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Finding Translation in Stress Research

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Abstract

In our ongoing efforts to advance understanding of human diseases, translational research across rodents and humans on stress-related mental disorders stands out as a field that is briskly producing discoveries that illuminate novel mechanisms of risk and pathophysiology. Here we offer a perspective on how a productive translational research dialogue between preclinical models and clinical studies of these disorders is being powered by an ever developing appreciation of the shared neural circuits and genetic architecture that moderate the response to stress across species. Working from these deep foundations, we discuss the approaches, both traditional and innovative, which have the potential to deliver a new generation of risk-biomarkers and therapeutic strategies for stress-related disorders.

The ubiquity of stress and stress-related illness

All organisms must overcome some adversity to survive and thrive in unpredictable and often unforgiving environments. The ubiquity of stress has shaped highly conserved biological machinery that function to acutely mobilize bodily resources and generate responses to myriad environmental dangers that threaten injury or death. Higher animals, in particular, have evolved elaborate physiological and neurobiological systems to perceive, react, and adapt to psychological stressors.

Central to these systems is the hypothalamic-pituitary-adrenal (HPA)-axis, activation of which directs energy away from routine homeostatic functions, such as immunity and tissue repair, to processes such as increased cardiovascular activity and glucose metabolism necessary for immediate survival. In the brain, highly complex neural circuits distributed in cortical, limbic, and midbrain areas integrate, encode, and establish memories of stressful stimuli and events to guide future behaviors [1]. The functional dynamics of these circuits are modulated, in turn, by equally complex and intersecting molecular signaling cascades, and the genes that encode for their constituent components. Across species, the capacity of neural and neuroendocrine systems to mount an appropriate response to stress is a core facet of adaptive success and can even build resilience to subsequent stress challenges.

But stress has a dark side. Mental illnesses directly linked to stress, including Anxiety disorders, Depressive disorders and the newly categorized Trauma-and stressor-related disorders (which we hereafter refer to by the former moniker, PTSD) [2], are now so

widespread that their prevalence rivals emerging global health pandemics such as obesity [3]. The diagnostic symptoms of stress-related disorders are many and varied, but what they typically have in common is an excessive reaction to isolated or recurring stressful experiences that persists over time, such that it becomes difficult for the sufferer to lead a normal life.

What goes awry in the body and brain when the response to stress stops being a healthy reaction to life's inevitable challenge and starts to become a chronic illness? Why do seemingly similar stressors and stressful life histories make one person sick, but leave another unaffected? And how can we leverage an ever-increasing understanding of the brain and behavior to design new ways to alleviate the suffering of people afflicted by stress-related illness and, ultimately, prevent them altogether?

These are long-standing questions that continue to occupy the work of psychologists, neuroscientists, and geneticists. The more circumscribed focus of our Perspective is to highlight the growing potential for marrying preclinical work, predominantly in rodents, with studies in healthy humans and clinical populations. Though the need for greater translational efforts is a common refrain across all of psychiatry, we believe stress research, with its rich and illustrious history (Figure 1), offers a particularly promising opportunity to integrate research at the bench, laboratory, and clinic to provide real advances in our understanding of the biological basis of stress-related disorders and illuminate a clear path to new strategies for treatment and prevention.

Stress recruits highly conserved biological machinery

Translational research on stress-related disorders is predicated on the existence of highly conserved biological machinery functioning to deal with the challenges encountered in the environment. Efforts to finding translation in stress research is not new and can be traced back to the seminal research of the endocrinologist, Hans Selye [4]. Selye's work was the genesis for the systematic study of stress manifest as both a critical adaptive physiologic response to the environment (i.e., eustress) and a maladaptive, non-specific dysregulation of this same physiology (i.e., distress or toxic stress). In addition to detailing numerous effects of stress on the body, Selye identified the HPA-axis as the anatomical brain-body substrate of the stress response and demonstrated the powerful regulatory role of glucocorticoid signaling in regulating this response [5].

