August 2016

Neural Plasticity of Extinction: Relations with Anxiety and Extinction Retention

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NEURAL PLASTICITY OF EXTINCTION: RELATIONS WITH ANXIETY AND EXTINCTION RETENTION

by

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A Dissertation Submitted in

Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

in Psychology

at

University of Wisconsin-Milwaukee

August 2016

ABSTRACT

NEURAL PLASTICITY OF EXTINCTION LEARNING: RELATIONS WITH ANXIETY AND EXTINCTION RETENTION

by

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The University of Wisconsin-Milwaukee, 2016
Under the Supervision of Associate Professor Christine Larson

Anxiety is a significant public health problem characterized by substantial psychological, physical, and economic burden. A key feature of anxiety is the inability to regulate fear. Aberrant extinction of conditioned fear is one prominent model of the etiology of anxiety disorders. Previous studies have shown that the neural circuitry underlying anxiety pathology overlaps with that mediating fear extinction learning. Recently, more precise pathways supporting the expression (CMA-aMCC) and inhibition (BLA-vmPFC) of conditioned fear have been identified, and dysfunction in these pathways has been linked with anxiety. However, this work has focused on examining these pathways at one point in time, outside of the context of learning, and no one has examined plastic changes in functional activity before and after extinction learning. In addition, no one has applied this inquiry to individual differences in anxiety and extinction retention. This gap in knowledge is a problem because deficits in extinction-induced neural plasticity may be a substantial contributing factor to sustained fear responses in anxiety. The aim of this project was to examine changes in the strength of CMA-aMCC and BLA-vmPFC pathways from before to after extinction learning and how this is related to anxiety and retention of

extinction. In a more exploratory fashion, I investigated the degree to which extinction-related plasticity varies as a function of white matter integrity within these pathways. Our results indicated that extinction learning is associated with enhanced plasticity in fear inhibition circuits (BLA-vmPFC and CMA-vmPFC). Plasticity in these circuits appears to be intact in high anxious individuals. However, trait anxiety was positively associated with strengthened connectivity in a fear expression pathway (BLA-aMCC). Enhanced plasticity within a fear expression circuit likely contributes to fear inhibition problems, a core feature of anxiety problems.

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ACKNOWLEDGEMENTS

I would like to thank my dissertation committee, Dr. Christine Larson, Dr. Fred Helmstetter, Dr. Adam Greenberg, Dr. Debbie Hannula, and Dr. Ira Driscoll for their helpful guidance and feedback on the project. I would especially like to thank Christine Larson for her dedicated mentorship and unwavering support. Additionally, I would like to thank Walker Pedersen and Tara Miskovich for all of their help with data collection for the project.

The Public Health Impact of Anxiety Disorders

Anxiety disorders are the most common class of mental health disorders, with a lifetime prevalence of 28.8% (Kessler et al., 2005). According to the World Health Organization, by 2020 anxiety and depressive disorders combined will represent the second greatest illness burden universally (WHO, 2001). The high prevalence of anxiety disorders comes with a large societal burden, costing the United States an estimated $42.3 billion (Greenberg, et al., 1999), as well as a substantial burden on sufferers and their families. (e.g., Mendlowicz & Stein, 2000). The Research Domain Criteria (RDoC) project developed by the NIMH emphasizes a focus on underlying mechanisms (e.g., core brain dysfunction) that may cut across different disorder categories and normal/abnormal psychological functioning. Trait anxiety, which involves a general tendency to respond to mild threat with exaggerated negative reactivity, has been shown to be a core vulnerability marker underlying all anxiety disorders (e.g., Brown, Chorpita, & Barlow 1998; Gershuny & Sher, 1998), and accounting for up to 50% of the genetic contribution to anxiety pathology (Hettema, Neale, Myers, Prescott, & Kendler, 2006). Therefore, characterizing the neural mechanisms implicated in trait anxiety will be important for gaining a better understanding of the etiology of anxiety disorders.

Extinction Learning is a Central Model of Impaired Fear Inhibition in Anxiety Pathology

A prominent model for assessing underlying fear regulation problems, a core feature of anxiety pathology (Barrett & Armony, 2009; Blechert, Michael, Vriends, Margraf, & Wilhem, 2007; Hermann, Ziegler, Birbaumer, & Flor, 2002; Michael, Blechert, Vriends, Margraf, & Wilhem, 2007), is fear extinction learning, a process by which an organism learns that an object that was previously associated with threat no longer predicts a threatening outcome. Deficits in extinction *retention* in particular (Berry, Rosenfield, & Smits 2009; Anderson & Insel, 2006;

Milad et al., 2009) likely contribute to anxiety pathology (e.g., Larson, Nitschke, & Davidson, 2007). Furthermore, when examined with neuroimaging, initial extinction learning and extinction retention have been shown to share neural circuitry also implicated in anxiety (e.g., Barret & Armony, 2009; Milad et al., 2009). Given that extinction learning maps onto core behavioral symptoms and closely aligns with the dysfunctional neural circuitry seen in anxiety, several researchers have advocated conceptualizing anxiety disorders as disorders of abnormal fear extinction (Anderson & Insel, 2006; Insel et al., 2010).

Neural Mechanisms Supporting Expression and Extinction of Fear Responses

One of the most important brain structures mediating extinction learning is the amygdala (LeDoux, 2000). A substantial animal literature has demonstrated that the amygdala is a heterogeneous structure made of many nuclei (e.g., Pitkanen, 2000; Sah, Faber, Lopez De Armentina, & Power, 2003). Recently, researchers working at the human level have also begun to parse the amygdala into three core subregions including the basolateral amygdala, the centromedial amygdala, and the superficial amygdala (e.g., Baur, Hangii, Langer, & Jancke, 2013; Bzdok, Laird, Zilles, Fox, & Eickhoff, 2013; Etkin et al, 2009; Roy et al., 2009, 2013). A wealth of laboratory animal research and some human research has suggested that the basolateral amygdala and the centromedial amygdala have a prominent role in fear extinction learning (see Milad & Quirk, 2012 for a review). The basolateral amygdala has been shown to play a pivotal role in the inhibition of fear (Barad, Gean, & Lutz, 2006; Milad & Quirk et al, 2012). Animal research has also demonstrated that the basolateral amygdala is important for the development of extinction induced neural plasticity and the formation of a stable fear extinction memory (Amano, Unal, & Pare, 2010; Laurent, Marchand, & Westbrook, 2008; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011). On the other hand, the centromedial amygdala has been shown to be

involved in the expression of fear (LeDoux, 2003).

In addition to the amygdala subregions, the anterior midcingulate cortex (aMCC) and the ventromedial prefrontal cortex (vmPFC) also play a critical role in the expression and inhibition of fear responses (e.g., Linnman et al, 2012; Milad, Quirk, Pittman, Orr, Fischl, & Rauch, 2007a; Milad, Wright, Orr, Pittman, Quirk, & Rauch, 2007b; Phelps, Delgado, Nearing, & LeDoux, 2004). The aMCC, considered to be the human homologue of the rat prelimbic cortex, has been linked to the expression of fear (Burgos-Robles, Vidal-Gonzalez, Santini, & Quirk, 2009; Linnman et al, 2012; Milad, Quirk, Pittman, Orr, Fischl, & Rauch, 2007a). Greater activation of the aMCC has been shown to be correlated with greater skin conductance responses to the CS+ (conditioned stimulus paired with a shock) during fear acquisition (Milad et al., 2007a). Additionally, increased aMCC resting state metabolism has been linked to poorer extinction retention (Linnman et al, 2012). In contrast to the role of the aMCC in fear extinction learning, the vmPFC, the human homologue of the rat infralimbic cortex, has been shown to play a role in the inhibition of fear (Quirk, Russo, Barron, Lebron 2000, Milad & Quirk, 2002; Milad et al., 2007b; Phelps et al., 2004). Enhanced vmPFC activity to the CS+ during late fear extinction learning has been demonstrated in healthy humans (Milad et al, 2007b). Enhanced vmPFC recruitment has also been linked to greater extinction recall (Milad et al., 2007b; Phelps et al, 2004).

Along with their separable roles, these regions also form critical neural pathways that support the expression and inhibition of fear. Following extensive animal research, recent studies at the human level have begun to examine different functional connections between the amygdala subregions and the rest of the brain (Blackford, Clauss, Avery, Cowan, Benningfield, & VanDerKlok, 2014; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; Roy et al, 2009,

2013; Qin et al, 2013). These studies demonstrated that the basolateral amygdala shows stronger resting state functional connectivity with the vmPFC compared to the centromedial amygdala whereas the centromedial amygdala shows stronger resting state connectivity with the aMCC compared to the basolateral amygdala (Roy et al, 2009; 2013). Together, this evidence suggests that the centromedial amygdala forms stronger connections with the aMCC to facilitate the expression of fear, whereas the basolateral amygdala forms stronger connections with the vmPFC to facilitate the inhibition of fear.

Neural Mechanisms Supporting Fear Extinction Learning are Altered in Anxiety

The same neural mechanisms that support the expression and inhibition of fear have also been shown to be altered in anxiety. In studies of participants performing fear acquisition and extinction learning in the scanner, both individuals with subclinical levels of trait anxiety as well as those diagnosed with anxiety disorders show greater amygdala activity during presentation of the CS+ during fear extinction (Barrett & Armony et al., 2009; Milad et al., 2009). Of the few studies examining individuals with subclinical levels of trait anxiety, one study showed that higher levels of trait anxiety is associated with less activation in the aMCC to the CS+ compared to the CS- (conditioned stimulus never paired with a shock) during fear extinction (Sehlmeyer et al., 2011). Another study investigating trait anxiety relationships with activation in the vmPFC during fear conditioning and extinction failed to find any significant relationships (Barrett & Armony, 2009). This stands in contrast to studies that assessed neural mechanisms underlying fear conditioning and extinction learning in individuals with posttraumatic stress disorder (PTSD), a disorder characterized by excessive anxiety in the aftermath of a traumatic event. These studies find that PTSD is associated with less vmPFC activation to the CS+ compared to the CS- during initial extinction learning and extinction recall and greater activation in the aMCC

during extinction recall (Milad et al., 2009).

Along with studies examining relationships between trait anxiety and brain activity during fear conditioning and extinction paradigms, researchers have also begun to investigate trait anxiety and altered resting state connectivity in regions supporting fear extinction learning (Bjsterbosch Smith, Forster, John, & Bishop, 2014; Kim, Gee, Loucks, Davis, & Whalen, 2011; Vytal, Overstreet, Charney, Robinson, & Grillon, 2014). One study has shown that high levels of trait anxiety are associated with less resting state functional connectivity between the whole amygdala and the vmPFC (Kim et al., 2011). Additionally, individuals with high levels of trait anxiety failed to show decreased connectivity between the whole amygdala and the dorsomedial prefrontal cortex (dmPFC; including the aMCC), which was a pattern demonstrated by the low trait anxiety group (Kim et al., 2011). Other more recent studies have shown that higher levels of trait anxiety are associated with increased amygdala-aMCC/dmPFC functional connectivity both at rest (Bijsterbosch et al., 2014) and under the threat of shock (Vytal et al., 2014) and a trend toward decreased connectivity between the amygdala and vmPFC (Bijsterbosch et al., 2014).

In addition to examining relationships between anxiety and whole amygdala functional connectivity with other brain regions, researchers have also recently begun to examine more precise relationships with amygdala subregions (Brown et al, 2014; Baur et al., 2013; Blackford et al., 2014, Etkin et al., 2009, Roy et al., 2013, Qin et al., 2014). Only one of these studies specifically examined relationships between trait anxiety and amygdala subregion connectivity with other brain structures (Baur et al, 2013). However, this particular study only reported amygdala subregion-insula connectivity, and they only found significant associations for state anxiety and not trait anxiety (Baur et al, 2013). The remaining studies examined other related dimensions of anxiety or clinical anxiety disorder populations (Blackford et al., 2014; Etkin et

al., 2009, Roy et al., 2013, Qin et al., 2014). Of the studies examining trait anxiety-related constructs, one study found that greater social inhibition was associated with reduced connectivity between the CMA and the aMCC (Blackford et al., 2014). Additionally, children with greater levels of anxious temperament showed greater connectivity between the basolateral amygdala and vmPFC (Qin et al., 2014). Within anxiety disorder populations, one study found that individuals with PTSD show greater BLA-aMCC resting state connectivity compared to trauma-exposed controls (Brown et al, 2014). Decreased CMA-vmPFC resting state connectivity has been observed amongst adolescents with generalized anxiety disorder (Roy et al., 2013). Another study of generalized anxiety disorder found a less differentiated pattern of CMA and BLA whole-brain resting state connectivity (Etkin et al, 2009; Roy et al, 2013). Together, these studies provide a mixture of evidence for relationships between anxiety and altered resting state connectivity between the amygdala subregions and the rest of the brain. The mixed results are likely due to differences in using clinical or subclinical populations, the dimensional measure of anxiety that is used, as well as developmental differences between the populations that have been studied. It is still unknown how trait anxiety may be associated with alterations in resting state connectivity between the CMA and BLA with other regions important to the expression and inhibition of fear (aMCC, vmPFC).

The Importance of Examining Extinction-Related Resting State Connectivity Changes

In order to study dynamic processes likely needed to support and retain different forms of learning, such as fear extinction, researchers have begun to incorporate a pre-learning resting state scan and a post-learning resting state scan to study learning-related neural changes (Daselaar, Huijbers, de Jonge, Goltstein, & Pennartz, 2010; Schultz, Balderston, & Helmstetter, 2012; Feng, Feng, & Chen, 2013; Feng, Feng, Chen, & Lei, 2014). To date this pre-post learning

resting state paradigm has not been used to study neural changes supporting fear extinction learning. However, a few studies have begun to examine resting state neural changes before and after fear acquisition learning (Schultz, Balderston, & Helmstetter, 2012; Feng, Feng, & Chen, 2013; Feng, Feng, Chen, & Lei, 2014). These researchers found altered connectivity in structures also important to the extinction of fear, including increased amydgala-aMCC/dmPFC connectivity, a pathway known to support the expression of fear (Schultz et al., 2012; Feng, Feng, Chen, & Lei, 2014). Additionally, Feng and colleagues (2014) found that higher subjective ratings of fear to the CS+ during fear acquisition were associated with decreased pre- to post-fear acquisition resting state connectivity changes between the amygdala and vmPFC. Given that impairments in fear extinction learning, particularly extinction retention, are a core feature of anxiety problems, it is important to extend this work to this type of learning. Examining pre- to post extinction related neural changes may allow for a better understanding of aberrant dynamic neural processes that underlie poor extinction and extinction retention in anxious individuals.

