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INVESTIGATING THE FUNCTIONAL CONNECTIVITY OF THE BED NUCLEUS OF THE STRIA TERMINALIS DURING CONDITIONS OF THREAT AND SAFETY USING HIGH RESOLUTION 7 TESLA FMRI

by

Walker S. Pedersen

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Requirements for the Degree of

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ABSTRACT

INVESTIGATING THE FUNCTIONAL CONNECTIVITY OF THE BED NUCLEUS OF THE
STRIA TERMINALIS DURING CONDITIONS OF THREAT AND SAFETY USING HIGH
RESOLUTION 7 TESLA FMRI

by

Walker S. Pedersen

The University of Wisconsin – Milwaukee, 2017
Under the Supervision of Professor Christine L. Larson

An influential model of the extended amygdala defines fear as the immediate response to phasic threat and anxiety as the prolonged response to unpredictable or sustained threat (Davis, Walker, Miles & Grillon, 2010). This model proposes that in response to unpredictable threat, the centromedial amygdala (CeA) activates the bed nucleus of the stria terminalis (BNST), which coordinates the anxiety response, and, in turn, inhibits the CeA. Connectivity between the BNST and both the basolateral amygdala (BLA) and hippocampus may also play an important role in the coordination of the anxiety response (Davis et al., 2010; Herman et al., 2003; Zhu, Umegaki, Suzuki, Miura & Iguchi, 2001). However, there is a dearth of human research investigating whether state anxiety is accompanied by increased connectivity between the BNST and CeA, BLA and hippocampus. To test whether sustained threat elicits increases connectivity between the BNST and these areas, I monitored participants' resting brain activity via high resolution 7 tesla fMRI during two five minute resting state scans, one while under threat of unpredictable shock and one while safe. I predicted that each of these areas would exhibit greater connectivity with the BNST during periods of threat vs. safety. To test whether BNST connectivity during periods of threat is altered in anxiety prone individuals, I collected self-reported behavioral inhibition. I predicted that greater behavioral inhibition would predict increased connectivity during periods of threat (vs. safety) between the BNST and the CeA, BLA and hippocampus. I

also tested whether connectivity in these areas changes over time following the onset of threat by examining connectivity for three time windows, corresponding roughly to the first, second and fifth minute following threat onset. I predicted positive threat vs. safe BNST-CeA connectivity during the first time window, negative threat vs. safe BNST-CeA connectivity during the second time window, and no difference in BNST-CeA connectivity during the final time window. I found a marginally significant trend toward greater BNST-BLA connectivity during threat vs. safety. I found no evidence for increased BNST-hippocampus connectivity during threat, or that BNST connectivity with either the BLA or hippocampus is modulated by behavioral inhibition. Threat condition, behavioral inhibition, and time window interacted to affect BNST-CeA connectivity, although a lack of significant follow-up tests makes interpreting this interaction challenging. Further research is needed to characterize how individual differences alter the time course of BNST-CeA connectivity during conditions of threat and safety, and the conditions under which threat may elicit BNST connectivity with the hippocampus and BLA.

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Investigating the Functional Connectivity of the Bed Nucleus of the Stria Terminalis During

Conditions of Threat and Safety Using High Resolution 7 Tesla fMRI

Researchers have proposed a distinction between fear and anxiety by defining fear as the

response to short-term, phasic threat and anxiety as the response to unpredictable or sustained

threat (Davis, Walker, Miles & Grillon, 2010; Grillon, 2008; Herrmann et al., 2016; Somerville,

Whalen & Kelley, 2010). In this framework the fear response consists of active defensive

behaviors in response to imminent threat (LeDoux, 1998), while the anxiety response consists of

behaviors associated with increased vigilance and apprehension elicited by threats that are

sustained and often unpredictable or physically distant (Barlow, 2000).

Davis et al. (2010) has proposed that connectivity between the centromedial amygdala

(CeA) and bed nucleus of the stria terminalis (BNST) plays a key role in the anxiety response to

sustained threat (Davis et al., 2010). Research also suggests that connectivity between the BNST

and both the basolateral amygdala (BLA) and hippocampus may play an important role in the

coordination of the anxiety response (Herman et al., 2003; Walker & Davis, 1997, Davis &

Whalen, 2001; Zhu, Umegaki, Suzuki et al., 2001; Zhu, Umegaki, Yoshimura et al., 2001).

However, there is little human research investigating this circuitry. Further research into the role

that BNST connectivity plays in the anxiety response is necessary for a better understanding of

basic human emotion, as well as anxiety related disorders. The need for this research is

underscored by the prevalence and debilitating nature of anxiety disorders (Kessler, Chiu,

Demler, & Walters, 2005).

 In Davis et al.'s (2010) conceptualization of the anxiety response, sustained threat elicits

activity in the CeA, which sends projections via corticotropin-releasing factor-containing

neurons to stimulate activity in the BNST (see Figure 1). The BLA may also play a critical role

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in the initiation of the anxiety response by relaying sensory information related to signals of threat to the BNST (Walker & Davis, 1997; Davis & Whalen, 2001). The BNST then coordinates an anxiety response via projections to a variety of targets involved in the production of autonomic and behavioral changes associated with anxious arousal. This model (Davis et al., 2010) of the anxiety response has been proposed based largely on observations in rodent studies. In part due to the difficulty of resolving BNST activation with standard 3T imaging, no one has tested whether state anxiety invoked via periods of prolonged threat is accompanied by changes in BNST-CeA connectivity. Furthermore, past studies have found that behavioral inhibition, a trait related to the dispositional anxiety (Van Ameringen, Mancini & Oakman, 1998) that predicts pathological anxiety, (Biederman et al., 1990; Barker et al., 2015; Van Ameringen et al., 1998) and is associated with a variety of anxious behaviors (Kagan, Snidman, Zentner, & Peterson, 1999; Fox, Henderson, Marshall, Nichols & Ghera, 2005), is associated with altered function of this circuitry in non-human primates (Fox, Shelton, Oakes, Davidson & Kalin, 2008; Oler et al., 2009). However, no one has examined whether behavioral inhibition predicts changes in BNST-CeA connectivity during periods of threat (vs. safety) in humans. The current study will address these issues by investigating the connectivity of the BNST under conditions of threat and safety, and examining whether changes in this connectivity are associated with behavioral inhibition.

The amygdala is made up of several nuclei. The BLA consists of the lateral, basal and accessory basal nuclei (Davis & Whalen, 2001; LeDoux, 2007). The central and medial nuclei form the CeA, while the cortical nuclei are known as the superficial amygdala (Bach, Behrens, Garrido, Weiskopf & Dolan, 2011; Davis & Whalen, 2001; LeDoux, 2007). It should be noted, however, that some classification schemes group the CeA and superficial amygdala together,

either under the name CeA, or cortico-medial amygdala (Sah, Faber, Lopez de Armentia & Power, 2003). The BLA serves as a major input to the CeA. While the BLA and CeA are grouped together under the term amygdala, it has been noted that the nuclei in the CeA are more similar anatomically to each other and to the other targets of the BLA, than they are to the nuclei in the BLA itself (Davis and Whalen, 2001). In light of this observation, the targets of the BLA are often referred to as the extended amygdala. In addition to the CeA, the extended amygdala includes the nuclei of the BNST, the nucleus accumbens shell, and the interstitial nucleus of the posterior limb of the anterior commissure (Alheid, 2003).

The BLA receives sensory information from the thalamus and sensory cortices, which may allow the BLA to integrate and transmit environmental cues related to threat and reward (McDonald, 1998). In addition to sensory areas, activity in the BLA can also be influenced by input from the medial prefrontal cortex and ventral hippocampus, allowing these regions to modulate threat-related responding (Felix-Ortiz et al., 2013; Herry et al., 2008). In turn, the BLA projects to a variety of areas, including orbital frontal cortex (Krettek & Price, 1977; Schoenbaum, Chiba & Gallagher, 1998), hippocampus (Huff, Emmons, Narayanan & LaLumeire, 2016), and dorsal (Kelley, Domesick & Nauta, 1982; Murray et al., 2015) and ventral striatum (Ambroggi, Ishikawa, Fields & Nicola, 2008; McDonald, 1991). These projections can modulate behavior and memory consolidation in a variety of ways relevant to emotional processing (Davis & Whalen, 2001). The BLA also projects to key nodes in the extended amygdala, including the CeA and the BNST (Krettek & Price, 1978; Pitkänen et al., 1995; Dong, Petrovich & Swanson, 2001). These inputs are thought to provide sensory information to these areas, which may allow them to respond to signals of potential threat in the environment (Davis et al., 2010; Davis & Shi, 1999).

The list of targets for CeA and BNST are largely overlapping, and include a number of areas implicated in autonomic and somatic aspects of fear and anxiety (Alheid, 2003; Davis & Whalen, 2001; Davis, 1998). Shared outputs of the CeA and BNST include the lateral hypothalamus, motor nucleus of vagus, nucleus ambiguous, parabrachial nucleus, ventral tegmentum, locus coeruleus, lateral dorsal tegmental nucleus, reticular formation, central gray, facial and trigeminal nuclei, and paraventricular nucleus of the hypothalamus (Davis, 1998). These projections are thought to allow the extended amygdala to initiate fear and anxiety responses. Projections from the CeA and BNST to the lateral hypothalamus may activate the autonomic response to fear and anxiety, including tachycardia, pupil dilation, and elevated blood pressure (Dong & Swanson, 2004; LeDoux, Iwata, Cicchetti & Reis, 1988; Gritti, Mainville & Jones, 1994; Kim et al., 2013). Projections to the vagus nerve may be related to urination, defecation, and bradycardia (Gray & Magnuson, 1987; Holstege, Meiners & Tan, 1985; Hopkins & Holstege, 1978; Porges, Doussard-Roosevelt, 1994; Schwaber, Kapp, Higgins & Rapp, 1982; Takeuchi, Sachi, Ryotaro & Hopkins, 1983), while those to the parabrachial nucleus may be associated with panting and respiratory distress (Cohen, 1979; Dong & Swanson, 2004; Harper, Frysinger, Trelease & Marks, 1984; Holstege et al., 1985; Moga & Gray, 1985; Kim et al., 2013). Activation in the ventral tegmentum, locus coeruleus, and lateral dorsal tegmental nucleus is associated with increased vigilance (Beckstead, Domesick & Nauta, 1993; Dong & Swanson, 2004; Holstege et al., 1985; Kudo et al., 2012; Rajkowski, Kubiad, & Aston-Jones, 1994; Simon, LeMoal & Calas, 1979; Van Bockstaele, Colago, & Valentino, 1998), and activation of the reticular formation is associated with increased startle responses (Dong & Swanson, 2003; Holstege et al., 1985; Koch & Ebert, 1993; Lingenhohl & Friauf, 1994). Projections to the central gray are thought to mediate freezing behaviors during conditioned fear

(Gray & Magnuson, 1987; LeDoux et al., 1988). Projections to the facial and trigeminal nuclei may mediate fearful facial expressions (Gothard, 2014; Gray & Magnuson, 1987; Holstege et al., 1985; Post & Mai, 1980), while those to the paraventricular nucleus of the hypothalamus may elicit a stress response via corticosteroid release (Dong & Swanson, 2006; Gray, Carney & Magnuson, 1989; Hsu & Price, 2009; Van de Kar & Blair, 1999). These outputs allow the extended amygdala to elicit several aspects of the fear and anxiety responses.

