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High anxiety trait: A vulnerable phenotype for stress-induced depression

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Abstract

A great deal of research aims to identify risk factors related to individual vulnerability to develop stress-induced psychopathologies. Here, we summarize evidence that point at anxiety trait as a significant contributor to inter-individual differences in stress-vulnerability. Specifically, we underscore high anxiety trait as a key vulnerability phenotype. Highly anxious individuals show both behavioral alterations and cognitive deficits, along with more reactive physiological stress responses. We discuss efforts and progress towards the identification of genetic variants and polygenetic scores that explain differences in trait anxiety and vulnerability to stress. We then summarize molecular alterations in the brain of individuals with high anxiety trait that can help explaining the increased vulnerability to stress of these individuals. Variation in such systems can act as risk factors, which in combination with severe/prolonged stressful life events can pave the way towards the development of depression. Our viewpoint implies that the consideration of high anxiety trait as a key vulnerability phenotype in stress research can support the overall aim to obtain improved or novel therapeutic approaches.

Introduction

To help the organism overcome challenging situations, the stress response [including the activation of the sympathetic nervous system and the hypothalamus-pituitary-adrenal gland (HPA) axis] stimulates metabolic and neurobiological changes that, typically, provide the organism with additional energy and coordinate brain responses to organize behavioral adaptation. Depending on the context, these reactions can facilitate species-specific "fight" or "flight" responses to cope with the specific threat (Smith and Vale, 2006; Ulrich-Lai and Herman, 2009). The process including such active physiological and behavioral responses of the body to a specific threat is termed "allostasis" and allows organisms to reestablish and maintain homeostasis (de Kloet et al., 2005; McEwen and Gianaros, 2011). While organisms have mechanisms to counterbalance potentially damaging side effects of short-term stress responses, exposure to prolonged stress can lead to adverse physiological and behavioral changes (de Kloet et al., 2005). This chronic impact has been termed "allostatic overload" and examples include the metabolic syndrome, as well as anxiety and mood disorders (McEwen et al., 2015).

Despite the large evidence supporting a deleterious impact of cumulative stress exposure on brain and behavior, the existence of considerable individual differences in the way organisms respond to and are affected by exposure to stressors is becoming increasingly recognized. While the so-called "vulnerable" individuals develop psychopathological alterations, "resilient" individuals do not show clear signs of psychopathology in response to repeated stress exposure (Del Giudice et al., 2011; Ebner and Singewald, 2017; Franklin et al., 2012).

Focusing research on stress vulnerability can greatly help to reveal the mechanisms that lead to stress-related disorders and improving therapeutic opportunities. In recent years, several animal studies (Duclot and Kabbaj, 2013; McEwen et al., 2015; Russo et al., 2012; Sandi and Richter-Levin, 2009) have revealed processes and mechanisms differentially altered in vulnerable individuals by stratifying subjects, as either vulnerable or resilient, based on *a posteriori* assessment of the behavioral symptoms exhibited after stress exposure. However, only by coupling such an approach with the identification of risk factors can eventually allow recognizing *a priori* individuals at risk. Such an approach would enable investigating fundamental differences determining individual susceptibility to stress.

Vulnerability to stress is generally accepted to result from both genetic factors and exposure to environmental adversity; in particular, adversity that occurs during early life (Gillespie et al., 2009). A role for genetic factors in stress vulnerability has been supported by early biometrical genetic studies showing that stress-related psychopathologies aggregate in families and are moderately heritable (Smoller, 2016). However, the identification of genetic factors has turned out as quite arduous. So far, only a few risk loci have been identified for these disorders, which strongly argues for their polygenic nature (Smoller, 2016). Consequently, each of the identified genetic risk variants seems to make small contributions to the vulnerable phenotype. On its turn, parental behavioral traits seem to also being propagated across generations via non-genetic (epigenetic) mechanisms (Mitchell et al., 2016; Sigal et al., 1988; Toth, 2015), clearly indicating the overall complexity of the underlying factors involved in stress-vulnerability. Especially early life adversity is the leading non-genetic risk factor for the development of stress-related psychopathologies later in life (Huh et al., 2017; Teicher et al., 2016; Vrijsen et al., 2017) and, importantly, not all individuals are equally affected by early life adversity. There are excellent examples of the moderate impact of specific genes, particularly from the monoaminergic system and the HPA axis, in defining subsequent behavioral adaptations (Nugent et

al., 2011; Scheuer et al., 2016; Zannas and Binder, 2014). However, the field is still exploring the relevance of sensitive periods and the suitability of different theoretical models (e.g., diathesis-stress; differential susceptibility) to guide studies on the role of gene-environment interactions (GxE) in explaining vulnerability to psychopathology (Leighton et al., 2017).

