Common Neural Engagement during Cognitive Reappraisal across Internalizing Psychopathology

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THESIS

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Dedication

To Mom and Dad, who provided me with the best of all educations outside the classroom, instilling in me the values of reading, travel, self-guidance, and the dual-importance of intellectual humility and curiosity. To my brothers James, Connor and Garrett, who are more capable than I in many important matters of the world, principal among them a sense of adventure and fearlessness to bend, break, and go beyond the rules. And to my husband, Nathan, whose perspective on what truly matters continues to impress me on a daily basis. I love you with all my heart.

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AAL	Anatomical Automatic Labeling
AD	Anxiety Disorder
ACC	Anterior Cingulate Cortex
BA	Brodmann Area
BOLD	Blood Oxygenated Level Dependent
CBT	Cognitive Behavioral Therapy
dACC	dorsal Anterior Cingulate Cortex
DLPFC	Dorsolateral Prefrontal Cortex
DMPFC	Dorsomedial Prefrontal Cortex
FWE	Family Wise Error
fMRI	functional Magnetic Resonance Imaging
GAD	Generalized Anxiety Disorder
GLM	General Linear Model
HC	Healthy Control
ID	Internalizing Disorder
IPL	Inferior Parietal Lobe
LSAS	Liebowitz Social Anxiety Scale
MDD	Major Depressive Disorder
MNI	Montreal Neurological Institute
MPFC	Medial Prefrontal Cortex
OFC	Orbitofrontal Cortex
PPI	Psychophysiological Interaction

PTSD	Posttraumatic Stress Disorder
rACC	rostral Anterior Cingulate Cortex
SAD	Social Anxiety Disorder
sgACC	subgenual Anterior Cingulate Cortex
SPM	Statistical Parametric Mapping
SSRI	Selective Serotonin Reuptake Inhibiter
VLPFC	Ventrolateral Prefrontal Cortex
VMPFC	Ventromedial Prefrontal Cortex

SUMMARY

Individuals who suffer from excessive anxiety often also have excessive depression. A parsimonious model would suggest that both anxiety and depression reflect a core deficit in emotion regulation, demonstrated by a inefficient or ineffective down-regulation of negative affect using cognitive strategies such as reappraisal. Prior neuroimaging work in discrete samples of patients with anxiety and depressive disorders (e.g., generalized anxiety disorder [GAD], social anxiety disorder [SAD], major depressive disorder [MDD]) has commonly implicated under-engagement of the prefrontal cortex (PFC) during emotion regulation; however, findings have been mixed in regard to magnitude, locality and extent of the dysfunction across the PFC. Differences between disorders (anxiety vs. depression) and across individuals (extent of anxiety and/or depression symptoms severity) could contribute to this heterogeneity. To address this question, I examined PFC engagement/activation and its functional connectivity to the amygdala - a region instrumental for negative affect - using functional magnetic resonance imaging (fMRI) in a large sample of *N*=238 individuals with a wide range of anxiety and depression symptomatology (*n*=64 without psychiatric illness, *n*=47 GAD, *n*=78 SAD, *n*=49 MDD) during a reappraisal-based emotion regulation task. Across the sample, results showed that: 1) greater anxiety symptom severity, as measured by the Hamilton Anxiety Rating Scale, was related to less engagement of the dorsolateral prefrontal cortex (DLFPC), ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (DMPFC) and dorsal anterior cingulate (dACC); and 2) greater depression symptom severity, as measured by the Hamilton Depression Rating Scale, was also related to less engagement in the DLPFC and VLPFC. Both anxiety and depression symptom severity were related to less functional connectivity between the amygdala and VLPFC. Focal results held when accounting for depression severity, but not when accounting for

anxiety severity. These findings demonstrate that individual differences in anxiety and depression severity can help explain extent of PFC dysfunction observed across anxiety and depressive disorders, and that much of this dysfunction is driven by anxiety but not depression.

I. INTRODUCTION

A. Prevalence of Anxiety and Depression

Internalizing disorders (IDs) are a group of psychiatric illnesses with similar emotional and behavioral disturbances (American Psychiatric Association, 2013). Epidemiological research demonstrates that, by far, the two most common IDs are anxiety and depression. Nearly 18% of U.S. adults are diagnosed with an anxiety disorder and 16% with a depressive disorder (Ronald C. Kessler, Chiu, Demler, & Walters, 2005), making these two disorders two of the most common psychiatric illnesses. While there are current effective treatments for both anxiety and depression, interventions do not work equally well in all individuals (Cuijpers et al., 2013). The lack of a "one-size-fits-all" treatment option is likely due to substantial variability within these disorders in terms of symptom manifestation and course of illness (Binelli et al., 2015; Fried & Nesse, 2015; Unick, Snowden, & Hastings, 2009). Therefore, despite significant need on the part of the healthcare system to treat those with anxiety and depression (Berto, D'Ilario, Ruffo, Virgilio, & Rizzo, 2000; Ronald C. Kessler et al., 2009), more information is required to learn about how these disorders develop within individuals.

The category of anxiety disorders (ADs) can be classified further into individuals diagnosed with generalized anxiety disorder (GAD), social anxiety disorder (SAD), specific phobias (SP), panic disorder (PD), or obsessive-compulsive disorder (OCD). Two of the most common ADs are GAD and SAD, disorders that are related as the development of anxiety in both occurs in the presence of perceived threat with differences between the two in terms of what is considered threatening. For instance, anxiety symptoms include general yet excessive worry that spans major life issues and day-to-day stressors in GAD (American Psychiatric Association, 2013). In contrast, in SAD, anxiety develops around social interactions and fear of rejection from

others (American Psychiatric Association, 2013). In both GAD and SAD, anxiety related to these threats is difficult to control and accompanies feelings of restlessness or agitation, difficulty concentrating, irritability, physical symptoms, and sleep disturbances (American Psychiatric Association, 2013). Similar to ADs, symptoms of depression – classified as major depressive disorder (MDD) – include difficulty concentrating, sleep disturbances, physical symptoms, irritability, and psychomotor disturbances that may result in restlessness or agitation. Depressed mood and decreased interest or pleasure are cardinal symptoms of MDD and distinguishes the disorder from ADs (American Psychiatric Association, 2013).

Likely related to the fact that anxiety and depression share several symptoms, these disorders are highly co-morbid (Hirschfeld, 2001). Upwards of 60% of individuals diagnosed with MDD qualify for an AD (Ronald C. Kessler et al., 1996), and it is common to meet diagnostic criteria for more than one AD at the same time. In particular, the incidence for comorbidity among GAD, SAD, and MDD is high. Among individuals with a primary diagnosis of GAD or SAD, the lifetime rate of also having MDD exceeds 50% (R.C. Kessler et al., 1994; Ronald C. Kessler et al., 1996). In addition, nearly 60% of those with GAD meet criteria for SAD (Noyes, 2001), and SAD is the most common comorbid AD in those with GAD (Brown, Campbell, Lehman, Grisham, & Mancill, 2001). Based on these findings, comorbidity is the norm rather than the exception among those with GAD, SAD, and MDD, making it difficult to tease out behavioral, psychological, or biological vulnerabilities for one single disorder.

B. Emotion Dysregulation as a Prominent Feature of GAD, SAD, and MDD

While anxiety and depression disorders share several symptoms, heightened negative affectivity in particular is a shared and central disturbance (American Psychiatric Association,

2013). The presence of this system may be conceptualized in terms of emotion dysregulation, or the occurrence of atypical responding to an emotional trigger and/or difficulty in regulating this response (Gross, 1998). The idea that emotion dysregulation is a trans-diagnostic feature of both anxiety and depression is gaining traction; indeed, in recent years several publications have been put forth suggesting that these disorders are linked due to disturbances in emotion dysregulation as a common feature (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Amstadter, 2008; Cisler, Olatunji, Feldner, & Forsyth, 2010; Fernandez, Jazaieri, & Gross, 2016; Hostinar, Nusslock, & Miller, 2017; Shapero, Abramson, & Alloy, 2016; Tripp, McDevitt-Murphy, Avery, & Bracken, 2015; Tull, Bardeen, DiLillo, Messman-Moore, & Gratz, 2015). Evidence for emotion dysregulation in all samples comes from clinical and behavioral research. For instance, individuals with GAD (Decker, Turk, Hess, & Murray, 2008; Mennin, Heimberg, Turk, & Fresco, 2005; Mennin, McLaughlin, & Flanagan, 2009), SAD (Helbig-Lang, Rusch, & Lincoln, 2015; Jazaieri, Morrison, Goldin, & Gross, 2015; Kashdan & Farmer, 2014) and MDD (Millgram, Joormann, Huppert, & Tamir, 2015; Werner-Seidler, Banks, Dunn, & Moulds, 2013) all self-report difficulty in regulating negative emotions. Further, inability to regulate negative reactions is reported as a significant moderator in the relationship between negative affect responding (e.g., the development of significant fear symptoms) and diagnosis of anxiety (Cisler et al., 2010) and between life stress and development of depression (Hopfinger, Berking, Bockting, & Ebert, 2016). Finally, when skills in emotion regulation (e.g., how to effectively manage one's emotions) are taught using emotion-focused cognitive behavioral therapy (CBT) techniques, symptoms of worry in the case of GAD (Mennin, Fresco, Ritter, & Heimberg, 2015), social fear in the case of SAD (Kneeland, Dovidio, Joormann, & Clark, 2016), and depression in the case of MDD (Wirtz, Radkovsky, Ebert, & Berking, 2014) decline. Together, this suggests

that emotion dysregulation is clinically relevant, and may be integrally tied to the development of each disorder. In addition, when exploring possible treatment options for the care of both anxiety and depression, emotion dysregulation seems promising as a target for remediation.

C. Neurobiology of Emotional Reactivity

As emotion dysregulation may transpire due to excessive reactivity in response to emotional stimuli and/or in difficulty regulating emotional reactions (Gross & John, 2003), disturbances in either domain may contribute to defining this symptom in anxiety and depression. In order to explore the contribution of both aspects, studies of functional magnetic resonance imaging (fMRI) have been completed, first to investigate the extent to which subcortical brain regions involved in the processing of emotional material and the mounting of an arousal response are activated in those with GAD, SAD, and MDD during exposure to negative material.

Here, the neurobiology of emotion reactivity focusing on involvement of the amygdala in particular, considered the body's "alarm signal" as it is activated in response to motivationally-salient stimuli (Herman, Ostrander, Mueller, & Figueiredo, 2005). Emotional material, particularly stimuli that signals threat, produce robust engagement of the amygdala, although the region is also activated in response to positive stimuli (Costafreda, Brammer, David, & Fu, 2008) and stimuli that are novel (Herman et al., 2005; Urry, 2006). Engagement of the amygdala may coincide with heightened arousal response measured using skin conductance (e.g., sweat response) (Laine, Spitler, Mosher, & Gothard, 2009) that signal the launching of a the hypothalamo-pituitary-adrenocortical (HPA) axis (Weidenfeld, Newman, Itzik, Gur, & Feldman, 2002). However, increases in arousal responses measured in the periphery using skin

conductance do not always relate to enhanced amygdala responding (Critchley, Elliott, Mathias, & Dolan, 2000). Therefore, while engagement of the amygdala is considered necessary for detection and perception of salient content, this information contributes to the mounting of an arousal response (Barrett, Mesquita, Ochsner, & Gross, 2007) but is not be considered synonymous with it (Touroutoglou, Bickart, Barrett, & Dickerson, 2014). Rather, the amygdala plays a larger role in the integration of arousal-related neuromodulatory changes based on the detection of salient cues (de Voogd, Fernández, & Hermans, 2016).

D. Neurobiological Alterations during Emotional Reactivity in GAD, SAD, and MDD

Using the above literature as a framework for understanding which brain regions are central in emotional reactivity in healthy individuals, individuals with GAD, SAD, and MDD may show disruptions in engagement of these regions, and which may indicate neural underpinnings of emotion dysregulation. With regard to individuals with GAD, several studies report increased amygdala reactivity during exposure to negative scenes and faces in comparison to healthy controls (HCs) (e.g., individuals without psychiatric illness) (Andreescu et al., 2011; Buff et al., 2016; Fitzgerald et al., 2017; Fonzo et al., 2015; McClure et al., 2007; Monk et al., 2008; Nitschke et al., 2009; Park, Kim, Jeong, Chung, & Yang, 2016). Individuals diagnosed with SAD also show increased engagement of the amygdala during exposure to negative scenes and faces (Brühl et al., 2011; Carré et al., 2014; Fonzo et al., 2015; Heitmann et al., 2017; Phan, Fitzgerald, Nathan, & Tancer, 2006; Shah, Klumpp, Angstadt, Nathan, & Phan, 2009; Simon, Becker, Mothes-Lasch, Miltner, & Straube, 2016; M.B. Stein, Goldin, Sareen, Eyler-Zorrilla, & Brown, 2002; Murray B Stein, Simmons, Feinstein, & Paulus, 2007; Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004; Straube, Mentzel, & Miltner, 2005). In addition, individuals with

SAD show similar increased activation of the amygdala during exposure to stimuli that this group specifically perceives as threatening, such as pictures of individuals giving a speech (Heitmann et al., 2016) or during anticipation of giving a speech themselves (Boehme et al., 2014; Guyer et al., 2008; Lorberbaum et al., 2004; Tillfors et al., 2001). Finally, compared to HCs, individuals with MDD also display greater amygdala in response to negative scenes, faces, and words (Ai et al., 2015; Doerig et al., 2016; Fournier et al., 2013; Grotegerd et al., 2014; Hall et al., 2014; Jenkins et al., 2016; Matthews, Strigo, Simmons, Yang, & Paulus, 2008; Mingtian et al., 2012; Monk et al., 2008; Peluso et al., 2009; Pulcu et al., 2014; Sheline et al., 2001; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007; Stuhrmann et al., 2013; Stuhrmann, Suslow, & Dannlowski, 2011; Surguladze et al., 2005; Suslow et al., 2010; Tao et al., 2012; van Tol et al., 2012; van Wingen et al., 2011; Victor, Furey, Fromm, Öhman, & Drevets, 2010; Yang et al., 2010; Zhong et al., 2011).

Together, this research shows that heightened amygdala response is common across anxious and depressed patients, suggesting heightened reactivity to negative stimuli. However, deficits in regulating heightened negative affect may also contribute to emotion dysregualation in these disorders. Evidence for this possibility stems from clinical reports that deficits in effectively regulating negative affect spurs the use of excessive and uncontrollable worry as a maladaptive coping mechanism for the regulation of reactivity as a signature symptom of GAD (Mennin et al., 2015, 2005; Mennin, Holaway, Fresco, Moore, & Heimberg, 2007). Inability to regulate a fear response to social situations or unfavorable critique is also a core symptom of SAD (Moscovitch, 2009), while inability to inhibit negative affect using another maladaptive emotion regulation strategy of rumination is a central feature of MDD (D'Avanzato, Joormann, Siemer, & Gotlib, 2013; Joormann & Gotlib, 2010). That is, inability to regulate negative

emotions is a common feature of GAD, SAD, and MDD, linked to central symptoms of each disorder.