These observations suggest that the CeA and BNST are both involved in responding to threat-related stimuli. Davis et al. (2010) have suggested that the function of the CeA and BNST can be distinguished by their separable roles in phasic and sustained fear responses. According to this framework, imminent threats elicit a fear response, while more unpredictable and sustained threats elicit anxiety. While fear is thought to dissipate quickly after the imminent threat is no longer present, anxiety represents a sustained state of vigilance and apprehension.

Davis et al. (2010) argues that this distinction is supported by rodent research on predatory imminence which demonstrates that when physical contact with a predator is imminent circa-strike defense is activated, in which an animal will either actively flee or attempt to ward off a predator by attacking it. Davis et al. (2010) conceptualizes these behaviors as being associated with the fear response. On the other hand, signals of a potential predator activate defensive behaviors associated with sustained risk assessment and freezing behaviors (Fanselow, 1986; Blanchard, Yudko, Rodgers & Blanchard, 1993). The Davis et al. model (2010) would characterize these behaviors as an anxiety response.

It is important to note that differentiating fear and anxiety is challenging. Grillon (2008) notes that distinguishing between fear and anxiety has proven "difficult and controversial" given that these constructs have "overlapping characteristics" (p. 2). Due to this, researchers have yet

to establish a consensus on how to operationally define fear and anxiety in humans (Perusini & Faneslow, 2015), or whether a clear distinction is even possible (e.g., Shackman & Fox, 2016).

Due to the lack of consensus on how to operationally define fear and anxiety, research on the human threat response is often not designed to distinguish between these constructs. Fear conditioning – in which a cue predicts an aversive stimulus – is often used as a measure of the human threat response (Sehlmeyer et al., 2009; Lissek et al., 2005). Fear conditioning protocols using a completely reliable cue (i.e. the cue always predicts the aversive stimulus) exemplify tasks that elicit a fear response, based on the Davis et al. (2010) definition, as the threat in this task is predictable and discrete. However, fear conditioning protocols often use cues that are not completely reliable with the cue predicting threat only on some predetermined percentage of trials (Sehlmeyer et al., 2009; Lissek et al., 2005). As this introduces unpredictability, these tasks would be presumed to elicit anxiety.

The presentation of negatively valenced images or facial expressions is another common way of studying the human threat response (Fusar-Poli, 2009; Lang & Bradley, 2007; Olofsson, Nordin, Sequeira & Polich, 2008). Whether this type of task measures fear or anxiety depends on the parameters of the task. If the valence and timing of upcoming images is predictable and images are presented individually as discrete events, then the Davis et al. (2010) model would define this task as eliciting a fear response. However, if the valence or timing of the images are unpredictable this task would be defined as eliciting anxiety.

Another common method for eliciting the human threat response is by using the threat of unpredictable shock (Robinson, Vytal, Cornwell & Grillon, 2013). In this paradigm, participants are told they may receive an aversive electrical shock during some period of time, but the administration of the shock is unpredictable. This unpredictability may concern whether the

shock will occur (for example, on a given trial the shock may or may not occur), when the shock will occur, or both. This task is used to induce a prolonged state of apprehension (Robinson et al., 2013), and exemplifies a task that elicits the anxiety response based on Davis et al.'s (2010) definition.

Despite the current lack of consensus on how to distinguish fear and anxiety, Grillon (2008) argues that treating them as a single construct may impede researchers from gaining a full picture of affective states and individual differences. This view is supported by psychometric studies of questionnaire data indicating that trait anxiety and trait fear are related, but separable constructs (Perkins, Kemp & Corr, 2007; Sylvers, Lilienfeld & La Prairie, 2011). Similarly psychometric studies investigating the symptoms and comorbidity of internalizing disorders demonstrate two factors, one that has been described as including disorders associated with fear, such as phobias and panic disorder, and one that has been described as representing anxiety and misery disorders, such as generalized anxiety disorder, posttraumatic stress disorder and depression (Cox, Clara, & Enns, 2002; Kruger, 1999). Furthermore, patients with posttraumatic stress disorder display normal startle toward a brief threat cue that signals impending shock, but show increased contextual fear conditioning (Grillon & Morgan, 1999; Grillon et al., 1994; Grillon et al., 1998; Pole et al., 2003), in which an aversive stimulus is paired with a particular environment and is thought to elicit an anxiety response, as the contextual cues of threat are sustained and ambiguous (Davis et al., 2010). This could suggest that individuals with posttraumatic stress disorder have an altered anxiety response, while exhibiting a normal fear response.

Human psychopharmacology studies not only provide further evidence for a distinction between fear and anxiety, but also suggest that fear and anxiety are mediated by different neural

mechanisms. A series of studies have investigated the effects of benzodiazepines, a class of

drugs used to treat anxiety disorders, on the fear and anxiety response in humans.

Benzodiazepines have been shown to reduce contextual fear, but not startle potentiated by brief

threat cues (Baas et al., 2002; Grillon et al., 2006). It should be noted, however, that some

researchers have not replicated these results (Bistios et al., 1999; Graham et al., 2005). Grillon et

al. (2006) argue that differences in study protocol that may have conflated brief and contextual

threat may account for these replication failures. Studies have also demonstrated that alcohol

reduces startle potentiated by unpredictable, but not predictable, shock (Bradford, Shapiro &

Curtin, 2013; Hefner & Curtin, 2012; Hefner, Moberg, Hachiya & Curtin, 2013; Moberg &

Curtin, 2009). These results suggest that alcohol, at least at moderate doses (blood alcohol

content = .08%), selectively reduces the anxiety response to unpredictable threat, but not the fear

response to predictable threat. Taken as a whole, these findings suggest that anxiety and fear are

distinguishable constructs that can be differentially pharmacologically targeted.

In Davis et al.'s (2010) model the fear response is mediated by the CeA, while anxiety is

produced via interactions between the CeA and BNST. In this model the CeA is activated in

response to signals of threat, mediated largely by inputs from the BLA. The CeA then activates a

phasic fear response via projections to brain stem and hypothalamic regions. Shortly after the

initiation of this phasic fear response, more lateral nuclei in the CeA release corticotropin-

releasing factor (CRF) into the BNST, which stimulates the BNST to initiate a sustained fear

reaction. Feedback from the BNST to the CeA then inhibits CeA activation, allowing for a

transition from a phasic to sustained fear response.

Davis et al. (2010) proposed this model of phasic and sustained threat responding based

primarily on evidence from rodent studies. Iwata et al. (1986) and Ledoux et al. (1988)

demonstrated that the CeA mediates the conditioned fear response. Building on these findings, Hitcock and Davis (1986, 1991) found that lesions of the CeA, but not the BNST, disrupt fear-potentiated startle during brief presentations of a conditioned stimulus that has been paired with electric shock. These results suggest that the CeA is a critical component of the response to immediate threat (Davis et al., 2010).

While these results demonstrate the role of the CeA in the response to brief threat, Walker and Davis (1997) used light-enhanced startle to investigate the neural mechanisms underlying the response to sustained threat. In the light-enhanced startle paradigm, rats are exposed to a prolonged, bright light, capitalizing on the observation that these nocturnal animals are averse to bright light (Crawley, 1981; File & Hyde, 1978). Studies demonstrating that rodents exposed to bright light exhibit an increased startle response to an acoustic stimulus (Walker & Davis, 1997), which is reduced by anxiolytic drugs, suggest that prolonged exposure to light enhances anxiety in rodents (de Jongh et al., 2002; Walker & Davis, 1997; Walker & Davis, 2002). Walker and Davis (1997) demonstrated that light-enhanced startle is blocked by infusion of an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist into the BNST, but not the CeA. This result supports Davis et al. (2010) by suggesting that the BNST plays an important role in the anxiety response during prolonged exposure to light.

The finding that AMPA antagonist infusions into the BNST decreased startle potentiation during the second half of an aversive conditioned stimulus presented for 8 minutes (Meloni, Jackson, Gerety, Cohen & Carlezon, 2006) gives further evidence that prolonged threat is mediated by the BNST. Similarly, blocking BNST neurotransmitter release via cobalt chloride infusions reduces freezing behavior in a context in which rodents have received foot shocks (Resstel et al., 2008). These findings led to Davis et al.'s (2010) hypothesis that the CeA

mediates the fear response toward brief, immediate threats, while the BNST mediates the anxiety response to sustained threat.

Walker and Davis (1997) also found that disrupting activation of the BLA with infusions of an AMPA antagonist interferes with both fear-potentiated startle and light-enhanced startle. Davis et al. (2010) interpret this finding as suggesting that input from the BLA – which projects to both the CeA and BNST – may be important for both the CeA-mediated fear response, and the BNST-mediated anxiety response. BLA projections to the CeA and BNST may carry sensory information to these areas, allowing them to respond to signals of threat in the environment (Davis & Whalen, 2001). As such, projections from the BLA to the BNST may be a critical component of the circuitry supporting the anxiety response toward sustained threat.

