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Resilience as a Translational Endpoint in the Treatment of PTSD

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CONFLICT OF INTEREST

Steven T Szabo has served on advisory boards for Jazz Pharmaceuticals, and as a consultant speaker for Neurocrine Biosciences, Teva
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Abstract

Resilience is a neurobiological entity that shapes an individual's response to trauma. Resilience has been implicated as the principal mediator in the development of mental illness following exposure to trauma. Although animal models have traditionally defined resilience as molecular and behavioral changes in stress responsive circuits following trauma, this concept needs to be further clarified for both research and clinical use. Here, we analyze the construct of resilience from a translational perspective and review optimal measurement methods and models. We also seek to distinguish between resilience, stress vulnerability, and posttraumatic growth. We propose that resilience can be quantified as a multifactorial determinant of physiological parameters, epigenetic modulators, and neurobiological candidate markers. This multifactorial definition can determine PTSD risk before and after trauma exposure. From this perspective, we propose the use of an 'R Factor' analogous to Spearman's g factor for intelligence to denote these multifactorial determinants. In addition, we also propose a novel concept called 'resilience reserve', analogous to Stern's cognitive reserve, to summarize the sum total of physiological processes that protect and compensate for the effect of trauma. We propose the development and application of challenge tasks to measure 'resilience reserve' and guide the assessment and monitoring of 'R Factor' as a biomarker for PTSD.

Introduction

Trauma exposure and the ensuing response poses major challenges to the psychological and physiological homeostasis of an individual. Trauma exposure triggers a host of behavioral and biological responses that interact with the individual's biology and genetics (1). This neurobehavioral response leads to pathophysiologic consequences that can protect against or precipitate the development of psychiatric symptoms. Broadly, factors that protect against the development of such psychiatric symptoms are referred to as "resilience". More specifically, the term resilience signifies a non-pathologic or adaptive behavioral and neurobiological response to traumatic stress (2, 3). Numerous mechanistic frameworks of trauma response have emerged to account for the development of psychiatric symptoms following trauma, such as allostatic load, stress inoculation, early life adversity, stress epigenetics, and transgenerational inheritance. Although the ability to apply these concepts to clinical situations is unproven, these frameworks do emphasize that there is a complex relationship between trauma and mental health that is influenced by genetic and environmental load effects. Gene-environment interactions and their role in etiology and pathology of illness are implicated in multiple reviews of trauma tolerance and resilience (3, 4).

While there is evidence that trauma can shape psychopathology over an individual's lifespan (5), consensus on the neurobiology of clinically-significant trauma and its effect on psychopathology continues to be elusive. While exposure to trauma in the general population is high (approximately 90%), prevalence of post-traumatic stress disorder (PTSD) is about 7–8 % (6). Multiple factors contribute to variability in development of

PTSD including gender, type and level of trauma exposure and age (6). In a seminal study, 20% of women and 24% of men developed PTSD following neglect, 8.8% of women and 6.3% of men developed PTSD following accidents, and 46% of women and 65% of men developed PTSD following rape (7). In addition, mounting evidence indicates an increased risk of PTSD in individuals exposed to trauma in childhood (8). Given the degree of variability in developing PTSD after trauma exposure, it becomes imperative to fully understand the effect of trauma on physiology and psychopathology to optimize clinical application. The concept of resilience is critical in conceptualizing maintenance of optimal functioning after trauma exposure.

The presence of multiple inconsistent and sometimes conflicting definitions of resilience points to the need for a consensus (2, 9). A few contemporary definitions focus on positive adaptation after trauma or a positive trajectory after trauma (2). The American Psychological Association (2014) defines resilience as the process of adapting well in the face of adversity, trauma, tragedy, threats, or significant sources of stress. Masten's definition of resilience is predicated on the capacity of a dynamic system to adapt successfully after disturbances that threaten the viability, the function, or the development of a system (2).

Definitions proposed by Southwick and Yehuda involve not succumbing to the negative effects of trauma (2, 10). Southwick proposes resilience as the ability of an individual to maintain an optimal trajectory after trauma. Yehuda proposes that resilience would involve a reintegration of self that includes a conscious effort to move forward in an insightful, integrated, and positive manner as a result of lessons learned from an adverse experience. This implies that resilience can co-exist with PTSD as opposed to the absence of symptoms following trauma. These definitions conceptualize resilience to be a mutable and scalable characteristic across the lifespan of an individual (10–12).

Resilience must be distinguished from stress vulnerability (1) and post-traumatic growth (13–15). Both stress vulnerability and resilience share common mechanisms that predispose individuals to develop PTSD upon exposure to stress. However, stress vulnerability only quantifies risk for developing PTSD, whereas resilience encompasses the effects of developing PTSD from exposure to stress, both positive and negative. Post-traumatic growth includes only positive changes occurring in an individual after an adverse event (13, 15). Our proposed consensus definition of resilience is a multifactorial construct that is determined from biological mechanisms and physiological parameters that mediate maintenance of an optimal functional trajectory after a traumatic event. This definition differs from both post-traumatic growth and stress vulnerability in that they are not multifactorial constructs. In addition, resilience encompasses adaptive behavioral and neurobiological responses to trauma, which are specific to the construct. Modeled as a Venn diagram, we postulate that stress vulnerability and post-traumatic growth are subsets of resilience (Figure 1).

Frequent criticisms of resilience include the difficulty to quantify it as a multifactorial construct or the need to combine multiple contributors into a single score of resilience (16). The two most widely used scales for resilience include the Connor–Davidson Rating Scale (CD-RISC) (17) and Deployment Risk and Resilience Inventory-2 (DRRI-2) (18). The CD-

RISC is a 25 item self-report instrument that has drawn from research by Suzanne Kobasa (19), Michael Rutter (20), Judith Lyons (21), and Ernest Shackleton. The scale was initially validated in populations drawn from outpatient primary care and psychiatry practices as well as clinical trials for generalized anxiety disorder and PTSD (17). Subsequent studies have validated the CD-RISC's predictive value for PTSD occurrence and severity among civilians and military veterans exposed to combat trauma. In both civilians and military veterans, CD-RISC scores were negatively correlated with PTSD symptom severity (22–25).

