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HPA AXIS GENETIC VARIATION AND LIFE STRESS INFLUENCES ON FUNCTIONAL
CONNECTIVITY IN RESTING STATE NETWORKS

by

Tara A. Miskovich

A Dissertation Submitted in

Partial Fulfillment of the

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ABSTRACT

HPA AXIS GENETIC VARIATION AND LIFE STRESS INFLUENCES ON FUNCTIONAL CONNECTIVITY IN RESTING STATE NETWORKS

by

Tara A. Miskovich

The University of Wisconsin – Milwaukee, 2018
Under the Supervision of Professor Christine Larson

Stressful or traumatic experiences are a key risk factor for developing psychopathology, primarily through the impact that chronic stress has on hypothalamic-pituitary-adrenal (HPA) axis functioning. The HPA axis regulates the stress response but can become dysregulated with chronic activation and impact brain functioning. In addition to environmental stressors, genetic variation in genes in the HPA axis appear to influence HPA axis functioning and is also related to disruption in brain functioning, particularly in the context of high life stress. The current study focused on examining potential mechanisms through which trauma and stress interacts with HPA axis genes to impact key networks involved in emotional processing and regulation that are disrupted in stress-related psychopathology (i.e. depression and anxiety). I found that individuals with high cumulative genetic risk in the HPA axis showed weaker functional coupling between the amygdala and visual cortices as number of traumatic experiences increased. I found no evidence that genetic variance in HPA axis-related genes was associated with altered connectivity in the default mode network or salience network in the context of environmental stress. The current findings provide evidence that environmental factors interact with genetic variation in the HPA axis to influence fear-related circuitry in the brain of emerging adults, possibly elucidating mechanism through which these factors confer risk for stress-related psychopathology.

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Stressful events across the lifetime have been linked to several types of psychopathology including internalizing disorders (Dohrenwend, 2000; Green et al., 2010; Kendler, Karkowski, & Prescott, 1999; Kessler et al., 2010; McLaughlin et al., 2010; Monroe & Reid, 2009) and have been shown to be an important factor in gene-environment influences on the brain (Bogdan, Pagliaccio, Baranger, & Hariri, 2016; Corral-Frías, Michalski, Di Iorio, & Bogdan, 2016). This is thought to occur as a result of sustained activation and eventual dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Herman, 2013; Lupien, McEwen, Gunnar, & Heim, 2009). Understanding the mechanisms linking stress and psychopathology may help inform how individual differences confer risk for developing one of these burdensome disorders. The aim of the current study is to expand on previous work (see Bogdan et al., 2016) and link aberrations in brain connectivity in large-scale functional networks to polymorphisms in the HPA axis and interactions with stressful life experiences. First, I review some of the key neural networks disrupted in depression and anxiety: the emotion regulation circuit, default mode network (DMN), and salience network (SN). Next, I review the HPA axis and the relationship of HPA axis dysfunction and anxiety and depression as well as the impact of stress on the brain. Finally, I review the limited research available examining the impact of polymorphisms in the HPA axis on key networks that are dysfunctional in internalizing disorders.

Altered Brain Networks in Anxiety and Depression

Emotion regulation network. Internalizing disorders have been associated with disruption in several brain networks responsible for emotional processing and regulation. Extensive research has documented functional aberrations of the amygdala. Meta-analyses demonstrate that the amygdala is a key region associated with emotional experience (Sergegie, Chochol, & Armony, 2008) and is essential for detecting environmental salience, such as threat

(LeDoux, 2000). Aberrations in amygdala functioning are linked to disruptions in the fronto- limbic circuitry that regulates emotions (Davidson & Irwin, 1999) and are characteristic of internalizing disorders. For instance, Individuals with depression (Hamilton et al., 2012) and anxiety (Etkin & Wager, 2007) display greater activity in the amygdala, as well as other paralimbic regions implicated in emotion processing such as the anterior cingulate cortex (ACC; depression) and insula (depression and anxiety), in response to negative and threatening stimuli. This literature repeatedly implicates dysfunction in a limbic system-based circuit for emotion expression and regulation.

In addition to hyperactivation of the amygdala and other limbic regions, regions important for emotion regulation are also altered in these disorders. Successful regulation of emotional responses is associated with increased activation of the lateral and medial prefrontal cortex, IPFC and mPFC respectively (Delgado, Nearing, LeDoux, & Phelps, 2008; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner & Gross, 2005; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). This top-down regulation of emotions is coupled by reductions in amygdala reactivity and is thought to be mediated by activation in the mPFC (Delgado et al., 2008; Etkin, Egner, & Kalisch, 2011; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Urry et al., 2006), which has direct connections with both IPFC and amygdala regions (Kim & Whalen, 2009; E. K. Miller & Cohen, 2001) and is involved in fear extinction (Phelps, Delgado, Nearing, & LeDoux, 2004). Therefore, mPFC activation is thought to regulate amygdala activity and in turn, emotional responses and better emotion regulation is posited to stem from stronger functional coupling between these two regions (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Bishop, Duncan, Brett, & Lawrence, 2004; Quirk, Likhtik, Pelletier, & Pare, 2003). Internalizing disorders, which are characteristic of affect dysregulation, have demonstrated abnormalities in

mPFC function. For instance, reduced mPFC activation in the face of emotionally laden stimuli or symptom provocation has been noted in PTSD (Bremner et al., 1999; Shin et al., 2004; Shin, Rauch, & Pitman, 2006) and generalized anxiety disorder (Etkin, Prater, Hoefl, Menon, & Schatzberg, 2010). Additionally, mPFC hypoactivity has been noted at rest in depression (Drevets et al., 1997), and social anxiety (Evans et al., 2009). Moreover, internalizing conditions are associated with diminished connectivity between amygdala and mPFC at rest (Connolly et al., 2017; Hahn et al., 2011). This indicates that hyperactivation of the amygdala in these disorders is likely due to the attenuation of top-down regulation over affect.

In short, disruption in the function of limbic and prefrontal regions that are implicated in emotion and emotional regulation is one of the core neural characteristics of anxiety and depression, and understanding the factors that influence disruption of this network will provide us with a greater understanding of the etiology of these disorders.

Default mode network. The DMN is a neural network that primarily is active during wakeful rest. It is comprised of the ACC, the posterior cingulate cortex (PCC), and hippocampus (Raichle et al., 2001). These regions are both structurally and functionally connected (Fox et al., 2005; Greicius, Supekar, Menon, & Dougherty, 2009; Horn, Ostwald, Reiser, & Blankenburg, 2014) and are thought to support internally-focused processing, such as self-referential thought, autobiographical memory, and mind wandering (Buckner, Andrews-Hanna, & Schacter, 2008; Mason et al., 2007). This network is also known as the task-negative network, as the network deactivates when participants are engaged in active goal-focused tasks (Fox et al., 2005). Failure to deactivate the DMN in cognitive tasks is associated with worse performance (Anticevic, Repovs, Shulman, & Barch, 2010; Daselaar, Prince, & Cabeza, 2004; Li, Yan, Bergquist, & Sinha, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006) suggesting excessive engagement

of DMN may be related to cognitive problems, such as difficulties with attentional control, which are common to internalizing disorders (Austin, Mitchell, & Goodwin, 2001; Eysenck, Derakshan, Santos, & Calvo, 2007). Variation in the function of this network has been linked to a number of neuropsychiatric diseases, such as Alzheimer's, schizophrenia, depression, anxiety and autism (see Broyd et al., 2009). In depression and anxiety, DMN dysfunction is thought to underlie excessive self-referential processing such as worry and rumination (Berman et al., 2011; Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010; Hamilton et al., 2011; Paulesu et al., 2010; Servaas, Riese, Ormel, & Aleman, 2014). Therefore, understanding patterns of DMN dysfunction in internalizing disorders may provide insight into the neural correlates of key symptomology.

In depressed individuals compared to controls, the DMN is hyperactive during self-focused tasks like rumination (Cooney et al., 2010), when asked to engage in externally-focused thought (Belleau, Taubitz, & Larson, 2015), and when directed to reappraise and passively view negative stimuli (Sheline et al., 2009), indicating difficulty disengaging from self-referential processing. Hamilton and colleagues (2011) demonstrated that relative dominance of DMN activation at rest in depressed individuals was associated with maladaptive rumination. Additionally, individuals with depression demonstrate greater functional connectivity between regions of the DMN at rest (Berman et al., 2011; Greicius et al., 2007). Berman and colleagues (2011) linked this greater functional connectivity to trait rumination, suggesting this increased connectivity may reflect the increased self-focused attention characteristic of depression.

The DMN is also disrupted in anxiety disorders (Sylvester et al., 2012). One study looked at DMN deactivation in patients with a Chinese Classification of Mental Disorders (CCMD)-III (Y. F. Chen, 2002), which has similar classifications to the Diagnostic and Statistical Manual of

Mental Disorders (American Psychiatric Association, 2013), diagnosis of any anxiety disorder showed reduced deactivation in the mPFC activity and increased deactivation PCC/precuneus activity when passively listening to alternating threat and emotionally neutral words (Zhao et al., 2007). However, this study did not find differences between controls and anxiety patients when alternating between neutral words and rest, which does not imply a general alteration of this network at rest (Broyd et al., 2009; Zhao et al., 2007). Another study found that individuals with social anxiety displayed increased activation of the DMN during a face perception task (Gentili et al., 2009). Individuals with PTSD demonstrate increased DMN activation during tasks (Daniels et al., 2010). In addition to altered responses to emotional stimuli, there is evidence linking the experience of worry to activation of regions in the DMN (Servaas et al., 2014), a finding that persisted following a rest in individuals with generalized anxiety disorder (Paulesu et al., 2010). There is also evidence to suggest alterations in this network in anxiety at rest (Peterson, Thome, Frewen, & Lanius, 2014) as well, for research has demonstrated altered DMN connectivity associated with social anxiety disorder (Liao, Chen et al., 2010), obsessive-compulsive disorder (Jang et al., 2010; Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012), and PTSD (Bluhm et al., 2009; Lanius et al., 2010; L. Qin et al., 2012; Sripada et al., 2012). Additionally, depressed elderly individuals had increased functional connectivity in posterior regions of the DMN and weaker connectivity in the anterior regions, only in the presence of comorbid anxiety (Andreescu et al., 2011), suggesting a potential interaction of symptomologies on DMN dysfunction. Therefore, although the pattern of DMN disruption differs across disorders, it seems to be a common neural correlate of anxiety (Peterson et al., 2014).

Overall, research has implicated disruption in the DMN as an important neurophenotype of anxiety and depression. Underlying network abnormalities in these disorders may instantiate

symptoms of excessive self-focus characteristic of depression and anxiety, as well as cognitive symptoms, such as difficulty in engaging attentional control (Austin et al., 2001; Eysenck et al., 2007).

Salience network. The SN includes cortical regions implicated in cognitive control, such as the dorsal anterior cingulate (dACC) and anterior insula, as well as subcortical regions involved in emotional processing, most notably, the amygdala (Menon & Uddin, 2010; Seeley et al., 2007). This network is thought to be involved in detecting salient events that may require increased cognitive resources, events such as the detection of errors or conflict (Botvinick, Cohen, & Carter, 2004; Carter et al., 1998; Menon & Uddin, 2010; Seeley et al., 2007). Therefore, the SN is thought to play an important role in switching between larger scale brain networks. For instance, at rest one may need to disengage attention from internal focus (DMN) to an important task in their environment (e.g. getting called on while daydreaming in class), thus engaging the central executive network (CEN) (Seeley et al., 2007). The SN is the intermediate between this transition (Sridharan, Levitin, & Menon, 2008), and therefore disruption of attentional switching may be related to attentional control problems and excessive self-focus (rumination & worry) in depression (Belleau et al., 2015; Hamilton et al., 2011) and anxiety (Eysenck et al., 2007).

Regions involved in the SN demonstrate abnormal functioning in internalizing disorders. In addition to hyperactivity of the amygdala, anxiety and depression have been linked to increased insula activation (Etkin & Wager, 2007; Etkin, 2009; Gentili et al., 2008; Hamilton et al., 2012; Mitterschiffthaler et al., 2003; Stein, Simmons, Feinstein, & Paulus, 2007). Furthermore, increased connectivity between the amygdala and insula has been associated with

state anxiety (Baur, Hänggi, Langer, & Jäncke, 2013), indicating alterations in the SN in anxiety disorders and depression may be linked to maladaptive states of anxiety.

Several studies have linked anxiety disorders and depression to SN connectivity dysfunction. For instance, individuals with major depressive disorder have demonstrated decreased intrinsic functional connectivity in the right frontal insula within the SN (Manoliu et al., 2013). This pattern was also found in elderly depressed individuals, but only if they had high levels of apathy (Yuen et al., 2014), possibly linking this pattern of SN dysfunction to symptoms of anhedonia. Furthermore, Hamilton and colleagues (2011) demonstrated that activation in the right frontal insula was increased when switching to the CEN in depressed individuals, whereas controls demonstrated SN increases when switching to the DMN, indicating abnormalities in attentional switching.

Findings of functional connectivity are more mixed across anxiety disorders (Peterson et al., 2014). For instance, PTSD patients exhibited increased functional connectivity between the left insula and limbic regions (Sripada, Wang, Sripada, & Liberzon, 2012; Sripada et al., 2012). Alternatively, patients with social anxiety have demonstrated decreased functional connectivity between the insula and the “core network”, similar to the SN, but increased with the cingulate and the network (Liao et al., 2010; Peterson et al., 2014). Other studies have linked abnormalities in functional connectivity between nodes of the SN and other regions at rest in generalized anxiety disorder and panic disorder (see Peterson et al., 2014). Additionally, trait anxiety is associated with greater axial diffusivity between the insula and basal lateral amygdala, indicating altered brain structure and network efficiency between these regions (Baur et al., 2013). This could represent a vulnerability to dispositional anxiety or perhaps plasticity changes due to chronic anxiety. While there is much more variation across studies of anxiety disorders and SN,

in general the literature suggests there is an association between anxiety and disruptions in the SN.

In short, each of the aforementioned networks have been shown to be disrupted in anxiety and depressive disorders, but there is still limited research in how individual differences such as life experiences and genetic variation may be associated with variation in cortical connectivity that may confer risk for internalizing disorders. Understanding how these individual factors are linked to this disruption can further aid in the understanding of the biological mechanisms related to broader dysregulation of these key networks.

