Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2017 March ; 174(2): 156–177. doi:10.1002/ajmg.b.32459.

The Genetics of Anxiety-Related Negative Valence System Traits

Jeanne E. Savage, BA^{1,*}, Chelsea Sawyers, BS^{1,*}, Roxann Roberson-Nay, PhD^{1,2}, and John M. Hettema, MD, PhD^{1,2}

¹Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA

²Department of Psychiatry, Virginia Commonwealth University, Richmond, VA

Abstract

NIMH's Research Domain Criteria (RDoC) domain of negative valence systems (NVS) captures constructs of negative affect such as fear and distress traditionally subsumed under the various internalizing disorders. Through its aims to capture dimensional measures that cut across diagnostic categories and are linked to underlying neurobiological systems, a large number of phenotypic constructs have been proposed as potential research targets. Since “genes” represent a central “unit of analysis” in the RDoC matrix, it is important for studies going forward to apply what is known about the genetics of these phenotypes as well as fill in the gaps of existing knowledge. This article reviews the extant genetic epidemiological data (twin studies, heritability) and molecular genetic association findings for a broad range of putative NVS phenotypic measures. We find that scant genetic epidemiological data is available for experimentally-derived measures such as attentional bias, peripheral physiology, or brain-based measures of threat response. The molecular genetic basis of NVS phenotypes is in its infancy, since most studies have focused on a small number of candidate genes selected for putative association to anxiety disorders (ADs). Thus, more research is required to provide a firm understanding of the genetic aspects of anxiety-related NVS constructs.

Keywords

negative valence; anxiety; twin study; heritability; candidate gene; genome-wide association study

INTRODUCTION

As reviewed elsewhere (Cuthbert and Insel, 2013; Insel et al., 2010), the National Institute of Mental Health (NIMH)'s strategic plan for research has undergone a paradigm shift regarding the phenotypic outcomes proposed as targets for investigation. Launched in 2009, the Research Domain Criteria (RDoC) project proposes the creation of a new psychiatric research nosology informed by genetics, neurobiology, and behavioral observations rather than clinical diagnoses. RDoC supports a framework for conducting psychiatric research

Correspondence to: John M. Hettema, MD, PhD, Department of Psychiatry, PO Box 980126, Richmond, VA 23298-0126. Phone: (804) 828-8592, Fax: (804) 828-1471, john.hettema@vcuhealth.org.

*Indicates equal contributions

aimed at fundamental brain circuits, physiology, and experimental paradigms that probe dimensions of neural functioning that extend beyond traditional diagnostic categories. Simmons and Quinn (2014) recently summarized the broad questions and possible implications surrounding this paradigm shift for genetics and other biologically-based psychopathology research under the NIMH.

In this article, we employ the RDoC framework as a lens through which to review the extant research relevant to understanding the genetics of anxiety. The genetic epidemiology of clinically defined anxiety symptoms and disorders is well studied (Shimada-Sugimoto et al., 2015; Smoller 2016); however, the variants underlying their genetic risk factors are mostly yet to be identified. We summarize genetic epidemiological and molecular genetic studies of dimensional psychological and physiological phenotypes shown to be associated with anxiety disorders (ADs). Many of these phenotypes naturally fall within one or more of the five suggested constructs of the RDoC domain of negative valence systems (NVS): acute threat (“fear”), potential harm (“anxiety”), sustained threat, loss, and frustrative non-reward. As constructed, the NVS domain attempts to reflect an organism’s fundamental responses to aversive situations or contexts, such as fear, anxiety, and distress, more traditionally included under the rubrics of anxiety and mood disorders. However, rather than focusing on clinical symptom sets aggregated under diagnostic syndromes, NVS phenotypic expressions may include emotional, biological, or behavioral responses to these experiences with the ultimate aim of understanding their neural, cellular, and genetic mechanisms.

In the context of this special issue, we exclude loss-related phenotypes, which are more specific to mood disorders. The genetics of biological phenomena such as neural activation and cognitive, emotional, or physiological responses to threat, harm, and frustration are the primary focus of this review. The RDoC matrix is meant to be an evolving, empirically-informed framework, so we also consider other dimensional risk markers of anxiety pathology not formally included in NVS such as anxious temperament (but excluding factors of normal personality like neuroticism and harm avoidance). NIMH has referred to such higher-order, more complex constructs as “intermediate phenotypes” (Insel & Cuthbert 2009), although this term does not necessarily imply a mediational mechanism (see next paragraph). A guide to the abbreviations used herein for commonly referenced phenotypes and other terms can be found in Table I. A list of gene names corresponding to the gene symbols used throughout this paper can be found in Table II.

Before embarking on this review, one clarification is needed. Most of the measures we review herein have not yet met the necessary criteria to be considered as “endophenotypes”. As proposed by Gottesman and Gould (2003), endophenotypes are measureable traits (e.g., biochemical, neuroanatomical, physiological, or neuropsychological) associated with a disorder that lie closer to the underlying genetic risk variants in the chain of expression leading to manifest pathophysiology. These measures must be associated with the illness (i.e., seen in affected patients), heritable, and co-segregate with the illness in families (i.e., share genetic factors with that of the illness). Some have emphasized the important distinction between endophenotypes for which the genetic factors correlate with those of the disorder (“liability index”) versus those that actually mediate the effects of genes on the disorder (Kendler and Neale, 2010). Most extant studies have not attempted to distinguish

these. Other considerations such as experimental design, psychometric properties of the measurement instrument, and data analytic approaches are important but outside the scope of this review. Given the wide variety of measures being investigated by RDoC-inspired research, we focus on the fundamental criterion that a construct is heritable, i.e., has a genetic basis. This is traditionally accomplished with genetic epidemiological study designs, primarily twin and family studies. With genome-wide SNP arrays, one can also now estimate “chip heritability” via genome-wide complex trait analysis (GCTA) using all of the common SNP variation on the array present in a sample of “unrelated” subjects to predict the outcome phenotypic measure (Yang et al., 2011). We note that there are subtle but important differences between the types of heritability assessable with these two different approaches. Without established heritability of one form or another for a phenotype, there is questionable value in conducting genetic association analyses or estimating genetic covariance with disease outcomes.

In the last few decades of molecular genetic advances leading to wide-spread availability of low-priced, high quality genetic markers, many researchers have “put the cart before the horse”, i.e., sought molecular genetic signatures for potential endophenotypes for which there are no available estimates of heritability or insight into genetic architecture. Most of these studies investigate a few candidate markers in a narrow range of “usual suspect” genes in neurotransmitter systems (e.g. serotonin, dopamine) that have tentative support, at best, in relation to the etiology of the higher level clinical phenotypes; thus, they provide poor coverage of human genetic variation that could contribute to NVS genetic susceptibility. In addition, candidate gene studies are generally fraught with issues that increase their likelihood of producing both false positives (Type I error) and false negatives (Type II error), such as inconsistent phenotypic assessment between studies, biased selection of a narrow range of genetic variants with little *a priori* evidence, underpowered samples, failure to correct for multiple testing and ancestry admixture, and lack of replication (Sullivan et al., 2001).

The aim of this review is to provide a comprehensive overview of the existing genetic studies of dimensional anxiety-related phenotypes. We include genetic epidemiology studies estimating the heritability of these phenotypes and molecular genetic studies that seek to identify specific genes/variants underlying the heritability. Despite the shortcomings noted above that exist across much of the body of molecular work, we attempt to survey the rapidly expanding genetic association literature for NVS phenotypes with emphasis on research conducted, where available, in large, well characterized samples, meta-analyses, and genome-wide association studies (GWAS). In the absence of meta-analyses, we briefly summarize the findings of individual association studies. Detailed reviews of the genetic research on some individual phenotypes, tasks, or of a set of genes (e.g. serotonin system) involved in a particular phenotype have previously been conducted; we will only briefly summarize those data herein. Our goal is to create a single concise source of current information about the heritability and gene identification findings for a broad suite of NVS traits relevant to anxiety/ADs in order to highlight the current state of the field and identify areas in need of further research efforts.

METHOD

We conducted this literature review through a search of the PubMed database by cross-typing two sets of search terms: genetic keywords and NVS phenotype keywords. The genetic keywords were intended to identify both heritability and genetic association studies (e.g. “twin”, “heritability”, “genetic epidemiology”, “gene”, “genetic”, “polymorphism”, “GWAS”). Phenotypic search terms were primarily taken from the RDoC NVS matrix, with auxiliary searches when needed to further flesh out the category or to include different terms used by researchers to describe the same construct. Reference lists of articles resulting from this search were also used to identify additional relevant sources for inclusion, and we conducted a secondary search with each identified phenotype and the keywords “meta-analysis” or “review” to ensure comprehensive coverage of the extant literature.

We group the results of our literature search under specific phenotypes/traits within the four NVS constructs related to ADs: responses to acute threat, responses to potential harm, responses to sustained threat, and frustrative non-reward. Given the high degree of overlap between biological and cognitive systems involved in these constructs, many phenotypes do not fit neatly under a single construct and may, for example, be involved in both appraising potential threats and reacting to acute threats. Where phenotypes did not clearly belong to a single construct, we organize them according to the best fitting category of their specific operationalization in the studies reviewed. Within constructs, we roughly group phenotypes by the units of analysis that make up the columns in the RDoC matrix: functional or structural brain **circuits** associated with ADs, threat-related **physiology**, trait-like **behaviors** that predict AD risk, and laboratory **paradigms** that tap into anxiety-relevant NVS constructs. For each of these NVS phenotypes, we summarize heritability estimates and results from candidate gene studies and, where available, GWAS and other molecular genetic approaches. For genetic association studies, we limit our reports to the main effects of variants, given the more tentative nature of gene-by-gene and gene-by-environment interactive effects. We limit our focus to studies of human samples, although we note a few phenotypes for which more extensive genetic research has been conducted in model organisms or for which translational cross-species studies have been reported. As the RDoC constructs are conceptualized as transdiagnostic, dimensional entities, we include studies of both healthy individuals and patients with anxiety-related disorders.

RESULTS

Responses to Acute Threat

RDoC defines acute threat as: “Activation of the brain’s defensive motivational system to promote behaviors that protect the organism from perceived danger. Normal fear involves a pattern of adaptive responses to conditioned or unconditioned threat stimuli (exteroceptive or interoceptive). Fear can involve internal representations and cognitive processing, and can be modulated by a variety of factors.” The NVS construct of acute threat maps on to the domain typically thought of as “fear” and encompasses neurobiological systems responsible for reacting to perceived, immediate danger or threatening stimuli. Acute threat systems mobilize resources (primarily physiological) needed to cope with a threat at hand, in what is commonly known as the fight-or-flight response. Well-characterized phenotypes that fall

within this construct include cognitive systems of threat appraisal and conditioned learning and physiological systems of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenocortical (HPA) axis that underlie the fight-or-flight response.

Circuits

Amygdala reactivity: The amygdala is a small, bilateral structure in the temporal lobe that plays a major role in fear and emotional memory (Domschke and Dannlowski, 2010; Scharinger et al., 2010). Amygdala reactivity, or the magnitude of response of the amygdala to a stimulus, is typically assessed with a functional magnetic resonance imaging (fMRI) task in which participants are shown pictures of emotional faces (expressing threat-relevant emotions of fear or anger) or non-facial affect-arousing imagery, and the hemodynamic response in the amygdala is measured (Domschke and Dannlowski, 2010; Sumner et al., 2015). Following an early report by Hariri and colleagues (2002) that the 5-HTTLPR functional polymorphism was associated with amygdala reactivity to fear-relevant stimuli, there has been an abundance of genetic association studies investigating the role of 5-HTTLPR and other candidate genetic variants in amygdala reactivity. Despite this, there have been scant genetic epidemiological studies of the heritability of amygdala reactivity. To our knowledge, a single published twin study (Wolfensberger et al., 2008) of 32 MZ twin pairs demonstrated that bilateral amygdala reactivity to emotional faces was higher for concordant pairs at high genetic risk for anxiety/depression than concordant pairs at low genetic risk. However, the extent to which genetic or environmental factors influence amygdala reactivity to threat has not been quantified.

Numerous human candidate gene association studies have been conducted in this area since the original Hariri et al. study, many of which are described in a recent review focusing specifically on the genetics of NVS acute threat systems (Sumner et al., 2015) and prior reviews by Scharinger et al. (2010) and Savitz and Drevitz (2009). We briefly summarize those findings and discuss a few studies not previously covered. The most well-studied genetic variant is the 5-HTTLPR, for which two large meta-analyses (Munafò et al., 2008; Murphy et al., 2013) have confirmed a small but significant association of the S allele with greater amygdala reactivity. As previously reviewed, other studies have provided additional evidence of the role of the serotonergic system genes (*HTR1A*, *HTR2A*, *HTR3A*, *TPH2*, and *MAOA*) in amygdala reactivity. The *MAOA* VNTR association has been subsequently replicated in a more recent study (Denson et al., 2014). An epigenetic study of the *SLC6A4* gene demonstrated that methylation of CpG sites around the transcription start site (indicating potential genetic regulatory effects) was positively correlated ($r = 0.07$) with left amygdala reactivity even after accounting for 5-HTTLPR genotype (Nikolova et al., 2014).

The dopaminergic system has also been investigated in several studies. As reviewed by Scharinger et al. (2010), conflicting evidence has been found for a role of the *COMT* Val158Met polymorphism (rs4689), with both alleles being reported as the risk allele in different studies. More recent evidence supports the idea that these conflicting findings may be due to sex differences, as Domschke et al., (2012) found a strong association with the Val allele that was evident only in females. Other dopamine-related genes have been associated with amygdala reactivity as well, including the dopamine transporter *DAT1/SLC6A3* (9-

repeat allele of the VNTR with higher left amygdala activation) (Bergman et al., 2014), the receptor *DRD2* (rs1076560; GG homozygotes with greater left amygdala activation) (Blasi et al., 2009), and the polymorphism rs1800497 in the *DRD2/ANKK1* region (homozygotes for either the A1/A1 or A2/A2 allele with higher amygdala reactivity than heterozygotes) (Lee et al., 2011).

A variety of other candidate genes have been investigated for their role in amygdala reactivity in the past few years, although most still require replication. Sumner et al. (2015) and Savits and Drevits (2009) review evidence of association for the *BDNF* Val66Met polymorphism, with the evidence pointing to greater reactivity in carriers of the Met allele. In other individual studies of genes putatively associated with internalizing disorders, variants in the androgen receptor (*AR*; trinucleotide repeat), acid-sensing ion channel 1 (*ASIC1/ACCN2*; rs10875995), fatty acid amide hydrolase (*FAAH*; rs324420), FK506 binding protein 5 (*FKBP5*; rs1360780), neuropeptide Y (*NPY*; rs16147), mineralocorticoid receptor (*NR3C2*; rs5522), and monoaminergic transmission-related *PCLO* (rs2522833) genes were significantly associated with amygdala reactivity to emotional faces (Bogdan et al., 2012; Domschke et al., 2010; Hariri et al., 2009; Holz et al., 2015; Manuck et al., 2010; Smoller et al., 2014; White et al., 2012; Woudstra et al., 2012). A mouse model evidencing impaired fear after acute administration of a *FAAH* inhibitor provides translational support for the role of this gene (Gunduz-Cinar et al., 2013). Another murine-human translational study identified abnormal fear conditioning in a knockout model of the *Pet-1* (*Fev*) gene and found that a SNP within the human ortholog gene *PET-1* (rs860573; A allele) was associated with higher amygdala activation as well as psychopathology and “general distress” in humans (Wellman et al., 2007; Wellman et al., 2013). The adenylate cyclase 7 (*ADCY7*) gene was identified through an assay of differential gene expression in both mouse and human depression phenotypes, and a polymorphism in this gene (rs1064448; T allele) was associated with amygdala reactivity in two human samples (Joeyen-Waldorf et al., 2012).

Finally, a few studies have used molecular genetic methods beyond candidate gene association. A GWAS of 224 schizophrenia/bipolar disorder (BPD)/psychosis cases and controls identified a single genome-wide significant association in the homeobox gene *PHOX2B* (rs10014254) with left amygdala reactivity to emotional faces in the combined case-control sample (Ousdal et al., 2012). However, there was little evidence for association enrichment in the surrounding genomic region, and this association did not replicate in a second sample. Another study compared gene expression in blood mononuclear cells between mood disorder (MDD/BPD) cases and controls and detected 12 differentially-expressed genes, of which *APBB3*, *CFD*, *NFKBIZ*, and *NUCKS1* expression levels were significantly related to amygdala activation (Savitz et al., 2013). Arloth and colleagues (2015) located expression quantitative trait loci (eQTL) underlying glucocorticoid response and used these markers to create polygenic risk scores. These scores predicted blunted amygdala response to angry and sad faces. The lower response was primarily due to an exaggerated reactivity to neutral faces, which suggests that these glucocorticoid response genes might promote an overgeneralized threat response.

Fronto-limbic connectivity: The critical role of the amygdala in threat appraisal and response, emotion processing, and memory necessitates a great deal of connectivity with

numerous other brain structures, especially those in frontal regions that modulate cognitive processing of threatening and emotionally valenced stimuli. Decreased coupling of activation of these regions during threat/emotion processing, specifically between the amygdala and the anterior cingulate cortex (ACC) or prefrontal cortex (PFC), is theorized to represent a loss of inhibitory cortical control over amygdala reactivity (Scharinger et al., 2011). The underlying genetic architecture of this fronto-limbic connectivity is not well understood. A single twin study implicated genetic effects on amygdala-ACC and amygdala-PFC coupling during processing of emotional faces, although heritability estimates were not computed (Miskowiak et al., 2015). The S allele of the 5-HTTLPR and the Met allele of *COMT* have been linked to changes in functional coupling of the amygdala with the PFC and ACC (see Sumner et al., 2015 for a review), and to lower coupling of the amygdala with an “emotional processing network” (PFC, occipital regions, superior temporal gyrus and superior temporal sulcus) (Surguladze et al., 2012). Alexander et al. (2012) also report greater amygdala-hypothalamus coupling in 5-HTTLPR S allele carriers, indicating a role in HPA axis regulation. Won and Ham (2016) discuss two additional studies showing an association between the *COMT* Met allele and greater amygdala-orbitofrontal cortex connectivity. Scharinger et al. (2011) identify two studies of the role of the *MAOA* uVNTR on amygdala-ACC coupling but they report opposite directions of effect; a more recent study supported the low-activity variant having greater functional coupling of these regions (Denson et al., 2014). A variant (rs1625579; T allele) in the microRNA gene *MIR137*, which affects brain development and neurogenesis, was associated with greater connectivity between the amygdala and frontal regions such as the cingulate and PFC (Mothersill et al., 2014).