Less than 30% of veterans with high combat exposure and high CD-RISC scores develop PTSD; 80% of veterans with high combat exposure but low CD-RISC scores develop PTSD (22). Although clinically significant, these outcomes do not explain much of the variance in PTSD symptom severity (25–28). This adds support to the hypothesis that resilience is not just the absence of PTSD (23, 27, 28). Additionally, the CD-RISC has been criticized for lacking internal consistency and construct validity (29). Factor analyses designed to address these issues have led to both a 10-item and a 2-item scale (30, 31). However, the CD-RISC continues to be plagued by the lack of a solid theoretical basis for resilience and discrepancies in consistency (29).

The DRRI-2 is a 17-item self-report instrument that assesses deployment related risk and resilience. The instrument also assesses previous exposure to trauma including childhood trauma, adult stressors, and harassment. The DRRI-2 has been shown to have good internal consistency and reliability (18). However, the DRRI-2 is also prone to criticism, as its method for quantifying the degree of trauma, stress, or adversity using self-report scales can be considered subjective and imprecise (32).

In order to quantify resilience, the validity and precision of resilience measures needs to be improved. Imprecision in measuring resilience does not negate the validity of established resilience measures but rather calls for improved methods of quantification. The varied psychopathology observed among individuals exposed to similar trauma type and severity clearly highlights a complex relationship between genes and environment (33). There is merit to investigating how such gene-by-environment interactions mediate a variety of neurobiological endpoints with regard to trauma exposure and resilience (14). Recent findings also support transgenerational inheritance of epigenetic markers of trauma exposure to children of affected parents (34).

We postulate that resilience is a multifactorial construct that comprises parameters that span psychological, biological and environmental domains. We propose machine learning as a tool to identify resilient individuals following trauma exposure. This would require a cohort of individuals monitored longitudinally for physiological parameters, epigenetic modulators, neurobiological markers, and psychosocial factors (35). The pattern classifier would use the measures from these individuals to identify the multifactorial contributors and specify their relative weights to determine resilience (36, 37). As such, over time some of these individuals would be identified as resilient while others would be identified as non-resilient. This sample could be then used to train a pattern classifier to evaluate resilience in new cohorts. The same factors used to calculate resilience work in concert to influence the development of PTSD following trauma exposure.

Identifying personalized biomarker signatures of resilience can help us characterize biologically vulnerable individuals, individuals prone to being traumatized (e.g. high risk taking), and individuals likely to experience trauma (e.g., maltreated children, first responders, military personnel exposed to combat). Better understanding biomarkers of resilience may also help in applying these biomarkers to guide treatment discovery and ultimately treatment selection in the clinical setting. In turn, we can use these biological measures alongside discoveries in basic neuroscience research to make predictions regarding resilience and trauma exposure. As such, we propose a framework of candidate biomarker categories drawn from translational studies that are likely to serve as comprehensive measures of resilience in healthy individuals with trauma history as well as patients with PTSD or other trauma-related disorders.

In order to develop resilience into a quantifiable construct with predictive power, the construct of resilience must be successfully translated from preclinical animal models to humans. Candidate biomarkers from both neuroscience and psychobiological research could be used to develop a quantitative measure of resilience; in turn, such a measure of resilience could be used to screen individuals who are biologically vulnerable to developing PTSD. We suggest three broad strategies to help operationalize resilience as a multifactorial determinant for translation into clinical settings: (1) psychobiological challenge tasks designed to evoke a resilient behavioral response, (2) pharmacotherapies that enhance resilience (Table1), and (3) neuromodulation strategies (e.g. brain stimulation, mindfulness) whose effects are characterized by neuroimaging of circuits that mediate resilience. Intervention and treatment strategies may be tested as enhancers of resilience, which significantly curb the risk of developing PTSD.

Translational barriers to clinical applicability of resilience

Experimental manipulations can be used to examine brain circuits that mediate stress reactions responsible for post-trauma compensatory mechanisms. These circuits can either be adaptive (i.e., building resilience) or pathophysiologic (i.e., leading to symptoms of mental illness). In animal models, the absence of pathophysiologic changes in trauma-response circuits that curtail maladaptive behaviors post-trauma are regarded as a resilience phenotype. In humans, key environmental parameters that influence resilience include, but are not limited to, prenatal stress, childhood trauma, childhood neglect/abuse, nutrition, and psychosocial variables such as family and community support, poverty, and community violence (38–40). Key biological (intrinsic) parameters that influence resilience include genotype, gene expression (41, 42) serum markers (43, 44), structure and function of the brain (neuroimaging) (45, 46), epigenetics (4), cognitive appraisal skills (40), psychophysiological and autonomic response, gut microbiome, and gut biology(47). Given their dynamic nature, longitudinal human clinical trials capturing these key parameters before and after trauma exposure will significantly advance the field but require tremendous resources. Finally, mounting evidence supports the distinction between passive resilience, referring to the absence of deleterious behavioral or molecular changes following trauma, and active resilience, signifying the presence of dynamic molecular, genetic, and other adaptations that enhance behavioral function (3).

Resilience can alternatively be conceptualized as a clinical risk prediction rule, such as those that are commonly applied in other branches of medicine. For instance, the CHADS has been used in cardiology to stratify risk of stroke (48), while Well's criteria has been used in pulmonology to stratify risk of pulmonary embolism (49). These risk-scores are derived from multi-factorial determinants that have been well validated in their respective fields. Psychiatry has generally greeted the proposition of developing clinical prediction rules with a degree of skepticism, particularly in the area of trauma-related disorders. An important exception in psychiatry is the formulation of predictors used to identify ultra-high risk for schizophrenia and psychosis (50). However, this clinical risk-prediction tool has only been applied in research and not yet used in clinical practice (50). Furthermore, there is no such clinical prediction tool developed to detect resilience specifically. This approach was recently advocated by Fernandes et al (35) who propose using systems biology and computational psychiatry tools to produce a bio-signature. When applied to individuals and populations, this bio-signature will produce better diagnoses, endophenotypes, classifications, and prognosis, as well as tailored interventions for better outcomes.