Stress and Alterations in Brain Circuitry

Chronic stress has been linked to the development of a number of psychiatric and physiological illnesses, such as heart disease, and mood and anxiety disorders (Dohrenwend, 2000; Rozanski, Blumenthal, & Kaplan, 1999). Vulnerability to these illnesses is linked to dysfunction in the HPA axis (E. R. De Kloet, Joëls, & Holsboer, 2005; G. E. Miller, Chen, & Zhou, 2007), which regulates the stress response system through feedback loops between three endocrine glands: the hypothalamus, the pituitary, and adrenal glands. This system acts to both up-regulate the stress response in response to situational demands as well as down-regulate it once the stressor has passed, but has shown to become dysregulated in response to chronic stress (Herman, 2013). The system is activated when the hypothalamus releases corticotropin-releasing factor (CRF), which triggers the pituitary gland to release adrenocorticotropic hormone (ACTH) (Herman, Ostrander, Mueller, & Figueiredo, 2005; Herman, 2013). ACTH then stimulates the adrenal cortex to release glucocorticoids, cortisol in humans, which binds to two types of receptors: mineralocorticoid (MR) and glucocorticoid (GR) receptors (Reul & Kloet, 1985). MRs are primarily found in the hippocampus and have high affinity to cortisol, so they are often

occupied even at low levels of cortisol (E. R. De Kloet et al., 2005). These receptors have a regulatory role in inhibiting CRH and subsequent ACTH (Joels, Karst, DeRijk, & de Kloet, 2008). Additionally, MR occupation is thought to play an important role in regulating cortisol levels associated with the circadian rhythm (Buckley & Schatzberg, 2005). GRs are more ubiquitous receptors and have a lower affinity, and therefore, are only stimulated when there are larger amounts of cortisol in the system and are responsible for down-regulating the HPA axis response during times of stress (Corral-Frías et al., 2016; E. R. De Kloet et al., 2005; E. R. De Kloet et al., 2000). Therefore, the system is regulated through a negative feedback loop in which higher levels of cortisol bind to these MR and GR receptors and, in turn, reduce the release of ACTH in the pituitary, which then leads to the reduced release of cortisol and down-regulation of the stress response (E. R. De Kloet, Vreugdenhil, Oitzl, & Joels, 1998). This intricate process can become dysregulated in mental health disorders (Corral-Frías et al., 2016). Previously it was thought that depression and anxiety disorders, such as PTSD, were characterized by hyper- and hypocortisolemia, respectively (G. E. Miller et al., 2007). However, recent meta-analyses have shown that the nature of HPA dysfunction is complex and dynamic and is influenced by factors such as the nature of the stressor or trauma, time since the stressor, as well as individual differences (G. E. Miller et al., 2007). Therefore, the exact nature of dysregulation may vary due to environmental factors, but genetic risk may be common across disorders.

A number of brain regions play an important role in regulating the stress response system. Limbic regions, including the amygdala and hippocampus, as well as prefrontal cortical regions are important in detecting or recognizing if something in the environment is a stressor (McEwen & Gianaros, 2010). These brain regions are rich in glucocorticoid receptors and cortisol binds to these regions to impact learning, memory and emotions when the HPA axis is

activated (Bremner, 1999; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). These brain regions also overlap with those that are altered in many mental disorders as discussed above, and animal studies as well as some human studies have suggested that altered HPA axis activation may be an important mediator between disease and brain aberrations (McEwen & Gianaros, 2010). Indeed, a substantial body of research has focused on the impact of elevated glucocorticoids throughout the body, including effects on the brain (McEwen, Nasca, & Gray, 2016). Animal studies examining exposure to excessive stress and stress hormones have demonstrated deleterious consequences of elevated glucocorticoid concentrations on the brain, specifically in the hippocampus, amygdala, and prefrontal cortex. At the neuronal level, stress or increased glucocorticoids in non-human animals can reduce dendritic spine density and impact neuronal structure in the hippocampus and prefrontal cortex (Cerqueira et al., 2005; Cook & Wellman, 2004; McEwen, 1999; McEwen et al., 2016; Radley et al., 2004), as well as cell reduction in the hippocampus dentate gyrus (Pham, Nacher, Hof, & McEwen, 2003; Sousa, Paula-Barbosa, & Almeida, 1999). Hypertrophy, on the other hand, has been noted in the basolateral amygdala (Mitra & Sapolsky, 2008; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). As noted, these regions are essential for emotion regulation, and chronically stressed animals display more anxious behaviors (Bondi, Rodriguez, Gould, Frazer, & Morilak, 2008), indicating that these brain changes are associated with emotional disturbances (McEwen, 2004).

Consistent with animal research, stress in humans also impacts brain functioning and is associated with cognitive and memory deficits (Goosens & Sapolsky, 2007; Lupien et al., 2007). HPA axis dysregulation is a risk factor for depression and anxiety disorders in humans (E. R. De Kloet et al., 2005), and the relationship is thought to be mediated by the brain changes associated with chronic cortisol exposure (Frodl & O'Keane, 2013; McEwen, 2004). In humans, a causal

effect of increased HPA activity on psychiatric symptoms has been demonstrated in Cushing's disease. Individuals with Cushing's disease show problems with coping and excessive arousal (Loosen, Chambliss, DeBold, Shelton, & Orth, 1992), symptoms characteristic of hypercortisolemia that remit upon treatment (Kelly, 1996; Loosen et al., 1992), and alterations in volume of the hippocampus much like in animals (Starkman, Gebarski, Berent, & Scheingart, 1992). There are also observational studies linking stress in humans to changes in brain structure in regions central to memory and emotion expression and regulation (Gianaros & O'Connor, 2011). Adversity is linked with volume reductions in the hippocampus and increases and decreases in the amygdala (Frodl & O'Keane, 2013; Tottenham & Sheridan, 2009; Tottenham, 2012). Additionally, research has shown higher stress was correlated with gray matter volume reductions in the hippocampus and prefrontal cortex in postmenopausal women (Gianaros et al., 2007a; McEwen & Gianaros, 2010). Similar findings have been observed in healthy populations faced with a common stressor, such as in individuals with low social standing (reduced ACC volume) (Gianaros et al., 2007b) and in individuals near the World Trade Center on September 11, 2001 (Ganzel, Kim, Glover, & Temple, 2008; Gianaros & O'Connor, 2011). In addition to structure, there is evidence that stress may alter functioning of some of these brain networks in humans. For instance, individual differences in cortisol secretions predict successful engagement of ventral mPFC inhibitory control and reductions in amygdala when participants were asked to decrease negative emotions (Urry et al., 2006). Additionally, childhood stress in girls is related to HPA axis dysfunction through increased levels of cortisol, and was linked to both mental health outcomes as well as reduced amygdala-ventral mPFC coupling (Burghy et al., 2012). As noted above, this fronto-limbic circuitry is key in emotional regulation and there seems to be a close association with HPA axis dysfunction and fronto-limbic functioning.

Collectively, the impact of stress on brain networks important for emotion regulation and cognitive functioning may be a mechanism predisposing one to mental illness. Animal studies demonstrate that increasing stress and the amount of circulating glucocorticoids results in alterations to limbic structures and prefrontal regions important for emotion regulation. These overlap with regions that demonstrate abnormal function and structure in anxiety and depression. The few neuroimaging studies examining the neural correlates of HPA axis dysfunction have pointed to altered fronto-limbic functioning, implicating HPA axis dysfunction as a potential mediator of stress and altered function in brain regions implicated in internalizing disorders.

Genetic Variation in HPA Axis Involved in Internalizing Disorders and Altered Brain Networks

Dysfunction in the HPA axis has been linked to internalizing disorders (E. R. De Kloet et al., 2005; Lupien et al., 2009), and environmental stress is linked to dysregulation of the system suggesting HPA axis functioning may mediate the association between stress and mental illness (Herman, 2013; McEwen, 2004). In addition to environmental factors, genetic variation in genes that are linked to HPA axis functioning can also put one at risk for internalizing disorders (Binder, 2009; Heim & Binder, 2012; Mehta & Binder, 2012; Minelli et al., 2013). Most studies have highlighted the role of gene-environment interactions in HPA dysregulation, but there is less information on how this, in turn, impacts brain functioning in humans (see Bogdan et al., 2016; Corral-Frias et al., 2016). Assessing genetic variation in HPA axis functioning and how it relates to differential brain functioning may elucidate important biological mechanisms that can help us better understand the etiology and development of psychopathology related to stress. Recent evidence has demonstrated that genetic variation in the regulation of the HPA axis may be an important factor for how life stressors impact brain structure and function (Bogdan et al.,

2016; Corral-Frías et al., 2016); however, the research in the field is limited and has been focused much on the impact of amygdala structure and function. Additionally, several studies are limited to examining one candidate gene within the HPA axis system, limiting the findings to examining variation in one aspect of HPA axis functioning. That said, these data have implicated the structural and functional relevance of polymorphisms across multiple HPA axis genes. Bogdan et al. (2016) and Corral-Frias et al. (2016) offer extensive reviews in this area, and below I will briefly summarize some of the key genes linked to both internalizing disorders and alterations in brain structure and function.

The FK506 binding protein 5 (FKBP5) gene is arguably the most well characterized gene in HPA axis gene with polymorphisms that several studies have implicated in risk for psychopathology (Appel et al., 2011; Binder et al., 2004; Binder et al., 2008; Binder, 2009; Lekman et al., 2008; Mehta & Binder, 2012; Minelli et al., 2013; Zimmermann et al., 2011). This gene codes a protein that aids in cortisol and GR binding, which is important for the negative feedback loop that down-regulates HPA axis activity (Binder et al., 2004; Zannas & Binder, 2014). Variation across this gene has been linked to increased expression of FKBP and a decrease affinity to GR in healthy individuals resulting in elevated cortisol levels (Binder et al., 2008) and slower recovery (Ising et al., 2008). There is also evidence of an important gene-environment interaction between risk alleles and trauma, particularly childhood trauma, in influencing risk to mental illness (Appel et al., 2011; Binder et al., 2008; Bogdan et al., 2016; Zannas & Binder, 2014). However, evidence of the influence of the risk alleles on brain functioning has been mixed as to whether this influence is a main effect or dependent on an environmental interaction (Bogdan et al., 2016). White et al. (2012) examined genetic variation in FKBP5 and found that polymorphisms in this gene interacted with childhood neglect to

predict increased amygdala activity in a face-viewing paradigm. Holz et al., (2015) examined a sample of high risk young adults and found heightened amygdala activity to fearful faces as well as larger amygdala volumes was associated with a main effect of the FKBP5 SNP rs1360780, indicating that functional differences in the amygdala may not be dependent on a gene-environment interaction. Additionally, risk alleles were associated with altered amygdala connectivity with the hippocampus and orbitofrontal cortex. They did find a gene-environment interaction with amygdala activity increasing with level of childhood adversity in homozygotes for the risk allele. Collectively, genetic variation in FKBP5 seems to play an important factor in susceptibility to stress-related psychopathology and neural functioning (Bogdan et al., 2016; Corral-Frias et al., 2016).

Genetic variation in the corticotropin-releasing hormone receptor 1 (CRHR1), the main receptor for CRH, has also been linked to differences in cortisol reactivity (Heim et al., 2009; Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2014; Tyrka et al., 2009) and is implicated in development of depression and anxiety often in the context of stress (Binder & Nemeroff, 2010; Liu et al., 2006). Studies examining the impact of CRHR1 polymorphisms on brain functioning have been mixed on whether there is a main effect of genetic variation or if there is only an interaction with environmental influences. Chen et al. (2010) assessed the effect of polymorphisms in CRHR1 on brain functioning using event-related potentials and found genetic variation was associated with differences in cognitive control related activity. Additionally, Hsu et al. (2012), examined the single nucleotide polymorphism (SNP) rs110402 and found genetic variation in CRHR1 was associated with brain activity in the subgenual ACC cortex in clinically depressed individuals when engaging in an emotional processing task. They found that minor alleles had differential effects in the depressed group compared to controls with for those with

major depressive disorder who carried an A allele demonstrating less activity in the hypothalamus, amygdala and left nucleus accumbens than controls with an A allele, while depressed G homozygotes demonstrated greater activity in the subgenual cingulate cortex than control homozygotes (Corral-Frías et al., 2016; Hsu et al., 2012). Finally, Bogdan et al. (2011) found no main effect of genetic variation in a CRHR1 SNP, rs12938031 feedback-related negativity, but found that A homozygotes showed indicators of altered reward processing when under stress (Corral-Frías et al., 2016). Together this may imply that polymorphisms in CRHR1 show differential patterns of activity under certain environmental conditions and that carriers of certain alleles may be particularly susceptible to the effects of stress on reward processing, similar to what is seen in depression (Bogdan et al., 2011).

Polymorphisms for the two key receptors of the HPA axis, GR, coded by the NR3C1 gene, and MR (NR3C2), have shown to result in differential HPA axis functioning and also confer risk for internalizing disorders (DeRijk et al., 2006; Ising et al., 2008; Plieger, Felten, Splittgerber, Duke, & Reuter, 2018; van Rossum et al., 2006; Van West et al., 2006; Vinkers et al., 2015). GRs and MRs bind to cortisol, but have different affinities, and both help to regulate the HPA axis, but at different levels of cortisol concentration, and therefore, the functioning of these receptors is important for the negative feedback loop in the HPA axis (Corral-Frías et al., 2016). Bogdan et al. (2012) examined a NR3C2 variant (rs5522) in children that those with the risk allele, and those who experienced neglect demonstrated amygdala activity during an emotional task. There was also an interaction with risk carriers showing the heightened amygdala in low stress context, and neglect being associated with amygdala activity in those without the risk allele. This mimics amygdala activity alterations seen in depression and anxiety, implying that genetic variation in MR functioning may be a risk factor (Bogdan et al., 2012; Bogdan et al.,

2016; Corral-Frías et al., 2016). Ridder et al. (2012), found brain activation during a fear-conditioning task was moderated by variation in three SNPs on the NR3C1 gene. Individuals with more minor alleles across the 4 SNPs demonstrated greater amygdala activity during fear conditioning as well as differential coupling between the amygdala and PFC in individuals with two or more minor alleles across NR3C1 compared to those with 0 or 1. This indicates that NR3C1 variation may moderate fear expression during fear learning, a key characteristic of anxiety disorders (Lissek et al., 2005; Ridder et al., 2012).

