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Genetic Influences on the Neural and Physiological Bases of Acute Threat: A Research Domain Criteria (RDoC) Perspective

Jennifer A. Sumner[1,2], **Abigail Powers**[3], **Tanja Jovanovic**[3], and **Karestan C. Koenen**[2,4,5]

[1]Center for Behavioral Cardiovascular Health, Columbia University Medical Center, New York, NY

[2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[3]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA

[4]Psychiatric and Neurodevelopmental Genetics Unit and Department of Psychiatry, Massachusetts General Hospital, Boston, MA

[5]The Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, Cambridge, MA

Abstract

The NIMH Research Domain Criteria (RDoC) initiative aims to describe key dimensional constructs underlying mental function across multiple units of analysis—from genes to observable behaviors—in order to better understand psychopathology. The acute threat ("fear") construct of the RDoC Negative Valence System has been studied extensively from a translational perspective, and is highly pertinent to numerous psychiatric conditions, including anxiety and trauma-related disorders. We examined genetic contributions to the construct of acute threat at two units of analysis within the RDoC framework: 1) neural circuits and 2) physiology. Specifically, we focused on genetic influences on activation patterns of frontolimbic neural circuitry and on startle, skin conductance, and heart rate responses. Research on the heritability of activation in threat-related frontolimbic neural circuitry is lacking, but physiological indicators of acute threat have been found to be moderately heritable (35-50%). Genetic studies of the neural circuitry and physiology of acute threat have almost exclusively relied on the candidate gene method and, as in the broader psychiatric genetics literature, most findings have failed to replicate. The most robust support has been demonstrated for associations between variation in the serotonin transporter (*SLC6A4*) and catechol-O-methyltransferase (*COMT*) genes with threat-related neural activation and physiological responses. However, unbiased genome-wide approaches using very large samples are needed for gene discovery, and these can be accomplished with collaborative consortium-based research efforts, such as those of the Psychiatric Genomics Consortium (PGC) and Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium.

Correspondence to: Jennifer Sumner, Center for Behavioral Cardiovascular Health, Columbia University Medical Center, 622 W. 168th St, PH 9-319, New York, NY 10032. Tel.: 212-342-5503; Fax: 212-342-3431; js4456@cumc.columbia.edu.

Keywords

RDoC; acute threat; genetics; neural circuit; physiology

Psychiatric disorders are heritable (Kendler and Eaves, 2005), and studying their genetic basis has the potential to increase our understanding of risk for these conditions and inform intervention efforts. Over the years, the literature on the genetics of psychiatric syndromes has grown dramatically, particularly within the past decade (see Sullivan et al., 2012, for a review). Although replicable genetic findings have been detected for schizophrenia and bipolar disorder (e.g., Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), mapping the complex genetic architecture of psychiatric conditions is far from complete. Additional research is needed, and there have been calls for developing approaches that go beyond examining psychiatric diagnoses as defined by the current nosology in order to facilitate discovery of genetic mechanisms of psychiatric risk (e.g., Meyer-Lindenberg and Weinberger, 2006).

The Research Domain Criteria (RDoC) Project

The Research Domain Criteria (RDoC) project, spearheaded by the National Institute of Mental Health (NIMH), represents one such alternative approach. The RDoC research framework postulates that psychiatric conditions are disorders of brain circuits, and it emphasizes the study of neurobiological mechanisms that cut across psychiatric disorders as defined by current diagnostic classification systems (Morris and Cuthbert, 2012). With the RDoC approach, psychopathology is classified based on underlying dimensions of function that can be defined at multiple units of analysis, ranging from genes to molecules to neural circuits to physiology to observable behaviors (Cuthbert and Insel, 2013). These dimensions (or constructs) are grouped into major domains of functioning that reflect key aspects of motivation, cognition, and social behavior (e.g., Negative Valence Systems, Cognitive Systems). One of the ultimate goals of the RDoC initiative is to use the neurobiological data that characterize these dimensions to develop “biosignatures” of psychopathology that can then be utilized to guide clinical interventions (Morris and Cuthbert, 2012).

By focusing on the identification and characterization of neurobiological intermediate phenotypes that underlie psychiatric syndromes, the RDoC framework has promise for furthering our understanding of the genetic basis of psychopathology. Psychiatric disorders are complex phenotypes that are influenced by the contributions of multiple genetic variants of small effects (Sullivan et al., 2012). The effects of genes are not expressed directly at the level of the behavioral manifestations of psychiatric syndromes (Fisher et al., 2008), which limits the detection of associations with risk variants. In contrast, neurobiological intermediate phenotypes are proposed to lie closer to the underlying genetic architecture than more distal clinical outcomes, and thus it may be easier to identify links between genetic loci and intermediate phenotypes due to higher penetrance (Meyer-Lindenberg and Weinberger, 2006). Nevertheless, effect sizes observed for individual single nucleotide polymorphisms (SNPs) on intermediate phenotypes are likely to be modest (e.g., Stein et al., 2012) and still require large sample sizes to be adequately powered. In addition, researchers

have postulated that intermediate phenotypes should be observable in genetically vulnerable individuals who do not exhibit the symptoms of a psychiatric disorder (Meyer-Lindenberg and Weinberger, 2006). Studying genetic influences on quantitative traits that are related to clinical phenotypes and index underlying biological processes more directly than disorders thus has potential for mapping the genetic architecture of psychopathology.

Aims of the Review

Although the RDoC project is a relatively recent initiative that aims to guide future research efforts, a number of findings in the extant literature can be organized in terms of this framework. As noted above, RDoC emphasizes several systems, which comprise different constructs. The acute threat ("fear") construct of the Negative Valence System has been studied extensively from a translational perspective, with research conducted in both animals and humans. Not only is the acute threat construct highly pertinent to numerous psychiatric conditions, including various anxiety and trauma-related disorders, but it is also directly relevant to exposure therapy, the most effective treatment at present for fear and anxiety (Briscione et al., 2014; Institute of Medicine, 2008). Therefore, studying acute threat has the potential to impact understanding of various manifestations of psychopathology and inform clinical applications.

In this review, we focus on genetic contributions to the construct of acute threat at two units of analysis of the RDoC framework: 1) neural circuits and 2) physiology. First, we introduce relevant paradigms for the study of acute threat. Next, we summarize findings on the heritability of and molecular genetic influences on the neural and physiological bases of acute threat, focusing on findings from functional neuroimaging and physiology studies in humans. Finally, we make recommendations for future studies in order to address gaps in the extant literature, and we link the existing research base to the goals of the RDoC initiative.

The literatures on the neural and physiological bases of acute threat are closely related, and much research on the physiology of acute threat has focused on understanding how it aligns with underlying neural circuitry. Furthermore, neural and physiological indicators of acute threat have been shown to have substantial inter-individual variability (Baas, 2013), thereby permitting investigations along the entire range of these quantitative measures. Thus, studying genetic influences on the neural circuits and physiology of acute threat offers a prime opportunity for conducting a cross-cutting examination of dimensions of threat responses that can help to shed light on biological mechanisms of risk for and resilience to mental illness.

In the current paper, we survey papers on genetic influences on the neural and physiological underpinnings of acute threat that were published between 1995 and December 31, 2014. The following keywords were used in our literature search: *genetics* - *fear* - *physiology* - *circuits* - *neural* - *brain* - *conditioning* - *extinction*. Several relevant reviews on this topic have been published in recent years (e.g., Lonsdorf and Kalisch, 2011; Murphy et al., 2013). Although the current paper is comprehensive, it is not an exhaustive review, and we refer the reader to those papers for additional coverage of this topic. As described below, and

summarized in Table I, the vast majority of studies have examined biologically plausible candidate genetic variants that are thought to have neurochemical effects on the acute threat system or that have been associated with psychiatric disorders characterized by acute threat. Furthermore, consistent with the notion that intermediate phenotypes should be observable in genetically vulnerable individuals who do not exhibit the symptoms of a psychiatric disorder (Meyer-Lindenberg and Weinberger, 2006), almost all investigations have been conducted in individuals without a history of psychopathology (some exceptions are noted, however). Although the studies reviewed differ in the samples, genetic variants, and paradigms examined, they are united by the common goal of identifying the biological intermediates that translate genetic risk into behavior.

