays a central role in the processing of certain and uncertain threat, fear, anxiety, and other emotions broadly (Cannistraro & Rauch, 2003; Davidson, 2002; Davis & Whalen, 2001; LeDoux, 2007; Rauch et al., 2003).

The amygdala is important for the expression of cue-related fear and learning the associations among threatening stimuli (Davidson, 2002; LeDoux, 2007), and damage to it interferes with these processes (Aggleton & Passingham, 1981; LeDoux, 2007). In fear conditioning, the outputs of the central nucleus of the amygdala lead to defensive freezing, autonomic responses, and the release of stress-related hormones such as cortisol (LeDoux, 2007). The outputs of the basal nucleus of the amygdala are also involved in behavioral avoidance (Amorapanth, LeDoux, & Nader, 2000). The BNST is a small structure that has strong connections with the amygdala and is typically activated during sustained, unpredictable threat (Davis et al., 2010; Somerville, Whalen, & Kelley, 2010; Walker, Toufexis, & Davis, 2003). Although the BNST is associated with sustained threat, it is often overlooked in its role in anxiety disorders and trauma (Lebow & Chen, 2016).

In addition to these subcortical structures, Grupe and Nitschke (2013) also highlight several regions of prefrontal cortex as central to anxiety-related response to uncertainty. The insula, primarily the anterior portion, is commonly associated with autonomic and interoceptive sensitivity, emotional experience, and risk and uncertainty evaluation (Craig, 2003; Critchley et al., 2005; Paulus & Stein, 2006; Platt & Huettel, 2008; Simmons, Matthews, Paulus, & Stein, 2008; Wicker et al., 2003). Meta-analyses reviewing the neurocircuitry of anxiety also found elevated insula and amygdala during negative emotion processing, across anxiety disorders (Etkin & Wager, 2007; Rauch et al., 2003). The aMCC is a mid-frontal region that is considered the central "hub" of the "uncertainty and anticipation model of anxiety," sharing connections with the amygdala, insula, OFC, and other regions associated with uncertainty processing (Grupe & Nitschke, 2013; Shackman et al., 2011). The aMCC is associated with probability assessment, decision-making, and avoidance behaviors (Aupperle Robin & Martin, 2010; Knutson, Taylor,

Kaufman, Peterson, & Glover, 2005; Shackman et al., 2011). The OFC is a frontal structure that has been implicated in decision making and integrating information about the costs and value of future outcomes and states, including threatening ones (Padoa-Schioppa & Assad, 2006; Plassmann, O'Doherty, & Rangel, 2010; Wallis, 2012). Similarly, the vmPFC, a larger frontal region that contains the OFC, is thought to be involved in higher order processing such as safety learning and down-regulation of the amygdala (Milad et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004).

Support for the Role of Anxiety Circuitry in Response to Uncertainty

Human studies of anxiety and uncertainty have shown elevated amygdala activation specifically during conditions of uncertainty (Davis & Whalen, 2001; Rosen & Donley, 2006; Sarinopoulos et al., 2009). Likewise, recent research showed that increased amygdala activation and diminished insula deactivation relative to controls were significantly associated with uncertain cues in children with anxiety disorders, suggesting a dysregulation of the amygdala and insula during uncertain anticipation (Williams et al., 2015). Bornhovd and colleagues (2002) conducted a parametric single-trial fMRI study investigating neural responses to variation in stimulus intensities. Their results revealed that the amygdala responded similarly to the highest cued intensity and to the uncertain intensity cue, suggesting that the amygdala may be involved in coding uncertainty. Importantly, the amygdala tends to respond to transient, imminent threat, whereas sustained activation of the BNST has been associated with the anticipation of threat (Davis et al., 2010; Herrmann et al., 2016; Kalin, Shelton, Fox, Oakes, & Davidson, 2005; Walker et al., 2009; Walker et al., 2003).

Although the amygdala-BNST differentiation is well supported in the animal literature, this relationship may be more nuanced in humans. A recent human study examining response to

threatening images found that functional connectivity between BNST and amygdala positively correlated with trait anxiety, suggesting that the amygdala and BNST process phasic threat together in a way that varies depending on inter-individual differences in trait anxiety (Brinkmann et al., 2018). Studies from Somerville and colleagues (Somerville et al., 2010; Somerville et al., 2012) also aimed to elucidate the association of and distinction between the systems involved in processing transient and sustained uncertain anxious states. The authors found significant activation in the amygdala in response to negative compared to neutral images and peak transient responding of the amygdala during unpredictability as subjects' intolerance of uncertainty increased. Additionally, they found that the sustained activation of vmPFC during the blocks predicted downregulation of transient amygdala responsivity. However, during negative valence and unpredictable blocks, the insula and BNST showed sustained activation consistent with task-induced anxiety ratings. This sustained activation in the insula during unpredictable blocks was also associated with greater intolerance of uncertainty. These findings further support the complexity of the fear/anxiety network and highlight the importance to better understand this network across clinical and non-clinical populations.

One of the most common and anxiolytic types of uncertainty, temporal uncertainty, has also been studied in behavioral and neuroimaging studies (Bennett, Dickmann, & Larson, 2018; Grillon, Baas, Lissek, Smith, & Milstein, 2004; Grillon et al., 2008; Grillon et al., 2009; Herrmann et al., 2016; Shankman, Robison-Andrew, Nelson, Altman, & Campbell, 2011; Shankman et al., 2014; Williams et al., 2015). Herry and colleagues (2007) found that temporally unpredictable tones produced sustained activation in the amygdala. Hermann and colleagues (2016) also examined the neural response to temporally uncertain threat. They observed a phasic activation of the amygdala, ACC, and vmPFC to the onset of aversive versus neutral cues.

However, they also found a sustained activation of the BNST, insula, and several other regions during the threat versus neutral anticipation period. These results, coupled with their functional connectivity findings showing that phasic amygdala activation was positively associated with activation in sensory cortex areas and sustained BNST activation was negatively associated with these same areas, suggests that the amygdala plays a central role in preferential phasic responding to relevant stimuli, such as unpredictable cues.

Consistent with this amygdala-BNST association, Alvarez and colleagues (2015) found increased activation in the BNST, insula, and aMCC during unpredictable shock anticipation. They also provided evidence suggesting that low perceived control influenced the neural response to uncertain threat. Sarinopoulos and colleagues (2009) conducted an fMRI study in which they examined how uncertain cues affect subsequent neural responses to neutral and threatening stimuli. Their results revealed that compared to a certain cue (predictive of picture valence), an uncertain cue (not predictive of picture valence) led to a larger response in the insula and amygdala to the subsequent aversive pictures. These findings suggest uncertainty may "prime" the fear system to over-respond to the threat stimulus.

Many studies have also found recruitment of the ACC and insula when subjects were in conditions of uncertainty, exposed to uncertain stimuli, and when anticipating threat, further suggesting these regions may be important for processing uncertainty in anxious individuals (Critchley, Mathias, & Dolan, 2002; Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005; Krain et al., 2006; Krain et al., 2008; Mackiewicz, Sarinopoulos, Cleven, & Nitschke, 2006; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Paulus & Stein, 2006; Sarinopoulos, Dixon, Short, Davidson, & Nitschke, 2006; Shankman et al., 2014; Simmons et al., 2008; Williams et al., 2015). The relationship between anterior insula activation and unpredictable

threat has also been shown to vary depending on individual differences in self-reported intolerance of uncertainty, suggesting this region may be involved in an "anxious risk assessment" (Shankman et al., 2014). Overall, these findings assert that there is a core network of structures associated with the processing of and responding to uncertain threat in anxious individuals. These structures are also implicated in processing uncertain threat in anxiety-related disorders, such as PTSD (Aupperle, Melrose, Stein, & Paulus, 2012; Brinkmann et al., 2018; Dretsch et al., 2016; Grupe & Nitschke, 2013; Grupe, Wielgosz, Davidson, & Nitschke, 2016; Simmons et al., 2008; Simmons et al., 2013).

Response to Uncertain Threat in PTSD and Acute Trauma

There is a growing body of literature that suggests that neural activation during the anticipation of uncertain threat and emotional stimuli is important for differentiating PTSD from control populations (Aupperle et al., 2012; Brinkmann et al., 2018; Dretsch et al., 2016; Grupe & Nitschke, 2013; Grupe et al., 2016; Simmons et al., 2008; Simmons et al., 2013). Dretch and colleagues (2016) compared neural response to predictable and unpredictable threat in veterans with PTSD and deployment-exposed controls. They found that PTSD subjects exhibited preferential responding of portions of the amygdala and insula to unpredictable threat relative to predictable threat. The opposite was true for the deployment-exposed controls. A recent study from Brinkmann and colleagues (2018) examined the response to temporally unpredictable aversive and neutral sounds in female PTSD and healthy control samples. Consistent with findings in non-clinical populations, the authors found transient amygdala activation and sustained BNST activation to the anticipation of aversive versus neutral stimuli in PTSD patients compared to healthy controls. These findings suggest that in PTSD, phasic fear responses and sustained anxiety responses are enhanced when anticipating uncertain threat.

Recent research has also shown, in female PTSD patients compared to controls, greater activation in the anterior insula in the anticipation of negative images as well as temporally unpredictable emotionally negative images (Aupperle et al., 2012; Simmons et al., 2008; Simmons et al., 2013). Aupperle and colleagues (2012) also reported that greater activation in the dorsolateral PFC (dlPFC) when anticipating negative images was related to better cognitive task performance and decreased PTSD symptoms in women with intimate partner violence PTSD. The authors suggest that this pattern represents an imbalance between internally-focused affective and externally-focused cognitive control networks. Therefore, they posit that a more active dlPFC when anticipating threat may serve as part of a protective cognitive control network that is beneficial for emotional and cognitive functioning in women with PTSD, highlighting the relevance of understanding neural activity during threat anticipation.

In addition to differentiating PTSD patients from controls, imaging research in this area has also focused on understanding the nuances of PTSD symptomology (Grupe et al., 2016). Grupe and colleagues (2016) used a paradigm in which they used a ticking clock to simulate anticipation of unpredictable threat. The authors found more deactivation of the vmPFC when anticipating unpredictable threat relative to unpredictable safety. However, this relationship changed as a function of PTSD symptoms; as PTSD symptoms increased, activation of vmPFC to unpredictable threat increased. Moreover, they found that this effect was primarily driven by hyperarousal symptoms, suggesting potentially dysfunctional peripheral physiological systems in individuals with PTSD.

To our knowledge, there are no studies examining the neural response to uncertainty in acute trauma survivors. However, there is some evidence suggesting the uncertainty-related structures also play a role in response to threat in acute trauma survivors. For example, in a

sample of motor vehicle crash (MVC) survivors with DSM-IV acute PTSD, PTSD symptoms were positively correlated with amygdala activation to masked fearful faces (Armony, Corbo, Clément, & Brunet, 2005). Moreover, a similar MVC study using positron emission tomography (PET) examined regional cerebral blood flow (rCBF) in response to trauma script audio (Osuch et al., 2008). They found decreased rCBF in the amygdala in trauma subjects when listening to trauma versus neutral scripts. Symptom improvement at 3 months suggested that this decreased amygdala rCBF may serve as an adaptive process. A small sample of coal mining trauma survivors with acute PTSD exhibited reduced activation in right ACC compared to controls when viewing trauma-related images (Hou et al., 2007). Acute trauma survivors (within 25 days of earthquake) relative to controls also showed increased amplitude of low frequency fluctuations (ALFF; 0.01-0.08 Hz) of BOLD signals in resting state activity in the insula and amygdala (Lui et al., 2009).

These studies of PTSD populations and acute trauma survivors highlight the role of the amygdala and insula as core structures involved in the processing of uncertainty. However, the findings are mixed. For example, in some of the studies differentiating PTSD groups from controls, the amygdala tends to be activated in response to unpredictable threat and when anticipating negative or aversive stimuli (Brinkmann et al., 2018; Dretsch et al., 2016). In contrast, several other studies found increased insula but not amygdala activation (Aupperle et al., 2012; Simmons et al., 2008; Simmons et al., 2013). Moreover, the findings in the limited acute trauma literature are also mixed. Armony and colleagues (2005) found PTSD symptoms positively correlated with amygdala activation to masked fearful faces. However, Osuch and colleagues (2008) found *decreased* amygdala activation in trauma subjects when listening to trauma vs. neutral scripts. These findings suggest a need for better understanding the nuances of

response to uncertain threat in trauma-exposed populations. Furthermore, due to the lack of research within acute trauma populations, there is a clear need to understand these responses in such a unique and vulnerable population.