Recently, researchers have been taking a multiloci approach examining multiple SNPs across multiple HPA axis genes in order to examine the potential additive effects of risk alleles in this system (Bogdan et al., 2016; Corral-Frías et al., 2016). In addition to examining SNPs across NR3C1, Ridder et al., (2012) also incorporated the NR3C1 and CRHR1 genes and found that higher risk scores (as indicated by number of minor alleles across SNPs) across both NR3C1 and CRHR1 had reduced activation of the vmPFC during fear extinction (Corral-Frías et al., 2016). Prior work would indicate that this would result in reduced regulation of the amygdala and therefore, impaired extinction learning (Milad et al., 2007; Phelps et al., 2004), which is thought to be a fundamental deficit associated with the maintenance of anxiety disorders (Bitterman & Holtzman, 1952; Peri, Ben-Shakhar, Orr, & Shalev, 2000; Pitman & Orr, 1986). Additionally, Pagliaccio and colleagues (2014; 2015) examined risk profiles of 10 SNPs across the four HPA axis genes discussed above (CRHR1, NR3C2, NR3C1, and FKBP5) in two studies. In Pagliaccio et al. (2014) children between 3-5 years old were examined and they found that the genetic profile predicted increased cortisol and the interaction of stressful life events in early childhood and the genetic profile was associated with gray matter volume in the amygdala and hippocampus. This indicated that in the context of early adversity the number of risk alleles in

the HPA axis predicted aberrations in limbic structures. Using the same profile from these four genes Pagliaccio et al., (2015) sought to determine if genetic risk could predict functional differences within cortico-limbic structures as well. In a sample of 120 adolescences (aged 9-14) they found both main effects of genetic variation in HPA axis risk scores and childhood adversity on altered amygdala connectivity. Main effects indicated genetic risk scores were associated with reduced connectivity between the amygdala and caudate and greater connectivity between amygdala and the postcentral gyrus, while main effects of early life stressful events demonstrated an association with reduced negative amygdala -ACC connectivity. There was also an interaction suggesting that having both experience of early life stressful events and increased genetic risk was associated with reduced amygdala connectivity with regulatory and cognitive control PFC regions of the middle and inferior frontal gyrus. They were also able to link some of the neural findings with psychopathology symptoms, linking this neural difference to behavioral consequences.

In short, genetic variation in HPA axis functioning also presents a risk factor for psychopathology, particularly in the context of a gene-environment interaction (Binder et al., 2008; Bogdan et al., 2016; E. R. De Kloet et al., 2005; Mehta & Binder, 2012). Neuroimaging genetics research on the HPA axis is still in its infancy, but there is emerging research that suggests a main effect of genetic variation on brain function, and more evidence pointing to an important gene-environment interaction influence on brain networks (Bogdan et al., 2016; Corral-Frías et al., 2016). Therefore, moving forward, it is important to consider genetic risk factors in the context of environmental risk factors (i.e. stressful life events) in understanding how HPA axis genetic variation relates to altered brain functioning. Most research examining the effects of HPA axis dysregulation on brain networks has focused on the amygdala and

connectivity between this region and other regions implicated in the emotion regulation network (e.g. mPFC) (Corral-Frías et al., 2016), but given the impact stress has on other regions of the brain (e.g. hippocampus and PFC), and each of these regions' roles in large-scale intrinsic networks, examining the influence of genetic variation on these broader networks as well may help broaden our understanding of the neural impact of these gene and gene-environment influences on brain functioning.

The Current Study

Imaging genetics research has uncovered important polymorphisms in the HPA axis that impact brain structure, activity, and connectivity and contribute to risk for internalizing psychopathology. Research in this area has focused primarily on the function and structure of limbic regions (amygdala and hippocampus), given their pivotal role in internalizing psychopathology. However, as discussed above with the focus on larger intrinsic networks and their role in mental illness, examining these networks in the context of HPA axis polymorphisms may provide a broader view of how variation in HPA functioning may influence neural phenotypes similar to those seen in internalizing disorders. Additionally, much research in environmental stress and genetic interactions in the HPA axis have focused on early life events; however, there is also evidence to suggest HPA variability may interact with later life stressors, such as war combat, to confer risk for developing PTSD (van Zuiden et al., 2011). Therefore, investigating the influence of stress and gene interactions will help us understand if the alterations in brain functioning are similar to those studies focusing on childhood adversity. Importantly, I took a candidate gene approach in the current study to look at gene-environment risk factors for stress-related pathology. Although polymorphisms in the genes described above have been linked to relevant phenotypes to internalizing disorders in candidate gene studies,

genome-wide studies have yet to link these genes to these disorders. Therefore, the primary aims of the current study focused on influences of a well characterized SNP of the FKBP5 gene, rs1360780 (Binder et al., 2008; Mehta & Binder, 2012; Minelli et al., 2013; Zannas & Binder, 2014; Zimmermann et al., 2011). Secondary aims used a more exploratory multi-loci approach based on the work of Pagliaccio and colleagues (2014:2015) and examined the impact of cumulative risk across 4 HPA axis genes. I specifically chose available SNPs that overlapped with Pagliaccio et al. (2014:2015) for they used SNPs that have been linked to differences in cortisol functioning and risk for internalizing disorders, including on FKBP5 and found their genetic profile also predicted cortisol levels. Although there is evidence of a main effect of HPA axis genetic variation on brain functioning, noted in the above section, prior work has highlighted the potent interaction with stressful life events (Bogdan et al., 2016); therefore, my hypotheses focused on gene-environment interactions, but I explored main effects for both. **The aim of the current study was to assess how genetic variation in the HPA axis interacts with stressful and traumatic life events to influence brain connectivity in a few important brain networks in a sample of young adults.**

Emotion regulation network. Pagliaccio et al. (2015) demonstrated altered connectivity in fronto-limbic regions implicated in emotional regulation as a result of HPA genetic risk and early childhood adversity in adolescents, making this a primary target to examine in emerging adults as well. Additionally, there is some evidence to suggest a potential main effect of HPA genetic risk on altered functional connectivity in this circuit during fear conditioning (Ridder et al., 2012). The interaction of HPA axis genetic variation and stressful life on resting state functional connectivity in this circuit in adults has never been examined. **Therefore, I posited high HPA genetic risk will interact with stressful and traumatic life events to predict**

weaker fronto-limbic connectivity, with particular focus on amygdala and mPFC connectivity.

Default mode network. As stated, the DMN is a large-scale brain network underlying several internally-focused thought processes, and dysfunction in this network is tied to numerous mental health diagnoses, including internalizing disorders (Broyd et al., 2009). While there is some research linking genetic variability in the HPA axis to altered functional connectivity between the amygdala and other circuitry important for emotional regulation (Bogdan et al., 2016; Pagliaccio et al., 2015; Ridder et al., 2012), the impact of polymorphisms in HPA axis genes on other resting state networks is relatively unknown. With the focus on variation in these large intrinsic networks and their relationship to disease, examining the genetic contribution of the HPA axis can provide important insight into the etiology and vulnerability for these disorders.

Recently, some research has suggested that the DMN network dysfunction seen in internalizing disorders may be in part due to dysregulation of the HPA axis. Philip and colleagues (2013) investigated DMN resting state connectivity in adults with a history of early life stress and found reduced functional connectivity between the PCC and mPFC. Sripada and colleagues (2014) found reduced DMN resting state connectivity among adults who experienced childhood poverty compared to adults with a middle-class background. This was coupled with higher cortisol levels before a stressor (Sripada et al., 2014). Graham and colleagues (2015) found that parental conflict was related to hyperconnectivity between anterior and posterior regions of the DMN at rest in infants (ages 6-12 months-of-age). Of interest, both Graham et al. (2015) and Philip et al. (2013) also found abnormal amygdala connectivity with regions in the DMN, indicating DMN dysfunction may interact with emotional dysregulation in the amygdala

(Sylvester et al., 2012). Additionally, combat trauma in veterans has been associated with dysregulation of the DMN (Sripada et al., 2012). This indicates that the impact of stress on this brain network may not be limited to early life stress, but may be susceptible to disruptions over the course of the lifespan. These studies suggest that much like the emotion regulation network, the DMN may be susceptible to alterations as a result of stressful life events due to HPA dysregulation. However, there is little information available on how genetic variation in the HPA axis may also contribute to individual variation in DMN functioning. Given what is known about the genetic contribution to altered connectivity with the amygdala and other brain regions, it is likely that genetic variation may also contribute to other network dysfunction in the brain. Therefore, at this point it is unclear how genetic variation may interact with stressful life events to disrupt DMN functional connectivity. **I posited that if HPA axis function variation due to environmental stresses impacts the DMN, it is plausible that genetic variation in HPA axis function may also contribute to DMN functioning, and would moderate the relationship between DMN connectivity and life stress.**

Salience network. In addition to the DMN, there is some evidence tying HPA axis variation to differences in the SN. Thomason et al. (2011) demonstrated that in adolescents who underwent a stress test, stress responsivity, measured by cortisol, predicted connectivity with the subgenual ACC and the SN. This indicates that heightened HPA axis reactivity is associated with alterations within this network. Additionally, Sripada et al. (2012) showed individuals with PTSD displayed reduced functional connectivity in the DMN, but increased connectivity in SN regions, possibly underlying the hypervigilance characteristic of PTSD. Since PTSD is also associated with HPA dysfunction (C. De Kloet et al., 2006; G. E. Miller et al., 2007) and HPA dysfunction is thought to mediate the relationship between stress and pathology (E. R. De Kloet

et al., 2005; Lupien et al., 2009; McEwen, 2004), this suggests a possible link between HPA axis and the SN. So far only one recent study examined the SN and the relationship to FKBP5 genetic variance and found risk alleles were linked with altered SN connectivity (Bryant, Felmingham, Liddell, Das, & Malhi, 2016) . **Therefore, I posited that genetic variation in the HPA axis would influence SN connectivity, and moderate the relationship between stressful life events and connectivity.**

Method

Participants

One hundred and twenty-one undergraduates from the University of Wisconsin-Milwaukee volunteered to participate in the current study. From this sample, participants were excluded from final analyses due to diagnosis of bipolar disorder (n = 1), not completing resting state scan (n = 7), technical issues with the scanner and/or software (n = 4), excessive motion during scanning (n = 3), and failure of genetic assay (n = 9), leaving a final sample of 97 individuals. All study procedures were approved by the Institutional Review Boards of the University of Wisconsin-Milwaukee and the Medical College of Wisconsin. Subjects were compensated with monetary payment and/or extra credit towards psychology courses. All participants were right-handed and had no contraindications for an MR scan, including metal in the body, pregnancy, or claustrophobia. Additionally, participants reported no history of head trauma, neurological disorders, psychosis, or a bipolar disorder (for DSM-IV characteristics see Table 1). To minimize genetic variation and increase power to detect significant genetic effects, the sample was limited to European American individuals, a control common in imaging genetics research (Hariri et al., 2005).

Table 1*Participant DSM-IV Axis I Diagnoses*

DSM-IV Axis I Diagnosis	Current	Past
No Diagnosis	37	-
Major Depressive Disorder	3	41
Panic Disorder	4	9
Agoraphobia w/o panic	4	-
Agoraphobia with Panic	1	-
Posttraumatic Stress	3	-
Generalized Anxiety	6	-
Social Anxiety Disorder	2	-
Obsessive Compulsive	2	-
Alcohol Abuse	9	-
Alcohol Dependence	8	-
Marijuana Abuse	10	-
Marijuana Dependence	3	-
Benzodiazepine Abuse	1	-
Opioid Dependence	2	-

Note: major depressive disorder and panic disorder were assessed for past diagnoses. Data was not collected from 6 participants because they did not return for the second session.

Procedure

As part of a larger project, participants came in for two sessions separated by a week. Of relevance for the proposed study, for the first session participants provided written informed consent and completed questionnaires, a resting state scan, and provided a saliva sample at the Medical College of Wisconsin for genetic testing. The following week participants were administered the Mini International Neuropsychiatric Interview Version 6.0.0 for DSM-IV (M.I.N.I. Sheehan et al., 2010) at the University of Wisconsin-Milwaukee. This was used to assess psychiatric history and to exclude participants based on the lifetime presence of either bipolar disorder or psychotic disorders. No other diagnoses were excluded for

Scanning Protocol

At session one, a five-minute resting state fMRI scan was collect. Participants were instructed to keep their eyes open and stay awake during the scan. fMRI data were acquired on a 3.0 Tesla GE scanner equipped with a high-speed quadrature birdcage headcoil. Functional T_2^* -weighted echo-planar images (EPI) were collected (41 interleaved sagittal slices; repetition time [TR] = 2000 ms, echo time [TE] = 25 ms, flip angle [α] = 77° , field of view [FOV] = 240 mm, matrix = 64 x 64, slice thickness = 3.5 mm, slice gap = 0 mm). High-resolution T_1 -weighted whole-brain anatomical images were acquired for coregistration of functional data across subjects using a spoiled gradient-recalled echo scan (150 slices, TR = 8.2 ms; TE = 3.2 ms; α = 12° ; FOV=240 mm; matrix = 256 x 224; slice thickness = 1 mm).

fMRI Processing

AFNI (Cox, 1996) was used to reconstruct functional and structural volumes. For the resting state data, the following steps were applied for preprocessing. First, I removed the first 3 volumes to allow for scanner equilibration. Slice-timing correction and rigid body transformations were applied to account for movement in the scanner, using the first volume as reference. Additional steps included despiking to remove outliers, and bandpass filtering of 0.1-0.01 Hz to remove low-frequency drifts and physiological noise. TRs exceeding 3 mm or 3 degrees of movement in any direction or rotation were censored. Motion derivatives were added as covariates. Participants with 20% or more TRs censors were excluded from group analyses (n=3). Finally, a non-linear transformation using FSL's FNIRT was applied (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fnirt>) to normalized to MNI space.

Resting State Functional Connectivity Analysis

Functional connectivity was assessed using a seed based approach. Five regions from key nodes of each of the three networks were selected as seeds. These included the amygdala (bilateral) for the emotion regulation network, the PCC (one ROI at midline) for the DMN, and the anterior insula (bilateral) for the SN. Cortical ROIs were created by centering a sphere on each region using coordinates identified from previous studies, right/left anterior insula (8 mm sphere centered at MNI = 39, 23, -4/4; Yuen et al., 2014) and PCC (10 mm sphere centered at MNI = 0, -56, 20; Sripada et al. 2012). Right and left amygdala ROIs were created using the Harvard-Oxford probabilistic atlas included in FSL (Smith et al., 2004) with a voxel threshold of 25% probability of being labeled amygdala. The average time series was extracted from each of these seed regions and then correlated with every other voxel in the brain. Fisher's r to z transformations were applied to standardize r values.