Paradigms for the Study of Acute Threat

The acute threat construct has been investigated predominantly in the context of two particular scientific paradigms: 1) fear conditioning paradigms and 2) aversive picture processing paradigms. Fear conditioning paradigms are based on the principles of Pavlovian conditioning (Maren, 2001; Pavlov, 1927). Specifically, they involve the pairing of a neutral stimulus with an aversive unconditioned stimulus (US). With repeated pairings, the neutral stimulus elicits the same type of response as the US and becomes a conditioned stimulus (CS). The response evoked by the CS is termed the fear-conditioned response (CR), whereas the response evoked by the US is the unconditioned response (UR). Fear conditioning paradigms permit the study of several threat-related processes, including fear acquisition, fear inhibition, fear generalization, and fear extinction. Fear acquisition refers to the extent to which levels of fear responding to the CS are greater than those during baseline or inter-trial intervals (Lissek et al., 2005). Simple conditioning paradigms traditionally employ only one CS. In contrast, differential fear conditioning paradigms generally use two CSs: the CS+ is paired with the US and functions as a “danger signal,” whereas the CS- is not paired with the US and is a “safety signal” (Lissek et al., 2005). Comparing the CRs in response to the CS+ vs. the CS- permits an examination of whether individuals can discriminate between predictors of danger and safety. Fear inhibition is thought to occur when a fear response is suppressed in the context of safety cues (Lissek et al., 2005). Inhibition can be assessed by examining discrimination to the CS+ vs. CS- or by presenting the CS+ in conjunction with a neutral, safe stimulus. A recent meta-analysis of fear in anxiety disorders reported that heightened fear responses to safety cues is a robust finding in these patients (Duits et al., 2015). Fear generalization refers to when stimuli that are similar to the CS+ also come to elicit the CR (Lissek et al., 2010; Norrholm et al., 2014). Fear extinction represents new learning that occurs when a previously reinforced CS+ is presented repeatedly without the US. This new extinction learning is thought to co-exist with the original fear memory (Sotres-Bayon and Quirk, 2010). High levels of fear during early extinction learning are thought to reflect persistent excitation, whereas high levels of fear during late extinction learning are thought to reflect deficits in fear inhibition (Norrholm et al., 2011).

The other major paradigm employed in studies of acute threat is aversive picture processing. In this task, individuals are presented with aversive pictures, often emotional faces (e.g., fearful or angry faces) or standardized unpleasant images from the International Affective Picture System (IAPS; Lang et al., 1999). Individuals typically passively view these images

(e.g., Stevens et al., 2014; Whalen et al., 2001), match the affect of an image with a target image (e.g., Hariri et al., 2002), or rate their fear in response to the images (e.g., Lau et al., 2010). Responses to the aversive pictures are compared to responses to control stimuli (e.g., neutral images).

Whereas fear conditioning paradigms permit an examination of influences on multiple aspects of fear responding, including acquisition of fear, generalization of fear to other stimuli, and extinction of fear, aversive picture processing paradigms primarily provide a window on how individuals respond to aversive stimuli. That is, unlike aversive picture processing paradigms, fear conditioning paradigms offer more of an opportunity to understand associative learning as it underlies threat responses. In addition, fear conditioning paradigms have frequently been employed in animal studies of acute threat, thereby permitting greater comparison of findings from animal models and investigations in humans.

Neural Circuitry of Acute Threat

The neural basis of acute threat has been studied extensively, and our understanding of fear circuitry in humans stems, in large part, from work conducted in animals (Shin and Liberzon, 2010). Based on this work, frontolimbic circuitry has been identified as playing a key role in threat responses. Critical components of this circuitry include the amygdala, hippocampus, anterior cingulate cortex (ACC), insula, and ventromedial prefrontal cortex (PFC; see Shin and Liberzon, 2010, for a review). For example, the amygdala is integral for the acquisition of fear, and activation of the ACC, insula, and hippocampus have also been implicated in fear conditioning. The ventromedial PFC plays an important role in extinction learning, and research suggests that the hippocampus may be involved in the contextual modulation of extinction (Milad et al., 2007). Furthermore, connections between these brain regions have important implications for responses to acute threat. For example, the medial PFC and ACC have an inhibitory influence on subcortical regions, such as the amygdala, and this regulatory effect is thought to occur during fear extinction (e.g., Milad et al., 2007).

Genetic Influences on the Neural Circuitry of Acute Threat

Heritability

Although findings from twin studies suggest that brain volume is heritable, with meta-analytic evidence indicating that brain structure is under strong genetic control (Blokland et al., 2012), the heritability of functional imaging phenotypes has received relatively little empirical investigation. As reviewed by Blokland et al. (2012), a few investigations have examined the heritability of task-related brain activity, although results across studies have been mixed. Functional activation in brain areas related to working memory circuits, including frontal areas and the middle cingulate cortex, has been found to be moderately heritable, with estimates ranging from 40-65% (Blokland et al., 2011; Koten et al., 2009), and there is initial evidence demonstrating the heritability of brain connectivity patterns (Shen et al., 2014). However, heritability estimates for activation in a number of regions of interest (ROIs) relevant to acute threat neural circuitry (e.g., the amygdala) in humans are lacking. Some functional neuroimaging work in monozygotic twins has examined

frontolimbic regions (Miskowiak et al., 2014; Wolfensberger et al., 2008), and reactivity in ROIs implicated in acute threat (e.g., the amygdala) has been found to be stable and trait-like (e.g., Manuck et al., 2007). Nevertheless, behavioral genetics research is needed that directly addresses the heritability of activation in these areas.

Molecular genetics findings: Candidate gene studies

There is a growing body of work demonstrating associations between variation in candidate genes and activation of the neural circuitry related to acute threat responses. As shown in Table I, most studies by far have examined the *5-HTTLPR* polymorphism in the promoter region of the serotonin transporter (*SLC6A4*) gene and the Val158Met polymorphism of the catechol-O-methyltransferase (*COMT*) gene, although additional genes have been considered as well. Even though we present all candidate gene findings in Table I, we limit our discussion in the text to only those that have been investigated in two or more independent studies. We first focus on serotonergic- and dopaminergic-related genes more broadly and then discuss results from some additional genes that have been investigated.

Serotonin has been identified as an important modulator of the corticolimbic circuit underlying acute threat (Fisher and Hariri, 2013), and several serotonergic-related genes have been studied with respect to the neural basis of acute threat, including the serotonin transporter (*SLC6A4*), tryptophan hydroxylase 2 (*TPH2*), monoamine oxidase A (*MAOA*), and serotonin 1A receptor (*HTR1A*) genes. As noted above, the *5-HTTLPR* polymorphism of *SLC6A4* has received the greatest empirical attention. *SLC6A4* is involved in the regulation of reuptake of serotonin to the presynaptic neuron (Homberg and Lesch, 2011), and *5-HTTLPR* is a functional 44-base pair insertion/deletion polymorphism in the promoter region of the gene. *5-HTTLPR* has two common alleles: short (S) and long (L). Compared to the L allele, the S allele has been associated with reduced serotonin transporter protein availability and function and, consequently, higher synaptic serotonin concentrations (Homberg and Lesch, 2011). Some research also suggests that an A/G single SNP (rs25531) upstream of *5-HTTLPR* may modify the function of L alleles, such that the L_G allele is associated with decreased transcriptional efficiency that is similar to that of the S allele (e.g., Hu et al., 2006). Whereas some research has examined a biallelic classification of *5-HTTLPR* (i.e., S vs. L alleles), other work has considered a triallelic classification whereby S and L_G alleles are compared to L_A alleles. Although we refer to the S and L alleles below for simplicity, we note that some of this research is based on comparisons of the S/L_G vs. L_A alleles.

Across numerous studies, there is evidence that, compared to the L allele, the S allele of *5-HTTLPR* is associated with greater activation in several frontolimbic areas implicated in acute threat, including the amygdala, hippocampus, cingulate gyrus, medial PFC, and ACC, in response to processing of aversive vs. neutral stimuli (e.g., Bertolino et al., 2005; Hariri et al., 2002; Heinz et al., 2005; Lonsdorf et al., 2011; Smolka et al., 2007; Surguladze et al., 2008; Williams et al., 2009). Furthermore, research suggests that *5-HTTLPR* genotype is also characterized by differential patterns of brain connectivity in frontolimbic neural circuitry (e.g., Heinz et al., 2005; Pezawas et al., 2005; Surguladze et al., 2008). The association between *5-HTTLPR* genotype and amygdala activation has been especially well-

supported. A recent meta-analysis of 34 independent samples demonstrated support for a statistically significant association between *5-HTTLPR* genotype and both left (Hedge's g = 0.22) and right (Hedge's g = 0.21) amygdala activation in response to affective stimuli (Murphy et al., 2013). However, effect sizes were small; approximately 1% of the variance in amygdala activation was estimated to be accounted for by *5-HTTLPR* genotype. This estimate is smaller than the percentage of amygdala activation explained by *5-HTTLPR* variation (10%) in a previous meta-analysis (Munafò et al., 2008). Interestingly, differences in study design (e.g., imaging method, task requirements, stimulus type) or sample composition (e.g., ancestry, patient vs. non-patient population) were not found to account for the between-study heterogeneity observed in effect sizes, although statistical power was often low for these comparisons (Murphy et al., 2013). Murphy et al. (2013) suggested that inadequate sample sizes most likely contributed to variability in effect size across investigations. Indeed, all published studies to date were found to be statistically underpowered to demonstrate an association between *5-HTTLPR* genotype and amygdala activation.