Notably, personality traits have been shown to explain a significant share of the variance observed in both individuals' responsiveness to stress and susceptibility to develop stress-induced psychopathologies (DiGangi et al., 2013; Duggan et al., 2003; Tosevski et al., 2010), particularly depression (Bagby R. M., Joffe R. T., Parker J. D. A., Kalemba V., 1995; Enns and Cox, 1997; Kendler et al., 1993). Personality traits are defined as behavioral predispositions that reflect a reliable behavioral responsiveness of a given individual across time and circumstances. Their predicting value in this context might be to some extent due to their polygenic character (Noblett and Coccaro, 2005). Human personality is typically considered to comprise five major factors: "openness" (person's degree of intellectual curiosity, creativity, and preference for novelty and variety), "conscientiousness" (tendency to show self-discipline, act dutifully, and aim for achievement), "extraversion" (describes energy, positive emotions, assertiveness, sociability, talkativeness, and the tendency to seek stimulation in the company of others), "agreeableness" (tendency to be compassionate and cooperative towards others rather than suspicious and antagonistic) and "neuroticism" (vulnerability to unpleasant emotions like anger, anxiety, depression, or vulnerability); each of these factors comprising different traits (Digman, 1990; Goldberg, 1993; McCrae and John, 1992). Notably, many studies examining the link between personality and stress-related psychopathologies have highlighted the factor neuroticism as the personality factor that captures the largest proportion of genetic risk for depression (Barlow et al., 2014; Brown and Rosellini, 2011; Kendler and Myers, 2010; Ormel et al., 2013).

Here, we argue that high anxiety trait is relevant to define vulnerability to develop stress-induced depression. To this end, we provide an overview about the literature presenting evidence that high anxiety trait is an important vulnerability factor for stress-induced psychopathology. Then, we summarize work dealing with molecular alterations in individuals with high anxiety trait, including neurotransmitters, neuroendocrine factors and mitochondrial function, and their potential role in mediating stress-vulnerability. As animal models allow performing in-depth investigations into neurobiological mechanisms, we also include studies done in animal models for stress-susceptibility and anxiety.

Behavioral and neurobiological evidence in support of high anxiety trait as a vulnerability factor to stress

Substantial work from a variety of species, including human and non-human primates highlights high anxiety trait as a critical risk factor for hyper-responsiveness to stress and vulnerability to develop psychopathologies, in particular anxiety disorders and depression (Rogers et al., 2013; Sandi and Richter-Levin, 2009). For example, following chronic stress exposure, high anxious rats [classified according to their behavioral responses in a variety of anxiety tests (see Box 1)] exhibit increased passive coping responses to environmental challenges, which are considered in the literature as depression-like behaviors (e.g., increased floating time in the forced swim test) (Castro et al., 2012; Sandi et al., 2008). Similar results were reported for rats genetically selected for their high or low trait anxiety (Frank et al., 2006). In addition, recent work in inbred C57BL/6 mice, characterized for their anxiety levels in the light dark test, further showed that the high anxiety-related phenotype is

predictive of higher susceptibility to develop depressive-like behaviors (i.e., reduced sucrose preference, increased floating in the forced swim-test, impaired coat fur state) following exposure to chronic unpredictable stress (Nasca et al., 2015).

In addition to these depression-related outcomes, it is important to note that high-anxious individuals were also reported to display alterations in other behavioral and cognitive functions, which can eventually contribute to a process whereby stress leads to depressive-like behaviors. Specifically, both rodent (Herrero et al., 2006; Salehi et al., 2010; Venero et al., 2004) and human (Thoresen et al., 2016) studies indicated inferior performance in learning tasks for high compared to low anxious individuals when performing under novelty or arousing conditions. Under stress, high anxious individuals show as well lower social competitiveness than low anxious ones (Goette et al., 2015; Hollis et al., 2015; Larrieu et al., 2017; van der Kooij et al., 2017). The latter observations are particularly relevant given the proposed link between social defeat and the emergence of depression (Krishnan et al., 2007).

Individuals with high anxiety trait show hyper-responsiveness to threatening, to moderate or ambiguous, stimuli, as well as attentional biases that facilitate the detection of threats and aversiveness (Bishop, 2007; Sandi and Richter-Levin, 2009; Stuijfzand et al., 2017). Along with these behavioral responses, they display increased amygdala activation and abnormal amygdala coupling with other brain regions, such as the hippocampus and prefrontal cortex (Bijsterbosch et al., 2015, 2014; Bishop, 2007; Forster et al., 2015; Indovina et al., 2011; Klumpp et al., 2011; Matt et al., 2016; Sandi and Richter-Levin, 2009). Accordingly, individuals with high trait anxiety show a higher vulnerability to display stress-induced alterations both, behaviorally and in their engagement of the amygdala. Frequently, they show concomitant HPA axis activation, increased glucocorticoid levels, enhanced negative memory consolidation and negative thoughts, which can lead to ineffective responses of individuals with high anxiety trait to major life stressors. Finally, these deficits can reinforce negative feelings characteristic for depression (i.e., hopelessness, helplessness, worthlessness, but also loss of motivation) and thus, can pave the way towards the development of depression. For details about the “neurocognitive model” linking high anxiety trait with stress-induced depression, see Sandi and Richter-Levin (Sandi and Richter-Levin, 2009).

