



Research paper

Prefrontal and amygdala engagement during emotional reactivity and regulation in generalized anxiety disorder



Jacklynn M. Fitzgerald^{a,b,*}, K. Luan Phan^{a,b,c,d}, Amy E. Kennedy^b, Stewart A. Shankman^{a,b}, Scott A. Langenecker^{a,b}, Heide Klumpp^{a,b}

^a University of Illinois at Chicago, Department of Psychology, Chicago, IL, USA

^b University of Illinois at Chicago, Department of Psychiatry, Chicago, IL, USA

^c University of Illinois at Chicago, Department of Anatomy and Cell Biology and the Graduate Program in Neuroscience, Chicago, IL, USA

^d Jesse Brown VA Medical Center, Chicago, IL, USA

ARTICLE INFO

Keywords:

Generalized anxiety disorder

Affect

Emotion regulation

Reappraisal

fMRI

ABSTRACT

Background: Emotion dysregulation is prominent in generalized anxiety disorder (GAD), characterized clinically by exaggerated reactivity to negative stimuli and difficulty in down-regulating this response. Although limited research implicates frontolimbic disturbances in GAD, whether neural aberrations occur during emotional reactivity, regulation, or both is not well understood.

Methods: During functional magnetic resonance imaging (fMRI), 30 individuals with GAD and 30 healthy controls (HC) completed a well-validated explicit emotion regulation task designed to measure emotional reactivity and regulation of reactivity. During the task, participants viewed negative images ('Look-Negative' condition) and, on some trials, used a cognitive strategy to reduce negative affective response ('Reappraise' condition).

Results: Results from an Analysis of Variance corrected for whole brain multiple comparisons showed a significant group x condition interaction in the left amygdala and left inferior frontal gyrus (IFG). Results from post-hoc analyses showed that the GAD group engaged these regions to a greater extent than HCs during Look-Negative but not Reappraise. Behaviorally, the GAD group reported feeling more negative than the HC group in each condition, although both groups reported reduced negative affect following regulation.

Limitations: As comorbidity was permitted, the presence of concurrent disorders, like other anxiety disorders and depression, detracts our ability to classify neural engagement particular to GAD alone.

Conclusions: Individuals with GAD exhibited over-engagement of amygdala and frontal regions during the viewing of negative images, compared to HCs. Together, these aberrations may indicate that deficits in emotional reactivity rather than regulation contribute to emotion dysregulation in those with GAD.

1. Introduction

Generalized anxiety disorder (GAD) is a prevalent, disabling and difficult disorder to treat (Gould et al., 2004; Hofmann and Smits, 2008; Mennin et al., 2005). While Cognitive Behavioral Therapy (CBT) is an empirically-supported psychotherapy for this disorder, symptoms persist in upwards of 50% of patients who complete treatment (Fisher, 2006; Hunot et al., 2007; James et al., 2013). Metacognitive therapy, which attempts to reduce 'reactivity' to salient cues and increase emotion regulation skills, fares better (Heiden, 2013), but still leaves upwards of 23% of those with GAD with residual symptoms (van der Heiden et al., 2012). In addition, although various pharmacotherapies have been used to treat the disorder, up to 50% of patients with GAD do

not experience a significant symptom decline following treatment (Buoli et al., 2013). Together these data demonstrate that a sizable portion of the GAD population remains symptomatic, despite undergoing currently available interventions.

One possible explanation for mixed efficacy in the treatment of GAD is that the neural underpinnings of symptoms central to the disorder remain largely unknown and, therefore, possibly untreated. Notably, while excessive and uncontrollable worry and an array of somatic symptoms (e.g., restlessness, muscle tension) characterize GAD (American Psychiatric Association, 2013), these complaints have been hypothesized to stem from emotion dysregulation as a common feature (Mennin et al., 2015, 2007, 2005). Even so, not much is known about the neurobiology associated with emotion dysregulation in GAD.

* Corresponding author at: University of Illinois at Chicago, Department of Psychiatry, 1747 West Roosevelt Street (M/C 747), Chicago, IL 60608 USA.
E-mail address: j Fitzgerald@psych.uic.edu (J.M. Fitzgerald).