While Davis et al.'s (2010) model remains influential, others have noted evidence that challenges specific aspects of this framework. Gungor and Paré (2016) cite evidence from rodent research suggesting BNST cells respond to both long and short cues (Haufler, Nagy & Paré, 2013; Meloni et al., 2006), and that BNST lesions reduce freezing behavior to brief conditioned stimuli (Duvarci, Bauer & Paré, 2009). Based on these results, Gungor and Paré (2016) conclude that while the BNST does not seem to be a necessary component of the circuitry that elicits a phasic fear response, evidence indicates that BNST activity can modulate this response. Similarly, Shackman and Fox (2016) have noted that human imaging studies have found mixed results concerning whether the BNST responds to brief signals of threat (Mobbs et al., 2010; Choi, Padmala & Pessoa, 2012; Grupe, Oathes & Nitschke, 2013; Klumpers et al., 2015). These findings challenge the assumption of the Davis et al. (2010) model that the response to brief, explicit threat cues are mediated by the CeA, independent of BNST activity.

The mixed evidence for whether the BNST responds to brief signals of threat may be due,

in part, to difficulties making a clear distinction between phasic and sustained threat. While the Davis et al. (2010) model suggests that the anxiety response involves an early phase, in which the CeA activates the BNST, a middle phase, in which the BNST inhibits the CeA, and a late phase, in which the BNST continues to mediate the anxiety response independently of CeA input, existing research does not allow for a clear specification of precisely when the transitions between these periods occur. Walker and Davis (1997) found that BNST inactivation does not disrupt fear-potentiated startle to a 3.2 second cue, while Davis, Schlesinger & Sorenson (1989) found that light-enhanced startle begins to appear at approximately one minute. Based on these findings, Davis et al. (2010) suggested that the transition between the phasic and sustained fear response begins somewhere between 4 and 60 seconds, but may take several minutes to become fully mediated by the BNST. Resstel et al. (2008) found that blocking neurotransmitter release in the BNST via cobalt chloride infusions resulted in reduced heart rate and blood pressure in rodents during contextual fear conditioning. These changes in blood pressure and heart rate associated with disrupted BNST neurotransmitter release appeared within the first minute of contextual fear conditioning (Resstel et al., 2008). One human imaging study demonstrated increased BNST activity during 118 s blocks of unpredictable negative images (Somerville et al., 2010), while another found increased BNST activity during 40 s blocks of unpredictable threat (Alvarez, Chen, Bodurka, Kaplan & Grillon, 2011). These studies demonstrate that BNST activation can occur within the first minute following the onset of threat, and imply that BNST-CeA connectivity thought to be responsible for initiating the anxiety response should be also increased within that time period. While this gives some insight into how early BNST-CeA connectivity begins following the onset of a threat, there is very little research investigating when the BNST begins to inhibit the CeA. Further research is needed to examine the time course

of BNST-CeA interactions in response to sustained threat.

Another reason studies may have difficulty drawing a sharp distinction between the CeA mediated fear response and the BNST mediated anxiety response is that the CeA may be under tonic inhibition by the BNST (Davis et al., 2010), implying that BNST activity may be able to modulate the phasic fear response. Thus while there may be differences in the degree to which the response to phasic and sustained threat are mediated by the CeA and BNST, respectively, it may not be possible to draw a clear-cut double dissociation between the two.

While research demonstrating a possible role for the BNST in responding to brief threat is a potential limitation of Davis et al.'s (2010) model of the extended amygdala, growing evidence supports their argument that BNST-CeA connectivity is an important component of the anxiety response. Anatomical studies have shown that CRF-expressing neurons in the CeA project to the BNST (Dong et al., 2001; Sakanaka, Shibasaki, Lederis, 1986; Swanson, Sawchenko, Rivier & Vale, 1983), over-expression of CRF in the CeA mimics the effects of chronic stress in rodents (Flandreau, Ressler, Owens & Nemeroff, 2012; Keen-Rhinehart et al., 2009), and infusions of a CRF receptor antagonist into the BNST disrupts contextual fear conditioning (Asok, Schulkin & Rosen, 2016), as well as both light-enhanced and CRF-enhanced startle (Lee & Davis, 1997). Additionally, while systemic yohimbine administration increases anxiety-like behaviors in rats in an elevated plus maze, this effect is disrupted in rats with lesions designed to disconnect the CeA from the BNST (Cai, Bakalli & Rinaman, 2012). These results support the Davis et al. (2010) model's prediction that connectivity between the CeA and BNST is critical for the initiation of the anxiety response.

Connectivity between the BNST and hippocampus may also serve an important role in mediating the anxiety response. The hippocampus has been implicated in contextual fear

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conditioning, which is thought to elicit an anxiety response (Maren, 2001). Rats with hippocampal lesions exhibit reduced signs of anxiety in response to a bright light, and in an elevated plus-maze task (Kjelstrup et al., 2002), and exhibit less predator-induced freezing behaviors (Blanchard & Blanchard, 1972). The hippocampus may play a role in the anxiety response (File, Kenny & Cheeta, 2000; Gray & McNaughton, 1996) through interactions with the hypothalamic-pituitary-adrenal axis – a key node in the endocrine system for regulating and releasing stress hormones (Jacobson & Sapolsky, 1991). The BNST relays signals from the hippocampus to the hypothalamic-pituitary-adrenal axis, and likely helps mediate hippocampal regulation of the hypothalamic-pituitary-adrenal axis stress response (Herman et al., 2003; Zhu, Umegaki, Suzuki et al., 2001; Zhu, Umegaki, Yoshimura et al., 2001). As such, connectivity between the hippocampus and BNST may also play an important role in mediating the anxiety response.

While there is little human research investigating the role of BNST connectivity in anxiety, several neuroimaging studies have found BNST activation in response to sustained signals of threat. Somerville et al. (2013) presented participants with blocks of negative or neutral images. In half of these blocks the timing of image presentation was predictable, while in the other half it was not. This study found greater amygdala activation in response to the presentation of negative (vs. neutral) images, and sustained activation in the BNST during blocks of negative (vs. neutral) images, as well as during blocks in which the timing of presentation of images was uncertain (vs. certain). Furthermore, BNST activation was associated with self-reported anxiety during the task. The BNST is also activated during the anticipation of an unpredictable aversive stimulus (Alvarez et al., 2011; Grupe et al., 2013; Herrmann et al., 2016; McMenamin, Langeslag, Sirbu, Padmala & Pessoa, 2014; Münsterkötter et al., 2015), and

uncertainty during a gambling task (Yassa, Hazlett, Stark & Saric, 2012). While these studies have implicated BNST activity in state anxiety, none of these studies investigated whether state anxiety is associated with changes in BNST connectivity.

Two recent studies investigated BNST connectivity at rest (Avery et al., 2014; Torrisi et al., 2015). However, these studies did not investigate changes in functional connectivity of the BNST during periods of safety and sustained threat. McMenamin et al. (2014) investigated network-level connectivity changes during periods of safety and threat, finding that the amygdala becomes more central to network function during threat across participants, while the BNST becomes more central to network function during threat for participants high in trait anxiety. However, McMenamin et al. (2014) did not specifically test whether connectivity between the BNST and CeA, BLA and hippocampus was altered during periods of threat vs. safety.

If connectivity between the BNST and the CeA, BLA and hippocampus is involved in the generation of anxious states, both pathological anxiety and dispositional traits related to anxiety may be expected to modulate BNST connectivity with these regions. While this question has received little attention, several studies have demonstrated altered BNST activity in pathological anxiety and anxiety prone individuals. BNST activation is associated with hypervigilant threat monitoring in individuals with high trait anxiety (Somerville et al., 2010), as well as increased reactivity to uncertainty in generalized anxiety disorder patients (Yassa et al., 2012). Spider phobics exhibit increased BNST responses in anticipation of images of spiders (Straube et al., 2007). Additionally, anxious temperament – a construct defined by behavioral inhibition and pituitary-adrenal activity – is associated with altered BNST metabolism in non-human primates (Fox et al., 2008; Oler et al., 2009). These studies demonstrate altered BNST activity associated with dispositional and pathological anxiety. As rodent research suggests that connectivity

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between the BNST and the CeA, BLA and hippocampus is important for the anxiety response (Asok et al., 2016; Cai et al., 2012; Davis et al., 2010; Herman et al., 2001; Lee & Davis, 1997; Walker & Davis, 199rez7; Zhu, Umegaki, Suzuki et al., 2001; Zhu, Umegaki, Yoshimura et al., 2001), further research is needed to test whether BNST connectivity with these regions is modulated by measures of dispositional anxiety.

One anxiety-related trait that is likely to modulate BNST activity and connectivity is behavioral inhibition. This trait is tied to the dispositional tendency to react to unfamiliar or uncertain situations with restraint and discomfort (Reznick, Hegeman, Kaufman, Woods & Jacobs, 1992). Behavioral inhibition is related to the trait anxiety (Van Ameringen et al., 1998), correlates with pathological anxiety, (Biederman et al., 1990; Barker et al., 2015; Van Ameringen et al., 1998) and is associated with a variety of anxious behaviors (Kagan, Snidman, Zentner, & Peterson, 1999; Fox, Henderson, Marshall, Nichols & Ghera, 2005). Behavioral inhibition has also been associated with greater reactivity of stress-related systems (Fox et al., 2005), including increased cortisol responses (Nachmias et al. 1996; Short et al. 2014). Given that the hypothalamic-pituitary-adrenal axis is thought to be a critical target of the extended amygdala response to sustained threat (Flandreau et al., 2012; Keen-Rhinehart et al., 2009), behavioral inhibition may be closely related to extended amygdala activity. Indeed, as stated above, anxious temperament – which is a measure of behavioral inhibition – is associated with altered BNST activity in non-human primates (Fox et al., 2008; Oler et al., 2009).