The Current Study

The proposed study compared the neural response to predictable and unpredictable threat in an acute trauma population. The results from this study helped clarify the role of the response to uncertain threat in fear circuitry in individuals who are especially vulnerable to future negative mental health outcomes, such as anxiety disorders and PTSD. The findings also informed our understanding of the brain's response to threat immediately following a traumatic event, further informing the nature of the development of PTSD in the context of uncertain threat. We used fMRI to examine the neural activation in response to both anticipation of and in response to threatening images (Grupe et al., 2016) in four conditions: 1) predictable threat, or certainty of knowing when a threatening image will appear, 2) unpredictable threat, or uncertainty of knowing when a threatening image will appear, 3) predictable safe, or certainty of knowing when a neutral image will appear, 4) unpredictable safe, or uncertainty of knowing when a neutral image will appear. Subjects were acute trauma survivors, ages 18-60, recruited from the Emergency Department at the Medical College of Wisconsin (MCW)/Froedtert hospital. The recent nature of the trauma (within 2 weeks) provided a unique opportunity to understand how exposure to trauma may rapidly affect the neural response to uncertain threat.

I addressed three primary research questions. The first research question addressed whether neural activation in anticipation of unpredictable threat differs from that in response to anticipation of predictable threat in acute trauma survivors. First, based on prior literature I predicted that subjects will demonstrate greater amygdala, BNST, and insula activation during

anticipation of threat compared to neutral images, as well as during uncertain vs. certain anticipation.

The second research question focused on differentiating the transient and sustained response to predictable and unpredictable threat. I predicted that the amygdala will preferentially respond to the threatening images, or transient threat, and that this will be even more pronounced for unpredictable vs. predictable negative images. I also predicted that the insula and BNST will show stronger sustained activation during unpredictable threat blocks compared to transient unpredictable threat.

The third research question aimed to better understand the relationship between acute trauma symptoms and the neural response to uncertain threat. This question is particularly relevant because understanding the severity of trauma and its relationship with response to uncertainty will lend itself to better predictability of pervasive trauma symptoms, such as PSTD. There is a paucity of data regarding acute trauma symptoms and response to uncertain threat. A small portion of PTSD literature, however, provides a basis for the following predictions of the relationship between trauma symptoms and response to uncertainty. I predicted that trauma symptom severity will be positively associated with activation of the amygdala, insula, BNST and vmPFC during the anticipation of uncertain compared to certain threat. This prediction is consistent with findings suggesting that the response to uncertain threat is also a function of trauma symptoms (Grupe et al., 2016). I also predicted that acute trauma symptoms will positively correlate with amygdala activation in response to uncertain blocks compared to certain blocks.

For an exploratory analysis, I also examined how individual differences in the intolerance of uncertainty are associated with the neural response to uncertain threat. Consistent with studies

from Somerville and colleagues (2010; 2013), I predicted that increased amygdala and insula activation during uncertain blocks will be positively correlated with IUS scores.

Method

Participants

One hundred twenty-nine traumatic injury survivors that were recruited from the Emergency Department and Trauma/Surgery Unit at the Medical College of Wisconsin (MCW)/Froedtert Hospital completed a portion of the uncertainty MRI task. Participants were between 18 and 60 years old, proficient in English, had normal hearing in both ears, normal or corrected-to-normal vision and were recently (within two weeks) exposed to a traumatic event as defined by the DSM-5 (American Psychiatric Association, 2013). Participants completed an MRI screening and provide written informed consent prior to starting the experiment. The final sample consisted of 54 participants (M_{age}=32.8, SD_{age}=9.83; Male=44.6%, Female=55.4%; Black/African American=51.8%; White=30.4%; Multiracial=8.9%; Asian=1.8%; Missing/Unknown=7.2%). Participants in the final sample experienced the following mechanisms of injury: motor vehicle crash=43 (79.6%); assault=4 (7.4%); other=4 (7.4%; chemical exposure, dog attack/bite, light bulb broke into face); pedestrian struck=1 (1.9%); crush injury=2 (3.7%), reported a range from 0 to 19 (M=4.3, SD=4.1) of alcohol use in the past year (AUDIT-10), and screened positive for the following drugs at scan day: marijuana=26 (48.1%); oxycodone=8 (14.8%); opiates=5 (9.3%); benzodiazepines=4 (7.4%); amphetamines=3 (5.6%) cocaine=1 (1.9%). Twenty-three subjects were excluded due to structural-EPI alignment issues, 24 due to excessive movement (29 subjects with >20% TRs censored), 17 due to incomplete uncertainty imaging data, 2 due to missing questionnaire data, and 9 due to processing errors.

Screening Procedures

Patients ages 18-60 (M_{age}=32.8) at Froedtert Hospital that presented with a trauma related injury or diagnosis were either approached in person or contacted by phone after discharge if they had a GCS > 13, and are not pregnant. Once the subject was deemed to meet these initial eligibility criteria, subjects approached in person who were willing to participate were provided written informed consent to complete a more in-depth screening. However, if the subject was called for recruitment, verbal consent was provided in order to complete the screening process. These subjects provided written informed consent to continue participation at their first session. The subjects then completed a Predicting PTSD Questionnaire (PPQ) to determine if they at high risk for developing PTSD (PPQ ≥ 3 or endorsed that the traumatic event was "clearly severe," "very severe," or "near death"), a study screen, and an MRI safety screen. Subjects were excluded from the study if they met the following screening criteria: Global Coma Scale (GCS) < 13, admitted due to self-inflicted injuries, evidence of moderate to severe cognitive impairment, loss of consciousness greater than 30 minutes, currently pregnant, clear presence of substance abuse (from chart review), prescribed antipsychotic, anticonvulsant, or mood stabilizer medications, history of psychotic or manic symptoms, unable to lie on back for at least 2 hours, presence of metal in body, contraindications for MRI scanning, history of heart surgery, spinal cord injury with neurological deficit, deafness or severe hearing loss, weight greater than 300 pounds or BMI greater than 40, unknown invasive injury, history of cancer, respiratory disease, blood disease, renal disease, breathing problems, motion disorder, seizures, claustrophobia, radiation, or chemotherapy.

Study Flow

This project is part of a larger study. Briefly, for the parent study within two weeks of the traumatic event, subjects came to Froedtert Hospital's Translational Research Unit and

completed a full study consent, self-report questionnaires, a series of tasks assessing attention, cognition, and memory, and a blood draw. Subjects then completed a resting state, structural, and functional brain imaging scans on a Tesla 3.0 (3T) magnetic resonance imaging (MRI) scanner. The functional scan of interest examined brain responsivity to predictable and unpredictable neutral and negative images.

Materials and Procedure

NPU Image Task. Subjects completed four runs of the temporal uncertainty image task, in which they viewed negative and neutral images presented either in a temporally predictable or unpredictable manner. The task included two blocks of each of the four conditions, Predictable Neutral; Predictable Negative; Unpredictable Neutral; and Unpredictable Negative, for a total of eight blocks. The eight blocks were collected across four separate scan runs. Each run contained two different condition blocks. In each block, subjects saw a three second start cue providing a description of the block condition (predictable neutral, predictable negative, unpredictable neutral, unpredictable negative). Each block contained 13 picture trials, with pictures displayed for three seconds. Prior to each picture was an anticipation period in which a "ticking" clock was displayed for one to eight seconds (Figure 1). In the predictable blocks, the clock countdown accurately predicted the onset of the negative or neutral image. In the unpredictable blocks, the movement of the hand was not related to the onset of the picture. After 13 trials, a three second stop cue was presented at the end of the block signaling that it was finished. There were eight blocks, 2 of each condition, that lasted for approximately 91 seconds each. These blocks were presented pseudorandomly, such that there was never two blocks of the same condition within one run. In each trial, subjects determined if the presented neutral or negative image was either indoors or outdoors with a button press. This aspect of the task was to keep the subjects focused

on the images. Consistent with Sommerville and colleagues (2010), all trails were included in fMRI analysis because accuracy was acceptable ($M_{accuracy}$=72.6%).

Participants viewed 52 negatively-valenced, high-arousal images and 52 neutral, low-arousal images, for a total of 104 images (26 per condition). Half of the images were from the International Affective Picture Set (Lang & Bradley, 2007) and half from the Nencki Affective Picture System (Marchewka, Żurawski, Jednoróg, & Grabowska, 2014). Half of the images took place indoors and half outdoors. Images were matched for number of images displaying people and images showing visible faces. The neutral images from the two picture sets were matched for valence (NAPS: *M*=5.4, *SD*=.57; IAPS: *M*=5.42, *SD*=.47) and arousal (NAPS: *M*=4.81, *SD*=.47; IAPS: *M*=3.51, *SD*=.56). The negative images were also matched for valence (NAPS: *M*=2.09, *SD*=.35; IAPS: *M*=2.04, *SD*=.38) and arousal (NAPS: *M*=7.28, *SD*=.41; IAPS: *M*=6.33, *SD*=.64).

Stimuli were presented using E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA) interfaced with an MRI compatible response box to record key presses when subjects determined if the image took place indoors or outdoors and during the subject rating portion after each block. Stimuli were visually presented during scanning onto a back-projection screen at one end of the scanner bore with a BrainLogic MR Digital Projection System. Blocking the conditions allowed us to examine the sustained activation of particular brain regions, whereas the clock countdown and image presentations allowed us to examine the transient neural responsivity during anticipation and in response to the picture.

Subjective Ratings of Anxiety. At the end of each block of trials, participants completed a brief subjective rating to assess their level of anxiety associated with the block. They were asked to rate their anxiety on a scale from 1 “not at all anxious” to 9 “very anxious”: “How anxious did you feel during the (first, second) set of trials in the previous run, which had

(predictable, unpredictable) timings and (negative, neutral) images?" These subjective ratings were used as a manipulation check to determine if the anticipation and exposure to negative images elicited more anxiety than that of the neutral images. These ratings were be used to examine differences in subjective anxiety between predictable and unpredictable blocks of trials.

Self-report Assessment of Symptoms. The PTSD Checklist (PCL-5) was used to measure participants' PTSD symptoms (Weathers et al., 2013). It contains 20 items rated using a 5-point Likert scale (e.g., 0=not at all, 4=extremely). The main measure of PTSD severity is the total PCL-5 score, calculated as the sum of four factors directly related to PTSD diagnostic symptom categories: reexperiencing, avoidance, negative alterations in cognition and mood, and hyperarousal. The PCL-5 has good test-retest reliability (r = 0.82-0.84), good internal consistency (α = 0.94-0.96), and good convergent and discriminant validity in samples of trauma-exposed college students and Veterans (Blevins, Weathers, Davis, Witte, & Domino, 2015; Bovin et al., 2016). The final sample's (N=54) total scores ranged from 1 to 73 (M=27.5, SD=17.7).

The Intolerance of Uncertainty Scale (IUS) was used to measure participants' level of intolerance of uncertain threats, situations, and outcomes (Buhr & Dugas, 2002; Freeston, Rhéaume, Letarte, Dugas, & Ladouceur, 1994). The IUS has good test-retest reliability at a five-week interval (r = 0.74), excellent internal consistency (α = 0.94), and good internal and external validity with measures of anxiety, depression, and worry (Buhr & Dugas, 2002). The final sample's (N=54) total scores ranged from 13 to 51 (M=32.2, SD=8.5).