Further, in defining what is meant by emotion dysregulation, this symptom consists of two separate, yet related, abnormalities: atypical emotional reactivity and regulation of reactivity (Lewis et al., 2010). Thus, emotional dysregulation observed in GAD may be the result of neural perturbations tied to exaggerated reactivity to salient stimuli and/or deficit or inefficient capacity to dampen emotional reactivity. As a result, while emotion dysregulation may be a central component of GAD, more information is needed to qualify the extent to which exaggerated reactivity and deficiency in down-regulation characterize emotion dysregulation as it presents in this disorder.

Evidence from clinical and behavioral studies help qualify the nature of emotional dysregulation as it appears in GAD. This work documents that GAD is associated with intense, inappropriate (i.e., out of context) affective reactivity (Mennin et al., 2007, 2005). Perhaps as a result, compared to healthy controls, those with GAD report feeling more negative when exposed to emotional stimuli (e.g., negative faces) (Kirschner et al., 2016; Mennin et al., 2005; Turk et al., 2005) and experience more physiological symptoms of anxiety during and following negative mood inductions (e.g., upset stomach, feeling restless) (MacDonald et al., 2015). Exaggerated negative reactivity may also be in part explained by increased attention towards emotional stimuli, as studies have demonstrated attentional bias to negative images (Roy et al., 2008; Weinberg and Hajcak, 2011) and emotional expressions in this population (Bui et al., 2017). In addition to exaggerated reactivity to negative stimuli, however, individuals with GAD also self-report difficulty in down-regulating negative affect when intending to do so (Amstadter, 2008; Cisler et al., 2010; Mennin et al., 2009, 2005; Salters-Pedneault et al., 2006; Turk et al., 2005), suggesting that deficits related to explicit regulation of negative affect are also present. It has also been shown that self-reported deficiency in emotion regulation uniquely predicts GAD symptoms when controlling for underlying symptoms of affect reactivity (Mennin et al., 2005), suggesting that regulation-related deficits may be a unique element of emotion dysregulation in GAD. Nevertheless, as theoretical work suggests that deficits in regulating emotions in GAD may stem from underlying exaggerated affective reactivity (Mennin et al., 2007), more work is needed to help clarify the prominence of each component of emotion dysregulation in GAD. Neuroimaging work that measures the extent to which neural functioning is compromised during reactivity to and regulation of negative content may help clarify and extend this work.

The neural mechanisms of reactivity to negative stimuli are well-characterized in healthy individuals. This work demonstrates a central role for the amygdala, a region known for its involvement in the detection, encoding and organization of response to salient stimuli (Anderson et al., 2003; Cunningham and Brosch, 2012; Phelps and LeDoux, 2005; Wilson-Mendenhall et al., 2013). The amygdala is activated during negative picture viewing (Hariri et al., 2002; Ochsner et al., 2009) and activation in the region correlates with self-reported negative affect (Ochsner et al., 2009) and peripheral indices of emotional arousal, like skin conductance (Hariri et al., 2002; Raine et al., 1991; Williams et al., 2004, 2001). Therefore, amygdala engagement is related to both objective and subjective markers of an emotional experience.

In line with observations that anxiety disorders are qualified by greater emotional reactivity (Barlow, 2004), there is substantial neuroimaging evidence that, compared to healthy controls, common, disabling affective disorders such as social anxiety disorder (SAD) (Carré et al., 2014; Fonzo et al., 2015; Stein et al., 2007) and panic disorder (PD) (Feldker et al., 2016; Fonzo et al., 2015; Rauch et al., 2003; van den Heuvel et al., 2005) are characterized by hyper-engagement of the amygdala during the viewing of negative images. However, despite exaggerated reactivity reported clinically in GAD, results are inconsistent with regard to whether this disorder is also characterized by exaggerated amygdala response. While some research has found hyper-engagement of the amygdala during viewing of negative images in GAD compared to healthy controls (HCs) (Fonzo

et al., 2015; McClure et al., 2007; Monk et al., 2008; Nitschke et al., 2009), there are also cases of hypo-engagement (Andrescu et al., 2011; Blair et al., 2008) or a failure to find group differences (Whalen et al., 2008). Despite the fact that excessive reactivity to negative stimuli is a prominent symptom of GAD, given such contrasting findings, more work is needed to better understand the neurobiology of emotional reactivity as it presents in this disorder.