Genetic and epidemiological evidence linking trait anxiety with stress-related vulnerability to depression

As indicated above, anxiety trait is one of the main facets of the personality factor neuroticism. Based on twin studies and early biometrical genetic studies, neuroticism was reported to exhibit substantial heritability, with genetic contributions ranging from 40-60% (Bouchard and Loehlin, 2001; Clark et al., 1994; Kendler et al., 2003; Power and Pluess, 2015). Recent genome-wide association studies (GWAS) have found genetic loci associated with neuroticism (Genetics of Personality Consortium et al., 2015; Okbay et al., 2016; Smith et al., 2016) and genome-wide single nucleotide polymorphisms (SNPs) explaining around 6-15% of the variance in neuroticism (Vinkhuyzen et al., 2012). Importantly, most of the studies that assessed a link between the big-five personality factors found that the largest proportion of the genetic risk for major depression is captured by neuroticism, suggesting shared genetic risk factors for neuroticism, anxiety and depression (Kendler and Myers, 2010; Lo et al., 2017; Middeldorp et al., 2011). A recent study involving polygenic risk scores for neuroticism applied to samples from Han Chinese descendants showed their ability to predict neuroticism across ancestry (Docherty et al., 2016). Importantly, a personality broad study assessing links with perceived job strain

also specifically identified high neuroticism as related to perception of high demands and low control (Törnroos et al., 2013).

Trait anxiety is most frequently evaluated by the trait subscale of the Spielberger's State-Trait Anxiety Inventory (STAI-T). Importantly, individuals with major depression are known since long to exhibit elevated scores in the STAI-T (Mathews et al., 1996). Conversely, low trait anxiety and its association with defensive functioning or high resilience have been indicated to contribute to better treatment response in depressed patients (Min et al., 2012; Sukul et al., 2009). Very few GWAS have specifically addressed the genetics of trait anxiety. One of the few exceptions is a recent study that, taking into consideration the different facets involved in neuroticism, specifically identified an association for the ITPR1 with anxiety (Kim et al., 2017). ITPR1 encodes the inositol 1,4,5-trisphosphate receptor and modulates the concentration and release of Ca^{2+}, affecting synaptic activity and plasticity. It is enriched in the central nucleus of the amygdala in mice, where it affects fear and anxiety (Chung et al., 2016). As a parenthesis, note that, interestingly, ITPR1 knockout mice showed a higher vulnerability to display depression-like behaviors (Cao et al., 2013). In fact, most of the existing genetic evidence for trait anxiety has been obtained with the candidate gene approach, which presents important biases and needs to be taken with great cautiousness (Colhoun et al., 2003; Duncan et al., 2014).

Several SNPs have been reported in relationship with trait anxiety (Savage et al., 2017). Probably the best studied one is a SNP in the promoter of the serotonin transporter (frequently abbreviated as 5-HTT or SERT). 5-HTT is encoded by the *SLC6A4* gene and its transcription is modulated by a repetitive sequence, the SLC6A4-linked polymorphic region (5-HTTLPR). 5-HTTLPR is either expressed as a short or long allele. The short allele leads to the synthesis of less 5-HTT protein than the long one, leading to higher serotonin concentration in the synaptic cleft (Canli and Lesch, 2007). Notably, the lower expressing 5-HTTLPR short variant allele was found to be associated with trait anxiety in various human studies (Greenberg et al., 2000; Kuhnen et al., 2013; Lesch et al., 1996; Minelli et al., 2011; Munafò et al., 2009b; Schinka et al., 2004; Sen et al., 2004a, 2004b; Zhang et al., 2015). Although most studies focused on adult populations, some studies also reported associations of the 5-HTTLPR short variant allele with increased shyness and inhibited temperament in children (Battaglia et al., 2005; Davies et al., 2013; Hayden et al., 2007) and in a rhesus monkey model for inhibited temperament (Bethea et al., 2004). However, it should be noted that some studies failed to find an association with shyness in children (Schmidt et al., 2002) or even described that the long, not the short, variant allele is associated with more shyness (Arbelle et al., 2003; Jorm et al., 2000). These differences in the literature were suggested to be at least partially due to a moderation of the impact of 5-HTTLPR on high anxiety trait by environmental factors, such as maternal care and social support, which are not always considered in genetic association studies [(for review, see (Clauss et al., 2015)].

