The Neuroscience of Resilience

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ABSTRACT Although the surge in research into the neuroscience of resilience is relatively new, it has been able to elucidate the brain structures that underlie resilience and identify strategies for supporting brain health and mental health across the lifespan. Despite advances, neuroscientists need the input of social work clinicians and clinical researchers to continue to move the field forward. This article provides a narrative review of the recent literature on the neuroscience of resilience with the goal of informing social workers and social work researchers about the state of knowledge in this field. We restricted our review to research in the past 20 years on resilience to stress and trauma, including only those papers that relate to neuroscience or mental functioning. We summarize recent developments in the neuroscience of resilience—notably the neural circuitry and physiology that underlie resilience in humans and animals. We go on to identify a number of interventions likely to promote resilience and resilient brain function, including parenting and community-based interventions for children and adolescents, hardiness training, meditation and mindfulness approaches, and aerobic exercise. Recommendations are made for future cross-disciplinary work.

KEYWORDS: trauma, neural plasticity, epigenetics, hypothalamic pituitary adrenal axis, hippocampus, evidence-based intervention

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In recent years, resilience has become a significant target for research in a number of contexts, including the field of social work, which aims to create and support resilience in clients and communities. Social work researchers, neuroscientists, psychologists, and psychiatrists—particularly those researchers involved in child development, mental health, and crisis intervention—are increasingly identifying resilience as an important area of study. The rise in interest in resilience research has emerged out of the observation that whereas stress and trauma are common events in human lives that can result in a variety of lasting pathologies, many individuals—if not most—will show some degree of resilience to the negative effects of stressful or traumatic events. Further, the development of life-course health devel-

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opment (LCHD) approaches to the causes of human disease has increased the attention given to how biological, psychological, and social factors, as well as developmental context, either contribute to or degrade resilience (Halfon, Larson, Lu, Tullis, & Russ, 2014).

The LCHD approach views the development of disease in the context of the multiple biological, psychological, and social factors that influence individual susceptibility to disease (Halfon et al., 2014). LCHD seeks to move past earlier models of disease that focused on particular pathogens or molecular targets for which a "magic bullet" (Williams, 2009) in drug form might be concocted. The latter approach was highly successful with regard to the treatment of bacterial infections with antibiotics, but it has been much less so for complex chronic diseases, particularly mental disorders, where the causation is complex. LCHD approaches recognize that although a disorder like atherosclerosis typically emerges in middle age, its origins lie not only in the present state of the patient's physiology, but also in their developmental, social, and psychological history (Baird et al., 2017). The developmental focus is particularly significant and arises from a large body of epidemiological research identifying stress and adversity in early life as risk factors for disease at later stages of the life course (Anda, Butchart, Felitti, & Brown, 2010; Baird et al., 2017; Edwards, Holden, Felitti, & Anda, 2003; Felitti et al., 1998; Halfon et al., 2014). Work in the neurosciences has begun to reveal how developmental history is embedded in human biology, contributing either susceptibility or resilience to the development of pathology in later life.

As we discuss in this review, resilience may derive from multiple factors, including early environment, social support, genetics, epigenetics, and coping strategies, as well as pharmacological and other therapeutic interventions. Because social workers often operate within and across the disciplines involved in building resilience, they are likely to be central to the delivery of resilience-promoting interventions and in the research and development of those interventions. The inter- and trans-disciplinary nature of social work places social workers in a unique position to both research and promote resilience. In this paper, we discuss resilience research developments within our own field of neuroscience to promote better understanding of the neurobiological aspects of resilience within the field of social work. Our hope is to increase the sort of interdisciplinary work we believe is needed to move the neuroscience field forward.