We argue that the conceptualization of resilience needs to capture the combined effect of physiological processes that serve to protect and compensate for the effect of trauma. As such, we propose the existence of a mechanism within resilience called “resilience reserve”. Resilience reserve is similar to the concept of “cognitive reserve,” which indicates the ability of neural networks to compensate for the effect of insults (51), or to “fault tolerance” in mechanical and electrical systems. Candidate physiological processes are detailed in the form of an equation (Equation 1) and a graphic representation (figure 2).

We also propose an ‘R factor’ that quantifies resilience as a multifactorial construct, analogous to ‘g factor’ (52). The ‘g factor’ is a heritable variable that accounts for variance in cognitive task performance and refers to a measure of general intelligence. Our proposed ‘R factor’ is derived via Equation 1. We define ‘R factor’ as the sum of four principal terms. The first represents biological contributors to resilience (B). ‘B’ encompasses genetic risk score, serum markers, and brain imaging measures, epigenetic changes, psychophysiological and autonomic response, and gut microbiome assessments. The second term represents environmental contributors (E) to resilience. ‘E’ would encompass elements such as prenatal stress, childhood trauma exposure, social support systems, psychosocial deprivation, and other psychosocial variables. The third term is the interaction of biological and environmental variables (B X E). From here on, we collectively refer to the combination of B and E as the ‘precision predictive panel’. Finally, a fourth term represents the latent factor. Figure 2 shows a visual representation of biological variables (B), environmental variables (E) and how they interact with each other (BXE). The figure also shows how preclinical models can inform the concept and help design therapeutic modalities.

A successful operational framework requires defining resilience as a determinant of the trajectory following exposure to trauma (2). Similar to the manner in which trauma interacts with illness onset in predisposed populations, resilience may reduce the probability of developing trauma-related illness or reduce the severity of illness in individuals following exposure to trauma (2, 10, 11). Once factors contributing to resilience are quantified, studies can be designed to characterize its behavioral and endophenotypic components and examine

its evolution over the life course. This approach is consistent with the recent introduction of the Research Domain Criteria (RDoC) by the National Institutes of Mental Health that aim to classify mental disorders based on behavioral dimensions and neurophysiological endpoints. Psychobiological challenge tasks from animal studies, such as fear conditioning and extinction, could be translated to humans to quantify resilience by interrogating the endophenotypic and behavioral responses (53–55). Such a framework provides opportunities to develop interventions that might enhance resilience while also predicting onset of PTSD following trauma exposure.

$$R \text{ factor} = \sum_{k=0}^n (B) + \sum_{k=0}^n (E) + \sum_{k=0}^n (B \times E) + \sum_{k=0}^n (\text{Latent Factor}) \quad \text{Equation 1}$$

Perspective

Neurobiological surrogates can help pinpoint multifactorial determinant signatures of resilience and operationalize an ‘R factor’ in individuals exposed to trauma. This novel approach could help in the development of screening tools, potentially identify individuals prone to developing trauma-related illness following trauma exposure, and allow for early intervention, preferably well before the onset of illness. Indeed, formulating a translationally-driven and clinically useful neurobiological approach to the development of resilience measures in psychiatry by detailing differences in the effect of trauma among groups of individuals has been proposed (10–12, 56) as a step towards precision medicine for trauma-exposed individuals. A comprehensive and quantifiable measure of resilience could help identify specific vulnerabilities at the individual level as well (e.g., gene expression from a specific protein). Interventions that are able to supplement or replace specific deficits could promote post-traumatic growth and minimize the negative impact of PTSD-related symptoms (12). This approach is already being used for several medical conditions. For instance, viral vectors carrying the gene for Factor IX, introduced into patients with hemophilia (Factor IX deficiency), integrate into the cell machinery to manufacture this essential protein. Initial trials show hemophilia patients have typically experienced a complete cure after receiving this experimental treatment (57). It would not be unreasonable then to hypothesize that treatment modalities that are aimed at enhancing resilience could have the potential to curb the onset of trauma-related illnesses like PTSD. We acknowledge of course that hemophilia is a deficiency of a single protein, whereas PTSD is far more complex multifactorial entity due to myriad environmental, biologic, and genetic influences.

Distinguishing between vulnerability and resilience in subjects exposed to trauma remains a challenge (4). As shown in equation 1 and figure 2, there has been a tremendous focus on detailing changes in neural connectivity, epigenetics, hormones, and other processes like neurogenesis that contribute to the pathophysiology of the trauma response (1, 3, 38, 41). Examining the effect of gene-environment interaction and quantifying the influence of environmental events on vulnerability or resilience requires longitudinal studies with a focus on epigenetic mechanisms. Epigenetic mechanisms are key to understanding the effects of

childhood stress, such as poverty, nutritional deprivation, and sexual abuse, on the epigenome. In their seminal work, Meaney and collaborators demonstrated that environmental changes including mother-child interactions (58) and child abuse (59) produce epigenetic changes to glucocorticoid receptor signaling in the hippocampus. Individual and cumulative epigenetic changes induced by upstream mediators of trauma responsiveness might be promising candidates for intervention. One such intervention would be designing molecules that can modulate trauma response, vulnerability, and resilience (4, 42). One promising candidate drug to enhance epigenetic determinants of resilience are histone deacetylase inhibitors. Table 1 provides an overview of studies that have used histone deacetylase inhibitors in animal models (58, 60–81). The literature has also proposed translational paradigms for modulation of resilience in human clinical trials. To assess modulation of resilience with the candidate molecules mentioned in Table 1, we propose using the CD-RISC or DRRI-2 with conditioned fear virtual reality paradigms.