Although small in effect size, the association between *5-HTTLPR* genotype and amygdala activation appears to be robust. However, what drives the S allele-amygdala activity relation is not entirely clear. For example, some research suggests that the link between *5-HTTLPR* genotype and amygdala response is due to differences in activation to neutral or control stimuli, rather than to increased reactivity to aversive stimuli (e.g., Canli et al., 2005b; Canli et al., 2006), although findings are somewhat inconsistent across studies. More research is needed to better understand what underlies the association between *5-HTTLPR* genotype and amygdala activation. Additional research is also needed to better comprehend the time course of *5-HTTLPR*-related differences in frontolimbic activation, as initial evidence suggests a lack of amygdala habituation to aversive faces over time for S allele carriers but not L allele homozygotes (Lonsdorf et al., 2011).

Most research has examined the link between *5-HTTLPR* genotype and neural activation during aversive picture processing, but a handful of studies have investigated *5-HTTLPR* genotype and neural responses to fear conditioning paradigms. In this work, compared to the L allele, the S allele has been associated with greater reactivity in fear network regions (e.g., amygdala, insula, thalamus, occipital cortex, dorsomedial PFC) during fear conditioning (Klucken et al., 2013; Klucken et al., 2014; Klumpers et al., 2014), elevated amygdala-insula coupling during fear conditioning (Klucken et al., 2014), and stronger late conditioned and unconditioned responses in the right insula during fear conditioning (Hermann et al., 2012).

As is characteristic of the broader literature on genetic influences on the neural circuitry of acute threat, the vast majority of research on *5-HTTLPR* genotype and acute threat neural response has been conducted in adults without a history of psychopathology (e.g., Klucken et al., 2013; Klucken et al., 2014; Murphy et al., 2013). However, there is some evidence that the S allele is associated with increased amygdala activation to clinically relevant triggers in individuals with psychopathology. For example, in one study, S allele carriers with social phobia exhibited greater amygdala activation in response to a public speaking task than L allele homozygotes (Furmark et al., 2004). Furthermore, initial findings in

healthy children and adolescents indicated that S allele carriers exhibited greater activation in limbic, parietal, and frontal regions in response to negative stimuli compared to L allele homozygotes, which suggests that the association between *5-HTTLPR* genotype and frontolimbic neural activation is present earlier in development (Thomason et al., 2010).

Some studies have also begun to examine whether the association between *5-HTTLPR* genotype and neural activation is moderated by the environment. There is some initial support that S allele carriers who also report high levels of life stress exhibit the greatest levels of reactivity in acute threat-related neural regions during processing of emotional stimuli and fear conditioning (e.g., Klucken et al., 2013; Williams et al., 2009). However, not all studies have demonstrated this pattern of results (e.g., Canli et al., 2006). Differences in the environmental variables examined across these few investigations (e.g., early life stress vs. lifetime stressful life events) and variation in the paradigms and comparisons used make it difficult to draw conclusions. More research is needed, but there is at least initial support for the presence of Gene × Environment interactions for *5-HTTLPR* variation and neural activity related to acute threat.

Although the literature on other serotonergic-related genes and the neural circuitry of acute threat is smaller than the body of work on *5-HTTLPR*, there is some support for associations with *TPH2*, *MAOA*, and *HTR1A*. Specifically, a SNP (rs4570625) in the promoter region of the *TPH2* gene, which encodes a rate-limiting enzyme involved in the synthesis of serotonin in the brain (Walther et al., 2003; Zill et al., 2004), has been linked to amygdala reactivity to emotional stimuli, such that T allele carriers exhibit greater amygdala activation to emotional stimuli than G allele homozygotes (Brown et al., 2005; Canli et al., 2005a; Canli et al., 2008). Furthermore, the association between the T allele of rs4570625 with greater amygdala activation during fear conditioning was potentiated among individuals reporting a higher number of traumatic events (Hermann et al., 2012).

Variation in *MAOA*, a gene involved in the degradation of serotonin, has also been linked to threat-related neural activation. A variable number tandem repeat (VNTR) polymorphism in the promoter region of *MAOA* has been identified that has higher expression (i.e., associated with increased transcription and therefore greater breakdown of serotonin) and lower expression variants (Deckert et al., 1999; Sabol et al., 1998). Compared to the higher expression variant, the lower expression variant has been associated with increased limbic activation to aversive stimuli in individuals without a history of psychopathology (Meyer-Lindenberg et al., 2006). Additionally, in a sample of patients with panic disorder with agoraphobia, those with the low expression variant showed increased neural responses to the CS+ vs. CS- during fear acquisition in the ACC, precuneus, and left parahippocampus compared to individuals with the high expression variant (Reif et al., 2014). Furthermore, the low expression group also showed patterns of neural activation consistent with improved discrimination between the CS+ and CS- after completing 12 weeks of cognitive behavioral therapy (CBT). In contrast, the high expression group did not exhibit such evidence of differential neural responses to the CS+ vs. CS- after CBT, which may reflect fear overgeneralization processes at the neural level.

Components of the neural circuitry of fear (e.g., the amygdala and ACC) are also influenced by serotonin 1A receptor-mediated serotonergic signaling. The serotonin 1A receptor is a major inhibitory serotonergic receptor in the brain, with high density of the receptor in cortical and subcortical regions, including limbic areas (Varnas et al., 2004). Compared to the C allele, the G allele of a functional SNP in the promoter region of *HTR1A* (rs6295) has been associated with reduced serotonergic signaling (Lemonde et al., 2003), and there is initial evidence linking *HTR1A* variation to amygdala activation. In healthy individuals, C allele homozygotes exhibited increased amygdala activation to emotional faces vs. shapes compared to G allele carriers (Fakra et al., 2009). However, in a sample of patients with panic disorder with agoraphobia, G allele homozygotes exhibited greater amygdala activity to threat and safety cues during early acquisition of fear conditioning (Straube et al., 2014). In addition, patients homozygous for the G allele showed diminished effects of 12 sessions of CBT on neural correlates of fear conditioning, whereas C allele homozygotes exhibited changes in neural responses in these areas after CBT consistent with differential conditioning (Straube et al., 2014). Differences in the nature of the samples (i.e., individuals with vs. without psychopathology) and paradigms (i.e., emotional processing vs. fear conditioning tasks) make it challenging to compare the results of these two studies. Nevertheless, these investigations provide preliminary evidence that *HTR1A* variation may influence threat-related processes at the neural level, although additional work is needed to better understand this association.

Dopaminergic-related genes have also been of interest when examining genetic influences on the neurocircuitry of acute threat given that dopamine has been shown to play a key role in fear conditioning, especially with respect to fear memory stabilization (Fadok et al., 2009; Pezze and Feldon, 2004). The *COMT* gene is involved in the degradation of dopamine, particularly in the prefrontal cortex (Mannisto and Kaakkola, 1999). Several studies have examined patterns of acute threat-related neural activation that are associated with a functional A/G SNP in *COMT* (rs4680) that results in the substitution of valine (Val) by methionine (Met) at codon 158 (the Val158Met polymorphism). Compared to the Val allele, the Met allele is associated with lower enzymatic activity and, consequently, higher dopamine levels (Mannisto and Kaakkola, 1999), and it has been characterized by greater activation in frontolimbic regions (e.g., the amygdala, hippocampus, cingulate gyrus, and dorsal and ventrolateral PFC) in response to aversive stimuli (Drabant et al., 2006; Lonsdorf et al., 2011; Smolka et al., 2005; Smolka et al., 2007; Williams et al., 2010). There is also initial evidence of increased functional coupling between limbic and prefrontal regions in Met allele homozygotes (Drabant et al., 2006).

One exception to this overall body of work comes from a study by Kempton et al. (2008), which found a different pattern of association between *COMT* genotype and neural reactivity to fearful faces when considering interactions with gender (given that estrogen reduces *COMT* activity). In this investigation, the Val/Val genotype was associated with increased limbic response during fearful affect recognition compared to the Met/Met genotype, primarily in females. Most research has been conducted in adults without a history of psychopathology, but in one study of patients with panic disorder, Val allele carriers (compared to Met allele homozygotes) exhibited greater amygdala activation to fearful faces

(Domschke et al., 2008). Although preliminary, the findings of Kempton et al. (2008) and Domschke et al. (2008) suggest that differential associations between *COMT* genotype and activation of acute threat neural circuitry may emerge when considering gender and psychopathology as potential moderators.