E. Emotion Regulation using the Strategy of Cognitive Reappraisal

In order to consider how regulation of negative reactivity occurs, we first consider what is meant by emotion regulation broadly. Emotion regulation is defined as a change in the onset, duration, intensity, or valence of an emotional experience (Gross & Thompson, 2007). The process model of emotion considers an emotional experience as one that unfolds along a continuum of time, and which can be defined at four discrete stages (**Figure 1**). The first, *situation*, describes instances that instigate an emotional reaction, which may be either internally- or externally-generated. The second, *attention*, describes the process by which an individual attends to this situation, while the third, *appraisal*, is the process by which individuals give meaning to this situation. In the end, a *response* is made which may occur at the behavioral, physiological, psychological, or neural level (Gross & Thompson, 2007).

Taking the process model of emotion as a framework, emotion regulation is defined as the ways in which an individual influences the emotional experience by interjecting at any one or multiple points along the continuum in order to change the onset/offset, duration, magnitude, or valence of an emotional experience (Gross, 1998). For example, emotion regulation may reflect delaying the start of an emotion, shortening its duration, decreasing its intensity, or changing it from negative to positive. Multiple strategies exist for completing emotion regulation, with variety in what process is targeted (Gross & Thompson, 2007). For instance, individuals may modify the situation in which they put themselves based on the probability that situations induce an emotional experience (*situation selection/modification*), attend to or away from emotional

triggers (*attentional deployment*), change cognitive thinking regarding the appraisal of a stimulus (*cognitive reappraisal*), or hide the manifestation of the emotional response (*suppression*).

Although each form of regulation uses distinct mechanisms to change an emotional reaction, cognitive reappraisal is the most widely-used strategy in healthy individuals (Cutuli, 2014) and is considered the most beneficial, in terms of reducing subjective feelings of negative affect (Gross, 2002; Hajcak & Nieuwenhuis, 2006; Ray, McRae, Ochsner, & Gross, 2010; Zhang, Li, Qin, & Luo, 2012) and objective physiological responses like startle eye-blinks to aversive stimuli (Dillon & LaBar, 2005; Eippert et al., 2007; Ray et al., 2010) and heart rate (Pavlov et al., 2014). In addition, frequent use of cognitive reappraisal in daily living (e.g., outside the laboratory) is associated with long-term psychological health and well-being (Cutuli, 2014; Gross, 2002). Defined further, cognitive reappraisal is as an antecedent emotion regulation strategy that occurs prior to or when an emotional experience is unfolding and involves the cognitive transformation of an emotional experience in order to change its emotional meaning (Gross, 1998). While cognitive reappraisal can be used to alter different aspects of an emotional experience, it is commonly studied in the context of changing the valence of an emotional experience, particularly when making negative stimuli appear less negative. For example, cognitive reappraisal may be used in the context of a scene of women crying outside a funeral in order to re-interpret it as one that depicts tears of joy at a wedding, rather than sorrow at a funeral (Phan et al., 2005).

Although use of cognitive reappraisal is linked to positive psychological, physiological, and behavioral outcomes in healthy individuals, individuals with GAD, SAD, and MDD all possess specific deficits in the ability to use cognitive reappraisal (Andreescu et al., 2015; D'Avanzato et al., 2013; Ehring, Tuschen-Caffier, Schnülle, Fischer, & Gross, 2010; Han et al.,

2014; Werner, Goldin, Ball, Heimberg, & Gross, 2011). As such, inability to use cognitive reappraisal is theorized to strengthen the use of maladaptive strategies such as rumination (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), worry (Millgram et al., 2015), or the use of suppression to mask negative affect (Ehring et al., 2010). While use of rumination as a maladaptive emotion regulation strategy is common in MDD, it is also common in ADs (Nolen-Hoeksema & Watkins, 2011), demonstrating that individuals with anxiety and depression are similar in the use of maladaptive strategies to regulate negative affect, perhaps arising due to common deficit in using cognitive reappraisal. Indeed, in a recent meta-analysis that surveyed over 100 studies involving over 2,000 individuals investigating the link between both adaptive (e.g., cognitive reappraisal) and maladaptive (e.g., rumination) strategies for emotion regulation and symptoms of both anxiety and depression, use of cognitive reappraisal was negatively related to both anxiety and depressive symptoms (Aldao et al., 2010). Further, this work shows that cognitive reappraisal may be specifically associated with decreased internalizing symptoms, as the relationship to severity eating disorder symptoms - an externalizing disorder - was not found (Aldao et al., 2010).

F. Neurobiology of Cognitive Reappraisal

In light of the strong link between use of cognitive reappraisal and psychological health, dozens of functional magnetic resonance imaging (fMRI) studies have been completed to-date investigating the underlying neurobiology that supports cognitive reappraisal in healthy individuals. To note, the vast majority of this work requests individuals to engage in the strategy of cognitive reappraisal to down-regulate negative emotions in response to highly aversive images taken from the validated International Affective Pictures Stimuli (IAPS) database (Lang,

Bradley, & Cuthbert BN, 2008). The first study to demonstrate neural processes supported during cognitive reappraisal was that completed by Ochsner and colleagues, who found that engaging in cognitive reappraisal relied on engagement of the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC) and dorsomedial prefrontal cortex (DMPFC) (Ochsner, Bunge, Gross, & Gabrieli, 2002). In factoring in regulation success through self-reported decline in negative affect, greater decreases in negative affect during cognitive reappraisal was associated with greater engagement of the dorsal anterior cingulate cortex (dACC) (Ochsner et al., 2002). Further, engagement of the VLPFC was inversely correlated with engagement of the amygdala (Ochsner et al., 2002).

In the years since this seminal study, several meta-analyses have been done to combine findings from 49 studies and close to 1,000 participants to confirm these results while shedding light on the involvement of additional brain regions (Buhle et al., 2014; P. Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011; Messina, Bianco, Sambin, & Viviani, 2015; Ochsner, Silvers, & Buhle, 2012). Findings from this work provide several observations regarding the neurobiology of cognitive reappraisal (**Figure 2**, adapted from (Buhle et al., 2014)). First, this research demonstrates that cognitive reappraisal relies on functioning in a broad network of regions including the DLPFC, VLPFC, DMPFC, dACC, ventromedial prefrontal cortex (VMPFC), middle and superior temporal gyri, and the inferior parietal lobe (IPL). Second, these regions are consistently activated across nearly 1,000 participants, showing a high-degree of reliability across studies. Third, engagement across many of these regions is associated with reductions in amygdala responding (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; M. Beauregard, Levesque, & Bourgouin, 2001; Ochsner et al., 2002; Phan et al., 2005; Schaefer et al., 2002; Urry, 2006). As the functioning of each of these cortical regions is diverse, their

involvement in cognitive and affective processes relevant to the task of cognitive reappraisal is detailed below.

1. Dorsolateral Prefrontal Cortex (DLPFC)

The DLPFC includes both middle and superior frontal gyri (Brodmann Area (BA) 9 and 46) is located on the lateral surface of the prefrontal cortex. The region forms numerous connections with other brain regions, predominantly with sensory cortices, including premotor areas, and the IPL (Hoshi, 2006). In contrast, the DLPFC does not form many direct connections with sub-cortical regions involved in emotional response, such as the amygdala, and so must receive this information through the involvement of intermediate brain regions, predominantly the VMPFC and anterior cingulate cortex (ACC) (Barbas, 2000; Ghashghaei, Hilgetag, & Barbas, 2007; Stefanacci & Amaral, 2002). The DLPFC is involved in executive functioning broadly-defined, and is implicated in working memory (Arnsten & Jin, 2014; Barbey, Koenigs, & Grafman, 2013; Edin et al., 2009), decision making (Lee & Seo, 2007), attentional control (Brosnan & Wiegand, 2017), and response selection (Yamagishi et al., 2016). Given these functions, DLPFC's role may be described as the active generation of strategies in order to execute goal-directed behavior (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002).

2. Ventrolateral Prefrontal Cortex (VLPFC)

The VLPFC is located on the inferior frontal gyrus (BA 47, 45, and 44). The right and left VLPFC are attributed to different functioning, with the right involved in motor inhibition (Aron, Robbins, & Poldrack, 2004), spatial attention and re-orienting attention to objects (Badre & Wagner, 2007; Corbetta et al., 2008; Corbetta & Shulman, 2002). The left VLPFC is implicated more in semantic processing (Marumo et al., 2014), categorization of objects (Corbetta et al., 2008; Corbetta & Shulman, 2002), and memory for semantic information

(Machizawa, Kalla, Walsh, & Otten, 2010; Novick, Kan, Trueswell, & Thompson-Schill, 2009; Snyder, Banich, & Munakata, 2011). During emotion processing, the VLPFC is involved in the generation of inner speech (Geva et al., 2011; Jones & Fernyhough, 2007; Morin & Hamper, 2012), which helps individuals categorize emotions (Kohn et al., 2014).

3. Dorsomedial Prefrontal Cortex (DMPFC)

The DMPFC (BA 9) is located on the medial wall of the prefrontal cortex, rostral of the premotor cortex. The ventral border of the DMPFC forms the ACC. Activation in the DMPFC occurs during exposure to negative content (Britton, Taylor, Sudheimer, & Liberzon, 2006; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Sabatinelli, Bradley, Lang, Costa, & Versace, 2007) and may be generally involved in the experience of affect based on evidence that it is involved in evaluation of one's own emotional experience (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Paradiso et al., 1999) as well as the emotional experiences of others (Isoda & Noritake, 2013). Evidence that the DMPFC is strongly connected with the fronto-parietal network that is implicated in attention underscores the DMPFC's role in attentional processes generally (Eickhoff, Laird, Fox, Bzdok, & Hensel, 2016). However, given that the DMPFC has strong connections with the amygdala, hippocampus, anterior midcingulate cortex, and bilateral insula, all regions important for the generation of emotion and internal monitoring of this state, the region likely plays a role in attention that is guided inwards (Eickhoff et al., 2016). Finally, other work demonstrates that participants display greater activation in medial prefrontal regions (e.g., DMPFC) during self-focused regulation relative to externally-focused regulation (Ochsner et al., 2004), suggesting again that the DMPFC plays an important role in emotional self-monitoring as it serves emotion regulation goals (Ochsner et al., 2004).

4. Ventromedial Prefrontal Cortex (VMPFC)

Located ventral and rostral to the DMPFC is the VMPFC (BA 10, 14, 25, 31), which forms the medial tissue situated ventral to the genu of the corpus callosum and may include the medial orbitofrontal cortex (OFC) by some accounts. The VMPFC has heavy reciprocal connections with the amygdala and other sub-cortical structures as well as with the lateral cortex; therefore, function of the VMPFC is viewed as a relay-station for "bottom-up" information from limbic and sub-cortical structures signaling emotion detection, and lateral PFC signaling response selection and control (Banks et al., 2007). Owing to dense projections with the amygdala, the VMPFC is involved in implicit, automatic emotion regulation that occurs without input from lateral cortical regions (Quirk & Gehlert, 2003; VanElzakker, Kathryn Dahlgren, Caroline Davis, Dubois, & Shin, 2014).

5. Dorsal Anterior Cingulate Cortex (dACC)

The ACC is composed of several different regions based on functional specialization. The most widely-recognized sub-division involves dichotomizing this region along a dorsal (dACC) and ventral (vACC) boundary (Bush, Luu, & Posner, 2000). The vACC (BA 12), which may subsume the subgenual ACC (sgACC) and rostral ACC (rACC), is involved in detection of emotion (Quirk & Gehlert, 2003; VanElzakker et al., 2014) based on its strong connections with the amygdala (Beckmann, Johansen-Berg, & Rushworth, 2009). The dACC (BA 32), in contrast, is involved in conflict control, response selection, and error detection (Bush et al., 2000; Etkin, Egner, & Kalisch, 2011) and forms little direct connection to the amygdala (Beckmann et al., 2009). In the context of cognitive reappraisal, the dACC is involved in monitoring and balancing the mismatch between bottom-up affective responses generated in limbic and sub-cortical regions with top-down reappraisals occurring in lateral portions of the cortex. However, the dACC is also involved cold-cognition and the experience of pain (Lieberman & Eisenberger,

2015), and is therefore involved generally in the monitoring of interoceptive and exteroceptive states (Mechias, Etkin, & Kalisch, 2010).

6. Temporal Gyrus

The temporal gyrus runs the length of the temporal lobe and is involved in high-level sensory and language recognition (Chao, Haxby, & Martin, 1999; Spitsyna, Warren, Scott, Turkheimer, & Wise, 2006). Although the contribution of the temporal gyrus to the act of cognitive reappraisal is not clearly defined, it is theorized to play a role in the reinterpretation process, by re-framing emotional content (Ochsner et al., 2012). In addition, involvement of the temporal gyrus likely contributes to reappraisal through semantic and perceptual associations among emotional material (Aggelopoulos & Rolls, 2005; Levy, Bayley, & Squire, 2004).

7. Inferior Parietal Lobe (IPL)

The IPL is located ventral to the intraparietal sulcus and caudal to the postcentral sulcus. The region is made up of two smaller regions: the supramarginal gyrus (BA 40) and angular gyrus (BA 39), together involved in the perception of faces (Sarkheil, Goebel, Schneider, & Mathiak, 2013). The IPL is located at the cross-section of both ventral and dorsal visual streams that project information from visual cortex embedded within the occipital lobe. In this way the IPL is involved in relaying information both regarding spatial information (‘where’ pathway located dorsally) and object identification (‘what’ pathway located ventrally) (Singh-Curry & Husain, 2009). Owing to its joint involvement in both streams, the IPL may uniquely be responsible for integrating both types of information (Singh-Curry & Husain, 2009). With regard to function of the IPL during cognitive reappraisal, it may provide semantic information to aid in the interpretation of emotional material (Messina et al., 2015).

8. Connectivity with Amygdala

Additional insight on the neurobiology of cognitive reappraisal comes from studies on functional connectivity that assess temporal correlations of neural activity across spatially distributed brain regions to provide information on the functioning of whole brain neurocircuitry. This work utilizes psychophysiological interaction (PPI) methods (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012) to test whether co-activation among discrete brain regions changes as a function of cognitive reappraisal. In this approach, a (i) 'psychological' variable representing the time of cognitive reappraisal, (ii) a 'physiological' variable representing timecourse of activation in a specified brain region (e.g., a 'seed' region), and (iii) the interaction of these two variables are modeled at the individual level. The interaction term therefore provides a measure of which brain regions are statistically correlated with the seed regions as a function of the task condition (e.g., cognitive reappraisal).

The majority of PPI studies during cognitive reappraisal utilizes the amygdala as a seed region to study brain areas that increase or decrease activation as a function of amygdala responding. This work shows that greater activation within the amygdala is positively related to the prefrontal cortex (PFC) during cognitive reappraisal – specifically within the DLPFC (Banks et al., 2007; Paschke et al., 2016), inferior frontal gyrus corresponding to the VLPFC (Morawetz, Bode, Baudewig, & Heekeren, 2016), OFC (Banks et al., 2007), ACC (Banks et al., 2007), DMPFC (Banks et al., 2007; Sripada et al., 2014), VMPFC (Delgado, Nearing, LeDoux, & Phelps, 2008), MPFC (Paschke et al., 2016), and IPL (Banks et al., 2007). In contrast, limited work has found an inverse correlation between amygdala activation and engagement of the inferior frontal gyrus (Winecoff, LaBar, Madden, Cabeza, & Huettel, 2011); however, positive correlation between the amygdala and cortical regions has been found to facilitate the dampening of an amygdala response (Silvers et al., 2016), is related to greater reduction in negative affect

(Banks et al., 2007; Morawetz et al., 2016), and is associated with greater self-control (Paschke et al., 2016). Therefore, positive connectivity between the amygdala and PFC during cognitive reappraisal is related to emotion regulation success.

