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Review Article

Understanding resilience: New approaches for preventing and treating PTSD

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ABSTRACT

All individuals experience stressful life events, and up to 84% of the general population will experience at least one potentially traumatic event. In some cases, acute or chronic stressors lead to the development of posttraumatic stress disorder (PTSD) or other psychopathology; however, the majority of people are resilient to such effects. Resilience is the ability to adapt successfully in the face of stress and adversity. A wealth of research has begun to identify the genetic, epigenetic, neural, and environmental underpinnings of resilience, and has indicated that resilience is mediated by adaptive changes encompassing several environmental factors, neural circuits, numerous neurotransmitters, and molecular pathways. The first part of this review focuses on recent findings regarding the genetic, epigenetic, developmental, psychosocial, and neurochemical factors as well as neural circuits and molecular pathways that underlie the development of resilience. Emerging and exciting areas of research and novel methodological approaches, including genome-wide gene expression studies, immune, endocannabinoid, oxytocin, and glutamatergic systems, are explored to help delineate innovative mechanisms that may contribute to resilience. The second part reviews several interventions and preventative approaches designed to enhance resilience in both developmental and adult populations. Specifically, the review will delineate approaches aimed to bolster resilience in individuals with PTSD. Furthermore, we discuss novel pharmacologic approaches, including the *N*-methyl-D-aspartate (NMDA) receptor ketamine and neuropeptide Y (NPY), as exciting new prospects for not only the treatment of PTSD but as new targets to enhance resilience. Our growing understanding of resilience and interventions will hopefully lead to the development of new strategies for not just treating PTSD but also screening and early identification of at-risk youth and adults. Taken together, efforts aimed at dissemination and implementation of novel interventions to enhance resilience will have to keep pace with the growth of new preventive and treatment strategies.

Contents

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1. Introduction

Resilience is broadly defined as the ability to adapt successfully in the face of adversity, trauma, tragedy or significant threat (Charney, 2004; Feder et al., 2009). Many definitions of resilience have been offered in the literature, including dimensional conceptualizations recognizing different levels of resilience, as well as longitudinal perspectives (Bonanno et al., 2012; Pietrzak et al., 2014; Southwick et al., 2014; Sapienza and Masten, 2011). The last decades have witnessed significant advances in our understanding of individual strengths, protective factors, and the normative function of human adaptational responses to environmental adversity and trauma (Russo et al., 2012; Yehuda et al., 2006b). Although trauma and adversity are extremely prevalent lifetime occurrences, ranging from 50 to 84% in the general population (Benjet et al., 2016; Breslau et al., 1998; Breslau et al., 2014; Kessler et al., 1995), a wide range of studies have shown that most people are resilient to trauma (Bonanno and Mancini, 2012; Feder et al., 2009). For example, the prevalence of PTSD, a condition arising post-trauma exposure by definition, is approximately 10% in the general population (Kessler et al., 1995; White et al., 2015). Of note, studies have also shown that resilience is less common after more severe traumas (e.g., assaultive trauma, higher trauma load or chronic severe adversity) (Alim et al., 2008; Breslau et al., 1998; Hobfall et al., 2011; Kessler et al., 1995).

The first part of this review outlines developments in resilience research, providing examples of interactions between environmental and genetic factors with resulting adaptive function at multiple phenotypic levels, including psychological, behavioral, neuroendocrine, and brain circuitry phenotypes (Cicchetti and Blender, 2007; Feder et al., 2011; Wu et al., 2013). Delineating the mechanisms underlying resilience is a key step toward designing successful preventive and treatment interventions. The second part reviews a range of interventions aimed at enhancing resilience, including examples of several types of interventions. In keeping with a broader definition of resilience, the present review also discusses approaches to enhancing resilience in individuals with PTSD, a psychiatric disorder that emerges in trauma-exposed individuals and is characterized by dysregulation of stress response systems. Individuals with PTSD present with core symptoms of re-experiencing (e.g., intrusive memories or nightmares about the trauma), avoidance of trauma-related reminders, negative alterations in cognitions and mood (e.g., inability to experience positive emotions), and alterations in arousal and reactivity (e.g., sleep disturbance and irritability) (American Psychiatric Association, 2013).

2. Genomics

Twin studies have estimated the overall heritability of PTSD at 30–40% (Cornelis et al., 2010). To date, the most frequently used approach in PTSD studies has been the candidate gene approach (Logue et al., 2015a), with gene × environment (G × E) effects on PTSD and resilience as primary findings. The most extensively studied candidate gene in PTSD is the gene coding for FK506 binding protein 5 *(FKBP5)*, a chaperone protein that modulates glucocorticoid receptor (GR) sensitivity (Binder et al., 2008; Smoller, 2016). The effect of *FKBP5* variation on risk for PTSD lies in G × E interaction, as a set of FKBP5 haplotypes increase risk for PTSD in adults exposed to childhood trauma (Klengel and Binder, 2015). Several other genes in stress response system pathways have been implicated in PTSD (Cornelis et al., 2010; Smoller, 2016). Recently, research on the genetics of PTSD has advanced to large collaborative genome-wide association studies (GWAS) (Logue et al., 2015a).

Further advances have come from the field of epigenetics, the study of stable and heritable changes in chromatin structure (e.g., DNA methylation or histone acetylation). Epigenetic modifications, often triggered by environmental exposures at sensitive periods during development, regulate gene expression, thus contributing to enhanced resilience or vulnerability to psychiatric disorders (Dudley et al., 2011; Zannas et al., 2015). The earliest study of relevance to resilience found that higher levels of maternal licking and grooming (LG) and arched-back nursing (ABN) behavior in rats was associated with lower DNA methylation in the glucocorticoid receptor (GR) gene promoter region in the hippocampus of offspring, with resulting higher GR expression, lower anxiety-like behaviors, and lower baseline and post-stress corticosterone secretion compared to offspring of low LG-ABN mothers (Fish et al., 2004; Weaver et al., 2004). Additional preclinical studies have substantiated a role of epigenetic modifications in the hippocampus following exposure to stress during development (Benoit et al., 2015; McGowan et al., 2011). These studies demonstrate the potential impact of early life environments on stress sensitivity into adulthood via epigenetic mechanisms.

Additionally, recent human studies have identified epigenetic changes of direct relevance to PTSD, in the form of allele-specific epigenetic modifications of the *FKBP5* gene that modify risk for PTSD following exposure to childhood trauma (Klengel and Binder, 2015). Genome-wide gene expression studies in humans and in animal models of PTSD have begun to identify differential expression of genes associated with resilience vs. vulnerability to PTSD within signaling pathways implicated in PTSD, in particular genes responsive to glucocorticoid signaling (Daskalakis et al., 2014; Logue et al., 2015b). Recent studies have also identified differential expression of inflammatory response genes in relation to resilience (Fredrickson et al., 2013; Lee, 2015).