Importantly, 5-HTTLPR was reported in humans to modulate the relationship between stress and depression (Caspi et al., 2003; Holden, 2003; Karg et al., 2011). In particular, a seminal study by Caspi et al. (Caspi et al., 2003) reported an interaction between 5-HTTLPR gene variants and exposure to stressful life events during the previous five years. Specifically, stressed individuals with one or two copies of the short allele exhibited more depressive symptoms, diagnosable depression, and suicidality than individuals homozygous for the long allele (Caspi et al., 2003). These observation were confirmed by more recent studies (Karg et al., 2011; Sharpley et al., 2014). However, it has to be noted that the association of 5-HTTLPR polymorphism and depression remains still controversial, as other studies could not find such an association in other populations (Culverhouse et al., 2017; Fergusson et al.,

2011; Munafò et al., 2009a; Risch et al., 2009). In addition, the mechanisms whereby alterations in the monoamine system might predispose individuals to psychopathology is still a matter of research. As reported, 5-HTTLPR short allele carriers exhibit reduced gray matter volume in limbic regions and alterations in neural circuit activation (e.g., amygdala, hypothalamus) during stress and emotional processing (Alexander et al., 2012; Canli et al., 2006; Dannlowski et al., 2008; Fortier et al., 2010; Heinz et al., 2007; Kruschwitz et al., 2015; Murphy et al., 2013; Pezawas et al., 2005; Zhang et al., 2015). Furthermore, HPA axis hyper-reactivity to stress observed in subjects carrying the 5-HTTLPR short allele might also underlie their increased vulnerability to develop depression (Alexander et al., 2009; Fogelman et al., 2016).

In addition, variation in genes from the catecholamine systems have also been associated with high anxiety trait. Evidence includes variants in several dopamine receptor genes (e.g., D2, D4) (Jönsson et al., 2003; Kim et al., 2013; Tochigi et al., 2006; Wacker et al., 2005) [but see also (Henderson et al., 2000; Hibino et al., 2006; Urata et al., 2007)] and different monoamine transporters such as the norepinephrine transporter (Marques et al., 2017) and the vesicular monoamine transporter 1 (Lohoff et al., 2008). Furthermore, a functional SNP (Val158Met) in the catechol-O-methyltransferase (*COMT*) gene, leading to decreased activity of this catecholamine catabolic enzyme, has been associated with high scores of neuroticism and lower scores of extraversion (Eley et al., 2003; Hoth et al., 2006; Stein et al., 2005).

Given the role of the GABAergic system in anxiety, alterations in this system may also predispose individuals to pathological anxiety traits (Domschke and Zwanzger, 2008), it is not surprising that several SNPs in genes that regulate GABA synthesis or signaling have been reported to contribute to individual differences in trait anxiety and, more globally, in neuroticism (Hettema et al., 2006; Sen et al., 2004b) and inhibited temperament (Smoller et al., 2001; Unschuld et al., 2009). For example, several SNPs in the GABA(A) α6 receptor subunit gene (*GABRA6*) were associated with higher neuroticism scores [for the Pro385Ser polymorphism; (Sen et al., 2004b)] and with "harm-avoidance" (anticipatory worry, fear of uncertainty, shyness, and fatigability) [for the T1521C polymorphism; (Arias et al., 2012)]. Furthermore, healthy subjects homozygous or heterozygous for the T allele in the T1521C SNP in the *GABRA6* gene were found to exhibit increased levels of HPA axis hormones to acute stress, including increased adrenocorticotropin (ACTH) and cortisol levels (Uhart et al., 2004). Importantly, GABA content in the ventromedial prefrontal cortex is positively correlated with trait anxiety (Delli Pizzi et al., 2016; Ritov et al., 2016). In line with the studies in human, anxiety-related behavior (HAB) mice, a model of pathological trait anxiety, exhibit a variety of alterations of the GABAergic system in their amygdaloid nuclei (i.e., basolateral, medial and central) (Tasan et al., 2011), and imbalances in the GABAergic system have been implicated with increased anxiety-like behavior in rodents (Kash et al., 1999; Shekhar et al., 1996; Stork et al., 2003). As emotional processing is regulated by GABAergic transmission in the amygdala (Nuss, 2015), these studies suggest that an imbalanced GABAergic neurotransmission might affect emotion processing and regulation by causing greater amygdala activity and thus, higher levels of anxiety. Notably, stress can lead to alterations of the GABAergic system in central stress circuits (Bowers et al., 1998; Makinson et al., 2015; Wilson and Biscardi, 1994).