Several additional genes have been explored with respect to acute threat-related neural circuitry, often based on preclinical findings that hold promise for understanding threat-related processes in humans. For example, genes related to memory consolidation and stabilization have emerged as candidates of interest given their roles in processes related to fear memory formation. One such gene is the brain-derived neurotrophic factor (*BDNF*) gene, which codes for the BDNF growth-factor protein. The BDNF growth-factor protein plays an important role in neuronal survival and learning and memory via its regulatory influence on synaptic plasticity (Bath and Lee, 2006). A SNP in the *BDNF* gene (rs6265) that results in a valine to methionine amino acid substitution at codon 66 (the Val66Met polymorphism) has been found to alter the intracellular processing of BDNF, with the Met allele associated with less secretion of BDNF and reduced hippocampal synaptic activity compared to the Val allele (Egan et al., 2003). Growing evidence suggests that carriers of the Met allele exhibit greater activation of limbic fear circuitry (e.g., the amygdala, hippocampus, insula) during fear conditioning and extinction compared to Val allele homozygotes (Lonsdorf et al., 2014; Soliman et al., 2010). Furthermore, there is an initial finding that the Met allele is associated with reduced vmPFC activation during extinction compared to the Val allele (Soliman et al., 2010), a pattern of neural activation suggestive of weaker fear extinction. However, the incorporation of a reversal learning phase prior to extinction training complicates interpretation of this extinction finding.

Additional work is also needed regarding the time course by which variation in *BDNF* influences neural activation during extinction, as some initial research has found that *BDNF* genetic variation is differentially associated with neural activation during extinction primarily during early extinction trials (Lonsdorf et al., 2014). Furthermore, although prior research has detected associations between the Val66Met polymorphism and neural activation during threat-related processing in adults without any history of psychopathology (Lonsdorf et al., 2014; Soliman et al., 2010), one study in adolescents found that Met allele carriers (compared to Val allele homozygotes) exhibited increased amygdala and hippocampal activation during emotional processing only in individuals with anxiety disorders or unipolar depression (Lau et al., 2010). This finding suggests that associations between *BDNF* Val66Met genotype and activation of acute threat-related neural circuitry may be more pronounced in individuals with psychopathology, although more research is needed to better understand this issue.

Translational work has also suggested a role for neuropeptide S (NPS) and its G-protein coupled receptor (NPSR1) in fear responding, with findings from animal models indicating that NPS has anxiolytic effects on the central nervous system (Pape et al., 2010). As a result, researchers have been interested in whether variation in the neuropeptide S receptor 1 (*NPSR1*) gene is associated with acute threat-related neural circuitry. Compared to the A allele, the T allele of the rs324981 SNP in *NPSR1* is characterized by greater NPSR expression and NPS efficacy at the receptor, although binding affinity is not affected

(Reinscheid et al., 2005). Interestingly, in contrast to animal research suggesting an anxiolytic effect of NPS, in humans, the T allele has been associated with exaggerated fear responses at the neural level. Specifically, the T allele has been linked to stronger ACC and dorsomedial PFC activation to the CS+ during fear acquisition (Raczka et al., 2010) and to greater amygdala responsiveness to negative faces (vs. shapes; Dannlowski et al., 2011). In a sample of individuals with panic disorder, the T allele was associated with decreased dorsolateral PFC, lateral orbitofrontal cortex, and ACC activation when processing fearful faces (vs. a control shape stimulus), although no significant differences were observed for amygdala activation (Domschke et al., 2011). Tupak et al. (2013) also examined rs324981 variation with respect to activation in the medial and dorsolateral PFC during an emotional Stroop task. Only A allele homozygotes, and not T allele carriers, exhibited increased activation to fear-relevant (vs. neutral) stimuli in the medial and dorsolateral PFC during the task (i.e., only those homozygous for the A allele showed an emotional Stroop effect). These results may reflect an adaptive inhibitory emotional regulation response to threat that was present in those with the A/A genotype but was less efficient in T allele carriers. Despite differences in the paradigms employed (e.g., fear conditioning vs. processing of emotional stimuli), overall findings from these studies begin to suggest that the T allele of the rs324981 SNP may be associated with heightened neural reactivity to fearful stimuli, as reflected by greater amygdala activation and less prefrontal inhibitory activity.

Preclinical work has also implicated the endocannabinoid system in threat-related processes, with the endocannabinoid anandamide in the amygdala implicated in fear extinction in particular (Gunduz-Cinar et al., 2013). Anandamide is degraded by fatty acid amide hydrolase (FAAH; Spradley et al., 2010), which is encoded by the *FAAH* gene. Two studies have linked the lower-expressing A allele of the rs324420 SNP in *FAAH* to threat-related amygdala activation, with one investigation demonstrating blunted amygdala reactivity to threatening faces (Hariri et al., 2009) and another indicating quicker habituation of the amygdala to aversive faces (Gunduz-Cinar et al., 2013).

Gene × Gene interactions—Most studies have examined the association between variation in a single candidate gene with acute threat-related neural activation, but a few studies have considered the contributions of multiple genes in a single investigation. The influence of genes is rarely limited to a single biological system, and there is often cross-talk between genes and/or systems that may, in turn, contribute to acute threat-related processes. Examining the joint contributions of genetic variants from multiple biological systems is thus of interest, and this approach is consistent with the notion that activation of the neural circuitry underlying threat processes is polygenic. Two studies found support for additive effects of variation in two serotonergic-related genes (*TPH2* and *5-HTTLPR*) on neural activity. Canli et al. (2008) detected additive effects of the *TPH2* T allele and *5-HTTLPR* S allele on putamen and amygdala activation to emotional stimuli, such that effects were amplified when both genotypes, rather than just a single gene, were examined. In addition, Hermann et al. (2012) found a combined effect of the *TPH2* T allele and *5-HTTLPR* S allele on increased activation of the dorsal ACC during extinction, which may suggest prolonged fear expression. Even though formal tests of Gene × Gene interactions were not significant in these studies, these findings nevertheless suggest that considering the contributions of

multiple genetic variants, including those related to the same family of neurotransmitters, may increase our understanding of genetic influences on the neural circuitry of acute threat and shed light on underlying mechanisms.

Physiology of Acute Threat

As noted above, the neural circuitry of acute threat is aligned with physiological processes, and several physiological metrics have been used to assess the construct of acute threat, including startle, skin conductance, and heart rate responses. The startle response is a frequently used translational methodology for measuring learned fear and basic defensive physiology in response to threat (Briscione et al., 2014). Two distinct, yet interrelated, circuits underlie the startle response: 1) a basic reflex response that is initiated by the nucleus reticularis pontis caudalis (Davis et al., 1982), and 2) a modulatory influence on the reflex by the amygdala (Davis et al., 1997). Startle is typically assessed by measuring the strength of the eye blink (as indexed by electromyographic activity from the orbicularis oculi muscle) in response to a startle probe (e.g., a loud noise or air puff; e.g., Norrholm et al., 2013; Vaidyanathan et al., 2014). The overall startle response provides a baseline index of startle reactivity, and startle can be modulated by the presence of emotional stimuli. For example, potentiation of the startle response occurs in the presence of aversive stimuli, and this response (known as fear-potentiated startle) is of particular interest with respect to threat-related processes. This potentiation is influenced by the amygdala, and it occurs independently of cortical influences, thereby providing a measure of threat responding that is distinct from cognition (Davis, 1992). A variety of threatening cues have been found to potentiate the startle response in humans, including aversive images (e.g., Klauke et al., 2012; Lang et al., 1990) and darkness (e.g., Grillon and Ameli, 1998).

Skin conductance response reflects the extent to which the electrical conductance of the skin is altered by a state of arousal via increased sweat gland activity (e.g., Lykken and Venables, 1971). Threat-related increases in skin conductance response have been observed, and these have been found to co-occur with engagement of components of the neurocircuitry of threat, including the amygdala and medial PFC (e.g., Williams et al., 2001), although dissociation of skin conductance and neural fear network activation during fear conditioning has been observed (Tabbert et al., 2006). Many studies have incorporated skin conductance response as a physiological indicator of acute threat, but some research suggests that it may be a more nonspecific measure of arousal that is not as closely tied to threat-related neurocircuitry as other physiological indicators, such as fear-potentiated startle (e.g., Lonsdorf et al., 2014). Furthermore, differential skin conductance responses in fear conditioning are thought to require an awareness of contingencies related to the conditioning paradigm (Hamm and Weike, 2005; Tabbert et al., 2006). These differences may explain, at least in part, discrepancies in associations between genetic predictors and different physiological indicators.

Although not investigated as frequently as fear-potentiated startle or skin conductance response, heart rate is a third physiological measure that has been employed in some studies of acute threat-related processes. Heart rate, generally measured with pulse oximetry,

provides an index of autonomic arousal that parallels brain activity in response to emotional stimuli in several regions, including the amygdala and insula (e.g., Critchley et al., 2005).

Genetic Influences on the Physiology of Acute Threat

Heritability

Evidence from twin studies suggests that physiological measures of acute threat are heritable. Heritability of fear conditioning based on skin conductance responses has been estimated to range between 35-45% (Hettema et al., 2003). Resting heart rate and stress-induced heart rate reactivity have also been shown to be heritable, with heritability estimates of 63% and 52%, respectively, in a sample of middle-aged twins (de Geus et al., 2007). Substantial heritability has been demonstrated for overall startle response as well, with estimates ranging, on average, from 50-70% (Anokhin et al., 2003; Anokhin et al., 2007; Vaidyanthan et al., 2014). However, findings regarding the heritability of emotional modulation of the startle response (e.g., fear potentiation of startle) are less consistent. In an initial study, Carlson et al. (1997) demonstrated that affectively-modulated startle responses showed greater concordance for monozygotic than dizygotic twins, suggesting that emotional modulation of startle may be mediated, in part, by genetic factors. However, subsequent investigations (Anokin et al., 2007; Vaidyanthan et al., 2014) have found little support for heritability of difference scores reflecting affective modulation of startle.