A large component of stress research since has focused on the importance of glucocorticoid signaling in mediating the adaptive and maladaptive effects of stress-triggered HPA-axis activity on the brain [6, 7]. This work reveals how dysregulated glucocorticoid signaling in animals subjected to chronic stress and humans suffering from stress-related mental disorders is a nexus through which genetic and environmental risk impairs neural circuit functions to cause aberrant behavior. A wide array of stressors can produce such effects, ranging from the direct physical and chemical insults studied by Seyle, to more indirect and insidious stressors such as environmental instability. In fact, we now know that witnessing traumatic events, non-physical forms of childhood neglect, and low-levels of perceived

social support are types of commonly encountered stressors experienced by individuals who go on to develop anxiety disorders or PTSD.

We also now have a deep understanding of how the brain perceives and processes these experiences. A tripartite corticolimbic circuit comprising the amygdala, hippocampus, and prefrontal cortex (PFC) operates across species to regulate both the immediate response and long-term impact of stress [8, 9]. The amygdala is a highly conserved brain structure with multiple functions [10, 11], the best known of which is to detect potential danger, mount physiologic and behavioral responses to avoid these threats, and establish lasting memories to predict, and appropriately direct, behavior in the face of future threats. A series of studies dating back to the 1960s provided the first evidence that the amygdala regulated the HPA-axis via projections to the paraventricular nucleus [12, 13]. The critical importance of the amygdala in the generation of cue-elicited or learned fear responses in rats was subsequently described in the early 1970s by Blanchard and Blanchard [14]; an observation replicated in many different settings in the years since [15]. In recent times, the field has been extraordinarily active in its efforts to delineate the subregions and neuronal subpopulations in the rodent amygdala that mediate both learned fear behaviors and the extinction of these responses [8, 16].

The hippocampus and PFC are often considered to play supporting, but no less integral roles, to the amygdala in stress regulation. Two major contributions of the hippocampus in this regard are the encoding of complex, multi-sensory (e.g., contextual) environmental information associated with threat and the provision of an important source of negative feedback to the HPA-axis via glucocorticoid receptors. This is evidenced by the observation that rodents with hippocampal lesions fail to use context to adaptively gate responses to threat cues [17, 18], and exhibit elevated circulating levels of the glucocorticoid, corticosterone, after stress challenge [19]. With regard to the PFC, various subregions in the rodent (e.g., anterior cingulate, prelimbic, infralimbic cortices) gate learned associations between cues and threat, but in some cases only in distinct settings, such as when associations have been extinguished or were formed in the remote past [20–23]. These findings illustrate how the amygdala, hippocampus, and PFC operate in a highly integrated neural circuit, along with critical input from other brain regions, including midbrain monoaminergic nuclei and the thalamus [24, 25], to filter the immediate and lasting impact of stress.

One of the major pillars of translational research on stress is the highly conserved nature of these brain circuits [26]. Clinical lesion and neuroimaging studies in humans dating back some twenty years demonstrate a prominent role for the human amygdala in processing and learning about sources of threat [27, 28]. Moreover, patients with stress-related disorders such as PTSD have been shown to display hyperactivity of the amygdala during fear conditioning and extinction, which correlates with their sustained levels of fear [29–31]. In a similar vein, some of the well-defined functions of the rodent hippocampus and PFC map onto analogous stress-related functions in humans [21, 32]. For example, functional neuroimaging studies in healthy humans have shown that the hippocampus is active during contextual processing of threat [33] and that both the hippocampus and PFC are recruited during fear extinction [34, 35]. And in clinical populations, such as individuals with PTSD, deficiencies in extinction are

closely linked to hypoactivity of the hippocampus and (ventromedial) PFC [31, 36], as has been observed in rodents [37]. The clear functional convergence of these and other well-defined stress-related processes is a boon to the cross-fertilization of parallel research streams in rodents and humans.

The genetic architecture of stress moderation

Identifying the molecular mechanisms through which this conserved neural circuitry is modulated brings us one step closer to understanding the pathophysiology of stress-related disorders and, ultimately, to the development of more effective therapeutic targets. Hence, a cornerstone of translational research is the identification of DNA sequence variation in organismal genomes that contribute to variability in the functioning of stress-modulating molecules [38, 39].