Trait anxiety and variation in the HPA axis

Alterations in HPA axis activity in high anxiety trait might also constitute a crucial vulnerability factor for stress-induced psychopathology. Several studies in humans have reported higher basal or activated cortisol levels in anxious humans (Gerritsen et al., 2009; Goette et al., 2015; Goldsmith and Lemery,

2000; Laceulle et al., 2015; Nater et al., 2010; Portella et al., 2005; Puig-Perez et al., 2016; Tyrka et al., 2008; Van den Bergh et al., 2008). During task performance, trait anxiety can have a moderator effect on cortisol secretion, suggesting that HPA activation due to performance pressure is stronger in individuals with high anxiety trait (Goette et al., 2015; Schlotz et al., 2006); however, note that some studies surprisingly found blunted cortisol responses to stress (Oswald et al., 2006). Similarly, in both rodents and primates, animals with high-anxiety trait were found to exhibit enhanced activation of the HPA axis following exposure to environmental stressors (Castro et al., 2012; Jakovcevski et al., 2011; Kalin et al., 1998; Landgraf and Wigger, 2003; Márquez et al., 2006; Salomé et al., 2006; Wigger et al., 2004). Glucocorticoids such as cortisol or corticosterone (depending on the species), final products of the activated HPA axis, and their receptors (i.e., glucocorticoid and mineralocorticoid receptor) are main mediators of the stress response and can act via both genomic and non-genomic (fast) mechanisms (Gray et al., 2017; Groeneweg et al., 2011). Genetic variation in the glucocorticoid (Montag et al., 2013) and mineralocorticoid (DeRijk et al., 2011) receptors have also been associated in humans with higher neuroticism scores.

More insights are provided by rodent studies showing that high-anxiety mice, as compared to low-anxiety ones, exhibit increased levels of hippocampal glucocorticoid receptor transcript and protein at basal conditions (Jakovcevski et al., 2011) and show enhanced novelty-induced plasma corticosterone secretion upon acute stress (Jakovcevski et al., 2008). Interestingly, systemic injection of the glucocorticoid receptor antagonist mifepristone decreases the stress-induced activation of the HPA axis and anxiogenic effects in high-anxiety mice (Jakovcevski et al., 2011), suggesting that the variability in stress responsiveness between high- and low-anxiety mice might result from changes in their glucocorticoid signaling. This is in line with a recent genome wide expression profiling study in rats in which differential expression of genes related to glucocorticoid receptor signaling in the amygdala and hippocampus was associated with inter-individual vulnerability to stress (Daskalakis et al., 2014). Furthermore, in the rat hippocampus, lower levels of the mineralocorticoid receptor were observed in high-anxiety animals (Herrero et al., 2006). Conversely, in the hippocampal dentate gyrus of C57BL/6 mice that were classified as high-anxious and identified as high sensitive to stress, mineralocorticoid receptor expression levels were shown to be higher than in resilient mice (Nasca et al., 2015), suggesting a link between mineralocorticoid receptor expression and trait anxiety. In mice, mineralocorticoid receptor overexpression in the forebrain leads to a decrease of anxiety-like behavior and to a moderate suppression of the corticosterone response to stress (Rozeboom et al., 2007), further supporting a role of the mineralocorticoid receptor for trait anxiety. High levels of glucocorticoids were shown to enhance glutamatergic transmission in the hippocampus and the basolateral amygdala via non-genomic actions of the mineralocorticoid receptor (Karst et al., 2010, 2005). In the basolateral amygdala, the enhancement in glutamatergic transmission is long-lasting and is maintained in a mineralocorticoid and glucocorticoid receptor-dependent manner. Physiologically this might provide an important time window for the encoding of emotional aspects by the amygdala during stressful events (Karst et al., 2010). A second exposure of treated brain sections with glucocorticoids, but also glucocorticoid treatment of brain sections of animals with prior stress exposure, leads to a decrease in glutamatergic transmission. Thus, high glucocorticoid levels can have excitatory to inhibitory effects on the basolateral amygdala, depending on the recent stress history of the organism and might be crucial for emotional processing via the amygdala in stressed conditions (Karst et al., 2010). These observations strongly suggest a potential relevance of imbalanced glucocorticoid and mineralocorticoid receptor expression and signaling in the link with high anxiety

and stress vulnerability. Notably, current aims target to overcome HPA axis dysregulation and changes in glucocorticoid signaling as observed in patient for major depression by restricting glucocorticoid receptor effects with antiglucorticoid treatment or steroid synthesis inhibitors [reviewed in (Joëls et al., 2012)].

Corticotropin-releasing-hormone (CRH or CRF), a primary effector of the HPA axis acts via two receptors, CRHR1 and CRHR2, which are distinctly different in localization and affinities for CRH (Laryea et al., 2012). In addition, CRH can also act in extra-thalamic brain regions (Laryea et al., 2012; Risbrough and Stein, 2006). Several studies have implicated CRH in anxiety and depression (Laryea et al., 2012; Risbrough and Stein, 2006). Rat studies investigated the question how CRH might act as a vulnerability factor for stress-induced psychopathology in individuals with high anxiety trait. CRH has a potentiating effect on the electrophysiological response of the basolateral amygdala (Ugolini et al., 2008), an effect reduced in animals exposed to chronic, unpredictable stress, and accompanied by an increase in depression-like behavior (Sandi et al., 2008). Interestingly, the degree of the reduction in basolateral amygdala response to CRH is dependent on the animal's trait-anxiety, with the observation that high-anxiety animals reveal more disturbed amygdala responses to CRH than low-anxiety animals (Sandi et al., 2008). These results suggest that individual differences in anxiety trait are related to differences in the susceptibility of the amygdaloid CRH system to be affected by chronic stress exposure.