Physiology

Cardiovascular response: Changes in cardiovascular functioning in reaction to stressors are essential to mobilize an adaptive physiological fight or flight response. Higher heart rate (HR) and lower heart rate variability (HRV) in response to threat are associated with internalizing psychopathology (Carney et al., 1988; Kemp and Quintana, 2013). A number of twin studies have found that resting HR and related measures like blood pressure, respiratory sinus arrhythmia, and pre-ejection period are moderately heritable (31–70%) (De Geus et al., 2007; Ditto, 1993; Van Hulle et al., 2000; Zhang et al., 2004) as are their stress-response component (26–74%, with meta-analysis estimates for HR at 43–45%) (De Geus et al., 2007; Ditto, 1993; Wu et al., 2010). However, the genetic factors influencing individual differences in resting versus stress-response HR appear to be distinct (Ditto, 1993; Wu et al., 2010). HRV is also moderately heritable, with estimates from four studies at around 50% (Neijts et al., 2014; Riese et al., 2007; Su et al., 2010; Wang et al., 2009), although heritability varied for different types of measures such as high versus low frequency spectral power. Unlike HR, 60–81% of the latent genetic influences were shared between resting and stress-response HRV (Wang et al., 2009), possibly because variation in heart rate intrinsically reflects an organism’s changing response to the immediate environment.

Candidate gene studies have primarily been conducted with many of the “usual suspect” neurotransmitter genes as well as genes related to stress response. In the serotonergic system, the 5-HTTLPR S allele has been associated with lower HR and HRV reactivity to

stress in two studies (Agorastos et al., 2014; Taylor et al., 2014) and in a third in the context of an interaction with stressful life experiences (Brummett et al., 2011). An additional study found no association with either HR or HRV response (Mueller et al., 2012), while another found that the L allele was associated with higher basal HR but only in the context of child abuse exposure (Shinozaki et al., 2011). The *MAOA* VNTR predicted higher HR in an anxiety-provoking task and a failure to habituate to the task as well as experience of panic attacks and anxiety during the task (Reif et al., 2014). In the dopaminergic system, the *COMT* Val158Met polymorphism was associated with a time-dependent effect on HR and HRV in one study (Mueller et al., 2012); that is, the Val allele carriers had a greater HR increase, blunted HR recovery, and decreased HRV after a stressor. However, another study showed no main effects of the SNP and evidence that, among MDD patients, it was the Met allele that had lower HRV (Woody et al., 2014). In the cholinergic system, a large meta-analysis of seven cohorts (N = 6,740) found no evidence for association of genes in the acetylcholine gene pathway with HRV (Riese et al. 2014).

Stress-response candidate genes thus far implicated in HR response include the glucocorticoid and mineralocorticoid receptors *NR3C1* and *NR3C2* (DeRijk et al., 2006; Taylor et al., 2014; van Leeuwen et al., 2011) and the adrenergic receptor *ADRA2C* (Kurnik et al., 2008). In mouse models, the corticotropin-releasing factor gene *Crf2* had no effect on HR or HRV stress response (Stiedl et al., 2003; Tovote et al., 2005). Angiotensin-related genes *Ace* and *At1a* were associated, respectively, with multiple measures of resting HRV and with decreased HR and blood pressure reactivity to acute stress in a mouse knockout model (Busjahn et al., 1998; Davern et al., 2009).

Several studies have also examined the *BDNF* Val66Met variant, with conflicting results reported. The Val allele was associated with higher HR reactivity in one study (Alexander et al., 2010), which was similar among females in another study, but with the opposite effect in males (Met > Val) (Shalev et al., 2009). A third study showed no association of *BDNF* with basal or reactive HR or blood pressure (Colzato et al., 2011). One further study demonstrated an association between the Met allele and lower high-frequency (parasympathetic nervous system-influenced) HRV and greater low-frequency/high-frequency ratio (sympathetic nervous system-influenced) HRV at rest (Yang et al., 2010). Clearly there is a need for further efforts to resolve the role of *BDNF* in cardiovascular functioning. A variant in the related nerve growth factor *NGF* gene (rs6330; T allele) was associated with lower HRV for men but not women (Chang et al., 2014). Other candidate genes investigated include the G protein beta-3 subunit (*GNB3*), which was associated with HR response (Kurnik et al., 2008), and two G-protein coupled receptors: the oxytocin receptor (*OXTTR*, rs53576, A allele), which showed inconsistent associations with HR-related measures across two studies (Norman et al., 2012; Rodrigues et al., 2009), and the neuropeptide S receptor *NPSR1* (rs324981; T allele), which was associated with higher basal HR but not HR response in females (Domschke et al., 2011).

Respiratory response: Respiration changes are also an important aspect of the body's mobilization of resources in response to acute threat. Measures of resting pulmonary function are moderately heritable (Ingebrigtsen et al., 2011), but heritability of the respiratory stress response has not been estimated. One candidate gene study found that a

variant in the adenosine receptor *ADORA2A* (previously implicated in panic and caffeine response) was associated with increased respiratory rate among blood-injection-injury phobia patients exposed to venipuncture (Hohoff et al., 2009). Tidal volume is another related component of the respiratory response although its genetics are not well-studied; a single murine experiment found that the heritability of tidal volume in response to a stressful task was significantly increased (from 21% to 37%) with early caregiver separation, indicating an environmental augmentation of genetic predisposition (D'Amato et al., 2011).

Skin conductance response: Skin conductance, or electrodermal activity of the skin's sweat glands, is a marker of ANS activity and physiological arousal. An increase in activity in response to acute threat is known as the skin conductance response (SCR), and higher responses have been reported in patients with ADs (Roth et al., 1990). An early twin study (Lykken et al., 1988) suggested genetic influences on SCR from MZ twin correlations that were nearly twice as high as that of DZ twins; subsequent twin studies have estimated heritability at 43–56% (Tuvblad et al., 2012; Vaidyanathan et al., 2014a) while estimates from a genome-wide measured gene (GCTA) model are somewhat lower, 21–32% (Vaidyanathan et al., 2014a). A genetically informative factor model of multiple ANS indicators reported that SCR is genetically correlated with other sympathetic nervous system factors such as heart rate (Tuvblad et al., 2010). One candidate gene study of the 5-HTTLPR and *COMT* Val158Met polymorphisms found no main effects of either variant, but reported a time-by-genotype interaction for 5-HTTLPR indicative of S allele carriers having greater habituation of the SCR (Lonsdorf et al., 2011). A recent GWAS in 4,424 individuals found no significant associations with SCR (Vaidyanathan et al., 2014a).

Alpha-amylase response: Alpha-amylase, measured in the saliva (sAA), is a putative ANS biomarker, with salivary concentrations positively correlating with ANS activation and norepinephrine secretion in response to stressors (Granger et al., 2007). sAA response to laboratory challenges corresponds to other physiological stress response markers and subjective anxiety ratings (Granger et al., 2007). A multivariate twin study found that a single set of genetic factors influenced both basal sAA and sAA stress response, with heritability of both between 51% and 62% (Out et al., 2011). In candidate gene studies, the L allele of the 5-HTTLPR was associated with stronger sAA stress response but also faster recovery in one study of adults (Mueller et al., 2012). Neither *COMT* (Mueller et al., 2012) nor *BDNF* (Tsuru et al., 2014) showed association with sAA levels in other studies.

Cortisol response: Cortisol, a glucocorticoid hormone, is secreted by the HPA axis in response to stress and can be measured in plasma or saliva. Acute cortisol response correlates with ANS/physiologic stress response and subjective anxiety ratings (Chrousos and Gold, 1992). Cortisol response to various physical and mental stressors (experimentally constructed via the Trier Social Stress Test, dexamethasone/CRH administration, or the cold-pressor test) had negligible heritability estimates in early, small twin studies. However, Federenko et al. (2004) determined that this was likely due to contextual effects, as heritability of cortisol response increased from 32% to 98% with repeated exposure to a stressor task.

HPA axis candidate genes with strong support for a role in the cortisol stress response include *CRH*, *CRHR1*, *CRHBP*, the glucocorticoid/mineralocorticoid receptors *NR3C1* and *NR3C2*, and *FKBP5*, which moderates the function of the glucocorticoid and mineralocorticoid receptors (DeRijk et al., 2006; DeRijk et al., 2011; Heim et al., 2009; Ising et al., 2008; Mahon et al., 2013; Oberlander et al., 2008; Sheikh et al., 2013; Tyrka et al., 2009; van Leeuwen et al., 2011). A polygenic risk score constructed from variants in these genes also positively predicted cortisol response curves with stronger effects in females than males (Pagliaccio et al., 2014). Two studies, including one with over 1,000 participants, found a significant association of the angiotensin converting enzyme (*ACE*) gene with cortisol response (Ancelin et al., 2013; Baghai et al., 2002).

Several studies have investigated the role of the 5-HTTLPR in cortisol response, and a recent meta-analysis of 11 samples (Miller et al., 2013) identified a small but significant association of the S allele with greater reactivity, which was also evident in newborns (Mueller et al., 2010). This effect may be moderated in adults by methylation of the *SLC6A4* gene, possibly indicating epigenetic compensatory mechanisms in the stress response (Alexander et al., 2014). Variants in the serotonin receptor genes *HTR2A* and *HTR2C* have also been associated with higher cortisol response (Brummett et al., 2012; Fiocco et al., 2007).

The *BDNF* Val66Met polymorphism has had conflicting reports of association, with higher cortisol reactivity in carriers of the Val allele in one study (Alexander et al., 2010), the Met allele in another (Tsuru et al., 2014), and neither in a third (Colzato et al., 2011). Variants in the *DRD4* and *GABRA6* genes have demonstrated a relationship with cortisol response in one study each (Armbruster et al., 2009; Uhart et al., 2004), but not in another in which both genes were investigated (Frigerio et al., 2009). Individual studies requiring replication have also found significant genetic effects on cortisol response in the genes *IL-1 β* , *NPSR1*, and *SLC6A15* (Kumsta et al., 2013; Sasayama et al., 2011; Schuhmacher et al., 2013).

Startle response: The startle response is a reflexive muscular reaction to an acute unexpected stimulus such as a sudden loud noise or mechanical/tactile stimulation (e.g. strong puff of air to the forehead or neck) that facilitates the fight or flight response (Lang, 1995). In humans this can be experimentally quantified by measuring the electrical activity produced by the orbicularis oculi muscle during an eye-blink response; murine models often assess whole-body startle reflex. Some evidence indicates that basal/resting startle is exaggerated in ADs (Mineka et al., 1998), although most research has focused on fear-potentiated (FPS) or emotion-modulated startle, which represent an augmented reaction to startle probes administered in the presence of fear-relevant or emotionally-valenced stimuli (Vaidyanathan et al., 2009).

An early study in 29 pairs of twins found greater correlations for MZ twins than DZ twins in the overall startle response and in the negative and positive emotional modulation of startle, although the sample was too small for formal model testing (Carlson et al., 1997). A decade later, Anokhin et al. (2007) estimated overall startle heritability at 64% in 123 twin pairs but found no evidence for genetic factors influencing emotional modulation of startle. Recently, a very large (N = 3,323) hybrid twin and molecular genetic study (Vaidyanathan et al.,

2014b) estimated heritability of overall startle across positive, negative, and neutral stimuli at 37–52% using a biometric twin model and at 49% via GCTA using genome-wide SNPs; they also found no evidence for significant genetic effects on emotional modulation. In contrast, a mouse model indicated additive (but not dominant) genetic effects impacting FPS, with a heritability of 46% (McCaughan et al., 2000). Measurement issues may play a role here, given that startle potentiation measures are typically standardized within person prior to analysis to remove inter-individual variability in overall response.

Candidate gene studies have primarily focused on the serotonergic and dopaminergic systems. As reviewed by Sumner et al. (2015), the 5-HTTLPR S allele has generally been associated with higher overall startle response to neutral and affective imagery but not emotional modulation of the startle response, although its association with fear- (rather than emotion-) potentiated startle was somewhat more consistent. One study found that the S allele was associated with greater FPS only under the threat conditions and not during safety cues, indicating that the conflicting findings may be due to this variant having an effect on defensive reactions rather than fear regulation (Klumpers et al., 2012). A study of the *TPH2* gene (rs4570625) found no association for basal startle or FPS (Armbruster et al., 2010). A murine study found that increasing expression of the 5-HT1B receptor in the dorsal raphe nucleus led to attenuated FPS (Clark et al., 2004).

In the dopaminergic system, conflicting evidence has been found for the *COMT* Val158Met polymorphism (rs4689), with some reporting an association of the Val allele with higher basal (Comasco et al., 2013) and potentiated startle (Domschke et al., 2015), others reporting higher basal (Armbruster et al., 2011) and potentiated startle (Norrholm et al., 2013) in carriers of the Met allele, and others reporting no modulation effects (Armbruster et al., 2011; Comasco et al., 2013). Sumner et al. (2015) reviewed three additional *COMT* studies with conflicting findings regarding potentiated startle. The *DAT1* VNTR 10-repeat allele has also been associated with higher basal/overall but not emotion-modulated startle (Armbruster et al., 2011). Investigation of other candidate genes *BDNF*, *CRP*, and *STMN1* did not yield significant basal or potentiated startle associations (Brocke et al., 2010; Heldt et al., 2007; Michopoulos et al., 2015), though there was some evidence for a gene-by-sex interaction for *STMN1* in overall response (Brocke et al., 2010). The *FMR1* gene may play a role in FPS, as individuals carrying a premutation in this gene for the Mendelian fragile X disease lacked a potentiated startle response to fearful face images (Hessl et al., 2007). Mouse knockout models of the *Npy* (Karl et al., 2010) and *Npsr1* (Zhu et al., 2010) genes indicate that these may play a role, as both were associated with a reduced acoustic startle response and related anxiety/arousal phenotypes.

A few studies have also implemented other molecular genetic approaches. Nelson et al. (2014) tested FPS during a threat-of-shock task among individuals of Asian, Caucasian, and Latino ethnicity. They found that Asians had the lowest baseline startle and FPS during unpredictable threat conditions. Furthermore, in order to link these results with a possible genetic mechanisms, they correlated baseline startle response with ethnicity principal components derived from ancestry informative genetic markers. They found Asian ancestry was negatively correlated with startle while European ancestry was positively correlated, indicative that genetic variants of lower frequency in Asian ancestry groups may be related

to startle response. The first published GWAS of startle response found no genome-wide significant SNP associations for overall or emotion-modulated startle, although post-hoc candidate gene and genome-wide gene-based association tests implicated *GRIK3* in overall startle and *PARP14* in aversive modulation (Vaidyanathan et al., 2014b). Finally, a genome-wide sequencing study investigating the role of rare variants in physiological endophenotypes found that a greater burden of rare variants in the genes *KIF18A* and *SLC27A6* predicted higher differential startle response to pleasant and aversive imagery, respectively (Vrieze et al., 2014).

Paradigms

CO₂ challenge: Hypersensitivity to carbon dioxide (CO₂), indicated by provocation of panic symptoms when exposed to CO₂, is a well-replicated marker of genetic liability to ADs, particularly PD (Coryell, 1997). Paradigms to assess this involve acute administration of CO₂-enriched air, most commonly either as a single vital capacity inhalation of 35% CO₂ enriched air or a sustained (5–10 minute) inhalation of air with 5–7.5% concentration of CO₂. Virtually all published genetic studies of CO₂ challenge paradigms have used the 35% single-inhalation version (see Amaral et al. [2013] and Battaglia et al. [2014] for reviews). Early twin and family studies found that CO₂ hypersensitivity was familial and showed a higher concordance for CO₂-provoked panic attacks in MZ than DZ twins (Bellodi et al., 1998; Perna et al., 1996). Larger twin studies have estimated the heritability of CO₂ sensitivity at around 40%, and this genetic risk is shared with separation anxiety and PD (Battaglia et al., 2009; Roberson-Nay et al., 2013). Some evidence suggests that the acetylcholine system may be involved (Battaglia, 2002), and one human candidate gene study of the 5-HTTLPR polymorphism found greater CO₂ sensitivity in L carriers than S allele carriers (Schmidt et al., 2000), although this failed to replicate in another study (Verschoor and Markus, 2012). Two murine studies, however, have implicated a role of the serotonin system in sensitivity to CO₂ (Li and Nattie, 2008; Puissant et al., 2015). In another human study, SNPs from multiple candidate genes previously implicated in ADs/traits (*CCKBR*, *SLC6A4*, *GAD1*, *COMT*, *BDNF*, *TMEM132D*, *ASIC1*, *ASIC2*, *ADCYAP1R1*, and *FKBP5*) were evaluated with respect to respiratory response to a sustained carbon dioxide challenge task (Savage et al., 2015a). Of these, only the *ASIC1* gene was significantly associated with basal respiratory rate and none with respiratory response to the task.