Molecular genetics findings: Candidate gene studies

As with the literature on genetic influences on the neural circuitry of acute threat, nearly all of the studies investigating the genetics of acute threat-related physiology have employed the candidate gene approach. Lonsdorf and Kalisch (2011) provided a comprehensive review of genetic association studies of physiological indicators of fear conditioning and extinction. We build on the research discussed in that paper here, discussing candidate genes that were investigated in two or more investigations in the text (as above) and emphasizing studies that were published in the time since that review (see Table I). The vast majority of research has focused on the *5-HTTLPR, COMT* Val158Met, and *BDNF* Val66Met polymorphisms, although some additional genes have been examined as well.

Similar to the literature on neural circuits of acute threat, several serotonergic-related genes have been examined with respect to threat-related physiology. The *5-HTTLPR* polymorphism has been the subject of the most research, and, of the different serotonergic variants examined, it has received the most robust support for a role in physiological threat responses. Across numerous studies, the S allele has been associated with greater physiological responding to fearful stimuli compared to the L allele. Findings are most robust for startle responses (Armbruster et al., 2009; Klumpers et al., 2012; Klumpers et al., 2014; Lonsdorf et al., 2009; Wendt et al., 2014; Williams et al., 2009; although see Heitland et al., 2013; Larson et al., 2010; Pauli et al., 2010, for exceptions) and less consistent for skin conductance response (Crisan et al., 2009; Garpenstrand et al., 2001; Glotzbach-Schoon et al., 2013; Hartley et al., 2012; Hermann et al., 2012; Klucken et al., 2014; Klumpers et al., 2014; Lonsdorf et al., 2009). Some evidence also supports greater emotional task-elicited

heart rate among S allele carriers compared to L allele homozygotes (Williams et al., 2009; although see Gatt et al., 2009, for an exception).

Greater startle among S allele carriers (vs. L allele homozygotes) has been observed during several phases of fear conditioning paradigms, including fear acquisition, reconditioning, and extinction (Lonsdorf et al., 2009; Wendt et al., 2014). Additionally, greater resistance to extinction has been documented based on skin conductance response in S allele carriers compared to those with the L/L genotype (Agren et al., 2012). There is also initial evidence that *5-HTTLPR* genotype may be linked to fear reacquisition after extinction. Extinction training that occurs inside (i.e., 10 minutes), but not outside (i.e., 6 hours), the reconsolidation interval has been associated with weakened return of fear (Schiller et al., 2010). Compared to L allele homozygotes, S allele carriers exhibited greater reacquisition of fear (as indicated by skin conductance response) when fear was extinguished outside, rather than inside, the reconsolidation interval (Agren et al., 2012). This research provides an initial demonstration of *5-HTTLPR* allelic differences on fear memory reconsolidation.

Although most investigations have examined the main effect of *5-HTTLPR* genotype on acute threat physiology, three studies investigated whether *5-HTTLPR* genotype might interact with life stress to contribute to physiological measures of threat responsivity. Williams et al. (2009) found support for a significant *5-HTTLPR* Genotype × Early Life Stress interaction in predicting heart rate during nonconscious processing of fearful faces, such that S allele carriers who reported high levels of early stress exhibited the greatest increase in heart rate when subliminally presented with fearful vs. neutral faces. Additionally, Hermann et al. (2012) demonstrated that, compared to L allele homozygotes, S allele carriers who reported a higher number of traumatic events exhibited stronger skin conductance responses during late fear acquisition trials. However, Armbruster et al. (2009) failed to find that *5-HTTLPR* genotype significantly interacted with multiple measures of life stress, including early stress, cumulative lifetime stress, and recent (past 18 months) stress, to impact startle response when viewing emotional pictures. Differences between these investigations (e.g., emotional stimuli presentation, physiological outcome measure) make it challenging to draw conclusions, and thus more research is needed to better understand whether *5-HTTLPR* genotype is differentially associated with the physiology of acute threat as a function of environmental experience.

Nevertheless, overall, a growing literature suggests that the S allele of *5-HTTLPR* is associated with heightened fear responding at the physiological level. However, some inconsistencies in findings across studies may reflect differences in study design and measure selection. For example, several studies that used aversive pictures to modulate the startle response failed to find an association between *5-HTTLPR* genotype and fear-potentiated startle (e.g., Armbruster et al., 2009; Brocke et al., 2006; Larson et al., 2010; Pauli et al., 2010), even though genotype was often related to overall startle response (Armbruster et al., 2009; Brocke et al., 2006). In contrast, the S allele of *5-HTTLPR* was more consistently linked to augmented physiological indicators of threat in studies that used Pavlovian fear conditioning paradigms with aversive US (e.g., unpleasant, but not painful, electrical stimulation; e.g., Lonsdorf et al., 2009; Wendt et al., 2014). These findings suggest that Pavlovian fear conditioning paradigms may produce more robust affective modulation

of the startle response. In addition, the greater consistency of findings of *5-HTTLPR* genotype modulation for startle responses than for skin conductance responses may reflect differences in the nature of these two physiological outcomes. As mentioned above, some researchers have noted that fear-potentiated startle may be a stronger indicator of amygdala-driven defensive responding than skin conductance response, which is influenced by additional factors that are not specific to reactions to threat, such as cognitive factors related to contingency awareness (Lonsdorf et al., 2009; Wendt et al., 2014). Therefore, this pattern of results suggests that even though several measures may reflect physiological processes, various indicators may tap into different underlying neurobiological pathways and thus show different degrees of association with genetic markers. These findings demonstrate the importance of conducting cross-cutting research that investigates connections across multiple units of analysis in order to better understand the factors that contribute to a given outcome measure.

Three studies have also examined variation in *MAOA* with respect to the physiology of acute threat. Compared to the T allele of the rs6323 SNP of *MAOA*, the G allele has been associated with higher MAOA enzyme activity (Hotamisligil and Breakefield, 1991). In one investigation, women with the G/G genotype showed greater startle potentiation to emotional stimuli than T carriers (Larson et al., 2010). Similarly, among patients with panic disorder with agoraphobia, those with the higher expression variant of the VNTR polymorphism in the promoter region of *MAOA* had higher heart rates during a behavioral avoidance task designed to provoke anxiety compared to patients with the lower expression variant (Reif et al., 2014). These findings provide some initial evidence that higher MAOA activity levels may be associated with increased physiological responses to threat, although no significant differences in skin conductance response during fear conditioning and extinction were observed in another study as a function of *MAOA* promoter VNTR genotype (Garpenstrand et al., 2001).

COMT is also one of the most-studied genes with respect to the physiology of acute threat, however findings regarding associations between *COMT* Val158Met genotype and startle response to aversive pictures have been mixed. Montag et al. (2008) found that Met allele homozygotes of the Val158Met polymorphism exhibited exaggerated startle to aversive pictures compared to Val allele carriers, whereas Klauke et al. (2012) found that Met allele homozygotes had a blunted startle response to aversive pictures when compared to Val allele carriers. Pauli et al. (2010) failed to detect a significant association between *COMT* genotype and startle responses in an affective picture startle paradigm.

A more cohesive set of findings has emerged from studies employing fear conditioning paradigms. Across several investigations, the Val158Met polymorphism has not been associated with differential responding during fear acquisition, but Met allele homozygotes have been found to show deficits in fear inhibition and extinction and/or greater fear memory consolidation. For instance, compared to Val allele carriers, Met allele homozygotes showed pronounced startle response during a conditional discrimination paradigm despite the presence of a safety signal (Wendt et al., 2014), as well as a greater startle response to the CS+ during extinction (Lonsdorf et al., 2009). With respect to fear-related psychopathology, the Met/Met genotype was associated with increased startle

response during fear inhibition trials in individuals with posttraumatic stress disorder (PTSD), suggesting that trauma and trauma-related psychopathology may exacerbate these genetic deficits (Norrholm et al., 2013). Researchers have suggested that the increased dopamine availability among Met allele carriers may underlie deficits in learning safety cues (Wendt et al., 2014). Initial evidence from fear reacquisition studies after extinction also suggests that Val allele homozygotes may maintain and update fear memories more effectively than Met allele carriers. Compared to carriers of the Met allele, individuals with the Val/Val genotype responded differentially to a reconsolidation manipulation on reacquisition such that they exhibited greater reacquisition of fear (as indicated by skin conductance response) when fear was extinguished outside (i.e., 6 hours) rather than inside (i.e., 10 minutes) the reconsolidation interval (Agren et al., 2012). Finally, preliminary support for a Gene × Environment interaction of *COMT* genotype with childhood trauma was provided by Klauke et al. (2012), who found that, only among Val allele homozygotes, greater childhood trauma was associated with increased potentiation of the startle response to unpleasant stimuli during an affective picture-startle paradigm.