In healthy individuals, mechanisms of explicit emotion regulation are frequently studied using the strategy of cognitive reappraisal, in which individuals modulate the emotional salience of a stimulus by changing its meaning (Gross, 2013; Ochsner et al., 2012). Cognitive reappraisal is considered an adaptive form of emotion regulation, based on research demonstrating its positive association with psychological health and well-being (Cutuli, 2014). As a result, the neural mechanisms that underlie cognitive reappraisal are well-known in individuals without psychopathology. Studies have consistently shown that cognitive reappraisal involves recruitment of several cortical regions, including the inferior frontal gyrus (IFG), dorsolateral PFC (DLPFC), dorsomedial PFC (DMPFC), ventrolateral PFC (VLPFC), anterior cingulate cortex (ACC), middle and superior temporal gyri, and parietal regions including the angular gyrus (Buhle et al., 2014; Kohn et al., 2014; Messina et al., 2015; Ochsner et al., 2012). The recruitment of specific frontal regions during reappraisal (e.g., DLPFC, VLPFC, ACC) is also associated with reduced amygdala responding, thought to reflect down-regulation of the negative emotional experience (Banks et al., 2007; Eippert et al., 2007; Frank et al., 2014; Ochsner et al., 2012). Though the inverse relationship between cortical engagement and amygdala activity is consistent with a “top-down” model of emotion regulation (Banks et al., 2007; Eippert et al., 2007; Frank et al., 2014; Ochsner et al., 2012), there are also reports of amygdala engagement during reappraisal in non-psychiatrically-ill samples (McRae et al., 2012; Nelson et al., 2015). Inconsistent findings may reflect sub-processes that underlie regulation, one of which involves establishing and elaborating on the emotional meaning(s) of a stimulus so that it can be subsequently re-interpreted (McRae et al., 2012). Therefore, “success” in emotion regulation at the neural level may not be best qualified by changes in amygdala responding (Morawetz et al., 2016) as regulation may be associated with amygdala response or attenuated activation.

Relative to other internalizing disorders such as SAD and PD (Ball et al., 2013; Blair et al., 2012; Goldin et al., 2008; Reinecke et al., 2015; Zilverstand et al., 2016; Ziv et al., 2013), less is known in GAD regarding neural activity during cognitive reappraisal. In fact, only two fMRI studies of explicit emotion regulation in GAD have been conducted and findings from this work must be considered in light of methodological complications that make it difficult to draw firm conclusions about the nature of aberrations in GAD. For instance, one study found that those with GAD exhibited less activation in frontal (e.g., DLPFC, DMPFC) and visual areas (e.g., middle occipital gyrus, fusiform gyrus) compared to HCs when using reappraisal to decrease negative reactivity to aversive images (Ball et al., 2013). However, in this study, the HC group did not show *differential* engagement of these regions between the viewing of negative images and when using reappraisal to down-regulate, making it difficult to conclude that under-engagement of these regions represented a deficiency related to reappraisal in GAD. In another study, HCs selectively engaged the dorsal ACC and inferior and superior parietal cortices to a greater extent than those with GAD when using reappraisal to down-regulate reactivity to negative images compared to negative reactivity as a baseline condition (Blair et al., 2012). However, the GAD group displayed elevated engagement in these regions across conditions of negative reactivity and reappraisal (Blair et al., 2012). As a result, aberrations in GAD may be explained by reduced capacity to effectively modulate limbic hypersensitivity to negative stimuli as an underlying disturbance, although this possibility was not fully explored by the authors (Blair et al., 2012). In both studies, while GAD participants reported

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