3. Developmental factors

Developmental experiences have long been established as critical contributors to differential stress responses in animal studies, often persisting into adulthood (McCormack et al., 2006; Walker and Woodside, 2015). Human studies have also widely documented the negative impact of childhood trauma and adversity on the development of stress response systems (Heim, 2013; Heim and Nemeroff, 2001), and on brain structure and function, including deficits in cognitive (e.g., memory, executive functioning) and affective (e.g., reward processing) functions (De Bellis et al., 1999; Nemeroff and Binder, 2014; Pechtel and Pizzagalli, 2011). Yet, in the face of early life adversity, outcomes significantly differ from one individual to another (Hovens et al., 2010; Masten et al., 1999). While maltreatment victims may suffer serious negative consequences, including psychopathology, many abuse survivors do surprisingly well.

Resilience research originated in the 1970s with studies of children at risk for mental health problems stemming from family history of

Table 1
Psychosocial correlates of resilience in childhood and adulthood.

Childhood	Adulthood
Positive bonds with caregivers/adults	Positive emotions, optimism
Consistent parenting	Active coping
Self-regulation, executive function	Cognitive reappraisal
Intelligence, problem-solving	Altruism
Mastery	Mastery
Positive friendships	Social support
Motivation for achievement	Facing fears
Meaning	Meaning, sense of purpose

mental illness or exposure to adversity (Masten et al., 1990). The finding that some children were able to thrive despite substantial risk stimulated a series of innovative studies searching for protective factors in these resilient children (Garmezy, 1974; Masten, 2001; Werner et al., 1971; Werner and Smith, 1977). Later studies investigated survivors of childhood traumatic events including maltreatment, community violence, and chronic illness (Luthar et al., 2000). In these studies, consistent parenting and positive bonds with a caregiver or other adults were identified as key predictors of child competence and resilience (Masten, 2001; Pastorelli et al., 2015; Wyman et al., 1991). Children's natural disposition and behavior might also influence the quality of parenting they receive (Pastorelli et al., 2015; Patterson et al., 1992).

Additional protective personal and psychosocial characteristics linked to resilience in children include advanced maturity, rapid response to danger, information-seeking skills, positive relationships, optimism, self-discipline, and higher cognitive functioning (see Table 1) (Burt and Paysnick, 2012; Mrazek and Mrazek, 1987; Sapienza and Masten, 2011; Wu et al., 2013). Protective factors identified in studies of children exposed to the extreme adversity of war and related traumas (e.g., child soldiers, rape, bombing, forced displacement) include positive bonding with a caregiver, strong social support systems, a shared sense of values, religious beliefs that identify meaning in suffering, humor, and altruism (Leavitt and Fox, 2014; Masten, 2001; Werner, 2012).

Severity and duration of early life stress also matter greatly, as well as timing of positive interventions. For example, studies of children raised in orphanages and later adopted into stable families consistently found that earlier adoption is linked to better outcomes (Rutter, 1998; Rutter, 2013; Tottenham et al., 2010). Developmental timing of adversity itself is also a key factor, with resulting differential impact on lifelong trajectories of well-being and health (Gee and Casey, 2015). Infancy and adolescence are considered particularly sensitive developmental periods, marked by heightened brain plasticity and thus enhanced susceptibility to modeling by both positive and negative environmental influences (Gee and Casey, 2015).

An individual's degree of agency and control over the stressor is also of key significance (Southwick and Charney, 2012b). For example, while unpredictable and inescapable shocks administered to animals have been linked to “learned helplessness” (Overmier and Seligman, 1967), animals administered shocks that were avoidable by behavioral modification did not develop helplessness (Seligman and Maier, 1967). Similarly, individuals who are able to master a moderate stressor successfully, for example the death of a family member, might become more resilient to later stressors, a phenomenon referred to as “stress inoculation” (Southwick and Charney, 2012a). In preclinical studies, Lyons et al. (2009) conducted experiments in young monkeys, causing stress in the form of weekly short maternal separations over 10 weeks. Despite acute behavioral and hormonal stress responses during separations, stress-inoculated monkeys demonstrated more adaptive behaviors, greater cognitive control, and lower basal stress hormone levels at later time points, as well as larger ventromedial PFC (vmPFC) volume by three years of age, a brain region mediating fear extinction and downregulation of arousal (Lyons et al., 2009).

Although less-well studied in humans, exposure to manageable levels of stress may have a “steeling” effect on later stress reactivity (Southwick et al., 2013). For example, children hospitalized for a range of illnesses showed lower levels of stress during hospitalization if they had a history of early parental separation (Stacey, 1970). Mild and “naturally occurring stress” during childhood has also been linked to lower sympathetic nervous system responses (e.g., heart rate, blood pressure) to distressing laboratory tests in adolescence (Boyce and Chesterman, 1990). Garmezy has noted that children facing adversity may develop new methods for coping with stress (Garmezy, 1983). It is important to note, however, that complex interactions between individual, environmental, and trauma characteristics such as genetic makeup, severity and timing of stress exposure, family dynamics, culture, and social support may impact individual responses to stress, even milder forms of stress, in complex ways (Masten and Narayan, 2012; Southwick et al., 2013).

4. Psychosocial factors in adulthood

A rich and growing body of literature has focused on psychosocial factors linked to resilience in adults, more recently investigating their biological underpinnings in interaction with environmental influences (Bar-Shai and Klein, 2015; Iacoviello and Charney, 2014). Personal characteristics, including emotion regulation capacity, being able to face fears, certain personality traits, use of adaptive coping strategies, and the ability to harness social support, among others, all contribute to resilience (see Table 1) (Feder et al., 2009; Southwick and Charney, 2012a). Research conducted by Fredrickson and colleagues suggests that positive emotions give rise to novel and exploratory thoughts and actions (Fredrickson, 2004; Garland et al., 2010; Kok et al., 2013), promote adaptive coping and openness to social support (Ong et al., 2006), and are associated with more rapid cardiovascular recovery after stress (Fredrickson and Levenson, 1998) Additionally, positive emotions have been linked to lower levels of inflammatory cytokines in healthy adults (Stellar et al., 2015).