The time course of connectivity between the BNST and CeA is another factor that must be considered by researchers investigating this circuitry. According to the Davis et al. (2010) model, the early response to a sustained threat stimulus will be dominated by CeA activation of the BNST. Once the BNST has been activated, inhibitory projections from the BNST to the CeA

allow for the inhibition of CeA activation, resulting in a transition between the CeA fear response, and the BNST anxiety response. As such, during the early stages of responding to a threatening stimulus, there may be positive BNST-CeA connectivity, as the CeA recruits BNST activation. During the intermediate stage, there may be negative BNST-CeA connectivity, as the BNST inhibits CeA activation. Finally, once threat responding has fully transitioned to the BNST mediated anxiety response, there may be little connectivity between the BNST and CeA.

The need for further research into the factors affecting activity and connectivity in the extended amygdala is compounded by the difficulty in confidently assessing BNST activation and connectivity at resolutions afforded by 3-Tesla (3T) fMRI scanning, due to its small size (~190 mm^3; Avery et al., 2014). Researchers have urged caution in labeling clusters appearing to capture BNST activation in 3T studies (Shackman & Fox, 2016) and have acknowledged a need for high resolution studies to investigate activity of the BNST with greater confidence (Somerville et al., 2010). As such, the existing literature may not give a full picture of BNST function, as significant clusters containing BNST activity may also capture activity in surrounding areas. This is especially true in studies using whole-brain analysis, where clusters of activation are only likely to survive correction for multiple comparison based on cluster extent if they extend outside of the BNST. Thus, research implementing high resolution fMRI is needed to investigate BNST activity and connectivity with greater specificity.

To test whether sustained threat elicits increased connectivity between the BNST and the CeA, BLA and hippocampus, I monitored participants' resting brain activity via fMRI during two five minute resting state scans, one while under threat of unpredictable shock and one while safe. I collected this data at high resolution (.86 mm × .86 mm × 1 mm) using 7-Tesla MRI, in order to capture this connectivity. I predicted that each of these areas would exhibit greater

connectivity with the BNST during periods of threat vs. safety.

To test whether individual differences in behavioral inhibition modulates resting-state connectivity during periods of threat, I collected self-reported behavioral inhibition with Current Self-Reported Inhibition (CSRI) scale. I predicted that greater behavioral inhibition would predict increased connectivity during periods of threat (vs. safety) between the BNST and the CeA, BLA and hippocampus.

To investigate whether the BNST connectivity with these areas – particularly BNST-CeA connectivity – differs between the early, middle and late stages of threat responding, I also investigated BNST connectivity during the first, second and last minutes of the threat and safe scans. I predicted that there would be greater connectivity during the threat vs. safe scan during the first time window, as the early stages of threat responding should be characterized by the CeA recruiting BNST activation. Although it is difficult to specify the exact time frame in which one would expect the inhibition of CeA via BNST projections to begin, I anticipated that the second time window may be characterized by less connectivity between the BNST and CeA during threat than safety. I predicted that our final time window would capture a period of time in which the transition between the BNST and CeA had already occurred, and as such, expected to find no difference in BNST-CeA threat vs. safe connectivity during this time window. I expected connectivity between the BLA and hippocampus to be constant for the entire period during which participants were under threat. As such, I expected greater connectivity between the BNST and both the BLA and hippocampus during the threat than safe scan, regardless of time window.

Method

Participants

Thirty-five right-handed University of Wisconsin – Milwaukee undergraduate students participated in the study. Participants gave written inform consent before participating, and were given monetary compensation. Those who were pregnant or had a metallic implant were excluded from participation. Individuals were also excluded from participation if they reported a history of seizures, Tourette's syndrome, significant head trauma, claustrophobia, hallucinations, manic episodes, Obsessive-Compulsive Disorder, recurrent panic attacks, substance use disorders, alcohol dependence, or having ever been unconscious for over a minute while not asleep or anesthetized. Those who reported currently taking antipsychotics, anticonvulsants or mood stabilizers were also excluded from participation.

Two participants withdrew from the study before completing the resting state scans, five participants were excluded from analysis due to excessive motion during the scan, two participants were excluded due to signal loss during the fMRI scan that affected the BNST region, and one was excluded due to equipment failure. Because the purpose of the study was to investigate changes in BNST connectivity associated specifically with state anxiety, 7 participants who reported experiencing as much, or more, anxiety during the safe vs. threat scan were also excluded. This resulted in data from 18 participants (14 female) being included in the analysis. Participants included in the analysis had a mean age of 21.2 years old (SD = 3.1). See Table 1 for participant demographics.

Measure of Behavioral Inhibition

The CSRI contains 31 items asking participants to report current anxious or inhibited behavior on a five-point likert scale. This measure shows high internal consistency (CSRI Cronbach's $\alpha = .78$; Reznick et al., 1992) and is correlated with the trait anxiety subscale of the State-Trait Anxiety Inventory ($r = .44$), as well as other measures of inhibition including the

Retrospective Self-Report of Inhibition scale (r = .51), the Adult Measure of Behavioral

Inhibition (r = .62), and the Retrospective Measure of Behavioral Inhibition (r = .41; Caulfield,

McAuley & Servatius, 2013). Participants used for data analysis in the current study had a mean

CSRI score of 68.39 (SD = 11.7, Minimum = 49, Maximum = 97).

Resting State Scans

Participants were asked to lie still with their eyes open during two five minute resting

state scans. Before the first scan participants were shown the following instructions: "You will

be under threat of shock during this scan, meaning that you may receive the electrical stimulus at

any time during this scan. You may receive multiple electrical stimulations during this scan."

Before the second scan, the following instructions were shown to participants: "You will be safe

from shock during this scan, meaning that you will not receive the electrical stimulus at any time

during this scan."

Participants did not receive any shocks during either the threat or safe scan. Prior to these

scans, participants completed an n-back task, which included a threat of shock component. The

procedures of this task were based on the procedures of Vytal et al. (2013). Participants

completed 1-back and 3-back tasks during 16 alternating blocks, during half of which

participants were under threat of shock. During this task, participants received six presentations

of the shock. The electrodes were be attached above the participant's right ankle before the n-

back task, and remained in place during the threat of shock resting state scan. I reasoned that

having participants complete a task involving the administration of shocks before this scan

would increase the plausibility of receiving shocks during this scan, even though none were

actually be administered.

After the threat of shock scan, a researcher removed the electrodes from the participant's

leg, ensuring that the participant knew that they would not be shocked during the safe scan. The threat and safe scans were separated by a 6 minute anatomical scan, as well as a brief single-volume EPI scan with reverse phase encode polarity. This design ensured that participants had approximately 8-10 minutes for the anxious arousal elicited by the threat of shock to subside before the safe scan began. Order of threat and safe blocks were not be counter-balanced, in order to eliminate anticipation effects, wherein participants may exhibit heightened anxiety during the safe scan if they know that a threat scan will follow shortly.

MRI Data Acquisition

MRI data were acquired on a 7-Tesla MR950 General Electric (GE Healthcare, Waukesha, WI) scanner. High-resolution T_1-weighted whole-brain anatomical images were acquired using a BRAVO gradient echo sequence (inversion time/repetition time/echo time/flip angle/field of view/matrix/slice thickness: 1050 ms/7.972 ms/3.776 ms/5°/220 mm/276 × 276 mm/.8 mm).

Partial-brain functional scans were obtained using a T_2*-weighted echo-planar image (EPI) sequence (repetition time/echo time/flip angle/number of excitations/field of view/matrix: 2300 ms/24 ms/73°/1/220 mm/224 × 224; 28 × 1-mm coronal slices; gap: 0 mm; 131 volumes) with voxel resolution of .86 mm × .86 mm × 1 mm. The scan coverage was determined for each participant by positioning the most anterior edge of the coverage just anterior to the amygdala, and then checking that coverage spanned at least 5 millimeters anterior to the anterior commissure to ensure coverage of the BNST. After the task, an additional single-volume EPI scan with reverse phase encode polarity was collected and used for susceptibility-related distortion correction.

FMRI Data Analysis

In order to avoid problems associated with global signal regression (Fox, Zhang, Snyder & Raichle, 2009; Murphy, Birn, Handwerker, Jones, & Bandettini, 2009) data were analyzed using the Analysis of Functional NeuroImages (AFNI) software package's ANATICOR processing stream (Cox, 1996). The first 3 volumes were discarded to allow spins to achieve a steady state and volumes with excessive motion were censored (Euclidean norm > .2).

Remaining EPI volumes were slice time corrected and motion corrected. To create a distortion correction template, the third volume from the task EPI data and the reverse polarity EPI scan was aligned to each participant's anatomical scan, and warped together using the "plusminus" option in AFNI's 3dQwarp (Cox, 1996). Anatomical scans were corrected for intensity field bias (Advanced Normalization Tools 2.1; Avants, Tustison & Song, 2009). EPI data were aligned to the anatomical image, non-linearly warped to the distortion correction template, and then non-linearly warped to the anatomical image. These transformations were calculated and applied in a single step to reduce the number of times the data are interpolated.

AFNI's 3dDeconvolve was used to fit the EPI data to a regression. Several regressors of no interest were modeled and the resulting residual time-series was used for performing voxel-wise correlations. Regressors of no interest included six head motion parameters and their derivatives, as well as 0.01 - 0.1 Hz bandpass filter regressors. Using the signal remaining after modeling regressors of no interest, a correlation between the mean time series for the BNST and the rest of the brain was computed. This was done separately for the left and right BNST, resulting in two correlation maps – one with the left BNST as a seed, and one with the right BNST as a seed. As correlation values do not follow a normal distribution, the values within these correlation maps were converted to Z-values using a Fisher's Z-transformation for use in group-level statistics.