Assessments

Participants completed questionnaires that assessed history of trauma and stress. Much like traumatic experiences, there is evidence linking stressful life events to health and overall well-being (Dohrenwend, 2000); therefore, I examined stressful life events over the past year in addition to lifetime traumatic events. The Life Events Checklist (LEC) assesses the number of lifetime traumatic experiences, including car accidents, physical and sexual assault, and military combat (Gray, Litz, Hsu, & Lombardo, 2004). I scored this measure by totaling the number of personally experienced traumatic events (range of possible scores = 0-17). I assessed stressful life events using the Life Events Scale (LES) adapted from the Holmes-Race Social Readjustment Rating Scale (Holmes & Rahe, 1967) and modified for young adults/students (Padilla, Rohsenow, & Bergman, 1976). Specifically, I used the student version. The LES lists

39 stressful life events and each event has a value attached to it representing the severity of the stressful life event. Participants were asked to indicate which events, and the number of occurrences over the past year. The total score is the sum of these severity values (range of possible scores = 0-10,970). The total score of the original scale has been validated in predicting illness (Rahe, Mahan, & Arthur, 1970).

In addition to assessing stressful and traumatic events, participants completed measures of symptom inventories. Specifically, participants completed the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). This is a 40-item measure of state (e.g. “I feel at ease”) and dispositional anxiety (“I am a steady person”), with good psychometric properties (Barnes, Harp, & Jung, 2002). Additionally, participants completed the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). This measurement is a 20 item self-report measure that asks participants to report the frequency of depression symptoms in the past week. This measurement has demonstrated good reliability (Radloff, 1977; Roberts, 1980; Roberts, Andrews, Lewinsohn, & Hops, 1990). Finally, I assessed emotion regulation difficulties with the Difficulties in Emotion Regulation Scale (DERS) (Gratz & Roemer, 2004). This is a 36-item self-report scale that assess difficulties in emotion regulation across six subscales: 1) non-acceptance of emotion, 2) difficulties engaging in goal-directed behaviors during negative emotional experiences, 3) difficulties with impulse control during negative emotional experiences 4) lack of emotional clarity, 5) lack of emotional awareness, and 6) limited strategies for regulating emotions. Prior studies have validated the DERS psychometric properties (Gratz & Roemer, 2004).

DNA Analysis and Creation of Genetic Profiles

DNA was extracted from saliva samples provided at session one, and assays were performed at the Gene Expression Center/Biotechnology Core at the University of Wisconsin-Madison. SNPs were selected across four HPA axis genes: CRHR1 (rs110402), NR3C1 (rs41423247, rs10052957), NR3C2 (rs5522, rs6195), and FKBP5 (rs1360780) based on literature linking the SNP genotypes to variation in neural functioning in key regions/processes linked to internalizing disorders (Pagliaccio et al., 2015; Ridder et al., 2012). Other HPA axis SNPs were excluded for lack of substantial evidence of the function and relevance to internalizing disorders, as well to as closely match the profile to previous studies (Pagliaccio et al., 2014; Pagliaccio et al., 2015). All SNPs were given a risk score (1 or 0) based on which genotypes have been linked to cortisol dysfunction or internalizing disorders as done in Pagliaccio et al. (2014). The FKBP5 SNP (rs1360780) is the most established SNP in both its function as well as the link to psychopathology (Zannas & Binder, 2014), and therefore, I analyzed the risk score for this SNP separately. Next, I took a multiloci approach and combined HPA genetic risk scores for each SNP to make a polygenetic risk score as done in previous research of neuroimaging genetics of the HPA axis (see Table 2) (Bogdan et al., 2016; Pagliaccio et al., 2014; Pagliaccio et al., 2015; Ridder et al., 2012). HaploView was used to test Hardy-Weinberg equilibrium. All SNPs are in equilibrium ($p > 0.05$: see Table 2) (Barrett, Fry, Maller, & Daly, 2004). Additionally, HaploView was used to test linkage disequilibrium (LD) with all pairwise $r^2 < 0.01$. SNPs with allele frequencies $< 5\%$ were dropped from further analyses (i.e. rs6195) (Barrett et al., 2004).

Table 2.*Participant Genotyping Results*

Gene	Polymorphism	Alleles	MAF	Major HZ	Minor HZ	Heterozygotes	HWpval
NR3C1	rs41423247	G>A	35	43 (coded 1)	14 (coded 1)	40 (coded 0)	0.45
	rs10052957	G>A	32	45 (coded 0)	10 (coded 1)	42 (coded 0)	1
NR3C2	rs5522	A>G	11	76 (coded 0)	1 (coded 1)	20 (coded 1)	1
CRHR1	rs110402	C>T	50	29 (coded 0)	28 (coded 1)	40 (coded 0)	.11
FKBP5	rs1360780	C>T	25	54 (coded 0)	5 (coded 1)	38 (coded 1)	0.87

Note: MAF is abbreviated for minor allele frequencies. Major HZ are defined as homozygotes for the major allele and Minor HZ are for the minor allele. HWpval is abbreviated for Hardy-Weinberg p values. Genotype risk coding based off of (Pagliaccio et al., 2014; Pagliaccio et al., 2015).

Analytic Approach

Exploratory analyses of genetic profile predicting symptoms. First, I assessed the ability for our gene profile and gene profile-environment interaction to predict current symptoms and emotion regulation problems in individuals. As our genetic risk profiles are assuming an additive effect of risk (Bogdan et al., 2016; Pagliaccio et al., 2014; Pagliaccio et al., 2015), I sought to see if indeed greater values would predict relevant symptoms for internalizing disorders. Linear multiple regression was used to test gene-environmental influences on individual's levels of trait and state anxiety (STAI), depression (CESD), and the six scales of difficulties in emotion regulation (DESR). I ran separate models with LES (stressful) or LEC (traumatic) scores as the environmental stress. Predictors included genetic profile score, environmental stress (LES or LEC scores), genetic profile-environmental stress interaction, gender, gender X genetic profile, and gender X environment, consistent with recommended practices (Bogdan et al., 2016; Keller, 2014; Pagliaccio et al., 2015). Only genetic profile score, environmental stress, and their interaction were interpreted. Importantly, I only ran these

analyses with the genetic profile as the genetic factor and not with the FKBP5 rs1360780 risk genotype, our main SNP of interest, for there exist much evidence linking this variant to relevant psychopathology (Zannas & Binder, 2014).

Effects of environment independent of genetic risk. Linear multiple regression was used to assess the influence of environmental stress and genetic factors on functional connectivity at the whole brain level with AFNI's 3dRegana. Prior to examining gene-environment influences, I examined main effects of lifetime exposure to trauma (LEC) and stressful life events in the past year (LES scores). For these models, I entered predictors of environmental stress (LEC or LES), gender, and gender X environment to adequately control for effects of gender. Then I examined subgroups of each gender. This helped me gain an understanding of the influence of environmental stress on brain networks without controlling for effects of genes.

Effects of FKBP5 and stress. Next, I examined carriers of the risk variant of SNP rs1360780 of the FKBP5 gene. As above, separate models were run for lifetime exposure to traumatic events (LEC scores) and past year exposure to stressful events (LES scores) as the environmental factor. Environmental stress, rs1360780 risk genotype, and their interaction were added as predictors, as well as gender, gender X environment, and gender X genotype to control for gender effects (Keller, 2014), with the whole-brain z-correlation maps for each of the 5 seeds separately as the dependent variable. Environmental stress predictors were centered. Additionally, follow-up regressions were conducted separately for each gender. AFNI's 3dClustStim, with the new AutoCorrelation Function, which offers a more adequate false positive rate (Cox, Chen, Glen, Reynolds, & Taylor, 2017) was used for Monte Carlo based thresholding to correct for multiple comparisons with a voxelwise threshold of $p = 0.001$. For the

whole group, clusters greater than 41 voxels achieved a corrected $p < 0.05$. For analyses of women only the cluster size threshold was 42 voxels and for men it was 40 voxels. I extracted average z correlations for any significant cluster to parse significant interactions using simple slope plots.

Effects of genetic profile and stress. Finally, using the same regression model described above, I also examined the influence of the genetic profile scores (centered) I created across four HPA axis genes with separate models for lifetime exposure to trauma (LEC scores) and lifetime stress (LES scores) with correlation maps of each of the network seeds as the dependent variable. I also examined each gender separately, as above.

Results

Participants

LEC scores ranged from 0 to 9 experienced traumatic events, with an average of 2.81 and standard deviation of 2.05. Scores on the LES ranged from 0 to 2043 (after removing two outliers), with a mean score of 577.67 and standard deviation of 418.05. As noted above, LES scores weigh the severity of each stressful life event in addition to adding the total, and therefore, the score represents both number of events and severity of those events in the past year. Two participants had scores more than 3+SDs from the mean and were excluded from further analyses with LES scores as a predictor. Scores on the genetic profile ranged from 0 to 4, with a mean of 1.91 and standard deviation of 0.94. See Table 3 for participant characteristics including other assessment measures.

Table 3*Participant Characteristics*

	Mean	SD	Minimum	Maximum
Age	21.84	3.721	18	35
Genetic Profile	1.91	.94	0	4
LES Score*	577.67	418.05	0	2043
LEC score	2.81	2.05	0	9
CES-D	14.14	10.95	0	46
STAI(trait)	40.21	11.00	21	66
STAI(state)	34.84	9.27	20	59
DERS				
Goals	13.81	4.88	5	24
Imp Con	10.32	4.15	6	23
Non Acc	12.54	6.08	6	30
Lim Strat	15.62	7.24	7	37
Lack Aware	12.97	4.88	6	28
Lack Clar	10.05	4.29	5	22
	N Female	N Male		
Sex	65	32		

Note: Data excluded for 2 individuals due to LES scores being over 3 SDs above the mean.

Gene Environment Interaction Predicts Symptoms

Prior to examining the imaging findings, I tested how well the genetic profile, and the interaction with life stress predicted symptoms and relevant traits: STAI Trait-State, CES-D, and the DERS subscales. I ran separate models for traumatic stress (LEC) and stressful life events (LES). I entered the following predictors into a regression model in three steps: step1: gender, step2: genetic profile scores and environment (LEC or LES scores), and step 3: genetic profile X environmental variable, genetic profile X gender, environment X gender.

LES stressful events model. In the model with LES, there was no main effect of genetic profile or LES scores on trait anxiety, depression, or current anxiety. There was a trend towards the genetic profile X LES score interaction predicting the lack of emotional awareness scale (see Table 4).

Table 4*Genetic Profile X LES Interaction and Emotion Regulation*

GP x LES	R ²	R ² Change	Change p	Beta	p	GP Lo	GP Lo p	GP Hi t	GP Hi p
STAI Trait	.069	.022	.566	.151	.174	-	-	-	-
STAI State	.080	.009	.828	.048	.434	-	-	-	-
CESD	.029	.011	.809	.094	.407	-	-	-	-
DERS									
Goals	.121	.023	.519	.144	.183	-	-	-	-
Imp Con	.085	.035	.350	.189	.088	-	-	-	-
Non Acc	.040	.009	.850	-.014	.901	-	-	-	-
Lim Strat	.086	.038	.309	.204	.066	-	-	-	-
Lack Awar	.136	.067	.086	.236	.029	-	-	-	-
Lack Clar	.089	.040	.286	.166	.133	-	-	-	-

Note: DERS Scales: the Impulse Control, Non Acceptance of Emotions, and Limited Strategies. Genetic profile X LES interaction did not significantly predict any symptom measure or emotion regulation. Betas are standardized.

LEC traumatic events model. In the model with LEC scores as the environmental factor I found that the LEC and Genetic profile interaction predicted scales on the DERS. Specifically, individuals with high genetic profiles scores had a significant positive relationship between LEC scores and the Non-Acceptance of Emotions and Limited Strategies scales. Individuals with a low genetic risk profile showed a negative relationship between experience of traumatic events and the Impulse Control scale (see Table 5 for overall model values and simple slope post hoc tests if applicable).

Table 5*Genetic Profile X LEC Interaction and Emotion Regulation*

GP x LEC	R ²	R ²	Change p	Beta	p	GP Lo t	GP Lo	GP Hi t	GP Hi p
STAI Trait	.078	.048	.205	.217	.040	-	-	-	-
STAI State	.053	.008	.855	.050	.636	-	-	-	-
CESD	.098	.040	.267	.192	.066	-	-	-	-
DERS									
Goals	.074	.005	.924	.067	.523	-	-	-	-
Imp Con	.105	.089	.036	.303	.004	-2.026	.046	1.935	.056
Non Acc	.105	.082	.047	.268	.011	-1.373	.173	2.163	.033
Lim Strat	.103	.081	.050	.289	.006	-1.740	.085	2.053	.043
Lack Awar	.049	.017	.656	.113	.288	-	-	-	-
Lack Clar	.056	.055	.164	.229	.033	-	-	-	-

Note: DERS Scales: Impulse Control, Non Acceptance of Emotions, and Limited Strategies. Presented Betas are standardized. Follow-up post hoc simple-slopes analyses demonstrated LEC was significantly associated with the Non Acceptance of Emotions and Limited Strategies scales in individuals with high genetic profiles (1 + SD above the mean), and that LEC scores negatively predicted Impulse Control in individual with low genetic profiles (1 – SD above the mean).

Emotion Regulation Network Imaging Results

Main effects of environment. A whole brain regression was run for each of the environmental predictors (LEC traumatic event or LES stressful event scores) covarying for gender and their interaction, to understand the environmental effects on connectivity independent of risk genotypes. I did not find either a main effect of LEC or LES scores on right or left amygdala connectivity. When examining men and women separately, I found that males demonstrated a negative relationship between number of traumas (LEC scores) and connectivity between the right amygdala and the left middle frontal gyrus (BA9, 55 voxels, MNI = -27, 23, 24, $t = -5.11$) and the left lateral fronto-orbital cortex (BA47, 40 voxels, MNI = -24, 23, -8, $t = -4.6157$; see Figure 1). There was no effect of either LEC or LES scores in women.