Aberrant White Matter Integrity may underlie Extinction-Related Neural Dysfunction seen in Anxiety Problems

In addition to extinction-related neural dysfunction seen in those with high levels of trait anxiety and anxiety disorders, altered integrity in the white matter connecting these regions has been seen in those with anxiety problems (Kim & Whalen, 2009; Eden et al., 2015). These studies have shown that higher levels of trait anxiety are associated with decreased white matter integrity within the uncinate fasciculus, a direct pathway that connects the amygdala to the vmPFC (Kim & Whalen, 2009; Eden et al., 2015). However, Eden and colleagues (2015) also examined indirect connections between the amygdala and dmPFC/aMCC and failed to find any associations with trait anxiety within this pathway. Given the large extent of the dmPFC,

examining tracks that specifically reach voxels within the aMCC, may potentially be fruitful in observing anxiety-related differences in the integrity of these dorsal pathways. Researchers have also begun to parcellate subregions of the amygdala utilizing diffusion imaging methods (Saygin, Osher, Augustinack, Fischl, & Gabrieli, 2011; Solano-Castiella et al., 2010; Balderston, Schultz, Hopkins, & Helmstetter, in press), however it is still unknown how unique white matter pathways between amygdala subregions and different parts of the brain are influenced by varying levels of trait anxiety. Additionally, it is unknown how aberrant white matter integrity may influence aberrant functioning in fear extinction-related neural pathways seen in those with anxiety problems.

The Current Study

The purpose of the current study was to examine the dynamic processes supporting extinction learning in more precise amygdala subregion pathways by incorporating a resting state scan both before and after a fear extinction learning paradigm. Given that fear extinction is a core process that is impaired in anxiety, it is important to better understand the neural processes that may contribute to poor extinction retention and greater severity of anxiety symptomology. At this point, we have some understanding of anxiety-related neural dysfunction during extinction learning and within a single resting state scan, but plastic processes likely needed to support the retention of fear extinction learning have not yet been explored. Thus, I explored changes in resting state connectivity resulting from extinction learning and their relationships with trait anxiety.

Additionally, with diffusion imaging methods, I examined how white matter integrity in amygdala subregion pathways may be associated with individual differences in extinction-related neural changes and trait anxiety. Following the assessment of extinction-related neural changes

and white matter integrity, participants completed an extinction retention task outside of the scanner one week later. This extinction retention task was correlated with measures of BOLD activation during extinction learning, extinction-related neural plasticity, white matter integrity, and individual difference in a measure of trait anxiety.

Given what is known about the functioning of amygdala subregion pathways within the context of extinction learning, following extinction learning I expected to find a strengthening in resting state connectivity within the BLA-vmPFC pathway, known to be involved in the inhibition of fear responses, and a dampening in connectivity within the CMA-aMCC pathway, known to be involved in the expression of fear. Additionally, I predicted that having increased white matter integrity in the BLA-vmPFC network would be associated with stronger BLA-vmPFC resting state connectivity following extinction learning. I also predicted that decreased white matter integrity within the CMA-aMCC network would be associated with diminished CMA-aMCC resting state connectivity following extinction learning. With regards to how individual differences in trait anxiety may influence neural changes within these pathways, I predicted that trait anxiety would be associated with less strengthening in the BLA-vmPFC fear inhibition pathway and less dampening of the CMA-aMCC fear expression pathway from pre- to post-fear extinction. I also expected that trait anxiety would be associated with less white matter integrity within the BLA-vmPFC pathway and greater white matter integrity within the CMA-aMCC pathway.

Regarding extinction retention, I expected that poorer retention would be predicted by greater activation in the amygdala and aMCC and less vmPFC activation to the CS+ versus the CS- during extinction learning. With respect to relationships between extinction retention and extinction-related neural plasticity, I expected that poorer extinction retention would be

associated with less strengthening of the BLA-vmPFC pathway and less dampening of the CMA-aMCC pathway following extinction learning. In turn, inefficient extinction learning was also expected to be associated with decreased white matter integrity within the BLA-vmPFC pathway and increased white matter integrity in the CMA-aMCC pathway. Given the hypothesized relationships between trait anxiety, extinction-related resting state connectivity changes, and white matter integrity, I predicted that altered brain activity during extinction learning, extinction-related plasticity, and white matter integrity may mediate the relationship between trait anxiety and poor extinction retention abilities.

The knowledge gained from this project will help provide a more precise understanding of altered neural pathways supporting impaired maintenance of fear extinction learning in anxious individuals. Additionally, understanding these impaired extinction processes in anxiety have a number of long-term implications. First, impaired extinction-induced neural plasticity and subsequent recall of extinction learning may serve as a biomarker that can lead to early detection of anxiety problems. Investigators have already begun to show that extinction learning has promise in this area (Guthrie et al., 2006). In addition, such understanding may help to further elucidate potential mechanisms of change in exposure therapy, a prominent therapy for anxiety rooted in fear extinction principles (Goosens, Sunaert, Peeters, Griez, & Schruers, 2007; Hauner, Mineka, Voss, & Paller, 2012; Straube, Glauer, Dilger, Mentzel, & Miltner, 2006), and inform attempts to maximize the efficacy of this intervention. Recently, it has been shown that successful exposure therapy results in the normalization of neural processes supporting extinction learning (Goosens, Sunaert,Peeters, Griez, & Schruers, 2007; Hauner, Mineka, Voss, & Paller, 2012; Straube, Glauer, Dilger, Mentzel, & Miltner, 2006). Thus, knowledge gained from the present project may ultimately help those at risk for or suffering from anxiety by aiding

in early detection and informing and optimizing extinction-based treatments for anxiety disorders.

Method

Participants

One hundred and ten undergraduates from the University of Wisconsin-Milwaukee volunteered to participate in the study. From this sample, participants were excluded from the final analyses due to the presence of manic episodes (n= 1), technical issues with the scanner (n = 2), excessive motion during scanning (n = 12), technical issues with electrical stimulation (n = 2) and a failure to show signs of implicit or explicit learning (n = 2) during fear conditioning. This resulted in a final sample of 91 participants (53 females, mean age: 22.05, SD = 3.94). All participants were right-handed and had no contraindications for an MR scan including metal in the body, pregnancy, or claustrophobia. Additionally participants reported no history of head trauma, neurological disorders, psychosis, or mania.

General Procedures

Participants completed two sessions, one week apart. The first session took place at the Medical College of Wisconsin and included a fear conditioning and extinction paradigm in the MRI scanner. A week later, participants were tested on retention of extinction learning. This second session took place in a laboratory in the Department of Psychology at the University of Wisconsin-Milwaukee. At the end of the first session, subjects completed the State-Trait Anxiety Inventory-Trait (STAI-Trait; Spielberger et al., 1983). The STAI-Trait is a 20-item measure of dispositional anxiety (e.g. *I worry too much over something that doesn't really matter, I try to avoid facing crisis or difficulty, I take disappointments so keenly that I can't put them out of my*

mind). The STAI-Trait has been shown to exhibit high internal consistency (r = .89) and test-retest reliability (r = .88; Barnes, Harp, & Jung, 2002).

Session One: Fear Conditioning and Extinction Paradigm

While in the scanner, participants completed a differential delay fear conditioning and extinction paradigm similar to those used in previous studies (Armony & Dolan, 2002; Knight, Smith, Cheng, Stein, & Helmstetter, 2004). The conditioned stimuli (CS) consisted of two different fractals. The unconditioned stimulus (UCS) was a 500 ms shock tailored to each individual's tolerance level. Before completing this task, participants underwent a procedure to determine what level of electrical stimulation was aversive but tolerable for them on a 0 to 10 scale (0=no sensation, 10=painful, but tolerable). The level of electrical stimulation was increased until the participant indicated that the level was painful, but tolerable or had reached a maximal current level of 7.5 mA (Schultz et al., 2012). Participants then underwent a conditioned fear acquisition protocol (5 min). Participants were presented with five visual presentations of the CS+ (CS associated with an aversive shock) and five presentations of the CS- (CS not associated with a shock). For 100% of the five CS+ trials, the UCS coterminated with the CS+. Following acquisition, participants completed a five-minute resting state scan during which they were instructed to close their eyes but remain alert (Schultz et al., 2012). Then participants completed a fear extinction protocol (5 min), in which they received five presentations each of the CS+ and CS-, with no presentation of the UCS. After extinction learning, another five minute resting state scan was performed (See Figure 1 on next page). The CSs were presented for 8 s followed by a 16-24 s intertrial interval (mean= 20 s). The CS+ and CS- were displayed in a quasi-random order, with no more than two presentations of the same condition in a row. Two pseudorandomized trial order sequences were used and counterbalanced

across subjects in order to control for order effects. Skin conductance responses (SCR) and expectancy ratings were collected throughout the task. Additionally, a subset of participants (n = 65) completed a diffusion weighted imaging scan after the fear conditioning and extinction task.

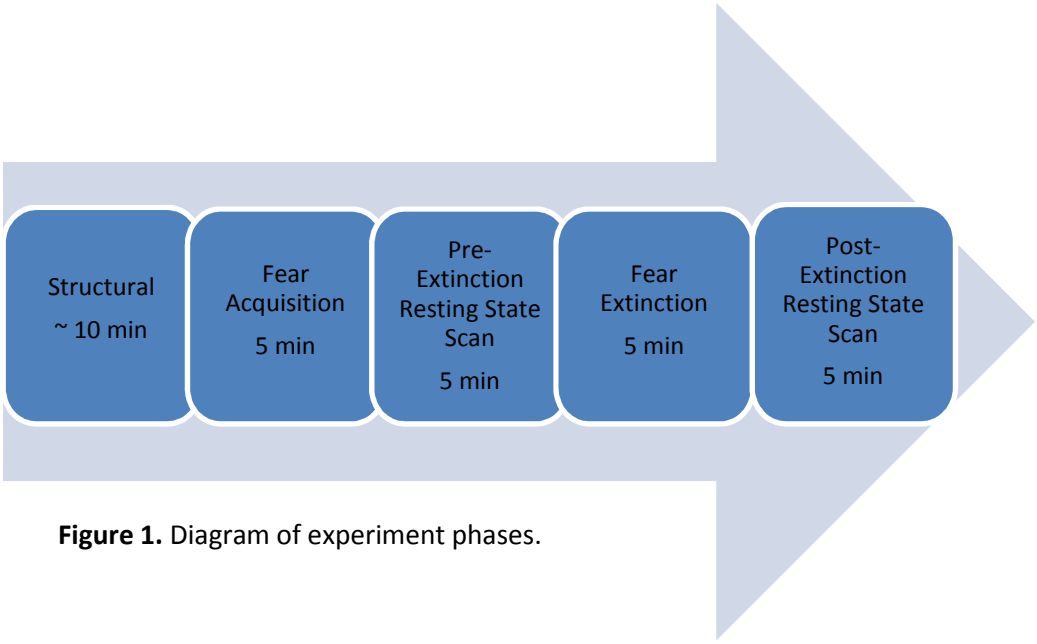

Figure 1. Diagram of experiment phases.

Session Two: Extinction Retention Paradigm.

Participants completed an extinction retention paradigm outside of the scanner environment. The paradigm included five presentations each of the CS+ and CS-, with no presentation of the UCS. Throughout the task, skin conductance and expectancy ratings were assessed. Additionally participants underwent a clinical interview, the Mini International Neuropsychiatric Interview Version 6.0.0 for DSM-IV (M.I.N.I.; Sheehan et al., 2010) to exclude participants with lifetime episodes of mania or psychosis. At the end of the task, the participants were compensated for their completion of both sessions.

Apparatus and Data Collection

Electrical stimulus. The 500 ms electrical stimulus was delivered by an AC (60 HZ)

source (Contact Precision Instruments, Model SHK1, Boston, MA) through two surface cup electrodes (silver/silver chloride, 8 mm diameter, Biopac model EL258-RT, Goleta, CA). The electrodes were filled with electrolyte gel and positioned on the participant's right tibial nerve above the right medial malleolus (ankle).

Visual stimulus. The fear conditioning and extinction protocol was programed with Presentation software (Albany, CA) and presented to participants in the scanner using a back projection system with prism glasses mounted on the head coil. Stimuli were presented on a desktop PC during session two.

Skin conductance. SCRs were collected with a SC5 24-bit digital amplifier (Contact Precision Instruments, Boston, MA), sampled at 80Hz. Electrodes (Biopac, Goleta, CA; Model EL258-RT) were filled with electrolytic gel and placed 2 cm apart on the sole of the left foot (Knight et al., 2004).

Expectancy ratings. Throughout fear acquisition and extinction learning, participants were given a button box in order to respond to a rating scale at the bottom of the screen. Participants practiced using the button box prior to beginning the experiment. Participants were instructed that if they felt that they were absolutely not going to receive the UCS, they would press the left button to move their cursor toward 0%. If the participants were absolutely certain they would receive the UCS, they were told to press the right button to move their cursor toward 100%. If they were unsure, they were directed to move the cursor toward the middle near 50%.

MRI. Whole brain imaging was conducted using a 3T short bore GE Signa Excite MRI system. Functional images were acquired using a T2* weighted gradient-echo, echoplanar pulse sequence. We collected 41 interleaved sagittal slices (TR=2 s; TE=25 ms; FOV=24 cm; flip

angle=77º; slice thickness = 3.5 mm). High resolution spoiled gradient recalled (SPGR) images were acquired in a sagittal orientation (TR=8.2 ms; TE=3.2 ms; FOV=24 cm; flip angle=12º; voxel size=0.9375 x 0.9375 x 1 mm) and served as an anatomical map for the functional images. Diffusion weighted images were collected using echoplanar imaging with 70 contiguous 2 mm thick axial slices and 38 non-collinear diffusion gradients (TR=10 s; TE= 77.9 ms; *b* value=800 s/mm^2; FOV=25.6 cm; flip angle=90º; voxel size=2 x 2 x 2 mm).