To date, some of the most influential research here has not resulted from the sequencing of the reference human genome, as many had expected, but rather the targeted study of candidate genes. In 1995, Lesch, Murphy and colleagues first described the existence of common functional DNA sequence variation in the human gene encoding the serotonin transporter (*SLC6A4*). This gene was targeted because the serotonin transporter regulates a neurotransmitter system long implicated in stress [40]. The authors findings, that *SLC6A4* variation associates with differences in trait anxiety across individuals, represented a watershed not only for translational stress research but also psychiatric genetics and imaging genetics [41]. This discovery was also instrumental in providing the impetus for the generation of rodent strains with functional mutations of the serotonin transporter [42, 43]. These rodent studies helped parse the neural circuit consequences of disrupting the serotonin transporter, stimulating work on the neural correlates of *SLC6A4*-related anxiety and threat processing in humans [44]. While defining the precise role of the *SLC6A4* variant has proven contentious over the years, the type of research it stimulated remains a guide for a rational translational approach to the study of stress-related disorders.

A recent illustration of this approach is the case of fatty acid amide hydrolase (FAAH), a regulatory component of the brain endocannabinoid, anandamide, which has been tied to stress-related behaviors and disorders by clinical and pharmacological studies alike [45–48]. A single-nucleotide polymorphism (SNP) in the human *FAAH* gene was found to be associated with reduced mRNA expression, enhanced fear extinction, and lower scores on PTSD-risk personality traits in healthy subjects [49]. At the neural level, imaging genetics studies mapped this phenotype to a capacity of the amygdala to rapidly habituate to threat [50, 51]. Further insight into how this genetic variant could impact amygdala function to affect behavior followed from rodent pharmacological studies, which mimicked the effects of the low-functioning human gene variant by inhibiting FAAH activity. This led to the demonstration that decreasing FAAH activity enhanced fear extinction and protected against the damaging effects of chronic stress on the amygdala [52]. In parallel, mice engineered to carry the low-functioning human *FAAH* variant were found to show that the resultant improvement in extinction produced by this genetic mutation was associated with increased functional coupling between the amygdala and PFC [49]. These multiple lines of evidence put forward a model whereby genetically-driven variation in *FAAH* signaling titrates anandamide levels in

the amygdala and PFC to moderate stress-related behavior. More generally, this work exemplifies how the dynamic back and forth between rodent and human studies can not only nominate new candidate genes, but also stimulate novel directions for drug development.

Another recent example illustrates how candidate genes can be studied to provide a rich biological understanding of how genetic variants work through cellular signaling cascades and brain circuits to impart their effects on stress-related behaviors. This is the case of the *FKBP5* gene (encoding FK506 binding protein 51). Common genetic polymorphisms in *FKBP5* were found to predict the occurrence of PTSD symptoms in people who had experienced varying degrees of abuse in childhood [53]. This classic gene×environment effect was described not only in terms of behavior and clinical symptoms, but also at the level of neural circuit function. *FKBP5* risk variants have been found to be associated with an exaggerated amygdala response to threat in individuals having suffered emotional neglect [54]. Moreover, a comprehensive series of experiments in rodents, led by Binder and colleagues among others, detailed a mechanism by which FKBP5 acts to reduce the sensitivity of the glucocorticoid receptor to cortisol. Together these observation present a model by which a *FKPB5* gene variation regulates brain activity to buffer the effects of stress and mitigate risk for stress-related disorders [55]. It is worth pointing out that the identification of the glucocorticoid system as central to these effects also brings us full circle to the work originated by Seyle almost a century earlier.

Towards biomarkers of risk for stress-related disorders

As in other areas of psychiatry and medicine more broadly, the hope has been that a growing knowledge base of genes that reliably predict stress-related phenotypes would allow us to forecast the likelihood someone will succumb to a stress-related disorder. We have not yet reached this point and there remain no definitive genetic markers [41], but the outlook may improve as the results of highly powered genome-wide association studies (GWAS) emerge. Additionally, there are initial signs that quantifying individual differences in the structure and function of stress-mediating neural circuits moderated by genes might be a tractable path towards ‘neural biomarkers.’