G. Neurobiological Alterations during Cognitive Reappraisal in GAD, SAD, and MDD

Building from what is known about the underlying neurobiology of cognitive reappraisal in healthy individuals, the nature of aberrations in those with GAD, SAD, or MDD during reappraisal of negative affect hint at dysfunction particular to this domain. Research examining aberrations in these disorders utilizes a diagnosis-specific approach to study either patients with GAD, SAD, or MDD in comparison to a group of HCs. Therefore, results of this work reflect the study of discrete group differences in brain functioning. While some studies tested patients without any comorbid conditions (Mario Beauregard, Paquette, & Levesque, 2006; K. S. Blair et al., 2012; Erk et al., 2010; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007), other work utilized samples with comorbid internalizing conditions, specifically GAD, SAD, and MDD as co-existing diagnoses (Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013; Fitzgerald et al., 2017; Goldin, Manber, Hakimi, Canli, & Gross, 2009; Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009). Therefore, results of neural aberrations in individuals with GAD, SAD, and MDD may be the result of elevated anxiety or depressed symptoms.

During cognitive reappraisal in the context of making negative images appear less negative, compared to HCs, individuals diagnosed with GAD under-engage of the dACC (K. S. Blair et al., 2012) and DMPFC (Ball et al., 2013). We recently demonstrated that individuals with GAD display hyperactive amygdala and hyperactive VLPFC responses during the viewing of negative images and fail to alter these responses during cognitive reappraisal (Fitzgerald et al.,

2017). That is, deficits in cortical recruitment during cognitive reappraisal in those with GAD was confirmed in our sample, along with evidence that underlying reactivity to negative affect may be related to this disturbance (Fitzgerald et al., 2017).

In individuals with SAD, prior work shows under-engagement of the dACC (K. S. Blair et al., 2012; Goldin, Manber, et al., 2009), as well the DLPFC and superior temporal gyrus (STG) (Goldin, Manber, et al., 2009) when using cognitive reappraisal to decrease negative affect in comparison to HCs. In another study, individuals with SAD engaged cortical regions during cognitive reappraisal to an equivalent extent as HCs, but did so later in the task condition than HCs. That is, SAD showed later increased engagement of the dACC, DMPFC, MPFC, and VLPFC during cognitive reappraisal, while HCs engaged these regions earlier (Goldin, Manber-Ball, et al., 2009). In addition, individuals with SAD did not exhibit inverse connectivity between the amygdala and DLPFC, VLPFC and IPL, while inverse relationships between the amygdala and these regions were found in HCs (Goldin, Manber-Ball, et al., 2009).

Finally, individuals with MDD exhibit less activation in the DLPFC (Erk et al., 2010). With regard to connectivity with amygdala, positive connectivity between the amygdala and VLPFC was found in HCs during cognitive reappraisal of negative affect, but absent in those with MDD (Erk et al., 2010). In contrast, other studies have found that individuals with MDD exhibit greater engagement in dACC and temporal regions during cognitive reappraisal of negative affect (Mario Beauregard et al., 2006). Finally, other work shows that HCs engage the left VLPFC during reappraisal but individuals with MDD showed both left and right VLPFC, showing no sign of hypo-activation (Johnstone et al., 2007).

Together, this work provides a framework for understanding neural aberrations tied to cognitive reappraisal as an emotion regulation strategy for negative reactivity in GAD, SAD, and

MDD. Specifically, this work suggests that there may be differential effects of anxiety versus depression on brain functioning in the context of cognitive reappraisal, characterized by under-engagement of cortical regions involved in top-down regulation of negative affect in anxiety, but mixed findings, particularly in depression, detract from this conclusion.

H. The Role of Individual Differences during Cognitive Reappraisal

As the above work on group differences in brain functioning during cognitive reappraisal suggests, although anxiety and depressed individuals share emotion dysregulation particular to negative stimuli as a common symptom, dysfunction at the neural level may be more pronounced in anxiety rather than depression. However, mixed samples of individuals with anxiety and depression in at least half of this work make this difficult to conclude. Recent work in the neural mechanisms of cognitive reappraisal demonstrates variability in cortical and amygdala engagement in IDs based on a number of individual difference factors, meaning that individual differences in these factors are meaningful for the interpretation of neural aberrations.

First, individual differences in neural functioning in those with anxiety and depression are tied to individual differences in self-reported negative affect in this process (Goldin, Manber-Ball, et al., 2009). Specifically, under-engagement of the DLPFC is related to individual differences in greater feelings of self-reported negative affective during reappraisal in those with SAD (Goldin, Manber-Ball, et al., 2009). Second, greater use of habitual use of cognitive reappraisal has been found to relate to less amygdala reactivity during cognitive reappraisal in individuals with MDD (Philipp Kanske, Heissler, Schönfelder, & Wessa, 2012) and posttraumatic stress disorder (PTSD) (Fitzgerald et al., 2016). That is, variability in engaging in adaptive emotion regulation strategies, specifically reappraisal, in daily activities outside the

laboratory relates to individual differences in the ability to dampen amygdala reactivity in IDs. Use of reappraisal is correlated with anxiety and depression symptom severity (Aldao et al., 2010); therefore, variability in severity of these illnesses may also play a role in shaping deficits in neural engagement during reappraisal.

In support of this hypothesis, prior work demonstrates a relationship between severity of illness with neural functioning in the context of cognitive reappraisal in GAD, SAD, and MDD. Although, this work has been completed in relatively small sample sizes ($n < 25$) and again tested within each diagnostic group separately, without assessing whether anxiety or depression relates to neural functioning trans-diagnostically. Nevertheless, this work shows that greater severity of anxiety as measured using the Liebowitz Social Anxiety Scale (LSAS) is related to greater early response in the inferior frontal gyrus in individuals with SAD (Goldin, Manber-Ball, et al., 2009). In addition, greater anxiety symptoms again measured using LSAS is related to greater amygdala responding during the viewing of negative images as a baseline comparison for neural activity during cognitive reappraisal (Goldin, Manber, et al., 2009) while under-engagement of the DLPFC and DMPFC is related to greater anxiety severity in individuals with GAD and SAD as measured using the Overall Anxiety Severity and Impairment Scale (OASIS) (Ball et al., 2013). With regard to individuals with MDD, greater symptoms of depression as measured using the Hamilton Anxiety Rating Scale (HAM-D) is related to less down-regulation of the amygdala during reappraisal (Erk et al., 2010). However, much of the work investigating neural functioning during cognitive reappraisal, the relationship between variability in neural engagement and symptom severity has not been tested (K. S. Blair et al., 2012; Fitzgerald et al., 2017; Johnstone et al., 2007).

I. Summary

Together, this work demonstrates that individuals with GAD, SAD and MDD share common symptoms of emotion dysregulation and exaggerated amygdala responding during exposure to negative stimuli. When instructed to use the strategy of cognitive reappraisal for the down-regulation of negative reactivity, findings summarized across discrete studies (e.g., in separate samples) suggest under-engagement of prefrontal cortical regions in those with anxiety, although discrepant findings exist with regard to MDD and much of this work has utilized samples with comorbid conditions (e.g., individuals with MDD with comorbid anxiety). Therefore, neural dysfunction during cognitive reappraisal may be the result of increased anxiety, but not depression. Additionally, other work suggests the existence of individual differences in cortical recruitment during cognitive reappraisal that may be tied to severity of each illness. That is, although anxiety and depression are related illnesses, more work is needed to determine whether the individual differences in of anxiety and depression symptoms relate to aberrations in neurocircuitry during the execution of cognitive reappraisal.

II. STATEMENT OF AIMS AND HYPOTHESES

The purpose of this study was to evaluate how anxiety and depression symptom severity rated on continuous measures relates to neural functioning during cognitive reappraisal in adults diagnosed with GAD, SAD, and MDD. Neural functioning was examined as activation in discrete cortical regions and as functional connectivity with bilateral amygdala during active use of cognitive reappraisal in the context of negative images. In addition and in order to test the utility of a trans-diagnostic approach in comparison to a between-group comparisons among separate disorders, we tested whether there were group differences in neural functioning between HCs and patients (combined) and, within patients, between those with GAD, SAD, and MDD as primary diagnoses (e.g., Axis I) in each neural measure.

Aim 1. Determine if neural functioning during cognitive reappraisal – measured by focal engagement and connectivity with amygdala during reappraisal of negative images – differed between HC and patient groups (GAD, SAD, and MDD combined). We hypothesized that HCs would show greater recruitment in any of the combined regions during cognitive reappraisal: DLPFC, VLPFC, DMPFC, dACC, temporal gyrus, and IPL. In contrast, we hypothesized that patients would show greater responding in the amygdala, suggesting deficit in down-regulation of negative affect at the neural level.

Aim 2. Determine if neural functioning during cognitive reappraisal – measured by focal engagement and connectivity with amygdala during reappraisal of negative images – differed between groups (GAD, SAD, MDD) using one-way ANOVAs. We hypothesized that neural engagement and connectivity with the amygdala would not differ as a function of Axis I diagnosis in the patient group (e.g., no group differences would emerge).

Aim 3. Determine if neural functioning during cognitive reappraisal was correlated with symptoms of anxiety versus depression as measured by Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Anxiety Depression Scale (HAM-D) scores, the two most widely-used clinician-administered scales for the presence of anxiety and depression severity. We hypothesized that reduced engagement in the prefrontal cortex (PFC) and dorsal anterior cingulate cortex (dACC) will be related to greater severity of both anxiety and depression.

Aim 4. Determine if connectivity with amygdala during cognitive reappraisal was correlated with symptoms of anxiety versus depression, again as measured by HAM-A and HAM-D scores. We hypothesized that reduced connectivity between the amygdala and the prefrontal cortex (PFC) will be related to greater severity of both anxiety and depression.

III. METHODS

A. Participants

Participants were recruited from the Chicago community for participation in parent studies that involved 12-weeks of cognitive behavioral therapy (CBT) or selective serotonin reuptake inhibiter (SSRI) for the treatment of "anxiety, worry, and/or depressed mood" as chief complaints in order to study how these treatments affect brain function, physiology, behavior, and mental health. Participants were included if they were (1) between the ages of 18-60, (2) able to give informed consent, (3) free from alcohol or drugs on the day of testing as confirmed by a urinary drug screen, (4) and had severe enough mood disturbances to warrant treatment as assessed by a physician-level clinician. Exclusion criteria included (1) history of congenital brain defects, (2) history or presence of schizophrenia or associated mental illness, (3) active treatment of primary mood disturbance either in the form of psychotherapy or medication. For fMRI testing, additional exclusion criteria included (1) the presence of ferromagnetic objects within the body, (2) being pregnant or actively trying to become pregnant, (3) fear of enclosed spaces (e.g., claustrophobia), and (4) inability to lie still in an enclosed space for up to one hour.

Participants who were eligible for entry into the parent study were secondarily assessed for entry into this study based on presence of an Axis I anxiety or depressive disorder through the use of an in-person Structured Clinical Interview for Diagnostic Statistical Manual-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002) conducted at screening by a clinically trained masters or PhD-level researcher. Individuals in the present study were allowed to have comorbid internalizing conditions, but were deemed ineligible based on the presence of a comorbid schizophrenic diagnosis, resulting in $N = 174$ eligible for entry into this study based on Axis I diagnosis of GAD ($n = 47$), SAD ($n = 78$), or MDD ($n = 49$). In addition, we recruited an

additional *n* = 64 HCs who were free of any major medical or neurological illness or Axis I disorder as confirmed by the SCID-IV.

After screening, all participants completed a two-day testing visit that included clinical assessment, behavioral studies, electroencephalogram, and fMRI testing as required by the parent study. Subsequently, all participants were randomized to receive either CBT or selective serotonin inhibitors (SSRIs) for the treatment of their mood systems over 12-weeks. Results of clinical assessments collected weekly and post-treatment testing procedures at Week 12 that were identical to baseline procedures are not included in this present study. All study procedures were approved by the Institutional Review Board (IRB) at the University of Illinois at Chicago (UIC) and all participants were compensated monetarily for their time throughout the study duration.

B. Materials

1. Clinical Assessments

In addition to the SCID-IV, all participants completed the:

a. Hamilton Anxiety Rating Scale (HAM-A): The HAM-A is a clinician-administered rating scale that measures severity of anxiety symptoms across 14 independent items (Hamilton, 1959). It is well-validated in both clinical and research settings (Borkovec & Costello, 1993; Miaer, Buller, Philipp, & Heuser, 1988). Each item measures severity of anxiety symptoms spanning anxious mood, tension, fear, sleep disturbance, difficulty in concentrating, somatic disturbances, and behavior at the time of the interview. Each item is assessed on a five-point Likert scale. In total, the HAM-A takes approximately 10-15 minutes to complete and a

composite score is calculated from tallying across the 14 independent items. Higher values on the HAM-A indicate greater anxiety severity.

b. Hamilton Depression Rating Scale (HAM-D): The HAM-D is a clinician-administered scale that measures severity of depression across 17 independent items spanning mood, guilt, suicidality, sleep disturbances, psychomotor disturbances, changes in weight and somatic disturbances (Hamilton, 1960). The scale is well-validated in clinical and research settings (Cole et al., 2004). Each item is scored on a three or five point Likert scale, depending on the item, and a composite score is calculated, with higher values indicating greater depression severity.

2. <u>Functional Magnetic Resonance Imaging (fMRI)</u>

During fMRI scanning, participants completed a block-design Emotion Regulation Task (ERT) that utilized cognitive reappraisal as a regulation strategy (**Figure 3**). The ERT was developed from previously-validated tasks (Ochsner et al., 2002) and used in prior published studies from our laboratory (Fitzgerald et al., 2016, 2017; MacNamara et al., 2016; Phan et al., 2005; Rabinak et al., 2014). During ERT, participants were shown 64 negative and 32 neutral images from the International Affective Picture System (IAPS; Lang et al., 2008) across three conditions (Reappraise, Look-Negative, Look-Neutral). Participants were instructed to: 1) use a cognitive strategy to reduce negative affect to aversive images (‘Reappraise’ condition); 2) attend to the emotional state elicited by aversive images (‘Look-Negative’ condition); or 3) view neutral images (‘Look-Neutral’ condition). Prior to scanning, participants were instructed on the strategy of cognitive reappraisal (Ochsner et al., 2002; Phan et al., 2005) and all conditions were practiced with eight images not used in the fMRI experiment to confirm understanding of task instructions.

The task consisted of four 20 s blocks of each condition (four images presented for 5 s each without inter-stimulus interval). Blocks were interspersed by 20 s blocks of a white fixation cross, shown on a black background to enable the hemodynamic response to return to baseline. Block order was pseudo-randomized over the course of two separate runs, with each run lasting a total of five minutes. Prior to each block, an instruction screen ("Reappraise" or "Look") was presented for 5 s. To assess self-reported negative affect in the form of behavioral responses, following each block, participants viewed a screen that asked them to answer the question "How negative do you feel?". Participants indicated their response on a 5-item Likert scale (1 = not at all; 5 = extremely) via a 5-button response with their dominant hand.