Cognitive reappraisal, an emotion regulation strategy involving the ability to monitor negative thoughts and replace them with more positive ones, is often employed by resilient individuals (McRae et al., 2012). Healthy individuals who habitually use cognitive reappraisal to cope with stress report less anger and exhibit lower levels of physiologic arousal than those who use suppression of emotional expression (Gross, 2002). Greater habitual reappraisal has also been linked to lower amygdala and higher prefrontal/parietal activation during processing of negative emotional stimuli (Drabant et al., 2009). In trauma-exposed samples, use of positive cognitive reappraisal was associated with lower reported stress-related and anxiety symptoms, in contrast to expressive suppression (Moore et al., 2008). Enhancing cognitive reappraisal skills might help build resilience in PTSD patients, an approach at the center of cognitive behavioral therapies (CBT) for this condition (Foa and Meadows, 1997; Foa et al., 2000). In brain imaging studies, higher prefrontal activation during reappraisal of negative images was found in resilient women with a history of sexual assault compared to women with PTSD (New et al., 2009), while reduced dorsal lateral PFC (dlPFC) activation was reported in veterans with PTSD during cognitive reappraisal of aversive images (Rabinak et al., 2014). These findings suggest functional deficits in prefrontal regions critical for cognitive control in PTSD patients (Buhle et al., 2014; MacNamara et al., 2015). A different line of studies has identified attentional biases in individuals with PTSD. Specifically, greater threat-related attention bias variability (toward and away from threat stimuli) has been reported in individuals with PTSD compared to trauma-exposed and unexposed controls (Fani et al., 2012; Iacoviello et al., 2014; Naim et al., 2015). Of note, in combat-exposed and unexposed soldiers, such differences were not observed pre-deployment (Iacoviello et al., 2014).

Another key psychosocial factor associated with resilience is the availability of social support, which has consistently been linked to better health outcomes and higher psychological well-being following stress (Boyce and Chesterman, 1990; Southwick and Charney, 2012a). Conversely, low levels of social support, including lower post-deployment social support in soldiers, have been linked to higher risk for PTSD (Pietrzak et al., 2009; Tsai et al., 2015), poor health outcomes (Ruggiero et al., 2009). Furthermore, in hurricane-exposed adults, low expression of the 5-HTTLPR polymorphism increased the risk of post-hurricane PTSD but only in individuals with low social support (Kilpatrick et al., 2007). In a study of Pakistani earthquake survivors, higher perceived social support was associated with higher levels of positive emotions, even after adjusting for PTSD symptoms (Feder et al., 2013). Social support might enhance resilience by counteracting

loneliness (Solomon and Mikulincer, 1990), and has been linked to decreased threat appraisal related to illness (Fontana et al., 1989).

Active coping strategies also characterize resilient individuals across trauma-exposed samples. Among adolescents exposed to war in Gaza, resilient youth were found to be more task-oriented and more likely to utilize problem-solving techniques, rather than avoidant coping and ventilation of feelings (Thabet et al., 2014). In a prospective study following the 9/11/01 terrorist attacks, active coping was associated with reduced distress levels (Silver et al., 2002). Being able to face one's fears also promotes active coping, including planning and problem-solving. Conversely, fears are likely to persist unchanged in individuals with PTSD as they avoid people, places, and situations that might trigger re-experiencing symptoms. Active coping at the time of the trauma or during re-exposure to traumatic reminders may attenuate fear conditioning by affecting underlying neural circuits (LeDoux and Gorman, 2002; Murray et al., 2015). Resilient individuals may avoid fear conditioning by facing their fears, a strategy that has been incorporated in exposure therapy paradigms for PTSD (Foa et al., 2005) or may be more successful at extinguishing conditioned fear responses (Briscione et al., 2014).

Use of humor is another coping strategy reported in diverse samples, including veterans, firefighters, and terminally ill patients (Sliter et al., 2014; Southwick and Charney, 2012a), which might help alleviate tension and attract social support (Sliter et al., 2014). The type of humor utilized might make a difference. In individuals who repeatedly witness trauma through their work (e.g., taskforce personnel working with child victims of abuse); "gallows humor," or humor at the expense of a victim, was found to be associated with higher secondary traumatic stress scores in contrast to lighthearted humor (Craun and Bourke, 2015). Physical exercise has also been linked to hardiness, improved mood, and self-esteem, and adaptive neurobiological changes including enhanced neural plasticity (Ding et al., 2006; Erickson and Kramer, 2009; Mueller, 2007) and healthy alterations in gene expression in the brain (Booth et al., 2002). Other characteristics found in resilient individuals include altruism, a sense of mastery, higher purpose in life, and the related ability to find meaning in the midst of adversity (Alim et al., 2008; Feder et al., 2013; Israel-Cohen et al., 2015; Leontopoulou, 2010; Pietrzak et al., 2010; Tsai et al., 2015).

5. Neurobiological profile

Several hormones, neurotransmitters, and neuropeptides have been implicated in the development of PTSD and as potential targets for enhancing resilience (Feder et al., 2011; Russo et al., 2012). It is well known that HPA axis activation upon stress exposure is protective in the short-term, but deleterious health effects can result from persistently high cortisol levels (Karatsoreos and McEwen, 2013). In animal and human studies, resilience has been linked to rapid activation and subsequent efficient termination of the stress response via an elaborate negative feedback system that includes optimal function and balance of glucocorticoid and mineralocorticoid receptors (Charney, 2004; de Kloet et al., 2005; de Kloet et al., 2007). Conversely, early life stress leads to chronically elevated corticotropin releasing hormone (CRH) levels, also found in patients with PTSD (Heim and Nemeroff, 2001; Yehuda, 2012). Chronic and unchecked hyper-responsiveness of the locus coeruleus-norepinephrine (LC-NE) system is also associated with anxiety disorders, while blockade of β-adrenergic receptors in the amygdala can help reduce the development of aversive memories in animal and humans (Cahill et al., 1994; Charney, 2003; McGaugh, 2004; Strange and Dolan, 2004). Such findings suggest that tempering LC-NE system responsiveness may help promote resilience (Krystal and Neumeister, 2009). The serotonergic system, which modulates neural responses to stress, has also been widely implicated in PTSD and resilience (Krystal and Neumeister, 2009). Additionally, dysfunction in dopaminergic transmission and reduced reward function may contribute to PTSD symptomatology (Enman et al., 2015).

Neuropeptide Y (NPY) has anxiolytic-like effects in rodents and may counteract the effects of CRH in the amygdala, hippocampus, hypothalamus, and LC (Sabban et al., 2015). In a study of Special Forces soldiers, considered to be highly resilient, higher NPY levels during rigorous military training correlated with better performance (Morgan et al., 2000). Higher NPY levels have also been linked with lower PTSD symptom levels (Yehuda et al., 2006a). Resilience might relate to the balance between NPY and CRH effects during stress (Sajdyk et al., 2008; Thorsell, 2010). Another key player is brain derived neurotrophic factor (BDNF), a key nerve growth factor that has been found to promote adult hippocampal and PFC function in rodent models (Duman and Monteggia, 2006). A resilient phenotype observed in mice following exposure to chronic social defeat stress has been linked to differential BDNF expression in the nucleus accumbens compared to vulnerable mice (Krishnan et al., 2007).