Data Reduction

Skin Conductance Preprocessing. To calculate SCR amplitude for each trial, the average SCR (in microSiemens) two seconds prior to the onset of the CS was subtracted from the highest SCR level during the eight-second duration of the CS (Milad et al., 2009; Schultz et al., 2012).

Expectancy Ratings Preprocessing. The UCS expectancy measure was operationalized as the mean self-reported ratings of the % chance of getting a shock during the last four seconds of the CS period for each trial for each participant (Schultz et al., 2012).

MRI Preprocessing. AFNI (Cox, 1996) was used to conduct image reconstruction and the following preprocessing steps for both the task data and the resting state data: 1) slice time correction, 2) remove first 3 images from each functional run to account for scanner equilibration, 3) rigid-body motion correction done in three translational and three rotational directions with all volumes registered to the first volume of each functional run (motion correction), 4) non-linear registration to MNI space using FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fnirt), 5) motion censoring above 0.3 mm and censoring based on outliers, and 6) apply motion derivatives. For the task-based data, the BOLD response

was modeled 0-14 seconds after the onset of the CS stimulus using 8 tent functions (0, 14, 8). For the resting state analyses, additional preprocessing steps were conducted including: 1) despiking to remove extreme time series outliers and 2) bandpass filtering to diminish frequencies above 0.1 Hz and below 0.01 Hz. Participants who exhibited excessive head motion (greater than an average value of 2.5 translational and/or 2.5 ° rotation) were excluded from further analysis. Diffusion weighted images were motion and eddy current corrected using FSL's eddy_current. The diffusion images were registered to the averaged B0 image. Probablistic tractography based on a ball-and-stick model (Behrens, Berg, Jababdi, Rushworth, & Woolworth, 2007) was implemented in FSL's probtrackx and fractional anisotropy (FA) maps were computed and FA values lower than 0.2 were thresholded out using FSL's DTIFIT.

Identification of amygdala subregions via resting state fMRI. Regions of interest (ROIs) for the amygdala subregions including the BLA and the CMA (according to definitions described in Ball et al., 2007), were determined using stereotaxic, probabilistic maps of cytoarchitectonic boundaries (Amunts et al., 2005) implemented in AFNI (Cox, 1996). Only voxels with at least a 50% probability of belonging to one of the subregions was included. In situations in which there was overlap, these voxels were assigned to the subregion that had the highest probability of inclusion. Each voxel was only assigned to one subregion. Each voxel's time series was weighted according to the probability of being included in a given subregion to ensure that the most reliable voxels in each subregion made the greatest contribution to the signal (Roy et al., 2009). For each subject, the mean time series was extracted by averaging across all voxels' probability weighted time series within each subregion.

Generation of amygdala-based connectivity maps. Correlational maps between the amygdala subregions and the time series from every other voxel in the brain were derived for the

pre-extinction resting state scan and the post-extinction resting state scan. The individual *r* statistics were normalized using a Fisher's *z* transformation and were resampled to 1 mm^3 voxels. Group level statistics were based on the normalized data.

Delineation of *a priori* connectivity regions and correction for multiple comparisons. The primary focus of the group analyses was on relations between the amygdala subregions and our *a priori* structures of interest, the aMCC and vmPFC. For all results found within the *a priori* neural pathways (BLA-vmPFC and CMA–aMCC) a small volume correction for multiple comparisons was applied to both a vmPFC (Mackey & Petrides, 2014) and an aMCC (Grupe et al., 2013) anatomical mask via cluster thresholding using Monte Carlo simulations. Using a voxel-based threshold of $p < 0.005$ and nearest-neighbor selection criteria, accounting for spatial correlation, clusters greater than 158 voxel for the vmPFC and 68 voxels for the aMCC achieved a corrected p-value of <0.05. A more stringent whole-brain correction through cluster thresholding (via Monte Carlo simulations) was applied to neural pathways that were not *a priori.* For post-hoc neural pathways, using a voxel-based threshold of $p<0.005$, clusters greater than 543 voxels achieved a corrected $p <0.05$.

DTI probablistic tractography. Tracking was performed from the CMA subregion (the seed mask) to the aMCC (way point and termination mask) and from the BLA subregion (seed mask) to the vmPFC (way point and termination mask). For the tracking of each pathway, an exclusion mask was created so that the other amygdala subregion would not be included in the pathway. Additional probabilistic tractography was performed based on resting state results involving the BLA, CMA, aMCC, and vmPFC that were not *a priori*. The same anatomical masks of the amygdala subregions that were generated for the resting state connectivity analyses were also used for the probabilistic tractography. Additionally, anatomical masks of the vmPFC

(Mackey & Petrides, 2014) and the aMCC (Grupe et al., 2013) that contained the voxels that showed significant resting state connectivity changes with amygdala subregions were used. Employing anatomical masks better ensured that the ROIs would be large enough to intersect with white matter. The final tracts were used as subject-specific masks for the extraction of fractional anisotropy (FA) values from individual maps (Baur et al., 2013). FA is interpreted as a measure of white matter strength or integrity, as it is thought to be influenced by axonal membrane thickness/diameter, amount of axon myelination, and parallel organization of axons (Basser & Pierpaoli, 1996; Beulieu, 2000).

Skin conductance response and expectancy ratings as indices of extinction retention. Given the different contexts in which GSR was collected during session 1 and session 2 (session 1 in the scanner and session 2 outside of the scanner), Milad's (2007) extinction retention index, which calculates each participants mean SCR to the first two CS+ trials and divides it by the maximum SCR to the CS+ during fear acquisition, was not used. Instead, an average of the participant's response to the first two trials during extinction retention was calculated. Only earlier extinction retention trials were used to avoid "new extinction learning" (Garfinkel et al, 2014). The same process was conducted on each participants mean expectancy ratings to the CS- for each trial.

Data Analysis: Conditioning Task Analyses

My primary hypotheses centered on the relationship between trait anxiety, changes in resting state functional connectivity as a result of fear extinction, retention of extinction learning, and the white matter pathways supporting these processes. Prior to addressing those hypotheses I first conducted basic analyses of the behavioral and imaging data from the conditioning tasks and examined relations between anxiety and acquisition and extinction of conditioned fear.

Acquisition and Extinction Behavioral Analyses. I conducted two CS Type X Trial repeated measure ANOVAs on the skin conductance response and expectancy ratings measures that were collected during fear acquisition. Additionally, I conducted two CS Type X Trial repeated measures ANOVAs on the skin conductance response and expectancy ratings measures during extinction. Then I generated a difference score for CS skin conductance responses during fear acquisition by subtracting the mean skin conductance to the CS- across trials minus the mean skin conductance response to the CS+ across trials. Similarly, I calculated a difference score for CS expectancy ratings during fear acquisition by subtracting the mean UCS expectancy rating to the CS- across trials minus the mean UCS expectancy rating across CS+ trials. For extinction learning, I repeated this same process and calculated difference scores for CS skin conductance responses and UCS expectancy ratings. I correlated each of these difference scores with self-reported trait anxiety.

Acquisition and Extinction Imaging Analyses. I conducted two whole-brain paired sample t-tests comparing CS+ versus CS- BOLD activation during fear acquisition and extinction learning, respectively.

To address my hypothesis that greater levels of trait anxiety would be associated with greater amygdala and anterior midcingulate (aMCC) BOLD activation as well as less ventromedial prefrontal cortex (vmPFC) BOLD activation to the CS+ compared to the CS- during fear extinction learning whole brain BOLD activation to the CS+ was subtracted from whole brain activation to the CS- during fear extinction learning. This difference score was then correlated with trait anxiety. For completeness, I also generated a whole brain CS+ minus CS- difference score during fear acquisition and correlated it with trait anxiety. I correlated trait

anxiety with activation associated with the CS+ and the CS- separately during fear acquisition and extinction.

Data Analysis: Extinction Retention

I examined whether the BOLD activation contrast between the CS+ and CS- during extinction predicted subsequent retention of extinction learning a week later. To test my hypothesis that poorer extinction retention would be associated with smaller differenced in vmPFC and greater differences in aMCC activation to the CS+ compared to the CS-, extinction retention indices were correlated with vmPFC and aMCC BOLD activation CS+ minus CS- difference scores.

Additionally, if there were significant relationships between a) trait anxiety and CS+ versus CS- difference scores, b) trait anxiety and extinction retention, as well as c) extinction retention and CS+ versus CS- difference scores, mediational analyses were conducted. The Multilevel Mediation and Moderation Toolkit (http://wagerlab.colorado.edu/tools/Mediation_help_11_6_08.pdf, Wager & Lindquist) was used to conduct single-level mediational analyses with a standard three-variable path model implemented with Baron and Kenny's (1986) four step method of establishing mediation through a series of linear regression analyses. Step 1: examine whether trait anxiety predicts extinction retention. Step 2: examine whether trait anxiety predicts the CS difference score in vmPFC BOLD activation during extinction learning. Step 3: examine whether the extinction related CS difference score in vmPFC BOLD activation predicts extinction retention. Step 4: enter both trait anxiety and the CS difference score in vmPFC activation during extinction learning as predictors and extinction retention as outcome. A reduction in the relationship between trait anxiety and extinction retention when the extinction-related CS difference score in vmPFC activation is entered in the model indicates that this

activation difference score mediates the relationship. In order to determine whether the association between trait anxiety and extinction retention is significantly different between step 1 and 3, a Sobel test was conducted (Sobel, 1982). These same steps were used with the CS difference in aMCC activation during extinction learning mediating the relationship between trait anxiety and extinction retention.

Data Analysis: Resting State and Structural Connectivity

Aim 1: **Examine plasticity underlying extinction learning in CMA-aMCC and BLA-vmPFC pathways and associations with the integrity of white matter connections within each pathway.**

Resting state connectivity changes. To address my hypothesis that successful extinction learning would be characterized by weaker CMA-aMCC and stronger BLA-vmPFC pathways, the *r* values between each of the amygdala subregions and the whole brain were calculated for the pre-extinction run and the post-extinction run separately. Then, a paired sample *t*-test comparing the CMA-whole brain correlational map during the pre-extinction run with the CMA-whole brain correlational map during the post-extinction run was conducted. Similarly, another paired sample *t*-test was conducted in order to compare the BLA-whole brain correlational map before extinction learning with the BLA-whole brain correlational map after extinction.

Resting state connectivity changes and white matter integrity. To test my prediction that less extinction-induced CMA-aMCC plasticity would be associated with less white matter integrity connecting these two regions, I computed a connectivity change score reflecting extinction learning plasticity by subtracting the pre- extinction CMA-whole brain correlational map from the post-extinction correlational map. Correspondingly, to test my hypothesis that greater extinction-induced BLA-vmPFC plasticity would be associated with greater white matter

integrity within this pathway, the pre-extinction BLA-whole brain correlational map was subtracted from the post-extinction correlational map. In addition, mean FA values for the CMA-aMCC pathway and the BLA-vmPFC pathways were calculated. The post-pre CMA-aMCC extinction learning difference value was correlated with the mean CMA-aMCC FA value. The BLA-vmPFC difference score was correlated with the mean BLA-vmPFC FA value.

Aim 2: **Assess the influence of trait anxiety on extinction-related neural plasticity and white matter integrity of BLA-vmPFC and CMA-aMCC pathways.**

I predicted that trait anxiety would be associated with a) a blunted increase in BLA-vmPFC connectivity, and b) less attenuation of CMA-aMCC connectivity from before to after extinction learning, as well as c) greater white matter integrity of the CMA-aMCC pathway, and d) reduced white matter integrity between the BLA and vmPFC. To test this, trait anxiety (STAI-Trait) was correlated with the post-pre CMA-whole brain difference score (described above) and with the post-pre BLA-whole brain difference score. To examine the relationship between trait anxiety and white matter fiber integrity, trait anxiety was correlated with the mean CMA-aMCC FA value and the mean BLA-vmPFC FA value.

Aim 3*:* **Examine whether extinction-related plasticity and the white matter integrity of BLA-vmPFC and CMA-aMCC pathways predict individual differences in retention of extinction learning a week later. In conjunction with this objective, if there were significant relationships between trait anxiety, extinction retention, white matter integrity, and extinction-related neural changes, I assessed whether extinction-related plasticity and the white matter integrity of these neural pathways mediate the relationship between anxiety and extinction retention abilities.**

I predicted that poorer extinction retention would be predicted by a) less strengthening of

BLA-vmPFC connectivity following extinction learning, b) less dampening of CMA-aMCC connectivity following extinction learning, c) less BLA-vmPFC white matter integrity, and d) greater CMA-aMCC white matter integrity. To test these hypotheses extinction retention indices (described earlier) were correlated with significant post-pre CMA-aMCC and the post-pre extinction BLA-vmPFC pathways. Likewise, extinction retention indices were also correlated with mean CMA-aMCC FA values as well as mean BLA-vmPFC FA values.

If there were significant relationships between a) trait anxiety and extinction-related neural changes or white matter integrity, b) trait anxiety and extinction retention, as well as c) extinction retention and plasticity or white matter integrity measures within *a priori* pathways, mediational analyses were conducted.

Additional Tests of Interest

The same tests conducted in Aims 1-3 described above were also conducted on post-hoc pathways that emerged, the BLA-aMCC and CMA-aMCC pathways.

Results

Participants

For our sample, trait anxiety scores ranged from 21 to 66, with a mean score of 40.21 and a standard deviation of 11.13.