Work along these lines remains at the earliest stages, but one encouraging recent observation has again involved variability in the human amygdala response to threat. In this research, premorbid amygdala hyperactivity predicts the likelihood of succumbing to a stress-related disorder, and does so independently of genetic or environmental risk. Separate studies have now shown that relatively exaggerated threat-related amygdala reactivity is linked to greater risk for presenting with PTSD-like symptoms after combat exposure in soldiers [56] and the experience of a terrorist attack in civilians [57]. Recently, one of our labs extended these findings by demonstrating that higher threat-related amygdala reactivity predicts broader risk for pathological mood and anxiety in response to common stressors, such as changing jobs or moving from home, that were experienced up to four years later [58] (Figure 2). Strikingly, the variability in the magnitude of amygdala reactivity independently was a better predictor of vulnerability than differences in self-reported symptoms, recent stressful experiences, and childhood trauma [58].

Preclinical models, in which exposure to stressors can be carefully controlled and monitored throughout life, are in many ways ideally suited to study and elaborate on such premorbid neural risk biomarkers. However, a barrier to prospective studies of brain-behavior associations in rodents is that precise analysis of neural anatomy and function is often performed *ex vivo*. This technical hurdle will be increasingly easy to overcome with the availability of higher resolution small animal imaging or technologies permitting chronic, repeated sampling of neuronal activity in the same animal. An alternative method is to take advantage of isogenic rodent strains exhibiting stable inter-individual and inter-generational variation in a neural phenotype of interest, such that one cohort of mice from each strain can be subjected to neural analysis and another cohort to behavioral testing. Using this approach, we have shown that reduced total volume of the amygdala, but not other brain regions such as the hippocampus, serves as a good predictor of higher learned fear behavior in mice [59] (Figure 2). Here again, we find parallels in the human brain, where differences in the gray matter volume of the amygdala are reported across adults with stress-related disorders, including one study suggesting that smaller amygdala volumes may predispose soldiers to combat-related PTSD [60].

Future work along these lines will be valuable to defining a set of neural biomarkers that, when considered individually or collectively, has the power to reliably predict any given person's susceptibility to stress-related illness. Likewise, the identification of specific genetic and epigenetic differences in rodents that account for variation in stress-related behaviors could prove key to pinpointing novel targets for studies in humans. This is not just an intellectual question, but a practical consideration, given neuroimaging-based assessment of neural biomarkers is highly unlikely in routine clinical settings. Continued translational research will help establish reliable genetic, epigenetic, and molecular markers of risk-related neural circuit function that can be readily assayed from peripheral tissues, such as blood and saliva, and serve as routine proxies of individual risk.

Advancing treatment of stress-related disorders

As is true across all of medicine, treatment of mental illness is costly, inefficient, and in the end largely ineffective. The ultimate value of biomarkers is to provide a means to prevent stress-related disorders from developing in the first place. In the interim, the value of translational research lies in the development of more effective strategies for treatment. So has the remarkable pace of translational discoveries in stress-related research borne therapeutic fruit? Over the course of a half century of research, involving 10,000 preclinical experiments on around 1,500 compounds, there has been a remarkable paucity of novel anxiolytic compounds that have successfully moved from the laboratory to the clinic [61].

Much has been said about the reasons for this apparent failure and the fact that the blame should not be apportioned solely to the poor predictive validity of our animal models. Even targets with significant therapeutic potential in animal studies can often be challenging to 'make druggable' and even then, turn out to be unsafe or poorly tolerated in patients. There is also the somewhat contentious issue of whether the current structure of clinical trials is truly optimal for identifying new drugs, particularly those that are not necessarily more effective than approved treatments, but do have a superior side-effect profile. Nonetheless,

we clearly need to do improve upon the drug process of discovering new anti-stress medications and, as we have outlined here, are confident that the growing trend towards 'joined up' translational research that exploits the power of basic neuroscience tools, neuroimaging, and detailed clinical profiling, can move the field forward.

Here, it is important to consider how translational research can also encourage non-pharmaceutical approaches to treatment, including cognitive restructuring and direct, non-drug manipulation of neural stress circuits. One example of the former comes from observations in rodents and humans that extinction-induced reductions in cue-elicited anxiety and associated amygdala responses can be improved with relatively simple modifications to behavioral procedures [62, 63 64]. Targeting the neural circuits that support fear learning and stress-responsiveness has also already provided compelling therapeutic findings. Most appealingly, non-invasive methods such as repetitive transcranial magnetic stimulation (rTMS) have been successfully used to manipulate neural circuits implicated in the pathophysiology of stress-related disorders [65]. For example, rTMS targeting the dorsolateral PFC, which is positioned to effect explicit top-down regulatory control of the amygdala via connections through the medial PFC, has resulted in reduced behavioral symptoms and HPA-axis reactivity associated with hyperarousal in patients with PTSD [66]. It will be interesting to see whether equally effective outcomes may be possible with even more accessible, non-invasive, techniques such as transcranial direct current stimulation (tDCS) [67].