Variations of the *CRHR1* gene have been associated with high anxiety trait and the risk to develop stress-induced psychopathology. In a study that examined three SNPs in *CRHR1* (rs110402, rs242924, rs7209436) in children, the CRHR1 genotype was found to moderate the association of maltreatment, that typically leads to less resilient functioning and increased risk for psychopathology, with neuroticism (DeYoung et al., 2011). Genetic associations of *CRHR1* with the cortisol response to acute psychosocial stress were reported in healthy adults, suggesting that inter-individual variation in HPA axis activity might represent a risk to develop psychopathologies (Mahon et al., 2013). Support for this view has been provided by studies in a rhesus macaque model for childhood anxious temperament. By using fluoro-2-deoxyglucose-positron emission tomography (PET) imaging to quantify local brain metabolic activity, increased metabolic activity in the dorsal amygdala, central nucleus of the amygdala and anterior hippocampus was shown to be predictive of anxious temperament (Oler et al., 2010). Functional SNPs in the *CRHR1* gene affecting exon 6, an exon assumed to impact CRHR1-signaling activity, seem to influence both anxious temperament and metabolic activity in neural circuits underlying anxious temperament, indicating that genetic variation in *CRHR1* affects the risk for affective disorders by influencing the function of the neural circuit underlying anxious temperament (Rogers et al., 2013). Based on these observations, the authors suggested that children with specific CRHR1 genotypes may exhibit differences in brain activity preceding the expression of clinically significant anxiety and depressive disorders (Rogers et al., 2013). Interestingly, *Crhr1* has been identified as a candidate epigenetic plasticity gene in the basolateral amygdala that responds to environmental stimuli (Sotnikov et al., 2014). Specifically, selectively bred high-anxiety (HAB) and low-anxiety (LAB) mice can be rescued from both ends of the anxiety continuum depending on whether they face an environmental stimulus that is beneficial or detrimental (environmental enrichment versus chronic mild stress). This rescue correlates with their amygdala activity (Avrabos et al., 2013) and with the methylation status and expression of the *Crhr1* (Sotnikov et al., 2014). Thus, this observation is in line with the idea that environmental conditions have modulating impact on the development of psychopathological symptoms in individuals with high anxiety trait.

Taking together, there is clear evidence that individuals with high anxiety trait exhibit alterations in HPA axis factors and increased HPA reactivity to stress. However, the precise impact of these alterations for developing stress-induced psychopathology will be a matter of further research.

The emerging link between trait anxiety and brain bioenergetics

Substantial work is implicating brain bioenergetics in the development of mental disorders, including depression and anxiety disorders (Gardner and Boles, 2011; Morava and Kozicz, 2013; Streck et al., 2014; Tyrka et al., 2016). Patients with mitochondrial disorders frequently exhibit psychiatric symptomology (Anglin et al., 2012; Fattal et al., 2006). Conversely, studies on individuals differing in anxiety levels are identifying key alterations in mitochondrial function. Mitochondrial DNA copy number, and thus likely mitochondrial biogenesis, is significantly higher in individuals with anxiety disorders (Tyrka et al., 2016). One study involving human placenta samples from a stress in pregnancy birth cohort has suggested a role for mitochondrial alterations in the development of infant temperament (Lambertini et al., 2015).

In rodents, a study in different inbred strains of mice performing gene expression profiling of brain regions regulating anxiety and fear led to the identification of genes with expression patterns that correlate with anxiety-like behavioral phenotypes (Hovatta et al., 2005). For two of those genes, the mitochondrial oxidative stress genes glyoxalase 1 (*Glo1*) and glutathione reductase (*Gsr*), the authors also showed a causal role in the genesis of anxiety, thus linking oxidative stress metabolism with anxiety-related behavior (Hovatta et al., 2005). Another study in mice has investigated into potential alterations in reactive oxygen species (ROS) levels in high anxiety trait. High-anxiety compared to low-anxiety animals exhibit increased ROS production in both neuronal and glial cells of the cerebellum and hippocampus and in neurons of cerebral cortex (Rammal et al., 2008). More recently, Filliou and colleagues applied omics approaches to characterize the molecular underpinnings of trait anxiety, and identified changes in mitochondrial pathways, especially in oxidative phosphorylation and oxidative stress (Filiou et al., 2014, 2011). Then, they applied MitoQ, a compound that enhances mitochondrial protection against oxidative damage (Kelso et al., 2001), to animals with high anxiety trait (Nussbaumer et al., 2016). Interestingly, MitoQ treatment had anxiolytic effects in these animals (Nussbaumer et al., 2016), suggesting that ROS might indeed affect trait anxiety due to altered oxidative stress in the brain.