The Brain at the Nexus of Stress

The brain is the principal organ for both the identification of and the response to stress (McEwen, 1998; McEwen & Gianaros, 2011). The brain also is a target of stressful events, as it adapts its structure, function, and gene expression in response to stressful events. These effects are mediated, in part, by stress hormones such as cortisol and trophic factors such as *brain-derived neurotrophic factor* (BDNF), as the brain

is rich in receptors for these messengers (Gray, Milner, & McEwen, 2013; McEwen, 2007). In humans and in animal models, chronic stress and stress-related disorders such as depression and post-traumatic stress disorder (PTSD) are associated with changes in brain structure and function that seem to recover to some extent with treatment or after a stress-free period (Bremner, Elzinga, Schmahl, & Vermetten, 2008; Gray, Rubin, Hunter, & McEwen, 2014; Sheline, Gado, & Kraemer, 2003; Warner-Schmidt & Duman, 2006). However, emerging evidence from studies of gene expression and epigenetics suggests that the recovery of structural markers is not the whole story; resilience itself may reflect a dynamic response to a stressful environment rather than an ability to remain rigid and unchanged by environmental insults, or a simple absence of vulnerability (Gray et al., 2014; Horn, Charney, & Feder, 2016; Hunter, Gagnidze, McEwen, & Pfaff, 2015; Hunter & McEwen, 2013; Hunter, McEwen, & Pfaff, 2013; Karatsoreos & McEwen, 2011).

Definitions of Resilience

We define *resilience* as the ability to achieve a successful outcome in the face of adversity (Karatsoreos & McEwen, 2011, 2013a, 2013b, 2014; McEwen, Gray, & Nasca, 2015). Although the exact definition of resilience is still subject to debate, this definition is the most commonly used in the neurosciences and is inclusive of most working definitions used in the field (Horn et al., 2016; Mancini & Bonanno, 2009; Russo, Murrough, Han, Charney, & Nestler, 2012; Southwick, Bonanno, Masten, Panter-Brick, & Yehuda, 2014; Yehuda, Flory, Southwick, & Charney, 2006). In the context of human health, what does resilience mean for prevention and treatment resulting from adversity? In the spirit of integrative medicine, it is important to let what Cannon referred to as the "wisdom of the body" prevail and to focus on strategies that center around the use of targeted behavioral therapies, along with treatments—including pharmaceutical agents—that open up "windows of plasticity" in the brain and facilitate the efficacy of behavioral interventions that change the trajectory of an individual's life (Cannon, 1932, p. 17183; Karatsoreos & McEwen, 2013a; McEwen, 2012). This type of approach is important because a major challenge throughout the life course is to find ways of redirecting future behavior and physiology in more positive and healthy directions (Halfon et al., 2014). Such "reversibility" is a redirection of those features of a species that can be modified by experiences (Karatsoreos & McEwen, 2011, 2013a). This means that although resilience may appear to be a return to normal behavior after a trauma, it is, in fact, an active process that involves using a person's (or animal's) adaptive capacity to achieve a positive outcome. Resilience, in other words, has a cost, and resilient individuals are changed by their experience, even if those changes are not immediately visible to an outside observer.

It is worth noting that the field of resilience research has not settled on a consistent definition of what resilience means (Southwick et al., 2014). Generally, re-

silience is defined by the capacities to resist, recover, or redirect oneself after an insult or trauma (Karatsoreos & McEwen, 2011). In preclinical models, resilience is typically defined by the improvement, or lack of deficit, in one or a few closely related endpoints, which may not adequately mimic the complexities of human experience. In the human-subjects literature, resilience appears to be more common in studies that look at only a few endpoints and less so in those that look at a larger number. For example, a hypothetical study that looks only at levels of delinquency would likely find higher levels of resilience on that axis than one that looks at delinquency as well as psychiatric symptoms, school performance, and lifetime earnings. This suggests that resilience or susceptibility is governed to some extent by accumulation of risk—an implication of the adverse childhood experiences (ACE) literature, which uses the "ACE score" to describe the number of different types of adversities to which a child has been exposed (Anda et al., 2010; Felitti et al., 1998; Jaffee, Caspi, Moffitt, Polo-Tomas, & Taylor, 2007; Nurius, Green, Logan-Greene, & Borja, 2015; Nurius, Prince, & Rocha, 2015). Thus, the more exposures to risk factors a population has, the lower the resilience, and the more protective factors that are present, the higher the level of resilience. The discrepancy in levels of observed resilience across studies may result from differences in the costs of adaptation. The lack of a consistent definition is perhaps impossible to avoid when assessing the complexity of human biopsychosocial interactions. However, we hope that the definition of resilience that we use is inclusive enough to cover most usages in the various disciplines.