Fear Acquisition: Behavioral Results

Two separate CS Type X Trial repeated measure ANOVAs were conducted on the skin conductance data and expectancy ratings during fear acquisition, respectively. Five participants did not have skin conductance data due to technical issues. During fear acquisition, there was a significant main effect of CS Type, $F(1, 85) = 14.67$, $p < .001$, with participants showing a greater skin conductance response to the CS+ compared to the CS-. There was also a significant

main effect of Trial, $F(4, 82) = 12.26$, $p < .001$. This main effect was qualified by a CS Type X Trial interaction, $F(4, 82) = 4.01$, $p = .005$. Simple effects tests revealed that the skin conductance response between CS+ and CS- did not differ during the first two trials ($p = .110$), but by the third, fourth and fifth trials, the skin conductance response was greater to the CS+ compared to the CS-, $p < .002$ (See Figure 2 on next page).

For expectancy ratings, there was a significant main effect of CS Type, $F(1, 90) = 481.18$, $p < .001$, with participants rating the CS+ higher compared to the CS- for expecting the UCS. There was also a significant CS Type X Trial Interaction, $F(4, 87) = 115.71$, $p < .001$, with participants initially rating higher UCS expectancy levels during the presentation of the CS- compared to the CS+, $p < .005$. However, by the second, third, fourth, and fifth trials, participants were rating higher UCS expectancy levels during the presentation of the CS+ versus the CS-, $p < .001$ (See Figure 2 on next page). Both the skin conductance and expectancy ratings results indicate that participants learned to associate the CS+ with a shock. Participants did not show a differential skin conductance to the CS+ compared to the CS- during early trials, but as the fear acquisition paradigm progressed, participants showed a greater skin conductance response to the CS+ compared to the CS-. This suggests that participants implicitly learned that the CS+ was specifically associated with a shock (Schultz & Helmstetter, 2010). Additionally, the UCS expectancy ratings also suggest that participants also explicitly learned the CS+-shock association early on during acquisition (Schultz & Helmstetter, 2010).

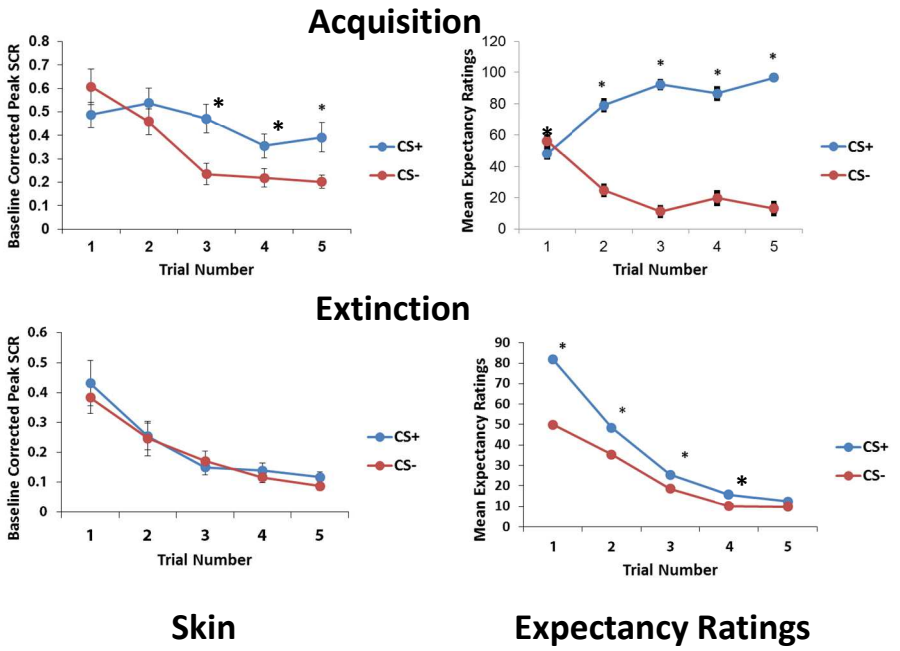

Figure 2. Skin conductance and Unconditioned Stimulus (UCS) expectancy ratings during fear acquisition and extinction learning. The top two graphs are the fear acquisition results and the bottom two graphs are the fear extinction results. The graphs on the left are graphs plotting the skin conductance results and the graphs on the right are plots of the expectancy ratings results. During fear acquisition, participants showed a greater skin conductance response to the CS+ compared to the CS- during the third, fourth, and fifth CS trials, $p < .002$. Additionally, by the second trial, participants rated that they expected the CS+ to be followed by the UCS more than the CS-, $p < .001$. During fear extinction, participants' skin conductance

Fear Acquisition: Associations between Behavior and Trait Anxiety

There was no significant correlation between trait anxiety and mean CS+ minus mean CS- skin conductance response (over all trials) during fear acquisition, $r = -.117$, $p = .284$. Additionally, there were no significant correlations between trait anxiety and the mean CS+ skin conductance response and the mean CS- skin conductance response separately, during fear acquisition, all $p > .30$. There were also no significant associations between trait anxiety and mean CS+ minus mean CS- expectancy ratings (over all trials), $r = -.114$, $p = .284$. Also, when examining relationships between trait anxiety and mean expectancy ratings for CS+ and CS-

separately, there were no significant associations, all $p > .100$. These results suggest that trait anxiety was not associated with difficulties in the ability to acquire a fear response.

Fear Extinction: Behavioral Results

Two separate CS Type X Trial repeated measure ANOVAs were conducted on skin conductance response and expectancy ratings during fear extinction. For skin conductance, there was a significant main effect of Trial, $F(4, 82) = 7.06$, $p < .001$. There was no significant main effect of CS Type, $F(4, 82) = .58$, $p = .449$, or CS Type X Trial interaction, $F(4, 82) = 0.64$, $p = .635$ (See Figure 2 above).

For expectancy ratings, there was a significant main effect of CS Type, $F(1, 90) = 34.92$, $p < .001$, with participants rating higher UCS expectancy levels during the CS+ compared to the CS-. There was also a significant main effect of Trial, $F(4, 87) = 89.35$, $p < .001$. Additionally, there was a significant CS Type X Trial interaction, $F(4, 87) = 14.78$, $p = .001$. During the first four trials, participants rated higher UCS expectancy levels to the CS+ versus the CS-, $p < 0.03$. However, by the final trial, participants were no longer significantly rating higher UCS expectancy levels to the CS+ compared to the CS-, $p = .200$ (See Figure 2 above). Together, these results suggest that the participants learned that the CS+ was no longer paired with a shock during extinction learning. The skin conductance results indicate that early on during extinction participants implicitly learned that the CS+ was no longer paired with a shock. The UCS expectancy rating results suggest that during later stages of extinction learning, participants began to explicitly learn that the CS+ was no longer being paired with a shock.

Fear Extinction: Associations between Behavior and Trait Anxiety

There was no significant correlation between trait anxiety and mean CS+ minus mean CS- skin conductance response (over all trials) during fear extinction, $r = -.001$, $p = .994$.

Additionally, there were no significant correlations between trait anxiety and mean CS+ skin conductance responses and mean CS- skin conductance responses, respectively, during fear extinction learning, all $p > .50$. There were also no significant associations between trait anxiety and mean CS+ minus CS- expectancy ratings (over all trials), $r = .067$, $p = .532$. Also, when examining relationships between trait anxiety and mean expectancy ratings for CS+ and CS- separately, there were no significant associations, all $p > .600$. These results suggest that both the skin conductance and UCS expectancy measures failed to capture meaningful trait anxiety related differences in the ability to learn that the CS+ was no longer paired with a shock during extinction.

Fear Acquisition: Imaging Results

A whole brain paired sample t-test revealed greater BOLD activation to the CS+ compared to the CS- in *a priori* regions, including the bilateral amygdala (left, 1394 voxels, 17, 3.5, -13; right, 1733 voxels, -27, 4.5, -16) and the aMCC (left, 5009 voxels, 8, -18, 29; right, 5916 voxels, -8, -9.5, 29) (See Figure 3). There was no significant CS+ versus CS- BOLD activation difference within the vmPFC during fear acquisition. These results are consistent with many prior fear conditioning studies that have shown greater activation to the CS+ within regions known to be involved in the expression of fear (amygdala, aMCC) (e.g., LeDoux, 2000).

Greater Activation in Fear Expression Regions to CS+ versus CS- during Fear Acquisition

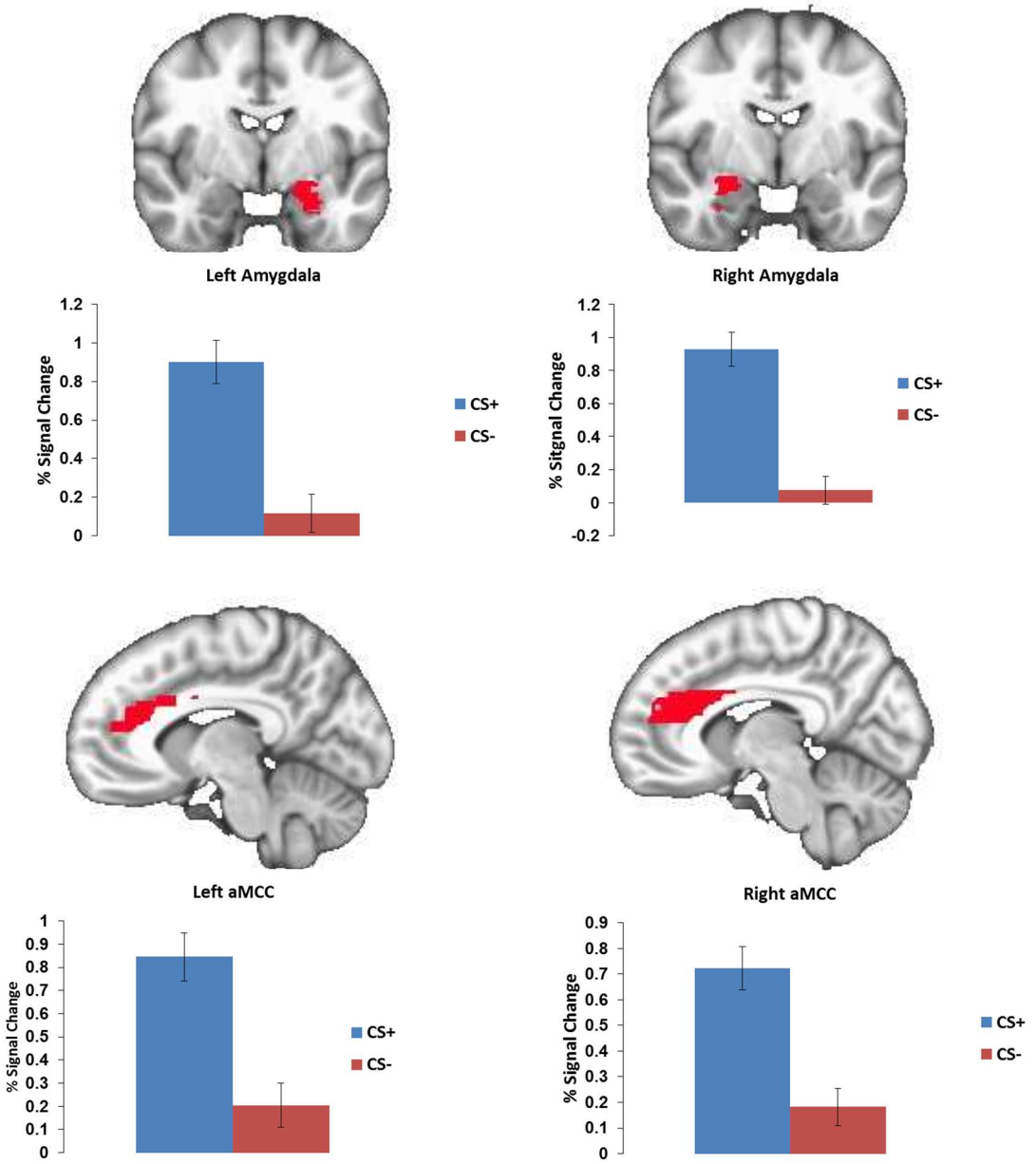

Figure 3. Participants showed greater BOLD activation in the bilateral amygdala and aMCC to the CS+ compared to the CS- during fear acquisition.

Fear Acquisition: Associations between BOLD Activation and Trait Anxiety

There were no significant associations between trait anxiety and a whole brain CS+ minus CS- difference score during fear acquisition. When taking amygdala and aMCC ROIs from the CS+ versus CS- minus contrast during fear acquisition, there were no significant correlations with trait anxiety, all $p > .70$. Additionally, when examining BOLD activation to the CS+ and the CS- separately, there were no significant associations with trait anxiety in our regions of interest (amygdala, aMCC, vmPFC). Consistent with the skin conductance and UCS expectancy rating results, these findings also suggest that higher trait anxiety levels may not be associated with deficits in the ability to acquire a fear response.

Fear Extinction: Imaging Results

A whole brain paired sample t-test revealed greater BOLD activation to the CS+ compared to the CS- in *a priori* regions including the bilateral amygdala (left, 202 voxels, 22, 8, -16; right, 267 voxels, -31, 6, -13), bilateral aMCC (Left: 395 voxels, 3, -21.5, 26, Right: 658 voxels, -10, -21.5, 29), and left vmPFC (456 voxels, -3, -46.5, -13) (See Figure 4). These results are consistent with prior studies that have implicated the amydala, aMCC, and vmPFC as important structures involved in a fear extinction network (Gottfried & Dolan 2004; Phelps et al., 2004).