MRI Acquisition. Imaging was performed on a General Electric Discovery MR750 3.0 Tesla scanner with a 32-channel head-coil (Waukesha, WI). A T1-weighted high-resolution anatomical scan was acquired for coregistration with the functional data and used the following

parameters: FOV = 240mm; matrix = 256x224; slice thickness = 1mm; 150 slices; TR/TE = 8.2/3.2; flip angle = 12º, voxel size = 0.9375x1.071x1. Functional T_2*-weighted echoplanar images (EPI) were acquired with the following parameters: FOV = 22.4mm; matrix = 64x64; slice thickness = 3.5mm; 41 sagittal slices; repetition time (TR)/echo time (TE) = 2000/25ms; flip angle = 77º. There were a total of four runs and each run was approximately 246 seconds (123 images). Transformation matrices were concatenated and applied to the EPI data.

fMRI Preprocessing and Analysis. Task-based fMRI data was analyzed using Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). Volumes with excessive motion were censored (Euclidian norm > .3). EPI data was slice-time corrected to adjust for non-simultaneous slice acquisition with each volume. Head movements were corrected using a six-parameter (rigid body) linear transformation followed by a nonlinear transformation, with the third volume as reference. Images were spatially smoothed (full-width-half-maximum [FWHM] = 4mm) to limit effects of anatomical variability. Images were transformed to Montreal Neurological Institute space (MNI 152; McGill University, Montreal, Quebec). EPI data was converted to percent signal change. Artifact covariates, such as head motion parameters (L/R, A/P, S/I, roll, pitch, yaw, and first derivatives), and outliers (censor TRs with >10% outliers) were regressed out to reduce signal-to-noise ratio. Due to the severity of injuries in this clinical population, movement was atypical. Therefore, individual subject data was removed from analysis if more than 20% of TRs are censored (29 subjects, 22.5% subjects).

To model the anticipation period, BOLD signal during the anticipation period prior to image onset was modeled for each condition using AFNI's duration modulation mini-block basis function, as the duration of the anticipation period was variable (1-8s). To model transient response to the images, BOLD signal at the onset of image presentation was modeled using

GLM and a 14-second tent function with seven tents in AFNI. Peak image activation was estimated by averaging across tents 3-5. Lastly, for sustained responses to uncertain and certain threat, a block function was used to model each 118 s block, measured from start cue offset to stop cue onset. For all deconvolution models, nuisance regressors were added to control for low-frequency drift (linear, quadratic and cubic) and motion (L/R, A/P, S/I, roll, pitch, yaw, and their derivatives). For the group level analysis the voxel-wise statistical threshold will be set at $p<.005$ and corrected for multiple comparisons across the whole brain at $p<.05$ using Monte Carlo simulations.

Group-level Analysis. To investigate neural activation during unpredictable vs. predictable threat anticipation periods and how it varies as a function of individual PTSD symptoms, I ran a voxel-wise linear mixed-effects model using AFNI's 3dLME (Chen, Saad, Britton, Pine, & Cox, 2013) with Valence (negative vs. neutral) and Predictability (predictable vs. unpredictable) as within-subjects factors, age, sex, urine drug screen (positive for any substance), as between-subjects factors, and PCL-5 scores as a within-subjects quantitative variable. For the first research question, I predicted greater activation in the amygdala, BNST, and insula during anticipation of unpredictable negative images. This would be reflected by an interaction of Valence and Predictability. For research question three, I predicted increased trauma symptom severity will be associated with greater activation in the amygdala, BNST, insula, and vmPFC during uncertain threat anticipation. A Valence × Predictability × PCL-5 interaction would support this prediction.

For my second research questions, I predicted greater transient amygdala activation to unpredictable negative images, and stronger BNST and sustained insula activation during unpredictable negative blocks. To test this, I calculated a separate linear mixed-effects model

with Valence, Predictability, and Duration (event vs. block) as within-subjects factors, age, sex, and urine drug screen as between-subjects factors, and PCL-5 and IUS scores as within-subjects quantitative variables. Support for my hypotheses would be provided by an interaction of Valence, Predictability, and Duration in the stated regions. For research question three, I also predicted that acute trauma symptoms will positively correlate with amygdala activation and negatively correlate with vmPFC activation during uncertain blocks relative to certain blocks. This would be reflected by an interaction of Predictability, Duration, and PCL-5. For an exploratory analysis, I predicted greater amygdala and insula activation during uncertain blocks will be positively correlated with IUS scores. This would be investigated with an interaction of Predictability, Duration, and IUS. All results, including main effects, interactions, and follow-up testing account for the between subjects factors included in each model: age, sex, and urine drug screen.

Results

Subjective Anxiety Manipulation Check

A within-subjects ANOVA was conducted to examine to determine if the negative images did indeed influence self-reported anxiety. Results revealed a main effect of Valence, $F(1, 55) = 52.91$, $p < .0001$, a nearly-significant main effect of Predictability, $F(1, 55) = 3.98$, $p = .051$, but no significant interaction, $F(1, 55) = 0.312$, $p > .57$. Pairwise comparisons (Bonferroni-corrected) indicated that anxiety reported during the negative blocks was higher than in neutral blocks, $p = .052$, and anxiety reported during unpredictable blocks was significantly higher than in predictable blocks (Figure 2).

Uncertainty Task Behavioral Manipulation Check

A within-subjects ANOVA was conducted to determine if subjects remained on-task during picture presentation across all conditions. Results revealed no main effects of Valence, $F(1, 55) = 0.005$, $p > .94$, and Predictability, $F(1, 55) = 1.217$, $p > .27$, and no significant interaction, $F(1, 55) = 0.196$, $p > .65$. Accuracy across conditions was above 70% (Figure 2).

Neural Activation During Unpredictable vs. Predictable Image Anticipation and PTSD Symptoms

A whole-brain voxel-wise linear mixed-effects model using AFNI's 3dLME was conducted with Valence (negative vs. neutral) and Predictability (predictable vs. unpredictable) as within-subjects factors, age, sex, and positive urine drug screen as between-subjects factors, and PCL-5 scores as a within-subjects quantitative variable. To estimate the probability of false positive voxel clusters, I used AFNI's 3dClustSim to determine the appropriate cluster-size given 3rd-nearest voxel neighbors (NN=3; face, edge, corner). Bi-sided thresholds of $\alpha = .05$ and $p < .005$ yielded a significant cluster size of 46.2. The interaction between Valence and Predictability was examined to address my first prediction: greater activation in the amygdala, BNST, and insula during anticipation of unpredictable negative images. The Valance × Predictability interaction did not yield any significant clusters, $p > .005$. To further explore results directly related to this prediction, follow-up comparisons using more liberal parameters were examined.

General linear tests examining neural response to unpredictable negative anticipation vs. predictable negative anticipation and unpredictable negative anticipation vs. unpredictable neutral anticipation both yielded no significant clusters, $p > .005$. However, there was increased activation when anticipating neutral relative to negative images (collapsed across Predictability) in the middle occipital gyrus (Figure 3). There was also increased activation when anticipating unpredictable relative to predictable (collapsed across Valence) images in the cuneus, but more

activation when anticipating predictable relative to unpredictable images in the superior parietal lobule (Figure 3; Table 1).

A Valence × Predictability × PCL-5 interaction was then tested to understand how response to the anticipation of unpredictable images varies as a function of Valence and acute trauma symptoms. The Valence × Predictability × PCL-5 interaction did not yield any significant clusters, p >.005. However, in order to understand the pattern of effects in this novel population, follow-up comparisons were used to explore research questions regarding activation during image anticipation. First, the Valence × PCL-5 and Predictability × PCL-5 interactions were examined. There were no significant clusters when comparing the anticipation of negative and neutral images as a function of acute trauma symptoms, but there were many significant clusters associated with decreased acute trauma symptoms in parietal and posterior regions to unpredictable relative to predictable image anticipation, $p < .005$ (Table 2). To directly address research question three, in which I predicted that increased trauma symptom severity will be associated with greater activation in the amygdala, BNST, insula, and vmPFC during uncertain threat anticipation, a general linear test compared unpredictable negative and predictable negative anticipation as a function of PTSD symptoms. Results did not reveal effects for the hypothesized regions, but revealed significant clusters in several regions in the frontal, parietal, and occipital areas of the brain, $p < .005$ (Figure 4; Table 2). Increased activation while anticipating unpredictable negative images relative to predictable negative images was associated with decreased PCL-5 scores in precuneus/superior parietal lobule, middle frontal gyrus, superior frontal gyrus, middle occipital gyrus, and lingual gyrus. However, there were no significant clusters when comparing anticipation of unpredictable negative images to unpredictable neutral and predictable neutral images as a function of PTSD symptoms, $p > .005$.

Transient and Sustained Neural Activation to Unpredictable and Predictable Images Associated with PTSD Symptoms

A whole-brain voxel-wise linear mixed-effects model using AFNI's 3dLME was conducted with Valence, Predictability, and Duration (transient vs. sustained) as within-subjects factors, age, sex, and positive urine drug screen as between-subjects factors, and PCL-5 scores as a within-subjects quantitative variable. To estimate the probability of false positive voxel clusters, I used AFNI's 3dClustSim to determine the appropriate cluster size given 3rd-nearest voxel neighbors (NN=3; face, edge, corner). Bi-sided thresholds of $\alpha = .05$ and $p < .005$ yielded a significant cluster size of 46.8 voxels. All main effects and follow-up analyses used a voxel cluster size threshold of 20 to improve detectability in this initial preliminary investigation.

A Valence × Predictability × Duration interaction was first tested to understand how neural response to unpredictable images varies as a function of Valence and Duration. The interaction did not yield significant clusters, $p > .005$. However, when the main effects of each factor were explored results revealed significant main effects of Valence and Predictability. The main effect for Predictability yielded findings of more activation to unpredictable relative to predictable images in the inferior frontal gyrus and superior medial gyrus. In contrast, there was more activation to predictable relative to unpredictable images in parietal and frontal regions, such as the inferior parietal lobule and superior frontal gyrus (Table 3). There was also a significant main effect of Duration, with sustained activation throughout blocks in middle occipital gyrus, inferior parietal lobule, and middle frontal gyrus, whereas greater response to transient stimuli (event images) was observed in precuneus, cuneus, and posterior cingulate (Table 3).

A general linear test comparing transient and sustained activation to unpredictable negative images was conducted to test the second research question. I predicted greater transient amygdala activation to unpredictable negative images, and greater sustained BNST and insula activation during unpredictable negative blocks. Results did not support this prediction, but revealed more sustained activation in unpredictable negative blocks in the lingual gyrus, and more transient response to unpredictable negative images in the superior occipital gyrus, $p < .005$ (Figure 5; Table 3).

A Valence × Predictability × Duration × PCL-5 interaction was also tested to better understand how transient and sustained neural response to predictability is related to acute trauma symptoms. The interaction did not yield significant clusters, $p > .005$. However, there were significant interactions between Valence and PCL-5, and Predictability and PCL-5, $p < .005$. Results revealed that increased activation to negative relative to neutral images was associated with decreased acute stress symptoms in mostly frontal and parietal regions (inferior frontal gyrus, somatosensory motor area (SMA), inferior parietal lobule) as well as the cerebellum, and was associated with increased acute stress symptoms in the middle frontal gyrus (Table 4). Results from the Predictability × PCL-5 interaction showed that more activation for unpredictable relative to predictable images was associated with increased acute trauma symptoms in the insula, superior temporal gyrus, cerebellum, and anterior cingulate, and was associated with decreased acute stress symptoms in the middle frontal gyrus (Table 4).

A general linear test comparing sustained activation to unpredictable and predictable images and its relationship with acute trauma symptoms was run to test research question three. I predicted increased acute trauma symptoms will be associated with sustained activation in the amygdala during unpredictable blocks relative to predictable blocks, and decreased trauma

symptoms will be associated with sustained vmPFC activation during unpredictable compared to predictable blocks. Results did not show effects in the predicted regions, but revealed that sustained activation in the insula during unpredictable versus predictable blocks was associated with increased acute trauma symptoms, whereas sustained activation in the superior frontal gyrus was correlated with decreased trauma symptoms, $p < .005$ (Figure 6; Table 4).

Sustained Activation to Unpredictable and Predictable Images Associated with Intolerance of Uncertainty (IUS)

A whole-brain voxel-wise linear mixed-effects model using AFNI's 3dLME was conducted with Valence, Predictability, and Duration as within-subjects factors, age, sex, and positive urine drug screen as between-subjects factors, and IUS scores as a within-subjects quantitative variable. To estimate the probability of false positive voxel clusters, I used AFNI's 3dClustSim to determine the appropriate cluster size given 3rd-nearest voxel neighbors (NN=3; face, edge, corner). Bi-sided thresholds of $\alpha = .05$ and $p < .005$ yielded a significant cluster size of 46.8 voxels. Follow-up analyses used a voxel significance threshold of 20 to improve detectability. An exploratory Predictability × Duration × IUS interaction was tested to examine the effects of intolerance of uncertainty on activation in unpredictable and predictable conditions. The interaction did not yield significant clusters, $p > .005$. A general linear test comparing sustained activation in unpredictable vs. predictable blocks and its relationship with intolerance of uncertainty was run as part of an exploratory analysis. Results revealed that sustained activation in unpredictable relative to predictable blocks was associated with increased intolerance of uncertainty in many areas of the brain, with the largest clusters in the inferior frontal gyrus/insula, middle frontal gyrus, superior frontal gyrus, and rolandic operculum, $p < .005$ (Figure 7; Table 5).