Most work on dopaminergic-related genes has examined *COMT* variation, but two studies investigated variation in dopamine receptor genes with respect to the physiology of acute threat. A VNTR polymorphism in the dopamine receptor D4 (*DRD4*) gene has been associated with dopamine function, with the long repeat variant linked to reduced dopaminergic efficiency compared to the short repeat variant (Asghari et al., 1995). Some evidence suggests that the long variant of *DRD4* was associated with blunted startle response to unpleasant stimuli (Pauli et al., 2010) and delayed extinction based on skin conductance response (Garpenstrand et al., 2001). However, there was no significant difference as a function of *DRD4* genotype when comparing good vs. poor fear acquisition participants as defined by skin conductance response (Garpenstrand et al., 2001). Initially believed to be located in the dopamine receptor D2 (*DRD2*) gene, the Taq1A restriction fragment length polymorphism has also been studied with respect to acute threat physiology. Although it has since been determined to be located in the nearby ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene, it is in linkage disequilibrium with *DRD2* variants, and the A1 allele has been associated with low DRD2 density (Munafò et al., 2007). However, no significant associations between *ANKK1* Taq1A genotype with startle or skin conductance responses during fear conditioning or emotional startle paradigms have been detected to date (Huertas et al., 2010; Montag et al., 2008).

Overall, there have been mixed findings regarding *BDNF* variation and physiological measures of acute threat, although some evidence suggests that the Met allele of the Val66Met polymorphism is associated with deficient fear-related physiology. For example, compared to the Val/Val genotype, the Met allele has been associated with slower or impaired extinction based on skin conductance response (Soliman et al., 2010), slower learning of safety cues based on skin conductance response (Soliman et al., 2010), a lack of fear-potentiated startle responses during late acquisition and early extinction (Lonsdorf et al., 2010), and attenuated startle to the CS+ (relative to the CS-) during differential conditioning (Hajcak et al., 2009). These findings may, in part, reflect enhanced fear memory retrieval. In addition, using a novel paradigm to examine generalization of cued

fear across contexts, Mühlberger et al. (2014) observed that only Met allele carriers—and not Val allele homozygotes—exhibited potentiated startle responses to the CS+ (vs. the CS-) in a novel context (indicative of generalization of fear). There was also a trend for Met allele carriers to show worse discrimination of fear vs. safety contexts during acquisition compared to Val allele homozygotes based on startle responses. These findings suggest that the Met allele may be associated with diminished learning of associations between context and conditioned fear. Despite this body of evidence, other studies, including those with large sample sizes, have failed to detect significant associations between *BDNF* Val66Met genotype and startle or skin conductance responses during several stages of fear conditioning (Lonsdorf et al., 2014, Torrents-Rodas et al., 2012). Furthermore, there is preliminary evidence that *BDNF* genotype in interaction with early life stress may contribute to task-elicited increases in heart rate: Among Met allele carriers, high (vs. low) levels of early life stress were associated with greater task-elicited heart rate increases (Gatt et al., 2009).

As in the literature related to the neural circuitry of acute threat, variation in the *NPRSR1* gene and the physiology of acute threat has been investigated as well. No significant associations between *NPSR1* rs324981 genotype and skin conductance response were found in individuals without a history of psychopathology during fear conditioning paradigms (Glotzbach-Schoon et al., 2013; Raczka et al., 2010), although an initial finding suggests that a link between *NPSR1* genotype and threat-related physiology may emerge in individuals with panic disorder. In a sample of patients with panic disorder who underwent a behavioral avoidance test of being locked in a small dark chamber for up to 10 minutes, T allele carriers exhibited greater heart rate compared to A allele homozygotes during anticipation of the behavioral avoidance test, exposure, and recovery (Domschke et al., 2011).

In addition, some sex-specific findings for candidate genes relevant to threat responsivity have emerged for physiological measures of acute threat. Variation in the gene coding for the pituitary adenylate cyclase-activating polypeptide (PACAP) receptor (*ADCYAP1R1*), which plays a key role in regulating prolonged stress circuit activation (Ressler et al., 2011), has been linked to differential startle response in adult women, although the sex-specific nature of the association has been found to vary with developmental stage. Specifically, compared to G allele carriers, adult women with the C/C genotype of rs2267735 were less able to discriminate danger from safety signals (as measured with startle response) during late acquisition of fear, and they showed greater dark-enhanced startle (Ressler et al., 2011). These genotype-related differences in startle response were not observed in adult men. In an investigation of children, C allele homozygotes exhibited greater dark enhanced startle compared to G allele carriers, but this finding was detected in both males and females (Jovanovic et al., 2013). The finding that C allele homozygote status was associated with potentiated startle in both male and female children, but only in adult women, suggests that *ADCYAP1R1*-related vulnerability for acute threat may only be present in females after adolescence due to changes in estrogen levels. This is consistent with the location of rs2267735 in an estrogen response element, in addition to the finding that *ADCYAP1R1* gene expression is influenced by estrogen (Ressler et al., 2011).

Gene × Gene interactions—Some research on the physiology of acute fear has also begun to investigate the joint contributions of multiple genetic variants. For example, several studies have suggested that the combination of the S allele of the *5-HTTLPR* polymorphism and homozygosity of the Met allele of the *COMT* Val158Met polymorphism is associated with particularly heightened physiological fear responsivity that is resistant to extinction and the presence of safety cues (Lonsdorf et al., 2009; Lonsdorf et al., 2011; Wendt et al., 2014). Although not studied as extensively as the potential interaction of *5-HTTLPR* with *COMT* genotype, there is some evidence that the *5-HTTLPR* S allele may also interact with variation in the corticotropin releasing hormone receptor 1 (*CRHR1*; the G allele of rs878886) and *NPSR1* (the T allele of rs324981) genes to contribute to heightened startle responses to threatening contexts (Glotzbach-Schoon et al., 2013; Heitland et al., 2013). Finally, one study detected a significant three-way interaction between early life stress and variation in two genetic variants implicated in biological systems that have been shown to modulate one another (i.e., the BDNF and serotonergic systems; Homberg et al., 2014). Specifically, Gatt et al. (2010) found that individuals who were carriers of the Met allele of the *BDNF* Val66Met polymorphism and homozygous for the C allele of the rs1062613 SNP in the serotonin receptor 3A (*HTR3A*) gene who also reported high levels of early life stress showed the greatest increases in heart rate in response to an emotional faces task. Although highly preliminary, the results of this study suggest that it may be promising to consider the joint contributions of related genetic variants and environmental factors when trying to elucidate the genetic underpinnings of the acute threat construct.

Molecular genetics findings: Genome-wide association studies (GWAS)

All of the work discussed thus far on molecular genetic influences on both the neural circuits and physiology of acute threat has utilized a candidate gene approach. Although some findings from this literature have been detected across independent investigations, relatively few meet a precise definition of replication (the same SNP, phenotype, and direction of association; Sullivan, 2007). Furthermore, there are significant limitations to this methodology. For one, with the candidate gene approach, genes are selected for study based on their involvement in biological pathways that are hypothesized to be implicated in acute threat. Even though the biological underpinnings of acute threat have been studied extensively from a translational perspective, with research conducted in animals and humans (Shin and Liberzon, 2010), our understanding is far from complete. This thus restricts the genes examined to those implicated in a limited number of biological systems. Another limitation is that many of the candidate gene studies are characterized by small sample sizes and vulnerable to Type I error. Indeed, in their meta-analysis of studies on *5-HTTLPR* variation and amygdala activation, Murphy et al. (2013) concluded that all the published research on this topic has been statistically underpowered.

In recent years, GWAS have become increasingly feasible with the mapping of the human genome and advances in high throughput genotyping. In contrast to the candidate gene approach, a GWAS implements an agnostic approach that tests for associations between variation in hundreds of thousands to millions of SNPs across the genome and a phenotype of interest. To date, one GWAS has been published with respect to the physiology of acute threat. Vaidyanathan et al. (2014) conducted the first GWAS of startle response in a sample

of over 3,000 twins and their parents. Over 527,000 SNPs across the genome were examined, but no variants exceeded the threshold for genome-wide statistical significance ($p < 5 \times 10^{-8}$) for either overall startle response or emotion-modulated startle. Vaidyanathan et al. (2014) also conducted a genome-wide scan that analyzed associations between more than 17,000 autosomal genes with startle responses. These analyses aggregated the contributions of all SNPs in a single gene; this is a more powerful approach when there are multiple causal variants within a gene. One gene emerged as statistically significant in the analysis of aversive modulated startle: the poly (ADP-ribose) polymerase family, member 14 (*PARP14*) gene on chromosome 3, which codes for a protein that aids in injured cell survival (Amé et al., 2004). *PARP14* has not been implicated in prior work on startle. Thus, notably, the genome-wide approach identified a variant in a novel pathway that would not have been examined using the biologically-driven candidate gene methodology, thereby highlighting the promise of using genome-wide methods for hypothesis generation. Vaidyanathan et al. (2014) also examined candidate SNPs that have been associated with startle response in the extant literature, and it is noteworthy that none of these SNPs was statistically significant after Bonferroni correction in their sample of over 3,000 individuals. The lack of significant candidate SNP-based findings in this sample, which far exceeds the sample sizes of studies in the candidate gene literature, thus raises some concerns regarding whether published findings represent true associations.