Definitions of Stress

As a scientific term, *stress* lacks specificity and a commonly understood meaning that represents all of the roles stress plays in biology and psychology. We have introduced a number of terms to clarify what stress means in the neurobiological context. *Toxic stress* refers to levels of stress that produce maladaptation and pathology; toxic stress is typically uncontrollable, severe, and/or chronic in nature. *Eustress* or "good" stress refers to varieties of stress that produce adaptive outcomes. Eustressful experiences are controllable stressors that increase our capacity to adapt to future stressors; for example, the stress of military boot camp is designed to increase resilience to the stress and trauma of combat and it could be viewed as eustress or at least a tolerable stress. In between are *tolerable stressors*, to which an individual is adapted enough to not develop pathology, but which produce no beneficial adaptations (McEwen & McEwen, 2016).

Underlying these concepts of stress is the concept of *allostasis*, or adaptation through change, which was developed as an addition to Walter Cannon's concept of homeostasis (Cannon, 1929). *Homeostasis* provides a conceptual framework to understand how the body maintains vital aspects of physiology, such as blood pressure or body temperature, which must be maintained within a certain range to maintain

life. Allostasis, in contrast, represents changes that do not threaten life in the short term and that often occur to protect the system from perceived or genuine threats to homeostasis. *Allostatic load* represents the net pressure on the organism to change in response to challenging life events; it includes both adaptive behaviors and external supports as well as the negative pressures often conceptualized as stress. *Allostatic overload* represents states where the allostatic load exceeds the capacity to adapt without damage or pathology, and it thus represents states where toxic stressors can produce pathology (Korte, Koolhaas, Wingfield, & McEwen, 2005; McEwen & Wingfield, 2003). The concept of allostasis emphasizes the adaptive nature of the stress response as well as the costs of adaptation.

It is important to note that allostasis and allostatic load and overload include the consequences of health-promoting and health-damaging behaviors that often result from tolerable and toxic stressors, such as physical activity as a positive aspect and poor diet, lack of sleep, alcohol use, and smoking as negative aspects. The key concept to allostasis and allostatic load and overload is that the same mediators that keep us alive via allostasis can turn against us and promote pathophysiology when they are overused and dysregulated among themselves (e.g., too much or too little cortisol, or too much or too little inflammatory response).

Stress, Adaptation, and the Brain

The allostatic framework fits well with our emerging understanding of *epigenetics*—the transmission of biological information by means other than the coding sequence of DNA itself. The term "epigenetic" was first used by Conrad Waddington (1940) to refer to the then-theoretical biological processes that governed the interaction between the genome and the environment in the development of the mature organism. Waddington was particularly interested in how organisms might produce what he called "trait adaptability," which is the inheritable capacity to adapt to one's environment, and he posited that epigenetic mechanisms must be responsible for this capacity of the environment to alter the program of development in an adaptive way (Waddington, 1942, 1957). We and others have argued that this idea of adaptability is fundamental to understanding how human biology allows adaptation to the developmental environment. This adaptability also explains how humans might, as a result, be pushed toward adapting in ways that might be suited to a difficult childhood but that canalize our development toward less resilience and higher probability of pathologies in later life (Halfon et al., 2014; Tronick & Hunter, 2016).

Even in adulthood, gene expression continually changes with experience (Gray et al., 2014), and there is loss of resilience with aging (Bloss, Janssen, McEwen, & Morrison, 2010) that can be redirected by exercise (Erickson et al., 2011) and possibly by pharmacological intervention (Pereira et al., 2014). Even chronic anxiety—possibly resulting from adverse childhood experiences—can respond to a behav-

ioral intervention in adulthood (Holzel et al., 2010). Indeed, mindfulness-based stress reduction and meditation increase functional connectivity within the brain and benefit fluid intelligence as well as improving function in aging (Gard, Holzel, & Lazar, 2014; Gard, Taquet, et al., 2014). Finding meaning and purpose in life also benefits overall health and cognitive function (Carlson et al., 2009; Fredrickson et al., 2013).