Greater BOLD Activation in vmPFC, aMCC, and Amygdala to CS+ versus CS- during Fear Extinction

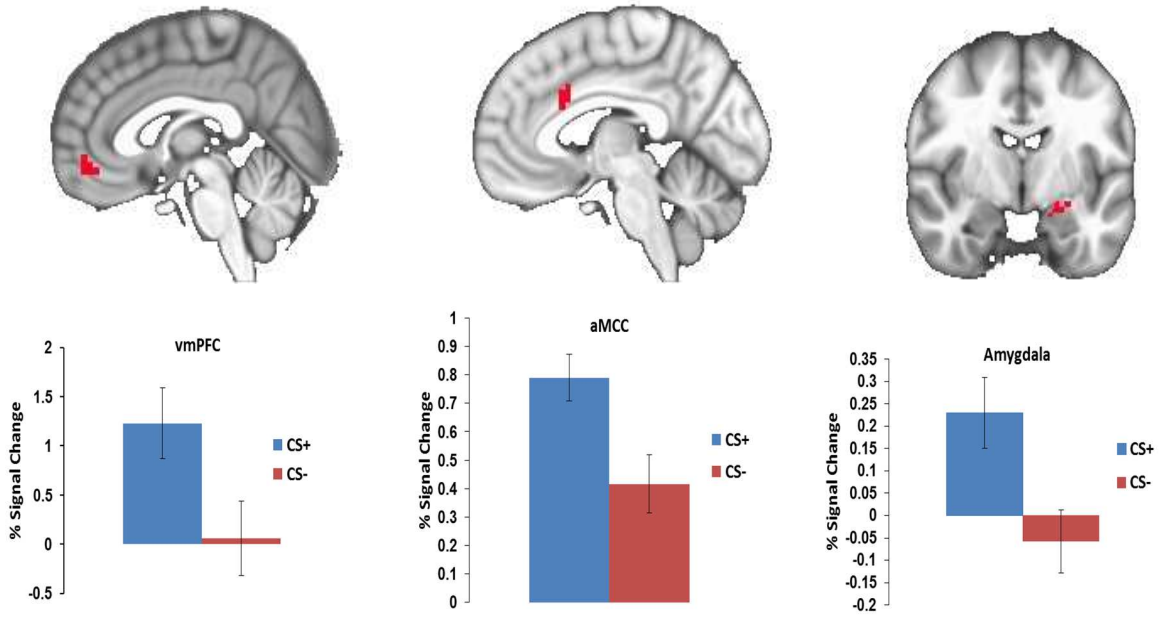

Figure 4. Participants showed greater BOLD activation in the left amygdala, bilateral aMCC (left shown) and bilateral amygdala (left shown) to the CS+ compared to the CS-.

Fear Extinction: Associations between BOLD Activation and Trait Anxiety

There were no significant associations between trait anxiety and a whole brain CS+ minus CS- difference score. Additionally, when using amygdala, aMCC, and vmPFC ROIs from the CS+ versus CS- minus contrast during fear extinction, there were no significant correlations with trait anxiety, all $p > .30$.

When looking at the CS+ and CS- separately, there were significant associations between trait anxiety and BOLD activation. Trait anxiety was significantly positively correlated with greater BOLD activation to the CS+ in *a priori* regions including the left vmPFC (1398 voxels, 11, -56.5, -20, $r = .34$, $p = .001$), right vmPFC (893 voxels, -13, -46.5, -16, $r = .32$, $p = .002$), and

right dorsal ACC/aMCC (1157 voxels, -10, -39.5, -6.0, r = .39, p < .001) (See Figure 5). For the correlation between trait anxiety and activity within the vmPFC to the CS+ a significant outlier was found (3SDs above mean BOLD activation). Therefore, these results were examined again without this outlier. The results remained significant even without the outlier participant (left vmPFC, r = .32, p = .002; right vmPFC r = .28, p = .007.

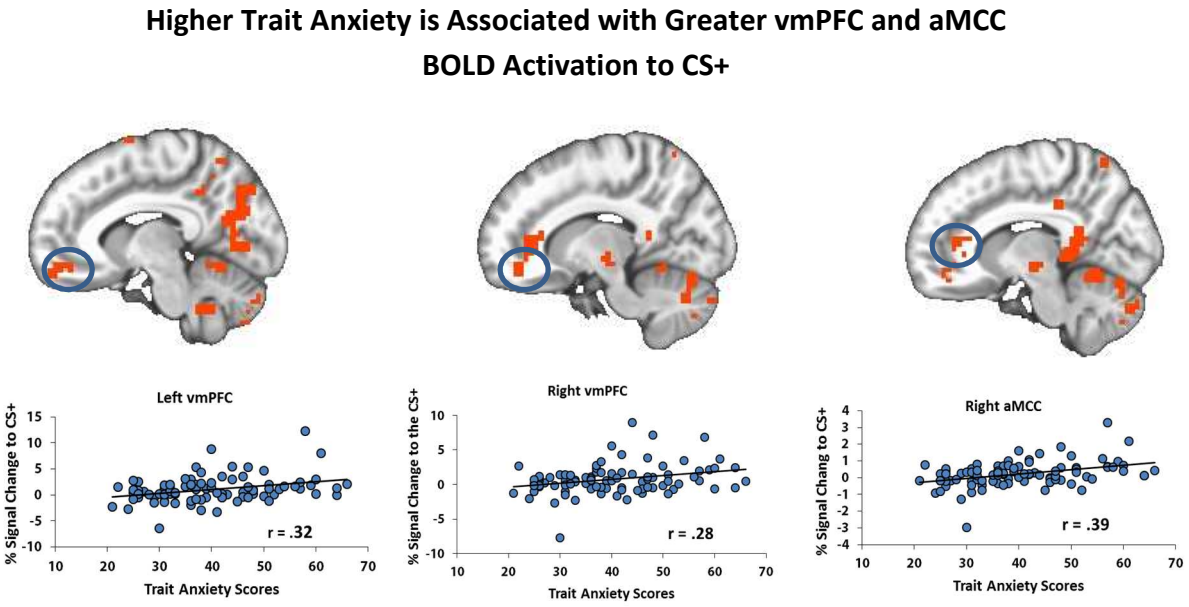

Figure 5. Higher levels of trait anxiety were associated with greater BOLD activation in the left vmPFC (r = .32, p = .002), right vmPFC (r = .28, p = .007), and right aMCC (r = .39, p = <.001). The vmPFC graphs have the outlier participant removed.

Higher trait anxiety levels were also significantly correlated with greater BOLD activation to the CS- in *a priori* regions including the right vmPFC (591 voxels, -3, -46.5, -13, r = .34) and left aMCC (984 voxels, 22, -39.5, 22, r = .33) (See Figure 6). Together, these results indicate that higher levels of trait anxiety are associated with amplified responding to both the CS+ and CS- in both fear expression (amygdala, aMCC) and fear inhibition (vmPFC) regions.

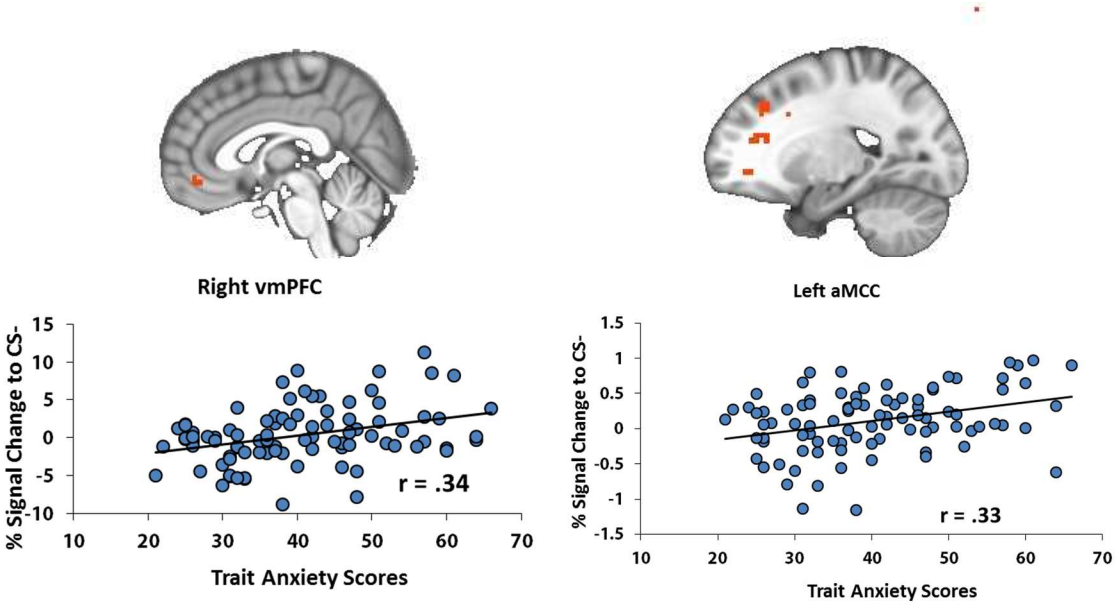

Figure 6. Higher levels of trait anxiety whereas associated with greater BOLD activation in the vmPFC (r = .34, p = .001) and aMCC (r = .33, p = .001) to the CS- during fear extinction learning.

Pre- to Post-Extinction Changes in Resting State Connectivity

Four separate paired t-tests were conducted to compare left BLA, right BLA, left CMA, and right CMA resting state connectivity changes with the whole brain from before to after extinction learning. As I expected, the left BLA showed a strengthening in its connection with the right vmPFC (184 voxels, BA32, -3.0, -36, -9 and 183 voxels, BA 11, -6, -29, -16) after extinction learning compared to before extinction learning (See Figure 7). There was no significant post- versus pre- fear extinction learning resting state connectivity changes within right BLA-vmPFC or right BLA-aMCC pathways. The findings suggest that extinction learning strengthens functional connections within a pathway that is known to be involved in the inhibition of fear.

Strengthening in BLA-vmPFC Resting State Connectivity Following Fear Extinction

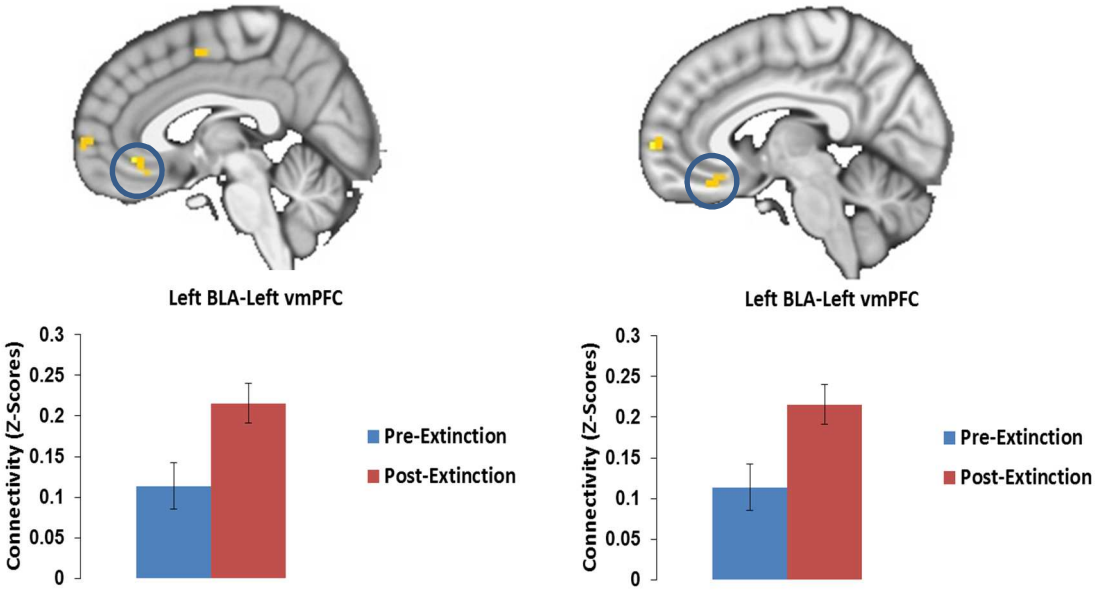

Figure 7. Participants showed a strengthening in resting state connectivity within the BLA-vmPFC pathway from pre- to post- fear extinction learning.

Additionally, the left CMA showed a strengthening in connectivity with the bilateral vmPFC (2235 voxels, BA 11, 25 and 32, 3, -32, -6) and the right CMA also showed greater connectivity with the right vmPFC (1236 voxels, BA 10 and 32, -16, -50, -23). Unexpectedly, fear extinction learning was associated with greater pre- to post- extinction-related connectivity within a fear expression pathway. The left CMA showed strengthened connections with the right aMCC (196 voxels, BA32, -11, -31, 15) and the right CMA also showed stronger connections with the right aMCC (455 voxels, BA32 and BA24, -10, -32, 12) following extinction learning (See Figure 8).

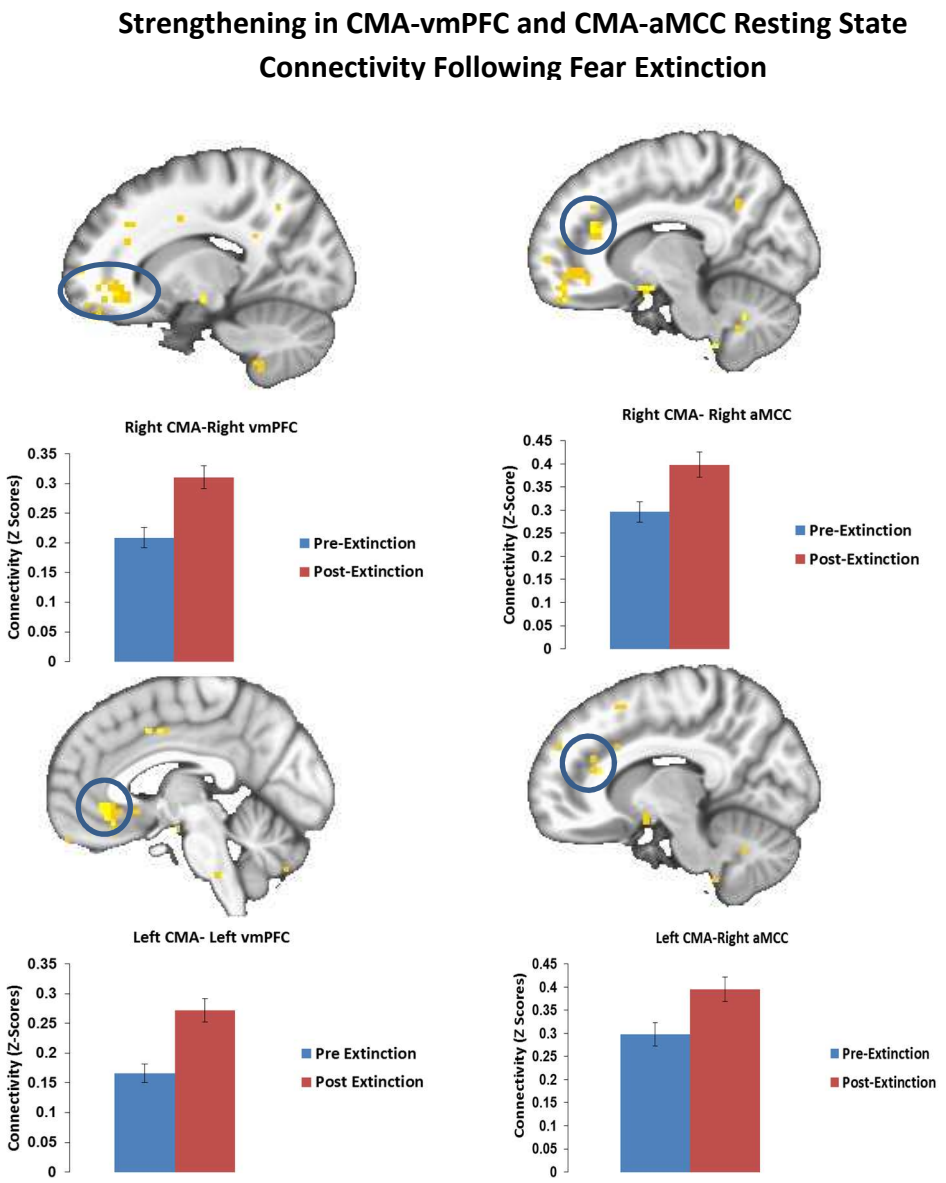

Figure 8. Participants showed a strengthening in connectivity within CMA-vmPFC and CMA-aMCC from pre- to post- fear extinction learning.