Fear conditioning: Fear conditioning (FC) is the process of associative learning by which a person develops fear towards an evolutionarily neutral stimulus (CS+) through its repeated pairings with an inherently aversive or threatening unconditioned stimulus (UCS). This is a critical learning mechanism that increases survival likelihood by enhancing avoidance of potential threats, and it is highly conserved across species. FC paradigms pair an aversive electrical shock or loud noise with either a neutral environment (contextual conditioning) or a neutral visual/auditory cue (cued conditioning) and assess the acquired fear response (typically self-report, startle response, or autonomic reactivity like SCR) to the CS+ versus a context or cue that has not been paired with the aversive stimuli, known as the CS-. FC paradigms encompass two phases: the acquisition of the conditioned fear association and the extinction of conditioned fear when the CS+ is no longer paired with the UCS. The neural

circuitry and cellular signaling pathways underlying FC are well-characterized in rodents, and several reviews on this topic already exist (Briscone et al., 2014; Pape and Pare, 2010; Tovote et al., 2015). A single twin sample has been used to investigate the heritability of FC using SCR as the physiological measure, which was estimated at 35–45% (Hettema et al., 2003). Further, in this sample the latent genetic factors influencing FC were distinct from those underlying episodic memory, and the genetic effects on the conditioned SCR were largely distinct from those influencing self-reported fears (Fredrikson et al., 2015; Hettema et al., 2008).

Much of the candidate gene research on FC has been reviewed in detail elsewhere, and we provide here only a brief overview of these, with a focus on discussing other studies not previously reviewed. Although not entirely consistent, a number of studies across both humans and mice have identified a role of the *BDNF* Val66Met polymorphism in FC, specifically that the Met allele is related to impaired fear extinction through its putative effects on reducing availability of the BDNF protein product, which has a role in synaptic plasticity (see Erhardt and Spoormaker [2013], Hartley and Casey [2013], Johnson and Casey [2015], Lonsdorf and Kalisch [2011], and Sumner et al. [2015] for relevant reviews). Bauer (2015) and Lonsdorf and Kalisch (2011) reviewed the evidence for serotonergic gene effects on FC, concluding that 5-HTTLPR S allele carriers express higher levels of conditioned fear and observational fear learning and poorer ability to inhibit fear in the context of the CS– or safety cues, although some studies only find this effect when including interactions with other genes or environmental stressors. The serotonin receptor gene *HTR1A* has also been associated with contextual FC (Baas and Heitland, 2014).

Lonsdorf and Kalisch (2011) and Sumner et al. (2015) also review evidence supporting effects on FC from dopaminergic genes (*COMT* in extinction resistance and deficits in fear inhibition in the presence of safety cues, *DAT1* in extinction, *DRD2* with conditioning but not extinction, and no association with *DRD4*). Other evidence reviewed by Lonsdorf and Kalisch (2011) includes an association of *NPSR1* with hypersensitivity to the CS+ and of *ADCYAP1R1* with impaired CS+/CS– discrimination, and no FC associations with *MAOA* or *ANKK1*. An initial association with *ADCYAP1R1* was not supported in two independent samples in a more recent human study (Pohlack et al., 2015). A review by Stoppel et al. (2006) discusses potential roles of glutamate receptors, ion channels such as *ASIC1*, genes involved in the CamK and MAPK cell signaling pathways, stress hormones (*CRH*), neuropeptides (CCK, SST), and cannabinoid receptors. Glucocorticoid genes (CRF receptors, *CRHR1*, and *NR3C1*) have received further support in mouse and human studies (Ridder et al., 2012; Risbrough et al., 2009), as have genes involved in the cannabinoid system such as *CBI*, *CB2*, and *FAAH* (Chhatwal et al., 2005; Choi et al., 2012; Dincheva et al., 2015; Gunduz-Cinar et al., 2013; Heitland et al., 2012).

Fear generalization: Related to FC, fear generalization is the tendency to associate a conditioned fear with objects or events that are similar to the conditioned stimulus. Overgeneralization of the fear response to stimuli that pose no true threat is posited as a maladaptive component of ADs and theorized as the mechanism by which individuals with PD develop widespread agoraphobia. Little genetic research has been conducted on this construct, with a single candidate human study of the *ADCYAP1R1* gene (rs2267735, C

allele) demonstrating an association with impaired threat/safety stimulus discrimination in a FPS task in females (Ressler et al., 2011). Knockout studies have identified a role for the mouse genes *Gad65* (Bergado-Acosta et al., 2008; Lange et al., 2014) and *Gabbr1* (Shaban et al., 2006), and *Grin1* (Vieira et al., 2015) in the biology of fear generalization and discrimination.

Responses to Potential Threat

The RDoC defines potential threat by the following: “Activation of a brain system in which harm may potentially occur but is distant, ambiguous, or low/uncertain in probability, characterized by a pattern of responses such as enhanced risk assessment (vigilance). These responses to low imminence threats are qualitatively different than the high imminence threat behaviors that characterize fear.” The potential threat construct is the closest approximation to clinical anxiety (as opposed to phobic fear) within the NVS domain. However the potential threat construct is not as well characterized as the other two threat-related constructs. There are only a few physiology-based phenotypes for sustained threat included in the RDoC matrix, so we have expanded to include others potentially relevant for NVS. While not included in the RDoC NVS matrix, we also summarize findings for specialized constructs of anxious temperament in this section.

Circuits

EEG asymmetry: Asymmetric brain electrical activity theoretically underlies the balance of approach versus avoidance motivation, with right-dominant asymmetry being associated with avoidance (Davidson, 1998; Jacobs et al., 2015) and linked to MDD and negative affect more broadly. This phenotype has been conceptualized as part of the Positive Valence System/reward motivation but is included here because the counterpart to the left-dominant reward motivation phenotype is an individual’s predisposition towards increased sensitivity to punishment and avoidance behaviors, which are relevant elements of NVS. A twin study of 123 pairs of female twins estimated the heritability of frontal asymmetry to be 0% and 27% for lateral-frontal and mid-frontal regions, respectively (Anokhin et al., 2006). Two larger twin studies ($N = 760\text{--}951$ individuals) found evidence for slightly higher heritability: 15% (lateral-frontal) and 25% (mid-frontal) (Gao et al., 2009) and 32–37% for overall frontal asymmetry (Smit et al., 2007), with the study by Smit and colleagues suggesting possible sex differences in heritability. Overall EEG alpha power has stronger genetic effects than asymmetry measures (heritability of 79–85% across all regions) (van Beijsterveldt and van Baal, 2002). Candidate gene studies have found support for greater right frontal asymmetry (in some regions) in child and adult carriers of the 5-HTTLPR S allele (Bismark et al., 2010; Christou et al., 2015). Other serotonergic genes have also been studied, with a polymorphism in *HTR1A* (rs6295; G allele) predicting greater right asymmetry across almost all frontal regions, while a variant in *HTR2A* was associated with right asymmetry in only one region (Bismark et al., 2010). There is modest evidence for a role of the *BDNF* Val66Met SNP (rs6265), with a trend level association between the Met allele and greater right frontal asymmetry in one study of mood disorder cases (Bulgin et al., 2008).

Physiology

Basal cortisol response: As described in the Acute Threat section, cortisol is a glucocorticoid hormone secreted by the HPA axis in response to stress; however, it also plays a major role in normal metabolism, immune response, and many physiological functions. Higher basal/resting cortisol levels are linked to trait anxiety and internalizing problems, although low basal levels and a blunted cortisol response has been seen in those with MDD or chronic stress, potentially indicative of a down-regulation of the HPA axis after prolonged stress exposure (Chrousos and Gold, 1992). A meta-analysis of five small twin studies of basal cortisol levels estimated its heritability at 62% (Bartels et al., 2003), and a large twin study of average daily cortisol levels reported a heritability of 42–48% (Franz et al., 2010). Candidate gene studies of basal cortisol have alternatively found an association between the 5-HTTLPR and waking cortisol levels (Chen et al., 2009) and no association between 5-HTTLPR or *COMT* genotype and cortisol levels assessed at baseline prior to a laboratory stressor (Lonsdorf et al., 2011). Significant associations have been identified between the *BDNF* and *NR3C2* genes and pre-stressor task cortisol levels (Colzato et al., 2011; DeRijk et al., 2011). A combined candidate gene/GWA study found significant effects of variants in the *FKBP5* candidate gene on average daily cortisol levels although no individual markers reached genome-wide significance (Velders et al., 2011). However, a GWAS of over 12,000 individuals identified a genome-wide significant association with morning plasma cortisol levels from three partially independent signals in a locus encompassing the *SERPINA6* and *SERPINA1* genes on chromosome 14, genes which code for corticosteroid-binding globulin and alpha1-antitrypsin, respectively (Bolton et al., 2014).

Behaviors

Behavioral inhibition: Behavioral inhibition (BI) to the unknown is a temperamental profile characterized as a stable proclivity to be cautious, quiet, and behaviorally restrained in novel situations. Primarily studied in younger children, BI has been identified as a developmental risk factor for social phobia (up to a seven-fold increase in risk (Clauss and Blackford, 2012)) and possibly panic, other ADs, and depression (reviewed by Hirshfeld-Becker et al. [2008]). Several twin studies provide heritability estimates for BI-related phenotypes: around 70% for shyness/inhibition in pre-school children (Eley et al., 2003), 40–60% for withdrawn behavior in a longitudinal study of children ages 3 to 12 (Hoekstra et al., 2008), and 45% for a measure of BI in older adults (Mosing et al., 2012).

Genetic association studies have tested a handful of candidate genes for their potential role in BI (recently reviewed in Clauss et al. [2015]). One study reported an association of the *RGS2* gene, linked to anxious temperament in rodents, with BI and other endophenotypes related to social phobia and introversion (Smoller et al., 2008), although another study failed to replicate this association (Hettema et al., 2013). This gene also has reported associations with panic and PTSD. A study of children of parents with PD found an association of the *CRH* gene with BI (Smoller et al., 2005). A large German study examined the candidate gene *AVPR1A*, part of the arginine-vasopressin system which has a role in affiliative behaviors, in relation to the behavioral inhibition system (BIS)/behavioral activation system (BAS) scales, reporting an association of BIS with SNP rs11174811 (Reuter et al., 2015).

Another German study, conducted in anxiety and depression cases and controls, created a BI proxy score by combining neuroticism and introversion, reporting association of this phenotype with *GAD2* (Unschuld et al., 2009), replicating a prior reported association of BI with this gene (Smoller et al., 2001). A SNP in an autism risk gene, *CNTNAP2*, was reported in association with social anxiety and retrospectively reported BI in adults and selective mutism in children (Stein et al., 2011). Association of the serotonin transporter gene 5-HTTLPR polymorphism with BI was reported in a small sample of Chinese toddlers (Chen et al., 2014), while larger studies in US children (Rubin et al., 2013), Brazilian adolescents (Bortoluzzi et al., 2014), and Australian adults (Jorm et al., 1998) failed to detect an association. The Rubin et al. study, conducted in 394 US children, tested association of 20 polymorphisms in 15 catecholaminergic candidate genes with Withdrawn Behavior Subscale Score (WBS) of the Child Behavior Checklist (CBCL), which combines items indicating inhibition or depression. After correction for age, sex, and multiple testing, they reported significant association of the WBS with two SNPs, one in *HTR2A* and the other in *ADRA2A* (Rubin et al., 2013). To date, no GWAS has examined BI.

Anxiety Sensitivity: Anxiety sensitivity (AS) is the fear of the emotional and physiological sensations stemming from anxious arousal. It is thought to arise from beliefs that these sensations have harmful consequences. When individuals high on AS become anxious, they also become alarmed by these arousal-related responses, leading to a further escalation in their level of anxiety (Reiss et al., 1986). Studies suggest that AS contributes to the risk of developing ADs, particularly panic (Schmidt et al., 2006). AS is moderately heritable in adults (45%) (Jang et al., 1999; Stein et al., 1999), adolescents (47%) (Zavos et al., 2012) and children (37%) (Eley et al., 2007). Genetic factors underlying AS predicted the development of anxiety symptoms in childhood (Eley et al., 2007), supporting its value as an endophenotype.

A handful of candidate genes have been tested for association with AS. One study reported association of *CCKBR* with AS and cholecystokinin-induced panic (Koszycki et al., 2012). A German PD research consortium reported association of AS with *NPSR1* (Domschke et al., 2011), *CRHR1* (Weber et al., 2015), and the gene coding for microRNA hsa-miR-4717-5p, which regulates the gene *RGS2* (Hommers et al., 2015), in conjunction with other PD-related phenotypes. Such findings are tentative until adequately replicated. One GWAS for AS has been conducted in a sample of 730 adult twin subjects. The authors reported genome-wide significant association for one SNP in the *RBFOX1* gene on chromosome 16, with indirect evidence for replication in an independent sample examining AD risk (Davies et al., 2015).

Trait Anxiety: Trait anxiety (TA) is a stable measure of overall stress responsiveness. Individuals with higher TA more likely become anxious when exposed to stress. TA has most often been characterized by the trait subscale of the Spielberger's State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970). The earliest twin studies in UK children report heritability of TA from the Revised Child Manifest Anxiety Scale ranging from 0% to 59% depending upon age and informant (Thapar and McGuffin, 1995). Similar results were obtained from a US twin sample (Topolski et al., 1999). Another UK study estimated STAI

TA heritability at 31%, with significant genetic correlations with state anxiety (Lau et al., 2006). A study in US children found lower heritability for TA in early childhood (15%) that increased by late adolescence to 45% (Garcia, et al., 2013). A recent study in Chinese children (ages 9–18) reported heritability estimates of 50–60% for STAI TA (Chen et al., 2015). We were unable to identify candidate gene studies or GWAS of TA as defined here.

Responses to Sustained Threat

RDoC defines sustained threat as “an aversive emotional state caused by prolonged (i.e., weeks to months) exposure to internal and/or external condition(s), state(s), or stimuli that are adaptive to escape or avoid. The exposure may be actual or anticipated; the changes in affect, cognition, physiology, and behavior caused by sustained threat persist in the absence of the threat, and can be differentiated from those changes evoked by acute threat.”

Sustained threat differs theoretically from the previous two constructs in that it includes negative emotional and physiological states that are the result of, rather than a proximal response to, threatening or aversive stimuli. This construct is closely connected in some ways to the idea of learned helplessness: psychological or physiological changes within a person that occur when immediate responses to a stressor (such as those recruited by acute threat response systems) are ineffective or impossible to achieve. Phenotypes included in this construct are somewhat more difficult to categorize because the definition of this construct implies a known etiological origin, and it is not always clear whether these psychological and physiological traits are a cause or an effect of psychopathology. However, we review in this section some phenotypes that are putatively altered in response to prolonged stress exposure.

Circuits

Attentional network: Vigilance towards, appraisal of, and response to threat are part of the core conceptualization of NVS traits and behaviors. The attentional network modulates cognitive resources in these domains, and patients with ADs have been shown to have altered functioning of this network. Panic disorder, for example, is associated with physiological hyperarousal and increased attention towards perceived or actual threats (Geiger et al., 2014), while hypervigilance is a key symptom of post-traumatic stress disorder. Although there is overlap with the RDoC “Cognitive Systems” domain, it is included in this review because of the relevance of attentional systems to core NVS elements (and AD correlates) like risk assessment, vigilance, and attentional biases. Brain circuits controlling attention can be reliably parsed into three cohesive anatomical sub-networks: alerting (arousal and response readiness), orienting (directing attention), and executive control (deciding which stimuli to attend/not attend to), each with distinct neural structures and neurotransmitters (Fan et al., 2001). In a small sample of 52 Chinese twin pairs, each sub-network was found to have genetic influences, with much lower heritability for alerting (18%) and orienting (16%) than for executive control (72%) (Fan et al., 2001). In a larger follow up in 202 pairs of Caucasian twins aged 6–9, somewhat larger but generally consistent estimates of 32, 27, and 55%, respectively, were found, and the latent genetic influences were shared across sub-networks and with working memory (Wang et al., 2012).

The norepinephrine-activated alerting network is of particular relevance to NVS as it relates to hypervigilance and attentiveness/attentional biases toward threat (Geiger et al., 2014). Genes demonstrating an association with the activation or function of the alerting network include *ADRA2A* (Green et al., 2008), *NET* (Green et al., 2008), *NPSR1* (rs324981) (Neufang et al., 2015), the NMDA receptor subunit *GRIN2B* (rs1806201) (Schulz et al., 2012), *CACNA1C* (rs1006737) (Thimm et al., 2011) and, at a trend level only, the dopamine transmitter *DAT1* (rs6350) (Konrad et al., 2010). Other tested variants having no significant associations with the alerting network included *TPH2* (rs4570625), *ZNF804A* (rs1344706), *DTNBPI* (rs1018381), and *COMT* (rs4689) (Balog et al., 2011; Reuter et al., 2007; Thimm et al., 2010).

Physiology

Error-related negativity (ERN): ERN is a characteristic deflection in the electrical event-related potential (ERP) emitted by the brain within 150 ms after an individual recognizes that they have committed an error. This is typically induced with timed cognitive tasks having a high probability of error, such as Go/NoGo or flanker tasks where individuals have to identify a visual cue against a difficult discrimination background. As reviewed by Olvet and Hajcak (2008), there is evidence that higher ERN is associated with, and a putative endophenotype for, depression, anxiety, and internalizing traits, likely through a mechanism of sensitivity to punishment. A single twin study of 274 pairs of adolescents estimated the heritability of ERN at 47% (no sex differences), with high correlations between the genetic factors underlying ERN and the related ERPs of correct response negativity (CRN) and error positivity (Pe) (Anokhin et al., 2008).

A study of Huntington's disease patients and controls identified a reduced ERN in patients that was correlated with the length of the trinucleotide CAG repeats within their *Huntingtin* gene, indicative of a potential role of the dopamine system in ERN (Beste et al., 2006) – which is conceptually consistent with the role of dopamine in feedback-related learning. As reviewed by Manoach and Agam (2013), several genes from the dopaminergic system have been associated with ERN or the related deltaERN measure (difference between the ERN and CRN), with an association of the *DAT1* VNTR and conflicting evidence across studies for an association of *DRD2*, *DRD4*, and *COMT*. The *DRD4* variant rs1800955 (T allele) was associated with increased ERN in one study included in the review (Kramer et al., 2007), but a more recent study reported an opposite direction of effect (Agam et al., 2014). An additional study of the *COMT* Val158Met polymorphism supported the association of the Val allele with increased ERN, an effect that was moderated by the acute administration of dopamine (Mueller et al., 2011). Also discussed by Manoach and Agam (2013) is conflicting evidence for association of the 5-HTTLPR across studies, and evidence from one study each reporting an association between HTR1A (rs6295, G allele) and BDNF (Val allele) and reduced ERN.