Intrinsic factors such as neuroimaging markers, serum neurosteroids, immune markers, gut microbiome, gene markers, proteins from gene expression, and epigenetic changes could be instrumental in characterizing both trauma-related illnesses and their treatment response. Neural markers revealed by structural and functional magnetic resonance imaging hold considerable promise in elucidating resilience profiles in individuals exposed to trauma (45, 46). Furthermore, portable devices like virtual reality headsets and devices with integrated capability for eye tracking(82), pupillometry(83), and electroencephalography (EEG) may be deployed for real-time monitoring of psychiatric symptoms that are developing in individuals exposed to traumatic events. These instruments may aid in measuring brain evoked-response potentials (ERPs)(84). ERPs are electrical responses recorded from the central nervous system, elicited by presentation of auditory or visual stimuli. These electrophysiological responses are recorded using techniques like EEG. In addition, eye-tracking systems can potentially serve as surrogates of brain function. Eye tracking methods can systematically measure eye movements such as saccades, smooth pursuit eye movements, and gaze fixation. Both ERP and eye tracking data have been found to correlate to disease states and have potential as biomarkers that may be combined with other types of biomarkers to predict resilience to trauma. Currently, exploring and quantifying biomarkers of resilience is more feasible in animal models of trauma; as such, we need to further explore how current models may help in preclinical translation of resilience.

1. Animal models of mood-anxiety disorders in preclinical evaluation of resilience

There is a dearth of scientific literature about translating animal studies of resilience to human clinical populations. This section details various animal models of PTSD, such as those directed at preclinical evaluation of treatments, with the aim of developing interventions that may enhance resilience in humans. Immunity to trauma-related symptoms observed in animal studies using PTSD model systems could be examined to learn characteristics and mechanisms of resilience. PTSD model systems incorporate elements of contextual encoding, retrieval, conditioning, exaggerated associative fear conditioning responses, failure of fear extinction, and generalization of conditioned fear responses (85). Examples of models that are based on these principles include the predator-based psychosocial stress, predator scent stress, and single prolonged stress paradigms (86). In

addition, the chronic social defeat stress paradigm approximates the behavioral phenotype of PTSD in rodents (87, 88).

In these model systems, a significant proportion of animals do not show the associated behavioral correlates and symptoms of PTSD even after being exposed to traumatic stress. This may represent differences in resilience phenotypes. In some animal models of PTSD, 30 to 40 percent of C57/BL6 mice exposed to the trauma paradigm escape any effects of the trauma exposure and are called unsusceptible (86, 89). Studies using the social defeat stress paradigm find that a certain percentage of rodents exposed to the paradigm do not exhibit social avoidance typically induced by exposure to social defeat (90, 91). Preclinical behavioral models of PTSD, such as single prolonged stress and chronic social defeat paradigms, capture the induction of conditioned fear responses and generalization; such models may also serve as stress models that can be applied in the preclinical assessment of resilience.

It is worth keeping in mind that resilience is not a concrete measure, like height or weight. Resilience is most often inferred from a population of individuals based on their neurobiological and environmental measures and performance on a battery of challenge tasks. Animals perform with varying levels of proficiency on challenge tasks that are designed to test the effects of stress. Given the varied performance in animal models, such challenge tasks may be able to serve as a proxy measure for resilience. The translational potential of a challenge task derived from animal models could be optimized by measuring human performance in a naturalistic setting. However, naturalistic trauma is challenging to study because it occurs infrequently, unpredictably, and is variable in its severity among individuals.

In order to quantify our proposed 'R factor', an ideal challenge task should have optimal specificity in measuring resilience over any other construct. The task would need to produce consistent results despite differences in populations and be based on a solid theoretical construct. For experimentation and validation, a plausible approach might be to administer the challenge task to groups of individuals who have consistently exceeded expectations after encountering real-life trauma. This group could be compared to another group of individuals that is untested or may have experienced significant symptoms following real-life trauma. A precision predictive panel could be measured before and after the proposed challenge task in both groups. For example, career Navy SEALs might be compared to reservists who struggled through boot camp as groups who have markedly different resilience. Developing a virtual reality-based challenge task with real-life military training scenarios overlaid with acoustic or visual startle mechanisms could be an effective method of measuring resilience in military personnel or veterans (53, 54). Although animals or humans may be more or less resilient for one particular task, it is reasonable to assert that the biological concept of resilience should mean something more robust than just task performance. As such, the ideal challenge task to measure resilience to trauma and thus help to quantify the 'R factor' should be specific to resilience and have optimal discriminant validity for distinguishing between resilience and symptoms of PTSD or another psychopathology.

2. Potential translational biomarkers of resilience in clinical trials

A recent review of changes caused by preclinical social defeat paradigm provides numerous candidate serum biomarkers which could serve as indirect measures of resilience (92). Potential candidates include neurosteroids, monoamine neurotransmitter metabolites, corticosterone, testosterone, fibroblast growth factor (FGF), and brain derived neurotrophic factor (BDNF). Immuno-modulatory molecules such as p38 mitogen activated protein (MAP) kinase and other pro-inflammatory cytokines such as interleukin (IL-1Beta), tumor necrosis factor (TNF-alpha), and interleukin IL-6 are known to be modulated by stress in both animal and human studies. As such, these molecules could be appropriate markers of stress-related illness if tethered to brain measures of circuit pathophysiology. P38 MAP kinase is a mitogen-activated protein kinase which is responsive to stress stimuli and has been linked to cell cycle, death and tumorigenesis (93). Immunological mediators are also emerging candidate biomarkers for PTSD (94) and for resilience.