C. Procedure

Participants for the parent study were recruited using standard recruiting methods (e.g., community flyers, posters, and by word-of-mouth). Research staff completed an initial phone screen to determine initial eligibility based on age and interest in the study, as well as severe enough mood disturbances as to warrant treatment. At in-person screening, participants completed the SCID-IV and gave a small urine sample for illicit drug and alcohol toxicology screen and a pregnancy test. Eligible participants then completed clinical assessments and electroencephalogram testing at the University of Illinois at Chicago (UIC) College of Medicine (COM) and functional magnetic resonance imaging at UIC COMs Center for Magnetic Resonance Research (CMRR) Center as required by the parent study.

Prior to fMRI testing participants were briefed at the CMRR and given detailed task instructions while practicing the ERT fMRI task on a laptop computer. Confirmation of reappraisal strategy was done verbally and confirmed by a research staff member. FMRI

scanning was performed on a 3T GE 3.0 Tesla GE MR 750 scanner (General Electric Healthcare; Milwaukee, WI) using a standard radiofrequency coil. Whole-brain functional images (i.e., BOLD) were collected using the following parameters: TR = 2s, TE = 25 ms, flip angle = 90°, field of view = 22 x 22 cm^2, acquisition matrix 64 x 64; 44 axial, 3-mm-thick slices with no gap. The first 4 volumes from each run were discarded to allow magnetization to reach equilibrium. The fMRI session lasted one hour and involved completion of the ERT task along with other tasks not part of the current study including: an emotional face assessment task, a contextual threat task, an emotional face interference task, resting state, and a high-resolution T1 structural scan.

IV. DATA ANALYSIS

A. fMRI Preprocessing

Conventional preprocessing steps were completed in Statistical Parametric Mapping (SPM8) software package (Wellcome Trust Centre for Neuroimaging, London www.fil.ion.ucl.ac.uk/spm). Images were temporally corrected to account for slice time acquisition differences and spatially realigned to the mean image. Motion realignment parameters were entered as regressors of no-interest to control for minimal head movement during scanning, however functional images from all participants included in analysis met criteria for high-quality with minimal motion correction (e.g., movements were < 3 mm and < 3 degrees rotation in any one direction). Images were subsequently normalized to a Montreal Neurological Institute (MNI) template using the echo-planar imaging template, resampled to 2 x 2 x 2 voxels and smoothed using an 8 mm isotropic Gaussian kernel.

A general linear model (GLM) was applied to the time series, convolved with the canonical hemodynamic response function and with a 128 s high-pass filter. Blocks of Reappraise, Look-Negative, and Look-Neutral were modeled separately in relation to implicit baseline (i.e., fixation cross), the effects of which were estimated for each voxel for each participant and taken to the second level for random effects analysis. Our primary objective was to measure neural functioning during cognitive reappraisal, controlling for variability in negative affect. Therefore, neural activity during Reappraise > Look-Negative was modeled as a primary contrast of-interest. However, all effects were also tested using Look-Negative > Look-Neutral contrast to assess for relationship between anxiety and depression severity during affect responding.

B. fMRI Analysis

1. Focal Analyses

For the completion of Aim I, we tested differences in whole brain neural functioning during Look-Negative > Look-Neutral and Reappraise > Look-Negative contrast between HCs and patients (GAD, SAD, and MDD combined) using a two-sample *t*-test, controlling for age, education, and gender as covariates. For the completion of Aim II, we used a one-way Analysis of Variance (ANOVA) to examine differences between GAD, SAD, and MDD patient groups in neural functioning during Reappraise > Look-Negative, again controlling for age, education, and gender as covariates. For the completion of Aim III, we conducted whole brain correlations between symptoms of (i) anxiety (HAM-A) and (ii) depression (HAM-D) with neural functioning during Reappraise > Look-Negative contrast, controlling for age, education and gender as covariates. Effects were first assessed independently and, in the case of significant effects, analyses were re-run controlling for the other factor (e.g., effect of HAM-A controlling for HAM-D). All analyses were repeated using the Look-Negative > Look-Neutral contrast in order to test specificity of results as it pertained to cognitive reappraisal.

2. PPI Analyses

Standard PPI analyses were completed using SPM8 (O'Reilly et al., 2012). First, condition onset times for Look-Neutral, Look-Negative, Reappraise, the preceding instruction screen, and the following affect rating period were separately convolved with the canonical hemodynamic response function for each condition to create psychological regressors. Next, deconvolved time series was extracted from a bilateral anatomical amygdala based on Anatomical Automatic Labeling (AAL)-defined mask using the SPM toolbox to create the physiological variable. Finally, interaction terms (e.g., PPIs) were computed by multiplying the

psychological and physiological variables. Effects representing connectivity values with bilateral amygdala were estimated for each voxel for each participant and taken to the second level for random effects analysis in a similar fashion to focal fMRI analyses listed above.

To test Aim IV, individual contrast images for Reappraise > Look-Negative were entered into separate second-level one sample *t*-tests to regress symptoms of (i) anxiety (HAM-A) and (ii) depression (HAM-D), controlling for age, education, and gender as covariates. A negative correlation of this interaction term with activity in other brain regions indicated that an activation increase in significant brain regions during cognitive reappraisal was inversely related with concurrent amygdala activity. In contrast, a positive correlation indicated that an activation increase in significant brain regions during cognitive reappraisal was associated with a concurrent increase in amygdala activity, or that a decrease in significant brain regions was associated with a concurrent decrease in amygdala activity. As before, all analyses were repeated using the Look-Negative > Look-Neutral contrast in order to test specificity of results as it pertained to cognitive reappraisal.

In all analyses (focal and connectivity), significant clusters of activation were identified using an uncorrected voxel threshold of $p<0.001$, and then subjected to correction for multiple comparisons across the entire brain within a gray matter mask excluding the cerebellum via simulation using the 3dClustSim utility (Dec. 16, 2015 updated release; 10,000 iterations; http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html; Eklund, Nichols, & Knutsson, 2016). Given smoothness estimates of the data, FWE correction at $\alpha<0.05$ was achieved using a voxel threshold of $p<0.001$ with minimum cluster sizes of 36 voxels (volume = 288 mm^3) for focal analyses, 49 voxels (volume = 392 mm^3) for connectivity analyses, and 36 voxels (volume 288 mm^3) for group comparisons. To clarify the direction of significant results

and complete secondary analyses, signal responses (β-weights in arbitrary units of activation/connectivity values) was averaged across voxels within a 5 mm radius sphere surrounding each peak maxima and extracted using the SPM MarsBar toolbox (Brett, Anton, Valabregue, & Poline, 2002).

C. Behavioral Data Analysis

Self-reported negative affect following each condition (Reappraise, Look-Negative, Look-Neutral) was averaged across blocks and runs within individuals. A repeated measures analysis of variance (ANOVA) was used to test differences in subjective negative affect as a function of condition (Look-Neutral, Look-Negative, Reappraise). Follow-up comparisons were done using paired sample *t*-tests were used to compare differences in self-reported negative affect between conditions of (i) Look-Negative and Look-Neutral and (ii) Reappraise and Look-Negative to measure changes in negative affect during the viewing of aversive images and after using the strategy of cognitive reappraisal, respectively. Planed comparisons were repeated within each group to study whether any particular group was driving effects.

V. RESULTS

A. Demographics

Participants ranged from 18-58 years of age (M=25.85, SD=7.37) and had 12-26 years of education (M=15.67, SD=2.85). Regarding gender distribution, 70.69% were female. Representation of different races included: 58% Caucasian, 21% African-American, 13% Asian, 2% American Indian or Alaskan Native, 1% more than one race, and 5% unknown. Sixteen percent of the sample identified as Hispanic.

B. Behavioral Data

Ratings of self-reported negative affect were available for n = 231/236 participants due to missing responses from five participants (1 HC, 1 GAD, 3 SAD, 1 MDD). Results from the repeated measures ANOVA indicated a significant effect of condition ($F(2, 704)=319.84$, $p<0.001$). In follow-up comparisons, paired sample t-tests indicated greater self-reported negative affect following Look-Negative compared to Look-Neutral and a reduction in negative affect following Reappraise compared to Look-Negative ($t(46) = 2.50$, $p<.02$). These effects were similar across groups, as within each group individuals indicated greater negative affect (HC: $t(62) = 11.70$, $p<0.001$; GAD: $t(46) = 13.49$, $p<0.001$; SAD: $t(75) = 21.83$, $p<0.001$; MDD: $t(48) = 11.34$, $p<0.001$) and reduction in negative affect following reappraisal (HC: $t(62) = 4.29$, $p<0.001$; GAD: $t(46) = 2.50$, $p<0.02$; SAD: $t(75) = 5.11$, $p<0.001$; MDD: $t(48) = 3.34$, $p<0.01$). **Figure 4** displays subjective negative affect by condition (Reappraise, Look-Negative, Look-Neutral) and group (HC, GAD, SAD, MDD).

C. Group Differences in Focal Neural Engagement and Connectivity with Amygdala

Inconsistent with our hypothesis, no differences emerged between HCs and patients (GAD, SAD, and MDD combined) in focal neural engagement during either Look-Negative > Look-Neutral (p>0.05 corrected) or Reappraise > Look-Negative (p>0.05 corrected)

However, consistent with our hypothesis, no differences emerged between patient groups during either Look-Negative > Look-Neutral (p>0.05 corrected) or Reappraise > Look-Negative (p>0.05 corrected)

D. Focal Neural Engagement: Correlation with HAM-A and HAM-D

Significant correlations between HAM-A and HAM-D and engagement of the PFC and ACC are listed below. These and additional brain regions that reached significance are presented in Table 1.

Within the Look-Negative > Look-Neutral contrast, no significant correlations with HAM-A or HAM-D were found (p's>0.05 corrected).

Within the Reappraise > Look-Negative contrast, results indicated a negative relationship between HAM-A and the left VLPFC (peak MNI: -48, 24, 24; Z = 3.93; volume = 4,736 mm^3 and peak MNI: -50, 30, -12; Z = 3.68; volume = 672 mm^3), left DLPFC (peak MNI: -26, 18, 64; Z = 3.85; volume = 848 mm^3), right DLPFC (peak MNI: 36, 8, 34; Z = 3.54; volume = 952 mm^3), DMPFC (peak MNI: -8, 12, 52; Z = 3.43; volume = 456 mm^3), and dACC (peak MNI: -8, 22, 32; Z = 3.33; volume = 456 mm^3). The negative correlation between left VLPFC and HAM-A remained when controlling for HAM-D (peak MNI: -52, 24, 22; Z = 3.40; volume = 368 mm^3). **Figure 5** displays location of significant clusters and scatterplots reflecting relationship between focal neural engagement and HAM-A.

In addition, we found evidence of a negative relationship between HAM-D and the left VLPFC (peak MNI: -38, -2, 34; Z = 3.62; volume = 608 mm^3) and right DLPFC (peak MNI: 26, 18, 56; Z = 3.50; volume = 576 mm^3). Effects did not remain when controlling for HAM-A (p>0.05 corrected). **Figure 6** displays location of significant clusters and scatterplots reflecting relationship between focal neural engagement and HAM-D.

In testing the relationship between self-reported negative affect and these regions, no significant relationships were found (p's>0.35).

E. Connectivity with Amygdala: Correlation with HAM-A and HAM-D

Significant correlations between HAM-A and HAM-D and connectivity of the PFC and ACC with bilateral amygdala listed below. These and additional brain regions that reached significance are presented in Table 2.

Within the Look-Negative > Look-Neutral contrast, no significant correlations with HAM-A or HAM-D were found (ps>0.05 corrected).

Within the Reappraise > Look-Negative contrast, results indicated a negative relationship between HAM-A and amygdala connectivity with a large cluster spanning right and left VLPFC (peak MNI: 30, 60, 2; Z = 5.72; volume = 31,096 mm^3). In addition, we found a negative relationship between HAM-D and amygdala connectivity with the right (peak MNI: 42, 44, -8; Z = 5.40; volume = 3,887 mm^3) and left VLPFC (peak MNI: -40, 42, 10; Z = 4.32; volume = 6,424 mm^3). The negative correlation between right VLPFC-amygdala connectivity (peak MNI: 28, 62, 6; Z = 4.48; volume = 2, 368 mm^3) and left VLPFC-amygdala connectivity (peak MNI: -22, 63, 6; Z = 3.87; volume = 1,672 mm^3) and HAM-A remained when controlling for HAM-D. In addition, the negative correlation between right VLPFC-amygdala connectivity and HAM-D

when controlling for HAM-A (peak MNI: 48, 36, -12; Z = 3.51; volume = 616 mm^3). **Figure 7** displays location of significant connectivity with amygdala and scatterplots reflecting relationship to HAM-A and HAM-D.

In testing the relationship between self-reported negative affect and these regions, no significant relationships were found (*p*'s>0.09).

VI. DISCUSSION

Findings from the current study provide evidence of similar deficits in (i) recruiting the DLPFC and VLPFC during cognitive reappraisal and (ii) reduced connectivity between the amygdala and left VLPFC during cognitive reappraisal related to severity of both anxiety and depression in individuals with GAD, SAD, and MDD. In addition, anxiety severity was related to less engagement of the DMPFC and dACC. When controlling for severity of depression, however, relationships between anxiety and under-engagement of the left VLPFC were sustained, while the relationships between focal neural measures and depression were abolished when controlling for the impact of anxiety. Together, this provides evidence that effects were strongest in regards to the relationship between anxiety severity and neural functioning during cognitive reappraisal of negative affect. Confirmation of heightened negative affect during the task, and reduction in negative reactivity during reappraisal, was confirmed by behavioral data.

The result that under-engagement of the VLPFC, DLPFC, DMPFC, and dACC during cognitive reappraisal related to anxiety severity replicates prior findings of under-engagement of the VLPFC in those with GAD (Ball et al., 2013; K. S. Blair et al., 2012; Fitzgerald et al., 2017) and SAD (Goldin, Manber, et al., 2009). The finding that under-engagement of the DLPFC during cognitive reappraisal relates to depression also replicates prior work in MDD (Erk et al., 2010). In addition, we found that less connectivity between the amygdala and VLPFC was related to greater depression symptoms, similar to prior work found less connectivity between the amygdala and VMPFC in MDD (Erk et al., 2010). However, we extend this prior work in two important ways. First, we demonstrate that these effects occur trans-diagnostically in individuals with GAD, SAD, and MDD. Second, we provide evidence that these deficits may be driven by anxiety symptoms primarily, owing to the fact that focal effects remained with regard

to anxiety – but not depressive – symptoms, when controlling for the contribution of the other symptom domain. That is, in a heterogeneous sample of patients with high comorbidity, focal neural deficits during cognitive reappraisal were primarily related to anxiety.

Atypical responding in the VLPFC emerged as a common deficit in the current study. Notably, lateralization effects were also found, as results were characterized by under-recruitment of the left VLPFC and less right VLPFC-amygdala connectivity tied to anxiety and depression. The left VLPFC is involved in semantic processing (Marumo et al., 2014), memory for semantic information (Nozari & Thompson-Schill, 2016), and categorization of objects (Corbetta et al., 2008; Corbetta & Shulman, 2002). During cognitive reappraisal, engagement of the left VLPFC may help in the generation of inner speech (Geva et al., 2011; Jones & Fernyhough, 2007; Morin & Hamper, 2012), which helps individuals categorize emotions for the reappraisal process (Kohn et al., 2014). That less connectivity between the VLPFC and amygdala was found in relation to both anxiety and depression severity hints at the possibility that greater severity of these illnesses is related to deficiency in the relationship between emotional responding, sub-served by amygdala, and language processesing for either the appraisal or re-appraisal process, sub-served by VLPFC.