Pre- to Post-Extinction Changes in Resting State Connectivity: Relationships with White Matter Integrity

Given the difficulties with examining contralateral-hemisphere structural connectivity relationships with standard diffusion methods (Wedeen et al., 2008), I only examined correlations between significant ipsilateral hemisphere extinction-related resting state

connectivity changes (left CMA-vmPFC, right CMA-vmPFC, and right CMA-aMCC pathways) with FA values within the same ipsilateral hemisphere. There were no significant associations between FA values and extinction related resting state connectivity changes within the left CMA-vmPFC pathway (r = -.037, p = .795, n = 13 participants missing this pathway) and the right CMA-vmPFC pathway (r = .101, p = .463, n = 10 participants missing this pathway). Contrary to my predictions, there were also no significant correlations between post- minus pre-extinction resting state connectivity changes and FA values within the right CMA-aMCC pathway (r = .052, p = .705, n = 9 participants missing this pathway). The results suggest that individual differences within the FA measure of white matter integrity were not related to neural changes associated with extinction learning.

Pre- to Post-Extinction Changes in Resting State Connectivity: Associations with Trait Anxiety

Trait anxiety was correlated with left BLA-whole brain, right BLA-whole brain, left CMA-whole brain, and right CMA-whole brain post- minus pre-extinction difference scores. Trait anxiety was associated with greater left BLA- bilateral aMCC resting state connectivity post-extinction learning versus pre-extinction r = .35, p = .001 (2067 voxels, -24, -39, 29; 274 voxels 14, -36, 19) (See Figure 9). Contrary to my predictions, there were no significant associations with trait anxiety and right BLA-vmPFC or right BLA-aMCC changes in resting state connectivity. There were also no significant correlations between trait anxiety and resting state connectivity changes between left CMA and right CMA with any *a priori* brain regions or other regions throughout the brain. These significant differences with trait anxiety did not emerge when conducting the correlations for the pre- and post-extinction resting state scans separately. These results suggest that trait anxiety is associated with aberrant extinction-related

neural changes via an alternative BLA-aMCC pathway.

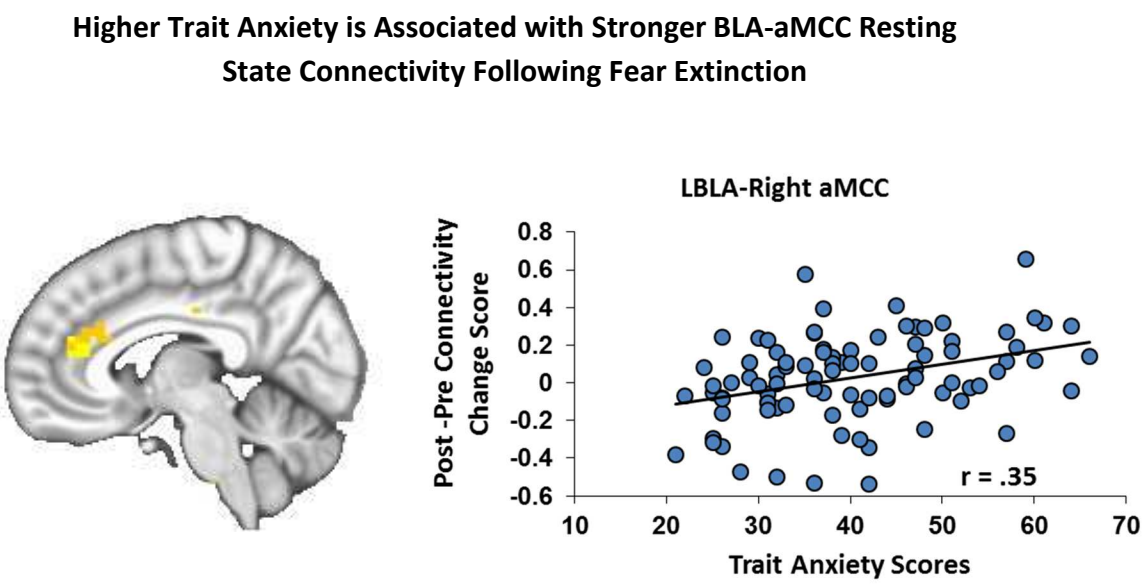

Figure 9. Higher trait anxiety levels were associated with a strengthening in the BLA-aMCC pathway following extinction learning (r = .35, p = .001).

Inconsistent with my predictions, trait anxiety scores were not significantly correlated with FA values within the left BLA-vmPFC (r = .031, p = .805) or right BLA-vmPFC pathways (r = -.123, p = .333, n = 1 participant missing this pathway). There were also no significant correlations between trait anxiety scores and FA values with the left CMA-aMCC (r = .209, p = .129, n = 11 participants missing this pathway) or right CMA-aMCC (r = -.125, p = .36). Additionally, there were no significant correlations with trait anxiety scores and FA values within post-hoc pathways (BLA-aMCC and CMA-vmPFC pathways), all p > .10. These results indicate that individual differences in trait anxiety was not associated with the white matter integrity in pathways thought to be involved in the expression and inhibition of fear.

Extinction Retention and Associations with Trait Anxiety and BOLD Activation during Extinction

In contrast to my predictions, extinction retention indices (skin conductance, expectancy ratings) were not significantly correlated with CS+ minus CS- BOLD activation difference scores in the amygdala, aMCC, or vmPFC during fear extinction learning, all $p > .055$. Additionally, extinction retention indices were not significantly correlated with trait anxiety, all $p > .15$. Given the lack of a relationship between extinction retention scores and BOLD activation, BOLD activation and trait anxiety, as well as extinction retention and trait anxiety, follow-up mediational analyses were not conducted. These results indicate that higher trait anxiety levels were not associated with difficulties in an extinction retention assessment conducted one week after the initial extinction session.

Extinction Retention and Associations with Pre- to Post-Extinction Resting State Connectivity Changes, White Matter Integrity, and Trait Anxiety

Unexpectedly, there were no significant correlations between extinction retention indices (skin conductance, UCS expectancy ratings) and pre- to post-extinction resting state connectivity changes within the BLA-vmPFC, CMA-vmPFC, or CMA-aMCC pathways, all $p > .102$. Extinction retention indices were also not significantly associated with the BLA-aMCC extinction-related resting state connectivity changes that were positively associated with trait anxiety levels.

With regard to white matter integrity, there was a negative correlation between the CS+ minus CS- UCS expectancy ratings difference score and FA values within the left CMA-aMCC pathway ($r = -.277$, $p = .043$, uncorrected). However, this result would not survive a multiple comparison correction using the Bonferroni-Holm method (for 6 tests, corrected = .008). There were no other significant results between extinction retention measures and FA values within any of the other *a priori* pathways. Additionally, trait anxiety was not significantly associated with

extinction retention indices (skin conductance: $r = .123$, $p = .270$; expectancy: $r = .010$, $p = .928$). Given the lack of relationships between trait anxiety, extinction retention measures, pre-post extinction resting state connectivity changes, and white matter integrity, follow-up mediational analyses were not conducted. The findings suggest that the integrity of the white matter connecting pathways important to the expression and inhibition of fear were not associated with extinction-related resting state connectivity changes.

Discussion

The aim of the current study was to examine changes in the strength of pathways thought to be involved in fear expression (CMA-aMCC) and inhibition (BLA-vmPFC) from pre- to post-extinction learning, and how these neural changes may be related to individual differences in trait anxiety and subsequent retention of extinction. I also investigated how extinction-related neural changes, trait anxiety, and the retention of extinction vary as a function of the integrity of the white matter connecting the structures within these pathways.

To lay the foundation for exploring these aims, I first demonstrated that participants exhibited normal learning patterns during fear acquisition and extinction, as indexed by the skin conductance and UCS expectancy measures. Additionally, as expected, during fear acquisition, participants showed greater activation to the CS+ in the amygdala and aMCC, areas known to play a crucial role in the expression of fear (e.g. Burgos-Robles et al, 2009; LeDoux, 2000; Linnman et al, 2012; Milad, et al., 2007). During fear extinction, participants also showed greater activation in the amygdala, aMCC, and vmPFC, all regions known to mediate this learning process (LeDoux, 2000, Burgos-Robles et al, 2009, Phelps et al, 2004).

When examining associations between trait anxiety and responses to the CS+ versus CS- during fear acquisition, consistent with previous studies of trait anxiety and anxiety disorder

patients, I did not find that trait anxiety was associated with enhanced differential responding to the CS+ versus CS- with either the skin conductance or UCS expectancy measure (e.g., Duits et al., 2015; Gazendam, Kamphuis, & Kindt, 2013; Joos, Vansteenwegen, & Hermans 2012; Torrents-Rodas et al., 2013). Also in keeping with previous studies (Barrett et al., 2009; Sehlmeyer et al, 2011), I failed to find associations between high levels of trait and anxiety and elevated activation of the amygdala and aMCC to the CS+ compared to the CS- during acquisition. This suggests that clinical and subclinical levels of anxiety are not associated with an enhanced ability to acquire a fear response.

Similar to the acquisition findings, I also did not find significant relationships between trait anxiety and differential skin conductance responses or UCS expectancy ratings to the CS+ versus CS- during extinction. I also found no significant relationships between trait anxiety and a CS+ minus CS- difference score within the amygdala, aMCC, or vmPFC during extinction. The skin conductance and UCS expectancy ratings findings are consistent with previous studies of trait anxiety (e.g., Gazendam, Kamphuis, & Kindt, 2013; Joos, Vansteenwegen, & Hermans 2012; Torrents-Rodas et al., 2013). However, previous studies that have used this difference score have found that higher trait anxiety is associated with sustained activation in the amygdala to the CS+ compared to the CS- during extinction, suggesting heightened threat reactivity when threat is no longer present in the environment (Barrett et al., 2009; Sehlmeyer et al., 2011). Additionally, one study found that trait anxiety was associated with reduced aMCC activation to the CS+ versus CS- during extinction (Sehlmeyer et al., 2011). Given that the aMCC also plays a role in cognitive control processes (Bush et al., 2000), the authors posited that trait anxious individuals fail to recruit mechanisms needed to inhibit fear responses (Sehlmeyer et al., 2011). Barrett & Armony (2009) found no significant relationships between trait anxiety and differential

activation to the CS+ compared to the CS- within the vmPFC during extinction (Barrett & Armony, 2009). When comparing our results to studies of anxiety disorder patients, our findings are largely inconsistent, with anxiety disorder patients showing an enhanced responding to the CS+, as indexed by a variety of psychophysiological and self-report measures (Duits et al., 2015). Studies of anxiety disorder patients have also shown that patients display greater amygdala and less vmPFC activation to the CS+ compared to the CS- during extinction learning (Milad et al., 2009). These studies suggest that anxiety disorders are associated with greater reactivity to threat (amygdala activity) and have inefficient regulatory mechanisms (vmPFC activity) to aid in inhibiting fear responses. While these previous studies used a similar paradigm as our study, they did not incorporate a 100% reinforcement rate of the CS+, which might contribute to the differing results. A 100% reinforcement rate is a strong manipulation that may have dampened the ability to find individual variability in responding to the CS+ versus CS- during extinction learning.

In contrast to the lack of trait anxiety relations with the CS+ versus CS- difference score, when I examined activation to the CS+ and CS- separately, I found that higher trait anxiety levels were associated with greater activation within the vmPFC and aMCC to both the CS+ and the CS-. Previous research has shown that clinical and subclinical levels of anxiety are associated with aberrant responding the CS- or the safety cue (Duits et al, 2015; Gazendam et al., 2013); therefore just examining difference scores may obscure significant relationships with trait anxiety. A number of possible explanations have been posited to explain aberrant responding to the safety cue or both the threat and safety cue in individuals with high levels of anxiety. One possible mechanism is that individuals with high anxiety levels may be unaware that the CS+ that was once paired with a shock during acquisition is no longer being paired with a shock

during extinction and that the CS- was never paired with a shock (Grillon, 2002). This mechanism does not seem to explain the current study results given that participants demonstrated normal learning irrespective of individual differences in trait anxiety. Additionally, other non-associative learning processes have been suggested such as a lack of physiological habituation (i.e. failure to dampen responses to repetitive stimuli; Clemens & Selesnick, 1967) and greater sensitization (i.e., enhanced responding to stimuli in an aversive environment; Ohman & Mineka, 2001). However, when looking at the fear acquisition results in the current study, irrespective of trait anxiety level differences, participants showed a general reduction in the skin conductance response as the acquisition learning progressed, despite the CS+ continuing to be paired with an aversive stimulus. This suggests that the association between trait anxiety and amplified responding to the CS+ and CS- is likely not due to a lack of physiological habituation or enhanced sensitization.