Paradigms

Dot probe paradigm: The dot-probe is a visual task that assesses attentional biases by presenting two visual stimuli side-by-side on a screen which are quickly replaced by a target cue whose location the participant must identify. Reaction time to locate the cue reflects

whether the participant was attending to the stimulus in the same or different location as the target cue. Attentional biases in relation to negatively valenced or threatening stimuli are commonly reported in AD patients. A small study of 12 pairs of twin children found some initial support (non-significant) for genetic factors underlying attentional orienting to fearful/threatening emotional faces using this task (Elam et al., 2010), but two larger studies of 125 and nearly 300 pairs found no evidence of heritability for attentional bias in either children or adults (Brown et al., 2013; Rijdsdijk et al., 2009). Despite this, several candidate gene studies have been conducted with the dot-probe task, with four independent studies finding that carriers of the 5-HTTLPR S allele had greater attentional orienting towards negative emotional stimuli, while L carriers focused their attention away from these (Beevers et al., 2007; Carlson et al., 2012; Osinsky et al., 2008; Perez-Edgar et al., 2010). In addition, a variant in the *FKPB5* gene (rs1360780, T allele) has been linked to greater attentional bias to threat (Fani et al., 2013), while the *BDNF* Val66Met polymorphism (rs6265) has shown modest evidence of an indirect effect on attentional threat bias through reductions in white matter tract integrity (Carlson et al., 2014). One study has demonstrated that variants in the *DBH* and *MAOA* genes have an interactive effect, but not individual main effects, on attentional bias towards negative faces (Gong et al., 2013).

Face emotion processing paradigms: Social cues, particularly facial displays of emotion, are used both to display threat and to convey information about external and potential threats. Emotional (angry/fearful) faces are used in many tasks (e.g. those measuring amygdala threat reactivity), but paradigms specifically investigating the mechanisms underlying face emotional processing typically require participants to correctly identify certain emotions presented in pictures of faces or use eye-tracking software to measure vigilance toward facial cues. Genetic epidemiological studies are lacking, but candidate gene studies have identified a role of the 5-HTTLPR S allele in greater emotion identification accuracy, increased fixation and attentiveness toward facial emotion cues, and a lower likelihood of perceiving neutral faces as happy (Boll and Gamer, 2014; Gohier et al., 2014). Other studies have identified genetic effects on gaze duration, recognition biases, and neural activation during facial emotion processing from the *HTR1A/HTR1B* (Mekli et al., 2011), *CBI* (Chakrabarti and Baron-Cohen, 2011), *COMT* (Gohier et al., 2014), *OXTR* (Puglia et al., 2015), and *TOMM40* (McFarquhar et al., 2014) genes, as well as a set of genes associated with NMDA receptor activation (Mattingdsdal et al., 2013).

Frustrative non-reward

RDoC defines this construct as “reactions elicited in response to withdrawal/prevention of reward, i.e., by the inability to obtain positive rewards following repeated or sustained efforts.” Frustrative non-reward is more tangentially related to ADs having overlap with other psychiatric disorders. Although not specifically listed in the RDoC NVS matrix, we also review irritability as an important transdiagnostic dimensional phenotype of negative affect related to frustration and aggression.

Behaviors

Reactive aggression: Reactive aggression (RA) is an aggressive response to a perceived threat (the “fight” dimension of the flight or fight response). Only one twin study of RA was

identified (Baker et al., 2008). This study used a US sample of 605 9-year-old twin pairs and found modest heritability estimates for RA in boys (0.38, 95% CI: 0.25–0.49). Girls were found to have no significant genetic influences; instead unique and shared environment likely explained their liability to aggression. In boys, RA measures were moderately correlated with proactive aggression, with a shared genetic correlation of 0.57 (95% CI: 0.38–0.74) ¹ (Baker et al. 2008). We were unable to identify candidate gene studies or GWAS of this phenotype.

Irritability: The DSM defines irritable mood as being “easily annoyed and provoked to anger” and usually refers to frustrative or angry responses to situations/stimuli (American Psychiatric Association, 2013). Few studies have directly examined the heritability of irritability; most were conducted in the context of related traits (e.g., aggression, depression) (Coccaro 2007; Savage et al., 2015b) or other psychiatric disorders (e.g., bipolar) (Hudziak 2005). Irritability is usually assessed via behavioral checklists on child self-reports or parents’ reports of their child. Available studies suggest that irritability is moderately heritable (around 30%, range 22–51%) (Coccaro 2007/1997, Stringaris 2008, Seroczynski 1999) and potentially developmentally dynamic with differential patterns based on sex. In a Swedish study of 1310 twin pairs, male irritability exhibited increased heritability from middle childhood to late adolescence while females exhibited decreasing heritability across the same developmental timespan. We were unable to identify GWAS or candidate gene studies.

DISCUSSION

The current review presented evidence from the existing epidemiological and molecular genetic literature on the genetic etiology of NVS traits, ranging from the biologically proximal brain systems and circuits to peripheral physiology to self-reports of anxious temperament. The wide variety of phenotypes included in this review precludes broad generalizations across the results, but a few consistent points may be noted. First, well-done genetic epidemiology studies for many NVS traits are lacking, especially for the laboratory-based measures that are difficult or expensive to measure on a large scale (e.g. fMRI, physiology). As discussed earlier, measures proposed as endophenotypes need to be heritable and share that heritability with clinical phenotypes (“co-aggregate in relatives”) to be relevant for further investigation in gene-finding studies. These various requirements have not been robustly demonstrated for most of the phenotypes reviewed herein. For the phenotypes for which some data are available, the results suggest that the heritability of simpler, biologically-based traits are in the same range or modestly higher than that found for their higher-level disorder-based counterparts. Whether putative endophenotypes are more strongly heritable has been an ongoing subject of debate (Flint and Munafo, 2007). However, the validity of any such conclusion depends on many factors, such as the power of the sample, the age of the subjects, the instrument used to assess the phenotype, its inherent stability and reliability, and the model used for analysis (Kendler and Neale, 2010). Furthermore, few twin or family studies have examined multiple NVS measures in the same sample, a requirement to determine their genetic risk structure (covariance), i.e., whether they represent the downstream effects of common or distinct sets of underlying genetic

factors. Such information can guide how multiple measures may be integrated to optimize the phenotypic targets chosen for studies that seek to discover novel genes and understand the mechanisms by which they produce clinical outcomes.

Second, although a great number of candidate gene association studies have been conducted over the past decade, these have almost exclusively utilized the same few variants in the same limited set of neurotransmitter system genes (e.g. 5-HTTLPR, *COMT* Val158Met, etc.). Confidence may be cautiously established in a few of these associations that have been consistently replicated or upheld in meta-analyses (e.g., 5-HTTLPR in amygdala reactivity, cortisol and glucocorticoid genes in cortisol response). These “usual suspect” candidates derive from the historical assumption that the etiology of clinical disorders lies in the same biologic systems as those affected by the drugs used to treat them, namely, the monoamine neurotransmitters (serotonin, dopamine, and norepinephrine). We note that this is analogous to studying the genes related to kidney function in order to detect the etiology of heart failure, since diuretics used to relieve its symptoms of fluid overload act in the kidney, not the heart. This has led to an abundance of neuropsychiatric genetic studies aimed at genes in these systems, often limited to one or another putative “functional” polymorphism rather than probing the large range of variation that can affect downstream gene expression. Thus, the available evidence base is both limited and biased, consisting largely of studies of the same few genetic polymorphisms that are those most frequently tested. This continues to occur despite an increasing level of certainty in the psychiatric genetics community that all complex human phenotypes are highly polygenic, influenced by at least hundreds of genetic variants of small effect (Agarwala et al., 2013), and evidence that the vast majority of genome-wide significant signals from GWAS thus far are novel and located outside of functional protein-coding regions (Maurano et al., 2012). We acknowledge that the limited choices of suitable candidates available for study drives this folly, as linkage studies have generally not identified more likely candidates for psychopathology, and few results from well-powered GWAS are available to date.

Additional caution is required in the interpretation of candidate gene studies in light of critical reviews of the candidate gene approach (Colhoun et al., 2003; Duncan et al., 2014), suggesting high rates of false positives due to publication bias, low prior probability of selecting a likely candidate, underpowered samples, and the “winner’s curse” of larger than expected effect sizes in the first published study. Indeed, even within one of the few meta-analyses available for experimental NVS traits (association between 5-HTTLPR and amygdala reactivity [Murphy et al., 2013]), evidence was detected of publication bias and unexpectedly large effect sizes in the published studies. Across the candidate gene studies reported here, the majority had samples of fewer than 200 individuals, especially for neuroimaging protocols, making them likely underpowered based on genetic effect sizes seen by groups such as the Psychiatric Genomics Consortium. Further, many of the reported associations were of marginal significance (p values between .01 and .05); while this does not negate the possibility of a true association, it also does not inspire confidence.

While the candidate gene approach has many limitations, the more conservative atheoretical GWAS design is also not without difficulties; namely, that it requires very large samples and small p -values estimated using strict multiple testing corrections that can be overly stringent.

Only a few GWAS of dimensional NVS traits have been published thus far, with no replicated genetic associations identified. Nevertheless, this leaves open a substantial gap in the literature, and recent technological advances and decreases in cost for large-scale molecular genetic studies may stimulate advances in this research area if funding agencies are willing to support them. Limitations due to sample size will likely require meta-analyses across datasets from individual studies like has proven successful in GWAS of clinical disorders; this approach is strongly encouraged and supported by NIMH's RDoC initiative. While novel gene discovery via GWAS is theoretically possible for laboratory-based NVS phenotypes, the effort and expense required to collect such data in sufficiently large samples makes this less plausible. The value of such data might more likely come from the ability to take new candidate genes identified in very large GWAS conducted with cruder, more easily assessed phenotypes (i.e., clinical symptoms or disorders as are being conducted presently) and investigate their mechanistic role in disorder expression through testing them in association with NVS phenotypes.

In conclusion, NVS traits across the range of the RDoC spectrum thus far studied in genetic epidemiological samples are moderately influenced by genetic factors. The first generation of candidate gene and GWAS studies has laid the groundwork to better appreciate and prepare to address the challenges that come along with genetic research of these complex traits. However, this field is still in its infancy; there remains a great deal of work to be done to fully understand the genetic mechanisms underlying these traits including replication and meta-analysis of current findings and GWAS and other innovative study designs to resolve the biological underpinnings of NVS traits and their associations with psychopathology. Their dimensional, possibly endophenotypic nature may lend itself to improved power and reliability for molecular genetic studies, but that is yet to be demonstrated. As recently cautioned by Kozac and Cuthbert (2016), the level and granularity of current RDoC-formulated constructs may still not map strongly onto molecular genetic signals: "perhaps such narrower constructs (as cognition, emotion, learning, memory, motivation, and perception) are still too broad for practical purposes, and *explananda* of even smaller grain size might be required for informative cross-level analyses of biological and psychological phenomena." Thus, the difficulties associated with identifying genes for NVS phenotypes will likely remain as challenging in the RDoC era as they have been for clinical phenotypes.

Acknowledgments

This work was supported by National Institutes of Mental Health grant R01MH098055 (JMH and CS), T32MH020030 (JS) and R01MH101518 (RRN).

References

- Agam Y, Vangel M, Roffman JL, Gallagher PJ, Chaponis J, Haddad S, Goff DC, Greenberg JL, Wilhelm S, Smoller JW, et al. Dissociable genetic contributions to error processing: a multimodal neuroimaging study. *PloS One*. 2014; 9:e101784. [PubMed: 25010186]
- Agarwala V, Flannick J, Sunyaev S, Go TDC, Altshuler D. Evaluating empirical bounds on complex disease genetic architecture. *Nat Genet*. 2013; 45:1418–1427. [PubMed: 24141362]
- Agorastos A, Kellner M, Stiedl O, Muhtz C, Becktepe JS, Wiedemann K, Demiralay C. The 5-HTTLPR genotype modulates heart rate variability and its adjustment by pharmacological panic challenge in healthy men. *J Psychiatr Res*. 2014; 50:51–58. [PubMed: 24342768]

- Alexander N, Osinsky R, Schmitz A, Mueller E, Kuepper Y, Hennig J. The BDNF Val66Met polymorphism affects HPA-axis reactivity to acute stress. *Psychoneuroendocrinology*. 2010; 35:949–953. [PubMed: 20079575]
- Alexander N, Klucken T, Koppe G, Osinsky R, Walter B, Vaitl D, Sammer G, Stark R, Hennig J. Interaction of the serotonin transporter-linked polymorphic region and environmental adversity: increased amygdala-hypothalamus connectivity as a potential mechanism linking neural and endocrine hyperreactivity. *Biol Psychiatry*. 2012; 72:49–56. [PubMed: 22418015]
- Alexander N, Wankerl M, Hennig J, Miller R, Zankert S, Steudte-Schmiedgen S, Stalder T, Kirschbaum C. DNA methylation profiles within the serotonin transporter gene moderate the association of 5-HTTLPR and cortisol stress reactivity. *Transl Psychiatry*. 2014; 4:e443. [PubMed: 25226552]
- Amaral JM, Spadaro PT, Pereira VM, Silva AC, Nardi AE. The carbon dioxide challenge test in panic disorder: a systematic review of preclinical and clinical research. *Rev Bras Psiquiatr*. 2013; 35:318–331. [PubMed: 24142095]
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5. Washington, DC: American Psychiatric Publishing; 2013.
- Ancelin ML, Carriere I, Scali J, Ritchie K, Chaudieu I, Ryan J. Angiotensin-converting enzyme gene variants are associated with both cortisol secretion and late-life depression. *Transl Psychiatry*. 2013; 3:e322. [PubMed: 24193727]
- Anokhin AP, Heath AC, Myers E. Genetic and environmental influences on frontal EEG asymmetry: a twin study. *Biol Psychol*. 2006; 71:289–295. [PubMed: 16054745]
- Anokhin AP, Golosheykin S, Heath AC. Genetic and environmental influences on emotion-modulated startle reflex: a twin study. *Psychophysiology*. 2007; 44:106–112. [PubMed: 17241146]
- Anokhin AP, Golosheykin S, Heath AC. Heritability of frontal brain function related to action monitoring. *Psychophysiology*. 2008; 45:524–534. [PubMed: 18503487]
- Arloth J, Bogdan R, Weber P, Frishman G, Menke A, Wagner KV, Balsevich G, Schmidt MV, Karbalai N, Czamara D, et al. Genetic differences in the immediate transcriptome response to stress predict risk-related brain function and psychiatric disorders. *Neuron*. 2015; 86:1189–1202. [PubMed: 26050039]
- Armbruster D, Mueller A, Moser DA, Lesch KP, Brocke B, Kirschbaum C. Interaction effect of D4 dopamine receptor gene and serotonin transporter promoter polymorphism on the cortisol stress response. *Behav Neurosci*. 2009; 123:1288–1295. [PubMed: 20001112]
- Armbruster D, Mueller A, Strobel A, Kirschbaum C, Lesch KP, Brocke B. Influence of functional tryptophan hydroxylase 2 gene variation and sex on the startle response in children, young adults, and older adults. *Biol Psychol*. 2010; 83:214–221. [PubMed: 20064585]
- Armbruster D, Mueller A, Strobel A, Lesch KP, Kirschbaum C, Brocke B. Variation in genes involved in dopamine clearance influence the startle response in older adults. *J Neural Transm*. 2011; 118:1281–1292. [PubMed: 21445667]
- Baas JM, Heitland I. The impact of cue learning, trait anxiety and genetic variation in the serotonin 1 receptor on contextual fear. *Int J Psychophysiol*. 2014 Epub ahead of print.
- Baghai TC, Schule C, Zwanzger P, Minov C, Zill P, Ella R, Eser D, Oezer S, Bondy B, Rupprecht R. Hypothalamic-pituitary-adrenocortical axis dysregulation in patients with major depression is influenced by the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene. *Neurosci Lett*. 2002; 328:299–303. [PubMed: 12147330]
- Baker LA, Raine A, Liu J, Jacobson KC. Differential genetic and environmental influences on reactive and proactive aggression in children. *J Abnorm Child Psychol*. 2008; 36:1265–1278. [PubMed: 18615267]
- Balog Z, Kiss I, Keri S. ZNF804A may be associated with executive control of attention. *Genes Brain Behav*. 2011; 10:223–227. [PubMed: 21040459]
- Bartels M, Van den Berg M, Sluyter F, Boomsma DI, de Geus EJC. Heritability of cortisol levels: review and simultaneous analysis of twin studies. *Psychoneuroendocrinology*. 2003; 28:121–137. [PubMed: 12510008]
- Battaglia M. Beyond the usual suspects: a cholinergic route for panic attacks. *Mol Psychiatry*. 2002; 7:239–246. [PubMed: 11920151]