Discussion

The findings from this study contribute to the limited research of response to uncertain threat in trauma-exposed populations (Aupperle et al., 2012; Brinkmann et al., 2018; Dretsch et al., 2016; Grupe & Nitschke, 2013; Grupe et al., 2016; Simmons et al., 2008; Simmons et al., 2013). Moreover, this is the first study to our knowledge that characterized the neural response to uncertainty in acute trauma survivors, an especially vulnerable population. Results from the clock countdown period showed that anticipating unpredictable relative to predictable negative images was not associated with differential activation in any brain regions. However, while anticipating unpredictable relative to predictable images regardless of valence, increased activation in superior parietal, middle frontal, and inferior posterior visual processing regions of the cortex was associated with decreased acute trauma symptoms. This finding was primarily driven by the response to anticipating unpredictable *negative* (compared to neutral) images, suggesting this network of frontoparietal regions may be associated with an adaptive mechanism for responding to unpredictable threat.

I also investigated differential neural activity to transient stimuli (images) compared to sustained response to unpredictable and predictable affective stimuli. Initial findings indicated a more transient response to unpredictable negative images in the lingual gyrus and a more sustained response to this condition in the superior occipital gyrus. Consistent with our anticipation findings, this relationship changed as a function of acute trauma symptoms. Increased PTSD symptoms was associated with more sustained activation during unpredictable compared to predictable blocks in the insula. By contrast those with more severe PTSD symptoms had greater response to transient (images) compared to sustained (blocks) unpredictable (vs. predictable) conditions in the superior frontal gyrus. These findings extend

previous work highlighting the insula's role in sustained responsivity to unpredictability in anxiety disorders and PTSD to symptomatology in acute trauma survivors (Aupperle et al., 2012; Dretch et al., 2016; Grupe & Nitschke, 2013; Shankman et al., 2014; Simmons et al., 2008; Simmons et al., 2013; Sommerville et al., 2012; Williams et al., 2015).

Finally, an exploratory analysis examining sustained activation to unpredictability and the intolerance of uncertainty found that widespread sustained activation of predominantly frontocentral and frontoparietal regions in unpredictable relative to predictable blocks was associated with increased intolerance of uncertainty. These findings emphasize the importance of understanding how trauma may influence the perception of uncertainty as aversive and threatening.

Anticipation Findings

The uncertainty task used in this study was modeled after a task created by Sommerville and colleagues (2012), which allows for modeling activation that occurs when anticipating predictable or unpredictable valenced stimuli. The first prediction for the anticipation period was that there would be greater activation in the amygdala, BNST, and insula during anticipation of unpredictable negative images. These regions have been strongly implicated in the processing of uncertain threat, including in trauma-exposed populations (Aupperle et al., 2012; Brinkmann et al., 2017; Dretsch et al., 2016; Grupe & Nitschke, 2013; Grupe et al., 2016; Simmons et al., 2008; Simmons et al., 2013). Surprisingly, the results from the anticipation period did not yield significant activation in any brain regions, including the hypothesized regions, when anticipating unpredictable relative to predictable negative images.

For the second prediction for the anticipation period, we expected increased acute trauma symptoms would be associated with greater activation in the amygdala, BNST, insula, and

vmPFC during uncertain threat anticipation. While we did not find support for any of these predicted effects, we did find that increased activation in frontoparietal and occipital regions during unpredictable relative to predictable image anticipation was associated with decreased acute trauma symptoms. A follow-up test examining unpredictable relative to predictable *negative* image anticipation yielded similar findings, suggesting this effect was primarily driven by the response to anticipating *negative* unpredictable images.

This finding suggests two possible explanations. First, this network of frontoparietal and occipital regions may be associated with an adaptive mechanism for responding to unpredictable threat. Second, it could also mean dysfunction in this circuitry with more resources preparing for predictable or looming threat in more symptomatic acute trauma survivors (Aupperle et al., 2012). Interestingly, Simmons and colleagues (2013) observed similar findings in these broad frontoparietal and occipital regions as well. They found that those with PTSD compared to combat-exposed controls exhibited greater activation when anticipating predictable relative to unpredictable negative images in the medial frontal gyrus, cuneus, and inferior frontal gyrus. Their findings support the idea that highly symptomatic trauma survivors have an attentional or cognitive bias to looming threat. Indeed, selective attention to threat via impairments in response inhibition and attention regulation has been found in individuals high on anxiety and posttraumatic stress symptoms, and these deficits are associated with activation in frontoparietal and occipital regions, such as the inferior frontal gyrus, medial frontal gyrus, cuneus, and lingual gyrus (Aupperle et al., 2012; Banich et al., 2009; Bishop, 2008; Blair et al., 2013; Fani et al., 2012; Simmons et al., 2013; White et al., 2015). Thus, together with previous work, our findings suggest that those experiencing posttraumatic stress symptoms do not effectively recruit neural

circuitry supporting attentional and cognitive control processes. This renders them particularly vulnerable to heightened anxiety in situations where an predictable threat is looming.

Response to Transient vs. Sustained Unpredictability and Valence

In addition to modeling the anticipation period, the uncertainty task also allows for modeling the differentiation between transient and sustained neural responsivity in unpredictable and predictable conditions. Consistent with prior work examining transient vs. sustained responses to uncertain threat (Brinkmann et al., 2018; Herman et al., 2007; Herry et al., 2007), I predicted greater transient amygdala activation to unpredictable negative images and greater sustained BNST and insula activation during unpredictable negative blocks. Our findings were not consistent with these predictions. We found more sustained superior occipital gyrus activation during unpredictable negative blocks relative to unpredictable negative images. In contrast, we there was more transient activation in the lingual gyrus to unpredictable negative images relative to unpredictable negative blocks. Because these regions are central to visuospatial processing and memory (Bremner et al., 1999; Fani et al., 2012), these findings indicate that in the context of unpredictable threat, acute trauma survivors may remain highly visually attuned to their environment and exhibit a heightened response to an unexpected negative stimulus. We also found main effects of Valence, Predictability, and Duration throughout many of the same frontoparietal, temporal, and occipital regions mentioned thus far.

The second prediction for these data posited that more sustained amygdala activation during unpredictable relative to predictable blocks would be associated with increased trauma symptoms, whereas more sustained vmPFC activation during this contrast would be associated with decreased trauma symptoms (Grupe et al., 2016). Although there were no significant effects in the proposed regions, we did find that sustained insula activation during unpredictable relative

to predictable blocks was associated with increased PTSD symptoms. This sustained activation of the insula in response unpredictable threat is consistent with uncertainty literature that focuses on differentiating the transient and sustained effects of common anxiety-related networks, which typically find sustained insula and BNST activation to uncertainty (Alvarez et al., 2015; Hermann et al., 2016; Somerville et al., 2010; Somerville et al., 2012). Shankman and colleagues (2014) suggested that the insula may be primarily involved in "anxious risk assessment" in contexts of uncertainty. Considering the insula is strongly associated with autonomic and interoceptive sensitivity, emotional experience, and uncertainty evaluation, it's role in risk assessment may be especially relevant in the immediate aftermath of a traumatic event (Craig, 2003; Critchley et al., 2005; Paulus & Stein, 2006; Platt & Huettel, 2008; Simmons et al., 2008; Wicker et al., 2003). For example, insula activation to threat has been linked with perceived threat of the trauma in two samples of combat-exposed soldiers (Van Wingen, Geuze, Vermetten, & Fernández et al., 2011). Thus, there is mounting evidence that the insula is a central region involved in response to sustained uncertainty, and that heightened activation of this region is associated with response to unpredictable threat in those with posttraumatic stress symptoms.

We also found sustained superior frontal gyrus activation during unpredictable relative to predictable blocks was associated with decreased PTSD symptoms. The superior frontal gyrus lies within the dlPFC, which is often associated with attentional control and down-regulation of fear responsivity (Crespo-Facorro et al., 2000; Miller & Cohen, 2001; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner & Gross, 2005). However, these processes can be disrupted in anxious populations, in the context of uncertainty, and in PTSD patients (Aupperle et al., 2012; Brinkmann et al., 2018; Ochsner & Gross, 2005; Gold, Morey, & McCarthy, 2015). Our results

suggest that in acute trauma survivors, sustained online recruitment of the dlPFC in the face of uncertain threat may represent the upregulation of an adaptive emotion regulation process, perhaps to compensate for heightened response to unpredictable threat. However, it is unclear if this process reduced in the moment feelings of anxiety, or if being less negatively impacted by the trauma allows for the dlPFC to more efficiently down-regulate the fear system facing uncertain threat.

Uncertainty, regardless of valence and duration, appears to be a significant predictor of posttraumatic stress symptoms in our acute trauma population. In particular, we found increased activation in the insula (consistent with block results), superior temporal gyrus, cerebellum, and anterior cingulate (ACC) in unpredictable relative to predictable conditions was associated with increased acute trauma symptoms. Our pattern of findings is broadly consistent with prior literature. Many studies have found recruitment of the ACC when subjects were in conditions of uncertainty, and suggest it is important for decision making in these contexts (Hermann et al., 2016; Krain et al., 2006; Krain et al., 2008; Nitschke et al., 2006; Sarinopoulos et al., 2010). Consistent with our findings, Brinkmann and colleagues found increased sustained cerebellum activation to uncertain threat in PTSD relative to controls. However, in contrast to our findings, the superior temporal gyrus has been shown to be activated during temporal unpredictability in combat exposed controls rather than PTSD subjects (Simmons et al., 2013). Our findings indicate that the pattern of findings regarding response to uncertainty observed in those with chronic PTSD, other anxiety, and even healthy controls is evident in, and potentiated, in those with more severe PTSD in the acute post-trauma period. Overall, examining this network of brain regions in acute trauma populations may be useful for understanding how response to

uncertainty varies as a function of the severity of trauma symptoms, and may indicate who is at risk for chronic PTSD.

Individual Differences in Intolerance of Uncertainty Associated with Sustained Activation to Unpredictable Threat

Finally, in an effort to understand how individual differences in intolerance of uncertainty may affect response to uncertain threat in acute trauma survivors, we completed an exploratory analysis predicting greater sustained amygdala and insula activation during unpredictable vs. predictable blocks would be associated with increased IUS symptoms. Both regions have strong support for their role in processing uncertain threat, but there are no studies to our knowledge that have examined how their role in acute trauma survivors varies as a function of intolerance of uncertainty. Consistent with our prediction and previous findings of affective ambiguity, we found that sustained insula activation in unpredictable vs. predictable blocks was associated with increased IUS (Simmons et al., 2008). Interestingly, we also found similar widespread effects in many frontocentral and frontoparietal regions such as the superior frontal gyrus, middle frontal gyrus, middle temporal gyrus, and superior parietal lobule, which have also been associated with IUS in several studies with anxious, non-anxious, and OCD samples (Krain et al., 2008; Rotge et al., 2015; Simmons et al., 2008). Together, these findings may indicate that when individuals who are especially intolerant of uncertainty are confronted with uncertain contexts immediately following a trauma, widespread activation in the brain may reflect hypervigilance and risk assessment.

Limitations and Future Directions

While our *a priori* predictions were grounded in extant literature, we did not find support for many of our predictions, especially those involving the amygdala, BNST, and vmPFC.