The brain's response to stressors is a complex process involving multiple interacting mediators that use both genomic and nongenomic mechanisms from the cell surface to the cytoskeleton to epigenetic regulation via the cell nucleus. Resilience in the face of stress is a key aspect of a healthy brain, even though gene expression shows a brain that continually changes with experience (McEwen, Gray, et al., 2015). Therefore, recovery of stress-induced changes in neural architecture after stress is not a "reversal" but a form of *neuroplastic adaptation* that may be impaired in mood disorders and reduced with aging. Resilience may be thought of as an active process that implies ongoing adaptive plasticity without external intervention (Russo et al., 2012).

On the other hand, resilience is decreased and vulnerability is increased by ACEs and the consequences of poverty and neglect, which lead to "biological embedding" of trajectories of response to stressful life events (Shonkoff, 2003). Such biological embedding includes epigenetic modifications such as CpG methylation of DNA (McGowan et al., 2009; see this paper's section on genetic, epigenetic, and developmental factors in resilience for more detail) that can persist throughout the life course (Halfon et al., 2014), contributing disproportionately to allostatic overload (McEwen, 1998; McEwen & Wingfield, 2003) in the form of physical and mental health disorders (Felitti et al., 1998) such as diabetes, depression, and dementia (Rasgon & McEwen, 2016).

Literature Review

This paper provides a narrative review of the research on resilience in the neurosciences and allied disciplines over the past 20 years in order to communicate these findings to social work practitioners and researchers. We restricted our review to research on resilience to stress and trauma and imposed the further constraint of only including papers that relate to neuroscience or mental functioning, except where reference to other approaches is necessary to provide context. For the purposes of this review we have defined *resilience* as the ability to achieve a successful outcome in the face of adversity. Our working definition of *stress* encompasses those environmental factors or events that are capable of producing pathological outcomes in susceptible individuals but may not do so in resilient individuals.

We have divided our discussion of the literature into sections covering work in preclinical animal models and those examining resilient outcomes in humans. We have done so for several reasons. First, animal studies are more able to examine

causal mechanisms, particularly at the cellular and molecular levels. Second, we wanted to avoid confusion between species that may have substantially different social and developmental biology. By way of illustration, rats and mice—which are the most common subjects for preclinical resilience research—do not display biparental behavior, which is present in less than 5% of mammalian species (Numan & Young, 2016). Therefore, caution must be used in extending findings about maternal behavior in rodents directly to humans. Third, translation from animal models has had limited success with regard to brain disorders for a number of reasons, including premature translation (Bahor et al., 2017; Drummond & Wisniewski, 2017). By separating the human from animal studies, we hope to avoid any confusion in this regard. Finally, by separating the two literatures, we hope to highlight those gaps where further translational research is warranted.

Animal Models of Resilience

Brain substrates of resilience. The use of animal models in neuroscience research has provided an essential window into the anatomical, electrophysiological, and molecular mechanisms of resilience as it is manifested in the brain's structure and function. Characterization of animals as *resilient* or *vulnerable* for comparison studies has relied on behavioral tests in which researchers infer the internal subjective state of the animals by measuring ethologically relevant behaviors. In rodents, several tests have been developed around the concept that as prey animals, rats and mice will tend to avoid open spaces where they might be subject to predation; tests such as the open field, elevated plus-maze, and light/dark box rely on this concept. Importantly, such tests show construct validity, in that rodents subjected to a stressor such as restraint or forced swimming will consistently spend less time in the open areas immediately after stress. Further, this stress-induced fear of open spaces can in most instances be reversed by anxiolytic or antidepressant medication. Therefore, studies of resilience in animal models have been based on the idea that after exposure to a stressor, some animals will exhibit anxiety-like behaviors (fear of the open area) and others will not. By comparing the neurobiological changes between these groups, researchers are beginning to understand the cellular and molecular mechanisms underlying resilience (Feder, Nestler, & Charney, 2009; Russo et al., 2012).