Conclusions and Recommendations for Future Research

Even though the RDoC project was only launched in 2009, it has already begun to influence the field's conceptualization of psychopathology. Indeed, research aimed at defining dimensions of observable behavior and neurobiological measures—across multiple units of analysis—that are proposed to cut across diagnostic categories has been accumulating in the years since RDoC was initiated. As summarized in this paper, in particular, there is a growing body of literature on the genetic influences on the neural circuitry and physiology of acute threat. The translational nature of this research is a major strength, as related processes have been observed across human and non-human species (Briscione et al., 2014). Furthermore, although some genetic variants and outcomes have only been investigated by one or (at most) a handful of studies, some findings have emerged that have been observed across independent investigations. Specifically, support in the extant literature is most robust for associations between the *5-HTTLPR* and *COMT* Val158Met polymorphisms with threat-related responses across both neural and physiological units of analysis. The *5-HTTLPR* S and *COMT* Met alleles have been associated with heightened activation in several frontolimbic areas, especially the amygdala, in response to aversive stimuli and with threat-related physiological responding, particularly potentiated fear acquisition (*5-HTTLPR*) and deficits in fear inhibition or extinction and/or greater fear memory consolidation (*COMT*). It is worth noting, though, that many studies have been statistically underpowered and that these two polymorphisms are some of the most widely-studied polymorphisms in all of psychiatric genetics. The robustness of findings for different genes thus needs to be considered in light of potential publication bias.

Despite these initial findings, our knowledge of the genetic architecture underlying acute threat remains limited, and further research is needed to better elucidate this construct across

multiple levels of analysis. Here, we make five recommendations for future research that aim to extend the growing body of work on this topic and ultimately improve our understanding of risk for psychopathology:

1. Test how genetic influences on acute threat-related neural circuitry and physiology contribute to the development of psychopathology

The vast majority of the extant literature on genetic influences on the neural and physiological bases of acute threat has been conducted in individuals without a history of psychopathology, which suggests that the detected associations between genetic variants and neural and physiological processes are not dependent upon fear or threat-related psychopathology. However, research in samples of individuals with psychiatric conditions is needed to better understand how these relations may result in functioning at the extreme end of the dimension of acute threat. Longitudinal studies, such as prospective high-risk cohort designs, are critical for testing how neural and physiological intermediate phenotypes may mediate the association between genetic vulnerability and the development of threat-related psychiatric conditions.

2. Continue to study acute threat at multiple levels of analysis

The research on the genetics of the neural and physiological bases of acute threat highlights some advantages to examining genetic influences on biological intermediate phenotypes. For example, in several studies, studying neural and physiological measures permitted detection of associations with genetic variants that did not emerge when investigating self-report clinical outcomes, such as subjective ratings of fear (e.g., Glotzbach-Schoon et al., 2013; Heitland et al., 2012; Heitland et al., 2013; Lonsdorf et al., 2009; Klumpers et al., 2012; Mühlberger et al., 2014; Pauli et al., 2010). Thus, incorporating more objective intermediate phenotypes that may lie closer to the underlying biological substrate may prove fruitful in elucidating the genetic architecture of dimensions of functioning, like acute threat, that are relevant to psychopathology. Moreover, some studies have found that genetic variations were significantly associated with neural activation patterns but not with more distal measures of symptoms of psychopathology (e.g., Stevens et al., 2014). In addition, some research suggests that genotype effect sizes on neural activation patterns are larger than effect sizes associated with psychopathology (e.g., Stevens et al., 2013; Stevens et al., 2014). It is worth noting that some researchers have questioned whether the contributions of specific genes to intermediate phenotypes are larger than they are to more complex phenotypes, such as psychiatric disorders (e.g., Flint and Munafò, 2007). However, even if the genetic architecture underlying intermediate phenotypes does not prove to be simpler than that for psychiatric illness, the existing research suggests that studying genetic influences on acute threat across multiple units of analysis is advantageous for providing a more comprehensive understanding of the factors that contribute to this construct.

Moreover, research that investigates the genetics of acute threat-related processes at multiple units of analysis and that examines links across these units in a single investigation has been especially encouraging, and more work of this nature is needed. For example, Klumpers et al. (2014) demonstrated that increased dorsomedial PFC responses to threat (vs. neutral) cues was associated with increased psychophysiological responding to threat, and this neural

activation mediated the relation between *5-HTTLPR* genotype and both skin conductance and startle responses to threat. This kind of research has particular promise for delineating how genetic vulnerability translates into behavior.

3. Use genome-wide methods and collaborative consortium efforts

Despite the growing findings on the genetics of acute threat-related neural circuits and physiology, the majority of studies have investigated variants of a single candidate gene, and this approach has been widely discredited (e.g., Kendler, 2013). Additional GWAS of acute threat-related neural circuits and physiology are of interest, particularly for hypothesis generation and identifying genetic variants that can then be explored with more targeted biological investigations. As described above, Vaidyanathan et al. (2014) provide an excellent model for how to comprehensively study variation across the genome with respect to a physiological outcome that is relevant to acute threat. Furthermore, GWAS of brain activation patterns have been conducted (e.g., Potkin et al., 2009), although not with respect to acute threat neural networks.

GWAS have produced fundamental knowledge about the genetic basis of psychiatric disorders (along with the methods to extract such knowledge; Sullivan et al., 2012), including the landmark paper in *Nature* which reported on the discovery of 108 genome-wide significant loci for schizophrenia in ∼36,000 cases and ∼113,000 controls (one of NIMH Director Insel's top five findings for 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). This knowledge needs to be extended to the genetics of acute threat-related neural circuits and physiology. However, GWAS require very large sample sizes for signal detection. Indeed, Vaidyanathan et al. (2014) noted that their sample of over 3,000 individuals—the largest study of genetic influences on acute threat-related physiology to date—was statistically underpowered for their GWAS. Collaborative consortium-based efforts, such as that of the Psychiatric Genomics Consortium (PGC; e.g., Sullivan et al., 2012) and the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium (e.g., Thompson et al., 2014), provide encouraging models for combining data from multiple samples and how this can be fruitful for identifying genetic variants. The PGC has demonstrated the potential for identifying genetic loci that show robust and replicable associations with psychopathology (particularly with respect to schizophrenia and bipolar disorder) with sufficiently powered GWAS. There are also working groups within the PGC, such as the genetics and imaging group within the PTSD working group of the PGC (Logue et al., 2015), focused on studying genetic influences on intermediate phenotypes that are relevant to psychopathology, such as neural structure and function. In addition, the ENIGMA Consortium is a network of researchers working collaboratively to conduct GWAS of brain imaging phenotypes. As part of this recently established collaborative effort, these scientists have already begun to identify genetic variants associated with brain structures (Hibar et al., 2015; Stein et al., 2012). Furthermore, both the PGC and ENIGMA have developed data processing pipelines that offer standardized methods for data preparation and analysis that can be used by different investigators. We believe that it is critical to employ these kinds of collaborative efforts for genome-wide investigations of loci implicated in the neural and physiological bases of acute threat. However, GWAS identify genetic variants that are associated with a phenotype, but

they do not necessarily identify causal variants or underlying mechanisms. Findings from GWAS thus need to be followed up with further investigations, such as deep sequencing and functional studies, in order to elucidate biological mechanisms.

4. Move beyond common genetic variation and single genetic loci

Both candidate gene and GWAS research have typically studied common genetic variation, and developing a diverse collection of genomic assessments, including copy number variants (a type of structural variant) and rare variants (both structural and exonic), may also deepen understanding of the different factors that comprise genetic contributions to the neural and physiological bases of acute threat. Recent methodological advances (e.g., in sequencing methods) will contribute to increased feasibility of these pursuits. In addition, incorporating the effects of multiple "-omics" data (e.g., GWAS, DNA methylation, and gene expression data), rather than only focusing on one level of genetic data, may help to shed light on underlying biological mechanisms.