Several limitations may have impacted the inconsistency between our *a priori* predictions and our results. First, using a whole-brain voxel-wise analysis may have limited our ability to find hypothesis-driven results in anatomically small structures such as the BNST or amygdala. The resulting cluster size needed to meet statistical threshold may be too large to find significant effects in these regions. Upon completion of the final sample we will either use small volume correction, in which correction for multiple comparisons is based on the number of voxels in that region rather than in the whole brain, or conduct our analyses of those regions based on anatomically-defined regions of interest (ROI). A combination of these approaches was utilized by Somerville and colleagues (2013) by using a whole-brain statistical analysis and constraining offline analysis to a priori affective ROIs, such as the amygdala, BNST, insula, and midbrain/periaqueductal grey. Despite this limitation, the main goal of this study was to fully characterize the neural responsivity of acute trauma survivors in response to uncertain threat, and ignoring regions not specified a priori may not capture the full breadth of effects. Moreover, the field has largely focused on mPFC and subcortical structures (amygdala, BNST, etc.) when examining neural response to uncertainty, as well as in investigations of PTSD (Alvarez et al., 2015; Grupe & Nitschke, 2013; Hermann et al., 2016; Herry et al., 2007; Rauch et al., 2003; Sarinopoulos et al., 2009; Shankman et al., 2014; Sommerville et al., 2010; Sommerville et al., 2012; Walker et al., 2009; Williams et al., 2015). This lack of attention to other regions outside this network that be detrimental for fully understanding how trauma may impact the processing of uncertain threat (Aupperle et al., 2012; Brinkmann et al., 2018; Dretsch et al., 2016; Grupe & Nitschke, 2013; Grupe et al., 2016; Simmons et al., 2008; Simmons et al., 2013). Indeed, our findings indicate that the field would be well-served by considering the role of structures and circuits beyond mPFC and subcortical regions.

Second, this acute trauma sample exhibited excessive movement throughout the task, which significantly reduced the final sample for analyses (N=54). After removing subjects for incomplete data and other processing errors, 25 subjects (24.3% of subjects) were removed from analyses due to excessive movement (>20% TRs censored; average TRs censored = 68.9, 14.4%). Moreover, movement may have contributed to structural-EPI alignment issues that also reduced the final sample by 25 subjects (17.8% of subjects). This movement and overall reduction of sample size may have reduced our ability to detect significant effects in the a priori regions of interest. However, our final sample size of 54 was comparable to the sample size of Sommerville's (2013) study (N=55), which our task was modeled after, suggesting the size of our sample was appropriate for this initial investigation. Additionally, after removal of subjects for all criteria the final sample's movement was minimal (average TRs censored = 38.4, 8.0%), reducing the impact on task-related activation. These movement-related difficulties will be taking into consideration when running the final analyses for our complete baseline dataset. Specifically, AFNI's newly updated @SSwarper will be used in the afni_proc.py processing pipeline for each subject to more accurately skull strip and warp the anatomical dataset for better structural-EPI alignment.

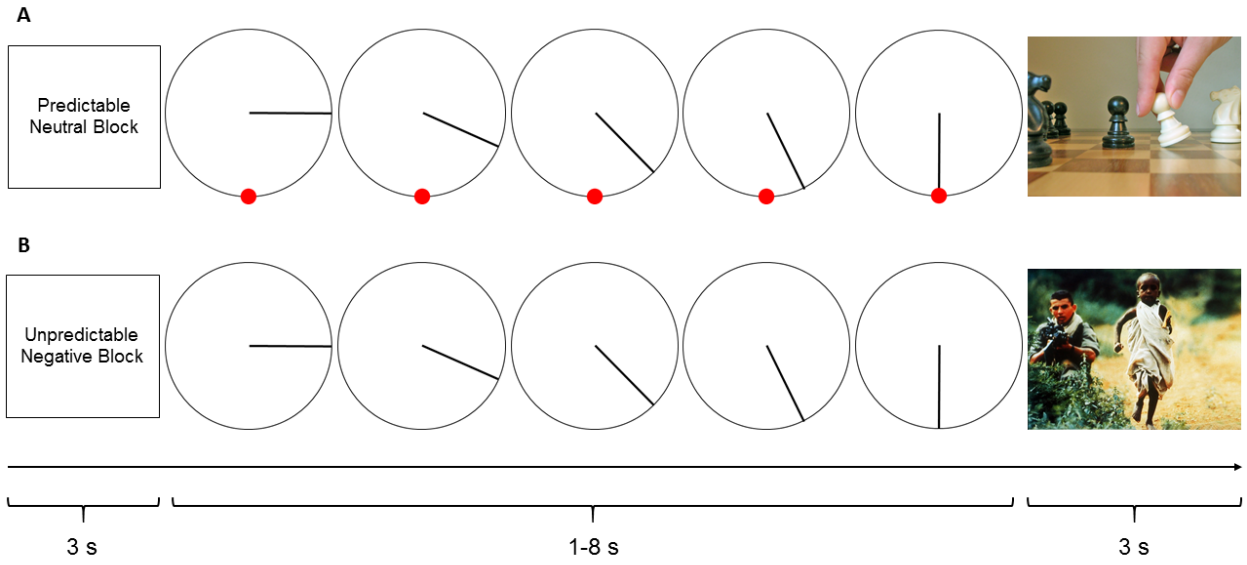
Conclusion

This is the first study to our knowledge that characterized the neural response to uncertainty in acute trauma survivors. To fully capture how acute trauma is associated with uncertainty, this study utilized a temporal uncertainty task which modeled the anticipatory, transient, and sustained response to uncertainty. The uncertain anticipation findings suggest that a network of frontoparietal and occipital regions that are typically associated with selective attention to threat may be dysfunctional in highly symptomatic acute trauma survivors. In terms

of transient and sustained responses to uncertainty, our results underscore the insula as a region primarily associated with sustained uncertain threat and highlight its role in anxious risk assessment in acute trauma survivors. Our findings also suggest that sustained dlPFC activation in response to uncertain threat may be associated with an adaptive process for down-regulating fear circuitry in acute trauma survivors. Finally, the results from our exploratory analysis indicated that encountering uncertain threat shortly after a trauma can ramp up hypervigilance and risk assessment processes in individuals that are especially wary of uncertainty.

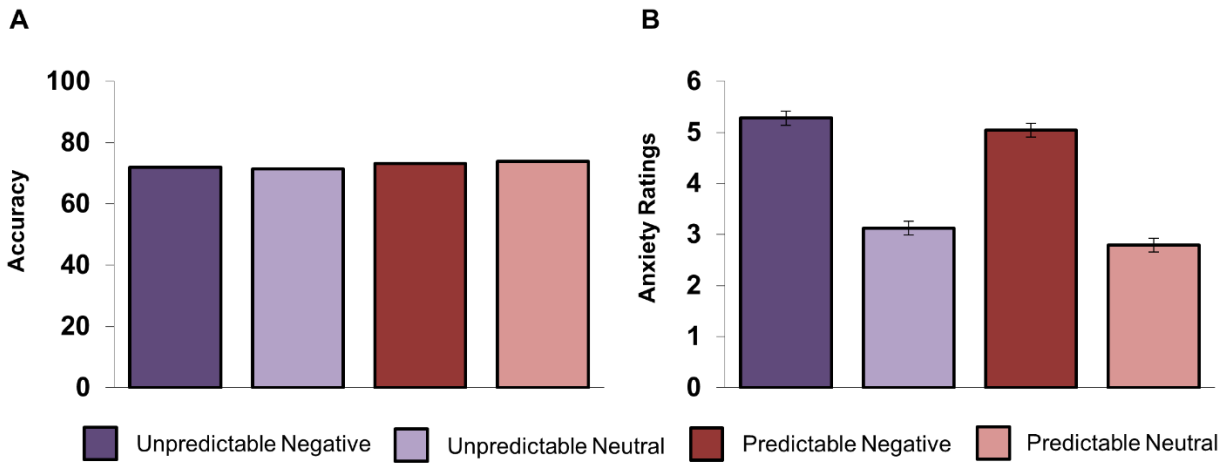
Overall, the findings from this study provide more information about the functional characteristics and neural underpinnings of uncertain threat in trauma exposed populations. These findings also provide novel insight into how uncertain threat is processed prior to the development of PTSD in acute trauma survivors. The acute window of time immediately following a trauma is an especially vulnerable period and, unfortunately, very little is known about the neural functioning during this time. Importantly, our findings shed light on the neural mechanisms during this acute period, which may help inform our understanding of the prediction and trajectories of risk and resilience following a trauma.

Figure 1. Example of Uncertainty Clock Task Trial



An example of a trial of the uncertainty task in which a predictable or unpredictable "clock" counts down to a neutral or negative image presentation. There are four conditions: unpredictable negative, unpredictable neutral, predictable negative, predictable neutral. Each block begins with a 3 s cue. Each trial consists of a 1-8 s countdown that precedes a 3 s image. **A.)** An example of a predictable neutral trial that has a predictable 5 s countdown, as depicted by the red dot. **B.)** An example of an unpredictable negative trial that has an unpredictable 5 s countdown, as depicted by no red dot.

Figure 2. Uncertainty Task Behavioral Performance and Anxiety Ratings



Uncertainty task manipulation check results. There are four conditions: unpredictable negative, unpredictable neutral, predictable negative, predictable neutral. **A.)** No main effect of Valence or Predictability on indoor-outdoor picture identification accuracy, *p*s > .25. Performance was above 70% in all conditions, suggesting on-task performance. **B.)** Main effect of Valence such that negative blocks produced more subject anxiety than neutral blocks, $p < .0001$. Near-significant main effect of Predictability, such that unpredictable blocks elicited more subjective anxiety than predictable blocks, $p = .052$.

Figure 3. Significant Activation During Anticipation of Negative vs. Neutral Images and Unpredictable vs. Predictable Images

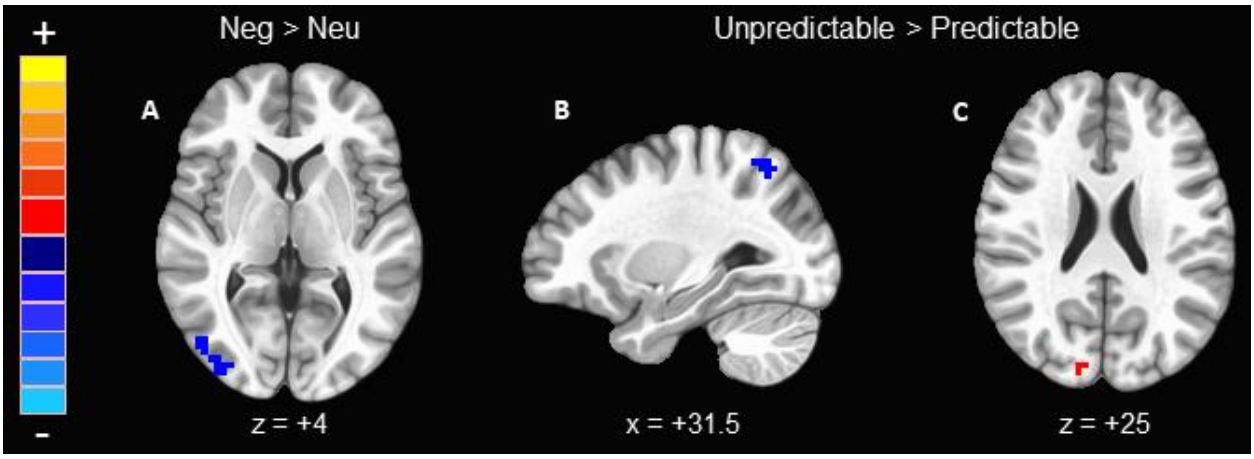


Image anticipation fMRI activation maps, MNI space. Neg, negative; Neu, neutral. From left to right: A. Greater activation to neutral relative to negative valence images in Middle Occipital Gyrus (z = -3.44). B. Greater activation to predictable relative to unpredictable images in Superior Parietal Lobule (z = -3.63), and C. Greater activation to unpredictable relative to predictable images in Cuneus (z = 3.24). Clusters of >20 voxels at α = .05, p < .005, uncorrected.