Studies have begun to outline the role of additional neuropeptide and neurotransmitter signaling systems in resilience and PTSD, including the endocannabinoid, oxytocin, and glutamatergic systems, among others, leading to potential novel pharmacological interventions. Dysregulation of endocannabinoid signaling, which modulates stress responses, has been reported in animals subjected to chronic stress (Hill et al., 2005) and in individuals with PTSD (Hill et al., 2013). Another focus of interest is oxytocin, a neuropeptide that is anxiolytic and promotes social attachment (Koch et al., 2015; Kosfeld et al., 2005). In a recent randomized controlled trial (RCT) employing magnetoencephalography (MEG), administration of oxytocin intranasally to combat-exposed veterans was associated with normalization of alpha activity in prefrontal regions involved in cognitive control and working memory, suggesting potential beneficial effects of this neuropeptide in trauma survivors (Eidelman-Rothman et al., 2015).

Another promising treatment target is the glutamate system, known to be involved in synaptic mechanisms underlying memory formation and fear learning (Riaza Bermudo-Soriano et al., 2012). Chronic stress induces changes in glutamate neurotransmission, causing synaptic atrophy in the hippocampus and PFC in rodent models, an effect that is rapidly reversed following administration of glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine (Duman, 2014; Li et al., 2011). Glutamate system dysfunction is thought to underlie the pathophysiology of stress-related disorders including PTSD (Popoli et al., 2011; Riaza Bermudo-Soriano et al., 2012). Both ionotropic and metabotropic glutamate receptors are potential treatment targets in PTSD, with promising initial results discussed below (Harvey and Shahid, 2012). Additionally, recent research has advanced our understanding of molecular signatures of resilience in animal models of stress (Pfau and Russo, 2015; Neylan et al., 2014). In chronic social defeat stress models, resilient mice exhibit higher molecular plasticity and adaptive changes in gene expression (Jung et al., 2015; Krishnan et al., 2007), suggesting that resilience does not simply result from absence of vulnerability but rather from unique and active neurobiological processes.

Glucocorticoids released in response to stress also regulate the immune response by blocking production of pro-inflammatory cytokines (e.g., interleukin-6 (IL-6)) (Silverman et al., 2005), which in turn induce hypothalamic secretion of CRH (Brattsand and Linden, 1996; Iribarren et al., 2005). A recent surge of research has focused on the role of inflammatory disturbances in stress-related psychiatric disorders. Central nervous system (CNS) cells with immune functions, such as astrocytes and microglia, and pro-inflammatory CNS cytokines have a role in learning and memory, highlighting the potential impact of the immune system on the resolution or worsening of fear-based memories (Baker et al., 2012; Yirmiya and Goshen, 2011). In a study employing the chronic social defeat paradigm, IL-6 was only up-regulated in mice developing a susceptible phenotype (Hodes et al., 2014).

Clinical studies of immune mediators in PTSD have focused on peripheral immune markers, such as IL-6 and C-reactive protein (CRP). Several studies have established a relationship between elevated CRP

and PTSD (Eraly et al., 2014; Groer et al., 2015; Heath et al., 2013; Spitzer et al., 2010), and polymorphisms within the *CRP* gene have been linked to higher PTSD symptom and CRP levels (Michopoulos et al., 2015). Abnormal inflammatory profiles in Gulf War veterans have been linked to higher PTSD symptom severity and reduced hippocampal volume, suggesting that inflammation might after brain function (O'Donovan et al., 2015). Studies have begun to report differential inflammatory profiles associated with resilience vs. PTSD, with resilient individuals showing similar profiles to those of unexposed controls (Gill et al., 2013). Studies of immune system dysregulation in PTSD patients might also shed some light on the roots of high comorbidity rates of PTSD with other health conditions (Friedman and Schnurr, 1995, Pacella et al., 2013) and generate potential avenues for novel interventions.

6. Neural circuitry

Brain imaging studies have identified several interconnected limbic regions in the forebrain that function as integrated parallel circuits regulating emotional responses and states (Duval et al., 2015; Feder et al., 2009). The neurocircuitry of fear comprises the amygdala, hippocampus, and vmPFC. Acquisition of fear conditioning is centered in the amygdala, while extinction of fear memories involves both the amygdala and the vmPFC (Schiller and Delgado, 2010). Activation of these structures and thickness of the vmPFC have been found to correlate with extinction success (Delgado et al., 2006; Milad et al., 2005). For example, traumatized civilians without PTSD exhibited stronger activation in the vmPFC during an inhibition task compared to those with PTSD. Furthermore, activation in the vmPFC was also negatively correlated with fear-potentiated startle responses and fear extinction learning (Jovanovic et al., 2013). PTSD is thought to arise in part from failure of extinction learning and extinction retention following trauma exposure. In a meta-analysis of brain imaging studies, PTSD patients exhibited hypoactivation of dorsal and rostral anterior cingulate cortex (ACC), and vmPFC, key regions involved in emotion regulation (Etkin and Wager, 2007), suggesting ineffective "top-down modulation" of amygdala and related subcortical structures (Liberzon and Sripada, 2007).

Conversely, resilience might be associated with lower threat-related amygdala reactivity, and more efficient emotion processing and regulation. In a recent prospective study of healthy volunteers, threat-related amygdala reactivity predicted higher psychological vulnerability to stressors 1 to 4 years later (Swartz et al., 2015). Functional magnetic resonance imaging (fMRI) studies have also reported higher cognitive control (associated with increased PFC activation) (New et al., 2009) and differences in functional connectivity in resilient individuals (Kennis et al., 2015) compared to PTSD patients and unexposed controls. Imaging studies in healthy volunteers suggest that resilience might be mediated by more appropriate emotional responses to stress (Reynaud et al., 2013). For example, firefighters with higher resilience scale scores showed higher right amygdala and left orbitofrontal activations while listening to a trauma script compared to a relaxing script (Reynaud et al., 2013). In another study, healthy volunteers with high-trait resilience showed insula and amygdala activation only to aversive pictures, while in low-trait resilience participants these regions activated to both types of pictures, suggesting that "resilient people flexibly and appropriately adjust the level of emotional resources needed to meet the demands of the (threatening) situation" – labeling this capacity "emotional flexibility" (Waugh et al., 2008) – and the importance of "accurate appraisal" in resilience (Southwick et al., 2015). Imaging genomics studies have also reported differential neural responses based genetically driven differences in stress vulnerability (e.g., Drabant et al., 2012).

Patients with PTSD also attempt to avoid re-exposure to trauma, possibly leading to over-generalization of external cues (e.g., startling to a loud telephone) (Mineka and Zinbarg, 2006), while in resilient individuals adaptive reconsolidation and extinction processes might prevent such overgeneralization (Liberzon and Sripada, 2007). Novel treatment interventions are beginning to emerge from these observations, as exemplified by a recent pilot study employing a reconsolidation impairment intervention for PTSD, in which reactivation of trauma memories under the influence of β-adrenergic blocker propranolol was associated with decreased PTSD symptom severity and increase in right ACC activation to fearful vs. happy faces during fMRI (Mahabir et al., 2015).