- Battaglia M, Pesenti-Gritti P, Medland SE, Ogliari A, Tambs K, Spatola CM. A genetically informed study of the association between childhood separation anxiety, sensitivity to CO₂, panic disorder, and the effect of childhood parental loss. *Arch Gen Psychiatry*. 2009; 66:64–71. [PubMed: 19124689]
- Battaglia M, Ogliari A, D'Amato F, Kinkead R. Early-life risk factors for panic and separation anxiety disorder: insights and outstanding questions arising from human and animal studies of CO₂ sensitivity. *Neurosci Biobehav Rev*. 2014; 46(Pt 3):455–464. [PubMed: 24793177]
- Bauer EP. Serotonin in fear conditioning processes. *Behav Brain Res*. 2015; 277:68–77. [PubMed: 25078294]
- Beevers CG, Gibb BE, McGeary JE, Miller IW. Serotonin transporter genetic variation and biased attention for emotional word stimuli among psychiatric inpatients. *J Abnorm Psychol*. 2007; 116:208–212. [PubMed: 17324031]
- Bellodi L, Perna G, Caldirola D, Arancio C, Bertani A, Di Bella D. CO₂-Induced Panic Attacks: A Twin Study. *Am J Psychiatry*. 1998; 155:1184–1188. [PubMed: 9734540]
- Bergado-Acosta JR, Sangha S, Narayanan RT, Obata K, Pape HC, Stork O. Critical role of the 65-kDa isoform of glutamic acid decarboxylase in consolidation and generalization of Pavlovian fear memory. *Learn Mem*. 2008; 15:163–171. [PubMed: 18323571]
- Bergman O, Ahs F, Furmark T, Appel L, Linnman C, Faria V, Bani M, Pich EM, Bettica P, Henningsson S, et al. Association between amygdala reactivity and a dopamine transporter gene polymorphism. *Transl Psychiatry*. 2014; 4:e420. [PubMed: 25093598]
- Beste C, Saft C, Andrich J, Gold R, Falkenstein M. Error processing in Huntington's disease. *PLoS One*. 2006; 1:e86. [PubMed: 17183717]
- Biehl SC, Dresler T, Reif A, Scheuerpflug P, Deckert J, Herrmann MJ. Dopamine transporter (DAT1) and dopamine receptor D4 (DRD4) genotypes differentially impact on electrophysiological correlates of error processing. *PLoS One*. 2011; 6:e28396. [PubMed: 22162768]
- Bismark AW, Moreno FA, Stewart JL, Towers DN, Coan JA, Oas J, Erickson RP, Allen JJ. Polymorphisms of the HTR1a allele are linked to frontal brain electrical asymmetry. *Biol Psychol*. 2010; 83:153–158. [PubMed: 20025927]
- Blasi G, Lo Bianco L, Taurisano P, Gelao B, Romano R, Fazio L, Papazacharias A, Di Giorgio A, Caforio G, Rampino A, et al. Functional variation of the dopamine D2 receptor gene is associated with emotional control as well as brain activity and connectivity during emotion processing in humans. *J Neurosci*. 2009; 29:14812–14819. [PubMed: 19940176]
- Bogdan R, Williamson DE, Hariri AR. Mineralocorticoid receptor Iso/Val (rs5522) genotype moderates the association between previous childhood emotional neglect and amygdala reactivity. *Am J Psychiatry*. 2012; 169:515–522. [PubMed: 22407082]
- Boll S, Gamer M. 5-HTTLPR modulates the recognition accuracy and exploration of emotional facial expressions. *Front Behav Neurosci*. 2014; 8:255. [PubMed: 25100964]
- Bolton JL, Hayward C, Direk N, Lewis JG, Hammond GL, Hill LA, Anderson A, Huffman J, Wilson JF, Campbell H, et al. Genome wide association identifies common variants at the SERPINA6/SERPINA1 locus influencing plasma cortisol and corticosteroid binding globulin. *PLoS Genet*. 2014; 10:e1004474. [PubMed: 25010111]
- Bortoluzzi A, Blaya C, Salum GA, Cappi C, Leistner-Segal S, Manfro GG. Anxiety disorders and anxiety-related traits and serotonin transporter gene-linked polymorphic region (5-HTTLPR) in adolescents: case-control and trio studies. *Psychiatr Genet*. 2014; 24:176–180. [PubMed: 24842237]
- Briscone MA, Jovanovic T, Norrholm SD. Conditioned fear associated phenotypes as robust, translational indices of trauma-, stressor-, and anxiety-related behaviors. *Front Psychiatry*. 2014; 5:88. [PubMed: 25101010]
- Brocke B, Lesch KP, Armbruster D, Moser DA, Muller A, Strobel A, Kirschbaum C. Stathmin, a gene regulating neural plasticity, affects fear and anxiety processing in humans. *Am J Med Genet B Neuropsychiatr Genet*. 2010; 153b:243–251. [PubMed: 19526456]
- Brown HM, McAdams TA, Lester KJ, Goodman R, Clark DM, Eley TC. Attentional threat avoidance and familial risk are independently associated with childhood anxiety disorders. *J Child Psychol Psychiatry*. 2013; 54:678–685. [PubMed: 23176633]

- Brummett BH, Siegler IC, Ashley-Koch A, Williams RB. Effects of 5HTTLPR on cardiovascular response to an emotional stressor. *Psychosom Med.* 2011; 73:318–322. [PubMed: 21364197]
- Brummett BH, Kuhn CM, Boyle SH, Babyak MA, Siegler IC, Williams RB. Cortisol responses to emotional stress in men: association with a functional polymorphism in the 5HTR2C gene. *Biol Psychol.* 2012; 89:94–98. [PubMed: 21967853]
- Bulgin NL, Strauss JS, King NA, Shaikh SA, George CJ, Fox NA, Barr CL, Kovacs M, Kennedy JL. Association study of theta EEG asymmetry and brain-derived neurotrophic factor gene variants in childhood-onset mood disorder. *Neuromolecular Med.* 2008; 10:343–355. [PubMed: 18543122]
- Busjahn A, Voss A, Knoblauch H, Knoblauch M, Jeschke E, Wessel N, Bohlender J, McCarron J, Faulhaber H-D, Schuster H, et al. Angiotensin-converting enzyme and angiotensinogen gene polymorphisms and heart rate variability in twins. *Am J Cardiol.* 1998; 81:755–760. [PubMed: 9527087]
- Carlson JM, Mujica-Parodi LR, Harmon-Jones E, Hajcak G. The orienting of spatial attention to backward masked fearful faces is associated with variation in the serotonin transporter gene. *Emotion.* 2012; 12:203–207. [PubMed: 21875187]
- Carlson JM, Cha J, Harmon-Jones E, Mujica-Parodi LR, Hajcak G. Influence of the BDNF genotype on amygdalo-prefrontal white matter microstructure is linked to nonconscious attention bias to threat. *Cereb Cortex.* 2014; 24:2249–2257. [PubMed: 23585520]
- Carlson SR, Katsanis J, Iacono WG, McGue M. Emotional modulation of the startle reflex in twins: preliminary findings. *Biol Psychol.* 1997; 46:235–246. [PubMed: 9360775]
- Carney RM, Rich MW, TeVelde A, Saini J, Clark K, Freedland KE. The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. *J Psychosom Res.* 1988; 32:159–164. [PubMed: 3404497]
- Chakrabarti B, Baron-Cohen S. Variation in the human cannabinoid receptor CNR1 gene modulates gaze duration for happy faces. *Mol Autism.* 2011; 2:10. [PubMed: 21714860]
- Chang CC, Fang WH, Chang HA, Chen TY, Huang SY. Sex-specific association between nerve growth factor polymorphism and cardiac vagal modulation. *Psychosom Med.* 2014; 76:638–643. [PubMed: 25162994]
- Chen J, Yu J, Li X, Zhang J. Genetic and environmental contributions to anxiety among Chinese children and adolescents--a multi-informant twin study. *J Child Psychol Psychiatry.* 2015; 56:586–594. [PubMed: 25109807]
- Chen MC, Joormann J, Hallmayer J, Gotlib IH. Serotonin transporter polymorphism predicts waking cortisol in young girls. *Psychoneuroendocrinology.* 2009; 34:681–686. [PubMed: 19128885]
- Chen X, Zhang G, Liang Z, Zhang M, Way N, Yoshikawa H, Ke X, Lu Z, Deng H. The association between 5-HTTLPR gene polymorphism and behavioral inhibition in Chinese toddlers. *Dev Psychobiol.* 2014; 56:1601–1608. [PubMed: 25196943]
- Chhatwal JP, Davis M, Maguschak KA, Ressler KJ. Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. *Neuropsychopharmacology.* 2005; 30:516–524. [PubMed: 15637635]
- Choi K, Le T, McGuire J, Xing G, Zhang L, Li H, Parker CC, Johnson LR, Ursano RJ. Expression pattern of the cannabinoid receptor genes in the frontal cortex of mood disorder patients and mice selectively bred for high and low fear. *J Psychiatr Res.* 2012; 46:882–889. [PubMed: 22534181]
- Christou AI, Endo S, Wallis Y, Bair H, Zeegers MP, McCleery JP. Variation in serotonin transporter linked polymorphic region (5-HTTLPR) short/long genotype modulates resting frontal electroencephalography asymmetries in children. *Dev Psychopathol.* 2015:1–12. Epub ahead of print.
- Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA.* 1992; 267:1244–1252. [PubMed: 1538563]
- Clark MS, Vincow ES, Sexton TJ, Neumaier JF. Increased expression of 5-HT1B receptor in dorsal raphe nucleus decreases fear-potentiated startle in a stress dependent manner. *Brain Res.* 2004; 1007:86–97. [PubMed: 15064139]
- Clauss JA, Blackford JU. Behavioral inhibition and risk for developing social anxiety disorder: a meta-analytic study. *J Am Acad Child Adolesc Psychiatry.* 2012; 51:1066–1075. [PubMed: 23021481]

- Clauss JA, Avery SN, Blackford JU. The nature of individual differences in inhibited temperament and risk for psychiatric disease: A review and meta-analysis. *Prog Neurobiol*. 2015; 127–128:23–45.
- Colhoun HM, McKeigue PM, Smith GD. Problems of reporting genetic associations with complex outcomes. *Lancet*. 2003; 361:865–872. [PubMed: 12642066]
- Colzato LS, Van der Does AJ, Kouwenhoven C, Elzinga BM, Hommel B. BDNF Val66Met polymorphism is associated with higher anticipatory cortisol stress response, anxiety, and alcohol consumption in healthy adults. *Psychoneuroendocrinology*. 2011; 36:1562–1569. [PubMed: 21596481]
- Comasco E, Hellgren C, Sundstrom-Poromaa I. Influence of catechol-O-methyltransferase Val158Met polymorphism on startle response in the presence of high estradiol levels. *Eur Neuropsychopharmacol*. 2013; 23:629–635. [PubMed: 22831878]
- Coryell W. Hypersensitivity to carbon dioxide as a disease-specific trait marker. *Biol Psychiatry*. 1997; 41:259–263. [PubMed: 9024948]
- Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med*. 2013; 11:126. [PubMed: 23672542]
- D'Amato FR, Zanettini C, Lampis V, Coccurello R, Pascucci T, Ventura R, Puglisi-Allegra S, Spatola CA, Pesenti-Gritti P, Oddi D, et al. Unstable maternal environment, separation anxiety, and heightened CO₂ sensitivity induced by gene-by-environment interplay. *PloS One*. 2011; 6:e18637. [PubMed: 21494633]
- Davern PJ, Chen D, Head GA, Chavez CA, Walther T, Mayorov DN. Role of angiotensin II Type 1A receptors in cardiovascular reactivity and neuronal activation after aversive stress in mice. *Hypertension*. 2009; 54:1262–1268. [PubMed: 19884564]
- Davidson RJ. Anterior electrophysiological asymmetries, emotion, and depression: Conceptual and methodological conundrums. *Psychophysiology*. 1998; 35:607–614. [PubMed: 9715104]
- Davies MN, Verdi S, Burri A, Trzaskowski M, Lee M, Hettema JM, Jansen R, Boomsma DI, Spector TD. Generalised anxiety disorder - a twin study of genetic architecture, genome-wide association and differential gene expression. *PloS One*. 2015; 10:e0134865. [PubMed: 26274327]
- De Geus EJ, Kupper N, Boomsma DI, Snieder H. Bivariate genetic modeling of cardiovascular stress reactivity: does stress uncover genetic variance? *Psychosom Med*. 2007; 69:356–364. [PubMed: 17510291]
- Denson TF, Dobson-Stone C, Ronay R, von Hippel W, Schira MM. A functional polymorphism of the MAOA gene is associated with neural responses to induced anger control. *J Cogn Neurosci*. 2014; 26:1418–1427. [PubMed: 24564461]
- DeRijk RH, Wust S, Meijer OC, Zennaro MC, Federenko IS, Hellhammer DH, Giacchetti G, Vreugdenhil E, Zitman FG, de Kloet ER. A common polymorphism in the mineralocorticoid receptor modulates stress responsiveness. *J Clin Endocrinol Metab*. 2006; 91:5083–5089. [PubMed: 17018659]
- DeRijk RH, de Kloet ER, Zitman FG, van Leeuwen N. Mineralocorticoid receptor gene variants as determinants of HPA axis regulation and behavior. *Endocr Dev*. 2011; 20:137–148. [PubMed: 21164267]
- Dincheva I, Drysdale AT, Hartley CA, Johnson DC, Jing D, King EC, Ra S, Gray JM, Yang R, DeGruccio AM, et al. FAAH genetic variation enhances fronto-amygdala function in mouse and human. *Nat Commun*. 2015; 6:6395. [PubMed: 25731744]
- Ditto B. Familial influences on heart rate, blood pressure, and self-report anxiety responses to stress: results from 100 twin pairs. *Psychophysiology*. 1993; 30:635–645. [PubMed: 8248455]
- Domschke K, Dannlowski U. Imaging genetics of anxiety disorders. *Neuroimage*. 2010; 53:822–831. [PubMed: 19944771]
- Domschke K, Dannlowski U, Hohoff C, Ohrmann P, Bauer J, Kugel H, Zwanzger P, Heindel W, Deckert J, Arolt V, et al. Neuropeptide Y (NPY) gene: Impact on emotional processing and treatment response in anxious depression. *Eur Neuropsychopharmacol*. 2010; 20:301–309. [PubMed: 19854625]
- Domschke K, Reif A, Weber H, Richter J, Hohoff C, Ohrmann P, Pedersen A, Bauer J, Suslow T, Kugel H, et al. Neuropeptide S receptor gene -- converging evidence for a role in panic disorder. *Mol Psychiatry*. 2011; 16:938–948. [PubMed: 20603625]

- Domschke K, Baune BT, Havlik L, Stuhmann A, Suslow T, Kugel H, Zwanzger P, Grotegerd D, Sehlmeier C, Arolt V, et al. Catechol-O-methyltransferase gene variation: impact on amygdala response to aversive stimuli. *Neuroimage*. 2012; 60:2222–2229. [PubMed: 22387174]
- Domschke K, Winter B, Gajewska A, Unterecker S, Warrings B, Dlugos A, Notzon S, Nienhaus K, Markulin F, Gieselmann A, et al. Multilevel impact of the dopamine system on the emotion-potentiated startle reflex. *Psychopharmacology*. 2015; 232:1983–1993. [PubMed: 25510857]
- Duncan LE, Pollastri AR, Smoller JW. Mind the gap: Why many geneticists and psychological scientists have discrepant views about gene–environment interaction (G×E) research. *Am Psychol*. 2014; 69:249–268. [PubMed: 24750075]
- Elam KK, Carlson JM, Dilalla LF, Reinke KS. Emotional faces capture spatial attention in 5-year-old children. *Evol Psychol*. 2010; 8:754–767. [PubMed: 22947832]
- Eley TC, Bolton D, O'Connor TG, Perrin S, Smith P, Plomin R. A twin study of anxiety-related behaviours in pre-school children. *J Child Psychol Psychiatry*. 2003; 44:945–960. [PubMed: 14531577]
- Eley TC, Gregory AM, Clark DM, Ehlers A. Feeling anxious: a twin study of panic/somatic ratings, anxiety sensitivity and heartbeat perception in children. *J Child Psychol Psychiatry*. 2007; 48:1184–1191. [PubMed: 18093023]
- Erhardt A, Spoormaker VI. Translational approaches to anxiety: focus on genetics, fear extinction and brain imaging. *Curr Psychiatry Rep*. 2013; 15:417. [PubMed: 24234873]
- Fan J, Wu Y, Fossella JA, Posner MI. Assessing the heritability of attentional networks. *BMC Neurosci*. 2001; 2:14. [PubMed: 11580865]
- Fani N, Gutman D, Tone EB, Almlil L, Mercer KB, Davis J, Glover E, Jovanovic T, Bradley B, Dinov ID, et al. FKBP5 and attention bias for threat: associations with hippocampal function and shape. *JAMA Psychiatry*. 2013; 70:392–400. [PubMed: 23407841]
- Federenko IS, Nagamine M, Hellhammer DH, Wadhwa PD, Wust S. The heritability of hypothalamus pituitary adrenal axis responses to psychosocial stress is context dependent. *J Clin Endocrinol Metab*. 2004; 89:6244–6250. [PubMed: 15579784]
- Ficcio AJ, Joobor R, Poirier J, Lupien S. Polymorphism of the 5-HT(2A) receptor gene: association with stress-related indices in healthy middle-aged adults. *Front Behav Neurosci*. 2007; 1:3. [PubMed: 18958185]
- Flint J, Munafò MR. The endophenotype concept in psychiatric genetics. *Psychol Med*. 2007; 37:163–180. [PubMed: 16978446]
- Franz C, York T, Eaves L, Mendoza S, Hauger R, Hellhammer D, Jacobson K, Levine S, Lupien S, Lyons M, et al. Genetic and Environmental Influences on Cortisol Regulation Across Days and Contexts in Middle-Aged Men. *Behav Genet*. 2010; 40:467–479. [PubMed: 20238238]
- Fredrikson M, Annas P, Hettima JM. Different genetic factors underlie fear conditioning and episodic memory. *Psychiatr Genet*. 2015; 25:155–162. [PubMed: 25967536]
- Frigerio A, Ceppi E, Rusconi M, Giorda R, Raggi ME, Fearon P. The role played by the interaction between genetic factors and attachment in the stress response in infancy. *J Child Psychol Psychiatry*. 2009; 50:1513–1522. [PubMed: 19686331]
- Gao Y, Tuvblad C, Raine A, Lozano DI, Baker LA. Genetic and environmental influences on frontal EEG asymmetry and alpha power in 9–10-year-old twins. *Psychophysiology*. 2009; 46:787–796. [PubMed: 19386046]
- Geiger MJ, Neufang S, Stein DJ, Domschke K. Arousal and the attentional network in panic disorder. *Hum Psychopharmacol*. 2014; 29:599–603. [PubMed: 25311787]
- Gohier B, Senior C, Radua J, El-Hage W, Reichenberg A, Proitsi P, Phillips ML, Surguladze SA. Genetic modulation of the response bias towards facial displays of anger and happiness. *Eur Psychiatry*. 2014; 29:197–202. [PubMed: 23769682]
- Gong P, Xi S, Shen G, Li S, Zhang P, Cao G, Zhang F, Shen Y, Feng T, Ma H. The effects of DBH, MAOA, and MAOB on attentional biases for facial expressions. *J Mol Neurosci*. 2013; 49:606–613. [PubMed: 23054588]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]