A recent study in rats highlighted the role of trait anxiety in mitochondrial function and its influence on social rank (Hollis et al., 2015). High-anxiety rats, that are more prone to become subordinate during a social encounter with low-anxiety rats, exhibit lower mitochondrial function (including reduced mitochondrial respiration, ATP levels, and increased ROS) in their nucleus accumbens (Hollis et al., 2015), a brain region implicated in depression (Nestler and Carlezon, 2006). Importantly, the manipulation of the activities of the mitochondrial complexes I and II, but not ROS production, was causally related to the outcome of the social competition and, thus, seems to play a vital role in the link between trait anxiety and social competitiveness (Hollis et al., 2015). More evidence for a crucial role of the energetic status of the nucleus accumbens for stress-vulnerability of individuals was shown by a subsequent study in mice (Larrieu et al., 2017). Metabolic profiling in subordinate and dominant mice revealed that subordinate mice, which are less vulnerable to chronic social defeat stress than dominant animals, exhibit under basal conditions lower levels of energy-related metabolites. Notably, these metabolites are increased by chronic social defeat stress only in subordinate but not dominant animals, suggesting that resilience in subordinate animals might be given by *a priori* differences in

energy metabolism and the capability of nucleus accumbens machinery to cope with the higher-energy demands given by stress (Larrieu et al., 2017). Another study in rat offspring of mice subjected to stress during pregnancy, which is considered as an animal model of depression with increased anxiety-related behavior, showed that these animals exhibit reduced protein levels of the key factor of mitochondrial biogenesis, peroxisome proliferator-activated receptor-coactivator (PGC-1α), in the two brain regions examined, the frontal cortex and hippocampus (Głombik et al., 2015). The authors suggested that decreased levels of PGC-1α in this animal model might limit mitochondrial biogenesis processes and lead to a reduction in the brain's energy supply (Głombik et al., 2015). Indeed, mitochondria seem to act as stress modulators and limited energy production caused by reduced mitochondrial activity is assumed to impair the adaptive neuronal capacity to stress exposure throughout life, which then eventually leads to the development of psychopathology (Picard et al., 2015, 2014). However, the molecular mechanisms how alterations in mitochondrial bioenergetics in individuals with high anxiety trait can act as a vulnerability factor for stress-induced psychopathology remain elusive. Glucocorticoids might be interesting candidate regulators of these processes, as recent studies in the brain have implicated the glucocorticoid receptor as an important regulator of mitochondrial function and gene expression (Du et al., 2009a, 2009b; Hunter et al., 2016).

Thus, impaired energy metabolism and/or the increase of ROS by alterations in mitochondrial function can be indeed a critical vulnerability factor for stress-induced psychopathology in individuals with high anxiety trait. Future research will show how mitochondrial dysfunction can precisely induce psychopathology and whether glucocorticoids as important mediators of the stress-response are involved in these processes.

Conclusion

The studies outlined in this review show increasing evidence that high anxiety trait is linked with alterations in stress sensitivity/reactivity and forms a vulnerability factor for stress-induced psychopathology. It is tempting to speculate that the high anxiety trait phenotype might be capturing a large part of genetic and environmental influences that lead to inadequate coping strategies of individuals towards stress, i.e., proactive versus passive/reactive or maladaptive copying styles, and, thus, make these individuals susceptible to stress. As further discussed here, stress-vulnerability of individuals with high anxiety trait is likely due to *a priori* differences in the genetic make-up of their brain. This at least partially seem to include (epi-) genetic alterations in factors involved in neurotransmitter and neuroendocrine systems and mitochondrial function, which can result in alterations in the way individuals experience, are affected and cope with stressful situations (Figure 1). Thereby, according to the "diathesis-stress model", high anxiety trait *per se* is not necessarily leading to the development of psychopathology, but it forms a severe risk factor, which in combination with suboptimal environmental conditions such as strong or prolonged stressful life events can lead to the development of anxiety disorders and/or depression. In contrast, positive environmental conditions can have mitigating effects on stress impact (Figure 1), reducing the risk to develop psychopathology [for details, see (Halldorsdottir and Binder, 2017), and references therein]. Particularly, positive social interactions can protect individuals from aversive stress effects and the development of stress-induced psychopathologies, a phenomenon called "social buffering of stress" (Sandi and Haller, 2015). Future functional studies will be required to elucidate the role of the identified risk factors and their downstream consequences for stress-induced psychopathology in individuals with high anxiety trait.