Early human studies on the effect of traumatic stress on PTSD and depression symptoms have focused on the hypothalamic-pituitary-adrenal axis and neurosteroid-induced receptor signaling (95). Specifically, preclinical studies using social isolation as an animal model of PTSD have demonstrated that selective serotonin reuptake inhibitors (SSRIs), which are the only class of drugs approved by the FDA for treatment of PTSD, ameliorate anxiety-like behaviors, fear responses, and aggressive behaviors through increasing corticolimbic levels of allopregnanolone (43, 44, 96). Other neurosteroids, such as serum dehydroepiandrosterone (DHEA), which are reduced in individuals with PTSD may also hold considerable promise as a biomarker of reduced resilience given its lack of diurnal variation(97). Recent studies also implicate trauma-induced release of cortisol in combination with the molecular complex comprising tetratricopeptide repeat proteins (TPR), such as FK506-binding protein 5 (FKBP5/FKBP51) and heat shock proteins (HSP70/90), as mediating a downstream cascade of actions that influence stress signaling through glucocorticoid and mineralocorticoid receptors (42).

A few human studies have demonstrated consistent candidate gene polymorphisms for resilience. Interestingly, human subjects at high risk for developing PTSD after trauma may be identified by a multifactorial additive score derived from polymorphisms of 10 previously identified genes associated with the traumatic stress-response: ADCYAP1R1, COMT, CRHR1, DBH, DRD2, FAAH, FKBP5, NPY, NTRK2, and PCLO (98). This is analogous to a polygenic risk score calculated from genome wide association data and is now widely recognized for its utility in stratifying complex traits (99, 100). In addition, veterans exposed to combat who developed PTSD were found to have lower NR3C1-1 F promoter methylation in peripheral mononuclear blood cells as compared to those who were exposed to combat but did not develop PTSD. This promoter of methylation is associated with measures of glucocorticoid activity in combat veterans with PTSD, such as cortisol level decline on the dexamethasone suppression test and urinary cortisol excretion (101).

As for neural correlates of resilience, there is overlap between neural correlates of PTSD, early childhood trauma, and resilience. Most studies have focused on the hippocampus, amygdala, and anterior cingulate cortex when examining neural correlations of PTSD. Individuals with a history of childhood maltreatment have a reduction in the size of the

hippocampal subfields, which may contribute to hampered resilience (102). A few candidate biomarkers of resilience include hippocampal subfield size (dentate gyrus and CA-3) in maltreated children, functional activity in medial prefrontal cortex and amygdala in PTSD (as correlates of fear extinction), and white matter changes in the corpus callosum in adolescents exposed to trauma (45, 103). Brain networks involving the amygdala, hippocampus, and prefrontal cortex are also potential candidates (46). Imaging studies have shown centrality measures unique to individuals who were exposed to trauma but did not develop PTSD, as opposed to individuals who have developed PTSD after trauma exposure (104–106). Ideal studies to determine possible neural correlates of resilience would need to compare groups of individuals exposed to trauma with differential trajectories of PTSD development (45). Another way of examining neural correlates of resilience would be to look at brain networks and functional activity using fMRI during a challenge task designed to evoke a resilient behavioral response.

Enhancement of resilience as measured by CD-RISC has been shown during treatment with venlafaxine in human clinical trials (23). Venlafaxine is a dual serotonin and norepinephrine transporter reuptake inhibitor. This suggests a serotonin-norepinephrine regulatory component to downstream behavioral phenotypes produced by stress. Adrenergic signaling has been highlighted as a critical component of the resilience phenotype (107), but other modulatory pathways have been implicated as well. These include brain derived neurotrophic factor (108), the GABAergic system within the nucleus accumbens (109), and, more recently, gut microbiota (47) and microRNAs 124 and 218 (110). Micro-RNAs are small, single stranded non-coding RNAs which post-transcriptionally repress target mRNAs and exert regulatory functions in a combinatorial manner. They have been predicted to regulate the majority of mammalian mRNAs (111). In the future, drug treatment trials may be designed to target neurobiological components that could enhance resilience and consequently curb the onset of stress disorders like PTSD. Enhanced resilience may translate to curbing the onset of trauma-related illnesses and as such serve as a neurobiological predictor of an individual's risk for illness and clinical treatment outcome.

3. Pharmacotherapeutics, epigenetic modulators, behavioral and neuromodulatory interventions to enhance resilience

SSRIs have shown to be effective in the treatment of subclinical PTSD in veterans (112). Antidepressants also enhance resilience as measured by the CD-RISC (23). The role of gene-environment interactions in enhancing resilience and vulnerability has led to focus on epigenetic modulation with pharmacotherapeutics. In particular, epigenetic modulation to enhance resilience has been the focus of numerous recent drug trials (72, 113). This is supported by SSRI-induced epigenetic changes, which impact intracellular signaling cascades, which are important neurobiological components of resilience and trauma-related disorders. Consequently, administration of SSRIs immediately following a trauma may help reduce the risk of developing trauma-related disorders in certain individuals (114, 115).

While SSRIs may not represent a novel approach to treatment of trauma-related illnesses, epigenetic modulation through administration of histone deacetylase (HDAC) inhibitors represents a promising avenue in ameliorating psychopathology in individuals with low

resilience (61). This is highlighted in Table 1. Various HDAC inhibitors such as vorinostat, MS-275, ACY-738, sodium butyrate and trichostatin have been used in rodent studies to reverse biological changes caused by chronic stress. These molecules could one day serve to enhance resilience in human clinical trials. The enhancement in resilience could be measured with a precision predictive panel.

In human trials, pharmacotherapeutics alongside psychological interventions that incorporate cognitive reappraisal, coping skills, and mindfulness may help reduce trauma-related pathophysiology and thus enhance resilience (116, 117). Some psychosocial interventions designed to increase resilience in children that have shown results are stress inoculation training, the CBT-based Bounce Back Program, the Positive Youth Development (PYD) program, and mentorship (38). In addition, non-invasive brain stimulation interventions like TMS (transcranial magnetic stimulation) and tACS (transcranial alternating current stimulation) have the potential to enhance neuroplasticity and brain circuits that confer resilience, making them ideal interventions (118, 119).