Though less applicable to all but the most severe cases, invasive techniques can get us even closer to the neural circuit nodes identified through translational research. Most prominent amongst these approaches is deep brain stimulation (DBS) wherein depth electrodes controlled by a subcutaneous pacemaker are implanted through stereotactic neurosurgery in target regions of interest [68]. Unlike rTMS or tDCS, the effectiveness of which is limited to the cortical mantle just below the skull, DBS can target any brain structure. For example, based on translational research areas adjacent to the ventromedial PFC are common targets in the DBS treatment of depression wherein there can be relief from lifelong debilitating illness in otherwise treatment resistant patients [69]. Although as yet untested, there is hope that DBS could provide therapeutic options in severe cases of other stress-related disorders, including PTSD.

It is further possible that invasive techniques like DBS may one day allow for direct translation of the increasingly precise mapping of neural circuits governing fear learning and stress responsiveness in preclinical models. Of course, such applications are predicated on convincingly demonstrating that analogous circuits exist in the human brain. While this may be possible with human functional neuroimaging at higher anatomical resolution using greater magnetic field strengths, many methodological challenges remain before such advances may be achieved. In the end, however, successful access to and therapeutic manipulation of an increasingly complex and fine-scale neural circuitry in humans may only be possible by expanding the catalogue of druggable targets.

Concluding remarks

In addition to the highly conserved biological machinery positioned to adaptively manage ubiquitously experienced stress, the ability to employ essentially identical behavioral measures, such as fear conditioning and extinction paradigms, that produce parallel metrics of corticolimbic circuit function and recruit analogous molecular and genetic factors, has driven translational discoveries in stress-related disorders (Figure 3). Translational stress research is thus positioned to be a standard bearer for the charge towards the recasting of mental illness as manifestations of disordered brain circuits and the behavioral processes they subserve, as formalized in the National Institute of Mental Health's Research Domain Criteria (RDoC) initiative [70]. Though not all mental disorders might prove ready fertile ground for such rapid and convergent discoveries, preclinical models have been developed for a wide range of disorders including drug addiction, depression, autism, and even schizophrenia. By emphasizing common environmental demands and resulting conservation of neural, physiological, and behavioral response repertoires across species, translational efforts around these disorders could find fertile ground as it has in the field of stress research.

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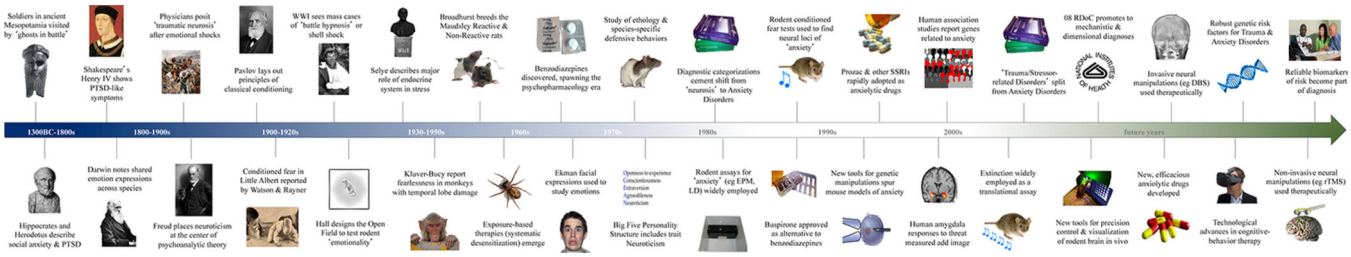

Figure 1.

A brief timeline of some major milestones - past, present and future - related to the observation, classification, and scientific study of stress and stress-related disorders.