Figure 4. Significant Activation During Anticipation of Unpredictable vs. Predictable Negative Images Associated with Decreased PCL-5 Scores

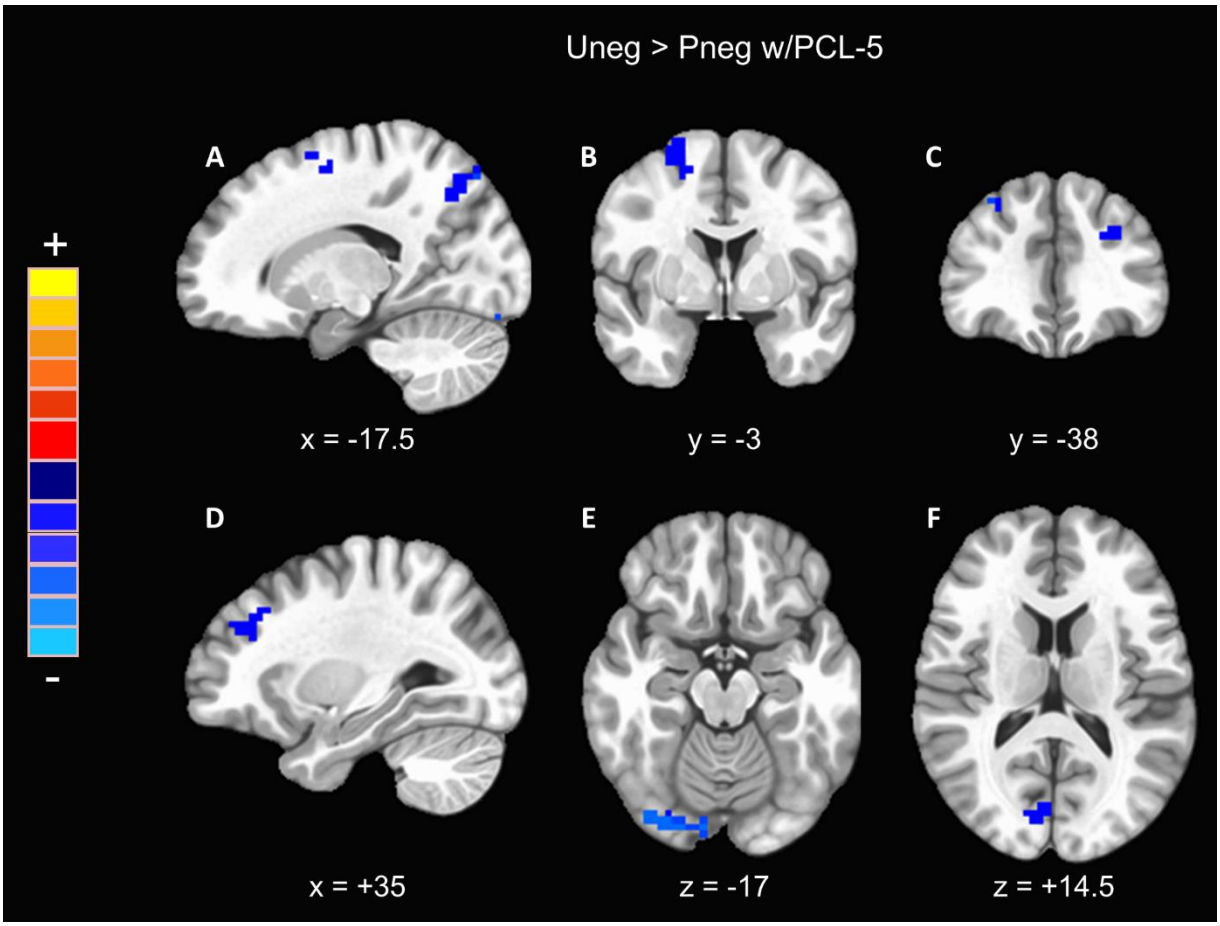
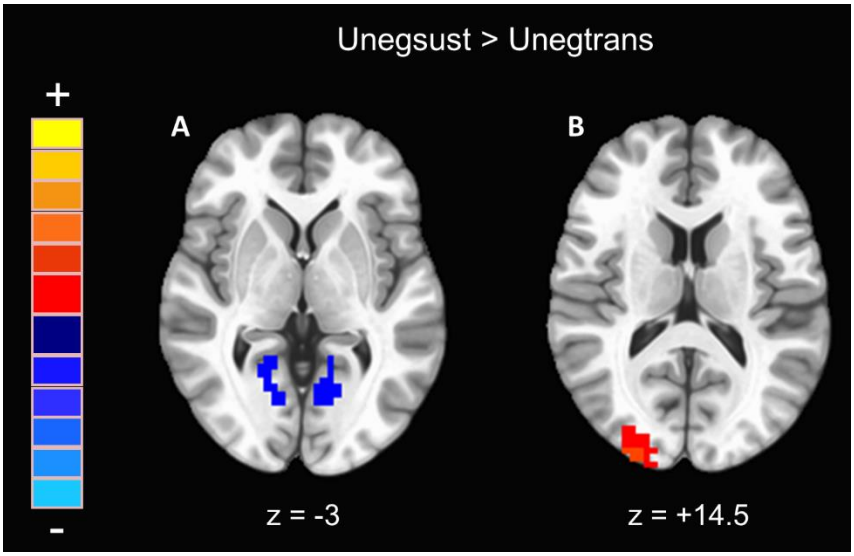


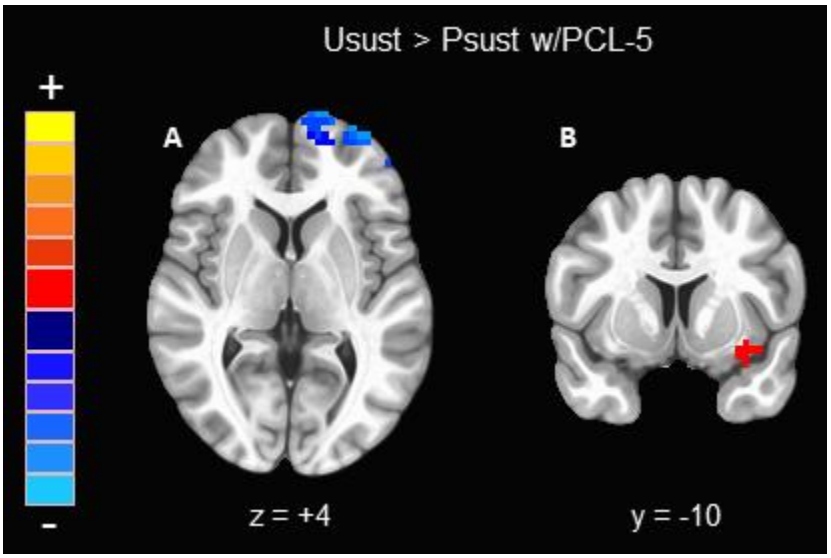
Image anticipation fMRI activation maps with PCL-5 scores, MNI space. Uneg, unpredictable negative; Pneg, predictable negative; PCL-5, PTSD Checklist for DSM-5. Top left to right: Greater activation anticipating unpredictable relative to predictable negative images is associated with decreased PCL-5 total scores in A. Superior Parietal Lobule (z = -3.14), B. Superior Frontal Gyrus (z = -3.21), C. Middle Frontal Gyrus (z = -3.38). Bottom left to right: Greater activation anticipating unpredictable relative to predictable images is associated with decreased PCL-5 total scores in D. Middle Frontal Gyrus (z = -2.96), E. Lingual Gyrus (z = -3.51), F. Cuneus (z = -5.13). Clusters of >20 voxels at $\alpha = .05$, $p < .005$, uncorrected.

Figure 5. Significant Transient and Sustained Activation in Unpredictable Negative Conditions



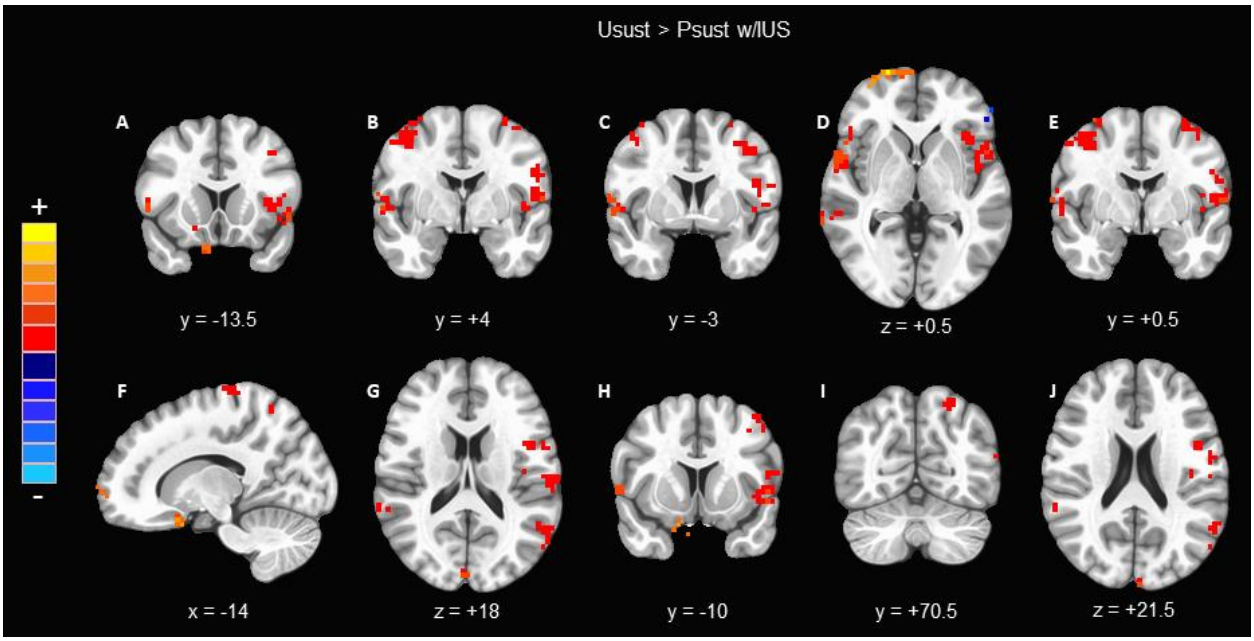
Duration fMRI activation maps, MNI space. Unegsust, unpredictable negative sustained. Unegtrans, unpredictable negative transient. Left: A. Greater transient relative to sustained activation to unpredictable negative images in Lingual Gyrus (Left z = -3.70; Right z = -3.32). Right: B. Greater sustained relative to transient activation in unpredictable negative blocks in Superior Occipital Gyrus (z = 4.11). Clusters of >20 voxels at $\alpha = .05$, $p < .005$, uncorrected.

Figure 6. Significant Sustained Activation in Unpredictable vs. Predictable Blocks Associated with PCL-5 Scores



Duration fMRI activation maps with PCL-5 scores, MNI space. Usust, unpredictable sustained; Psust, predictable sustained; PCL-5, PTSD Checklist for DSM-5. Left: A. Greater sustained activation in unpredictable relative to predictable blocks in Superior Frontal Gyrus (z = -4.63) associated with decreased PCL-5 total scores. Right: B. Greater sustained activation in unpredictable relative to predictable blocks in Insula (z = 4.03) associated with increased PCL-5 total scores. Clusters of >20 voxels at $\alpha = .05$, $p < .005$, uncorrected.

Figure 7. Significant Sustained Activation in Unpredictable vs. Predictable Blocks Associated with Increased IUS Scores



Duration fMRI activation maps with IUS scores, MNI space. Usust, unpredictable sustained; Psust, predictable sustained; IUS, Intolerance of Uncertainty. Top left to right: Greater sustained activation in unpredictable relative to predictable blocks is associated with increased IUS total scores in A. Inferior Frontal Gyrus/Insula (z = 4.48), B. Middle Frontal Gyrus/Superior Frontal Gyrus (z = 5.84), C. Rolandic Operculum (z = 4.15), D. Superior Frontal Gyrus (Left: z = 3.93) E. Superior Frontal Gyrus (Right: z = 4.27). Bottom left to right: Greater sustained activation in unpredictable relative to predictable blocks is associated with increased IUS total scores in F. Rectal Gyrus (z = 4.47), G. Middle Temporal Gyrus (z = 4.09), H. Middle Frontal Gyrus (z = 3.50), I. Superior Parietal Lobule (z = 3.02), J. Cuneus (z = 3.05). Clusters of >20 voxels at $\alpha = .05$, $p < .005$, uncorrected.

Table 1. Significant Activation During Anticipation of Neutral vs. Negative Images and Unpredictable vs. Predictable Images

Region	Lateralization	*x*	*y*	*z*	*z*-value	Voxels
		Negative > Neutral				
Middle Occipital Gyrus	R	-38.5	+88	+4	-3.44	21
		Unpredictable > Predictable				
Superior Parietal Lobule	L	+31.5	+63.5	+53	-3.63	22
Cuneus	R	-10.5	+88	+25	3.24	21

Neutral and Negative collapsed across Predictability; Unpredictable and Predictable collapsed across Valence; L, left; R, right; (*x*,*y*,*z*), MNI coordinates of maximally activated voxel (activation threshold: $p < .005$, uncorrected).