Applicability of the precision predictive panel of resilience and targeted reduction of trauma-related illnesses

The development of measures which can assess and monitor neurobiological components of resilience may hold promise to reduce the burden of mental illness through early identification and personalized treatment approaches in susceptible individuals. As an example, the Study to Assess Risk and Resilience in Service Members (STARRS) found that one-third of post-enlistment suicide attempts in the US Army were associated with pre-enlistment identification of mental disorders. This could signify that individuals with a previously diagnosed mental illness had poor resilience to trauma.

While the military places a great emphasis on equality of opportunity, the military is also deeply meritocratic. Certain positions in the US military (e.g. Army ranger or Navy SEAL) require rigorous demonstration of skills and capability. Indeed, the US Armed Forces have pioneered testing methods to assign individuals to duties, branches, or missions based on measuring skills with a battery of tests (120). The STARRS study aimed to evaluate whether mental illness in recruited soldiers represents a high vulnerability to trauma and whether these individuals would benefit from routine assessments of resilience. Furthermore, PTSD symptoms in soldiers prior to deployment are worsened following deployment; as such, such symptoms should be assessed at the time of recruitment (121). A quantified measurement of resilience would enable prediction of adverse outcomes in these potentially vulnerable populations, thereby enabling delivery of early personalized interventions.

Future Direction in Resilience Research

Mechanisms of resilience can most effectively be investigated longitudinally with the precision predictive panel before exposure to trauma and again at regular intervals following trauma. However, as mentioned above, exposure to trauma in the general population is infrequent, unpredictable, and variable in its severity. Nevertheless, several large-scale studies have embarked on collecting a wide array of measures similar to our proposed

precision predictive panel either prior to or immediately following trauma. Table 2 lists 4 longitudinal studies that aim to gather variables related to trauma exposure in various populations.

The High-Risk Cohort Study for Psychiatric Disorders has screened 9937 eligible children from 57 schools and further assessed 2512 of them considered to be high risk due to exposure to poverty, maltreatment, violence, and familial genetic loading for mental illness (122). To date, a significant percentage of youth have developed psychopathology including PTSD, OCD, GAD, panic disorder, MDD, ADHD, separation anxiety disorder, and conduct disorder. The AURORA study is another example of such a longitudinal study which is currently enrolling trauma survivors (target enrollment, n=5,000) from over 25 emergency departments across the United States. Study participants are followed over a period of one year, during which extensive data is collected including a variety of survey-assessed outcome measures, neurocognitive data, passive digital phenotyping data, and continual wearable/watch data. Biological (blood) samples are collected within 24 hours, and in a subset of individuals 2 weeks and 6 months following trauma exposure. In addition, a subset of the study participants (n=800) undergo more in-depth assessments including functional and structural MRI, laboratory administered startle tests, and quantitative sensory/pain testing at both 2 weeks and 6 months following trauma exposure. The information gained from this study will be useful in the development of diagnostic and predictive biomarkers. It will also be useful to identify novel preventive/treatment interventions for civilian trauma survivors and military veterans, in addition to investigating resilience.

The Marine Resiliency Study (MRS) and the Dutch 'Police-In-Action' study are 2 other studies that could yield valuable insights into mechanisms of resilience (123). The Marine Resiliency Study is a joint collaborative effort between Marine Corps, Navy, Veterans Affairs (VA) Health Services Research and Development (HSR&D), and various academic institutions (124). The goal of the study is to follow a cohort of Marines all through a deployment cycle. This will allow for an analysis of physiologic characteristics before deployment combined with future longitudinal data to ultimately identify modifiable risk and resilience factors for combat-related PTSD. The Police-In-Action study comprises 2 waves of assessments for police recruits and controls, separated by a period of 15 months. This study aims to compare biological variables among civilians and police recruits exposed to aversive situations as part of providing emergency aid.

These studies would greatly benefit from the use of a multifactorial score derived from neurobiological endpoints to measure resilience. The use of such an operationalization of resilience would also provide potential for directing personalized treatments with measurable outcomes. In addition to the precision predictive panel of resilience, clinical assessments will need to incorporate rating scales for resilience. Measuring the precision predictive panel and assessing response to a resilience challenge task concomitantly with mental health assessments will translate into a clinically relevant and useful assessment profile of resilience. This will subsequently help to assess risk for developing PTSD. Such an assessment could be used in clinical trials to identify military recruits or healthy individuals who would benefit from resilience interventions to maintain optimal trajectories in the aftermath of trauma exposure. These resilience interventions could curtail the

development of PTSD and provide neurobiological avenues for developing further modulatory interventions.

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Resilience in Relation to Post-traumatic Growth and Stress Vulnerability: A Venn Diagram

Figure 1.

The Venn diagram models how resilience relates to stress vulnerability and post-traumatic growth. We hypothesize that both post-traumatic growth and stress vulnerability are subsets of resilience. Both stress vulnerability and resilience share common mechanisms that predispose individuals to develop PTSD upon exposure to stress. However, stress vulnerability only quantifies risk for developing PTSD, whereas resilience encompasses the effects of developing PTSD from exposure to stress, both positive and negative. Post-traumatic growth includes only positive changes occurring in an individual after an adverse event. Our proposed consensus definition of resilience is a multifactorial construct that is determined from biological mechanisms and physiological parameters that mediate maintenance of an optimal functional trajectory after a traumatic event. This definition differs from both post-traumatic growth and stress vulnerability in that they are not multifactorial constructs. In addition, resilience encompasses adaptive behavioral and neurobiological responses to trauma, which are specific to the construct. Examining the relationship between these constructs requires longitudinal studies that collect our proposed precision predictive panel markers prior to and following trauma exposure. We elucidate further on this in table 2 and in the latter part of the article under 'Future Directions in Resilience Research'.

Figure 2.