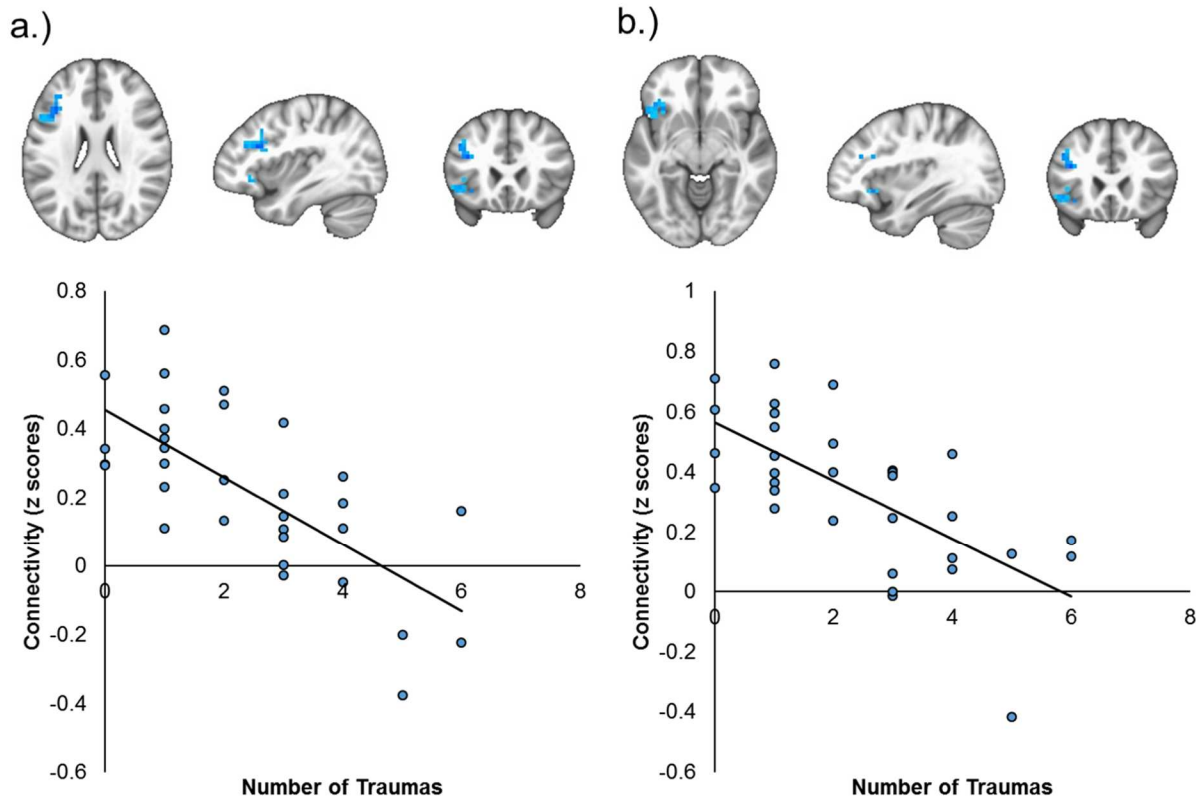


Figure 1. LEC scores predict right amygdala connectivity in men. Main effect of LEC scores in males without controlling for genetic risk factors. a.) Males demonstrated a negative relationship between right amygdala-left middle frontal gyrus connectivity and number of traumas (LEC scores). b.) LEC scores also negatively predicted right amygdala-left lateral fronto-orbital cortex in males.

FKBP5 risk genotype and stressful life events (LES scores). A whole brain regression with the rs1360780 risk genotype (coded 1 or 0), LES score, and rs1360780 risk genotype X LES as predictors of interest, controlling for gender, gender X risk genotype, and gender X LES score, predicting left or right amygdala connectivity did not reveal any significant main effects of FKBP5 genetic risk or LES score. There was also no significant effect of genotype and LES score interaction on right or left amygdala connectivity. There were also no effects when looking at women or men separately.

FKBP5 risk genotype and number of traumas (LEC scores). Using the same model above with LEC scores instead of LES scores predicting left or right amygdala connectivity, I did not find any significant main effects of genotype or LEC score. There was also no significant

effect of the interaction of genotype and LEC score on right or left amygdala connectivity. There were no effects when analyzing women or men separately.

Genetic profile scores and stressful life events (LES scores). Next, I ran a whole brain regression including the predictors of genetic profile, LES score, genetic profile X LES Score, gender, gender X genetic profile, and gender X LES score predicting left or right amygdala connectivity. There were no significant main effects of genetic profile score or LES score. There was also no significant effect of their interaction (LES score and genetic profile score) on right or left amygdala connectivity. There were also no significant effects when analyzing women or men separately.

Genetic profile scores and number of traumas (LEC scores). I ran the above model replacing LES scores with LEC scores. Neither main effects of genetic profile score or LEC score predicted right or left amygdala connectivity with any other regions in the whole brain analysis. However, the interaction between genetic profile and LEC score predicted right amygdala connectivity within two clusters, one in the left lingual gyrus and one in the right middle occipital gyrus (see Figure 2 and Table 6). The interaction of genetic profile and LEC scores also predicted left amygdala connectivity with the left middle occipital gyrus (see Figure 3 and Table 6). Average connectivity correlation values were extracted from each of the significant clusters and were plotted to determine the nature of the interaction. Simple slope post hoc analyses demonstrated that among individuals with high genetic risk profiles (+1 SD from mean), LEC scores positively predicted right amygdala connectivity with the right middle occipital gyrus, $t = 4.608$, $p < 0.001$, as well as the left lingual gyrus, $t = 3.386$, $p = 0.001$. In those with low genetic risk profiles (-1 SD from mean), LEC scores were associated with decreased connectivity between these regions (right middle occipital gyrus: $t = -3.497$, $p < 0.001$;

left lingual gyrus: $t = -2.930, p = 0.004$). Similarly, simple slope post hoc analyses demonstrated a similar finding for left amygdala connectivity with the left occipital lobe. LEC scores and left amygdala-occipital gyrus connectivity were significantly positively correlated when genetic risk was high ($t = 3.001, p = 0.003$), but negatively in individuals with lower genetic risk ($t = -3.023, p = 0.003$).

Table 6

Significant Clusters Predicted by Genetic Profile X LEC Interaction

Cluster	BA	X	Y	Z	Voxels	T
R Amygdala Connectivity						
R middle occipital gyrus	18*	-22	-82	-1	354	5.026
L Lingual gyrus	18*	19	-75	-18	68	4.531
L Amygdala Connectivity						
L middle occipital gyrus	18	-16	-93	13	48	4.589

*Peak coordinates were within white matter boundaries, and therefore nearest Brodmann Area was selected.

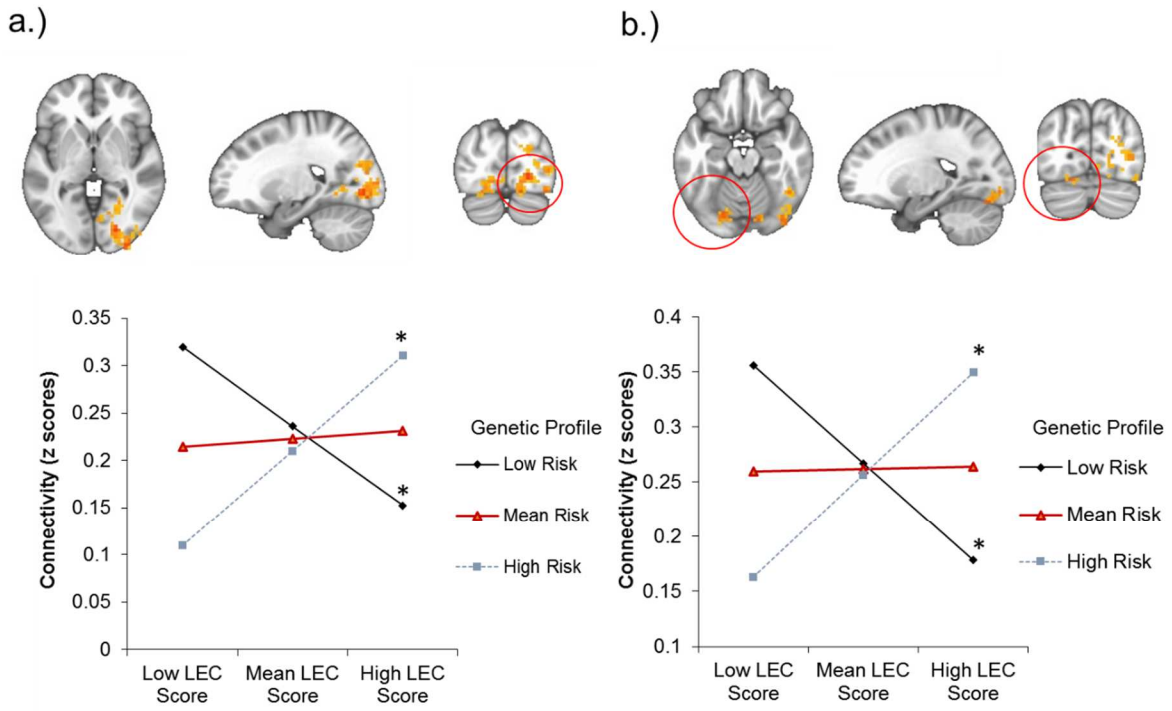


Figure 2. Genetic profile X LEC interaction predicts right amygdala connectivity. Participants with high genetic risk profile scores showed greater right amygdala and bilateral occipital connectivity was associated with LEC scores. The relationship is reversed in those with low genetic risk scores a.) right amygdala and right occipital connectivity b.) right amygdala and left occipital connectivity.

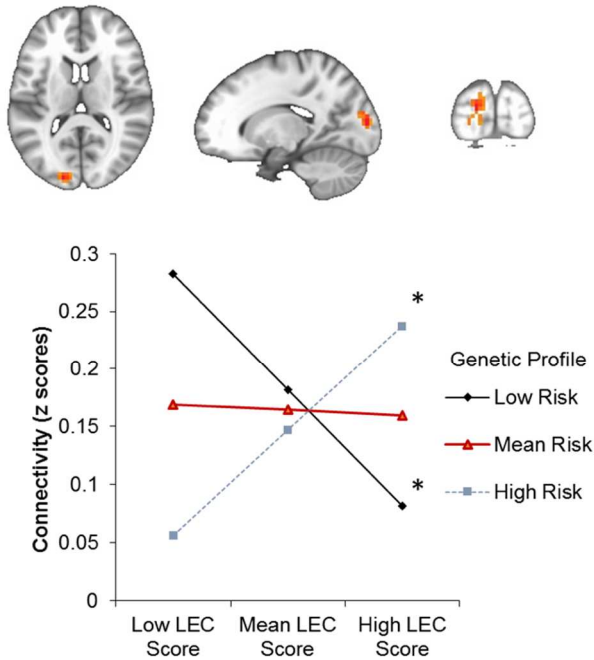


Figure 3. Genetic profile X LEC interaction predicts left amygdala connectivity. Participants with high genetic risk profile scores showed greater left amygdala left occipital connectivity was positively associated with LEC scores. The relationship was reversed in those with low genetic risk profile scores.

Gender differences in emotion regulation network connectivity as a function of genetic profile and trauma. I examined right and left amygdala connectivity associated with genetic risk profile scores, LEC scores, and the interaction between the two in men and women separately. In women, I found a similar pattern of results to that seen in the combined group, such that the genetic profile score X LEC score interaction predicted right amygdala connectivity with bilateral occipital lobe (right middle occipital gyrus: BA18, 220 voxels, MNI = 36, -93, 3, $t = 4.742$; left middle occipital gyrus: BA19, 47 voxels, MNI = -41, -79, 3, $t = 4.787$). Simple slope follow-ups demonstrated that the pattern of results were the same as seen in the combined findings, that higher genetic risk demonstrated a positive relationship between traumatic incidents experienced and greater amygdala and bilateral occipital connectivity (right occipital lobe: $t = 4.219$, $p < 0.001$; left occipital lobe: $t = 4.142$, $p < 0.001$; see Figure 4). In women with

low genetic risk profiles, I found weaker connectivity between the right amygdala and bilateral occipital lobe (right occipital lobe: $t = -3.270$, $p = .002$; left occipital lobe: $t = -2.722$, $p = .008$) associated with LEC scores (see Figure 4).

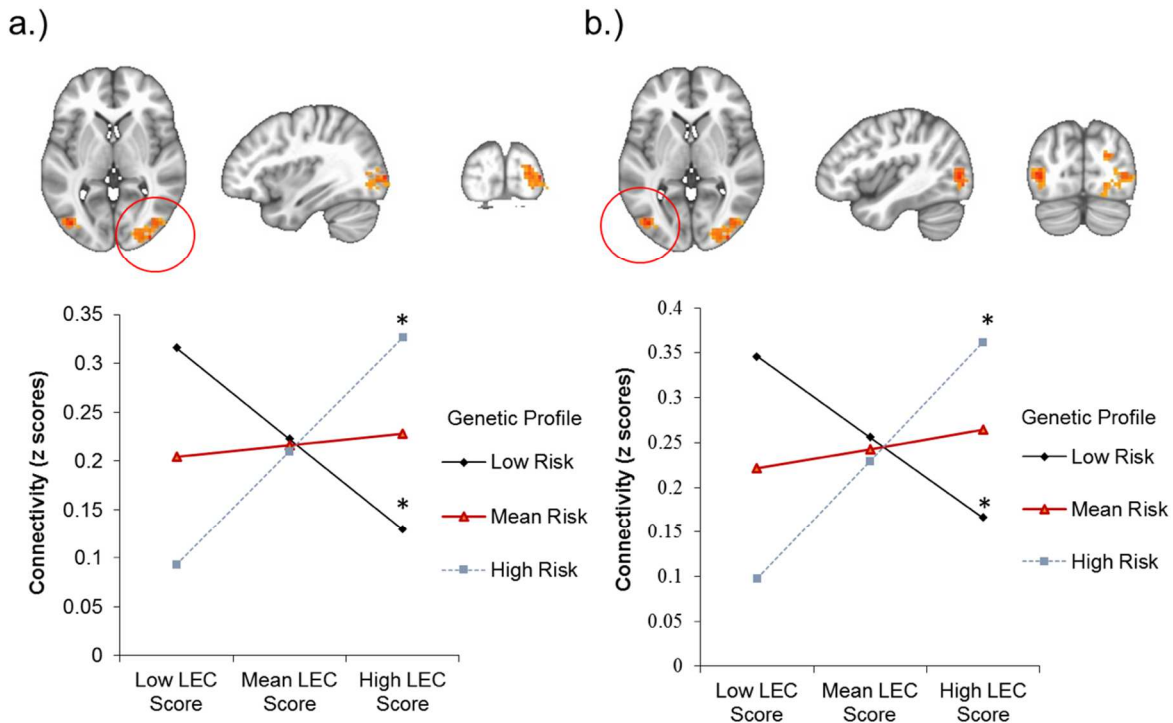


Figure 4. Genetic profile X LEC interaction predicts right amygdala connectivity in women. Women with high genetic risk profiles demonstrated greater right amygdala and bilateral occipital lobe connectivity in the context of high traumatic events. a.) right middle occipital gyrus and associated simple slopes plots. b.) left middle occipital gyrus and associated simple slope plots

In men, I found a main effect of LEC scores in several clusters. Since I have interpreted these findings without genetic covariate, I will not interpret these here. Additionally, I found that the gene profile X number of traumas (LEC score) interaction significantly predicted connectivity between the right amygdala and three clusters in midline occipital lobe in the lingual gyrus that extends bilaterally (BA18, 201 voxels, MNI -2, -96, -8, $t = 5.802$), midline PCC (BA32, 186 voxels, MNI 1, -33, 41, $t = 6.919$), right caudate (BA 48, 66 voxels, MNI 15, 2, 17, $t = 5.208$), and middle frontal gyrus (BA44, 41 voxels, MNI, 50, 19, 24, $t = 5.031$; see Figure

5). Similar to what I found in women, simple slope post hoc tests demonstrated LEC scores were associated with greater connectivity between the right amygdala and midline occipital lobe as well as the PCC, and right caudate in high genetic risk men (lingual gyrus: $t = 2.232, p = 0.034$; PCC; $t = 5.336, p < 0.001$; right caudate: $t = 3.224, p = 0.003$), but weaker connectivity when genetic risk profile was low (lingual gyrus: $t = -8.329, p < .001$; PCC: $t = -9.467, p < 0.001$; right caudate: $t = -5.259, p < .001$). This was also found when genetic risk profiles were at the mean in the lingual gyrus and PCC (lingual gyrus: $t = -4.994, p < 0.001$; PCC: $t = -3.841, p < 0.001$). Right amygdala connectivity with the DLPFC was also negatively associated with trauma in low genetic risk ($t = -6.553, p < .001$) and mean levels of genetic risk ($t = -4.158, p < 0.001$).