Table 2. Significant Activation During Anticipation of Unpredictable vs. Predictable Negative Images Associated with Decreased PCL-5 Scores

	Unpredictable > Predictable w/PCL-5					
Region	Lateralization	*x*	*y*	*z*	*z*-value	Voxels
Lingual Gyrus	R	-10.5	+88	-17	-3.84	101
Superior Parietal Lobule	R	-17.5	+77.5	+53	-3.19	72
Middle Occipital Gyrus	R	-42	+81	+11	-3.16	52
Superior Frontal Gyrus	R	-28	+4	+70.5	-4.03	43
Cuneus	R	-7	+81	+14.5	-5.21	34
Putamen	L	+28	+4	+4	-3.99	22
Precuneus	L	+17.5	+60	+14.5	-3.19	21
	Uneg > Pneg w/PCL-5					
Superior Parietal Lobule	R	-17.5	+77.5	+53	-3.14	96
Superior Frontal Gyrus	R	-28	-3	+67	-3.21	43
Middle Frontal Gyrus	R	-31.5	-38	+46	-3.38	32
Middle Frontal Gyrus	L	+35	-45	+35.5	-2.96	30
Lingual Gyrus	R	-31.5	+84.5	-17	-3.51	26
Cuneus	R	-7	+81	-14.5	-5.13	21

PCL-5, PTSD Checklist for DSM-5; Uneg, unpredictable negative; Pneg, predictable negative; L, left; R, right; (*x*,*y*,*z*), MNI coordinates of maximally activated voxel (activation threshold: $p < .005$, uncorrected).

Table 3. Significant Transient and Sustained Activation to Negative vs. Neutral and Unpredictable vs. Predictable Images

Region	Lateralization	*x*	*y*	*z*	*z*-value	Voxels
		Negative > Neutral				
Middle Orbital Gyrus	R	-28	-38	-24	3.93	3988
Inferior Frontal Gyrus	R	-52.5	-34.5	+14.5	6.14	721
Inferior Frontal Gyrus	L	+52.5	-38	+25	-4.24	251
Superior Medial Gyrus	R	-3.5	-27.5	+63.5	3.78	209
Precentral Gyrus	L	+63	-6.5	+32	-3.51	160
Paracentral Lobule	L	+7	+28.5	+81	4.54	120
Precuneus	L	+0.5	+60	+25	4.43	64
Middle Orbital Gyrus	R	-38.5	-59	-10	-4.14	43
Precuneus	L	+3.5	+56.5	+14.5	3.635	35
Parahippocampal Gyrus	L	+7	-6.5	-20.5	3.756	24
Precuneus	L	+14	+49.5	+74	-4.330	22
		Unpredictable > Predictable				
Inferior Parietal Lobule	R	-42	+56.5	+56.5	-4.649	76
Inferior Frontal Gyrus	L	+35	-38	-13.5	3.115	41
Superior Medial Gyrus	L	+7	-52	+42.5	3.795	33
Inferior Parietal Lobule	L	+38.5	+46	+49.5	-3.923	24
Superior Frontal Gyrus	L	+21	-69.5	+0.5	-3.427	23
Inferior Parietal Lobule	L	+63	+39	+42.5	-3.745	23
		Sustained > Transient				
IOG, CG, Cuneus	L	+56	+67	-13.5	-3.349	1337
SOG, MOG	R	-28	+98.5	+14.5	6.861	529
Middle Occipital Gyrus	L	+52.5	+77.5	+4	5.059	306
Superior Parietal Lobule	R	-17.5	+70.5	+63.5	5.121	258
Superior Parietal Lobule	L	+35	+60	+67	3.429	131
Supplementary Motor Area	L	+0.5	-13.5	+53	3.455	53
Superior Frontal Gyrus	R	-24.5	+7.5	+53	5.018	45
Caudate Nucleus	R	-17.5	-10	+21.5	2.885	33
		Unegsust > Unegtrans				
Lingual Gyrus	L	+14	+46	-3	-3.69	67
Superior Occipital Gyrus	R	-28	+98.5	+14.5	4.11	67
Lingual Gyrus	R	-3.5	+70.5	+7.5	-3.32	54

Unegtrans, unpredictable negative transient; Unegsust; unpredictable negative sustained; CG, Calcarine Gyrus; IOG, Inferior Occipital Gyrus; MOG, middle occipital gyrus; SOG, superior occipital gyrus; L, left; R, right; (*x*,*y*,*z*), MNI coordinates of maximally activated voxel (activation threshold: $p < .005$, uncorrected).

Table 4. Significant Transient and Sustained Activation to Unpredictable vs Predictable Images Associated with PCL-5 Scores

Region	Lateralization	*x*	*y*	*z*	*z*-value	Voxels
	Negative > Neutral w/PCL-5					
Inferior Frontal Gyrus	R	-59.5	-17	+7.5	-3.225	312
Inferior Parietal Lobule	L	+56	+28.5	+53	-2.918	160
Inferior Frontal Gyrus	L	+56	-10	+11	-3.815	90
Inferior Frontal Gyrus	L	+52.5	-41.5	-6.5	-3.654	57
Supplementary Motor Area	R	+0	-3	+56.5	-3.342	57
Cerebellum	L	+38.5	+88	-31	-5.473	31
Middle Frontal Gyrus	L	+38.5	-13.5	+53	3.511	30
Supplementary Motor Area	L	+10.5	+18	+53	-3.512	24
	Unpredictable > Predictable w/PCL-5					
Middle Frontal Gyrus	L	+38.5	-62.5	+4	-5.56	123
Insula	L	+35	-10	-20.5	4.40	46
Superior Temporal Gyrus	L	+52.5	+11	+7.5	3.46	33
Cerebellum	L	+31.5	+49.5	-45	2.85	26
Anterior Cingulate	L	+17.5	-31	-7.5	4.49	21
	Sustained > Transient w/PCL-5					
Middle Occipital Gyrus	L	+31.5	+91.5	+4	4.02	36
	Usust > Psust w/PCL-5					
Superior Frontal Gyrus	L	+14	-73	+4	-4.62	142
Insula	L	+25	-10	-20.5	4.03	25

PCL-5, PTSD Checklist for DSM-5; Usust, unpredictable sustained; Psust, predictable sustained; L, left; R, right; (*x*,*y*,*z*), MNI coordinates of maximally activated voxel (activation threshold: $p < .005$, uncorrected).

Table 5. Significant Sustained Activation in Unpredictable vs. Predictable Blocks Associated with IUS Scores

		Usust > Psust w/IUS				
Region	Lateralization	*x*	*y*	*z*	*z*-value	Voxels
IFG, Insula	L	+52.5	-13.5	-3	4.48	212
MFG, SFG	R	-35	+4	+67	5.84	196
Rolandic Operculum	R	+63	-3	+11	4.15	136
Superior Frontal Gyrus	R	-21	-69.5	+0.5	4.27	49
Superior Frontal Gyrus	L	+31.5	+0.5	+67	3.93	28
Rectal Gyrus	R	-14	-10	-24	4.47	26
Middle Temporal Gyrus	L	+59.5	+63.5	+18	4.09	26
Middle Frontal Gyrus	L	+45.5	-10	+56.5	3.50	25
Superior Parietal Lobule	L	+28	+70.5	+60	3.02	25
Cuneus	L	+3.5	+98.5	+21.5	3.05	20

IUS, Intolerance of Uncertainty; Usust, unpredictable sustained; Psust, predictable transient; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; L, left; R, right; (*x*,*y*,*z*), MNI coordinates of maximally activated voxel (activation threshold: $p < .005$, uncorrected).

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Williams, L. E., Oler, J. A., Fox, A. S., McFarlin, D. R., Rogers, G. M., Jesson, M. A., . . . Kalin, N. H. (2015). Fear of the unknown: Uncertain anticipation reveals amygdala alterations in childhood anxiety disorders. *Neuropsychopharmacology, 40*(6), 1428.

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CURRICULUM VITAE

Kenneth Bennett

Place of Birth: Detroit, MI

Education

B.S., Michigan State University, May 2012
Major: Psychology

M.S., University of Wisconsin-Milwaukee, December 2016
Major: Psychology

Ph.D., University of Wisconsin-Milwaukee, Expected August 2020
Major: Psychology

Dissertation Title: Response to Uncertain Threat in Acute Trauma Survivors

Awards and Fellowships

UWM Advanced Opportunity Program Fellowship (Fall 2016 – Spring 2019)
UWM Graduate Student Travel Award (2015, 2016, 2017, 2018)
UWM Department of Psychology Summer Graduate Research Fellowship (Summer 2016)
UWM Chancellor's Graduate Student Award (Fall 2014 – Spring 2016)
Michigan State University Dean's List (Spring 2009 – Spring 2012)

Clinical Experience

Predoctoral Internship – Residential Treatment for Trauma and Substance Use
RRTP, Montana VA Health Care System, Fort Harrison, MT July 2019 - Present
Supervisors: Ostin Warren, Ph.D, Curtis Tillotson, PsyD.

- Conduct psychodiagnostic assessment (biopsychosocial, CAPS-5, SCID-5), measurement-based care (BAI, BDI-II, PCL-5), and individual psychotherapy (Prolonged Exposure [PE], CBT for SUD, Behavioral Activation, Unified Protocol, and DBT-based skills) to Veterans with PTSD, SUD, and comorbidities.
- Facilitate group psychotherapy for PTSD and SUD: Seeking Safety, Anger Management, and Recovery Focus.
- Co-facilitate group psychotherapy for PTSD and SUD: Cognitive Processing Therapy (CPT), Moral Injury, Lifespan and Trauma Narrative, Trauma Recovery, and Individualized Treatment Team.
- Consultation and treatment planning with multidisciplinary treatment team, including nursing, pharmacy, physicians, peer support, case management, homeless Veterans program, and outside treatment providers.

Predoctoral Internship – Psychological Assessment (PTSD Focus)
Bozeman CBOC, MVHCS, Bozeman, MT July 2019 - Present
Supervisor: Dudley Blake, Ph.D.

- Conduct neurospsychological and psychodiagnostic assessment primarily for Veterans with attention and trauma-related concerns using the following measures: BAI, BDI-II, CAPS-5, CES, IES-R, LEC-5, MCMI-III, MMPI-2-RF, M-PTSD, MoCA, PAI, PCL-5, SCID-5, STAXI-2, WAIS-IV, and WRAT4.
- Provide outpatient trauma-focused psychotherapy for Veterans with training and supervision in PE.

Practicum in Clinical Health Psychology
Trauma Surgery Psychology Service, Medical College of Wisconsin, Milwaukee, WI 2018-2019
Supervisors: Terri deRoon-Cassini, Ph.D.; Joshua Hunt, Ph.D.; Tim Geier, Ph.D.

- Provided inpatient psychodiagnostic assessment (Psychosocial, PCL-5, HADS), bedside psychotherapy, and consultation to patients and families admitted for a traumatic injury or illness that required surgical intervention.
- Provided outpatient psychotherapy to trauma survivors with training and supervision in Behavioral Activation (BA), Prolonged Exposure (PE), and CBT-based anxiety reduction skills. Gained training and supervision in Biofeedback for chronic pain.

Practicum in Residential OCD Intervention 2017-2018
Adults Residential OCD Center, Rogers Memorial Hospital, Oconomowoc, WI
Supervisors: Bradley Reimann, Ph.D; Brenda Bailey, Ph.D.

- Conducted empirically-based CBT interventions for OCD and comorbid anxiety and depressive disorders, such as Exposure and Response Prevention (ERP) and BA.
- Created exposure hierarchies, assisted residents with exposures and ritual prevention in residential and public settings, monitored behavior, provided emotional support, implemented Mindfulness and relaxation skills, and participated in treatment team meetings on a multidisciplinary care team.
- Co-facilitated social anxiety communication, processing therapy, and dialectical behavior therapy (DBT) skill building groups.

Practicum in Therapy 2016-2019
Psychology Clinic, University of Wisconsin-Milwaukee
Supervisors: Shawn Cahill, Ph.D.; Robyn Ridley, Ph.D.

- Provided adult outpatient individual psychotherapy.
- Conducted empirically-based CBT interventions for adult ADHD, depression, and anxiety disorders.
- Received specialized training and supervision conducting empirically supported interventions for anxiety and trauma-related disorders; specifically, PTSD, panic disorder, and social anxiety disorder.