The neural circuitry of reward, comprising the nucleus accumbens (NAc), dlPFC, medial PFC (mPFC), orbitofrontal cortex (OFC), and ACC, is also implicated in resilience and PTSD (Felmingham et al., 2014;

Table 2
Examples of resilience interventions for children and adolescents.

Intervention type	Program example	Focus of intervention	Population
Family	Child-Parent Psychotherapy (Lieberman et al., 2005) Therapist-administered	Attachment, support child-mother relationship, reduce trauma-related fearfulness and maladaptive behaviors	Mother-child dyad (preschool children) exposed to marital violence
	Child and Family Traumatic Stress Intervention (CFTSI) (Berkowitz et al., 2011) Therapist-administered	Youth anxiety and traumatic stress symptoms, maladaptive behaviors Behavioral and cognitive intervention	Recently trauma-exposed children (7–17 years old) Child-caregiver(s)
Group	Multidimensional Treatment Foster Care for Preschoolers (MTFC-P) (Fisher and Kim, 2006) Therapist-administered	Children's playgroup: facilitate school readiness (supplemented by individual behavioral sessions) Foster parent group: enhance positive/consistent parenting	Foster preschool children; foster caregiver(s)
	Kids' Club and Moms' Empowerment (Graham-Bermann et al., 2007) Therapist-administered	Children's group: managing fears, coping with emotions Mothers' group: enhance positive parenting, educate mothers about trauma-related symptoms in children	School-aged children and their mothers exposed to domestic violence
School	Stress Inoculation Training (SIT) (Wolmer et al., 2011a) Teacher-delivered	Managing fears, coping skills, promoting positive emotions and emotion regulation	Children living in rocket attack zone
	Cognitive behavioral therapy-based Bounce Back program (Langley et al., 2015) School clinician-delivered	PTSD and anxiety symptoms Promote cognitive restructuring and social problem solving	Multicultural school-aged children exposed to traumatic events
Community	Positive Youth Development (PYD) (Catalano et al., 2004) Trained mentors	Five C's: competence, confidence, character, connection, caring Engage youth in community (prosocial approach) Enhance individual strengths, promote positive adult-youth relationships, boost self-regulation skills	High-risk and general community youth

Sailer et al., 2008). Hypofunction of reward circuitry might manifest in anhedonic and numbing symptoms in PTSD patients (Elman et al., 2009). "Sturdy" reward responses might instead characterize resilient individuals, as suggested by a study in Special Forces soldiers (Vythilingam et al., 2009). Reward circuitry function has also been linked to trait optimism, which positively correlated with ACC activation in healthy individuals as they imagined future positive events in an fMRI study (Sharot et al., 2007). Longitudinal studies in soldiers incorporating brain imaging pre-deployment have also begun to identify differences associated with resilience and vulnerability post-deployment (Admon et al., 2013; Geuze et al., 2012).

7. Interventions to enhance resilience

7.1. Resilience interventions during development

When adversity strikes in childhood or adolescence, it can potentially result in long-lasting abnormalities in stress response systems and increased lifetime risk for PTSD, depression, and other health disorders. Designing successful interventions to enhance resilience during development is thus a priority (see Table 2). The developmental period is also a time of increased plasticity and thus potentially increased responsiveness to preventive interventions. The Positive Youth Development (PYD) perspective focuses on individual strengths of developing youth, aligning closely with the Positive Psychology movement in its emphasis on positive outcomes and well-being (Lerner et al., 2005a). A PYD Evaluation Project (the 4-H study) studied 1700 fifth grade children participating in community youth development programs and followed their developmental trajectories through the second decade of life (Lerner et al., 2005b). Centered on the "5 C's" of competence, confidence, connection, character, and caring, the PYD perspective has given rise to a range of empirically-based intervention programs, fostering development from childhood through adolescence (Catalano et al., 2004; Lerner et al., 2005a). Emphasis on strong bonds with healthy adults and regular involvement in positive community activities may enhance resilience and prevent the onset of mental health problems (Catalano et al., 2004).

Resilience interventions designed to maximize adaptation and positive growth in youth exposed to trauma or significant adversity aim to enhance individual, family, and community factors that have been linked to resilience in observational studies of high-risk youth (Sapienza and Masten, 2011). Because positive caregiving during development is a well-established protective and potentially modifiable factor, several intervention paradigms for high-risk youth have centered on improving parenting skills in caregivers, and on strengthening family bonds (Scheeringa et al., 2006; Southwick et al., 2011). For example, one study evaluated the effectiveness of a brief preventive early intervention to mitigate risk for PTSD in trauma-exposed youth referred by a forensic sexual abuse program, the police, or through reviews of pediatric emergency records. Children assigned to the Child and Family Traumatic Stress Intervention (CFTSI), a four-session intervention focused on increasing caregiver emotional support, and communication between youth and caregiver(s), were significantly less likely to develop full or subsyndromal PTSD by the 3-month follow-up (Berkowitz et al., 2011). Another study assessed the effectiveness of the Mom's Empowerment and Kids' Club, a program designed to help mothers and children exposed to domestic violence. Mothers assigned to the parenting intervention arm, which fostered discussion of parenting concerns and focused on enhancing parenting competence in a supportive group setting, demonstrated significant improvement in positive parenting after controlling for demographic variables, violence severity, and mental health status (Graham-Bermann et al., 2007; Howell et al., 2015).

An RCT investigated the efficacy of the Attachment and Biobehavioral Catch-Up (ABC) Intervention, working with foster parents to improve attachment patterns and regulatory capabilities in young children relocated after Child Protective Service (CPS) referrals by teaching caretakers how to detect signals of distress from children and respond sensitively. Children whose foster parents were in the experimental intervention demonstrated significantly less avoidance than those whose parents were in the comparison educational intervention (Dozier et al., 2009). A similar approach with foster care children, the Multidimensional Treatment Foster Care for Preschoolers (MTFC-P), focuses on supporting caregivers to respond consistently and contingently to positive and negative behavior, yielding improvements in attachment security and fewer permanent foster placement failures than the comparison group (Fisher and Kim, 2006). Despite positive outcomes from this and other evidence-based interventions, challenges remain to their wider implementation within overburdened foster care systems, indicating a gap that needs addressing to enhance resilience in this high-risk population (Leve et al., 2012). Results from a different study evaluating the ABC Intervention with birth parents and children from families under CPS investigation for neglect showed a positive impact on neuroendocrine function, as cortisol production patterns were more typical in children in the treatment group, while children in the control arm demonstrated flatter cortisol rhythms with blunted morning levels (Bernard et al., 2015). Cortisol rhythms also normalized in children in the intervention arm of the MTFC-P program mentioned above (Fisher et al., 2006).