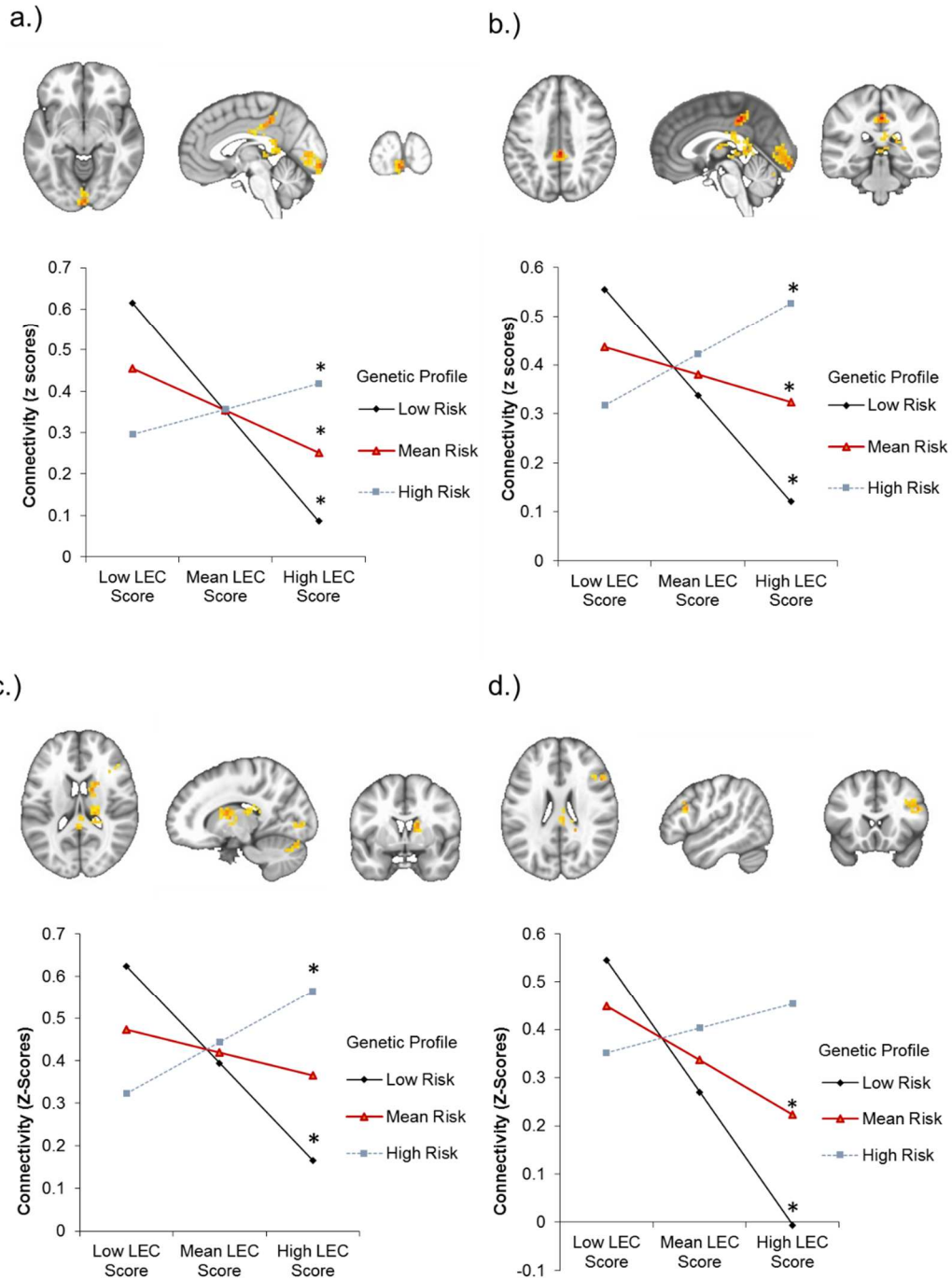


Figure 5. Genetic profile X LEC interaction predicts right amygdala connectivity in men. Effect of genetic profile X LEC interaction on right amygdala connectivity in males and post hoc simple slope plots **a.)** midline occipital lobe **b.)** posterior cingulate cortex **c.)** right caudate **d.)** right middle frontal gyrus

Default Mode Network Imagining Results

Main effects of environment. A whole brain regression with PCC as the seed region was run for each of the environmental predictors (LEC and LES scores) covarying for gender, and the environment-gender interaction to understand the environmental effects on connectivity independent of genetic risk. I did not find either a main effect of LEC or LES scores on PCC connectivity. There were also no effects for women or men when analyzed separately.

FKBP5 risk genotype and stressful life events (LES scores). A whole brain regression with the following predictors, the rs1360780 risk genotype (coded 1 or 0), LES score, genotype X LES score, gender, gender X genotype, and gender X LES score did not reveal any significant main effects of genotype or LES score in predicting PCC connectivity. There was also no significant effect of the genotype-LES interaction on PCC connectivity. There were also no effects for women or men when analyzed separately.

FKBP5 risk genotype and number of traumas (LEC scores). A whole brain regression using the same model as above, but switching stressful events (LES scores) with traumatic lifetime events (LEC scores), predicting PCC connectivity did not reveal any significant main effects of genotype or LEC score. There was also no significant effect of the interaction of genotype and LEC score on PCC connectivity. There were also no effects when looking at women or men separately.

Genetic profile scores and stressful life events (LES scores). A whole brain regression with predictors of genetic profile, LES score, genetic profile X LES score, gender, gender X genetic profile, and gender X LES score predicting PCC connectivity did not reveal any significant main effects of genetic profile or LES score. There was also no significant effect of

the interaction on PCC connectivity. There were also no effects when looking at women or men separately.

Genetic profile scores and number of traumas (LEC scores). A whole brain regression predicting PCC connectivity with the same predictors as above, with LES scores (rather than LEC scores) as the environment factor, did not reveal any significant main effects of genetic profile or LEC score. There was also no significant effect of the genetic profile-LEC score interaction on PCC connectivity. Once again there were also no effects for women or men when analyzed separately.

Salience Network Imaging Results

Main effects of environment. A whole brain regression using right or left insula as the seed region was run for each of the environmental predictors (LEC and LES scores) covarying for gender, to understand the environmental effects on salience network connectivity independent of risk genotypes. I did not find either a main effect of LEC or LES scores on right or left anterior insula connectivity independent of genetic risk. There were also no effects for women or men when analyzed separately.

FKBP5 risk genotype and stressful life events (LES scores). A whole brain regression with predictors, the rs1360780 risk genotype (coded 1 or 0), LES score, genotype X LES Score, gender, gender X genotype, and gender X LES score predicting left or right anterior insula connectivity did not reveal any significant main effects of genotype or LES score. I did not find a significant effect of the genotype-LES interaction on right or left anterior insula connectivity. There were also no effects when looking at women or men separately.

FKBP5 risk genotype and number of traumas (LEC scores). A whole brain regression using the same model as above, but with LEC scores instead of LES scores for environment,

predicting left or right anterior insula connectivity did not reveal any significant main effects of genotype or LEC score. There was also no significant effect of the genotype-LEC interaction on right or left anterior insula connectivity. I found no effect in men or women separately either.

Genetic profile scores and stressful life events (LES scores). A whole brain regression with predictors: genetic profile, LES score, genetic profile X LES Score, gender, gender X genetic profile, and gender X LES score predicting insula connectivity with other brain regions did not reveal any significant main effects of genetic profile or LES score with connectivity of either the left or right insula. I did not find a significant interaction between genetic profile and LES scores on right or left insula connectivity. There were also no effects for women or men when analyzed separately.

Genetic profile scores and number of traumas (LEC scores). A whole brain regression using the same model as above, but with LEC scores instead of LES scores for environment, did not reveal any significant main effects of genetic profile or LEC score in predicting right or left insula connectivity. There was also no significant effect of the genetic profile-LEC interaction on left or right insula connectivity. There were also no effects when looking at women or men separately.

Discussion

The aim of the current project was to examine how genetic risk in genes that regulate the HPA axis interact with lifetime stress and trauma to influence resting state connectivity of functional brain networks, presumably through dysfunction of the HPA axis. First, I examined a well-studied variant of the FKBP5 gene (rs1360780), that has been linked to stress related psychopathology as well as HPA axis dysfunction (Appel et al., 2011; Binder et al., 2008; Binder, 2009; Ising et al., 2008; Mehta & Binder, 2012; Zannas & Binder, 2014; Zimmermann et

al., 2011). Then, I took a multi-loci approach examining increased risk genotypes across four HPA axis genes (Bogdan et al., 2016; Pagliaccio et al., 2014; Pagliaccio et al., 2015). Specifically, the focus was on connectivity of nodes in three key networks relevant for stress-related psychopathology: the emotion regulation network, default mode network, and salience network. Additionally, I examined the influence of both traumatic stressful events, with the Life Events Checklist, as well as past year stressful life events, with the Life Events Scale for students. Additionally, I examined these effects separately in men and women in each network. Interestingly, for FKBP5, I found no main effect of genetic risk and no effect of the interaction with either measure of environmental stress. I did find that greater genetic risk across HPA axis genes interacts with traumatic experiences to predict functional connectivity with the amygdala and visual cortices. These findings have implications for understanding how brain connectivity may mediate relationships between both genetic and environmental risk in the stress system and emotional difficulties which will be discussed below.

FKBP5 and resting state functional connectivity

One of the primary aims of the current investigation was to characterize the relationship between genetic risk in the FKBP5 gene, specifically in the context of environmental stress, and resting state networks. Previous findings have linked FKBP5 rs1360780 to altered HPA axis functioning (Binder et al., 2008; Ising et al., 2008; Velders et al., 2011), attentional bias to threat (Fani et al., 2013) and increased depression (Appel et al., 2011; Binder et al., 2004; Zimmermann et al., 2011) and PTSD risk (Binder et al., 2008) as well as to both structural and functional abnormalities in the brain (Fani et al., 2013; Fani et al., 2014; Fani et al., 2016; M. G. White et al., 2012). Therefore, given the functional significance of FKBP5 genetic variation in the stress system, examining how this variant impacts larger scale brain networks that are

disrupted in stress-related psychopathology may be useful in understanding how this variant moderates risk for depression and anxiety. Contrary to my hypotheses, I found no main effect of the risk carriers or interaction between FKBP5 risk and either of our environmental measures on any of the three functional networks examined. I also did not find any effect of these predictors when examining men and women separately.

Two previously published studies have investigated the FKBP5 risk variant rs1360780 and fMRI resting state functional connectivity. Fani et al. (2016) examined rs1350780 risk homozygotes across women with and without PTSD. They found regardless of group, having two risk alleles was associated with weaker hippocampus-ACC connectivity, indicating possible DMN abnormalities. Another recent study examined the role of several FKBP5 SNPs, including rs1360780, in resting-state connectivity in healthy individuals (Bryant et al., 2016). Examining spectral power, they found individuals with more high-risk alleles demonstrated dysfunction in regions of the salience network. Although, the current study had a larger sample size, I focused on only one well characterized SNP in the FKBP5 gene. It is possible that inclusion of more risk variants of this gene may be more powerful for detecting subtle differences in brain functioning. Neither Bryant et al. (2016), nor the current study found differences in the DMN associated with FKBP5 variants. Together these findings suggest that risk variants of this gene may have little impact on DMN functioning (c.f. Fani et al., 2016). Overall, given the focus on examining relevant stress-related phenotypes of FKBP5 rs136780, our lack of findings add to the current literature, as even in the context of environmental stress, I found no impact of genetic risk on functioning in key networks implicated in internalizing disorders. Given the previous links of rs1360780 to brain structure and function and internalizing disorders (Bogdan et al., 2016; Corral-Frías et al., 2016; Holz et al., 2015; T. White, Andreasen, & Nopoulos, 2002; Zannas &

Binder, 2014), the current findings help us better understand how genetic risk in this variant influences brain functioning by showing that, at least in this sample of emerging adults, rs1360780 was not associated with altered connectivity of key networks that are disrupted in internalizing disorder. Given the mixed findings to date, there is a clear need to further investigate the link between relevant brain networks and this particular SNP, as well as to explore the influence of FKBP5 risk on brain functioning during symptom provocation and/or tasks based scans, within clinical samples (Bryant et al., 2016) and across development.