Practicum in Empirically Supported Interventions 2015-2016
Psychology Clinic, University of Wisconsin-Milwaukee
Supervisor: Shawn Cahill, Ph.D.

- Received didactics, specialized training, and supervision in empirically-supported assessment and treatment for anxiety related disorders (e.g., phobia, social anxiety, OCD, and panic disorder), eating disorders, depression, PTSD, and substance use disorders.

Practicum in Clinical Assessment 2015-2016
Psychology Clinic, University of Wisconsin-Milwaukee
Supervisors: Han Joo Lee, Ph.D.; Kristin Smith, Ph.D.

- Received training in conducting administration, scoring and interpretation of psychodiagnostic assessment batteries for cognitive, academic, and attention-related difficulties.
- Received training in report writing, and clinical interviewing for comprehensive assessments.
- Assessments administered: WAIS-IV, WIAT-III, WISC-V, MINI, Woodcock Johnson, DKEFs, CVLT-II, MMPI-II, PAI, NEO-PI-R, and other measurements of personality, academic, and cognitive functioning.

First Year Clinical Psychology Practicum 2014-2015
Psychology Clinic, University of Wisconsin-Milwaukee
Supervisors: Han Joo Lee, Ph.D.; Kristin Smith, Ph.D.

- Received training in psychological assessment, report writing, and clinical interviewing.
- Assessment administered: Woodcock-Johnson, DKEFs, CVLT-II, MMPI-II, PAI, NEO-PI-R, and other measurements of personality, academic, and cognitive functioning.

Administration of Diagnostic Interviews 2014-2019
Affective Neuroscience Laboratory, University of Wisconsin-Milwaukee
Milwaukee Veteran Affairs, Milwaukee, WI
Supervisors: Christine Larson, Ph.D.; Han Joo Lee, Ph.D.; Sadie Larsen, Ph.D.

- Administered and scored CAPS-5 and MINI psychodiagnostic interview for undergraduate college students, military Veterans, and acute trauma survivors.
- Received training and experience in administration and interpretation of structured suicidality assessment protocol for military Veterans.

Research Experience

Graduate Research Assistant 2014-2019
Affective Neuroscience Laboratory, University of Wisconsin-Milwaukee
Supervisor: Dr. Christine Larson

- Designed and conducted independent behavioral studies examining overgeneralization of

conditioned fear in anxious individuals, the negative cognitive affects associated with a mood induction, and the physiological indices of the anticipation of uncertain threat.
- Designed and conducted a collaborative psychophysiological study examining the effects of working memory training on anxiety, another examining the effects of working memory training on Veterans diagnosed with PTSD, and another examining the effects of threat on cognitive control.
- Conducting a NIMH-supported R01 collaborative psychophysiological and neuroimaging study examining the neurobiological underpinnings of the development of PTSD in acute trauma survivors.
- Designed and conducted a high-resolution imaging (7T fMRI) study examining fear learning, extinction, avoidance, and response to uncertain threat.
- Trained undergraduate research assistants in study protocols and use of ASAlab EEG and Biopac equipment.
- Responsible for maintaining data storage system, including a series of Linux-based external drives and part of a high-performance computing cluster service.
- Skills: fMRI and structural MRI analysis using AFNI; fMRI connectivity analysis using CONN; event-related potential analysis using Matlab, EEGLAB, ERPLAB, and Acqknowledge; experimental design with EPRIME; advanced statistical analysis with SPSS.

Professional Research Aide 2012-2014
Michigan Twins Project, Michigan State University
Supervisors: Dr. Kelly Klump, Dr. Alexandra Burt

- Responsible for updating and overseeing the growing database of a mailing research study consisting of approximately 30,000 twins throughout Michigan, including tracking and processing of information.

Research Assistant 2012-2014
Clinical Psychophysiology Lab, Michigan State University
Supervisor: Dr. Jason Moser

- Facilitated recruitment and scheduling of participants for a plethora of anxiety, emotion, and attention studies, and conducting electrophysiology research using BioSemi 64-Channel EEG equipment and E-Prime software.
- Consolidated EEG/ERP data using Brain Vision Analyzer software, and analyzing ERP, behavioral, and scored questionnaire data using SPSS and Microsoft Excel.
- Trained research assistants in proper EEG study protocols and delegating data entry and other daily tasks to research assistants, while checking and merging entered questionnaire data for further analyses.

Publications

Weis, C. N., Huggins, A. A., Bennett, K. P., Parisi, E. A., Larson, C. L. (*In Press*). High-resolution resting-state functional connectivity of the extended amygdala. *Brain Connectivity.*

Ward, R. T., Miskovich, T. A., Stout, D. S., Bennett, K. P., Lotfi, S., & Larson, C. L. (2019). Reward-related distractors and working memory filtering. *Psychophysiology.*

Larsen S. E., Lotfi, S., Bennett, K. P., Larson, C. L., Dean, C., & Lee, H. (2019). A pilot randomized trial of a dual n-back emotional working memory training program for Veterans with elevated PTSD symptoms. *Psychiatry Research.*

Bennett, K. P., Dickmann, J. S., & Larson, C. L. (2018). If or when? Uncertainty's role in anxious anticipation. *Psychophysiology.*

Schroder, H. S., Glazer, J. E., Bennett, K. P., Moran, T. P., & Moser, J. S. (2016). Suppression of error-preceding brain activity explains exaggerated error monitoring in females with worry. *Biological Psychology.*

Symposium Presentations

Bennett, K.P., Lotfi, S., Dean, C., Larsen, S.E., Larson, C.L., Lee, H. *Avoidance and autonomic inflexibility in veterans with chronic PTSD symptoms.* Oral presentation presented at the annual meeting of the International Society for Traumatic Stress Studies, November 8-10, 2018, Washington, DC.

Larson, C.L., Miskovich T., Stout, D., & Bennett, K.P. *Filtering of affective distracters from working memory: inefficient filtering of threat, but not reward*. Symposium presented at annual meeting of the Society for Psychophysiological Research, October 11-15, 2017 Vienna, Austria.

Poster Presentations

Weis, C. N., Huggins, A. A., Bennett, K. P., Parisi, E. A., Larson, C. L. *High resolution resting state functional connectivity of the extended amygdala*. Poster presented at the annual meeting of the Organization of Human Brain Mapping, June 9-13, 2019. Rome, Italy.

Huggins, A. A., Weis, C. N., Parisi, E. A., Bennett, K. P., & Larson, C. L. *Trait anxiety associated with differences in BOLD activation during fear generalization task.* Poster presented at the 74th annual meeting of the Society of Biological Psychiatry, May 16-18, 2019. Chicago, IL.

Parisi, E. A., Weis, C. N., Huggins, A. A., Bennett, K. P., Hajcak, G., Larson, C.L. *Amygdala and hippocampal activation to conditioned stimuli during extinction following threat avoidance.* Poster to be presented at the 74th annual meeting of the Society of Biological Psychiatry, May 16-18, 2019. Chicago, IL.

Weis, C. N., Huggins, A. A., Miskovich, T. A., Fitzgerald, J. M., Bennett, K. P., deRoon-Cassini, T. A., & Larson, C. L. *White matter integrity in individuals at-risk for PTSD development: a longitudinal investigation*. Poster to be presented at 74th Society of Biological Psychiatry Annual Meeting. May 16-18, 2019. Chicago, IL.

Lotfi, S., Bennett, K.P., Larsen, S.E., Larson, C.L., Dean, C., Lee, H. *Working memory and cognitive control performance among veterans with elevated PTSD symptoms*. Poster presented at the annual meeting of the International Society for Traumatic Stress Studies, November 8-10, 2018, Washington, DC.

Larsen, S.E., Lotfi, S., Bennett, K.P., Larson, C.L., Dean, C., Lee, H. *Emotional working memory training for chronic PTSD: Effects on PTSD symptoms and memory*. Poster presented at the annual meeting of the International Society for Traumatic Stress Studies, November 8-10, 2018, Washington, DC.

Bennett, K.P., Lotfi, S., Dean, C., Larsen, S.E., Larson, C.L., Lee, H. *Avoidance and autonomic inflexibility in veterans with chronic PTSD symptoms.* Poster presented at the annual meeting of the Society for Research in Psychopathology, September 20-23, 2018, Indianapolis, IN.

Lotfi, S., Bennett, K.P., Larsen, S.E., Larson, C.L., Dean, C., Lee, H. *Working memory and cognitive control performance among veterans with elevated PTSD symptoms*. Poster presented at the annual meeting of the Society for Research in Psychopathology, September 20-23, 2018, Indianapolis, IN.

Weis, C. N., Huggins, A. A., Bennett, K. P., Parisi, E. A., Larson, C. L. *High resolution resting state functional connectivity in anxiety*. Poster presented at the annual meeting of the Society for Neuroscience, November 3-7, 2018, San Diego, CA.

Lotfi, S., Ayazi, M., Bennett, K.P., Dommer, L., Mathew, A., Larson, C.L., Lee, H. *The prefrontal theta activity during thought suppression compared with thought free predicts lower working memory and higher worry symptoms and rumination in high trait anxiety.* Poster presented at the annual meeting of the Cognitive Neuroscience Society, March 24-27, 2018, Boston, MA.

Larson, C.L., Miskovich, T.A., Stout, D.M., Bennett, K.P. *Filtering of affective distractors from working memory: Inefficient filtering of threat, but not reward.* Poster presented at the annual meeting of the Society for Psychophysiological Research, October 11-15, 2017, Vienna, Austria.

Bennett, K.P., Lotfi, S., Lee, H., & Larson, C.L. *Working memory training does not modulate error-related negativity in anxious individuals*. Poster presented at the annual meeting of the Society for Psychophysiological Research, October 11-15, 2017, Vienna, Austria.

Miskovich, T.A, Bennett, K.P., Stout, D.M., Larson, C.L. *Impaired proactive control under threat of shock.* Poster presented at the annual meeting of the Cognitive Neuroscience

Society, March 25-28, 2017, San Francisco, CA.

Bennett, K.P., Dickmann, J.S., & Larson, C.L. *If or when? Uncertainty's role in anxious anticipation.* Poster presented at the annual meeting of the Society for Psychophysiological Research, September 21-25, 2016, Minneapolis, MN.

Bennett, K.P. & Larson, C.L. *Mood induction and working memory performance*. Poster presented at the annual meeting of the Society for Affective Science, March 17-19, 2016, Chicago, IL.

Miskovich, T.A, Bennett, K.P., Stout, D.M., & Larson, C.L. *Reward distracters and working memory filtering*. Poster presented at the annual meeting of the Cognitive Neuroscience Society, April 2-5, 2016, New York, NY.

Bennett, K.P., Schroder, H.S., Moser, J.S. (2014). *I think I can, I know I can: Implicit beliefs and motivation for change*. Poster presented at the annual convention for the Association for Psychological Science, May 22-25, 2014, San Francisco, CA.

Glazer, J.E., Bennett, K.P., Schroder, H.S., Moran, T.P., & Moser, J.S. (2013). *Error-preceding brain activity is reduced in worriers*. Poster presented at the annual convention for the Association for Psychological Science, May 23-26, 2013, Washington, D.C.

Teaching Experience

Teaching Assistant 2014-2016
University of Wisconsin-Milwaukee

- Psychology 205: Personality (Fall 2014 – Spring 2015)
- Psychology 325: Research Methods of Psychology (Fall 2015)
- Psychology 802: 1st Year Clinical Assessment Practicum (Spring 2016)

Professional Affiliations

- Founder, Treasurer, Association of Clinical and Cognitive Neuroscience at UWM (2017-2019)
- Member, Cognitive Neuroscience Society (2018-2019)
- Member, Society for Research in Psychopathology (2014, 2017-2019)
- Member, Society for Psychophysiological Research (2016-2019)
- Member, Society for Affective Science (2016-2017)
- Member, Sigma Xi Research Honor's Society (2014-2016)
- Member, PSI CHI – National Honor Society in Psychology (2011-2012)

Professional Workshops

- AFNI Boot Camp, University of Wisconsin-Milwaukee, Milwaukee, WI (April 2019)
- Learning the CONN Toolbox, Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA (May 2017)
- ERP Mini Boot Camp, Annual Meeting of the Society for Psychophysiological Research, Minneapolis, MN (September 2016)

Boards and Committees

- Psychology Student Representative, University of Wisconsin-Milwaukee Institutional Review Board (July 2016 – September 2018)