Data were extracted from the resulting Z-maps for each region of interest (ROI; other than the BNST seed region) for statistical analysis. Average Z-score was extracted for each subject for the CeA, BLA and hippocampus. For each ROI data was extracted for each side using the Z-map representing correlation with the ipsilateral BNST. For example, average Z-score for the left CeA was extracted from the Z-map representing correlation with the left BNST, and average Z-score for the right CeA was extracted from the Z-map representing correlation with the right BNST. None of the extracted values were more than 3.5 standard deviations from the mean. Extracted values were used in a linear mixed model using ROI (CeA vs. BLA vs. hippocampus), Condition (threat vs. safe) and self-reported Behavioral Inhibition (continuous) as fixed factors, and subject as a random factor. An ROI x Condition x Behavioral Inhibition x Side ANOVA was used to determine significant effects within this model. To investigate whether any of the ROIs included in this analysis exhibited significant connectivity with the BNST when analyzed individually, separate linear mixed models for each area were also run, using Condition x Behavioral Inhibition x Side ANOVAs within each ROI.

Time Window Analysis

Based on Davis et al.'s (2010) model of the extended amygdala, the threat response may be initially characterized by increased positive connectivity between the CeA and BNST, followed by negative connectivity as the BNST inhibits CeA activity, allowing for a transition from the CeA mediated fear response, to the BNST mediated anxiety response. After this transition takes place, there should be relatively little connectivity between the CeA as the BNST coordinates the anxiety response independent of CeA input. To test this hypothesis I extracted average connectivity Z-scores using the BNST as a seed from the CeA, BLA and hippocampus for three time windows, corresponding to early, middle and late connectivity. The first time

window included the first 26 TRs following the 3 TRs removed to allow the scanner to reach a steady state (6.9 – 66.7 s following onset of the scan). The second time window included the 26 TRs immediately following our first time window (66.7 – 126.5 s following the onset of the scan). The third time window included the last 26 TRs of the scan (204.2 – 300 s following the onset of the scan).

Average connectivity Z-values for these time windows were extracted from each ROI. Values that were greater than 3.5 standard deviations away from the mean were removed and treated as case-wise missing values in the analysis, there were three such values. Remaining observations were submitted to a linear mixed model with Time Window (early vs. middle vs. late), ROI (CeA vs. BLA vs. hippocampus), Condition (threat vs. safe) and self-reported Behavioral Inhibition (continuous) as fixed factors, and subject as a random factor. A Time Window x ROI x Condition x Behavioral Inhibition ANOVA was used to determine significant effects within this model. To investigate whether any of the ROIs included in this analysis exhibited significant connectivity with the BNST when analyzed individually, separate linear mixed models for each area were also run, using Time Window x Condition x Behavioral Inhibition x Side ANOVAs within each ROI.

ROIs

BNST ROIs were traced by hand in AFNI using the anatomical boundaries detailed by Avery et al. (2014). The ROIs were visually inspected by overlaying them onto the EPI data and adjusted if necessary, for example if the ROI encroaches onto lateral ventricle. Average ROI size was 69.95 mm^3 for the left BNST and 61.57 mm^3 for the right BNST.

For the CeA, BLA and hippocampus, spherical ROIs were created, using coordinates from Torrisi et al.'s (2015) study of resting state connectivity of the BNST. Torrisi et al.

investigated resting state connectivity at high resolution using 7T scanning. They reported significant connectivity between the BNST and the right CeA (MNI coordinates: x = 18.4, y = -3.4, z = -11.5), right BLA (MNI coordinates: x = 23.6, y = -2.2, z = -19.3) and left (MNI coordinates: x = -20.6, y = 13.8, z = -18) and right anterior hippocampus (MNI coordinates: x = 19.7 y = -15.2 z = -14.2). I used these coordinates to create individual ROIs by non-linearly warping each subject's anatomical scan to the MNI template using AFNI's 3dQwarp (Cox, 1996). The inverse of the resulting warp was used to warp these coordinates from MNI space into each individual's anatomical space. Spherical ROI's with a radius of 2.5 mm were created at each of these coordinates in anatomical space. While Torrisi et al. (2015) did not find clusters of connectivity between the BNST and either the left CeA of left BLA, connectivity between the amygdala and BNST has been implicated in anxiety bilaterally (Cai et al., 2012). As such, coordinates for the right CeA and right BLA were created by changing the sign of the x coordinate, allowing for the bilateral creation of these ROIs. Examples of each of the ROIs for one subject can be seen in Figure 2.

<div align="center">

Results

</div>

Initial Analysis

To test whether sustained threat elicits changes in BNST connectivity, and whether this effect is modulated by individual differences in behavioral inhibition, average connectivity Z-scores between BNST seed ROIs and the ipsilateral CeA, BLA and hippocampus ROIs were extracted and submitted to a linear mixed model using ROI (CeA vs. BLA vs. hippocampus), Condition (threat vs. safe) and self-reported Behavioral Inhibition (continuous) as fixed factors, and subject as a random factor. An ROI x Condition x Behavioral Inhibition x Side ANOVA was used to determine significant effects within this model. Mean connectivity Z-scores used in this

analysis can be seen in Figure 3.

None of the effects in this model were significant, including the main effect of Condition, $X^2(1) = .15$, $p = .7$, the Condition × Behavioral Inhibition interaction, $X^2(1) = .03$, $p = .86$, all interactions involving ROI (ps > .24), and all other effects (ps > .28).

To investigate whether any of the ROIs included in this analysis exhibited significant connectivity with the BNST when analyzed individually, I ran separate linear mixed models for each area, using Condition x Behavioral Inhibition x Side ANOVAs within each ROI. However, none of these analyses yielded any significant effects (ps>.1). Thus, this analysis found no evidence of differences in BNST connectivity between threat conditions or differences associated with individual differences in Behavioral Inhibition within the CeA, BLA or hippocampus.

Early vs. Late Threat Connectivity

To investigate how time course affects threat vs. safe connectivity between the BNST and CeA, BLA and hippocampus, connectivity values were extracted for each ROI for each condition, for three time windows, corresponding roughly to the first, second and fifth minute after threat onset. A linear mixed model with Time Window (early vs. middle vs. late), ROI (CeA vs. BLA vs. hippocampus), Condition (threat vs. safe) and self-reported Behavioral Inhibition (continuous) as fixed factors, and subject as a random factor was computed. A Time Window x ROI x Condition x Behavioral Inhibition ANOVA was used to determine significant effects within this model.

This analysis found no significant main effect of Condition, $X^2(1) = 2.1$, $p = .15$, or any other main effect (ps > .12). There was a trend toward an Area x Condition interaction, $X^2(1) = 5.96$, $p = .051$, with the BLA exhibiting a larger difference in connectivity scores between threat

(M = .009) and safe scans (M = -.012), $X^2(1) = 4.09$, $p = .13$, in comparison to both the CeA,

$X^2(1) = 2.63$, $p = .21$, and hippocampus, $X^2(1) = 1.29$, $p = .26$ (Holm-Bonferroni corrected).

However, none of these comparisons were statistically significant. There were no other

significant effects in this ANOVA (ps > .1)

To investigate whether any of the ROIs included in this analysis exhibited different

patterns of connectivity with the BNST when analyzed individually, I ran separate linear mixed

models for each area, using Condition x Behavioral Inhibition x Side x Time Window ANOVAs

within each ROI.

Using connectivity between the BNST and CeA as the dependent variable in a Condition

x Behavioral Inhibition x Side x Time Window ANOVA revealed no difference in connectivity

scores during the threat scan (M = .015) relative to the safe scan (M = -.001), $X^2(1) = 3.07$, $p =$

.08. There were no other significant main effects (ps > .21), and no Condition x Behavioral

Inhibition interaction, $X^2(1) = .003$, $p = .96$. There was, however, a trend toward a Condition x

Behavioral Inhibition x Time Window interaction within the CeA, $X^2(1) = 5.8$, $p = .055$ (see

Figure 4). This interaction suggests that the time course of BNST-CeA connectivity for threat vs.

safety was modulated by Behavioral Inhibition. While Behavioral Inhibition predicted greater

BNST-CeA connectivity during the safe (b = .002) than threat scan (b = -.001) for the early time

window, $X^2(1) = 3.44$, $p = .19$, the reverse was true during the middle (safe: b = .000; threat: b =

.002), $X^2(1) = 2.14$, $p = .29$, and late time windows (safe: b = -.0004; threat: b = .0003), $X^2(1) =$

.23, $p = .63$, although none of these comparisons were statistically significant.

A Condition x Behavioral Inhibition x Side x Time Window ANOVA using connectivity

between the BNST and BLA as the dependent variable revealed a trend toward greater

connectivity during the threat (M = .009) than during the safe scan (M = -.012), $X^2(1) = 3.61$, $p =$

.06. There was also a significant effect of Side, $X^2(1) = 4.4$, $p = .04$, with greater BNST-BLA

connectivity of the right (M = .01) than on the left (M = -.013) side. There were no interactions

between Condition and Time Window, $X^2(1) = 4.84$, $p = .09$, or Condition and Behavioral

Inhibition, $X^2(1) = .73$, $p = .39$, or any other significant effects in the BLA ($ps > .14$).

Using connectivity between the BNST and hippocampus as the dependent variable in a

Condition x Behavioral Inhibition x Side x Time Window ANOVA revealed no main effect of

Condition, $X^2(1) = 1.53$, $p = .22$, no interaction between Condition and Behavioral Inhibition,

$X^2(1) = .16$, $p = .69$, and no other significant effects ($ps > .3$).

Discussion

An influential model of the extended amygdala argues that connectivity between the CeA

and BNST are critical in the generation of the anxiety response to sustained threat (Davis et al.,

2010). This model also suggests that connectivity between these areas may occur in multiple

phases. The early stage of the anxiety response may be characterized by increased BNST-CeA

connectivity, as the CeA recruits the BNST to threat responding. The middle stage of the anxiety

response is thought to involve negative connectivity between these areas, as the BNST inhibits

the CeA, allowing for a transition between the CeA mediated fear response and the BNST

mediated anxiety response. The late stage of the anxiety response may involve little connectivity

between the BNST and CeA, as the BNST may coordinate the anxiety response independently,

once fully activated. Due to the paucity of human research testing whether state anxiety is

accompanied by increases BNST-CeA connectivity, I tested this prediction by having

participants complete high resolution resting state scans while under threat of an unpredictable

shock, and while safe. I also tested whether connectivity in these areas unfolds over time, by

investigating this connectivity in early, middle and late time windows, corresponding roughly to

the first, second and fifth minute after the onset of threat, respectively. As BNST activity is altered by behavioral inhibition (Fox et al., 2008; Oler et al., 2009), I also tested whether individual differences in behavioral inhibition is associated with changes in connectivity between the BNST and CeA during threat.