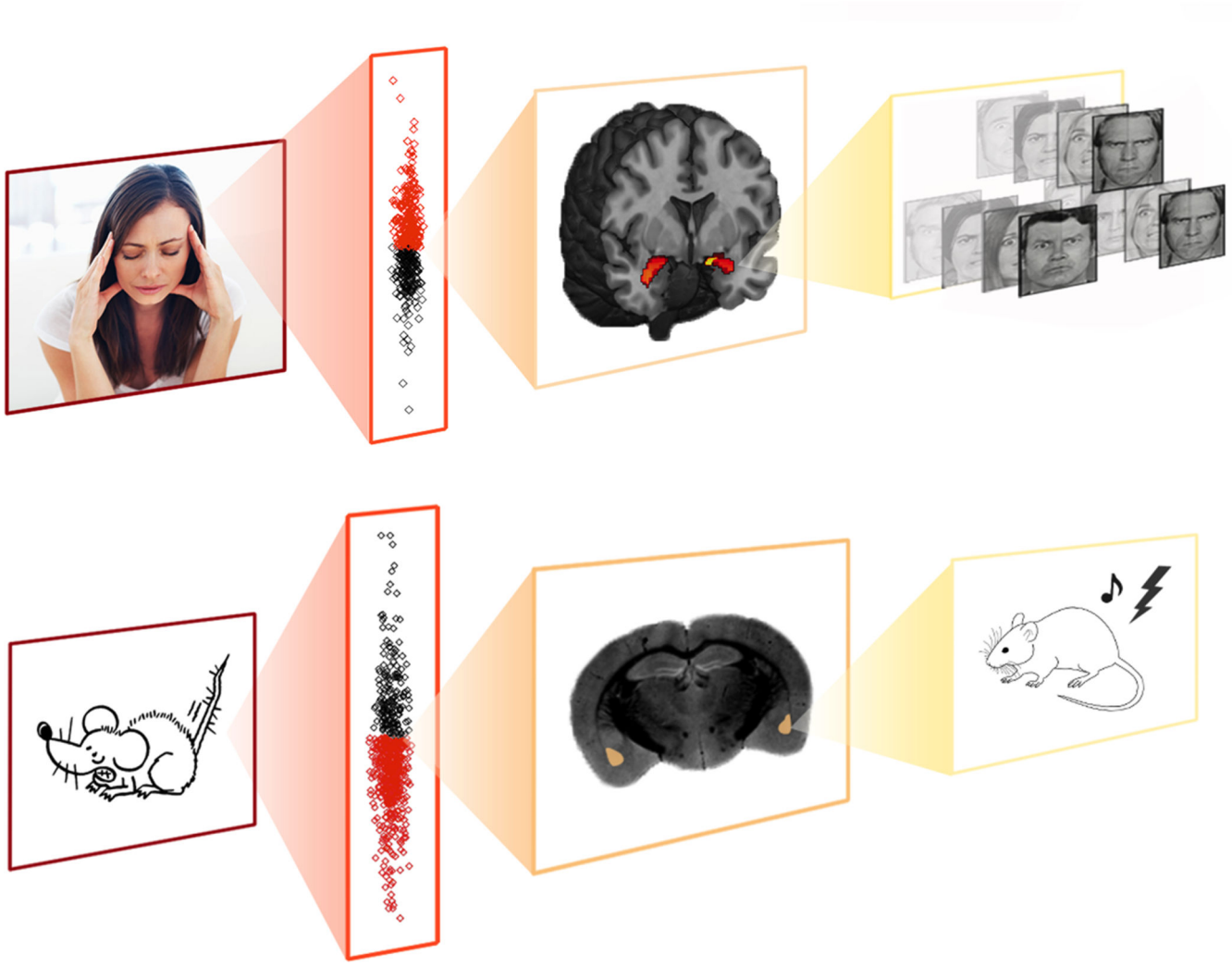

Figure 2.

Pre-existing variability in a highly conserved neural circuitry for stress responsiveness predicts vulnerability for stress-related dysfunction. Top Panel: Individual differences in human amygdala reactivity to threat-related facial expressions predict psychological vulnerability to future stress. Participants with relatively greater amygdala reactivity (red) are more likely to experience symptoms of depression and anxiety if they encounter stressors up to four years later. Bottom Panel: Individual differences in the volume of the basolateral amygdala in mice predict sensitivity to fear conditioning. Mice with a relatively smaller basolateral amygdala (red) are more likely to express persistent, extinction-resistant conditioned fear responses.