- Granger DA, Kivlighan KT, el-Sheikh M, Gordis EB, Stroud LR. Salivary alpha-amylase in biobehavioral research: recent developments and applications. *Ann N Y Acad Sci.* 2007; 1098:122–144. [PubMed: 17332070]
- Green AE, Munafo MR, DeYoung CG, Fossella JA, Fan J, Gray JR. Using genetic data in cognitive neuroscience: from growing pains to genuine insights. *Nat Rev Neurosci.* 2008; 9:710–720. [PubMed: 19143051]
- Gunduz-Cinar O, MacPherson KP, Cinar R, Gamble-George J, Sugden K, Williams B, Godlewski G, Ramikie TS, Gorka AX, Alapafuja SO, et al. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. *Mol Psychiatry.* 2013; 18:813–823. [PubMed: 22688188]
- Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. *Science.* 2002; 297:400–403. [PubMed: 12130784]
- Hariri AR, Gorka A, Hyde LW, Kimak M, Halder I, Ducci F, Ferrell RE, Goldman D, Manuck SB. Divergent effects of genetic variation in endocannabinoid signaling on human threat- and reward-related brain function. *Biol Psychiatry.* 2009; 66:9–16. [PubMed: 19103437]
- Hartley CA, Casey BJ. Risk for anxiety and implications for treatment: developmental, environmental, and genetic factors governing fear regulation. *Ann N Y Acad Sci.* 2013; 1304:1–13. [PubMed: 24147742]
- Heim C, Bradley B, Mletzko TC, Deveau TC, Musselman DL, Nemeroff CB, Ressler KJ, Binder EB. Effect of childhood trauma on adult depression and neuroendocrine function: Sex-specific moderation by CRH receptor 1 gene. *Front Behav Neurosci.* 2009; 3:41. [PubMed: 20161813]
- Heitland I, Klumpers F, Oosting RS, Evers DJ, Leon Kenemans J, Baas JM. Failure to extinguish fear and genetic variability in the human cannabinoid receptor 1. *Transl Psychiatry.* 2012; 2:e162. [PubMed: 23010766]
- Heldt SA, Stanek L, Chhatwal JP, Ressler KJ. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. *Mol Psychiatry.* 2007; 12:656–670. [PubMed: 17264839]
- Hessl D, Rivera S, Koldewyn K, Cordeiro L, Adams J, Tassone F, Hagerman PJ, Hagerman RJ. Amygdala dysfunction in men with the fragile X premutation. *Brain.* 2007; 130:404–416. [PubMed: 17166860]
- Hettema JM, Annas P, Neale MC, Kendler KS, Fredrikson M. A twin study of the genetics of fear conditioning. *Arch Gen Psychiatry.* 2003; 60:702–708. [PubMed: 12860774]
- Hettema JM, Annas P, Neale MC, Fredrikson M, Kendler KS. The genetic covariation between fear conditioning and self-report fears. *Biol Psychiatry.* 2008; 63:587–593. [PubMed: 17698042]
- Hettema JM, Sun C, Chen X, Kendler KS. Genetic association study between RGS2 and anxiety-related phenotypes. *Psychiatr Genet.* 2013; 23:92. [PubMed: 23277133]
- Hirshfeld-Becker DR, Micco J, Henin A, Bloomfield A, Biederman J, Rosenbaum J. Behavioral inhibition. *Depress Anxiety.* 2008; 25:357–367. [PubMed: 18412062]
- Hoekstra RA, Bartels M, Hudziak JJ, Van Beijsterveldt TC, Boomsma DI. Genetic and environmental influences on the stability of withdrawn behavior in children: a longitudinal, multi-informant twin study. *Behav Genet.* 2008; 38:447–461. [PubMed: 18548343]
- Hohoff C, Domschke K, Schwarte K, Spellmeyer G, Voge C, Hetzel G, Deckert J, Gerlach AL. Sympathetic activity relates to adenosine A(2A) receptor gene variation in blood-injury phobia. *J Neural Transm.* 2009; 116:659–662. [PubMed: 18629431]
- Holz NE, Buchmann AF, Boecker R, Blomeyer D, Baumeister S, Wolf I, Rietschel M, Witt SH, Plichta MM, Meyer-Lindenberg A, et al. Role of FKBP5 in emotion processing: results on amygdala activity, connectivity and volume. *Brain Struct Funct.* 2015; 220:1355–1368. [PubMed: 24756342]
- Hommers L, Raab A, Bohl A, Weber H, Scholz CJ, Erhardt A, Binder E, Arolt V, Gerlach A, Gloster A, et al. MicroRNA hsa-miR-4717-5p regulates RGS2 and may be a risk factor for anxiety-related traits. *Am J Med Genet B Neuropsychiatr Genet.* 2015; 168B:296–306. [PubMed: 25847876]

- Insel TR, Cuthbert BN. Endophenotypes: bridging genomic complexity and disorder heterogeneity. *Biol Psychiatry*. 2009; 66:988–989. [PubMed: 19900610]
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010; 167:748–751. [PubMed: 20595427]
- Ising M, Depping AM, Siebertz A, Lucae S, Unschuld PG, Kloiber S, Horstmann S, Uhr M, Muller-Myhsok B, Holsboer F. Polymorphisms in the FKBP5 gene region modulate recovery from psychosocial stress in healthy controls. *Eur J Neurosci*. 2008; 28:389–398. [PubMed: 18702710]
- Jacobs RH, Orr JL, Gowins JR, Forbes EE, Langenecker SA. Biomarkers of intergenerational risk for depression: a review of mechanisms in longitudinal high-risk (LHR) studies. *J Affect Disord*. 2015; 175:494–506. [PubMed: 25687188]
- Jang KL, Stein MB, Taylor S, Livesley WJ. Gender differences in the etiology of anxiety sensitivity: a twin study. *J Gend Specif Med*. 1999; 2:39–44. [PubMed: 11252860]
- Joeyen-Waldorf J, Nikolova YS, Edgar N, Walsh C, Kota R, Lewis DA, Ferrell R, Manuck SB, Hariri AR, Sibille E. Adenylate cyclase 7 is implicated in the biology of depression and modulation of affective neural circuitry. *Biol Psychiatry*. 2012; 71:627–632. [PubMed: 22264442]
- Johnson DC, Casey BJ. Easy to remember, difficult to forget: the development of fear regulation. *Dev Cogn Neurosci*. 2015; 11:42–55. [PubMed: 25238998]
- Jorm AF, Henderson AS, Jacomb PA, Christensen H, Korten AE, Rodgers B, Tan X, Easteal S. An association study of a functional polymorphism of the serotonin transporter gene with personality and psychiatric symptoms. *Mol Psychiatry*. 1998; 3:449–451. [PubMed: 9774781]
- Karl T, Chesworth R, Duffy L, Herzog H. Acoustic startle response and sensorimotor gating in a genetic mouse model for the Y1 receptor. *Neuropeptides*. 2010; 44:233–239. [PubMed: 20096928]
- Kemp AH, Quintana DS. The relationship between mental and physical health: Insights from the study of heart rate variability. *Int J Psychophysiol*. 2013; 89:288–296. [PubMed: 23797149]
- Kendler KS, Neale MC. Endophenotype: a conceptual analysis. *Mol Psychiatry*. 2010; 15:789–797. [PubMed: 20142819]
- Clumbers F, Heitland I, Oosting RS, Kenemans JL, Baas JM. Genetic variation in serotonin transporter function affects human fear expression indexed by fear-potentiated startle. *Biol Psychol*. 2012; 89:277–282. [PubMed: 22061270]
- Konrad K, Dimpfle A, Friedel S, Heiser P, Holtkamp K, Walitza S, Sauer S, Warnke A, Remschmidt H, Gilsbach S, et al. Familiality and molecular genetics of attention networks in ADHD. *Am J Med Genet B Neuropsychiatr Genet*. 2010; 153b:148–158. [PubMed: 19418498]
- Koszycki D, Prichard Z, Fiocco AJ, Shlik J, Kennedy JL, Bradwejn J. CCK-B receptor gene and response to cholecystokinin-tetrapeptide in healthy volunteers. *Peptides*. 2012; 35:9–13. [PubMed: 22414867]
- Kozak MJ, Cuthbert BN. The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics. *Psychophysiology*. 2016; 53:286–297. [PubMed: 26877115]
- Kramer UM, Cunillera T, Camara E, Marco-Pallares J, Cucurell D, Nager W, Bauer P, Schule R, Schols L, Rodriguez-Fornells A, et al. The impact of catechol-O-methyltransferase and dopamine D4 receptor genotypes on neurophysiological markers of performance monitoring. *J Neurosci*. 2007; 27:14190–14198. [PubMed: 18094258]
- Kumsta R, Chen FS, Pape HC, Heinrichs M. Neuropeptide S receptor gene is associated with cortisol responses to social stress in humans. *Biol Psychol*. 2013; 93:304–307. [PubMed: 23466585]
- Kurnik D, Friedman EA, Muszkat M, Sofowora GG, Xie HG, Dupont WD, Wood AJ, Stein CM. Genetic variants in the alpha2C-adrenoceptor and G-protein contribute to ethnic differences in cardiovascular stress responses. *Pharmacogenet Genomics*. 2008; 18:743–750. [PubMed: 18698227]
- Lang PJ. The emotion probe. Studies of motivation and attention. *Am Psychol*. 1995; 50:372–385. [PubMed: 7762889]
- Lange MD, Jungling K, Paulukat L, Vieler M, Gaburro S, Sosulina L, Blaesse P, Sreepathi HK, Ferraguti F, Pape HC. Glutamic acid decarboxylase 65: a link between GABAergic synaptic

plasticity in the lateral amygdala and conditioned fear generalization.

Neuropsychopharmacology. 2014; 39:2211–2220. [PubMed: 24663011]

Lau JY, Eley TC, Stevenson J. Examining the state-trait anxiety relationship: a behavioural genetic approach. *J Abnorm Child Psychol*. 2006; 34:19–27. [PubMed: 16557359]

Lee B-T, Lee H-Y, Han C, Pae C-U, Tae WS, Lee M-S, Joe S-H, Jung I-K, Ham B-J. DRD2/ANKK1 TaqI A polymorphism affects corticostriatal activity in response to negative affective facial stimuli. *Behav Brain Res*. 2011; 223:36–41. [PubMed: 21510979]

Li A, Nattie E. Serotonin transporter knockout mice have a reduced ventilatory response to hypercapnia (predominantly in males) but not to hypoxia. *J Physiol*. 2008; 586:2321–2329. [PubMed: 18356199]

Lonsdorf TB, Golkar A, Lindström KM, Fransson P, Schalling M, Öhman A, Ingvar M. 5-HTTLPR and COMTval158met genotype gate amygdala reactivity and habituation. *Biol Psychol*. 2011; 87:106–112. [PubMed: 21356267]

Lonsdorf TB, Kalisch R. A review on experimental and clinical genetic associations studies on fear conditioning, extinction and cognitive-behavioral treatment. *Transl Psychiatry*. 2011; 1:e41. [PubMed: 22832657]

Lykken DT, Iacono WG, Haroian K, McGue M, Bouchard TJ Jr. Habituation of the skin conductance response to strong stimuli: a twin study. *Psychophysiology*. 1988; 25:4–15. [PubMed: 3353484]

Mahon PB, Zandi PP, Potash JB, Nestadt G, Wand GS. Genetic association of FKBP5 and CRHR1 with cortisol response to acute psychosocial stress in healthy adults. *Psychopharmacology*. 2013; 227:231–241. [PubMed: 23274505]

Manuck SB, Marsland AL, Flory JD, Gorka A, Ferrell RE, Hariri AR. Salivary testosterone and a trinucleotide (CAG) length polymorphism in the androgen receptor gene predict amygdala reactivity in men. *Psychoneuroendocrinology*. 2010; 35:94–101.

Mattingsdal M, Brown AA, Djurovic S, Sonderby IE, Server A, Melle I, Agartz I, Hovig E, Jensen J, Andreassen OA. Pathway analysis of genetic markers associated with a functional MRI faces paradigm implicates polymorphisms in calcium responsive pathways. *Neuroimage*. 2013; 70:143–149. [PubMed: 23274185]

Maurano MT, Humbert R, Rynes E, Thurman RE, Haugen E, Wang H, Reynolds AP, Sandstrom R, Qu H, Brody J, et al. Systematic localization of common disease-associated variation in regulatory DNA. *Science*. 2012; 337:1190–1195. [PubMed: 22955828]

McCaughran JA Jr, Bell J 3rd, Hitzemann RJ. Fear-potentiated startle response in mice: genetic analysis of the C57BL/6J and DBA/2J intercross. *Pharmacol Biochem Behav*. 2000; 65:301–312. [PubMed: 10672983]

McFarquhar M, Elliott R, McKie S, Thomas E, Downey D, Mekli K, Toth ZG, Anderson IM, Deakin JF, Juhasz G. TOMM40 rs2075650 may represent a new candidate gene for vulnerability to major depressive disorder. *Neuropsychopharmacology*. 2014; 39:1743–1753. [PubMed: 24549102]

Mekli K, Payton A, Miyajima F, Platt H, Thomas E, Downey D, Lloyd-Williams K, Chase D, Toth ZG, Elliott R, et al. The HTR1A and HTR1B receptor genes influence stress-related information processing. *Eur Neuropsychopharmacol*. 2011; 21:129–139. [PubMed: 20638825]

Michopoulos V, Rothbaum AO, Jovanovic T, Almlil LM, Bradley B, Rothbaum BO, Gillespie CF, Ressler KJ. Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. *Am J Psychiatry*. 2015; 172:353–362. [PubMed: 25827033]

Miller R, Wankerl M, Stalder T, Kirschbaum C, Alexander N. The serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cortisol stress reactivity: a meta-analysis. *Mol Psychiatry*. 2013; 18:1018–1024. [PubMed: 22945032]

Miskowiak KW, Glerup L, Vestbo C, Harmer CJ, Reinecke A, Macoveanu J, Siebner HR, Kessing LV, Vinberg M. Different neural and cognitive response to emotional faces in healthy monozygotic twins at risk of depression. *Psychol Med*. 2015; 45:1447–1458. [PubMed: 25382193]

Mosing MA, Pedersen NL, Cesarini D, Johannesson M, Magnusson PK, Nakamura J, Madison G, Ullen F. Genetic and environmental influences on the relationship between flow proneness, locus of control and behavioral inhibition. *PloS One*. 2012; 7:e47958. [PubMed: 23133606]

- Mothersill O, Morris DW, Kelly S, Rose EJ, Fahey C, O'Brien C, Lyne R, Reilly R, Gill M, Corvin AP, et al. Effects of MIR137 on fronto-amygdala functional connectivity. *Neuroimage*. 2014; 90:189–195. [PubMed: 24361663]
- Mueller A, Brocke B, Fries E, Lesch KP, Kirschbaum C. The role of the serotonin transporter polymorphism for the endocrine stress response in newborns. *Psychoneuroendocrinology*. 2010; 35:289–296. [PubMed: 19647944]
- Mueller A, Strahler J, Armbruster D, Lesch KP, Brocke B, Kirschbaum C. Genetic contributions to acute autonomic stress responsiveness in children. *Int J Psychophysiol*. 2012; 83:302–308. [PubMed: 22133998]
- Mueller EM, Makeig S, Stemmler G, Hennig J, Wacker J. Dopamine effects on human error processing depend on catechol-O-methyltransferase VAL158MET genotype. *J Neurosci*. 2011; 31:15818–15825. [PubMed: 22049425]
- Munafò MR, Brown SM, Hariri AR. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biol Psychiatry*. 2008; 63:852–857. [PubMed: 17949693]
- Murphy SE, Norbury R, Godlewska BR, Cowen PJ, Mannie ZM, Harmer CJ, Munafò MR. The effect of the serotonin transporter polymorphism (5-HTTLPR) on amygdala function: a meta-analysis. *Mol Psychiatry*. 2013; 18:512–520. [PubMed: 22488255]
- Nelson BD, Bishop JR, Sarapas C, Kittles RA, Shankman SA. Asians demonstrate reduced sensitivity to unpredictable threat: a preliminary startle investigation using genetic ancestry in a multiethnic sample. *Emotion*. 2014; 14:615–623. [PubMed: 24708496]
- Neijts M, Van Lien R, Kupper N, Boomsma D, Willemsen G, de Geus EJ. Heritability of cardiac vagal control in 24-h heart rate variability recordings: influence of ceiling effects at low heart rates. *Psychophysiology*. 2014; 51:1023–1036. [PubMed: 24894483]
- Neufang S, Geiger MJ, Homola GA, Mahr M, Akhrif A, Nowak J, Reif A, Romanos M, Deckert J, Solymosi L, et al. Modulation of prefrontal functioning in attention systems by NPSR1 gene variation. *Neuroimage*. 2015; 114:199–206. [PubMed: 25842293]
- Nikolova YS, Koenen KC, Galea S, Wang CM, Seney ML, Sibille E, Williamson DE, Hariri AR. Beyond genotype: serotonin transporter epigenetic modification predicts human brain function. *Nat Neurosci*. 2014; 17:1153–1155. [PubMed: 25086606]
- Norman GJ, Hawkey L, Luhmann M, Ball AB, Cole SW, Berntson GG, Cacioppo JT. Variation in the oxytocin receptor gene influences neurocardiac reactivity to social stress and HPA function: a population based study. *Horm Behav*. 2012; 61:134–139. [PubMed: 22146101]
- Norrholm SD, Jovanovic T, Smith AK, Binder E, Klengel T, Conneely K, Mercer KB, Davis JS, Kerley K, Winkler J, et al. Differential genetic and epigenetic regulation of catechol-o-methyltransferase is associated with impaired fear inhibition in posttraumatic stress disorder. *Front Behav Neurosci*. 2013; 7:30. [PubMed: 23596403]
- Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*. 2008; 3:97–106. [PubMed: 18536531]
- Olvet DM, Hajcak G. The error-related negativity (ERN) and psychopathology: Toward an endophenotype. *Clin Psychol Rev*. 2008; 28:1343–1354. [PubMed: 18694617]
- Osinsky R, Reuter M, Kupper Y, Schmitz A, Kozyra E, Alexander N, Hennig J. Variation in the serotonin transporter gene modulates selective attention to threat. *Emotion*. 2008; 8:584–588. [PubMed: 18729589]
- Osinsky R, Hewig J, Alexander N, Hennig J. COMT Val158Met genotype and the common basis of error and conflict monitoring. *Brain Res*. 2012; 1452:108–118. [PubMed: 22425188]
- Ousdal OT, Anand Brown A, Jensen J, Nakstad PH, Melle I, Agartz I, Djurovic S, Bogdan R, Hariri AR, Andreassen OA. Associations between variants near a monoaminergic pathways gene (PHOX2B) and amygdala reactivity: a genome-wide functional imaging study. *Twin Res Hum Genet*. 2012; 15:273–285. [PubMed: 22856363]
- Out D, Bakermans-Kranenburg MJ, Granger DA, Cobbaert CM, van Ijzendoorn MH. State and trait variance in salivary alpha-amylase: a behavioral genetic study. *Biol Psychol*. 2011; 88:147–154. [PubMed: 21827821]