The initial analysis, looking at connectivity during the threat vs. safe scan as a whole, found no evidence for differences in BNST-CeA connectivity during threat vs. safety. This analysis also found no interaction between threat and individual differences in behavioral inhibition. However, the analysis investigating connectivity in these areas during early, middle and late time windows revealed a marginal trend toward a three way interaction between Threat Condition, Time Window and Behavioral Inhibition. While the lack of significant follow-up tests makes interpretation of this interaction difficult, this suggests that the time course of BNST-CeA connectivity is altered in participants who are high in behavioral inhibition. These results highlight the need for future researchers to consider time course when investigating the activity and connectivity of the extended amygdala in response to threat.

Based on research suggesting that the BLA may play a role in relaying sensory cues of threat to the BNST (Walker & Davis, 1997; Davis & Whalen, 2001), I predicted greater BNST-BLA connectivity during the threat vs. safe scan. While the initial analysis found no evidence for this, the analysis investigating connectivity within the early, middle and late time windows found a marginally larger BNST-BLA connectivity during threat vs. safety. Given that there was no interaction between Threat Condition and Time Window on BNST-BLA connectivity, it is interesting that the analysis including Time Window as a variable found a marginally significant effect of Threat Condition on connectivity between these areas, while the initial analysis without this variable did not. It is possible that although the main effect of Threat Condition did not

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interact with Time Window, that there was some variance in BNST-BLA connectivity associated with Time Window that, once accounted for, allowed the main effect of Threat Condition to become marginally significant. However, while this finding is in line with rodent research on BNST-BLA connectivity, this effect should be seen as preliminary, given that it was only marginally significant, and was non-significant in the initial analysis. If future research demonstrates that this effects is reliable, this could suggest increased relay of sensory signals of threat from the BLA to BNST during conditions of sustained threat.

While my analyses revealed some mixed evidence for greater BNST-BLA connectivity during threat than safety, my prediction that BNST-BLA connectivity would be modulated by individual differences in behavioral inhibition was not supported. This is somewhat surprising, given that the BLA is thought to relay signals of potential threat in the environment to the BNST (Walker & Davis, 1997; Davis & Whalen, 2001), and that high anxious individuals often exhibit increased attention toward threat cues (Bar-Haim, Lamy, Pargamin, Bakermans-Kranenburg & Van Ijzendoorn, 2007; Mathews, Mackinstosh & Fulcher, 1997). It may be that because the threat of unpredictable shock manipulation used in the current study did not involve any cues that signaled potential threat, there were no relevant cues to drive BNST-BLA connectivity. If this is the case, a threat manipulation that involves a cue that predicts the shock, but does so with some uncertainty (i.e. the cue is only a valid predictor of shock on some trials) would more effectively elicit BNST-BLA connectivity. It is also possible that measures of trait anxiety are better predictors of the increased attention toward threat in high anxious individuals, rather than the related, but separate construct of behavioral inhibition used in the current study. If this is the case, measures of trait anxiety may also be better predictors of changes in BNST-BLA connectivity during conditions of threat and safety. Alternatively, the current study may simply

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not have had adequate power to detect individual differences in this circuitry.

Based on past research implicating the hippocampus in the anxiety response (File, Kenny & Cheeta, 2000; Gray & McNaughton, 1996), as well as research suggesting that the BNST relays signals from the hippocampus to the hypothalamic-pituitary-adrenal axis, I predicted that BNST-hippocampus connectivity would increase during conditions of threat, and that this increase would be larger for participants who are high in behavioral inhibition. I found no evidence for either of these predictions. The most robust findings linking the hippocampus to the anxiety response comes from contextual fear conditioning (Maren, 2001). In contrast to contextual fear conditioning tasks, participants in the current study were explicitly told whether they were under threat of shock or safe from shock. This made contextual cues irrelevant. If the primary role of the hippocampus in the anxiety response is related to encoding contextual threat cues, this could explain the lack of changes in BNST-hippocampus connectivity during threat vs. safety in the current study.

Given that our results suggest that behavioral inhibition modulates the time course or BNST-CeA connectivity in response to threat, future research is needed to better characterize this interaction. The small sample size of the current study was likely inadequate to fully characterize individual differences in BNST-CeA connectivity, which likely contributed to the lack of significant differences in my follow-up tests. Future studies with larger sample sizes should seek to clarify the nature of the Threat Condition x Time Window x Behavioral Inhibition interaction found in the current study.

The design of the current study, with participants undergoing one threat scan and one safe scan, may have also contributed to a lack of power for detecting changes in connectivity between the extended amygdala through time. Research has demonstrated that the reliability of a resting

state scan is reduced as the length of the scan decreases (Birn et al., 2013). As such, the current study's analysis using three one minute time windows may have resulted in greater variation in connectivity estimates, resulting in a loss of power. Future studies investigating how connectivity in the extended amygdala changes during conditions of threat and safety would likely benefit from having participants undergo multiple transitions between threat and safety. This would allow researchers to average the time course of connectivity between these regions over several trials, enabling for more reliable estimates. Such a study would also lend itself to a more fine-grained analysis of dynamic functional connectivity, rather than the somewhat arbitrary one-minute time windows used in the current study.

One limitation to the current study is that order was not counterbalanced – the threat scan always came before the safe scan. This was done to remove anticipation effects, wherein a subject may experience increased anxiety anticipating a future threat of shock. This design means that the order of the conditions was confounded with the threat of shock manipulation. As such, it is impossible to eliminate the possibility that the reported effects are due to the order of condition presentation, rather than due to the threat of shock manipulation. For example, differences between the threat and safe scans could be due to the fact that the threat scan followed a prior n-back task that had alternating periods of threat and safety, while the safe scan followed the acquisition of the anatomical image. Future research is needed to test whether sustained threat is accompanied by changes in BNST connectivity in a counterbalanced design.

Another limitation of the current study is that substance use was not controlled for. Substance use is both correlated with anxiety (Conway, Compton, Stinson & Grant, 2006) and associated with altered functioning of affective neuro-circuitry (Quickfall & Crockford, 2006; Verdejo-Garcia, Perez-Garcia, Sanchez-Barrera, Rodriguez-Fernandez & Gomez-Rio, 2007).

Given that the current study was investigating individual differences in neural functioning associated with a behavioral inhibition, which is closely related to anxiety, substance use presents a potential confound.