It is noteworthy that the current therapeutic approaches to treat anxiety disorders or depression, while being effective to a large extent, can be accompanied by intolerability or can have mild or even no effect at all in certain individuals (Bystritsky et al., 2013; Penn and Tracy, 2012). Such drawbacks in treatment are more and more supporting the idea of applying "personalized medicine" approaches, which aim to consider each person's unique clinical, genetic, genomic, and environmental information in the application of a certain treatment (Chan and Ginsburg, 2011; Miller and O'Callaghan, 2013). Data reviewed here suggest that the high anxiety trait is a polygenic trait, i.e., several risk factors contribute to this vulnerable phenotype. The polygenic nature of high anxiety trait can explain much of the generally observed variance of genetic vulnerability to stress-induced psychopathology. Thus, research in stress resilience and susceptibility could strongly benefit from the classification of individuals in regards to their trait anxiety. This might eventually help to lead to improved or novel therapeutic approaches for the prevention and/or treatment of stress-induced psychopathologies such as anxiety disorders and/or depression.

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Figures

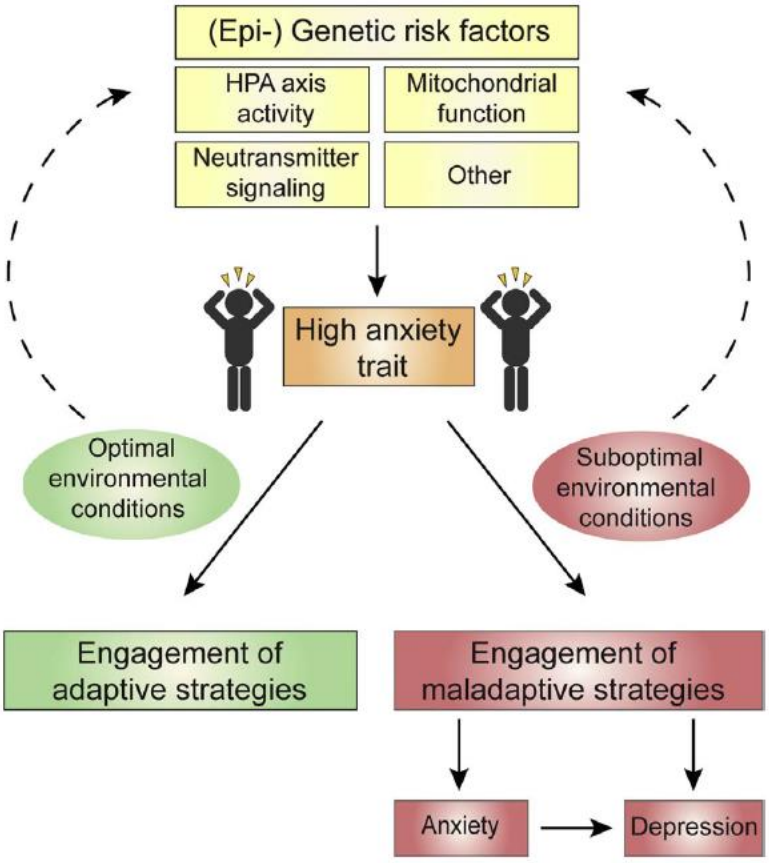

Figure 1. High anxiety trait as a key vulnerability phenotype for stress-induced psychopathology

Schematic illustrating how high anxiety trait can act as a vulnerability factor for stress induced psychopathology. In this model, molecular variations (i.e., epigenetic and/or genetic factors) in key neurobiological systems (i.e., neurotransmitter systems, HPA axis, mitochondrial function, other) might define the high anxiety trait phenotype. This phenotype is not *per se* leading to psychopathology and positive environmental conditions can have mitigating effects. Only in combination with suboptimal environmental conditions such as stressful life events, high anxiety trait provides a vulnerability phenotype for the development of psychopathology such as anxiety disorders and/or depression. The dashed lines indicate that environmental factors also can feedback in turn to (epi-) genetic factors targeting, for example, HPA axis activity.

Box 1. Animal tests for anxiety and stress-susceptibility

Animal studies allow to undertake in-depth investigations of neurobiological mechanisms (i.e., at the circuit and molecular level). Individual variation in anxiety responses in rodents is typically evaluated using the following tests:

Elevated plus maze: A test that exploits the trade-off experienced by animals between adventuring themselves to explore the unprotected, anxiogenic open arms (OA) of a cross, elevated maze or remaining in the protected closed arms (CA). Low values of percent time spent in the open, as opposed to the closed arms indicate high anxiety (HA). In low anxious (LA) animals these differences are less pronounced. See Figure A.

Light-dark box: A test in which animals are let to explore two adjacent, communicating chambers, one of them exposed to a bright, anxiogenic light (L) and the other one in darkness (D). Low values of percent time spent in the light compartment are considered an index of high anxiety. See Figure B.

Open field: A test in which animals are allowed to explore an empty arena. Thereby, the animal can choose to explore the protected periphery of the arena, usually in contact with the walls (thigmotaxis), or the unprotected center area. Animals that spend significantly less time exploring the center of the arena are regarded to be high anxious. See Figure C.

The validity of these tests to measure anxiety was confirmed many years ago in studies showing a reduction of anxiety-like behaviors in animals injected with anxiolytic drugs (Lister, 1987; Misslin et al., 1989).

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