One of the most studied models of resilience has been the *social defeat stress paradigm*, in which a naïve animal is exposed to a larger and more aggressive animal that establishes social dominance over the subject (Golden, Covington, Berton, & Russo, 2011). After a brief encounter with the aggressor, some defeated animals will exhibit increased anxiety-like behaviors, increased hypothalamic-pituitary-adrenal (HPA) stress-axis reactivity, and metabolic changes, whereas resilient animals will continue to exhibit normal behaviors. Early experiments comparing the brains of defeated tree shrews to nonstressed animals revealed atrophy of the den-

dritic trees of CA3 neurons in the hippocampus (Magarinos, McEwen, Flugge, & Fuchs, 1996) and reduced hippocampal neurogenesis (Gould, McEwen, Tanapat, Galea, & Fuchs, 1997), which together resulted in decreased hippocampal volume (Czeh et al., 2001). The discovery of neurogenesis (or the birth of new neurons) in the adult brain was one of the more significant findings in 20th century neuroscience, and it provided an important mechanism for understanding how experience shapes the physical structure of the brain. In mammals, the hippocampus is one of only two regions that show regular neurogenesis in adulthood. The hippocampus is a region of the brain important for spatial learning and memory, and it plays a role in the regulation of the HPA axis. As these results suggest, the hippocampus is also one of the brain regions most sensitive to stress in both humans and animals, and a loss of hippocampal volume is associated with risk for brain disorders such as PTSD. Further, chronic stress reduces hippocampal function, leading to memory impairments and placing additional burdens on the stressed individual (McEwen, Bowles, et al., 2015; McEwen, Nasca, & Gray, 2016).

In mice, initial findings revealed that susceptible (socially defeated) animals also had increases in the neurotrophic factor BDNF (brain-derived neurotrophic factor) in the *nucleus accumbens* (NAcc; Berton et al., 2006; Krishnan et al., 2007), a brain region implicated in motivated behaviors such as reward seeking. Subsequently, genome-wide expression profiling studies of this and other areas of the brain after social defeat have identified numerous changes, principally in genes related to neuroplasticity (Krishnan et al., 2007; Walsh et al., 2014; Wilkinson et al., 2009). The mesolimbic reward system that includes the NAcc is important not only for reward, but for the value of incentives like food, water, and drugs of abuse (Pierce & Kumaresan, 2006). Further, in animals and humans the system represents an important neural substrate for the formation of social bonds between sexual partners and between mothers and infants (Numan & Young, 2016). The mesolimbic system has also been conceptualized as governing "seeking" behaviors, whether food or social opportunities (Alcaro, Huber, & Panksepp, 2007). All of this points to a role for the mesolimbic system both in the production of resilience through self-care and seeking social support, as well as in its failure. Indeed, external modulation of mesolimbic dopamine neurons to increase their activity during social defeat in mice has been shown to increase susceptibility, while inhibition of midbrain to NAcc dopamine activity increased resilience (Chaudhury et al., 2013). Further, manipulation of these neurons in susceptible or "depressed" mice rescued them from the susceptible phenotype (A. K. Friedman et al., 2014). More recently, work integrating the actions of BDNF and dopamine in the NAcc has shown that dopamine's effects are dependent on BNDF signaling to achieve their effects (Wook Koo et al., 2016). However, it is important to note that although it influences neural plasticity in multiple regions of the brain, BDNF can have different effects in different areas of the brain (Casey et al., 2009; Gray et al., 2013). Thus, traditional pharmacological

interventions that aim to raise BDNF globally are less likely to be effective than more targeted interventions. The body of work identifying the reward system as a brain substrate for resilience in animals has implications for humans exposed to stress and trauma, as they often develop disorders such as depression and PTSD associated with impairments in motivation and anhedonia (American Psychiatric Association, 1994).

Researchers have also used other stressors prior to sorting animals as resilient or susceptible based on their behavior. Using an inescapable foot-shock paradigm, a subset of rats will develop learned helplessness behavior (decreased escape attempts from the shock chamber), whereas others will show behavior similar to unstressed rats (Berton et al., 2007). Other research groups have used exposure to predator odor and classified animals as resilient based on their behavior in the elevated plus-maze and their acoustic startle response (Cohen et al., 2012). In addition to fear of open spaces, researchers have also used presumptive measures of anhedonia, such as decreased sucrose consumption after stress, to discriminate between resilient and susceptible mice (Delgado y Palacios et al., 2011).