It is also of interest to consider the influence of multiple genetic loci on the neural circuits and physiology of acute threat. Intermediate phenotypes are likely to be polygenic in nature, and a number of the candidate gene systems investigated in the literature thus far (e.g., the serotonergic and BDNF systems; Homberg et al., 2014) have been found to act synergistically. Some studies have begun to examine epistatic effects by testing Gene × Gene interactions (e.g., Heitland et al., 2013; Wendt et al., 2014), and more research is needed, particularly with increased understanding of the underlying biological systems. However, sample sizes need to be sufficiently large to have adequate statistical power to detect interactions. In addition, polygenic scores for neural and physiological indicators of acute threat that aggregate the effects of multiple genetic loci are of interest, particularly as more GWAS findings accumulate. Polygenic scores are based on the notion that the role of multiple common variants in an outcome may be observed when considered collectively, and promising findings based on polygenic scores have emerged in the broader psychiatric genetics literature (e.g., International Schizophrenia Consortium, 2009).

5. Consider Gene × Environment interactions

Additional research investigating Gene × Environment interactions has potential for enhancing our understanding of the acute threat construct as well. Relatively few studies in the extant literature have considered environmental influences on neural and physiological measures of acute threat responses in interaction with genetic influences, despite evidence of environmental contributions to these outcomes. Research on Gene × Environment interactions may be especially helpful for elucidating how genetic vulnerability translates into pathological dysfunction of the acute threat dimension. As described in this review, a few studies have demonstrated evidence for Gene × Environment interactions in contributing to neural and physiological manifestations of acute threat (e.g., Canli et al., 2006; Gatt et al., 2009). However, further research, particularly work that goes beyond cross-sectional study designs, is needed to better understand how mechanisms of risk unfold.

Returning to the Aim of the RDoC Initiative

A sizeable, and growing, literature has begun to delineate genetic contributions to the neural circuits and physiology of acute threat, one of the key constructs of the RDoC framework that is relevant to various forms of psychopathology, particularly anxiety and trauma-related disorders. In concluding this review, we return to the aim of the RDoC initiative, which is to "accelerate the pace of research that translates basic science into clinical settings by understanding the multi-layered systems that contribute to mental function" (Chiodo, 2014). RDoC is still a relatively nascent initiative, and "biosignatures" of psychopathology that can be used to inform clinical intervention efforts remain far off. Nevertheless, we are optimistic that research on genetic influences on the neural and physiological bases of acute threat may influence the development of precision medicine in the future.

Indeed, initial results in the area of "therapygenetics" suggest that genetic variation may influence an individual's response to psychotherapy, and findings related to the genetic bases of the neural and physiological bases of acute threat in particular may prove useful for informing which patients receive certain therapeutic interventions in the future. For example, growing findings suggest that variation in some of the genes discussed in this review may inform which patients with panic disorder with agoraphobia are most likely to respond to CBT. Patients with panic disorder with agoraphobia with the higher expression variant of *MAOA* showed less of a response to CBT than those with the lower expression variant, and this was mirrored at the level of neural responses such that only carriers of the lower expression variant showed patterns of neural activation that were indicative of improved discrimination between danger and safety signals following completion of CBT (Reif et al., 2014). In addition, patients with panic disorder with agoraphobia with the risk genotype of *HTR1A* rs6295 (G/G) participated in fewer self-initiated exposure practices during the course of CBT treatment compared to those with the C/C genotype (Straube et al., 2014). G allele homozygotes also exhibited less of a neural response to CBT, such that CBT only impacted the neural correlates of fear learning in C allele, and not G allele, homozygotes. These neural changes in C allele homozygotes may have resulted from the greater number of exposure practices, although additional research is needed to better understand the underlying mechanisms.

Furthermore, research suggests that examining genetic influences on intermediate phenotypes, including at the neural level, may be particularly useful for understanding individual differences in treatment response. For instance, Lueken et al. (2015) examined *5-HTTLPR* as a predictor of response to CBT in patients with panic disorder with agoraphobia. No significant main effect of *5-HTTLPR* genotype on treatment response emerged but significant associations were detected when neural responsivity during fear conditioning prior to the start of treatment was taken into consideration. Lueken et al. (2013) previously demonstrated that a negative correlation between ACC and amygdala activation during fear conditioning was predictive of responding to CBT, and the authors found that among treatment responders, only L allele homozygotes exhibited a negative ACC-amygdala coupling. Thus, *5-HTTLPR* genotype appeared to modulate a neural pattern of connectivity implicated in fear extinction and predictive of treatment response. The findings of this study

indicate that particular patterns of neural activity may be relevant for understanding treatment response in individuals with a certain genotype.

Together, these findings begin to suggest that information about one's genetic background, in addition to individual differences at the neural and physiological levels, may one day be utilized to tailor intervention efforts. With its emphasis on studying dimensions of functioning across multiple units of analysis, the RDoC initiative encourages the rich characterization of psychological processes. We believe that this approach holds promise for studying mechanisms of risk for, and resilience to, psychopathology, and that this knowledge can ultimately be used to design more targeted and effective mental health treatment.

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Table I

Candidate gene findings for the neural circuitry and physiology of acute threat

			Frontolimbic Neural Circuitry[a]			Physiology[b]		
Gene	**Common Name**	**Location[c]**	**Published Reports**	**Significant Findings**	**Null Findings**	**Published Reports**	**Significant Findings**	**Null Findings**
Serotonergic System								
SLC6A4	Serotonin transporter	17q11.2						
5-HTTLPR	Serotonin transporter promoter polymorphism[d]		37	2217,29,34,35, 37,40,44,49,52,59,65,71	1520,49	19	131,3,6,12,19,22,29,36,37,40,43,69,71	620,26,27,35,38,51
STPP	Serotonin transporter polyadenylation polymorphism		0	---	---	1	126	0
TPH2	Tryptophan hydroxylase 2	12q21.1	4	48,10,11,29	0	1	129	0
MAOA	Monoamine oxidase A	Xp11.3	2	245,56	0	3	238,56	119
HTR1A	Serotonin receptor 1A	5p11.2-q13	2	218,64	0	1	14	0
HTR3A	Serotonin receptor 3A	11q23.1	0	---	---	1	121	0
Dopaminergic System								
COMT	Catechol-O-methyltransferase	22q11.21	7	714,16,32,40,59,60,70	0	8	71,33,40,43,47,50,69	151
DAT1 (*SLC6A3*)	Dopamine transporter	5p15.3	1	155	0	1	0	151
DRD2 (*D2R, D2DR*)	Dopamine receptor D2	11q23	0	---	---	1	130	0
DRD4 (*D4DR*)	Dopamine receptor D4	11p15.5	0	---	---	2	219,51	0
Additional Genes								
ACCN2 (*ASIC2*)	Amiloride-sensitive cation channel 2	12q12	1	161	0	0	---	---
ADCYAP1R1	Receptor for adenylate cyclase-activating polypeptide 1	7p14	1	163	0	2	231,57	0
ANKK1 (Taq1A)[e]	Ankyrin repeat and kinase domain containing 1	11q23.2	0	---	---	2	0	230,47
AVPR1a	Arginine vasopressin receptor 1A	12q14-q15	1	146	0	0	---	---
BDNF	Brain-derived neurotrophic factor	11p13	4	420,39,41,62	0	8	620,21,24,42,48,62	241,66
CNR1 (*CB1, CNR*)	Cannabinoid receptor 1	6q14-q15	0	---	---	1	128	0
CRHR1	Corticotropin-releasing hormone (CRH) receptor 1	17q12-q22	0	---	---	1	127	0
FAAH	Fatty-acid amide hydrolase	1p35-p34	2	223,25	0	0	---	---
GRIN2A	Glutamate receptor, ionotropic, N-Methyl D-Aspartate 2A	16p13.2	1	19	0	1	0	19
NPSR1	Neuropeptide S receptor 1	7p14.3	4	413,15,54,68	0	3	215,22	154
NPY	Neuropeptide Y	7p15.1	1	172	0	0	---	---
NRGN	Neurogranin	11q24	1	153	0	1	0	153

			Frontolimbic Neural Circuitry[a]			Physiology[b]		
Gene	**Common Name**	**Location[c]**	**Published Reports**	**Significant Findings**	**Null Findings**	**Published Reports**	**Significant Findings**	**Null Findings**
OPRL1	Opiate receptor-like 1	20q13.33	1	12	0	1	12	0
OXTR	Oxytocin receptor	3p25	1	167	0	1	158	0
PDYN	Prodynorphin	20p13	1	15	0	1	15	0
STMN1	Stathmin 1	1p36.11	0	---	---	1	17	0

Note: Superscript numbers refer to the relevant citations in the References list.

[a]Includes activation in the amygdala, hippocampus, anterior cingulate cortex, insula, and ventromedial prefrontal cortex.

[b]Includes startle, skin conductance, and heart rate outcomes.

[c]Location based on Entrez Gene database.

[d]Twenty-five of the studies on *5-HTTLPR* are reviewed in the Murphy et al.49 meta-analysis.

[e]Initially believed to be located in *DRD2*, the Taq1A restriction fragment length polymorphism has since been located in *ANKK1*.