Another mechanism that may best explain the findings of the current study is fear generalization (i.e., perceptual deficits in distinguishing between threat and safety cues (Haddad, Pritchett, Lissek, & Lau, 2012; Lissek et al., 2008). Studies examining fear generalization have demonstrated that successful discrimination between threat and safety cues is associated with declines in aMCC and amygdala activity and increases in vmPFC activity as the generalized stimulus becomes less perceptually similar to the CS+ (Lissek et al., 2008). The neural correlates of this process have been shown to be altered in those with anxiety problems (Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2012; Cha et al., 2014). Although I did not directly examine fear generalization, greater activation within the aMCC and vmPFC to the CS+ and CS- in those with higher levels of anxiety may potentially reflect a deficient discriminatory learning process.

After exploring anxiety-related differences during fear extinction learning, I examined dynamic interactions between the BLA, CMA, aMCC, and vmPFC, by incorporating a resting state scan before and after fear extinction learning. As expected, I found a strengthening in resting state functional connectivity between the BLA-vmPFC from before to after fear extinction learning. Connectivity between the CMA and vmPFC also increased following extinction learning. In addition to inhibitory relationships between the BLA and vmPFC, animal research has established that the vmPFC also contains projections to the lateral division of the CMA which aid to inhibit CMA output (McDonald, 1998; Vertes, 2004). This strengthening in BLA-vmPFC and CMA-vmPFC connectivity was unrelated to varying levels of trait anxiety. These findings indicate that fear extinction learning serves to strengthen pathways that are known to be involved in fear inhibition and that this pathway appears to be intact in those with high levels of trait anxiety. In contrast to what I expected, resting state connectivity between the CMA and aMCC, a pathway thought to be involved in the expression of fear did not dampen following extinction learning. This was not related to trait anxiety. This may be the result of the short length of our fear extinction protocol, which may have prevented a complete dampening of the fear response. Additionally, given that extinction learning is not a process in which the fear memory is erased (see Herry et al., 2010; Furini, Myskiw, & Izquierdo, 2014), the CMA-aMCC may be a representation of the still existing fear memory.

While trait anxiety was not associated with changes in BLA-vmPFC, CMA-vmPFC, or CMA-aMCC pathways, it was positively associated with strengthening in a BLA-aMCC pathway following fear extinction learning. This is consistent with a study that showed stronger resting state connectivity between the BLA and aMCC in individuals with PTSD compared to trauma-exposed controls (Brown et al., 2014). Based on animal research, it has been established

that the aMCC contains excitatory projections to the BLA, which serve to promote the expression of fear and impede fear extinction (McDonald, 1998; Vertes, 2004; Likhtik, Pelletere, Paz & Pare, 2005; Senn et al., 2014). In sum, our findings suggest that trait anxious individuals show strengthened connectivity in a fear expression circuit, but seem to have intact plasticity within a fear inhibition circuit. A number of studies of trait anxious samples have shown greater dysfunction in regions involved in the expression of fear (amygdala, aMCC) (e.g.; Barrett & Armony; Sehlmeyer et al, 2011). However, in studies of clinical populations such as PTSD, particularly within the context of fear extinction learning, additional vmPFC dysfunction is more often demonstrated (Milad et al, 2009). A causal model of PTSD suggests that dysfunction in the amygdala and aMCC may be predisposing factors to the development of PTSD whereas vmPFC deficits are acquired after the full development of the disorder (Admon, Milad, & Hendler., 2013). Given the nature of our sample, it is possible that we are examining predisposing factors or early markers of an anxiety disorder that are thought to involve dysfunction in fear expression circuits.

While I found significant relationships between trait anxiety and extinction-related resting state connectivity changes, I did not find significant associations between trait anxiety and white matter integrity as indexed by FA values. Previous studies that have found significant associations between anxiety problems (both clinical and subclinical) and white matter integrity within amygdala based pathways have used the whole amygdala and have not explored more precise amygdala subregion pathways (Eden et al., 2015; Kim et al., 2009; Tromp et al, 2012). This may contribute to differing results between our study and previous studies.

Additionally, I also did not find significant associations between resting-state functional connectivity changes and white matter integrity. A number of potential methodological issues

may have contributed to the lack of structure-function relationships. Our diffusion weighted images were collected with echoplanar imaging, which suffers from susceptibility artifacts (Koch et al, 2002). These susceptibility artifacts were found in the ventromedial/orbital frontal cortex, a primary target of the amygdala subregion pathways of interest. It is likely that these artifacts degrade the validity and sensitivity of the tractography and subsequent calculation of FA values. Additionally, tracking longer range connections, such as the one characterizing the largely indirect pathways connecting the amygdala subregions to the aMCC, are known to susceptible to bias due to challenges with tracking the complex local association fibres that underlie the cortex (Reveley, 2015). Also, structural connections represent anatomical connections and likely direct neuronal communication across structures whereas functional connections represent correlational patterns that don't always onto the direct neuronal communication. Therefore, it is plausible that functional connections don't always map onto structural properties of the pathway. Additionally, given that I only examined one index of the white matter properties within these amygdala based pathways, it may be possible that other diffusivity measures (e.g., axial diffusivity, radial diffusivity) may have been more sensitive to structure-function relationships. Studies have only recently begun to explore relationships between resting state connectivity and diffusion measures (e.g., Kehoe, Farrell, & Metzler-Baddley, 2015; Khalsa et al., 2014). Additionally, to our knowledge no one has explored relationships between resting state connectivity changes associated with a learning event and diffusion measures. Given the paucity of research, it will be important to further examine possible relationships between diffusion measures and extinction-related neural processes using more advanced techniques (e.g., diffusion spectrum imaging) that may more accurately portray specific amygdala subregion connections.

Given that poor extinction retention is thought to lie at the core of anxiety problems, I also sought to examine how individual differences in neural activity during initial extinction learning, extinction-related resting connectivity changes, white matter integrity, and varying levels of trait anxiety are related to extinction assessed one week later. In contrast to what I expected, I failed to find significant associations between both extinction retention indices (skin conductance, UCS expectancy rating) and CS+ minus CS- activation within the amygdala, aMCC, and vmPFC during initial extinction learning. Additionally, I did not find significant associations between both extinction retention measures and extinction-related changes within BLA-vmPFC or CMA-aMCC pathways or our post-hoc BLA-aMCC and CMA-vmPFC pathways. I also did not find significant relationships between trait anxiety and extinction retention indices.

The lack of relationships between extinction retention, brain activation, resting state functional connectivity changes, white matter integrity, and trait anxiety, may be due to a number of reasons. The extinction retention session was done in a different context (outside of the scanner in a different room) than the initial extinction learning session. Additionally, the extinction retention session occurred one week after the initial extinction session. In most studies, a typical extinction retention session occurs 24 hours after and within the same context as the initial extinction session (e.g. Milad et al., 2009; Milad et al., 2007b; Linnman et al., 2012). Given that extinction retention is context dependent and sensitive to the passage of time (Bouton et al., 2004), the differences in context and the greater length of time in between initial extinction learning and retention may have dampened the ability to detect individual variability.

Additionally, skin conductance and UCS expectancy measures often fail to capture extinction learning deficits in those with high but not clinical levels of trait anxiety (Gazendam et

al., 2013). Gazendam and colleagues (2013) found that using measures more within the affective domain such as distress level ratings and startle response measures (which captures valence and arousal) were better at capturing safety learning impairments in subclinical trait anxiety populations than skin conductance and UCS expectancy measures. Future work should incorporate more sensitive affective measures such as the startle response or distress ratings to assess how changes within these fear inhibition and fear expression networks may be associated with extinction retention impairments in anxiety. Also, our paradigm was a simple differential delayed conditioning paradigm in which the CS+ was 100% reinforced with a shock during fear acquisition. Given that difficulties with uncertainty and ambiguity are important features of anxiety problems, this type of 100% reinforcement paradigm may not be optimal for the assessment of individual differences (Arnaudova et al., 2013).

Additionally, it would be helpful to include an additional baseline scan before fear acquisition to clarify which neural changes are purely associated with extinction learning and which neural changes might have been influenced by the fear acquisition session. It would also be useful to incorporate a control task to more accurately test which neural changes are resulting from extinction learning and not other potential learning processes.

Despite some of these potential limitations, my study has some clear strengths: I used a novel paradigm to study plastic processes linked to fear extinction learning in a relatively large sample stratified on trait anxiety. In sum, my study showed that fear extinction learning is associated with a strengthening of connections involved in fear inhibition (BLA-vmPFC, CMA-vmPFC). However, higher levels of trait anxiety are associated with less dampening of a fear expression network (BLA-aMCC). For individuals with higher levels of trait anxiety, enhanced plasticity in fear expression circuits likely contributes to fear inhibition problems and undermines

the work of the intact fear inhibition plasticity. Given the current findings on neural dysfunction on trait anxious versus clinically anxious populations, deficits in fear expression plasticity may appear early on and additional deficient plasticity within fear inhibition circuits may evolve later on if the individual develops an anxiety disorder. Further understanding of extinction –related plasticity may help to guide our understanding of predisposing factors that may help to identify at risk individuals. Additionally, this work may ultimately aid in understanding and optimizing exposure based treatments for anxiety problems.

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Sehlmeyer, C., Dannlowski, U., Schoning, S., Kugel, H., Pyka, M., Pfleiderer, B., … &, Konrad, C. (2011). Neural correlates of trait anxiety in fear extinction. *Psychological Medicine, 41,* 789-798.

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Vytal, K. E., Overstreet, C., Charney, D.R., Robinson, O. J., & Grillon, C. (2014). Sustained anxiety increases amygdala-dorsomedial coupling: a mechanism for maintaining an anxious state in healthy adults. *Journal of Psychiatry & Neuroscience, 39,* 321-329.

Wedeen, V. J., Wang, R. P., Schmahmann, J. D., Benner, T., Tseng, W. Y., Dai, G., … & de Crespigny, A. J. (2008). Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage, 41,* 1267-77.

World Health Organization: The World Health Report 2001: Mental Health: New Understanding, New Hope. Geneva, World Health Organization.

Emily L. Belleau

Curriculum Vitae

Contact Information

University of Wisconsin-Milwaukee
Department of Psychology
2441 E. Hartford Ave.
Milwaukee, WI 53211

Education

2009 – Current	Ph.D. in Clinical Psychology: University of Wisconsin-Milwaukee Dissertation: *Neural plasticity of extinction learning: Relations with dispositional anxiety and extinction retention* Advisor: Christine L. Larson, Ph.D.
2012	M.S. in Clinical Psychology: University of Wisconsin-Milwaukee Master's Thesis: *Negative emotion's effect on cognitive load and cognitive load's effect on negative emotion: Is it emotional interference, emotion regulation, or both?* Advisor: Christine L. Larson, Ph.D.
2004 – 2008	B.S., in Psychology: Pennsylvania State University Schreyer Honors College Honor's Thesis: *Depression and emotion recognition* Thesis Advisor: Amy D. Marshall, Ph.D.

Honors and Awards

2014	UWM Chancellor Golda Meir Library Scholar Award Finalist
2013	UWM Psychology Department Summer Research Fellowship
2012-2013	UWM Clinical and Translational Science Institute Research Assistantship
2012	UWM Travel Award
2011	Society for Psychophysiological Research Training Fellowship
2008	Poster Award at the Penn State Undergraduate Psi Chi Conference
2007	Phi Kappa Phi

Research Experience

2009-Current	*Graduate Student Research Assistant* Affective Neuroscience Lab, University of Wisconsin-Milwaukee Supervisor: Christine L. Larson, Ph.D.

2008-2009	*Research Associate* Western Psychiatric Institute and Clinic, Pittsburgh, PA Supervisor: Cecile D. Ladouceur, Ph.D.
2007-2008	*Undergraduate Research Assistant* Relationship Research Lab, Pennsylvania State University Supervisor: Amy D. Marshall, Ph.D.
2008	*Undergraduate Research Assistant* Interdisciplinary Social Psychology Lab, Pennsylvania State University Supervisor: Stephanie A. Shields, Ph.D.
2007-2008	*Undergraduate Research Assistant* Personality, Psychopathology, and Psychotherapy Lab, Pennsylvania State University Supervisor: Kenneth N. Levy, Ph.D.

Publications

Belleau, E.L., Taubitz, L.E., & Larson, C.L. (2015). Imbalance of default mode and regulatory networks during externally focused processing in depression. *Social Cognitive and Affective Neuroscience 10,* 744-751.

Belleau, E.L., Phillips, M.L., Birmaher, B., Axelson, D.A., & Ladouceur, C.D. (2013). Aberrant executive attention in unaffected youth at familial risk for mood disorders. *Journal of Affective Disorders*, *147,* 397-400.

Snorrason, I., **Belleau, E.L.,** & Woods, D.W. (2012). How related are hair pulling disorder (trichotillomania) and skin picking disorder? A review of evidence for comorbidity, similarities and shared etiology. *Clinical Psychology Review, 32,* 618-629.

Marshall, A.D., Sippel, L.M., & **Belleau, E.L.** (2011). Negatively biased emotion perception in depression as a contributing factor to psychological aggression perpetration: A preliminary study. *The Journal of Psychology: Interdisciplinary and Applied*, *145,* 521-535.

Manuscripts in Preparation

Belleau, E.L., Larson, C.L., Jakubowski, E.J., & Siegle, G.J. (in prep). *Working memory capacity influences the effectiveness of reappraisal emotion regulation strategies*.

Belleau, E.L., Pedersen, W.S., Miskovich, T., & Larson, C.L. (in prep). *Neural plasticity of extinction: Relations with dispositional anxiety and extinction retention.*

deRoon-Cassini, T., Taubitz, L.E., **Belleau, E.L.,** Blaisdell, J., & Larson, C.L. (in prep). D*ysregulation in affect-related neural activity immediately post-trauma predicts chronic PTSD symptoms.*

Larson C.L., **Belleau, E.L.,** Steuer, E.L., Duke, M.W., & Kaad, L.M. (in prep). *The downward V is an emotionally meaningful environmental cue: An event related potential study*.