Importantly, these tests are based on the absence of specific behavioral changes, suggesting that resilience is passive or results from a lack of changes. However, researchers have begun to examine active coping mechanisms exhibited by resilient animals that may mitigate the effects of a stressor. For example, using the social defeat paradigm, Wood and colleagues showed that mice that exhibit a longer latency to submissive posturing during the attack have less social avoidance later, suggesting that some mice engage in specific behaviors that facilitate resilience (Wood, Walker, Valentino, & Bhatnagar, 2010). Interestingly, recent work has identified a potassium channel expressed in the *ventral tegmental area* (a part of the mesolimbic dopamine system) as an important mediator of active resilience. Drugs targeting this type of potassium channel have been shown to enhance resilience in mice and act in antidepressant-like fashion. Significantly, one of these drugs, ezogabine, is already approved by the U.S. Food and Drug Administration, raising the possibility of rapid translation to clinical settings (A. K. Friedman et al., 2016).

Genetic, epigenetic, and developmental factors in resilience. Exposure to different levels of maternal care or deprivation has been associated with susceptibility or resilience of rodent pups to stress exposure later in life. High levels of maternal care have been shown to decrease later stress reactivity, and this effect was associated with increased glucocorticoid receptor (GR) expression in the hippocampus (Meaney et al., 1985). Rodents with lower levels of maternal investment also show higher levels of anxiety and epigenetic changes in stress-sensitive hippocampal brain regions (Weaver et al., 2004). Significantly, the differences in maternal behavior are transmitted across multiple generations, as are the changes in epigenetic markers and GR expression (Zhang, Labonte, Wen, Turecki, & Meaney, 2013). This intergenerational and transgenerational epigenetic transmission of biological susceptibility

and resilience is one of the more significant contributions of the neurosciences in the past 20 years. The fact that parental experience can be biologically embedded in the child has significant implications for social workers and other clinicians, as it points to the importance of interventions targeting caregivers, children, and expectant parents to reduce risk and promote resilience (Griffiths & Hunter, 2014; Hunter & McEwen, 2013; Taouk & Schulkin, 2016).

Despite the extensive literature using stressors prior to sorting resilient animals based on their behavior, some researchers have now demonstrated that inbred rat and mouse strains exhibit a spectrum of responses in tests such as the light/dark test, even in the absence of a prior stress exposure (Nasca, Bigio, Zelli, Nicoletti, & McEwen, 2015). These studies have helped to establish the genetic heritability of these traits. Selective breeding of Sprague-Dawley rats based on their exploratory behavior in a novel environment led to the identification of a number of changes in gene expression and neuroendocrine markers that were associated with the rats' differences in reactivity (high vs. low responders; Stead et al., 2006). Further, wide-ranging differences in susceptibility to social defeat have been characterized between inbred rat (Vidal, Buwalda, & Koolhaas, 2011) and mouse strains (Golden et al., 2011), clearly establishing a genetic connection with resilient or susceptible behavioral phenotypes. Further, researchers have now shown that manipulation of genes in specific brain regions can alter susceptibility to stress. For example, increased levels of the epigenetic regulator sirtuin1 (SIRT1) in the nucleus accumbens were observed after social defeat stress in susceptible mice, and viral-mediated genetic manipulation of SIRT1 levels in the accumbens (both overexpression and knock down) could mediate the depressive- and anxiety-like behaviors of mice (H. D. Kim et al., 2016).

Although genetics plays a role in resilience, adaptive or maladaptive behaviors most often manifest themselves after environmental exposure to a stressor. To characterize these gene × environment interactions, researchers have turned to the field of epigenetics. In the context of molecular neuroscience, epigenetics refers to the study of changes in the structure of DNA, such as DNA methylation or covalent modifications of histones (e.g., methylation and acetylation), which result in changes in cell-type specific gene expression. Exposure to stressors has been shown to result in epigenetic changes in several brain regions, including the hippocampus (Griffiths & Hunter, 2014; Hunter et al., 2015). Thus, several groups have now started to identify differences in molecular markers between susceptible and resilient animals. For example, exposure to predator scent was associated with increased DNA methylation at the BDNF gene locus and decreased messenger RNA (mRNA) expression of BDNF in the hippocampus (Roth, Zoladz, Sweatt, & Diamond, 2011). Methylation of the glucocorticoid receptor has also been studied in the hippocampus of rats subjected to high and low maternal care, in which increased methylation was associated with low maternal care and decreased receptor expression (Weaver et al.,