Another characteristic often found in resilient individuals is the capacity for cognitive reframing, or arriving at more positive interpretations of events or situations, a central component of well-validated CBT interventions for both children and adults. A review of different intervention programs for trauma-exposed youth suggests that individual and group CBT can be effective in reducing negative psychological outcomes after trauma, as well as PTSD symptom levels (Giannopoulou et al., 2006; Wethington et al., 2008). One example is the Bounce Back program, a 10-session group CBT intervention for trauma-exposed children in elementary school, delivered by school clinicians, that demonstrated significantly greater efficacy in reducing PTSD, depression, and anxiety symptoms compared to the delayed intervention condition (Langley et al., 2015; McGrath and Noble, 2012).

Several psychosocial interventions have also been studied in children traumatized by war, but few have measured resilience as an outcome beyond reduction of PTSD, depressive, and somatic symptoms. Interventions have centered on enhancing family and social support, effective coping, problem-solving, and emotion regulation (Diab et al., 2015; Werner, 2012). Some programs are based at schools, and some even delivered by teachers, thus incorporating ecological systems central to children's life to enhance support in natural social networks (Diab et al., 2014; Wolmer et al., 2011a, 2011b). In one program, a teacher-delivered intervention for children following the second Lebanese war involved inviting children to share and seek support from peers; participating children demonstrated a decrease in PTSD symptoms and greater adaptive functioning (Wolmer et al., 2011a). Another teacher-delivered intervention for Israeli students exposed to persistent rocket attacks was based on Stress Inoculation Training (SIT), a resilience-enhancing intervention originally designed by Meichenbaum and colleagues as a treatment for anxiety disorders (Meichenbaum and Deffenbacher, 1988). The SIT intervention, involving practicing effective coping skills prior to exposure, was more successful in preventing PTSD symptom development than the control condition (regular curriculum) (Wolmer et al., 2011b). Some studies measuring resilient outcomes in children traumatized by war have yielded non-significant results, emphasizing the severity and complex nature of war-related trauma meriting further research (Diab et al., 2015; Tol et al., 2014).

7.2. Resilience interventions in adulthood

7.2.1. Pre-trauma training

Programs offering training before the occurrence of stressful or traumatic events aim to enhance resilience in a variety of ways.

One approach is through boosting preparedness in occupational groups encountering potentially traumatic situations, typically by incorporating specific skills (e.g., firefighting) and general stress management skills (e.g., relaxation training). This form of pre-trauma training is thought to work by enhancing coping self-efficacy, the perception that one is able to manage and recover from stressful life events (Southwick et al., 2013; Whealin et al., 2008). Coping self-efficacy has been linked to positive adjustment following trauma exposures ranging from combat to the unexpected death of a loved one (Hobfall et al., 2007). A higher sense of control might reduce levels of perceived threat and temper associated neurobiological responses, thus helping protect against the development of PTSD and other disorders (Southwick et al., 2011). Hardiness training, for example, which aims to enhance a set of attitudes and skills to help reframe stressful situations into opportunities for growth (Maddi, 2007), contributes to the appraisal of stressful events as less threatening and increases faith in one's coping abilities. Higher levels of hardiness have been linked to lower PTSD symptom levels, and have also been shown to buffer the impact of common stressful life events, including difficulties faced by students in college or adults at work (Kobasa et al., 1982; Southwick et al., 2013).

Other "resilience training" approaches have centered on maximizing additional personal attributes and attitudes characteristic of resilient individuals. A number of resilience-building programs have been developed for the U.S. military (Mulligan et al., 2011). For example, the Comprehensive Soldier Fitness program developed for the Army for implementation from pre- through post-deployment periods is based on the principles of Positive Psychology, focusing on personal strengths and enhancing positive emotion, engagement, and meaning (Cornum et al., 2011; Seligman et al., 2005). A different training program designed to build social resilience was developed for Army platoons, and in a recent RCT was associated with small but significant improvements in social cognition and military hardiness compared with the active control intervention (Cacioppo et al., 2015).

7.2.2. Early post-trauma interventions

Preventive interventions designed to be administered shortly after trauma exposure with the goal of preventing first onset of PTSD symptoms have recently regained momentum in the trauma field. These studies require caution given the discouraging results from early studies of psychological debriefing administered immediately post-trauma (Kearns et al., 2012). Some early intervention efforts have focused on survivors of rape and sexual assault. For example, a brief video intervention aimed at reducing the emergence of PTSD symptoms in female victims of sexual assault, administered within 72 h of the assault and including information on coping strategies, was associated with lower PTSD symptomatology both six weeks and six months later, primarily in women with prior rape history (Resnick et al., 2007). Technology-based brief preventive programs, if efficacious in boosting resilience and reducing the incidence of psychopathology in trauma-exposed individuals, can be cost-effective and easily implemented (Resnick et al., 2007).

A novel pilot study of three sessions of modified exposure therapy administered in the emergency department beginning only hours after trauma exposure was found to mitigate risk of emerging posttraumatic stress reactions, particularly in rape victims (Rothbaum et al., 2012). Among those participants who underwent genotyping, the intervention was most successful in those most at risk for PTSD based on particular genetic polymorphisms (Rothbaum et al., 2014b). Other early psychosocial interventions with varying degrees of success, reviewed by Kearns et al. (2012), have included a memory-structuring intervention for traffic accident survivors (Gidron et al., 2001; Gidron et al., 2007); the Battlemind intervention based on normalizing common posttraumatic reactions and developed to be administered to soldiers post-deployment (Adler et al., 2009a; Adler et al., 2009b); and collaborative studies incorporating a combination of early case management, CBT, and psychopharmacologic treatment for injured trauma survivors in acute care settings (Zatzick et al., 2004; Zatzick et al., 2009).

In addition to psychological interventions, early pharmacologic interventions also hold some promise in reducing the emergence of PTSD symptoms, possibly by preventing or reducing initial consolidation of traumatic memories. Human studies of pharmacologic agents administered shortly after trauma exposure have included pilot studies with the beta-adrenergic blocker propranolol, with mixed results (e.g., Pitman et al., 2002; Stein et al., 2007); naturalistic studies of morphine administration (Bryant et al., 2009; Holbrook et al., 2010); and studies testing the efficacy of high-dose glucocorticoid immediately following trauma exposure (Surís et al., 2010; Zohar et al., 2011). Additionally, recent studies in an animal model of PTSD have reported attenuated behavioral and neuroendocrine responses to single prolonged stress after intranasal NPY administration, suggesting a potential role of NPY administration for primary or secondary PTSD prevention (Serova et al., 2013).