Genetic risk profiles predict difficulties in emotion regulation

In a more exploratory approach, I aimed to examine how accumulated genetic risk across HPA axis relevant genes interact with stressful and traumatic life events to influence brain connectivity (Pagliaccio et al., 2015). To bolster the use of our genetic profile in predicting functional connectivity in networks associated with internalizing pathology I examined how well the models predicted related traits/symptoms. I found that the genetic profile-LEC score interaction revealed individuals with high genetic risk have difficulties with certain difficulties in emotion regulation in the context of high trauma. This provides us with some preliminary evidence that the current genetic profile interacts with traumatic life events to predict some difficulties in emotion regulation, which is linked to clinical outcomes (Bradley, 2000; Cole, Michel, & Teti, 1994; Gratz & Roemer, 2004; Gross, 1998). This could be related to chronic activation of the stress system, which during acute activation experimentally has been linked with decreased ability to use cognitive resources to regulate emotions (Raio, Orederu, Palazzolo, Shurick, & Phelps, 2013). Surprisingly, the model with LES scores (stressful events) did not predict any symptoms or emotion regulation difficulties. This could be due to the measurement only capturing that past year events. These findings suggest that the genetic profile interacts with

lifetime trauma to disrupt emotion regulation abilities. Therefore, this genetic profile may be most relevant to the emotion regulation network, or amygdala connectivity.

Genetic risk profiles and traumatic events predict amygdala connectivity

I found that variation in genetic risk in genes influencing the HPA axis interacted with experienced traumatic events to predict amygdala connectivity. Specifically, I found that individuals with higher genetic risk had a positive association between traumatic events and right amygdala connectivity with both the left and right occipital lobe. In individuals with low genetic risk, connectivity between these regions was weaker in the context of high trauma exposure. A similar finding was found in left amygdala connectivity with the left middle occipital gyrus. Brain areas involved in visual processing have been reported as hyperactive in response to fearful stimuli in anxious samples (Duval, Javanbakht, & Liberzon, 2015), and previous studies have suggested that greater connectivity between the amygdala and occipital cortices may represent a neural network underlying hypervigilance (Liao, Qiu et al., 2010). Consistent with this idea, connectivity between the amygdala and inferior occipital gyrus has been reported when participants view novel faces (Ousdal, Andreassen, Server, & Jensen, 2014). Greater functional connectivity between these regions has also been reported at rest in childhood anxiety (S. Qin et al., 2014), social anxiety disorder (Liao et al., 2010), and in PTSD under symptom provocation (Gilboa et al., 2004). Interestingly, normative patterns of amygdala-occipital cortex demonstrate negative functional connectivity (Roy et al., 2009) that remains consistent across development (Gabard-Durnam et al., 2014). Therefore, our results suggest that high genetic risk in genes in the HPA axis moderate how fear-related circuitry communicates with visual processing regions when individuals are exposed to traumatic stress. In the context of high traumatic stress, those at

higher genetic risk may have a stronger fear modulation over the visual cortex that is present even at rest.

Contrary to my original hypothesis, I did not find weaker coupling between the amygdala and mPFC. This failure to find an effect of amygdala-mPFC connectivity is consistent with other resting state investigations of trauma-based disorders (Rabinak et al., 2011). However, I did find that weaker connectivity between the right amygdala and other prefrontal regions (i.e. left lateral orbitofrontal and dorsal lateral PFC) was associated with trauma, in men only. This may indicate that cumulative trauma exposure in males is associated with weaker communication between the amygdala and regions implicated in cognitive control and emotion regulation (Banks et al., 2007; Ochsner & Gross, 2005). This is consistent with some previous research finding alteration in emotion regulation regions in trauma exposed youths during an emotion conflict task (Marusak, Martin, Etkin, & Thomason, 2015), but further research may highlight why I found a different relationship in men and women.

I also found different patterns of right amygdala connectivity associated with the genetic profile-trauma interaction in analyses conducted separately for men and women. Both genders showed the whole group pattern of greater right amygdala-occipital cortex connectivity in the context of high traumatic stress and high genetic risk, with men demonstrating this in more medial regions of the occipital cortex and women in more lateral. Additionally, men showed significant clusters of amygdala connectivity with the PCC, right caudate, and right middle frontal gyrus. These regions are similar to Pagliaccio et al. (2015) who found HPA gene-environment interactions influences on left amygdala connectivity with the left caudate tail as well as middle frontal gyrus. I found in men with higher genetic risk, trauma was associated with greater positive functional connectivity between the right amygdala and right caudate, but

weaker functional connectivity between these regions in the context of low genetic risk. However, Pagliaccio et al. (2015) reported the opposite pattern across their sample, which was not exclusively male. Additionally, our pattern of findings in men in the middle frontal gyrus were also different to Pagliaccio et al. (2015) with individuals with low genetic risk demonstrating weaker positive amygdala middle frontal gyrus connectivity in the context of stress. They found this group had greater negative connectivity and the reverse for those with high genetic risk. The differences here may reflect developmental differences in our samples; however, normative connectivity between the amygdala and the lateral PFC is a negative relationship in both adults (Roy et al., 2009) and children (Pagliaccio et al., 2015) at rest. During reappraisal, however, these two regions demonstrate increased coactivation (Banks et al., 2007). Therefore, it is possible that those with low genetic HPA axis risk demonstrate changes in this network in the context of trauma, whereas there is little influence in those with high genetic risk. Interestingly, these patterns of results were not seen in women, which is not surprising given literature highlighting different HPA functioning (see Kudielka & Kirschbaum, 2005) and neural functioning (Wang et al., 2007) in men and women in response to acute stress. Although the current findings examining men and women should be taken as exploratory given they were post-hoc and I did not examine a three-way gender-stress-gene interaction in order to preserve power for the group analyses, these findings signify the need for future research to examine gender-specific responses to stress and trauma.

Importantly, our overall group findings do not replicate Pagliaccio and colleagues (2015), who also examined HPA genetic risk and environmental stress influences on amygdala connectivity. This is not unexpected as they studied a sample of school-aged children, and given developmental changes in connectivity of the amygdala (Gabard-Durnam et al., 2014), genetic

and environmental influences on connectivity may change through development. Additionally, they included more SNPs in their profile, and therefore, likely had a greater range of genetic risk in their sample. Finally, they combined lifetime stressful life events with traumatic events and created a summed score, whereas I examined separate measurements of traumatic stress and stressful life events. Importantly, our results are consistent in demonstrating high genetic risk and high environmental stress (specifically traumatic) are associated with alterations in amygdala connectivity, which may have functional consequences in the threat-detection system.

Genetic risk profiles and stress did not predict default mode network connectivity

I did not find evidence that traumatic events or lifetime stress interacted with genetic risk profiles to predict altered functional connectivity within the DMN. To my knowledge, Bryant et al. (2016) and Fani et al. (2016) are the only other published studies that have examined genetic variation in genes influencing the HPA axis and the DMN. My predictions were based on the well-documented functional abnormalities in DMN in anxiety (Peterson et al., 2014; L. Qin et al., 2012; Sylvester et al., 2012) and depressive disorders (Belleau et al., 2015; Berman et al., 2011; Sheline et al., 2009), disorders which are also associated with stressful life events and dysfunctional HPA axis functioning (G. E. Miller et al., 2007), as well as research suggesting DMN activity is influenced by genetics (Fu et al., 2015; Glahn et al., 2010; Korgaonkar, Ram, Williams, Gatt, & Grieve, 2014). The DMN has been linked to some of the more cognitive aspects of internalizing disorders, such as worry (Servaas et al., 2014) and rumination (Berman et al., 2011). It is possible that given our findings demonstrating greater connectivity in hypervigilance networks, that HPA axis genetic influences and interactions with stress have less influence on networks underlying more cognitive symptoms of internalizing disorders, and may be linked to different neurobiological systems. For instance, previous research has linked a main

effect of variation in the serotonin transporter linked polymorphic region (5-HTTLPR) to alterations in DMN in children and adolescents (Wiggins et al., 2012). Polymorphisms in the dopamine D2 receptor gene have also been linked to alterations in DMN during cognitive tasks, possibility implicating dopamine systems (Sambataro et al., 2013). Additionally, the MAOA genotype was associated with differences in DMN functional connectivity, with those with the high activity genotype demonstrating increased connectivity (Clemens et al., 2015; Fu et al., 2015). Interestingly, Sripada et al. (2014) did find adults who have experienced greater childhood adversity demonstrated decreased DMN connectivity that was linked with higher cortisol levels, indicating that stressful environments and HPA dysregulation may be linked to DMN connectivity, but possibly through moderating effects of genes involved in systems other than the HPA axis. For instance, genetic variation in genes influencing the serotonin system, 5-HTTLPR, has also been associated with HPA axis reactivity (Gotlib, Joormann, Minor, & Hallmayer, 2008). I also did not find any main effects or interaction of genetic profile or environmental stress (trauma or stressful events) in men or women separately in the DMN. However, given the smaller sample size (men = 32), these subgroup analyses may not have been powered well enough to detect significant effects, particularly for men. The current findings are one of two studies to examine HPA genetic influences on DMN connectivity and offer some understanding to how genetic risk in this system influences functioning in this network.

Genetic risk profiles and stress did not predict salience network connectivity

I also predicted alterations within the salience network in the context of high genetic risk in the HPA axis system as well as environmental stress. There were no main effects of either environmental scores (LEC or LES scores) or genetic profiles and no significant effect of the interaction. The salience network is responsible for switching between the DMN and CEN, and

is thought to be disrupted in depressive disorders (Manoliu et al., 2013), and PTSD (Sripada et al., 2012). Similar to the DMN, cortisol reactivity has been linked to differential functioning in the salience network (Thomason et al., 2011), but our lack of findings in the salience network may indicate that genetic risk in genes influencing the HPA axis does not necessarily influence connectivity in this network. 5-HTTLPR risk allele carriers have demonstrated abnormalities in regions of the SN when viewing threat cues (Klumpers et al., 2015), and therefore, it is possible that other genetic factors are involved in the dysregulation of this brain network in internalizing disorders that interact with HPA axis functioning. As mentioned above, one study examining FKBP5 risk alleles found dysfunction in this network (Bryant et al., 2016), but I found neither FKBP5 risk or our genetic profile (which includes FKBP) had any impact on neural functioning in this network on its own, or in the context of high environmental stress.

Developmental Considerations

Importantly, our sample primarily focused on emerging adults, a critical period in development. Specifically, emerging adulthood is characterized as a period where cognitive functioning associated with the prefrontal cortex and other structures begin to mature (Gogtay et al., 2004). Although the transition into this developmental period is thought to be a sensitive period for the development of psychopathology, much less literature has focused on stress in this age range (Schulenberg, Sameroff, & Cicchetti, 2004). This is particularly relevant in the examination of HPA axis related genes, in which much of the literature has focused on the gene-environment interactions with either childhood or adult-related stress. To date much of this work has suggested that these gene-environment influences on phenotypes may be limited to early experiences (Binder et al., 2008; Hornung & Heim, 2014), although, some studies have found similar gene interactions with stress included stress during later developmental periods, closer to

the age range of our sample (Lessard & Holman, 2014; Zimmermann et al., 2011). Importantly, our traumatic experiences measure did not allow us to determine when in development these experiences have occurred, but I was able to show a unique pattern of amygdala dysfunction associated with trauma and HPA genetic risk in emerging adults, not detected in a similar study examining these influences in children (Pagliaccio et al., 2015). In addition to changes in the prefrontal cortex, the amygdala undergoes developmental changes in connectivity from childhood to adulthood (Gabard-Durnam et al., 2014; Gee et al., 2013), and it is possible that stressful experiences in this period may result in different alterations in connectivity from what is seen in children (Pagliaccio et al., 2015) or that gene and environment influences over the HPA axis are linked to different amygdala connectivity patterns later in development. Longitudinal studies of brain functioning examining factors related to the HPA axis will help clarify some of these questions.

Limitations

Candidate gene studies have several limitations such as the risk of producing a higher rate of false positives and difficulty replicating findings (Dunn et al., 2015). Given these limitations, I focused the primary aim on a well characterized SNP in the FKBP5 gene, which has good support for the relationship to HPA axis dysfunction (Zannas & Binder, 2014). Additionally, other SNPs included in the genetic profile were selected due to their previous associations with cortisol dysfunction and/or psychopathology (see Pagliaccio et al, 2014). Importantly, none of the current genes have been linked to any genome-wide association studies (GWAS) of depression or anxiety. Unfortunately, GWAS studies of internalizing pathology have not yet produced robust or replicable findings (Banerjee, Morrison, & Ressler, 2017; Dunn et al., 2015; Ripke et al., 2013), which could be due to the heterogeneity of such disorders and failure to

consider more precisely defined phenotypes. Additionally, many of these GWAS have not considered environmental interaction effects (Dunn et al., 2015). As discussed above, there is a strong relationship between internalizing disorders and environmental stress, and genetic effects are often detected only in the context of an environmental interaction (Dunn et al., 2015). One GWAS study of stress examined interactions of stress by matching on stress exposure, and they did not find any significant associated SNPs (Power et al., 2013). Therefore, I acknowledge the lack of GWAS studies to support the use of these candidate genes is a limitation to the current study, highlighting the need for replication of the current findings.

While there are some notable strengths of using polygenetic scores, the equal weighting of risk genotypes, may not truly reflect the contribution of each genotype to HPA axis variation (Bogdan et al., 2016; Pagliaccio et al., 2014). Also, there may be limitations in the range of the genetic profile used. I limited the number of SNPs used in the genetic profile to included only SNPs previously used in a multi-loci approach (Pagliaccio et al., 2014; Pagliaccio et al., 2015), which resulted in a smaller range of genetic profiles. However, this approach allowed us to look at the effect of increasing genetic risk and to keep our environmental variables continuous rather than categorizing them into high or low stress.

Another limitation is the small sample size of males. The findings within this group should be taken with caution, as there is a higher risk for false positives. Also, results may not be generalizable to other non-Caucasian ethnicities, for the risk allele may be different in other groups. Several studies have found similar associations of the risk alleles studied in the present study to cortisol reactive and risk for psychopathology in other populations (e.g. Binder et al., 2008; Fujii et al., 2014) but the current imaging findings may not be generalizable. I also did not have a measure of HPA axis activity through measurements of cortisol, which would have

allowed us to detect if our genetic profile does indeed predict increasing risk of HPA axis dysfunction. Importantly, I carefully selected SNPs from studies with such measures of cortisol (Pagliaccio et al., 2014; Pagliaccio et al., 2015). Finally, I did not exclude for various psychiatric disorders including substance abuse or the use of psychotropic medications which may introduce confounding factors. I also included individuals with substance use disorders, but did not include a comprehensive assessment of current substance use, which can impact brain functioning during development (Lisdahl, Gilbert, Wright, & Shollenbarger, 2013).