2004). More recently, maternal separation and deprivation in rodents has been shown to enhance susceptibility to stress in adulthood (a "two-hit" model), and this differential susceptibility appears to be regulated in part by orthodenticle homeobox 2, a developmentally important transcription factor in the mesolimbic dopamine system (Peña et al., 2017). Epigenetic regulation via small noncoding RNAs has also been implicated in resilience through the upstream regulation of small RNA processing by beta-catenin in the NAcc (Dias et al., 2014). Beta-catenin is a cell-adhesion molecule that plays a role in interactions between neurons and is known to be a significant player in neural plasticity and brain development (Maguschak and Ressler, 2012). Therefore, epigenetic regulation of beta-catenin can modify the amount of plasticity available to adapt to stress or trauma.

Interventions in animal models. In addition to characterizing these neurobiological differences, researchers have also sought to reverse the anxiety-like behaviors associated with susceptibility through pharmacological and behavioral interventions, as well as using techniques to manipulate the levels of specific genes. Not surprisingly, chronic administration of antidepressant medications that are used clinically has been shown to be effective at reversing the behavioral effects of social defeat stress (Tsankova et al., 2006; Wilkinson et al., 2009). Interestingly, researchers have found that the tricyclic antidepressant imipramine functions through epigenetic mechanisms by increasing histone acetylation (Tsankova et al., 2006). Another possibility is that antidepressant medications facilitate resilience by activating neurotropic pathways. Serotonin selective reuptake inhibitors (SSRIs) are known to increase BDNF levels in the hippocampus, which can facilitate increased neurogenesis and new dendritic spine formation; these changes have been associated with decreases in anxiety- and depressive-like behaviors in rodents (Martinowich & Lu, 2008). As noted earlier, the drug ezogabine may also prove useful in promoting resilient behaviors (A. K. Friedman et al., 2016) and is likely to see clinical use in the near future.

In addition to pharmacological manipulation, researchers have found that offering rodents the ability to exercise can have equally profound effects on reversing some of the negative behaviors observed after stress and restoring the underlying neurobiological changes associated with stress susceptibility. In rodents, voluntary running for extended periods increases hippocampal neurogenesis, dendritic length, and spine density (Eadie, Redila, & Christie, 2005), and it alters gene expression (Inoue et al., 2015). These changes may partly be due to increases in BDNF in the hippocampus with exercise (Adlard & Cotman, 2004; Vaynman, Ying, & Gomez-Pinilla, 2004). More recently, changes in neuronal morphology after exercise have been observed in the prefrontal cortex (Brockett, LaMarca, & Gould, 2015). Paradoxically, both exercise and stress are known to elevate corticosterone, which has been implicated in the negative changes associated with chronic stress and mood disorders. One possibility is that there are differential changes in the glucocorticoid

and mineralocorticoid (GR and MR) receptor systems in response to either stress or exercise, or that stress and exercise seem to have differential effects on medial prefrontal dopaminergic system (Chen et al., 2017). Increased dopamine in the *medial prefrontal cortex* (mPFC) has been demonstrated in response to numerous classes of antidepressants in rodents and after voluntary wheel running (Chen et al., 2016), in conjunction with reductions in anxiety- and depressive-like behaviors. Importantly, the positive effects of exercise on resilience after a stressor appear to directly translate to humans, as we discuss later.

In summary, research in preclinical animal models has identified many of the neural mechanisms underlying susceptibility to stressful events, as well as the brain regions most likely to be involved. Neural plasticity and epigenetics have shown that biology is not destiny. Rather, the brain can adapt, or maladapt, depending on life experience—particularly in early life. These studies also have biologically validated existing resilience-promoting interventions, such as antidepressant treatment, family-centered therapeutic approaches, and exercise. Most importantly, they have established that parental exposure to stress and trauma have biological effects that can be passed along to multiple generations, further emphasizing the importance of viewing trauma and resilience through a multigenerational lens.