7.2.3. Resilience-based interventions for adults with PTSD

While individuals who have developed PTSD are generally not considered "resilient", resilience can also be viewed as existing on a continuum (Southwick et al., 2014). Additionally, insights derived from studies of resilient trauma survivors can be applied to improve psychosocial functioning and promote recovery in patients with PTSD. Similar to pre-trauma training programs, emerging therapeutic options for adults with PTSD aim to enhance psychosocial factors commonly observed in resilient individuals, including higher social support, emotion regulation, positive affect, physical exercise, meaning-making, and purpose in life. These therapeutic approaches also aim to enhance resilient functioning and posttraumatic growth beyond reduction of PTSD symptoms (Burton et al., 2015). SIT, mentioned above, focuses on teaching resilience-based skills through psychoeducation, imagery, and behavioral rehearsal. Specific skills include active problem solving, cognitive reappraisal, relaxation training, and guided self-dialogue. In studies of female sexual assault survivors, SIT was associated with reductions in PTSD and depressive symptoms (Foa et al., 1999; Parcesepe et al., 2015).

Bolstering social and family support is also critical to recovery and boosting resilience in individuals with PTSD, who often distance themselves from others (Foa et al., 2005; Pietrzak et al., 2010; Schnurr et al., 2007). For example, in a 5-year longitudinal study of Veterans with PTSD, early PTSD symptom severity strongly predicted reduction in social support over time (King et al., 2006). In a small pilot study without a comparison group, Vietnam Veterans with PTSD who participated with their marital partners in exercises to increase communication and intimacy, and in partner-assisted anxiety reduction exercises, reported reduced avoidance, numbing, and overall PTSD symptom severity post-intervention (Sautter et al., 2009). Of note, survivors of certain types of trauma, such as sexual assault, might receive negative feedback from their social circle in the form of victim blaming (Moor, 2007; Ullman and Filipas, 2001; Zoellner et al., 1999). In this population, support within relationships that promote self-esteem is particularly critical (Hyman et al., 2003).

An innovative Veterans Affair approach for PTSD patients is the Moving Forward program, which has adapted problem-solving therapy to build resilience and reduce emotional distress in Veterans. The program is a four-session group "life skills program" providing training in emotional regulation and effective problem-solving in daily life. An evaluation of the Moving Forward program revealed that program participation was associated with improvements in social problem solving and in resilience measured with the Brief Resilience Scale (Tenhula et al., 2014). A recent review of psychological interventions for PTSD in military personnel and veterans, however, found that most RCTs to date have focused on cognitive-behavioral

approaches and calls for additional RCTs with novel interventions (Rose et al., 2014).

As traumatic experiences often shatter an individual's long-held assumptions about life, the ability to make sense of a traumatic experience is another important component of recovery post-trauma (Feder et al., 2013). Meaning-making, or incorporating a trauma into one's broader belief system, might facilitate recovery and enhance resilience (Park, 2010; Southwick et al., 2005). Logotherapy, developed by Viktor Frankl and centered on finding meaning in life, has been adapted for the treatment of Veterans with combat-related PTSD. This form of therapy specifically addresses patients' individual strengths, and helps guide them in their personal search for meaning and purpose in life. Similarly, Integrative Testimonial Therapy (ITT) with elderly survivors of World War II trauma, including a biographical approach aiming to integrate their experience of trauma into their life narrative and achieve a more coherent life story, was associated with PTSD symptom improvement and posttraumatic growth, both maintained at a 3-month follow-up (Knaevelsrud et al., 2014) Of note, a higher sense of purpose in life has been strongly linked to resilience in diverse trauma-exposed samples (Alim et al., 2008; Feder et al., 2013; Southwick et al., 2006; Tsai et al., 2015).

Recent years have also witnessed rising interest in the concept of mindfulness, the ability to focus one's awareness on the present moment while noticing, observing and describing sensations, perceptions, thoughts and feelings (Baer et al., 2006; Brown and Ryan, 2003; Kabat-Zinn, 2003). Mindfulness-based stress reduction (MBSR) (Kabat-Zinn, 2003) has been incorporated into a variety of resilience programs as mindfulness has been found to be associated with higher levels of physical and mental health in several studies (Smith et al., 2011; Stanley et al., 2011; Thompson et al., 2011). The Mindful Awareness and Resilience Skills Training (MARST) program is designed to increase resilience in human service professionals by enhancing mindfulness, positive cognitive reappraisal skills, and awareness of positive emotions (Pidgeon et al., 2014; Pidgeon et al., 2015). Overall, within the last five years, mindfulness-based interventions have produced initial evidence of their potential as a PTSD treatment, and have also been combined with other resilience-based approaches (e.g., focusing on personal mastery and positive emotions) (Banks et al., 2015; Kearney et al., 2012; Rapgay et al., 2014).

Along with mindfulness, yoga and meditation have become more widespread in treating PTSD and enhancing resilience. Yoga enables the integration of physical exercise, known to be protective against dysregulation of stress responses (Tsatsoulis and Fountoulakis, 2006). A recent RCT of a yoga intervention for 80 individuals with PTSD found that the program not only decreased PTSD symptoms but showed even greater improvements in measures of positive affect and resilience compared to those in the waitlist control condition (Jindani et al., 2015). Meditation, a common technique often combined with yoga, has also been adapted for the treatment of PTSD. A breathing-based meditation intervention combined with yoga with US military male veterans was associated with reductions in PTSD and anxiety symptoms (Seppälä et al., 2014). The practice of mindfulness meditation has been linked to increases in positive affect and in left-sided anterior temporal activation, as well as improved immune system functioning (Davidson et al., 2003; Jevning et al., 1978).

The best-validated evidence-based psychotherapies for PTSD are based on CBT models and gradual exposure to trauma memories. Brain imaging studies suggest that CBT might work by reducing amygdala activation and increasing rACC activation in PTSD patients (Felmingham et al., 2007), and that amygdala and ventral ACC activation predicts treatment response to CBT (Bryant et al., 2008). Recent studies are investigating the use of pharmacotherapeutic agents to augment the effect of exposure therapy for PTSD. For example, D-cycloserine, a partial agonist at the glycine regulatory site of the NMDA receptor shown to enhance fear extinction in pre-clinical studies (Davis et al., 2006), administered to PTSD patients prior to sessions of virtual reality exposure therapy, was associated with earlier and greater PTSD symptom improvement compared to placebo (Difede et al., 2014). While in another study of virtual reality treatment, administration of D-cycloserine was not superior to the comparison conditions, it was associated with more pronounced reduction in cortisol and startle reactivity (Rothbaum et al., 2014a). Further studies are needed on this and other cognitive enhancers of exposure therapy (Singewald et al., 2015).

Additionally, recent studies focusing on memory reconsolidation mechanisms and the possibility of disrupting reconsolidation of traumatic memories within a short window of time following memory retrieval (Schiller et al., 2010) are encouraging the development of novel cognitive and pharmacotherapeutic interventions to be administered upon memory retrieval. In a recent encouraging study of individuals with a different condition, spider phobia, a single dose of propranolol administered after brief exposure to a tarantula appeared to succeed in disrupting fear memory reconsolidation, as avoidance behavior was transformed into approach behavior, a change that persisted for at least one year post-intervention (Soeter and Kindt, 2015). Although it will likely be more challenging to adapt this type of intervention for a complex disorder like PTSD, in a small study with PTSD patients a traumatic memory reactivation exercise post-propranolol administration was associated with reduced thalamus and amygdala activation, and greater right anterior cingulate activation (Mahabir et al., 2015). Another novel treatment intervention currently under development is based on recent findings of attention to threat abnormalities in patients with PTSD (Iacoviello et al., 2014; Naim et al., 2015). Recent RCTs of a cognitive training intervention aimed at remediating abnormal allocation to threat have yielded promising results in combat Veterans (Badura-Bracks et al., 2015).