- Pagliaccio D, Luby JL, Bogdan R, Agrawal A, Gaffrey MS, Belden AC, Botteron KN, Harms MP, Barch DM. Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children. *Neuropsychopharmacology*. 2014; 39:1245–1253. [PubMed: 24304824]
- Pape HC, Pare D. Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. *Physiol Rev*. 2010; 90:419–463. [PubMed: 20393190]
- Perez-Edgar K, Bar-Haim Y, McDermott JM, Gorodetsky E, Hodgkinson CA, Goldman D, Ernst M, Pine DS, Fox NA. Variations in the serotonin-transporter gene are associated with attention bias patterns to positive and negative emotion faces. *Biol Psychol*. 2010; 83:269–271. [PubMed: 19723555]
- Perna G, Bertani A, Caldirola D, Bellodi L. Family history of panic disorder and hypersensitivity to CO₂ in patients with panic disorder. *Am J Psychiatry*. 1996; 153:1060–1064. [PubMed: 8678175]
- Puglia MH, Lillard TS, Morris JP, Connelly JJ. Epigenetic modification of the oxytocin receptor gene influences the perception of anger and fear in the human brain. *Proc Natl Acad Sci U S A*. 2015; 112:3308–3313. [PubMed: 25675509]
- Puissant MM, Echert AE, Yang C, Mouradian GC Jr, Novotny T, Liu P, Liang M, Hodges MR. RNASeq-derived transcriptome comparisons reveal neuromodulatory deficiency in the CO₂ insensitive brown Norway rat. *J Physiol*. 2015; 593:415–430. [PubMed: 25630262]
- Reif A, Richter J, Straube B, Hofler M, Lueken U, Gloster AT, Weber H, Domschke K, Fehm L, Strohe A, et al. MAOA and mechanisms of panic disorder revisited: from bench to molecular psychotherapy. *Mol Psychiatry*. 2014; 19:122–128. [PubMed: 23319006]
- Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behav Res Ther*. 1986; 24:1–8. [PubMed: 3947307]
- Reuter M, Ott U, Vaitl D, Hennig J. Impaired executive control is associated with a variation in the promoter region of the tryptophan hydroxylase 2 gene. *J Cogn Neurosci*. 2007; 19:401–408. [PubMed: 17335389]
- Reuter M, Cooper AJ, Smillie LD, Markett S, Montag C. A new measure for the revised reinforcement sensitivity theory: psychometric criteria and genetic validation. *Front Syst Neurosci*. 2015; 9:38. [PubMed: 25852497]
- Ridder S, Treutlein J, Nees F, Lang S, Diener S, Wessa M, Kroll A, Pohlack S, Cacciaglia R, Gass P, et al. Brain activation during fear conditioning in humans depends on genetic variations related to functioning of the hypothalamic-pituitary-adrenal axis: first evidence from two independent subsamples. *Psychol Med*. 2012; 42:2325–2335. [PubMed: 22410078]
- Riese H, Rosmalen JG, Ormel J, Van Roon AM, Oldehinkel AJ, Rijdsdijk FV. The genetic relationship between neuroticism and autonomic function in female twins. *Psychol Med*. 2007; 37:257–267. [PubMed: 17094814]
- Riese H, Munoz LM, Hartman CA, Ding X, Su S, Oldehinkel AJ, van Roon AM, van der Most PJ, Lefrandt J, Gansevoort RT, et al. Identifying genetic variants for heart rate variability in the acetylcholine pathway. *PloS One*. 2014; 9:e112476. [PubMed: 25384021]
- Rijdsdijk FV, Riese H, Tops M, Snieder H, Brouwer WH, Smid HG, Ormel J. Neuroticism, recall bias and attention bias for valenced probes: a twin study. *Psychol Med*. 2009; 39:45–54. [PubMed: 18377673]
- Risbrough VB, Geyer MA, Hauger RL, Coste S, Stenzel-Poore M, Wurst W, Holsboer F. CRF1 and CRF2 receptors are required for potentiated startle to contextual but not discrete cues. *Neuropsychopharmacology*. 2009; 34:1494–1503. [PubMed: 19020499]
- Roberson-Nay R, Moruzzi S, Ogliairi A, Pezzica E, Tambs K, Kendler KS, Battaglia M. Evidence for distinct genetic effects associated with response to 35% CO₂. *Depress Anxiety*. 2013; 30:259–266. [PubMed: 23349098]
- Rodrigues SM, Saslow LR, Garcia N, John OP, Keltner D. Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proc Natl Acad Sci U S A*. 2009; 106:21437–21441. [PubMed: 19934046]
- Roth WT, Ehlers A, Taylor CB, Margraf J, Agras WS. Skin conductance habituation in panic disorder patients. *Biol Psychiatry*. 1990; 27:1231–1243. [PubMed: 2191728]

- Rubin DH, Althoff RR, Ehli EA, Davies GE, Rettew DC, Crehan ET, Walkup JT, Hudziak JJ. Candidate gene associations with withdrawn behavior. *J Child Psychol Psychiatry*. 2013; 54:1337–1345. [PubMed: 23808549]
- Sasayama D, Hori H, Iijima Y, Teraishi T, Hattori K, Ota M, Fujii T, Higuchi T, Amano N, Kunugi H. Modulation of cortisol responses to the DEX/CRH test by polymorphisms of the interleukin-1beta gene in healthy adults. *Behav Brain Funct*. 2011; 7:23. [PubMed: 21726461]
- Savage JE, McMichael O, Gorlin EI, Beadel JR, Teachman B, Vladimirov VI, Hettema JM, Roberson-Nay R. Validation of candidate anxiety disorder genes using a carbon dioxide challenge task. *Biol Psychol*. 2015a; 109:61–66. [PubMed: 25913301]
- Savage J, Verhulst B, Copeland W, Althoff RR, Lichtenstein P, Roberson-Nay R. A genetically informed study of the longitudinal relation between irritability and anxious/depressed symptoms. *J Am Acad Child Adolesc Psychiatry*. 2015b; 54:377–384. [PubMed: 25901774]
- Savitz J, Frank MB, Victor T, Bebak M, Marino JH, Bellgowan PS, McKinney BA, Bodurka J, Kent Teague T, Drevets WC. Inflammation and neurological disease-related genes are differentially expressed in depressed patients with mood disorders and correlate with morphometric and functional imaging abnormalities. *Brain Behav Immun*. 2013; 31:161–171. [PubMed: 23064081]
- Savitz JB, Drevets WC. Imaging phenotypes of major depressive disorder: genetic correlates. *Neuroscience*. 2009; 164:300–330. [PubMed: 19358877]
- Scharinger C, Rabl U, Sitte HH, Pezawas L. Imaging genetics of mood disorders. *Neuroimage*. 2010; 53:810–821. [PubMed: 20156570]
- Scharinger C, Rabl U, Pezawas L, Kasper S. The genetic blueprint of major depressive disorder: contributions of imaging genetics studies. *World J Biol Psychiatry*. 2011; 12:474–488. [PubMed: 21830992]
- Schmidt NB, Storey J, Greenberg BD, Santiago HT, Li Q, Murphy DL. Evaluating gene x psychological risk factor effects in the pathogenesis of anxiety: a new model approach. *J Abnorm Psychol*. 2000; 109:308–320. [PubMed: 10895569]
- Schmidt NB, Zvolensky MJ, Maner JK. Anxiety sensitivity: prospective prediction of panic attacks and Axis I pathology. *J Psychiatr Res*. 2006; 40:691–699. [PubMed: 16956622]
- Schuhmacher A, Lennertz L, Wagner M, Hofels S, Pfeiffer U, Guttenthaler V, Maier W, Zobel A, Mossner R. A variant of the neuronal amino acid transporter SLC6A15 is associated with ACTH and cortisol responses and cognitive performance in unipolar depression. *Int J Neuropsychopharmacol*. 2013; 16:83–90. [PubMed: 22475622]
- Schulz S, Arning L, Pinnow M, Epplen JT, Beste C. N-methyl-D-aspartate receptor 2B subunit (GRIN2B) gene variation is associated with alerting, but not with orienting and conflicting in the Attention Network Test. *Neuropharmacology*. 2012; 63:259–265. [PubMed: 22484476]
- Shaban H, Humeau Y, Herry C, Cassasus G, Shigemoto R, Ciochi S, Barbieri S, van der Putten H, Kaupmann K, Bettler B, et al. Generalization of amygdala LTP and conditioned fear in the absence of presynaptic inhibition. *Nat Neurosci*. 2006; 9:1028–1035. [PubMed: 16819521]
- Shalev I, Lerer E, Israel S, Uzevsky F, Gritsenko I, Mankuta D, Ebstein RP, Kaitz M. BDNF Val66Met polymorphism is associated with HPA axis reactivity to psychological stress characterized by genotype and gender interactions. *Psychoneuroendocrinology*. 2009; 34:382–388. [PubMed: 18990498]
- Sheikh HI, Kryski KR, Smith HJ, Hayden EP, Singh SM. Corticotropin-releasing hormone system polymorphisms are associated with children's cortisol reactivity. *Neuroscience*. 2013; 229:1–11. [PubMed: 23131710]
- Shimada-Sugimoto M, Otowa T, Hettema JM. Genetics of anxiety disorders: Genetic epidemiological and molecular studies in humans. *Psychiatry Clin Neurosci*. 2015; 69:388–401. [PubMed: 25762210]
- Shinozaki G, Romanowicz M, Kung S, Mrazek DA. A new interaction between SLC6A4 variation and child abuse is associated with resting heart rate. *Depress Anxiety*. 2011; 28:227–233. [PubMed: 21394855]
- Simmons JM, Quinn KJ. The NIMH Research Domain Criteria (RDoC) Project: implications for genetics research. *Mamm Genome*. 2014; 25:23–31. [PubMed: 24085332]

- Smit DJ, Posthuma D, Boomsma DI, De Geus EJ. The relation between frontal EEG asymmetry and the risk for anxiety and depression. *Biol Psychol.* 2007; 74:26–33. [PubMed: 16875773]
- Smoller JW. The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders. *Neuropsychopharmacology.* 2016; 41:297–319. [PubMed: 26321314]
- Smoller JW, Rosenbaum JF, Biederman J, Susswein LS, Kennedy J, Kagan J, Snidman N, Laird N, Tsuang MT, Faraone SV, et al. Genetic association analysis of behavioral inhibition using candidate loci from mouse models. *Am J Hum Genet.* 2001; 105:226–235.
- Smoller JW, Yamaki LH, Fagerness JA, Biederman J, Racette S, Laird NM, Kagan J, Snidman N, Faraone SV, Hirshfeld-Becker D, et al. The corticotropin-releasing hormone gene and behavioral inhibition in children at risk for panic disorder. *Biol Psychiatry.* 2005; 57:1485–1492. [PubMed: 15953484]
- Smoller JW, Gallagher PJ, Duncan LE, McGrath LM, Haddad SA, Holmes AJ, Wolf AB, Hilker S, Block SR, Weill S, et al. The human ortholog of acid-sensing ion channel gene ASIC1a is associated with panic disorder and amygdala structure and function. *Biol Psychiatry.* 2014; 76:902–910. [PubMed: 24529281]
- Spielberger, C., Gorsuch, R., Luchene, R. The State-Trait Anxiety Inventory: Test manual for Form X. Palo Alto, Ca: Consulting Psychologists Press; 1970.
- Stein MB, Jang KL, Livesley WJ. Heritability of anxiety sensitivity: a twin study. *Am J Psychiatry.* 1999; 156:246–251. [PubMed: 9989561]
- Stein MB, Yang BZ, Chavira DA, Hitchcock CA, Sung SC, Shipon-Blum E, Gelernter J. A common genetic variant in the neurexin superfamily member CNTNAP2 is associated with increased risk for selective mutism and social anxiety-related traits. *Biol Psychiatry.* 2011; 69:825–831. [PubMed: 21193173]
- Stiedl O, Meyer M, Kishimoto T, Rosenfeld MG, Spiess J. Stress-mediated heart rate dynamics after deletion of the gene encoding corticotropin-releasing factor receptor 2. *Eur J Neurosci.* 2003; 17:2231–2235. [PubMed: 12786991]
- Stoppel C, Albrecht A, Pape HC, Stork O. Genes and neurons: molecular insights to fear and anxiety. *Genes Brain Behav.* 2006; 5(Suppl 2):34–47. [PubMed: 16681799]
- Su S, Lampert R, Lee F, Bremner JD, Snieder H, Jones L, Murrah NV, Goldberg J, Vaccarino V. Common genes contribute to depressive symptoms and heart rate variability: the Twins Heart Study. *Twin Res Hum Genet.* 2010; 13:1–9. [PubMed: 20158303]
- Sullivan PF, Eaves LJ, Kendler KS, Neale MC. Genetic case-control association studies in neuropsychiatry. *Arch Gen Psychiatry.* 2001; 58:1015–1024. [PubMed: 11695947]
- Sumner JA, Powers A, Jovanovic T, Koenen KC. Genetic influences on the neural and physiological bases of acute threat: A research domain criteria (RDoC) perspective. *Am J Med Genet B Neuropsychiatr Genet.* 2015 Epub ahead of print.
- Taylor MK, Larson GE, Lauby MD. Genetic variants in serotonin and corticosteroid systems modulate neuroendocrine and cardiovascular responses to intense stress. *Behav Brain Res.* 2014; 270:1–7. [PubMed: 24821403]
- Thimm M, Krug A, Kellermann T, Markov V, Krach S, Jansen A, Zerres K, Eggermann T, Stocker T, Shah NJ, et al. The effects of a DTNBP1 gene variant on attention networks: an fMRI study. *Behav Brain Funct.* 2010; 6:54. [PubMed: 20846375]
- Thimm M, Kircher T, Kellermann T, Markov V, Krach S, Jansen A, Zerres K, Eggermann T, Stocker T, Shah NJ, et al. Effects of a CACNA1C genotype on attention networks in healthy individuals. *Psychol Med.* 2011; 41:1551–1561. [PubMed: 21078228]
- Topolski TD, Hewitt JK, Eaves L, Meyer JM, Silberg JL, Simonoff E, Rutter M. Genetic and environmental influences on ratings of manifest anxiety by parents and children. *J Anxiety Disord.* 1999; 13:371–397. [PubMed: 10504108]
- Tovote P, Meyer M, Ronnenberg A, Ogren SO, Spiess J, Stiedl O. Heart rate dynamics and behavioral responses during acute emotional challenge in corticotropin-releasing factor receptor 1-deficient and corticotropin-releasing factor-overexpressing mice. *Neuroscience.* 2005; 134:1113–1122. [PubMed: 16039799]
- Tovote P, Fadok JP, Luthi A. Neuronal circuits for fear and anxiety. *Nat Rev Neurosci.* 2015; 16:317–331. [PubMed: 25991441]