Miskovich, T., Pedersen, W.S., Hansen, J., **Belleau, E.L.,** & Larson, C.L. (in prep). *Decreased local gyrification in the precuneus is associated with high trait anxiety*.

Symposia at National Conferences

Larson, C.L., deRoon-Cassini, T., Taubitz, L.E., & **Belleau, E.L.** *Neural markers of emotion dysregulation in acute trauma survivors predict chronic PTSD*. Symposium presentation at the annual meeting of the Society for Research in Psychopathology, September 18-21, 2014, Evanston, IL.

Belleau, E.L., Taubitz, L.E., & Larson, C.L. *Imbalance of default mode and regulatory networks during externally focused processing in depression.* Symposium presentation at the annual meeting of the Society for Psychophysiological Research, September 10-14, 2014, Atlanta, GA.

Larson, C.L., deRoon-Cassini, T., Taubitz, L.E., & **Belleau, E.L.** *Divergent neural correlates of hyperarousal and intrusive symptoms in acute trauma survivors*. Symposium presentation at the annual meeting of the Society for Psychophysiological Research, September 10-14, 2014, Atlanta, GA.

Ladouceur, C.D., **Belleau, E.L.**, Birmaher, B., Axelson, D.A., & Phillips, M.L. *Deficits in attentional control processes in youth at high familial risk for bipolar disorder and unipolar depression: Potential endophenotype for mood disorders?* Symposium Presentation at the annual meeting of the Society for Biological Psychiatry, May 12-14, 2011. San Francisco, CA.

Local Talks

Belleau, E.L. & Larson, C.L. *Fear and safety learning*. Invited talk at the Upward Bound Math and Science Data Blitz, July, 15, 2014, University of Wisconsin-Milwaukee.

Belleau, E.L. & Larson, C.L. *Neural plasticity of fear extinction learning: Relations with anxiety.* Invited talk given at Rogers Memorial Hospital, August 5th, 2013, Oconomowoc, WI.

Belleau, E.L. & Larson, C.L. *Neural plasticity of fear extinction learning: Relations with anxiety*. Invited talk given at the weekly Clinical Translational Science Research Seminar, April 11th, 2013, Medical College of Wisconsin, Milwaukee, WI.

Belleau, E.L., Taubitz, L.E., Castro, M., & Larson, C.L. *Neural correlates of rumination in depression*. Talk given at the annual Association of Graduate Students in Psychology (AGSIP) Research Symposium, April 5th 2013, University of Wisconsin-Milwaukee.

Belleau, E.L., Ladouceur, C.D., Birmaher, B., Axelson, D., & Phillips, M.L. *Deficits in executive attention in offspring at high familial risk for mood disorders.* Talk given at the annual Association of Graduate Students in Psychology (AGSIP) Research Symposium, April 9th, 2010, University of Wisconsin-Milwaukee.

Poster Presentations

Belleau, E.L., Taubitz, L.E., & Larson, C.L. *Imbalance of default mode and regulatory networks during externally focused processing in depression.* Poster presented at the annual meeting of the Society for Research in Psychopathology, September 18-21, 2014, Evanston, IL.

Belleau, E.L., Taubitz, L.E., & Larson, C.L. *Imbalance of default mode and regulatory networks during externally focused processing in depression.* Poster presented at the first meeting of the Society for Affective Science, April 24-26, 2014, Bethesda, MD.

Miskovich, T.A., Pedersen, W.S., **Belleau, E.L.**, & Larson, C.L. *Decreased cortical gyrification is associated with trait anxiety.* Poster presented at the first meeting of the Society for Affective Science, April 24-26 2014, Bethesda, MD.

Pedersen, W.S., Balderston, N.L., Miskovich, T.A., **Belleau, E.L.,** Schultz, D.H., Helmstetter, F.J., & Larson, C.L. *Independent effects of novelty and valence on the amygdala BOLD response.* Poster presented at the annual meeting of the Society for Affective Science, April 24-26, 2014, Bethesda, MD.

Pedersen, W.S., Shackman, A.J., Blaisdell, J.A., **Belleau, E.L.,** Stout, D.M., & Larson, C.L. *Posterior parietal cortex activation predicts working memory capacity for faces*. Poster presented at the annual meeting of the Cognitive Neuroscience Society, April 13-16, 2013, San Francisco, CA.

Belleau, E.L., Larson, C.L., Jakubowski, E.J., & Siegle, G.J. *Working memory capacity influences the effectiveness of reappraisal emotion regulation strategies*. Poster presented at the annual meeting of the Society for Psychophysiological Research, September 19-23, 2012, New Orleans, LA.

Belleau, E.L., Taubitz, L.E., Larson, C.L., & Castro, M. *The impact of neural functioning in response to emotional information.* Poster presented at the Biological Psychiatry Society Annual Convention, May 3-5, 2012, Philadelphia, PA.

Jakubowski, E., **Belleau, E.L,** & Larson, C.L. *Effect of negative emotion on cognitive load and mood.* Poster presented at the UWM Undergraduate Research Symposium, April 4, 2012, Milwaukee, WI.

Belleau, E.L., Taubitz, L., Larson, C.L. & Castro, M. *The impact of neural functioning in response to emotional information.* Poster presented at the 51st Annual Meeting of the Society for Psychophysiological Research, September 14-18, 2011, Boston, MA.

Lewis, K.L., Steuer, E.L., Duke, M.W., Taubitz, L., **Belleau, E.L.**, & Larson, C.L. *Frontal late positive potential predicts subsequent memory for pleasant pictures.* Poster presented at the Society for Psychophysiological Research, September 14-18, 2011, Boston, MA.

Lewis, K.L., Steuer, E.L., Duke, M.W., Taubitz, L., **Belleau, E.L.**, & Larson, C.L. *Frontal late positive potential predicts subsequent memory for pleasant pictures*. Poster presented at the Midwest Psychological Association meeting, May 2011, Chicago, IL.

Belleau, E.L., Taubitz, L. & Larson, C.L. *Ruminative thinking and cognitive reappraisal predict the experience of depressive symptomology*. Poster accepted at the Association for Behavioral and Cognitive Therapies 44th Annual Convention, November 18-21, 2010, San Fransisco, CA.

Taubitz, L.E., **Belleau, E.**, & Larson, C.L. *Decreased BAS reward sensitivity predicts anhedonia better than general distress symptoms of depression*. Poster presented at the Association of Behavioral and Cognitive Therapies' 44th annual meeting, November 18-21, 2010, San Francisco, CA.

Belleau, E.L., Steur, E.L., Duke, M.W., Kaad, L.M., & Larson, C.L. *The downward V is an emotionally meaningful environmental cue: An event-related potential study*. Poster submitted to the Social and Affective Neuroscience Society 4rth Annual Meeting, October 29-31, 2010, Chicago, IL.

Duke, M.W., Steuer, E.L., Taubitz, L.E., **Belleau, E.L.**, & Larson, C.L. *EEG responses to emotional images: examination of the effects of rumination and distraction in depression.* Poster presented at the Society for Social & Affective Neuroscience Society, October 29-31, 2010, Chicago, IL.

Duke, M.W., Steuer, E.L., Taubitz, L.E., **Belleau, E.L.**, & Larson, C.L. *EEG responses to emotional images: examination of the effects of rumination and distraction in depression.* Poster presented at the Society for Psychophysiological Research, September 29-October 3, 2010, Portland, OR.

Belleau, E.L., Ladouceur, C.D., Birmaher, B., Axelson, D., & Phillips, M.L. *Deficits in executive attention in offspring at high familial risk for mood disorders* Poster presented at the Annual Society of Biological Psychiatry 64th Annual Convention and Meeting. May, 2009, Vancouver, Canada.

Belleau, E.L. & Marshall, A.D. *Depression and emotion recognition* 1st runner up awarded Poster presented at the Psi Chi (Psychology Honors Society) Undergraduate Research Conference, April, 2008, The Pennsylvania State University, University Park, PA.

Belleau, E.L. & Marshall, A.D. *Depression and emotion recognition* Poster presented at the Columbia University Undergraduate Research Symposium, April, 2008, Columbia University, New York, NY.

Ad Hoc Journal Reviewer

Psychophysiology (with Christine Larson, Ph.D)
Cognition and Emotion
Psychiatry Research: Neuroimaging

Grants Applied For

Ruth L. Kirschstein National Research Service Award for Individual Predoctoral Fellowships (Parent F-31, PA-11-111) entitled N*eural plasticity of extinction: relations with anxiety and extinction retention.* (not funded)

Neuroimaging Training

Connectivity course: Structural and functional brain connectivity via MRI and fMRI
October 28th –November 1st 2013, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, Massachusetts
Coordinator: Robert L. Savoy, Director of fMRI Education, Athinoula A. Martinos Center for Biomedical Imaging

FSL Neuroimaging Training
June 3-6th 2013, University of Wisconsin-Milwaukee
Instructor: Laura Libby, University of California-Davis

Research Skills

- Task-based neuroimaging analyses with AFNI and FSL
- Resting state connectivity (both seed based and independent component analysis approaches) using AFNI and GIFT software packages
- Diffusion tensor imaging analyses using FSL and Tracula software packages
- EEG and ERP collection and analysis using EEGLAB, ERPLAB, and Neuroscan software packages
- Pupilometry, facial EMG, skin conductance collection and analysis
- SNP genotyping
- Programing experiments with Eprime
- Psychodiagnostic interviewing

Research Supervision Experience

2013-Current	Supervision of Undergraduate Thesis (with Christine Larson, Ph.D.) Student: Jessica Hanson
2010-2011	Supervision of Undergraduate Thesis (with Christine Larson, Ph.D,) Student: Lindsay Kaad B.S. Thesis: *Attention training for social anxiety in a single session: Using basic geometric shapes*

Teaching Experience

Spring 2015	Teaching Assistant, Psychology 320: Psychology of Women
Fall 2014	Teaching Assistant, Psychology 677: Experimental Social Psychology
Spring 2014	Teaching Assistant, Psychology 677: Experimental Social Psychology
Fall 2013	Teaching Assistant, Psychology 205: Personality

Clinical Experience

2014-Current **Traumatic Stress and Anxiety Disorders Specialty Clinic**
University of Wisconsin-Milwaukee
Supervisor: Shawn P. Cahill, Ph.D.

I am currently receiving training in prolonged exposure therapy for posttraumatic stress disorder. I am receiving live individual supervision as well as weekly group supervision.

2011-Current **General Psychology Clinic**
University of Wisconsin-Milwaukee
Supervisor: Robyn C. Ridley, Ph.D.

I received generalist training providing supportive, behavioral activation, and mindfulness based interventions for individuals with a range of mood, anxiety, and personality disorder characteristics. I participated in weekly group supervision as well as individual supervision that involved review of video recorded sessions. I am currently seeing a client in the clinic and receive supervision as needed.

2009-Current **Assessment Experience in a Research Context**
University of Wisconsin-Milwaukee
Supervisor: Christine L. Larson, Ph.D.

I have administered several semi-structured psychodiagnostic interviews for research studies on anxiety, depression, and posttraumatic stress disorder, including the Structured Clinical Interview for DSM-IV-TR Disorders (SCID), the Mini International Neuropsychiatric Interview (M.I.N.I.) and the Clinician -Administered PTSD Scale for DSM-5 (CAPS-5).

2012-2013 **Rogers Memorial Hospital, Eating Disorder Center**
Supervisors: Bradley C. Riemann, Ph.D. & Mary E. Fitzpatrick, Ph.D.

I received training in exposure and response prevention for comorbid eating and obsessive-compulsive disorder within a residential treatment setting. In addition to exposure and response prevention, I also got extensive training in interoceptive exposure interventions for panic disorder, cognitive-behavioral therapy for social anxiety disorder, and behavioral activation for major depressive disorder. I also co-facilitated three therapy groups: a coping skills group composed of female residents with eating disorders, a coping skills group composed of male residents with eating disorders and a cognitive-behavioral check-in group. Additionally, under the supervision of Dr. Fitzpatrick, I attended and later conducted consultation meetings with patients to determine their treatment needs in the cognitive-behavioral treatment program. I received weekly supervision as well as group supervision. I attended interdisciplinary treatment team meetings.

2011-2012 **Depression Specialty Clinic**
University of Wisconsin-Milwaukee
Supervisor: Jonathan W. Kanter, Ph.D.

I received training in behavioral activation and cognitive-behavioral therapy for individuals with major depressive disorder and comorbid personality disorder traits. On occasion, I also applied acceptance-based interventions. I received both weekly individual supervision which involved review of recorded sessions and group supervision.

2011 **Didactic in Empirically Supported Interventions**
University of Wisconsin-Milwaukee
Supervisor: Shawn P. Cahill, Ph.D.

I participated in a 1 ½ hour weekly practicum where we learned skills commonly implemented in empirically supported cognitive-behavioral interventions. This practicum involved role-play instruction on conducting Arthur Nezu's problem-solving interventions, hierarchy building, *in vivo* exposure, imaginal exposure, interoceptive exposure, and relaxation techniques.

2010-2011 **Assessment Practicums**
General Psychology Clinic & Depression Specialty Clinic
University of Wisconsin-Milwaukee
Supervisors: Bonnie P. Klein-Tasman, Ph.D., Han Joo Lee, Ph.D., & Jonathan W. Kanter, Ph.D.

I administered, scored, and interpreted objective measures of intelligence, achievement, memory, executive functioning, and personality in both adults and children. I also prepared integrated assessment reports and provided recommendations regarding treatment objectives to clients and their families. I completed four adult neuropsychology assessments and one child neuropsychology assessment. Additionally in the Depression Specialty Treatment Clinic, I conducted two comprehensive psychodiagnostic intake evaluations on two adults prior to entering therapy.

2007-2008 **Mental Health Technician, Meadows Psychiatric Center**

I provided support, psychoeducation, and taught problem-solving skills to adults, adolescents, and children in an inpatient mental health treatment facility.

Professional Organizations

2014-Current	Society for Research in Psychopathology
2010-Current	Social and Affective Neuroscience Society
2010-Current	Society for Psychophysiological Research
2010-Current	Sigma Xi
2009-Current	American Psychological Association