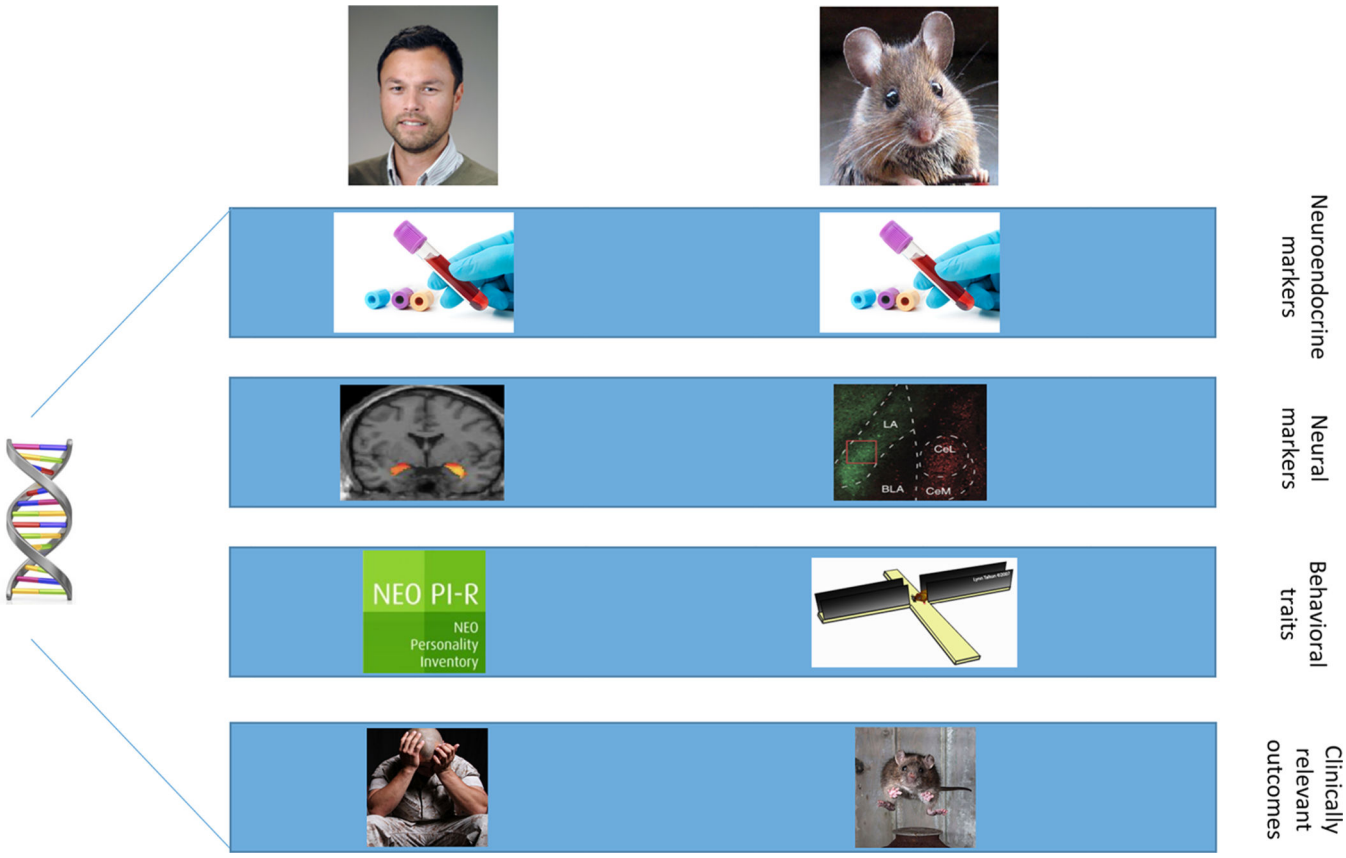

Figure 3.
Translational research has revealed convergent processes at multiple levels of analysis associated with the stress-related disorders.