That neural deficits during cognitive reappraisal were tied more to severity of anxiety, rather than depression, may indicate that individuals with depression without comorbid anxiety do not exhibit prominent difficulty in using cognitive reappraisal to down-regulate negative affect. That is, focal neural deficit in this process do not appear to be pronounced in individuals with depression and, if present, may be driven by severity of anxiety symptoms that may co-occur. This conclusion is supported by the fact that prior neuroimaging studies investigating neural abnormality in MDD patients report variability in engagement of the PFC during

reappraisal, reflecting either hypo- (Erk et al., 2010) or hyper-activation (Mario Beauregard et al., 2006; Johnstone et al., 2007) of this region. These findings combined with those of the present study suggest that depression is not characterized by *under*-engagement of the PFC and ACC regions during cognitive reappraisal of negative images.

In addition to a relationship between anxiety and depression and frontal cortical regions, we also found that greater anxiety and depression was related to less engagement in temporal, pre- and post-central gyri, midbrain, cerebellar, and basal ganglia structures. In regards to the temporal cortex, prior work suggests that it plays a role in cognitive reappraisal through semantic and perceptual associations among emotional material (Aggelopoulos & Rolls, 2005; Levy et al., 2004), both processes important for the reinterpretation of stimuli meaning (Ochsner & Gross, 2005; Ochsner et al., 2012). Additionally, although the involvement of primary motor and somatosensory cortices are not clearly understood as it relates to reappraisal, prior work has found greater engagement of these regions as individuals prepare for down-regulation, specifically with greater engagement of precentral gyrus related to less facial movement during this process (Vanderhasselt, Kühn, & De Raedt, 2013). Less is known about the involvement of the postcentral gyrus in reappraisal, although engagement of this region is reported during the perception of facial expressions, and also corresponds with sensory experiences during this process (Kragel & LaBar, 2016). Therefore, engaging motor and somatosensory regions may be important for both the emotional appraisal and anticipation of reappraisal, although more work is needed to directly test this hypothesis.

With regard to the involvement of the function of the midbrain, basal ganglia, and cerebellum, their involvement in reappraisal is not reported and so difficult to discern. Nevertheless, it has long been recognized that these regions play an important role in emotion

processing (Snider & Maiti, 1976). In particular, patients with damage to these regions possess affective disturbances (Schmahmann & Sherman, 1998). While generally these regions are known for their role in regulating motor responses and automatic systems important for central nervous system functioning, including sleep/wake cycles, arousal, and temperature, their functions extend as a regulator of emotional state as well (Lanciego, Luquin, & Obeso, 2012; Sacchetti, Scelfo, & Strata, 2009). Exactly what the contribution of these regions to the complex process of reappraisal is altogether unknown however, and more work needs to be done to explore their roles. Nevertheless, hypo-activation in these non-frontal regions that are diverse in their function suggests that symptoms of anxiety and depression are related not only deficits in cognitive control mechanisms, but other processes involved in the reinterpretation and appraisal process as well.

Notably, we did not find evidence of hyper-engagement of the amygdala between patients and controls, or in relationship to anxiety or depression symptom severity to neural functioning or connectivity to the amygdala during exposure to aversive scenes. The failure to find group differences in brain functioning during exposure to negative stimuli replicates prior work using a similarly-crafted large, trans-diagnostic sample of GAD, SAD, and MDD participants (MacNamara et al., 2017). In addition, although numerous prior studies report over-active amygdala in response to varied negative stimuli (e.g., scenes, faces, words), there are also number of studies that failed to find such effects in GAD and SAD (K. Blair et al., 2008; Burklund, Torre, Lieberman, Taylor, & Craske, 2017; Davies et al., 2017; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Mochcovitch, da Rocha Freire, Garcia, & Nardi, 2014; Nakao et al., 2011; Palm, Elliott, McKie, Deakin, & Anderson, 2011; Strawn et al., 2012; Whalen et al., 2008) or MDD (Almeida, Versace, Hassel, Kupfer, & Phillips, 2010; Mario Beauregard et al.,

2006; Davidson, Irwin, Anderle, & Kalin, 2003; Grimm et al., 2008; Irwin et al., 2004; Lawrence et al., 2004; Townsend et al., 2010). Therefore, findings of hyper-active amygdala response in anxiety and depression are varied, suggesting that this neural trait may not characterize all samples (Hägele et al., 2016).

The fact that we failed to find group differences in brain engagement during emotional responding and cognitive reappraisal underscores the need for individual differences approach in the study of emotion dysregulation in these populations. That is, when treated as a homogenous group, individuals with GAD, SAD, MDD, and HCs did not differ in neural engagement during emotional responding or regulation. Nevertheless, individual differences in anxiety and depression symptom severity related to neural deficiencies in expected regions across the patient sample (e.g., DLPFC, VLPFC, DMPFC, dACC). These findings are consistent with similar studies that have failed to find group differences in brain functioning but found that individual and trans-diagnostic measures of anxiety and depression related to differences in brain functioning in tasks of emotion processing (MacNamara, Klumpp, Kennedy, Langenecker, & Phan, 2017). Extending this work, we provide the first account of a similar relationship during a task of active explicit regulation in the form of cognitive reappraisal.

Results of the present study should be considered in light of several limitations. First, the current study did not include positive stimuli. Prior research suggests that the processing of positive stimuli, along with negative stimuli, may be disrupted be MDD (Grotegerd et al., 2014; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Matthews et al., 2008; van Tol et al., 2012). Therefore, neural deficits during cognitive reappraisal may be pronounced when using positive images in this population, perhaps as it relates to using reappraisal to up-regulate positive affect. Second, only individuals with GAD, SAD, and MDD were included. Thus,

results cannot be generalized to other anxiety disorders like panic disorder and specific phobia. Third, HAM-A and HAM-D may be more sensitive to measuring symptom severity in some groups, but not others. Specifically failure to find robust relationship between depression severity and neural functioning may be tied to qualities of the HAM-D as an instrument for measuring depression psychopathology (Watson et al., 2007).

Despite these limitations, the present study possesses many notable strengths. First, results leverage neuroimaging data from 174 patients. Prior work on the neural correlates of emotion regulation in those with GAD, SAD, and MDD report findings from $n < 25$ individuals in each discrete study, making the present study the largest to-date on the topic of neural functioning during cognitive reappraisal in anxiety and depression. Methodological differences across pre-existing studies in terms of recruitment methods, inclusion criteria, tasks used, stimuli selection, and in the reporting of results make it difficult to draw conclusions regarding the nature of shared neural deficit during cognitive reappraisal in that work. In contrast, findings from the present study that control for these effects in a single study design, and add greatly to our understanding of aberrations in cortical engagement during cognitive reappraisal tied to anxiety and depression. In addition, this is the first study to-date to combine findings from discrete focal brain regions and connectivity measures to further understanding regarding whole-brain neurocircuitry during reappraisal in anxious and depressed individuals.

VII. CONCLUSION

In conclusion, we found that anxiety symptom severity was related to under-engagement of the DLPFC, VLPFC, DMPFC, and dACC during cognitive reappraisal of negative affect, and depression symptom severity related to under-engagement of the DLPFC and VLPFC. In addition, both anxiety and depression severity were related to less connectivity between the amygdala and the VLPFC. In assessing independent effects of each symptom dimension, only anxiety severity uniquely accounted for focal reduction in VLPFC engagement. Results therefore suggest that while trans-diagnostic disturbances in neural engagement are related to measures of anxiety and depression severity, but neural deficits may be more closely tied to anxiety symptoms. Findings offer added insight into neurobiology underlying emotion dysregulation in anxiety and depression, and underscore that deficits in ability to explicit down-regulate negative affect may be tied to aberrations in cortical regions.

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Table 1.

Whole Brain Focal Engagement During Reappraise > Look-Negative

Condition	Brain region	Laterality	Volume (mm^3)	Z-score	peak MNI Coordinates x	y	z
Positive correlation with HAM-A							
	No significant clusters						
Negative correlation with HAM-A							
	Anterior lobe of the cerebellum	R	3,976	4.6	0	-48	-4
	Culmen	R	1,912	4.07	42	-48	-38
	Cuneus	R	3,936	3.97	24	-84	6
	VLPFC	**L**	**4,736**	**3.93**	**-48**	**24**	**24**
		L	**672**	**3.68**	**-50**	**30**	**-12**
	DLPFC	**L**	**848**	**3.85**	**-26**	**18**	**64**
	Precentral gyrus	L	1,320	3.82	-36	-4	30
	Midbrain	L	808	3.78	-10	-16	-18
	Postcentral gyrus	R	584	3.65	30	-28	36
		L	560	3.61	-32	-46	30
	Declive	R	1,184	3.61	30	-66	-30
	Supplemental motor area	L	1,144	3.58	-6	10	72
	Lingual gyrus	R	1,064	3.55	2	-82	-12
	DLPFC	**R**	**952**	**3.54**	**36**	**8**	**34**
	Cerebellar tonsil	L	1,088	3.51	-28	-36	-40
	DMPFC	**L**	**456**	**3.43**	**-8**	**12**	**52**
	Middle temporal gyrus	R	408	3.41	38	-62	4
	dACC	**L**	**456**	**3.33**	**-8**	**22**	**32**
	Lateral dorsal nucleus	L	336	3.25	-12	-18	16

	Caudate	L	296	3.22	-14	2	14
Positive Correlation with HAM-D							
	No significant clusters						
Negative Correlation with HAM-D							
	Declive	R	2,752	4.47	30	-66	-30
	Midbrain	L	37,168	4.16	-10	-18	-18
	Precuneus	L	560	4.07	-8	-54	76
	Supplemental motor area	L	424	3.95	-6	10	74
	Superior temporal gyrus	L	424	3.78	-50	12	-28
	Uncus	L	560	3.66	-22	0	-32
	VLPFC	**L**	**608**	**3.62**	**-38**	**-2**	**34**
	DLPFC	**R**	**576**	**3.50**	**26**	**18**	**56**
	Posterior lobe of the cerebellum	R	1,040	3.45	4	-84	-18
	Insula	L	696	3.30	-30	20	4
	Middle temporal gyrus	L	536	3.26	-10	-66	54

Note. Significant results at $p<0.001$ with minimum cluster sizes of 36 voxels (volume = 288 mm^3) correcting for multiple comparisons using 3dClustSim. **Bolded** regions indicate significant effects within the prefrontal cortex and anterior cingulate cortex.

Table 2

Whole Brain Connectivity with Amygdala During Reappraise > Look-Negative

Condition	Brain region	Laterality	Volume (mm^3)	Z-score	peak MNI Coordinates x	y	z
Positive correlation with HAM-A							
	No significant clusters						
Negative correlation with HAM-A							
	VLPFC	**R**	**31,096**	**5.72**	**30**	**60**	**2**
	Occipital lobe	R	512	4.04	26	-96	20
		L	1,888	4.02	-16	-86	12
		R	528	3.86	50	-82	-4
	Angular gyrus	R	1,376	3.6	46	-58	34
	Cuneus	R	265	3.43	10	-76	26
Positive Correlation with HAM-D							
	No significant clusters						
Negative correlation with HAM-D							
	VLPFC	**R**	**14,920**	**5.40**	**42**	**44**	**-8**
		L	**6,424**	**4.32**	**-40**	**42**	**-10**
	Pons	L	520	3.74	-2	-32	-36
	Caudate	R	440	3.43	14	26	-6
	Superior frontal gyrus	L	608	3.36	-16	54	26

Note. Significant results at $p<0.001$ with minimum cluster sizes of 49 voxels (volume = 392 mm^3) correcting for multiple comparisons using 3dClustSim. **Bolded** regions indicate significant effects within the prefrontal cortex and anterior cingulate cortex.

Figure Legends

Figure 1. "Process Model of Emotion Regulation". Figure adapted from Gross & Thompson, 2007

Figure 2. Significant brain regions engaged in cognitive reappraisal using identical, well-validated cognitive reappraisal task in healthy adults. Figure adapted from Fitzgerald et al, Under review. DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; IPL = inferior parietal lobe; DMPFC = dorsomedial prefrontal cortex; dACC = dorsal anterior cingulate cortex.

Figure 3. Task conditions during Emotion Regulation Task (ERT). Participants were shown neutral ('Look-Neutral') and negative images. During negative images, participants were instructed to experience negative affective naturally without instruction to change it ('Look-Negative') or use the strategy of cognitive reappraisal to down-regulate ('Reappraise'). At the end of each trial a Likert scale was shown for the collection of self-reported negative affect using a scale of 1=not at all to 5=extremely. s = seconds

Figure 4. Self-reported negative affect displayed by condition averaged (A) across groups, and (B) within each group. Error bars reflect ± SEM. ***p<0.001; **p<0.01; *p<0.05

Figure 5. (A) Significant negative correlation between anxiety (HAM-A) and left ventrolateral prefrontal cortex (VLPFC) during Reappraise > Look-Negative. (B) Significant negative correlation between anxiety (HAM-A) and dorsomedial prefrontal cortex (DMPFC) during Reappraise > Look-Negative. (C) Significant negative correlation between anxiety severity (HAM-A) and dorsal anterior cingulate cortex (dACC) during Reappraise > Look-Negative. HAM-A = Hamilton Anxiety Rating Scale.

Figure 6. Significant negative correlation between depression severity (HAM-D) and left ventrolateral prefrontal cortex (VLPFC) during Reappraise > Look-Negative. HAM-D = Hamilton Depression Rating Scale

Figure 7. (A) Negative correlation between anxiety severity (HAM-A) and right ventrolateral prefrontal cortex (VLPFC) connectivity with bilateral amygdala during Reappraise > Look Negative. Negative correlation indicates greater anxiety severity is related to less VLPFC-amygdala connectivity. (B) Negative correlation between depression severity (HAM-D) and right ventrolateral prefrontal cortex (VLPFC) connectivity with bilateral amygdala during Reappraise > Look Negative. Negative correlation indicates greater depression severity is related to less VLPFC-amygdala connectivity

Figure 1

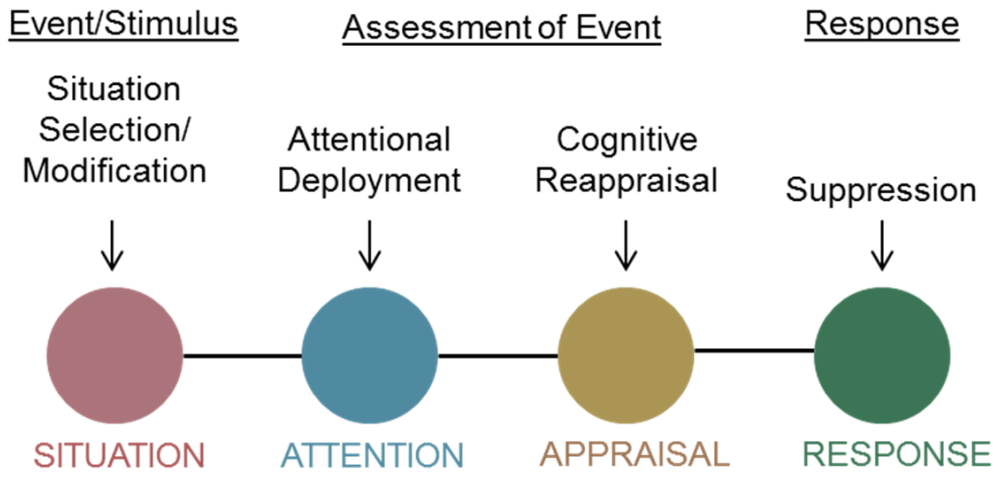

Event/Stimulus
Assessment of Event
Response
Situation Selection/ Modification
Attentional Deployment
Cognitive Reappraisal
Suppression
SITUATION
ATTENTION
APPRAISAL
RESPONSE

Figure 2.