- Tsuru J, Tanaka Y, Ishitobi Y, Maruyama Y, Inoue A, Kawano A, Ikeda R, Ando T, Oshita H, Aizawa S, et al. Association of BDNF Val66Met polymorphism with HPA and SAM axis reactivity to psychological and physical stress. *Neuropsychiatr Dis Treat*. 2014; 10:2123–2133. [PubMed: 25419135]
- Tuvblad C, Isen J, Baker LA, Raine A, Lozano DI, Jacobson KC. The genetic and environmental etiology of sympathetic and parasympathetic activity in children. *Behav Genet*. 2010; 40:452–466. [PubMed: 20162348]
- Tuvblad C, Gao Y, Isen J, Botwick T, Raine A, Baker LA. The heritability of the skin conductance orienting response: A longitudinal twin study. *Biol Psychol*. 2012; 89:47–53. [PubMed: 21945549]
- Tyrka AR, Price LH, Gelernter J, Schepker C, Anderson GM, Carpenter LL. Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor gene: effects on hypothalamic-pituitary-adrenal axis reactivity. *Biol Psychiatry*. 2009; 66:681–685. [PubMed: 19596121]
- Uhart M, McCaul ME, Oswald LM, Choi L, Wand GS. GABRA6 gene polymorphism and an attenuated stress response. *Mol Psychiatry*. 2004; 9:998–1006. [PubMed: 15197399]
- Unschuld PG, Ising M, Specht M, Erhardt A, Ripke S, Heck A, Kloiber S, Straub V, Brueckl T, Muller-Myhsok B, et al. Polymorphisms in the GAD2 gene-region are associated with susceptibility for unipolar depression and with a risk factor for anxiety disorders. *Am J Med Genet B Neuropsychiatr Genet*. 2009; 150B:1100–1109. [PubMed: 19229853]
- Vaidyanathan U, Patrick CJ, Cuthbert BN. Linking dimensional models of internalizing psychopathology to neurobiological systems: Affect-modulated startle as an indicator of fear and distress disorders and affiliated traits. *Psychol Bull*. 2009; 135:909–942. [PubMed: 19883142]
- Vaidyanathan U, Isen JD, Malone SM, Miller MB, McGue M, Iacono WG. Heritability and molecular genetic basis of electrodermal activity: A genome-wide association study. *Psychophysiology*. 2014a; 51:1259–1271. [PubMed: 25387706]
- Vaidyanathan U, Malone SM, Miller MB, McGue M, Iacono WG. Heritability and molecular genetic basis of acoustic startle eye blink and affectively modulated startle response: a genome-wide association study. *Psychophysiology*. 2014b; 51:1285–1299. [PubMed: 25387708]
- van Beijsterveldt CE, van Baal GC. Twin and family studies of the human electroencephalogram: a review and a meta-analysis. *Biol Psychol*. 2002; 61:111–138. [PubMed: 12385672]
- Van Hulle CA, Corley R, Zahn-Waxler C, Kagan J, Hewitt JK. An exploration of the genetic and environmental etiology of heart rate in infancy and middle childhood. *Twin Res*. 2000; 3:259–265. [PubMed: 11463147]
- van Leeuwen N, Bellingrath S, de Kloet ER, Zitman FG, DeRijk RH, Kudielka BM, Wust S. Human mineralocorticoid receptor (MR) gene haplotypes modulate MR expression and transactivation: implication for the stress response. *Psychoneuroendocrinology*. 2011; 36:699–709. [PubMed: 21095064]
- Velders FP, Kuningas M, Kumari M, Dekker MJ, Uitterlinden AG, Kirschbaum C, Hek K, Hofman A, Verhulst FC, Kivimaki M, et al. Genetics of cortisol secretion and depressive symptoms: a candidate gene and genome wide association approach. *Psychoneuroendocrinology*. 2011; 36:1053–1061. [PubMed: 21316860]
- Verschoor E, Markus CR. Physiological and affective reactivity to a 35% CO(2) inhalation challenge in individuals differing in the 5-HTTLPR genotype and trait neuroticism. *Eur Neuropsychopharmacol*. 2012; 22:546–554. [PubMed: 22209359]
- Vieira PA, Corches A, Lovelace JW, Westbrook KB, Mendoza M, Korzus E. Prefrontal NMDA receptors expressed in excitatory neurons control fear discrimination and fear extinction. *Neurobiol Learn Mem*. 2015; 119:52–62. [PubMed: 25615540]
- Vrieze SI, Malone SM, Vaidyanathan U, Kwong A, Kang HM, Zhan X, Flickinger M, Irons D, Jun G, Locke AE, et al. In search of rare variants: Preliminary results from whole genome sequencing of 1,325 individuals with psychophysiological endophenotypes. *Psychophysiology*. 2014; 51:1309–1320. [PubMed: 25387710]
- Wang X, Ding X, Su S, Li Z, Riese H, Thayer JF, Treiber F, Snieder H. Genetic influences on heart rate variability at rest and during stress. *Psychophysiology*. 2009; 46:458–465. [PubMed: 19226307]

- Wang Z, Deater-Deckard K, Cutting L, Thompson LA, Petrill SA. Working memory and parent-rated components of attention in middle childhood: a behavioral genetic study. *Behav Genet.* 2012; 42:199–208. [PubMed: 21948215]
- Weber H, Richter J, Straube B, Lueken U, Domschke K, Schartner C, Klauke B, Baumann C, Paner-Farre C, Jacob CP, et al. Allelic variation in CRHR1 predisposes to panic disorder: evidence for biased fear processing. *Mol Psychiatry.* 2015 Epub ahead of print.
- Wellman CL, Izquierdo A, Garrett JE, Martin KP, Carroll J, Millstein R, Lesch KP, Murphy DL, Holmes A. Impaired stress-coping and fear extinction and abnormal corticolimbic morphology in serotonin transporter knock-out mice. *J Neurosci.* 2007; 27:684–691. [PubMed: 17234600]
- Wellman CL, Camp M, Jones VM, MacPherson KP, Ihne J, Fitzgerald P, Maroun M, Drabant E, Bogdan R, Hariri AR, et al. Convergent effects of mouse Pet-1 deletion and human PET-1 variation on amygdala fear and threat processing. *Exp Neurol.* 2013; 250:260–269. [PubMed: 24100022]
- White MG, Bogdan R, Fisher PM, Munoz KE, Williamson DE, Hariri AR. FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. *Genes Brain Behav.* 2012; 11:869–878. [PubMed: 22979952]
- Wolfensberger SP, Veltman DJ, Hoogendijk WJ, Boomsma DI, de Geus EJ. Amygdala responses to emotional faces in twins discordant or concordant for the risk for anxiety and depression. *Neuroimage.* 2008; 41:544–552. [PubMed: 18396414]
- Won E, Ham BJ. Imaging genetics studies on monoaminergic genes in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* 2016; 64:311–319. [PubMed: 25828849]
- Woody ML, McGeary JE, Gibb BE. Brooding rumination and heart rate variability in women at high and low risk for depression: group differences and moderation by COMT genotype. *J Abnorm Psychol.* 2014; 123:61–67. [PubMed: 24661160]
- Woudstra S, Bochdanovits Z, van Tol MJ, Veltman DJ, Zitman FG, van Buchem MA, van der Wee NJ, Opmeer EM, Demenescu LR, Aleman A, et al. Piccolo genotype modulates neural correlates of emotion processing but not executive functioning. *Transl Psychiatry.* 2012; 2:e99. [PubMed: 22832909]
- Wu T, Snieder H, de Geus E. Genetic influences on cardiovascular stress reactivity. *Neurosci Biobehav Rev.* 2010; 35:58–68. [PubMed: 19963006]
- Yang AC, Chen TJ, Tsai SJ, Hong CJ, Kuo CH, Yang CH, Kao KP. BDNF Val66Met polymorphism alters sympathovagal balance in healthy subjects. *Am J Med Genet B Neuropsychiatr Genet.* 2010; 153b:1024–1030. [PubMed: 20213725]
- Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet.* 2011; 88:76–82. [PubMed: 21167468]
- Zavos HM, Gregory AM, Eley TC. Longitudinal genetic analysis of anxiety sensitivity. *Dev Psychol.* 2012; 48:204–212. [PubMed: 21842987]
- Zhang L, Rao F, Wessel J, Kennedy BP, Rana BK, Taupenot L, Lillie EO, Cockburn M, Schork NJ, Ziegler MG, et al. Functional allelic heterogeneity and pleiotropy of a repeat polymorphism in tyrosine hydroxylase: prediction of catecholamines and response to stress in twins. *Physiol Genomics.* 2004; 19:277–291. [PubMed: 15367723]
- Zhu H, Mingler MK, McBride ML, Murphy AJ, Valenzuela DM, Yancopoulos GD, Williams MT, Vorhees CV, Rothenberg ME. Abnormal response to stress and impaired NPS-induced hyperlocomotion, anxiolytic effect and corticosterone increase in mice lacking NPSR1. *Psychoneuroendocrinology.* 2010; 35:1119–1132. [PubMed: 20171785]

Table I

Abbreviations

Abbreviation	Definition
AD	anxiety disorder
AS	anxiety sensitivity
BI	behavioral inhibition
DZ	dizygotic
EEG	electroencephalogram
ERN	error-related negativity
ERP	event-related potential
FPS	fear-potentiated startle
GCTA	genome-wide complex trait analysis
GWAS	genome-wide association study
HPA axis	hypothalamic-pituitary-adrenocortical axis
HR	heart rate
HRV	heart rate variability
MDD	major depressive disorder
MZ	monozygotic
NVS	negative valence systems
RA	reactive aggression
RDoC	Research Domain Criteria
SCR	skin conductance response
SNP	single (simple) nucleotide polymorphism
TA	trait anxiety
VNTR	variable number of tandem repeats (genetic polymorphism)

Table II

Gene symbols

Gene Symbol	Definition
5-HTTLPR	serotonin transporter (5-HTT) linked polymorphic region; the most commonly studied polymorphism is a functional VNTR with a short, low-activity 'S' allele and a long, higher-activity 'L' allele
<i>ACE</i>	angiotensin I converting enzyme
<i>ADCY7</i>	adenylate cyclase 7
<i>ADCYAP1R1</i>	adenylate cyclase activating polypeptide 1 (pituitary) receptor type 1
<i>ADORA2A</i>	adenosine receptor A2a
<i>ADRA2A/ADRA2C</i>	adrenoceptor A2a/A2c
<i>ANKK1</i>	ankyrin repeat and kinase domain containing 1
<i>APBB3</i>	amyloid beta (A4) precursor protein-binding, family B, member 3
<i>AR</i>	androgen receptor
<i>ASIC1 (ACCN2)</i>	acid-sensing (proton-gated) ion channel 1
<i>At1a</i>	angiotensin II receptor, type 1a
<i>AVPR1A</i>	arginine vasopressin receptor 1A
<i>BDNF</i>	brain-derived neurotrophic factor; the most commonly studied variant is a functional SNP changing valine to methionine at position 66 (Val66Met)
<i>CACNA1C</i>	calcium channel, voltage-dependent, L type, alpha 1C subunit
<i>CB1/CB2</i>	cannabinoid receptor 1/2
<i>CCKBR</i>	cholecystokinin B receptor
<i>CFD</i>	complement factor D (adipsin)
<i>COMT</i>	catechol-O-methyltransferase; the most commonly studied variant is a functional SNP changing valine to methionine at position 158 (Val158Met)
<i>CNTNAP2</i>	contactin-associated protein-like 2
<i>CRH</i>	corticotropin releasing hormone
<i>CRHBP</i>	corticotropin releasing hormone binding protein
<i>CRHR1</i>	corticotropin releasing hormone receptor 1
<i>CRP</i>	C-reactive protein, pentraxin-related
<i>DBH</i>	dopamine beta-hydroxylase (dopamine beta-monoxygenase)
<i>DAT1 (SLC6A3)</i>	solute carrier family 6 (neurotransmitter transporter), member 3
<i>DRD2/DRD4</i>	dopamine receptor D2/D4
<i>DTNBP1</i>	dystrobrevin binding protein 1
<i>FAAH</i>	fatty acid amide hydrolase
<i>FKBP5</i>	FK506 binding protein 5
<i>FMR1</i>	fragile X mental retardation 1
<i>Gabbr1</i>	gamma-aminobutyric acid (GABA) B receptor, 1
<i>GABRA6</i>	gamma-aminobutyric acid (GABA) A receptor, subunit alpha 6
<i>GRIN1/2B</i>	glutamate receptor, ionotropic, N-methyl D-aspartate 1/2B
<i>GAD1/2</i>	glutamate decarboxylase 1/2
<i>GNB3</i>	guanine nucleotide binding protein (G protein), beta polypeptide 3

Gene Symbol	Definition
<i>GRIK3</i>	glutamate receptor, ionotropic, kainate 3
<i>HTR1A/1B/2A/2C/3A</i>	5-hydroxytryptamine (serotonin) receptor 1A/1B/2A/2C/3A
<i>IL-1B</i>	interleukin 1, beta
<i>KIF18A</i>	kinesin family member 18A
<i>MAOA</i>	monoamine oxidase A; the most commonly studied variant is a 30-base pair VNTR polymorphism in the promoter region with 2–5 repeats
<i>MIR137</i>	microRNA 137
<i>NFKBIZ</i>	nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, zeta
<i>NGF</i>	nerve growth factor (beta polypeptide)
<i>NPSR1</i>	neuropeptide S receptor 1
<i>NPY</i>	neuropeptide Y
<i>NR3C1/NR3C2</i>	nuclear receptor subfamily 3, group C, member 1/2
<i>NUCKS1</i>	nuclear casein kinase and cyclin-dependent kinase substrate 1
<i>OXTR</i>	oxytocin receptor
<i>PARP14</i>	poly (ADP-ribose) polymerase family, member 14
<i>PCLO</i>	piccolo presynaptic cytomatrix protein
<i>PET-1 (FEV)</i>	FEV (ETS oncogene family)
<i>PHOX2B</i>	paired-like homeobox 2b
<i>RBFOX1</i>	RNA binding protein, fox-1 homolog (C. elegans) 1
<i>RGS2</i>	regulator of G-protein signaling 2
<i>SERPINA1/SERPINA6</i>	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1/6
<i>SLC6A4 (SERT; 5HTT)</i>	solute carrier family 6 (neurotransmitter transporter), member 4 (serotonin transmitter)
<i>SLC6A15</i>	solute carrier family 6 (neutral amino acid transporter), member 15
<i>SLC27A6</i>	solute carrier family 27 (fatty acid transporter), member 6
<i>STMN1</i>	stathmin 1
<i>TMEM132D</i>	transmembrane protein 132D
<i>TOMM40</i>	translocase of outer mitochondrial membrane 40 homolog (yeast)
<i>TPH1/2</i>	tryptophan hydroxylase 1/2

Table III

Summary of heritability estimates and genetic associations identified in human studies of negative valence traits.

RD/C Unit	Phenotype	Heritability	Candidate Genes	Replicated	Needs Replication	Conflicting Evidence	GWAS	Other
Acute Threat Response	Amygdala Reactivity	-	5-HTTLPR, HTR1A, MAOA, FKBP5, FAAH, ADCY7	HTR1A, HTR2A, SLC6A3, DRD2, ANKK1, AR, ASIC1, ACCN2, NPY, NR3C2, PET-1, PCLO	TPH2, COMT	PHOX2B (did not replicate)		gene expression studies identified <i>APBB3</i> , <i>CFD</i> , <i>NFKBIZ</i> , <i>NUCKS1</i> ; polygenic risk score of glucocorticoid response genes
	Fronto-limbic Connectivity	-	5-HTTLPR, COMT	MIR137	MAOA			-
	Cardiovascular Stress Response	43–45% (HR); ~50% (HRV)	NR3C1, NR3C2	HTR1B, NGF, ADRA2C, GNB3	5-HTTLPR, COMT, BDNF, OXTR			-
	Respiratory Stress Response	-	-	ADORA2A	-			-
	Skin Conductance Response	43–65%	-	5-HTTLPR, COMT	-	no significant associations		-
	Alpha Amylase Stress Response	51–62%	-	GABRA6	5-HTTLPR			-
	Cortisol Stress Response	32–98%	CRH, CRHR1, CRHBP, NR3C1, NR3C2, FKBP5, ACE, 5-HTTLPR	HTR2A, HTR2C, DRD4, GABRA6, IL-1 β , NPSR1	BDNF			-
	Startle Response (fear/emotion potentiated)	0%	-	FMRI	5-HTTLPR, COMT	no significant associations		genome-wide gene-based association with <i>PARP4</i> ; rare variant burden in <i>KIF18A</i> and <i>SLC27A6</i>
	Startle Response (basal)	37–64%	5-HTTLPR	DAT1	COMT			genome-wide gene-based association with <i>GRK3</i> ; ancestry-informative markers correlated

RDoC Unit	Phenotype	Heritability	Candidate Genes	Replicated	Needs Replication	Conflicting Evidence	GWAS	Other
	CO2 Sensitivity	~40%	-	5-HTTLPR, COMT, DAT1, DRD2, BDNF, CBI, CB2, FAAH	-	5-HTTLPR	-	with basal startle
	Fear Conditioning	35–45%	-	5-HTTLPR, COMT, DAT1, DRD2, BDNF, CBI, CB2, FAAH	HTR1A, NPSRI, CRH, CRHR1, NR2C1, CCK, SST	-	-	-
	Fear Generalization	-	-	-	ADCYAPIR1	-	-	-
Potential Threat Response	EEG asymmetry	0–37%	5-HTTLPR	-	HTR1A, HTR2A, HTR2A, BDNF	-	-	-
	Cortisol (basal)	42–62%	-	-	FKBP5, BDNF, NR3C2	5-HTTLPR	SERPINA1/SERPINA6	-
	Anxiety sensitivity	37–47%	-	-	CCKBR, NPSRI, CRHR1, hsa-miR4717-5p (regulates RGS2)	-	RBFOX1	-
	Trait Anxiety	0–59%	-	-	-	-	-	-
	Behavior inhibition	40–60%	GAD2	-	CRH, AVPR1A, CNTNAP2, HTR2A, ADRA2A	RGS2, 5-HTTLPR	-	-
Sustained Threat Response	Attention Network (Alerting)	18–32%	-	-	ADRA2A, NET, NPSRI, GRIN2B, CACNA1C, DAT1	-	-	-
	Error-related Negativity	47%	COMT, DAT1	-	DRD2	5-HTTLPR, DRD4	-	-
	Dot-Probe	0%	5-HTTLPR	-	FKBP5, BDNF, DBH, MAOA	-	-	-
	Face Emotion Processing	-	5-HTTLPR	-	HTR1A, HTR1B, CBI, COMT, OXTR, TOMM40	-	-	-
Frustrative Nonreward	Reactive aggression	~35% (boys only)	-	-	-	-	-	-
	Irritability	22–51%	-	-	-	-	-	-

Gene abbreviations can be found in Table II. Dashes (-) within the table denotes a lack of existing studies within the specified phenotype/method. Findings of no significant associations are reported where applicable.