Findings from neurobiological studies of stress and resilience have also stimulated research on potential novel pharmacologic interventions for PTSD, as currently available first-line pharmacotherapies (selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors and other medications) are insufficiently effective for many patients (Institute of Medicine, 2008; Ravindran and Stein, 2009). In a rodent model of PTSD, studies have recently shown a protective effect of intranasal NPY administration immediately prior to or following exposure to traumatic stress, on behavioral, neuroendocrine, and molecular changes (Sabban et al., 2015). Intranasal NPY administration is currently under investigation as a potential treatment for patients with PTSD. The glutamate system represents another promising treatment target, including studies of exposure therapy enhancement with D-cycloserine mentioned above. Ketamine, a glutamate NMDA receptor antagonist, has demonstrated therapeutic efficacy for treatment-resistant depression when administered at sub-anesthetic doses (Murrough et al., 2014) and more recently preliminary efficacy for PTSD (Feder et al., 2014). In a recent proof-of-concept RCT, a single dose of intravenous (IV) ketamine was superior to IV midazolam in rapidly reducing PTSD symptom levels in patients with chronic PTSD (Feder et al., 2014). Follow-up studies of repeated ketamine administration for patients with PTSD are currently under way. Of potential relevance to enhancing resilience, recent studies in rodents suggest that ketamine might blunt biological responses to uncontrollable stress when administered prophylactically up to 2 weeks prior to stress exposure (Amat et al., 2016). Modulators of glutamate metabotropic receptors have also been studied in animal models and are currently under development for treatment of stress-related disorders (Harvey and Shahid, 2012). Compounds targeting the endocannabinoid system are also under investigation, including inhibitors of the catabolic enzyme fatty acid amide hydrolase (FAAH), which have yielded positive findings in animal studies (Neumeister et al., 2015). Other novel pharmacological interventions for PTSD are continuing to emerge. For example, intranasal administration of oxytocin was recently shown to

dampen amygdala reactivity to emotional faces and normalize amygdala functional connectivity in an fMRI study of PTSD patients (Koch et al., 2015; Koch et al., 2016).

8. Future directions: a roadmap for resilience studies and novel interventions

This is an exciting time for the broad field of resilience research, as increasing interdisciplinary collaboration and translational studies, combined with scientific and technological advances, are poised to yield novel interventions to mitigate the impact of stress and trauma. Neural and molecular studies in animal models of resilience are enabling a closer examination of adaptive neuroplastic changes within specific neural substrates mediating stress responses. This approach is exemplified by a series of elegant studies in rodents employing the chronic social defeat stress paradigm, which have characterized a range of neuroplastic events at the molecular level, beginning with the ventral tegmental area-nucleus accumbens reward circuitry. These studies have identified active adaptations occurring in resilient animals, providing insight into potential avenues for novel pharmacological interventions by inducing naturally existing mechanisms of resilience (Krishnan et al., 2007; Russo et al., 2012).

Further, new findings from combined genomic and molecular studies, along with new genome-wide studies in larger samples of trauma-exposed individuals, will yield more refined means of identifying individuals at high risk for stress- or trauma-related conditions. Well-designed series of studies can help identify new intervention targets based on specific mechanisms of risk. A prime example is the sequence of studies that uncovered a G × E interaction, and subsequently allele-specific epigenetic changes within this G × E interaction, involving the *FKBP5* gene and exposure to childhood trauma, associated with increased *FKBP5* gene expression and heightened GR resistance in individuals exposed to early life stress, and resulting higher risk for PTSD (Klengel and Binder, 2015). These findings have stimulated the development of *FKBP5* antagonists, currently being tested in rodent models of early trauma exposure. If successful, this type of intervention has the potential to prevent the development of maladaptive stress responses if implemented early in life (Gaali et al., 2015).

Additionally, research on novel interventions based on advancing knowledge of fear conditioning, reconsolidation, and extinction processes, as well as abnormalities in attention to threat, emotion regulation, coupled with new insights on neural abnormalities from brain imaging studies, will yield new approaches to enhance resilience, prevent or reduce PTSD symptom emergence after trauma exposure, and reduce PTSD symptom severity in patients with chronic PTSD. Novel interventions currently under development include cognitive training, combined cognitive and pharmacological interventions, and administration of extinction enhancers following reactivation of trauma memories, among others. Clinical trials over the next decade are also likely to yield novel pharmacological treatments aimed at reducing dysfunction in neurotransmitter, hormone, and neuropeptide systems involved in the stress response – including glutamate, NPY, endocannabinoid, HPA axis, oxytocin, among others –, as well as immune system abnormalities that might mediate PTSD symptom chronicity.

The extensive literature on the consequences of early life stress, complemented by studies of resilience in high-risk children, has highlighted the importance of early intervention during development with children and adolescents at risk for stress-related psychopathology (Masten, 2001). The type and timing of trauma exposure should increasingly inform the development and optimal timing of interventions for children (Gee and Casey, 2015). A range of interventions for at-risk youth have been studied in school-aged children and adolescents, but wider implementation lags behind. Fewer studies have examined preventive interventions for younger children at risk, such as the Kids' Club program (Howell et al., 2013) or child-parent interventions with preschool children exposed to marital violence (Lieberman et al., 2005). Much additional research is needed, including studies of interventions during earlier stages of development likely to maximize resilience (Gee and Casey, 2015). Further, interventions that are feasibly integrated into the child's natural environment (i.e., school, communities) such as the PYD programs are an exciting platform and direction to enhance resilience (Lerner et al., 2005a). Early screening tools, including psychological and neurobiological methods that improve identification of children at higher risk for psychopathology, is a newer area of research with strong implications for maximizing resilience (Bender et al., 2015; van Meijel et al., 2015).

Finally, a growing number of interventions are being developed for adults, based on accumulating knowledge about psychosocial factors that promote resilience, including hardiness training, mindfulness interventions, meaning-making, promoting adaptive coping, cognitive reappraisal, positive psychology interventions, and many others, with applications for the military, other groups with high rates of trauma exposure by virtue of their occupation (e.g., police, first responders), and individuals with chronic PTSD. The development of new strategies for screening and early identification of at-risk youth and adults, and efforts aimed at dissemination and implementation of novel interventions will have to keep pace with the growth of new preventive and treatment strategies.

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