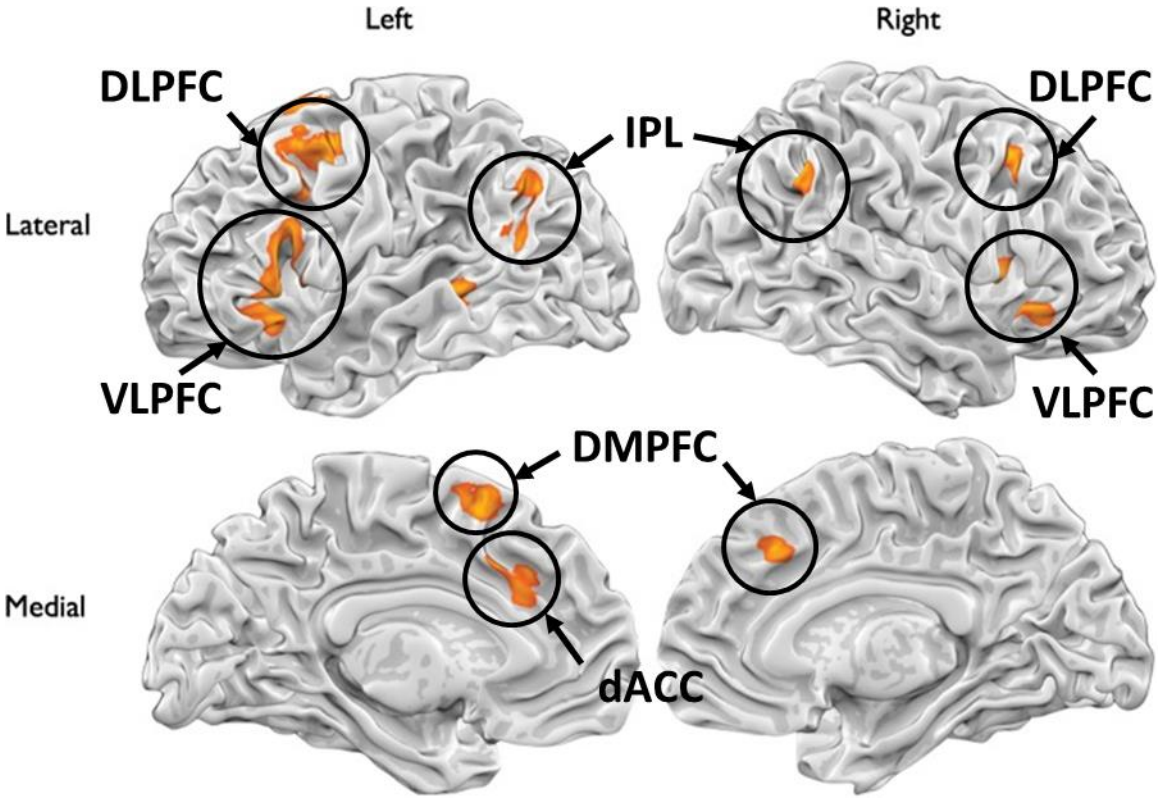

Left
Right
DLPFC
IPL
DLPFC
Lateral
VLPFC
VLPFC
DMPFC
Medial
dACC

Figure 3.

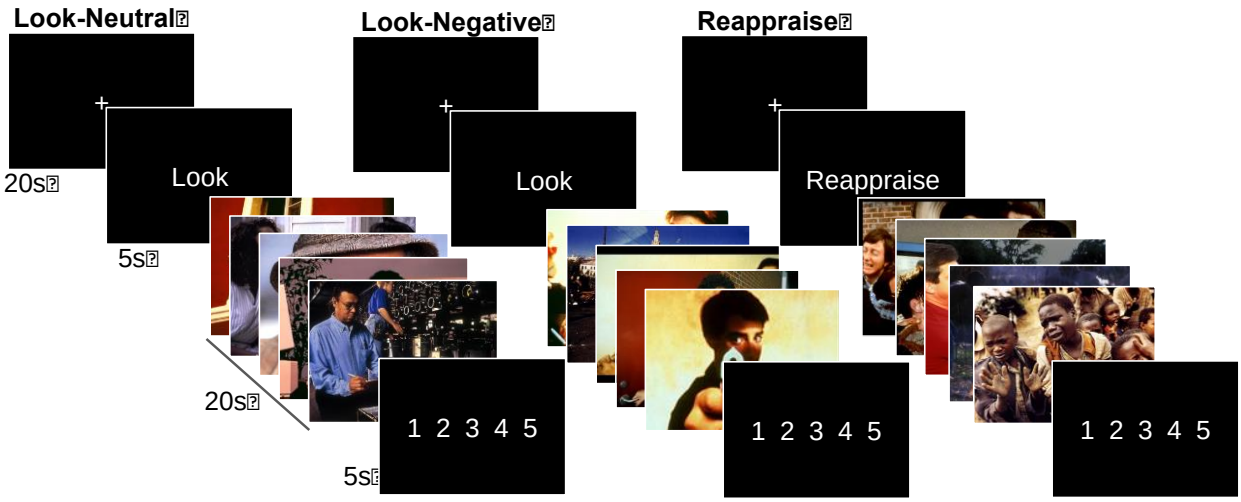

Look-Neutral
20s
Look
5s
20s
1 2 3 4 5
5s
Look-Negative
Look
1 2 3 4 5
Reappraise
Reappraise
1 2 3 4 5

Figure 4.

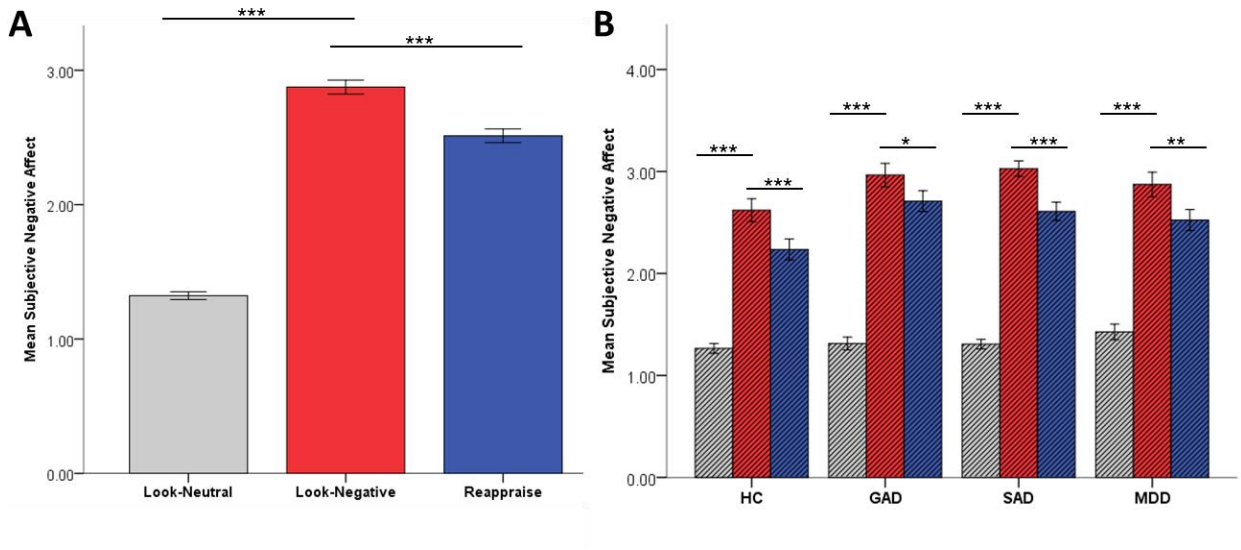

A
***
***
Mean Subjective Negative Affect
3.00
2.00
1.00
0.00
Look-Neutral
Look-Negative
Reappraise
B
Mean Subjective Negative Affect
4.00
3.00
2.00
1.00
0.00
***
***
***
*
***
***
**
HC
GAD
SAD
MDD

Figure 5.

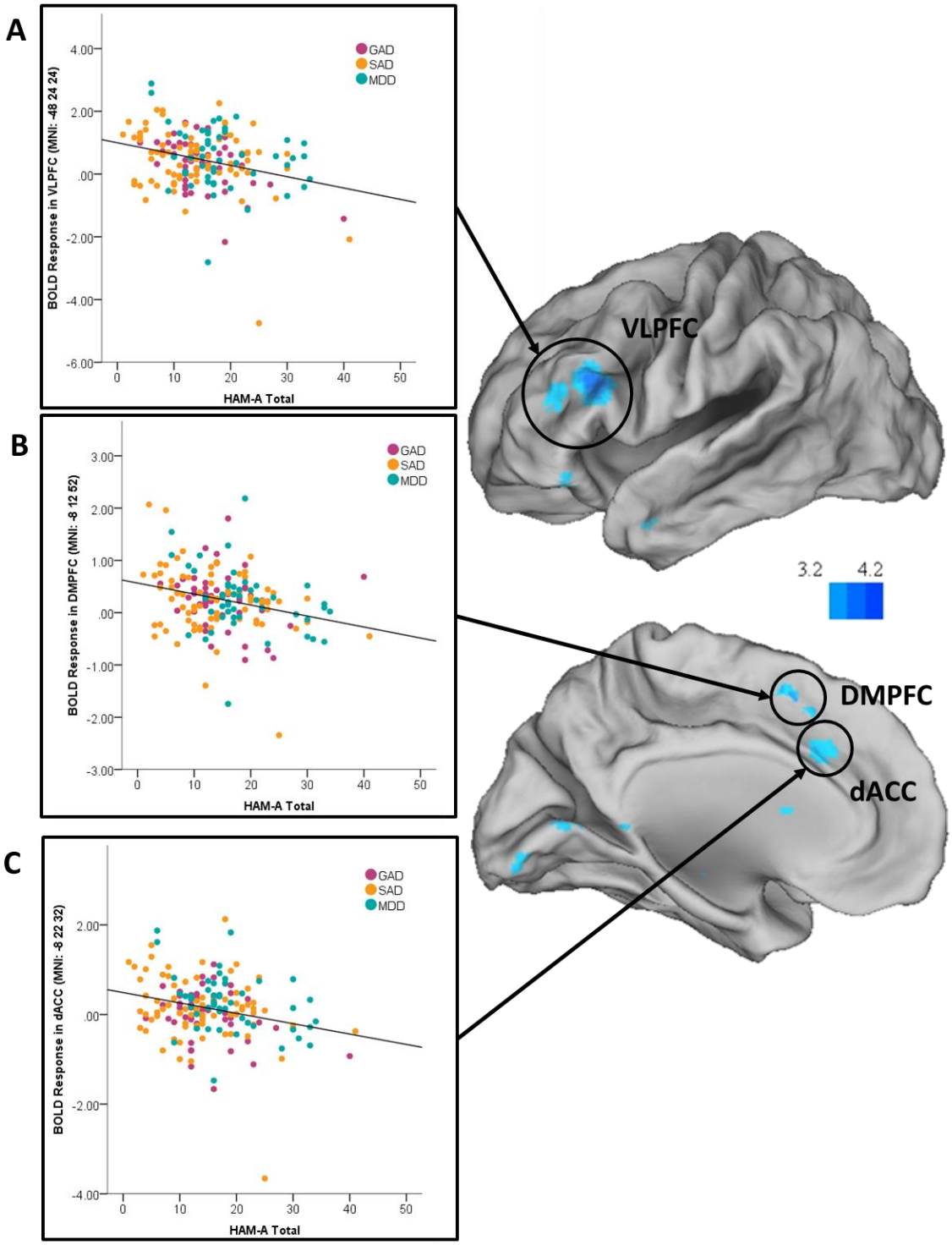

A
B
C
GAD
SAD
MDD
BOLD Response in VLPFC (MNI: -48 24 24)
BOLD Response in DMPFC (MNI: -8 12 62)
BOLD Response in dACC (MNI: -8 22 32)
HAM-A Total
VLPFC
DMPFC
dACC
3.2
4.2

Figure 6.

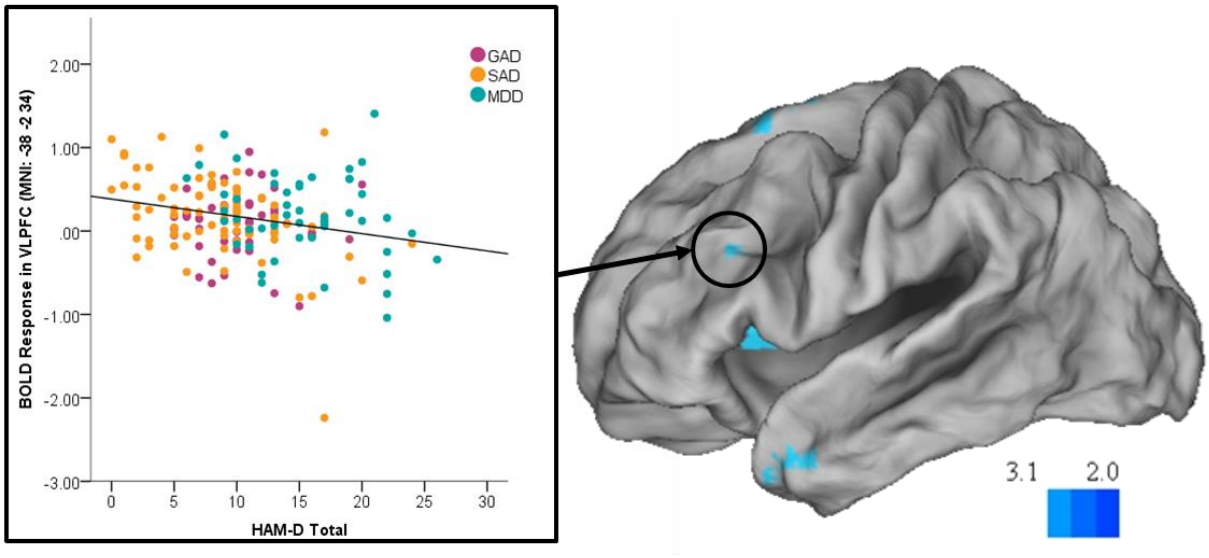
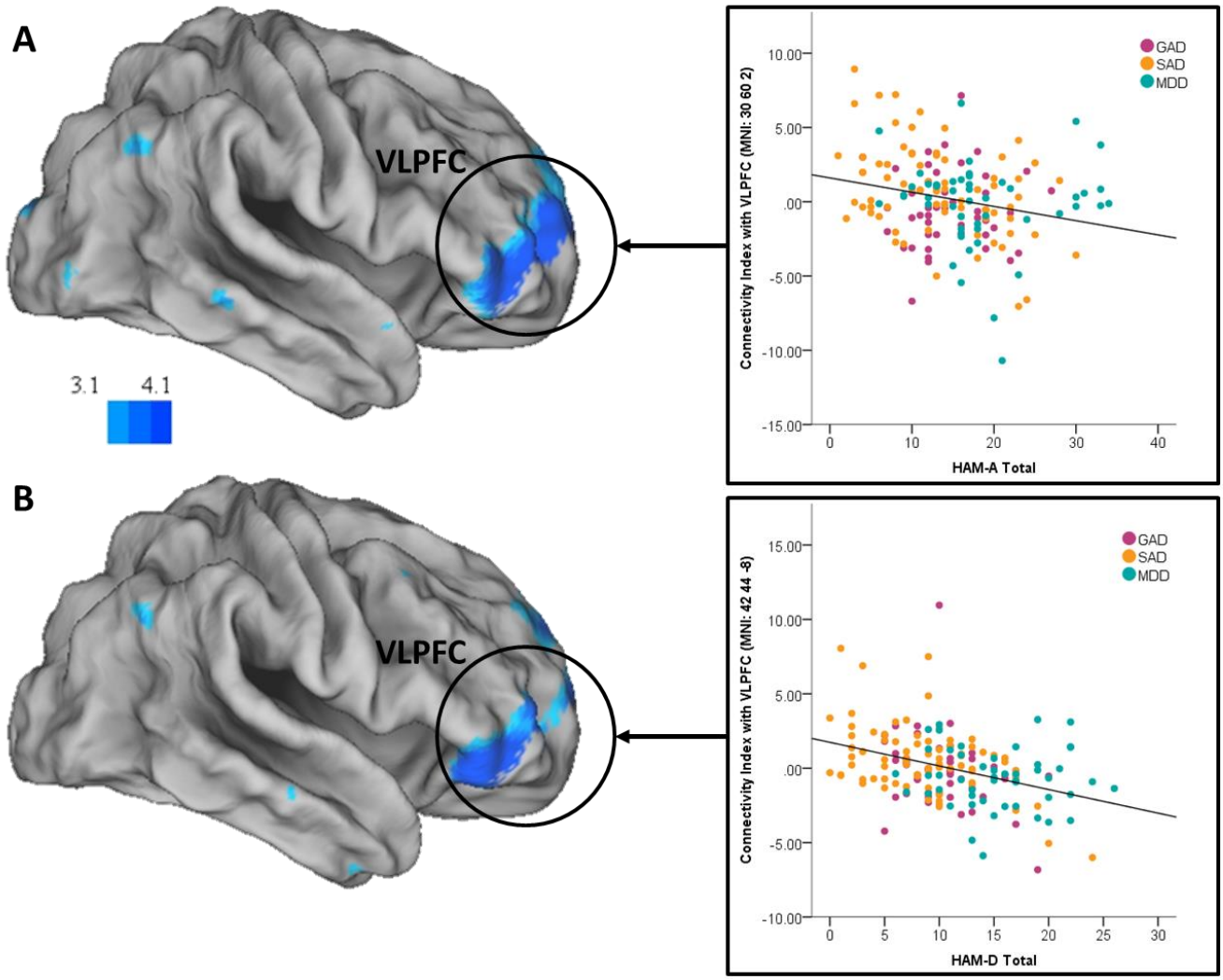