In this figure we provide a visual representation of components that help derive the R factor. Preclinical animal models of resilience support the use of a resilience challenge task that can be used to measure resilience. In humans, key environmental parameters that influence resilience include, but are not limited to, prenatal stress, childhood trauma, childhood neglect/abuse, nutrition, and psychosocial variables such as family and community support, poverty, and community violence. Key biological (intrinsic) parameters that influence resilience include genotype, gene expression serum markers, structure and function of the brain (neuroimaging), epigenetics, cognitive appraisal skills, psychophysiological and autonomic response, gut microbiome, and gut biology. R factor would provide an objective assessment of resilience as a multifactorial determinant using our proposed precision predictive panel. We hypothesize R factor as a measurable endpoint to assess 'resilience reserve' analogous to Stern's cognitive reserve. Assessing resilience in a quantified manner as a multifactorial determinant will help develop new treatment targets and strategies.

Table 1-

Novel Therapeutics to Enhance Resilience Based on Preclinical Animal Studies and Possible Translational Outcome Measures

Study	Animal Paradigm Used	Findings	Possible Human Clinical Trials to Enhance Resilience	Translational Human Outcomes to Assess Resilience
Wagner et al 2015 (75)	Contextual fear conditioning and extinction with drug administration in a neurodegenerative disease mouse model.	BRD4884 and BRD6688 are HDAC2 inhibitors that reversed p25 associated memory defects.	Randomized, double-blind, placebo controlled trial for HDAC2 inhibitors to ameliorate negative emotional state in civilians with recent exposure to stressful environments (i.e., bullying, workplace/school stress) and developed symptoms of acute stress disorder or PTSD.	<p>1 Skin conductance/ heart rate variability/ fear potentiated startle in response to conditioned fear using VR paradigms.</p> <p>2 Connor-Davidson (CD-RISC) scoring for resilience.</p>
Matsumoto et al 2013 (70)	Single prolonged stress	Vorinostat facilitated fear extinction by enhancing the hippocampal levels of NR2B and calcium/calmodulin kinase II (CaMKII) α and β proteins, with increase in the levels of acetylated histone H3 and H4.	Randomized, double-blind, placebo controlled trial with vorinostat in reducing hypervigilance and avoidance from prolonged stressors such as war in veterans with PTSD. Examining relationship between GABAergic, glutamatergic neurotransmitter systems and norepinephrine in PTSD.	<p>1 Pupillometry to assess noradrenergic activity in locus coeruleus which could correlate to resilience and modulate fear conditioning.</p> <p>2 Positron emission tomography (PET) imaging to measure glutamate and magnetic resonance spectroscopy (MRS) imaging to measure GABA.</p> <p>3 CD-RISC scores</p>
Fujita et al 2012 (64) Kirtley & Thomas 2010 (78) Stafford 2012 (74) Lattal 2007 (68)	Contextual fear conditioning and extinction with candidate molecule administration	All these studies looked at hippocampal administration of candidate molecules to modulate extinction of contextually conditioned fear. Vorinostat, a histone deacetylase inhibitor, facilitated fear extinction by increasing the expression of NMDA NR2B mRNA in the hippocampus (64). Hippocampal extinction of memory assessed with recombinant BDNF infusion and co-administration of antisense oligonucleotides targeting Zif268 (78). Intra-hippocampal and intra-medial prefrontal cortex administration of sodium butyrate mediates extinction of contextually conditioned fear (74). Intra-hippocampal trichostatin administration mediates contextual fear extinction (68).	Randomized, double-blind, placebo controlled trials of vorinostat, BDNF infusion, sodium butyrate and trichostatin to modulate fear extinction in civilian subjects with PTSD.	<p>1 Hippocampal volume, hippocampal connectivity to other brain regions.</p> <p>2 Cognitive paradigms to assess working memory and episodic memory performance.</p> <p>3 CD-RISC scores</p>
Bredy and Barad 2008 (60) Whittle et al 2013 (76)	Contextual fear conditioning and extinction	VPA induces H4 acetylation and BDNF gene changes in the PFC of rodents associated with fear extinction (60).	Randomized, double-blind, placebo controlled trial of VPA in individuals with	1 Hippocampal N-Acetyl Aspartate (NAA) levels assessed with magnetic resonance

Study	Animal Paradigm Used	Findings	Possible Human Clinical Trials to Enhance Resilience	Translational Human Outcomes to Assess Resilience
		Effects of VPA, AMN082, PEPA (AMPA receptor potentiator) and MS275 (mglur7 agonist) on fear extinction (76).	emotional dysregulation as part of PTSD.	<p>spectroscopy (MRS) imaging. Hippocampal neuronal/volume loss is a surrogate marker of toxicity from PTSD.</p> <p>2 Serum neurosteroid levels</p> <p>3 CD-RISC scores</p>
Gunduz-Cinar et al 2013 (79)	Contextual fear conditioning and extinction	Systemic infusion of anandamide degradation enzyme inhibitor AM3506 to amygdala in rodents before extinction decreased fear during a retrieval test.	Double blind RCTs for AM3506 infusions in war veterans with PTSD symptoms or military personnel with low resilience being trained for combat to prevent PTSD symptoms.	<p>1 Fear potentiated startle (using eye blink electromyogram or EMG) to conditioned fear using VR paradigms.</p> <p>2 CD-RISC scores</p>
Jochems et al 2014 (66), 2015 (67)	Chronic social defeat stress	ACY-738, a histone deacetylase 6 (HDAC6) inhibitor administered in the dorsal raphe nucleus, increased relative association of HSP90 with FKBP51 versus with FKBP52 and inhibited glucocorticoid receptor (GR) translocation thought relevant to enhancing resilience (67). ACY-738 and ACY-775 reversed pathophysiologic behaviors through HDAC6 inhibition (66).	A prospective trial using ACY-738 to increase resilience scores and decrease severity of PTSD symptoms from social rejection, bullying, hazing and ostracism.	<p>1 Functional (fMRI) anterior cingulate cortex (ACC) activity with cognitive control task to assess learned helplessness.</p> <p>2 CD-RISC scores</p>
Covington HE III et al 2009 (61), 2011 (63), 2015 (62)	Social defeat stress	Infusion of MS-275 into nucleus accumbens (NAC), hippocampus and medial prefrontal cortex in three separate studies. mRNA changes like those found in postmortem brains of depressed patients treated with fluoxetine seen in first study, changes caused by social defeat stress reversed in the other two studies.	Randomized, double-blind, placebo controlled trial using MS-275 in patients with reduced resilience.	<p>1 fMRI Functional connectivity between hippocampus and prefrontal cortex mediating symptoms in MDD.</p> <p>2 Neuro-steroid levels</p> <p>3 CD-RISC scores</p>
Nasca et al 2013 (71) Lin et al 2012 (69) Yamawaki et al 2012 (77)	Forced swim test (FST) and sucrose preference test	Antidepressant action of L-acetyl carnitine mediated by action on mGlu2 glutamate receptor transcription in the hippocampus and prefrontal cortex (71). MS-275 administered into the ventrolateral orbitofrontal cortex is associated with an increase in H3 acetylation and elevated CREB and BDNF levels (69). Intraperitoneal sodium butyrate administration decreased depressive behaviors (77).	Double blind placebo controlled RCTs of L-acetyl carnitine or sodium butyrate or MS-275 to modulate connectivity and therefore resilience in patients with reduced resilience.	<p>1 Functional connectivity between hippocampus and prefrontal cortex in MDD.</p> <p>2 Performance on working memory tasks (Glutamate target).</p> <p>3 CD-RISC scores in subjects and first-degree relatives</p>
Han et al 2014 (65)	Chronic restraint stress (CRS) applied and assessed with sucrose preference test, light dark test (LD), tail suspension test (TST), and forced swim test (FST).	Intra-hippocampal administration of sodium butyrate decreased HDAC2 and 5 mRNA and protein level with reversal of depressive behaviors (65).	Double blind RCTs of sodium butyrate in patients with low resilience.	<p>1 fMRI activity ventral striatum and dorsal ACC with the reward responsiveness task</p> <p>2 CD-RISC scores subjects and first-degree relatives</p>