The current study tested whether periods of sustained threat are accompanied by increased connectivity between the BNST and the CeA, BLA and hippocampus, respectively. In addition, I investigated how this connectivity may change over the course of a sustained threat, and whether behavioral inhibition predicts greater BNST connectivity with these areas in response to threat. I found no evidence that BNST-hippocampus connectivity increases during sustained threat or that this connectivity is altered in participants who are high in behavioral inhibition. However, I found a marginal trend toward increased BNST-BLA connectivity during conditions of threat, which could suggest increased relay of sensory signals of threat to the BNST during sustained threat. Although I did not find a significant main effect of threat on BNST-CeA connectivity, our results suggest an interaction in which the time course of BNST-CeA connectivity in response to threat is altered in those who are high in behavioral inhibition. Because the lack of significant follow-up tests make interpreting this effect difficult, future research should seek to further characterize how individual differences alter the time course of BNST-CeA connectivity during conditions of threat and safety. Doing so will allow researchers to develop a clearer picture of how the amygdala coordinates the anxiety response to sustained threat, and provide further testing of the Davis et al. (2010) model of the human extended amygdala.
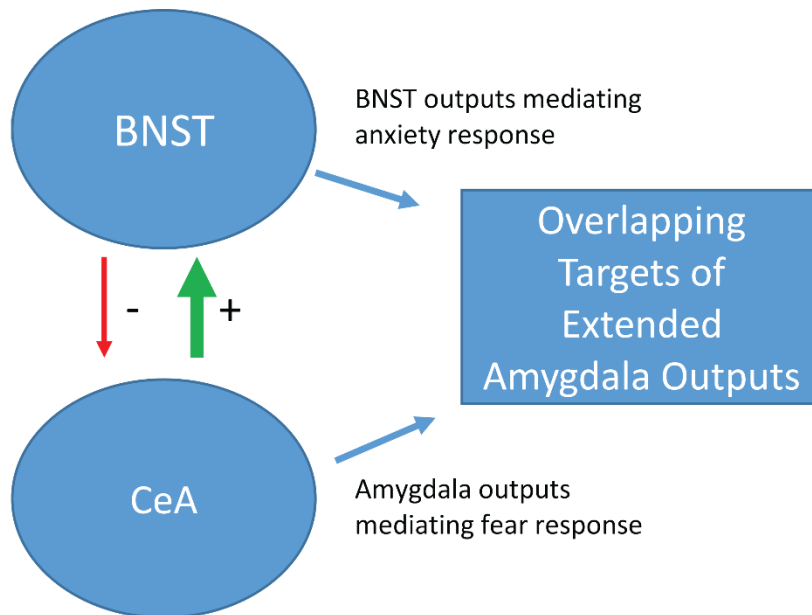
Figure 1. According to the Davis et al. (2010) model of the extended amygdala, outputs of the CeA mediate the fear response, while outputs of the BNST mediate the anxiety response. During immediate threat the CeA is activated and coordinates the fear response. When threat is sustained or uncertain, the CeA activates the BNST which coordinates the anxiety response. The BNST, in turn, inhibits the CeA, allowing for a smooth transition between fear and anxiety.
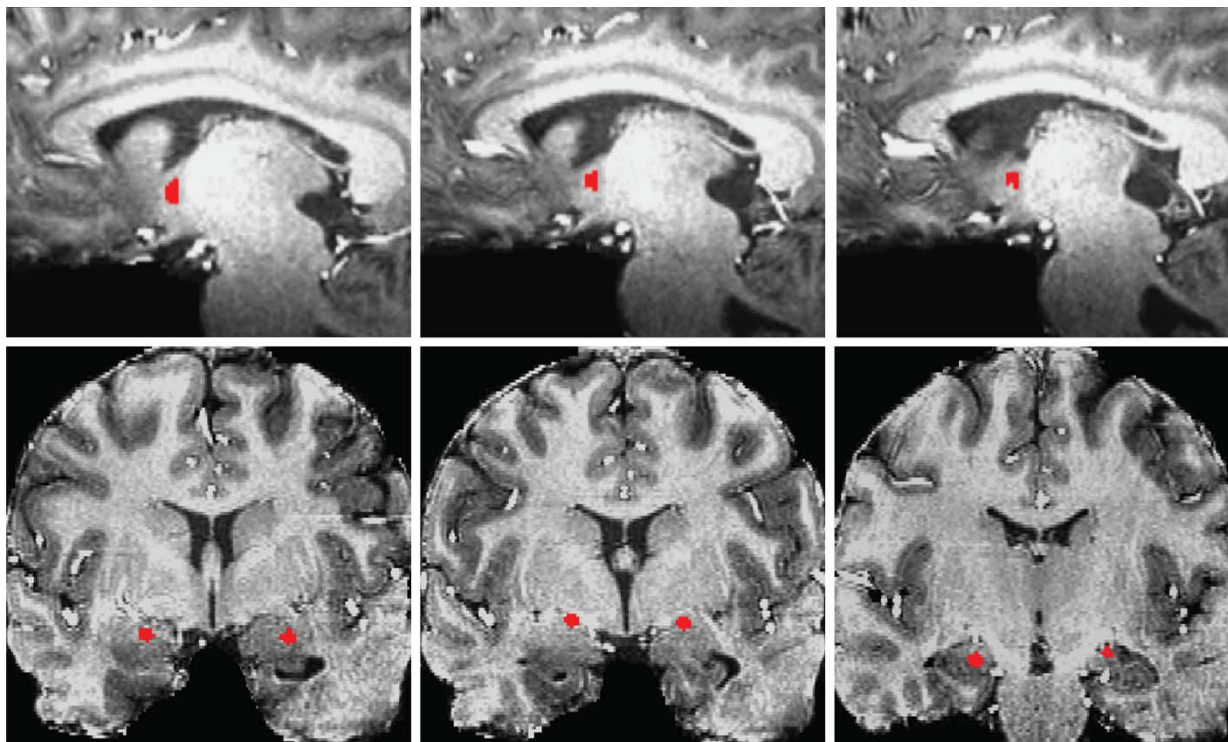
Figure 2. ROIs for BNST (top), BLA (bottom left), CeA (bottom center) and hippocampus (bottom right). BNST ROIs were traced by hand, using the anatomical boundaries detailed by Avery et el. (2014), and were used as a connectivity seed region. BLA, CeA, and hippocamus ROIs were created by generating spheres at locations previously found to have significant connectivity with the BNST (Torrisi et al., 2015).
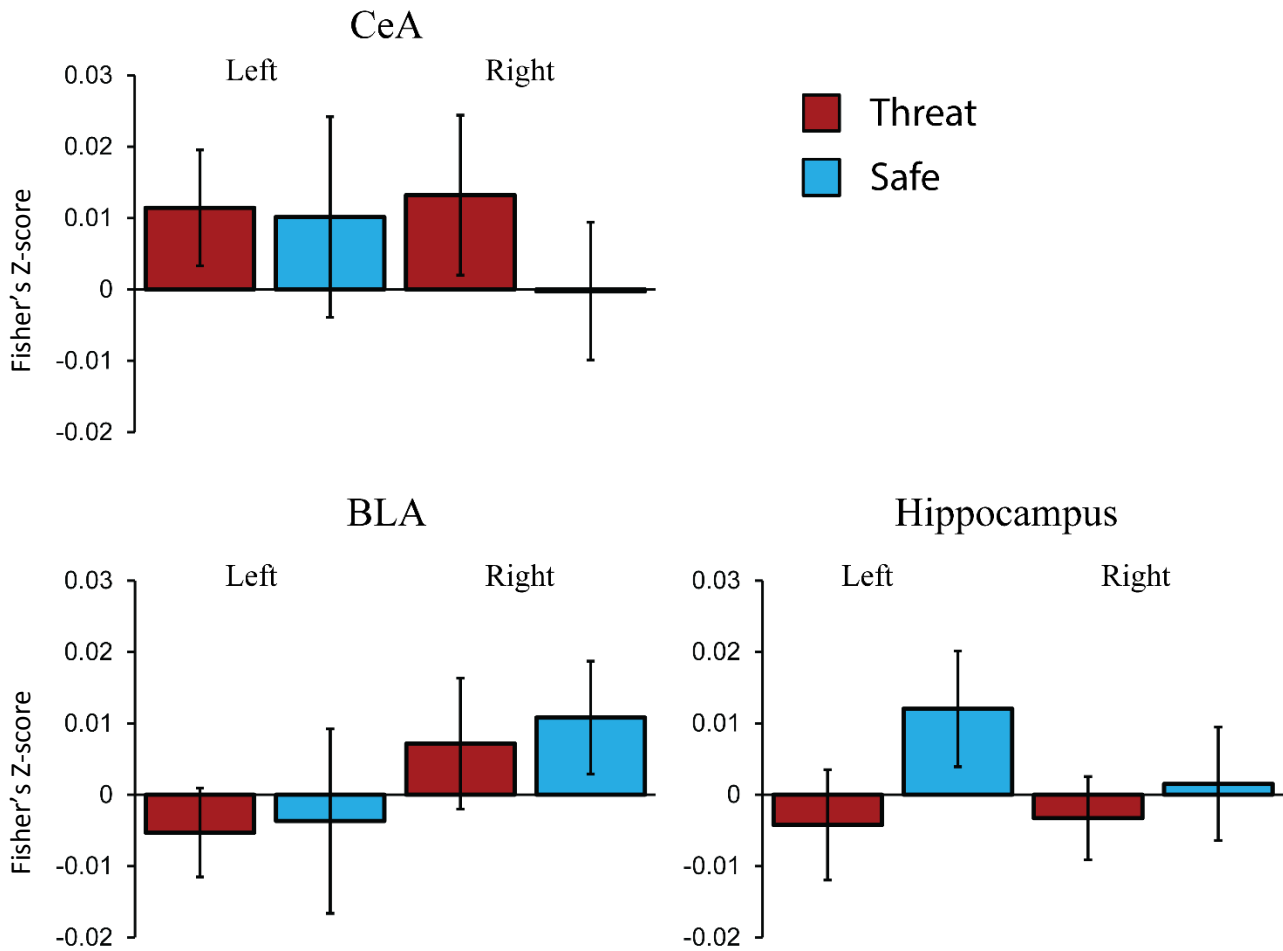
Figure 3. Mean connectivity between the BNST and the ipsilateral CeA (top left), BLA (bottom left) and Hippo-campus (bottom right). Bars depict mean Fisher's Z-score for connectivity between each ROI and the ipsilateral BST averaged across entire 5-minute scan, for threat (red) and safe (blue) conditions, respectively. Error bars depict standard error.

BNST-CeA Safe Connectivity
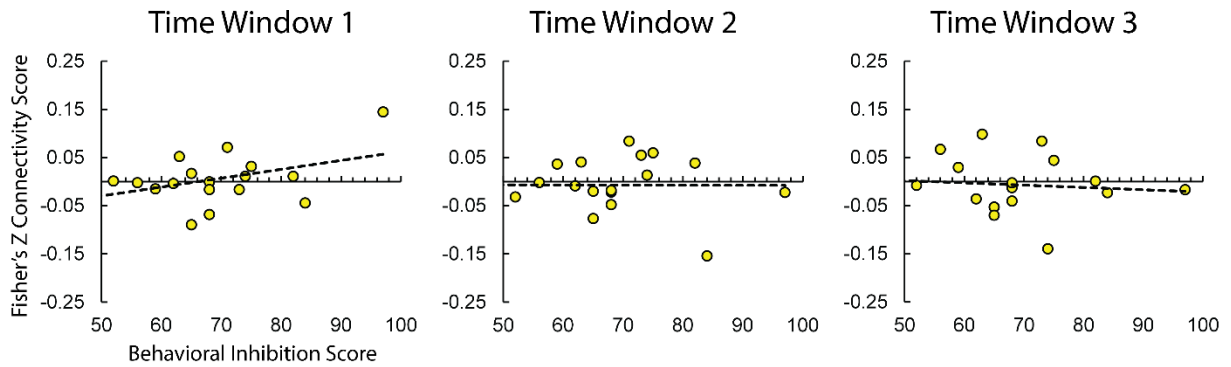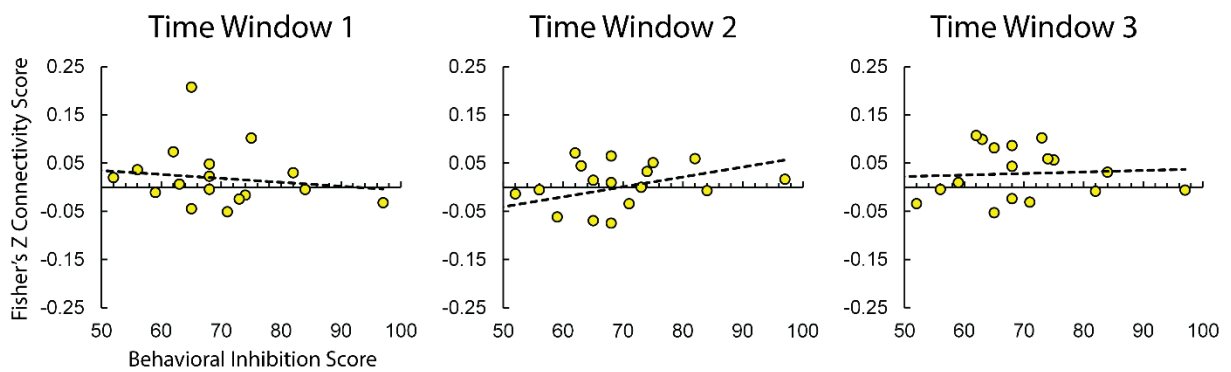

BNST-CeA Safe Connectivity

Figure 4. Regressions using self-reported behavioral inhibition to predict BNST-CeA connectivity during the early, middle and late time windows of the safe and threat scans. The marginally significant Time Window x Condition x Behavioral Inhibition interaction suggests that behavioral inhibition predicts BNST-CeA connectivity differentially across the time windows of the threat and safe scans. While none of the follow-up tests for this interaction were significant, the largest individual slopes involved Behavioral Inhibition potivitely predicting greater BNST-CeA connectivity during the first time window of the safe scan, and during the second time window of the threat scan.