GAD
SAD
MDD
BOLD Response in VLPFC (MNI: -38 -2 34)
2.00
1.00
.00
-1.00
-2.00
-3.00
0
5
10
15
20
25
30
HAM-D Total
3.1
2.0

Figure 7.


A
VLPFC
3.1
4.1
Connectivity Index with VLPFC (MNI: 30 60 2)
HAM-A Total
GAD
SAD
MDD
B
VLPFC
Connectivity Index with VLPFC (MNI: 42 44 -8)
HAM-D Total
GAD
SAD
MDD

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Continuing Review

November 3, 2016

Kinh Luan Phan, MD
Psychiatry
1747 West Roosevelt
Room 244 IJR, M/C 747
Chicago, IL 60612
Phone: (312) 355-5954 / Fax: (312) 413-1703

RE: Protocol # 2013-0325
"Negative Valence Brain Targets and Predictors of Anxiety and Depression Treatment"

Dear Dr. Phan:

Your Continuing Review was reviewed and approved by the Convened review process on October 25, 2016. You may now continue your research.

Please note the following information about your approved research protocol:

Protocol Approval Period: October 25, 2016 - October 25, 2017
Approved Subject Enrollment #: 400
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: UIC, University of Notre Dame
Sponsor: National Institutes of Health
PAF#: 00015514
Grant/Contract No: Pending
Grant/Contract Title: Negative Valence Brain Targets and Predictors of Anxiety and Depression Treatment
Research Protocol(s):

a) Negative Valence Brain Targets and Predictors of Anxiety and Depression Treatment, PI: K. Luan Phan, MD, Protocol, Version 16; 09/02/2016

Recruitment Material(s):

a) Brochure, Version 1, 03/22/2013
b) PTSD Ad; Version 1; 04/27/2016
c) "Do you have PTSD?" (Flyer w/ tear offs) ; Version 1; 04/27/2016
d) Massmail PTSD ; Version 1; 04/27/2016
e) UIC PTSD News Ad; Version 1; 04/27/2016
f) Doctor Letter/Email, Version 7, 4.13.15
g) HC-ResearchMatch.org, Version 6, 4.13.15
h) Patient Phone Screen, Version 6, 4.13.15
i) HC Phone Screen Version 3, 4.13.15
j) UIC Control News Ad, V5, 9/3/15
k) UIC Patient News Ad, V5, 9/3/15
l) HC Ad "Are you a healthy adult...", Version 9, 9.3.15
m) Flyer "Are you a healthy adult...", with pull tabs, Version 9, 9.3.15
n) Ad "Do you have problems with mood or anxiety", Version 9, 9.3.15
o) Flyer "Do you have problems with mood or anxiety", with pull tabs, Version 9, 9.3.15
p) Control Email/Webpage advertisement, Version 6, 3/3/16
q) Patient Email/Webpage advertisement, Version 7, 3/3/16
r) Massmail HC, Version 4, 3.3.16
s) Massmail Patient, Version 4, 3.3.16
t) Massmail HC Matching, Version 3, 3.3.16
u) Hospital flyer "A Research Study About Mood and Anxiety", Version 8; 2.16.16
v) Hospital flyer "Healthy Adult Volunteers Wanted for a Research Study", Version 8, 2.16.16
w) Online Survey, Version 2, 1/28/16
x) RDoC Massmail Panic V1 9/14/16
y) RDoC Massmail SAD V1, 9/14/16
z) RDoC Panic Ad, V1, 9/14/16
aa) RDoC Panic Flyer, V1, 9/14/16
bb) RDoC SAD Ad, V1, 9/14/16
cc) Colleague Letter/Email, Version 7, 4.13.15
dd) RDoC NIH Database Telephone Script, Version 1, 5/6/15
ee) Intake Recruitment Script, Version 2, 2/26/14
ff) Patient-ResearchMatch.org, Version 5, 2.26.14
gg) RDoC SAD Flyer, V1, 9/14/16
hh) Recruitment Questionnaire, Version 2, 3/6/14

Informed Consent(s):

a) Combined consent/HIPAA authorization: Predictors Anxiety & Depression Control, Version 14, 09/02/2016
b) Combined consent/HIPAA authorization: Predictors Anxiety & Depression Treatment;

Version 13, 09/02/2016

c) Waiver of Signed Consent Document 45 CFR 46.117 granted for the phone screening
d) Alteration of informed consent granted under 45 CFR 46.116(d) for the phone screening
e) RDoC db Consent Addendum, Version 1, 4/13/15

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
10/14/2016	Continuing Review	Convened	10/25/2016	Approved

Please remember to:

→ Use your **research protocol number** (2013-0325) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-3788. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Rachel Olech, B.A., CIP
Assistant Director, IRB # 3
Office for the Protection of Research Subjects

Enclosure (sent electonically):

1. **Informed Consent Document(s):**
   a) Combined consent/HIPAA authorization: Predictors Anxiety & Depression Control, Version 14, 09/02/2016
   b) Combined consent/HIPAA authorization: Predictors Anxiety & Depression

Treatment; Version 13, 09/02/2016

c) RDoC db Consent Addendum, Version 1, 4/13/15

2. Recruiting Material(s):

a) Brochure, Version 1, 03/22/2013
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ff) Patient-ResearchMatch.org, Version 5, 2.26.14
gg) RDoC SAD Flyer, V1, 9/14/16
hh) Recruitment Questionnaire, Version 2, 3/6/14

cc: Anand Kumar, Psychiatry, M/C 912
OVCR Administration, M/C 672
IDS, Pharmacy Practice, M/C 883

Jacklynn M. Fitzgerald

CURRICULUM VITAE

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EDUCATION

2017	**PhD**, University of Illinois at Chicago (UIC) Psychology (Behavioral Neuroscience) Advisor: Luan Phan, MD
2014	**MA**, University of Illinois at Chicago (UIC) Psychology (Behavioral Neuroscience) Advisor: Luan Phan, MD
2006	**BA**, University of Wisconsin – Madison Sociology

FELLOWSHIPS

2015-16	National Institute of Mental Health (NIMH) T32 MH67631 Pre-doctoral Fellowship ($36,976) "Training in the Neuroscience of Mental Health" (competitive reappointment)
2014-15	National Institute of Mental Health (NIMH) T32 MH67631 Pre-doctoral Fellowship ($35,104) "Training in the Neuroscience of Mental Health"

AWARDS

2017	Society of Biological Psychiatry (SOBP) Pre-doctoral Scholars Travel Fellowship Award ($2,000)
2016	Honorable Mention: Best Poster (top 5 out of 120) UIC Dept. of Psychiatry Research Forum
2016	UIC Michael J. Piorkowski Award for Scholarly Achievement
2015	UIC Chancellor's Student Service and Leadership Award
2014	UIC Dept. of Psychology Travel Award for Conference Participation

PUBLICATIONS

1. **Fitzgerald, J.M.**, Kennedy, A.E., Shankman, S.A., Langenecker, S.A., Phan, K.L., Klumpp, H. (2017). Prefrontal and amygdala engagement during emotion regulation in generalized anxiety disorder. *Journal of Affective Disorders*, 218, 398-406.

2. Klumpp, H., **Fitzgerald, J.M.**, Kerry, K., Fitzgerald, D.A., Piejko, K., Roberts, J., Kennedy, A.E., Phan, K.L. (2017). Prefrontal control and predictors of cognitive behavioral therapy response in social and generalized anxiety disorders. *NeuroImage: Clinical*, 15, 25-34.

3. **Fitzgerald, J.M.**, MacNamara, A., Kennedy, A.E., Rabinak, C., Rauch, S.A.M., Liberzon, I., Phan, K.L. (2017). Individual differences in cognitive reappraisal and emotion regulatory brain function in combat-exposed veterans with and without PTSD. *Depression and Anxiety,* 34(1), 79-88.

4. **Fitzgerald, J.M.,** MacNamara, A., DiGangi, J.A., Kennedy, A.E., Rabinak, C.A., Patwell, R.S., Greenstein, J.E., Proescher, E., Rauch, S.A.M., Hajcak, G., Phan, K.L. (2016). A psychophysiological investigation of directed emotion regulation in combat-associated posttraumatic stress disorder. *Psychiatry Research: Neuroimaging,* 249, 113-121.

5. Follette, V., Garfin, D., **Fitzgerald, J.M.,** McLean, C. (2016). Translational Trauma Research: Implications for Policy and Intervention. *Translational Issues in Psychological Science: Special Issue on The Psychology of Trauma,* 2(4), 350-355. [invited editorial]

6. Gorka, S.M., MacNamara, A., Aase, D.M., Proescher, E., Greenstein J.E., Walters, R., Passi, H., Kennedy, A.E., DiGangi, J.A., Rabinak, C.A., Afshar, K. **Fitzgerald, J.M.**, Hajcak, G., Phan, K.L. (2016). Impact of alcohol use disorder comorbidity on defensive reactivity to errors in post-traumatic stress disorder. *Psychology of Addictive Behaviors*, 30(7), 733-742.

7. **Fitzgerald, J.M.,** & Pavuluri, M.N. (2015). *Pediatric Bipolar Disorder*. Chapter in the Handbook of Adolescent Behavioral Problems: Evidence-based Approaches to Prevention and Treatment, Second Edition. Edited by T. Gullotta, R.W. Plant, & M.A. Evans, Springer: New York, NY. [invited book chapter]

8. Yang, H., Lu, L., Wu, M., Stevens, M., Wegbreit, E., **Fitzgerald, J.,** Levitan, B., Shankman, S., Pavuluri, M. (2013). Time course of recovery showing initial prefrontal changes at 16 weeks extending to subcortical changes by 3 years in pediatric bipolar disorder. *Journal of Affective Disorders*, 150(2), 571-7.

9. Passarotti, A.M., **Fitzgerald, J.M.**, Sweeney, J.A., Pavuluri, M.N. (2013). Negative emotion interference during a synonym matching task in pediatric bipolar disorder with and without attention deficit hyperactivity disorder. *Journal of the International Neuropsychological Society*, 19(5), 601-12.

10. Lu, L.H., Zhou, X.J., **Fitzgerald, J.,** Keedy, S.K., Reilly, J.L., Passarotti, A.M., Sweeney, J.A., Pavuluri, M.N. (2012). Microstructural abnormalities of white matter differentiate the pediatric and adult-onset bipolar disorder. *Bipolar Disorders*, 14(6), 597-606.

11. Pavuluri, M.N., Passarotti, A.M., **Fitzgerald, J.M.,** Wegbreit, E.S., Sweeney, J.A. (2012). Risperidone and divalproex differentially engage the fronto-striato-temporal circuitry in pediatric mania: A pharmacological fMRI study. *Journal of American Academy of Child and Adolescent Psychiatry*, 51(2), 157-170.

12. Pavuluri, M., Passarotti, A., Ellis, J., **Fitzgerald, J.,** O'Neil, J., Wegbreit, E. (2012). Functional connectivity of motor control in attention deficit hyperactivity disorder (ADHD) and pediatric bipolar disorder (PBD). *European Psychiatry Published Abstracts*, 27(1). [Published Conference Abstract]

13. Wegbreit, E., Ellis, J., Nandam, A., **Fitzgerald, J.M.,** Passarotti, A.M., Pavuluri, M.N., Stevens, M. (2011). Amygdala functional connectivity predicts pharmacotherapy outcome in pediatric bipolar disorder. *Brain Connectivity*, 1(5), 411-422.

14. Mayanil, T., Wegbreit, E., **Fitzgerald, J.,** Pavuluri, M. (2011). Emerging biosignature of brain function and intervention in pediatric bipolar disorder. *Minerva Pediatrica*, 63(3),183-200.

15. Pavuluri, M.N., Passarotti, A.M., Parnes, S., **Fitzgerald, J.M.,** Sweeney, J.A. (2010). A pharmacological functional magnetic resonance imaging study probing the interface of cognitive and emotional brain systems in pediatric bipolar disorder. *Journal of Child and Adolescent Psychopharmacology*, 20(5), 395-406.

UNDER REVIEW

Fitzgerald, J.M., DiGangi, J., Phan, K.L. (Under review). Functional neuroanatomy of emotion and its regulation in PTSD. *Harvard Review of Psychiatry Special Issue: Recent Advances in Understanding and Treatment of Posttraumatic Stress and Trauma-Related Disorders*.

Fitzgerald, J.M., Kinney, K., Phan, K.L., Klumpp, H. (Under review). Distinct neural engagement during implicit and explicit regulation of negative stimuli. *Neuropsychologia Special Issue: The Neural Basis of Emotion*

POSTER PRESENTATIONS

1. **Fitzgerald, J.M.**, DiGangi, J., Kujawa, A., Aase, D., Greenstein, J.E., Proescher, E., Schroth, C., Afshar, K., Kennedy, A., Phan, K.L. Neural indices of cognitive emotion regulation and course of PTSD symptom severity in combat-exposed veterans. 72nd Society of Biological Psychiatry Annual meeting. May 19, 2017. San Diego, CA.