Study	Animal Paradigm Used	Findings	Possible Human Clinical Trials to Enhance Resilience	Translational Human Outcomes to Assess Resilience
				3 Neuro-steroid levels
Schmauss et al 2015 (73)	Forced swim test (FST), tail suspension test and elevated maze test (EPM)	HDAC inhibition with trichostatin in fluoxetine treated rodents enhanced antidepressant and anxiolytic action by epigenetic stimulation of BDNF expression.	Double blind RCTs of combination treatments (fluoxetine +trichostatin) in patients with low resilience.	1 fMRI activity ventral striatum and dorsal ACC with the reward responsiveness task 2 CD-RISC scores subjects and first-degree relatives 3 Neuro-steroid levels
Moriguchi et al 2011(81), 2013 (80)	Olfactory bulbectomy (OBX) rodents subjected to tail suspension and forced swim tests. OBX rodents subjected to Y-maze, novel object recognition and passive avoidance task to study spatial, cognitive and conditioned fear memories respectively.	Chronic treatment with DHEA (dehydroepiandrosterone) for 14 days significantly improved hippocampal LTP impaired in OBX rodents. Chronic DHEA treatment also ameliorated depressive-like behaviors in OBX rodents (80). Chronic treatment with DHEA improved spatial, cognitive and conditioned fear memories in OBX (81) rodents.	Double blind RCTs of combination treatments DHEA in patients with low resilience.	1 N-Acetyl Aspartate measurement as a surrogate marker for neurogenesis using Magnetic resonance spectroscopy (MRS) imaging. 2 Neuro-steroid levels 3 CD-RISC scores in subjects and their first-degree relatives

Table 2 –

Longitudinal studies that seek to examine correlates of resilience

Study	Patient Sample	Sample size	Number of Time Points	Parameters examined
Dutch-In-Police Study	Police recruits and civilians	340 police recruits and 85 civilians	Two waves of assessments separated by 15 months	Parameters measured include structural brain imaging, functional brain imaging with an approach avoidance task; genetic and epigenetic measurements; serum testosterone and cortisol; childhood trauma and PTSD symptom questionnaires; behavioral performance tasks - psychophysiological responses assessed using a shooting task, assessment of fear conditioning based on a task where participants have to predict the occurrence of electrical stimulation based on cue and context, probabilistic reversal learning task, fearful avoidance task.
Marine Resiliency Study	Marines in 4 battalions deployed to Iraq or Afghanistan	2600 marines	Post deployment time points - 1 week, 3 months and 6 months	Parameters measured include questionnaires exploring PTSD symptoms physical and mental health, depressive and anxiety symptoms, substance use, stress exposure, resilience; serum epinephrine and norepinephrine, cortisol from saliva, C-Reactive protein, neurotrophin Y; psychophysiological measurements like acoustic startle, fear potentiated startle, prepulse inhibition, heart rate variability; neuropsychological performance tests like continuous performance test.
AURORA study	Participants arriving in the ER after trauma	5000 trauma survivors	Baseline, 2 weeks and 6 months after trauma exposure	After an initial evaluation and baseline collection of biological data from blood samples, participants are monitored longitudinally via use of mobile technology, wrist wearables and smart phones, to track factors like activity, sleep, and mood. Also include collection of functional brain imaging, laboratory administered startle tests, and quantitative sensory/pain testing in addition to other psychological tests.
High-Risk Cohort Study for Psychiatric Disorders	Children attending school in Brazil	9937 screened, 2511 children recruited	3 waves of assessments after screening (Baseline in 2010–2011, wave 2 in 2013–2014, wave 3 in 2017–18)	The study recruited children predisposed to develop psychiatric illnesses based on genetic loading and stressors. The study includes collection of following data:- Questionnaires assessing prenatal trauma, bullying, brain injury and head trauma, family cohesion, mental illness diagnoses for parents, use of psychotherapy services for children; neuropsychological tests for processing speed, attention, executive functions, general intelligence, working memory, visuospatial abilities, motor functions, verbal fluency; central auditory process and phonological awareness for children recruited into the study; genetic evaluation; neuroimaging.