Table 1

Sample Demographics

		N	Percent
Age	18-19	8	44.4
	20-21	4	22.2
	22-23	3	16.7
	24-25	1	5.6
	26+	2	11.1
Gender	Female	4	22.2
	Male	14	77.8
Ethnicity	African American	1	5.6
	American Indian / Alaskan Native	0	0
	Asian or Pacific Islander	1	5.6
	Caucasian	14	77.8
	Hispanic	1	5.6
	Other or unknown	1	5.6

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CIRRICULUM VITAE

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Education

A.S., Salt Lake Community College, April 2007
B.S., Brigham Young University, August, 2009
M.S., University of Wisconsin – Milwaukee, May, 2013
Ph.D., University of Wisconsin – Milwaukee, May 2017

Publications

Published

Pedersen, W. S., Balderston, N. L., Miskovich, T. A., Belleau, E. L., Schultz, D. H., Helmstetter, F. J., & Larson, C. L. (in press). Disentangling the effects of stimulus novelty and negativity in the amygdala, hippocampus, and bed nucleus of the stria terminalis. *Social, Cognitive and Affective Neuroscience*. Link

Pedersen, W. S., & Larson, C. L. (2016). State anxiety carried over from prior threat increases LPP amplitude during an instructed emotion regulation task. *Emotion 16*(5), 719-729. Link

Miskovich T.A., **Pedersen, W.S.**, Belleau, E. L., Shollenbarger, S., Lisdahl, K. M. & Larson, C. L. (2016). Cortical gyrification patterns associated with trait anxiety. *PLoS ONE, 11*(2): e0149434.

Taubitz, L.E., **Pedersen, W.S.**, & Larson, C.L. (2015). BAS reward responsiveness: A unique predictor of positive psychological functioning. *Personality and Individual Differences, 80*, 107-112.

Pedersen, W. S. (2013). Using BIS and BAS sensitivity to predict psychopathology, emotion regulation and well-being. *Theses and Dissertations, 145*. Link

Under Review

Pedersen, W. S., Muftuler, L. T. & Larson, C. L. (under revision at *Neuroimage*). Disentangling the effects of novelty, valence and trait anxiety in the bed nucleus of the stria terminalis, amygdala and hippocampus with high resolution 7T fMRI. Link

Belleau, E.L., **Pedersen, W.S.**, Miskovich, T., & Larson, C.L. (under review at *Neuropsychopharmacology*). Fear extinction-related neural plasticity in cortico-limbic pathways and relationships with trait anxiety.

Stout, D.M., Shackman, A.J., **Pedersen, W.S.**, Miskovich, T., & Larson, C.L. (under review at *Neuropsychopharmacology*). Neural circuitry governing anxious individuals' mis-allocation of working memory to threat.

In Preparation

Pedersen, W. S. & Larson, C. L. (in prep.). Resting state connectivity of the bed nucleus of the stria terminalis while under threat of unpredictable shock and while safe: a high resolution 7T fMRI study.

Pedersen, W. S. & Larson, C. L. (in prep.). Negative slow wave ERP amplitude altered by threat of unpredictable shock during the suppression of implicit race bias.

Presentations

Pedersen, W. S., Balderston, N. L., Miskovich, T. A., Belleau, E. L., Schultz, D. H., Helmstetter, F. J. & Larson, C. L. (2016). Disentangling the effects of stimulus novelty and affective valence in the amygdala, hippocampus, and bed nucleus of the stria terminalis. Presented at the Annual Society for Psychophysiological Research Conference, Minneapolis, MN.

Pedersen, W. S. & Larson, C. L. (2016). State anxiety carried over from prior threat increases LPP amplitude during an instructed emotion regulation task. Presented at The Society of Affective Science Conference, Chicago, IL.

Wenner, L. J., **Pedersen, W. S.** & Larson, C. L. (2016). The effects of state anxiety on race bias and brain activity related to cognitive control. Presented at the UW-System Symposium for Undergraduate Research and Creative Activity, Milwaukee, WI.

Danzynger, B. S., **Pedersen, W. S.**, & Larson C. L. (2015). Regulating under stress: The impact of state anxiety on instructed emotion regulation. Presented at the UWM Association of Graduate Students in Psychology Conference, Milwaukee, WI.

Jeske, A. R., **Pedersen, W. S.**, Tadych, A. S. & Larson, C. L. (2014). Too anxious to regulate: The effect of an ongoing stressor on instructed emotion regulation. Presented at the UW-System Symposium for Undergraduate Research and Creative Activity, Milwaukee, WI.

Miskovich T. A., **Pedersen W. S.**, Belleau E. L., & Larson, C. L. (2014). Decreased cortical gyrification associated with trait anxiety. Presented at The Society of Affective Science Inaugural Conference, Bethesda, MD.

Pedersen, W. S., Balderston, N. L., Miskovich, T. A., Belleau, E. L., Schultz, D. H., Helmstetter, F. J., Larson, C. L. (2014). Independent effects of novelty and valence on the amygdala bold response. Presented at the Annual Society for Affective Science Conference, Bethesda, MD.

Pedersen, W. S., Shackman, A. J., Blaisdell, J. A., Belleau E. L., Stout D. M. & Larson C. L. (2013). Posterior parietal cortex activation predicts working memory capacity for faces. Presented at the Annual Society for Cognitive Neuroscience Conference, San Fransisco, CA.

Tadych, A. S., Larson, C. L., **Pedersen, W. S.** (2013) The effect of mental fatigue on emotion regulation: An ERP study. Presented at the UW-System Symposium for Undergraduate Research and Creative Activity, Milwaukee, WI.

Grants

2015   MCW Imaging Center Daniel M. Soref Charitable Trust Grant, with Christine Larson, Ph.D.

Research Skills

fMRI

- Analysis of task-based and resting state data in AFNI

- Collection and analysis at 3T and 7T

- Event-related and block designs

- AFNI volume-based and SUMA surface-based analysis

- Non-linear registration in FSL and AFNI

- Freesurfer anatomical structural analysis and ROI identification

- Definition of the bed nucleus of the stria terminalis by hand

- ANTs N4 bias field correction

- Blip-up blip-down distortion correction in AFNI

- Automated fMRI analysis via C shell scripts

- Scripting for parallel processing on super computer in SLURM

ERP, SCR & EMG

- Data collection

- Analysis in the Matlab toolboxes, EEGLAB and ERPLAB

- Automated analysis via scripting in EEGLAB and ERPLAB

- Skin-conductance collection and analysis

- EMG collection and analysis

Experimental Design

- Designing cognitive and affective tasks in e-prime

- Event-related, block design, and resting state fMRI

- fMRI stimulus timing optimization using AFNI's RSFgen and 3dDeconvolve

- ERP and behavioral (accuracy and RT) task design

- Use of multiple paradigms including: Instructed emotion regulation, implicit association, joystick approach/avoidance, affective priming, change detection, attentional blink, go/no go, threat of shock, N-back, mental fatigue induction, novel image task, temporal uncertainty task

- Implementation of automated randomization and counter-balancing in e-prime

Statistical Analysis

- SPSS, R, SAS and Mplus

- Mixed linear modeling

- Between-subjects, repeated measures and mixed ANOVA

- Regression

- Structural equation modeling

- Correction for multiple comparison in AFNI, SPSS, R and SAS

Manuscript Preparation

- Compiling literature reviews and references

- Writing manuscripts and grant proposals

- Creation of effective, high-resolution graphics using excel, GIMP and adobe illustrator

Data Management

- Design and implementation of data backup strategy for ~20 TB of data involving RAID storage and computer networking

- C shell programming for automated fMRI and EEG data backup

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Awards

2015   Department of Psychology Summer Graduate Research Fellowship

2010-2011 UWM Chancellor's Graduate Student Award, Glenn E. and Olive W. Nielson Academic Scholarship

2007-2009 BYU Spring/Summer Academic Scholarship

2007-2009 BYU Dean's List

2006-2007 SLCC Dean's List

Ad Hoc Reviewer

Psychophysiology, *Cognition and Emotion*

Teaching Experience

Fall 2010   Teaching Assistant, Research Methods in Psychology

Spring 2011 Teaching Assistant, Research Methods in Psychology

Fall 2011   Teaching Assistant, Research Methods in Psychology

Spring 2012 Coordinating Teaching Assistant, Research Methods in Psychology

Fall 2013   Teaching Assistant, Research Methods in Psychology

Spring 2014 Teaching Assistant, Research Methods in Psychology

Fall 2014   Teaching Assistant, Research Methods in Psychology

Spring 2015 Coordinating Teaching Assistant, Cognitive Processes

Fall 2015   Coordinating Teaching Assistant, Research Methods in Psychology

Spring 2016 Teaching Assistant, Research Methods in Psychology

Fall 2016   Teaching Assistant, Research Methods in Psychology

Professional Organizations

2016-Present Society for Psychophysiological Research

2014-Present American Psychological Society

2014-Present Society for Affective Sciences

2013-Present Cognitive Neuroscience Society