2. MacNamara, A., **Fitzgerald, J.M.**, Phan, K.L. Using anxiety and depressive subtypes to predict electrocortical processing of distracting pictures. 72nd Society of Biological Psychiatry Annual meeting. May 19, 2017. San Diego, CA

3. **Fitzgerald, J.M.,** MacNamara, A., Kennedy, A.E., Rabinak, C., Rauch, S., Liberzon, I., Phan, K.L. Individual tendencies to use cognitive reappraisal and emotion regulatory brain function in combat-exposed veterans with and without PTSD. 71st Society of Biological Psychiatry Annual meeting. May 13, 2016. Atlanta, GA.

4. **Fitzgerald, J.M.**, MacNamara, A., Kennedy, A.E., Proudfit, G.H., Phan, K.L. A Psychophysiological investigation on sustained emotional response in combat-associated posttraumatic stress disorder. Wisconsin Symposium on Emotion Research. April 22, 2015. Madison, WI.

5. **Fitzgerald, J.M.**, MacNamara, A., Rabinak, C.A., Kennedy, A.E., Hajcak-Proudfit, G. Phan, K.L. Relationship between pre-deployment and combat stress exposure and neural response of cognitive reappraisal in OEF/OIF veterans. 34th Annual Anxiety and Depression Conference. March 28, 2014. Chicago, IL.

6. Wu, M., Hamm, L., Fitzgerald, D., **Fitzgerald, J.,** Lu, L.H., Jacobs, R.H., Monk, C., Phan, K.L. Development of amygdala-prefrontal circuitry from childhood to young adulthood. 9th Annual Center for Clinical and Translational Science Conference. March 27, 2014. Lexington, KY.

7. Iordanescu, L., Stevens, M.C., **Fitzgerald, J.**, Pavuluri, M.N. Multivariate analysis reveals sex differences in distributed neural networks of attention, language and emotion regulation in typically developing youth and pediatric mania. 43rd Annual Meeting of the Society for Neuroscience. November 9, 2013. San Diego, CA.

8. Passarotti, A.M., Ellis, J., O'Neil, J., Nandam, A., **Fitzgerald, J.M.**, Pavuluri, M.N. Emerging bio-signatures of impulsivity differentiate attention-deficit hyperactivity disorder and pediatric bipolar disorder with and without ADHD. American Academy of Child & Adolescent Psychiatry 59th Annual Meeting. October 23, 2012. San Francisco, CA.

9. Wu, M., Lu, L., Passarotti, A., Wegbreit, E., **Fitzgerald, J.**, Shah, N., Pavuluri, M. Altered affective, executive and sensorimotor resting state networks in psychotropic naïve patients. 18th Annual Meeting of the Organization for Human Brain Mapping. June 10, 2012. Beijing, China.

10. Stevenson, J.M., Bishop, J.R., **Fitzgerald, J.M.**, Wong, M., Pavuluri, M.N. Analysis of the relationship between lithium concentrations, symptom response and cognitive performance in adolescents with bipolar disorder. College of Psychiatric and Neurologic Pharmacists Annual Meeting. April 29, 2012. Tampa, FL.

11. Yang, H., Lu, L., Wu, M., Wegbreit, E., **Fitzgerald, J.**, O'Neil, J., Lowes, A., Levitan, B., Pavuluri, M. Three year longitudinal study of pediatric bipolar disorder illustrates reduction in striatal overactivity and connectivity. Pediatric Bipolar Conference at Massachusetts General Hospital. March, 2012. Boston, MA.

12. Passarotti, A.M., Ellis, J., **Fitzgerald, J.**, O'Neil, J., Wegbreit, E., Stevens, M.C., Pavuluri, M.N. Functional connectivity of response control in ADHD and pediatric bipolar disorder with and without ADHD. American College of Neuropsychopharmacology Annual Meeting. December 5, 2011. HI.

13. Lu, L.H., Zhou, X.J., **Fitzgerald, J.**, Umfleet, L.G., Keedy, S.K., Reilly, J.L., Passarotti, A.M., Sweeney, J.A., Pavuluri, M.N. White matter microstructure change in bipolar disorder across age spans. 41st Annual Meeting of the Society for Neuroscience. November 15, 2011. Washington, D.C

14. **Fitzgerald, J.**, Samala, M., Wu, M., Lu, L., Passarotti, A., Wegbreit, E., Saini, N., Pavuluri, M.. Functional connectomics reveal three abnormal resting state networks in pediatric mania. University of Illinois at Chicago College of Medicine Research Forum. November 11, 2011. Chicago, IL

15. Wegbreit, E., Ellis, J., Nandam, A., **Fitzgerald, J.**, Passarotti, A.M., Pavuluri, M.N., Stevens, M.C. Amygdala functional connectivity predicts pharmacotherapy outcome in pediatric bipolar disorder. University of Illinois at Chicago Annual Research Forum. September 15, 2011. Chicago, IL

16. Yang, H., Wegbreit, E., **Fitzgerald, J.**, Levitan, B., Wu, M., Lu, L., Pavuluri, M. Three year longitudinal study of pediatric bipolar disorder illustrates reduction in limbic overactivity with development. University of Illinois at Chicago Annual Research Forum. September 15, 2011. Chicago, IL

17. Wegbreit, E., Ellis, J., **Fitzgerald, J.M.**, Passarotti, A.M., Stevens, M., Pavuluri, M.N. Mechanistic differences in risperidone and divalproex on cognitive circuitry function in pediatric mania: a longitudinal study. Pediatric Bipolar Conference at Massachusetts General Hospital. March 25, 2011. Boston, MA.

18. Pavuluri, M.N., Passarotti, A.M., **Fitzgerald, J.M.**, Sweeney, J.A. Differential impact of risperidone and divalproex in modulating negative and positive emotions during an affective working memory task in pediatric mania. American College of Neuropsychopharmacology 29th Annual meeting. December 7, 2010. Miami, FL.

19. **Fitzgerald, J.M.**, Passarotti, A.M., Pullagurla, K.R., Pavuluri, M.N. Risperidone vs. divalproex in pediatric mania using affective working memory task: preliminary fMRI outcomes. American Academy of Child & Adolescent Psychiatry 57th Annual Meeting. Saturday, October 30, 2010. New York, NY.

ORAL PRESENTATIONS

CONFERENCE SYMPOSIA

1. **Fitzgerald, J.M. (Chair)**, Cruza-Guet, M. C. (Discussant), Gobin, R.L. (Discussant). *Obtaining a Teaching or Research-Focused Postdoc: Tips, Tricks and How-To's.* APA Annual Convention. August 4, 2017. (accepted)

2. **Fitzgerald, J.M. (Chair)**, Krieger, M. (Discussant), Cloutier, R. (Discussant), *How to Peer Review for a Journal as a Graduate Student*. August 4, 2017. (accepted)

3. Revelle, W.R. (Chair), Williams, M.W., (Discussant), Cloutier, R. (Discussant), **Fitzgerald, J.M. (Discussant).** *Introduction to the R Statistical System*. APA Annual Convention. August 6, 2017. (accepted)

4. Lamar, M. (Co-Chair), Price, C.C. (Co-Chair), Williams, O. (Discussant), Beason-Held, L. (Discussant), Tanner, J.J. (Discussant), Yeo, J. (Volunteer), **Fitzgerald, J.M. (Volunteer).** *TED Talk Learning Lounge: An interactive Guide to Neuroimaging in Psychology.* APA Annual Convention. August 4, 2017. (accepted)

5. **Fitzgerald, J.M.** *Affective Neuroscience Methodology: Flash Talk.* Presented at the Association for Neuropsychological Student Training (ANST). November 21, 2016. Chicago, IL.

6. Lee, K. (Chair), **Fitzgerald, J.M. (Discussant)**, Krieger, M. (Discussant). *Reviewing for a Journal As a Graduate Student* APA Annual Convention. August 5, 2016. Denver, CO.

7. **Fitzgerald, J.M. (Co-Chair)**, Winkeljohn Black, S. (Co-Chair). *Stats Phobia: How to Learn Stats (and Work Past Beginners Anxiety)* at the APA Annual convention. August 5, 2016. Denver, CO.

8. MacNamara, A., Rabinak, C.A., **Fitzgerald, J.M.**, Kennedy, A.E., Fitzgerald, D.A., Liberzon, I., Stein, M.B., Phan, K.L. Neural correlates of emotion regulation in PTSD: SSRI treatment mechanisms and predictors of change. Flash talk presentation at Society for Affective Science (SAS), March 19, 2016. Chicago, IL.

9. **Fitzgerald, J.M. (Co-Chair)**, Lopez, A.A. (Co-Chair), Doran, J. (Discussant), Cruza-Guet, C. (Discussant), & Brown, D.L. (Discussant) *Publish or Perish! What Everyone Needs to Know about Publication and Peer-Review* at the APA Annual Convention. August 5, 2015. Toronto, ON, Canada.

DEPARTMENTAL PRESENTATIONS

1. *Under-engagement of VLPFC during Emotion Regulation is Associated with Common Anxiety Symptoms across Internalizing Disorders*. Laboratory of Integrative Neuroscience Spring Symposium, UIC. April 20, 2017.

2. *Common and Disorder-Specific Neural Engagement during Cognitive Reappraisal across Internalizing Psychopathology*. Dept. of Psychology Current Topics in Behavioral Neuroscience, UIC. April 19, 2017.

3. *Preliminary Findings: Common and Disorder-Specific Neural Engagement during Cognitive Reappraisal across Internalizing Psychopathology*. Dept. of Psychiatry Neuroscience Seminar Series, UIC. April 10, 2017.

4. *Evidence for a Unique Posttraumatic Stress Disorder Neural Circuit during Emotion Regulation*. Dept. of Psychology Cross Program Conference, UIC. March 31, 2017.

5. *Change in Late Positive Potential during Cognitive Reappraisal Predicts PTSD Symptoms over 1 year in Combat-Exposed Veterans.* Dept. of Psychology Current Topics in Clinical Psychology Seminar, UIC. November 17, 2016.

6. *Neural Measures of Capacity for Up-Regulation of Positive Affect in Adolescents at Risk for Depression.* Dept. of Psychiatry Junior Scholars Colloquium Seminar, UIC. October 28, 2016.

7. *Individual Differences in Cognitive Reappraisal and Emotion Regulatory Brain Function in Combat-Exposed Veterans with and without PTSD.* Dept. of Psychology Current Topics in Behavioral Neuroscience Seminar, UIC. March 9, 2016.

8. *Rethinking Emotion Dysregulation in Combat-Associated PTSD.* Neuroscience Society, Loyola University. February 3, 2016.

9. *The Ups and Downs of Explicit Emotion Regulation in Combat Veterans: a Psychophysiological Investigation.* Dept. of Psychology Current Topics in Behavioral Neuroscience Seminar, UIC. February 28, 2015.

10. *Relationship between Stress Exposure and Neural Response during Emotion Regulation in Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) Veterans.* Dept. of Psychology Current Topics in Behavioral Neuroscience Seminar, UIC. March 12, 2014.

11. *The Neurobiology of Suicide in Pediatric Mania*. Dept. of Psychology Current Topics in Behavioral Neuroscience Seminar, UIC. February 27, 2013.

12. *Neurocircuitry Model of PTSD.* Dept. of Psychology Current Topics in Behavioral Neuroscience Seminar, UIC. November 13, 2012.

13. *Brain Networks Modulating Affect Self-Regulation in Pediatric Mania.* Dept. of Psychiatry Institute for Juvenile Research Intellectual Exchange, UIC. July 19, 2012.

INVITED LECTURES

1. *Post-traumatic Stress Disorder & Traumatic Brain Injury*. Behavioral Neuroscience (undergraduate course), UIC. December 3, 2013.

2. *Introduction to Brain-Based Neuropsychology*. Advanced Developmental Psychology & Educational Processes (graduate seminar), UIC. May 24, 2011.

RESEARCH POSITIONS

2013-17	Graduate Research Assistant Mood and Anxiety Disorders Research Program (MADRP) UIC, Department of Psychiatry PI: Luan Phan, MD
2010-13	Lab Manager Brain Research and Intervention (BRAIN) Center UIC, Department of Psychiatry PI: Mani Pavuluri, MD PhD
2009-10	Data Analyst Brain Research and Intervention (BRAIN) Center UIC, Department of Psychiatry PI: Mani Pavuluri, MD PhD
2006	Research Assistant Wisconsin Study of Families and Work (WSFW) Life Stress and Human Development Laboratory University of Wisconsin – Madison, Department of Psychiatry PI: Marilyn Essex, PhD
2004-05	Research Interviewer University of Wisconsin Survey Center (UWSC) University of Wisconsin – Madison, Department of Sociology

NON-ACADEMIC RESEARCH POSITIONS

2008-09	Data Associate Phase I Clinical Trials United BioSource Corporation (formally Cognitive Drug Research (CDR)) Chicago, IL
2006-08	Research Assistant Behavioral Sciences Department American Institutes for Research (AIR) Washington, DC

TEACHING POSITIONS

2013-14	Teaching Assistant, UIC, Introduction to Biopsychology
2013	Discussion Instructor, UIC, Research Methods in Psychology
2012	Discussion Instructor, UIC, Introduction to Psychology

SERVICE

2016-present	Society for Affective Science Student Committee (SASSC)
2016-17	National Liaison, Graduate Women in Science (GWIS) Chicago Chapter
2016-18	Member-at-Large for Research/Academic Affairs, American Psychological Association of Graduate Students (APAGS)
2016	Publication Manual Task Force, American Psychological Association (APA)
2016	Chair, UIC Psychology Cross-Program Conference Committee
2015-16	Student Liaison to the Board of Scientific Affairs, American Psychological Association (APA)
2015-16	President, Graduate Women in Science (GWIS) Chicago Chapter
2015-16	Student Representative, UIC Dept. of Psychology Committee on Graduate Studies
2015-16	Psychology Student Representative, UIC Graduate Student Council (GSC)
2014-16	Science Committee, American Psychological Association of Graduate Students (APAGS)
2014-15	Vice President, Graduate Women in Science (GWIS) Chicago Chapter
2016-16	UIC Dept. of Psychology Diversity Advancement Committee - Student Advisory Board

Reviewer
- Graduate Women in Science (GWIS) National Fellowship, 2016
- Junior Scientist Fellowship (APAGS), 2015- 2017
- Psychological Science Research Grant (APAGS), 2015-2017
- Student Poster Abstract Submissions (APA Convention), 2015-2017

EDITORIAL SERVICE

2016	Associate Editor, *Translational Issues in Psychological Science: Special Issue on The Psychology of Trauma*, 2(4), 350-355.
2015	Advisory Editor, *UIC Interdisciplinary Undergraduate Research Journal*
2014-16	Advisory Editor, *Translational Issues in Psychological Science*

Ad-Hoc Reviewer
- *Biological Psychology*
- *Psychological Medicine*
- *New School Psychology Bulletin*

MEMBERSHIPS AND SOCIETIES

Society for Neuroscience (sfN)
Social and Affective Neuroscience Society (SANS)
Society for Affective Science (SAS)
American Psychological Association of Graduate Students (APAGS)
Graduate Women in Science (GWIS)