Conclusions

The current study explored the impact of variation in genes that influence the HPA axis and stressful life events and trauma on resting state networks that are disrupted in internalizing disorders. In my primary aims focusing on the role of a well characterized SNP in the FKBP5 gene, I did not find any main genetic effects or interactions with the environment. Exploratory aims examining the impact of greater genetic risk across several HPA axis genes did reveal hyperconnectivity between fear and visual regions in the context of high genetic risk and more traumatic events, which may represent a neural circuitry related to hypervigilance. Therefore, cumulative genetic risk in the HPA axis may interact with traumatic experiences to disrupt neural connectivity in emerging adults, which may help inform how individual risk to the stress system impacts brain functioning in networks relevant for the excessive vigilance observed in many internalizing disorders.

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resting-state functional connectivity in children and adolescents: A preliminary report. *NeuroImage*, 59(3), 2760-2770.

Yuen, G. S., Gunning-Dixon, F. M., Hoptman, M. J., AbdelMalak, B., McGovern, A. R., Seirup, J. K., & Alexopoulos, G. S. (2014). The salience network in the apathy of late-life depression. *International Journal of Geriatric Psychiatry*, 29(11), 1116-1124.

Zannas, A., & Binder, E. (2014). Gene–environment interactions at the FKBP5 locus: Sensitive periods, mechanisms and pleiotropism. *Genes, Brain and Behavior*, 13(1), 25-37.

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Zimmermann, P., Brückl, T., Nocon, A., Pfister, H., Binder, E. B., Uhr, M., . . . Holsboer, F. (2011). Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: Results from a 10-year prospective community study. *American Journal of Psychiatry*, 168(10), 1107-1116.

Tara Ann Miskovich

Curriculum Vitae

EDUCATION

Veterans Affairs Northern California Health Care System Clinical Psychology Internship (APA accredited)	present
Expected Ph.D., University of Wisconsin, Milwaukee Clinical Psychology GPA: 4.0	present
M.S., University of Wisconsin, Milwaukee Clinical Psychology GPA: 4.0	2014
B.A., University of California, Davis Psychology GPA: 3.97	2010

AWARDS

American Psychological Association Dissertation Research Award (\$1,000) (2017)
University of Wisconsin-Milwaukee Travel Grant (2017)
University of Wisconsin-Milwaukee Travel Grant (2016)
University of Wisconsin-Milwaukee Department of Psychology Summer Research Fellowship (\$3,178) (2015)
Dean's Honor List at University of California, Davis (2007-2010)
Begley Merit Scholarship (\$8,000) (2006-2007)

PUBLICATIONS

- Stout, D. M., Shackman, A. J., Pedersen, W. S., **Miskovich, T. A.**, & Larson, C. L. (2017). Neural circuitry governing anxious individuals' mis-allocation of working memory to threat. *Scientific Reports*, 7(1), 8742.
- Pedersen, W. S., Balderston, N. L., **Miskovich, T. A.**, Belleau, E. L., Schultz, D. H., Helmstetter, F. J., & Larson, C. L. (2016). Disentangling the effects of stimulus novelty and affective valence in the amygdala, hippocampus, and bed nucleus of the stria terminalis. *Social, Cognitive and Affective Neuroscience*.
- Miskovich, T.A.** Pedersen, W.P., Belleau, E.L., Shollenbarger, S., Lisdahl K.M., Larson, C.L. (2016). Cortical gyrification patterns associated with trait anxiety. *PLoS ONE*.

Fisher, M., Loewy, R., Carter, C., Lee, A., Ragland, J. D., Niendam, T., Schlosser, D., Pham, L., **Miskovich, T.**, & Vinogradov, S. (2014). Neuroplasticity-based auditory training via laptop computer improves cognition in young individuals with recent onset schizophrenia. *Schizophrenia Bulletin*, sbt232.

PUBLICATIONS UNDER REVIEW

Miskovich, T.A., Anderson, N.E., Harenski, C.L, Harenski, K.A., Baskin-Sommers, A.R., Larson, C.L., Newman, J.P., Hanson, J.L., Stout, D.M., Koenigs, M., Shollenbarger, S.G., Lisdahl, K.M., & Kiehl, K.A. (revise and resubmit). Abnormal cortical gyrification in criminal psychopathy.

Belleau, E.L., Pedersen, W.S., **Miskovich, T.A.**, Helmstetter, F.J., & Larson, C.L. (revise and resubmit). Fear extinction-related neural plasticity in cortico-limbic pathways and relationships with trait anxiety.

Miskovich, T.A., Stout, D.M., Bennet, K., & Larson, C.L. (under review). Reward distracters and working memory performance.

PUBLICATIONS IN PREPARATION

Miskovich, T.A., Stout, D.M., Wild, A., & Larson, C.L. (in prep). Proactive control is impaired under threat of unpredictable shock.

Stout, D.M., **Miskovich, T.A.**, Sheppes, G., Luria, R., Shackman, A.J., & Larson, C.L. (in prep). Recovering from attention capture by threat is associated with sustained frontal activity neurophysiological evidence for the failure of attention to recover from threat

REVIEWED POSTERS AND PRESENTATIONS

Miskovich, T.A., Belleau, E.L, Pedersen, W.S., Larson, C.L. (2017). HPA axis genetic variation and lifetime trauma influences amygdala functional connectivity at rest. Presented at the annual meeting of the International Society for Traumatic Stress Studies, Chicago, IL. Student poster award finalist.

Hanson, J., Miskovich, T., deRoos-Cassini., Larson, C. (2017). Amygdala and visual cortex activations during trauma script and recall are associated with perceived life threat in the acute aftermath of a traumatic event. Presented at the annual meeting of the International Society for Traumatic Stress Studies, Chicago, IL.

Harvey, A. M., Yaroch, M. R., Pendleton, A. M., Huggins, A. A., **Miskovich, T. A.**, Larson, C. L., & Lee, H. (2017). The association between response inhibition and skin-picking symptoms. Presented at the annual meeting of the Association for Behavioral and Cognitive Therapies, San Diego, CA.

- Huggins, A.A., Belleau, E.L., **Miskovich, T.A.**, & Larson, C.L. (2017) Altered functional connectivity between right insular cortex and default mode regions associated with perceived stress and anxiety during undergraduate students' finals week. Presented at the Society of Biological Psychiatry Annual Meeting, San Diego, CA.
- Belleau, E.L., Pedersen W.S., **Miskovich, T.A.**, Helmstetter, F.J., Larson, C.L. (2017) Fear extinction-related neural plasticity in cortico-limbic pathways and relationships with trait anxiety. Presented at the annual meeting of the Anxiety and Depression Association of America, San Francisco, CA.
- Miskovich, T.A.**, Bennett, K., Stout, D.M., Larson, C.L. (2017) Impaired proactive control under threat of shock. Presented at the annual meeting of the Cognitive Neuroscience Society, San Francisco, CA.
- Miskovich, T.A.**, Stout, D.M., Wild, A., Larson, C.L. (2016) Proactive maintenance under threat of shock in the AX-CPT. Presented at the annual meeting of the Society for Psychophysiology Research, Minneapolis, MN.
- Pedersen, W., Balderston, N., **Miskovich, T.A.**, Belleau, E.L., Helmstetter, F., & Larson, C.L. (2016) Disentangling the effects of stimulus novelty and affective valence in the amygdala, hippocampus, and bed nucleus of the stria terminalis. Presented at the annual meeting of the Society for Psychophysiology Research, Minneapolis, MN.
- Miskovich, T.A.**, Bennett, K., Stout, D.M., & Larson, C.L. (2015) Reward distracters and working memory filtering. Presented at the annual meeting of the Cognitive Neuroscience Society, New York, NY.
- Miskovich, T.A.**, Hanson, J.L., Newman, J.P., Baskin-Sommers, A.R., Koenigs, M.R., Stout, D.M., Balderson, N.L., Kiehl, K.A., & Larson, C.L. (2014). Abnormal gyrification patterns in incarcerated males with psychopathy. Symposium presented at the 17th annual Association of Graduate Students in Psychology Symposium, Milwaukee, WI
- Miskovich, T.A.**, Hanson, J.L., Newman, J.P., Baskin-Sommers, A.R., Koenigs, M.R., Stout, D.M., Balderson, N.L., Kiehl, K.A., & Larson, C.L. (2014). Abnormal gyrification and white matter integrity in psychopathy. Presented at the annual meeting of the Society for Research in Psychopathology, Chicago, IL.
- Miskovich T.A.**, Pederson W.S., Belleau E.L., & Larson, C.L. (2014). Decreased cortical gyrification associated with trait anxiety. Presented at The Society of Affective Science Inaugural Conference, Bethesda, MD.
- Stout, D.M., Shackman, A.J., **Miskovich, T.A.**, & Larson, C.L. (2014). Unnecessary storage of threat in working memory: a proximal mechanism underlying anxiety and worry. Presented at The Society of Affective Science Inaugural Conference, Bethesda, MD.

- Pederson, W.S., Balderson, N.L., **Miskovich, T.A.**, Belleau, E.L., Schultz, D.H., Helmstetter, F.J., Larson, C.L. (2014). Independent effects of novelty and valence on the amygdala BOLD response. Presented at The Society of Affective Science Inaugural Conference, Bethesda, MD.
- Stout, D.M., Shackman, A.J., **Miskovich, T.**, & Larson, C.L. (2013). Neural measures of the access of threat to working memory in anxiety. Symposium presentation at the annual meeting of the Society for Psychophysiological Research, October 2-6, Florence, Italy.
- Fulford, D., Niendam, T., Floyd, E., **Miskovich, T.**, Carter, C., Mathalon, D., Vinogradov, S., & Loewy, R. (2012) Symptom dimensions in early psychosis: examining the unique contributions of depression and anxiety on functional outcomes. Presented at the 2012 International Early Psychosis Association, San Francisco, CA.
- Carter, C.S., Luck, S.J., Ragland, J.D., Ranganath, C., Swaab, T., Boudwyn, M., Lesh, T., **Miskovich, T.**, Kring, A. (2012) Domain general cognitive control deficits and prefrontal deficits in schizophrenia. Presented at the 2012 Annual Meeting of the Organization for Human Brain Mapping, Beijing, China.
- Niendam, T.A., Lesh, T.A., **Miskovich, T.**, Solomon, M., Ragland, J.D., Yoon, J., Minzenberg, M. & Carter, C.S. (2012) Association between age-at-onset and context processing in first episode schizophrenia. Presented at the 2012 Society of Biological Psychiatry Annual Meeting, Philadelphia, PA.

RESEARCH EXPERIENCE

Graduate Research Assistant

2012-Present

Affective Neuroscience Laboratory
 University of Wisconsin-Milwaukee
 Supervisor: Christine Larson, Ph.D.

- Responsible for recruitment, collection, processing, and analyzing of data for a fMRI and genetics study looking at the neural deficit in extinction of conditioned fear in individuals high in trait negative affect and examining the degree to which this deficit is modulated by genetic differences.
- Conducted independent ERP and behavioral studies examining cognitive control and attention filtering in the face of emotional distraction.
- Collaborating on an fMRI study examining the impact of inhibition cognitive training on neural networks in individuals with OCD symptoms.
- Research assistant for an NIMH-supported R01 using fMRI to examine affective and cognitive processing in individuals who have recently experienced a traumatic injury in order to assess neural predictors of PTSD.
- Successfully defended dissertation project that focuses on HPA axis candidate gene x environment influences on large-scale cognitive networks using fMRI.

- Skills: fMRI analysis using FSL, AFNI; structural MRI analysis with FreeSurfer; event-related potential analysis using EEGLAB, ERPLAB; experimental design with EPRIME; advanced statistical analysis with SPSS and SAS.

Graduate Research Assistant

2015-2017

Medical College of Wisconsin Trauma Surgery Department
Supervisor: Terri deRoon-Cassini, Ph.D.

- Recruitment participants and conduct psychodiagnostic assessments and symptom inventories for the Study on Trauma and Reliance (STAR).
- Assessments administered: The Clinically Administered PTSD Scale (CAPS), PTSD Checklist for DSM-5.

Junior Specialist/ Research Coordinator

2010-2012

Translational Cognitive and Affective Neuroscience Laboratory
University of California, Davis
Supervisor: Cameron Carter, M.D., J. Daniel Ragland, Ph.D.

- Study coordinator for a multi-site, multi-dimensional study investigating deficits in memory, attention, language, emotion, and cognitive control in schizophrenia. Responsible for recruitment, collection and analysis of neuroimaging data.
- Study site coordinator for “The Randomized Clinical Trial of Intensive Computer-Based Cognitive Remediation in Recent-Onset Schizophrenia”, a multi-site longitudinal study examining the effectiveness of computer-based cognitive training in patients with schizophrenia. Responsible for recruitment, conducting assessments, and managing site databases.

Research Assistant

2010

Dr. Simonton’s Lab of Creativity, Emotions, and Motivation
University of California, Davis
Supervisors: Dean Simonton, Ph.D., Rodica Damian, Ph.D.

- Ran subjects on computer based behavioral assessments, reliably entered assessment data, conducted research for future studies, and participated in constructive lab meetings.

PEER-REVIEW EXPERIENCES

Ad-hoc reviewer for *Cognition and Emotion* and *Cognitive, Affective, and Behavioral Neuroscience*

SPECIALIZED TRAINING

Cognitive Processing Therapy Rollout Training, Palo Alto, CA
Event-Related Potential Mini Bootcamp, Minneapolis, MN
Neuroimaging Journal Club, Milwaukee, WI

Analysis of Functional NeuroImages (AFNI) Bootcamp, Bethesda, MD
Introduction to Pattern Classification Analysis in fMRI with FSL, Milwaukee, WI
Functional Neuroimaging for SPM, Davis, CA
Responsible Conduct in Research, Wisconsin, WI
Symptom Inventories in Schizophrenia (BPRS, SAPS, SANS), Davis, CA

TEACHING EXPERIENCE

Teaching assistant for multiple sections of lower and upper division Personality Theory course. Duties included lesson planning for smaller discussion sessions, leading study sessions, and grading.

PROFESSIONAL AFFILIATIONS

Sigma Xi	2013-Present
Society of Affective Neuroscience	2013-Present
Cognitive Neuroscience Society	2015-Present
Society for Research in Psychopathology	2014-Present
American Psychological Association	2014-Present
American Psychological Association Division 56	2016-Present
American Psychological Association of Graduate Students	2014-Present
Society for Psychophysiological Research	2016-Present

LEADERSHIP AND SERVICE

Vice President of the Association of Graduate Student in Psychology at UW-Milwaukee (2014-2015)
Graduate Student Representative for the Future Success Program (2015)