The Neuroscience of Human Resilience

Brain substrates of resilience. Regarding human resilience, using the definition of "making a positive outcome out of adversity," self-regulation and locus of control are critical to how an individual is able to actively resist adversity or learn from bad experiences and recover (McEwen, Gray, et al., 2015, p. 1). These capabilities depend, at least in part, on the normal development of the prefrontal cortex and hippocampus (Russo et al., 2012). We know from animal models that these brain structures are altered by chronic stress and circadian disruption, and for humans, we can see negative effects of ACEs, including the experience of poverty. In the human brain, exposure to adverse early life experiences, including poverty, impairs development of the prefrontal cortex, which results in deficits in planning and working memory (Hackman, Farah, & Meaney, 2010). In another study, adults who had experienced lower family income at age 9 exhibited reduced ventrolateral and dorsolateral prefrontal cortex activity and failure to suppress amygdala activation during effortful regulation of negative emotion at age 24 (P. Kim et al., 2013), Moreover, childhood poverty is associated with risk of transmission of harsh parenting to the next generation. A possible mediator of this transmission is the finding that both men and women who grew up in poverty show an aversion to and altered limbic response to infant cry sounds, but with sex differences in the neural regions activated and how those emotional responses to infant cry sounds are expressed behaviorally among young adults growing up in poverty (Kim, Ho, Evans, Liberzon, & Swain, 2015).

Normal prefrontal cortical development involves initial positive connectivity followed by a valence shift to negative connectivity (Gee, Humphreys, et al., 2013). One study found that childhood adversity caused earlier development of negative connectivity of mPFC to the amygdala, resulting in some negative control of anxiety, although anxiety was still significantly higher in those who had experienced childhood adversity. From these findings, the authors postulated that accelerated amygdala–mPFC development is an ontogenetic adaptation in response to early adversity (Gee, Gabard-Durnam, et al., 2013). This accelerated development impairs planning and working memory (Hackman et al., 2010).

The hippocampus is another brain structure that is smaller in children who are exposed to adversity in poverty, as well as to abuse and neglect (Hanson, Chandra, Wolfe, & Pollak, 2011; Teicher, Samson, Anderson, & Ohashi, 2016). Underdevelopment of the hippocampus is accompanied by slower brain growth and less gray matter overall, as well as altered structure of the orbitofrontal cortex (Hanson et al., 2010, 2011, 2013). A smaller hippocampus is associated with slower shutoff and lack of habituation of a cortisol stress response after repeated Trier Social Stimulation Tests and with lower locus of control (Kirschbaum et al., 1995; Pruessner et al., 2005). Smaller hippocampal volume is associated with those with PTSD, including both risk for PTSD and the subsequent effects of PTSD to further decrease hippocampal volume (Gilbertson et al., 2002; Pitman, 2001; Pitman, Shin, & Rauch, 2001; Shalev et al., 1998). Reductions in hippocampal volume are also seen in chronic stress, low self-esteem, depression, and schizophrenia (Adriano, Caltagirone, & Spalletta, 2012; McEwen, 2006), suggesting convergent mechanisms of vulnerability. Given the common finding of reduced hippocampal volume in mental disorders, it is plausible that reduced hippocampal volume is a risk factor for reduced resilience in and of itself.

The function of the stress axis is another important factor in humans as in animals. Rapid activation and rapid, appropriate termination of the stress response are associated with resilience, whereas blunted or exaggerated responses are associated with disease states (Charney, 2004; de Kloet, Joëls, & Holsboer, 2005; Karatsoreos & McEwen, 2013a). Similarly, the activity of other stress-reactive neurotransmitter systems—such as corticotropin-releasing hormone and norepinephrine—is related to resilience or pathology depending on the capacity of the system to self-regulate (Cahill, Prins, Weber, & McGaugh, 1994; Charney, 2003; Heim & Nemeroff, 2001; McGaugh, 2004), and evidence exists to suggest that blocking the activity of these systems could effectively treat emotional memory disorders like PTSD (Strange & Dolan, 2004).

Other neurotransmitter systems may also contribute to resilience. Neuropeptide Y acts as a natural antagonist to the actions of corticotropin-releasing hormone in a number of stress-responsive brain regions (Sabban, Alaluf, & Serova, 2016). Neuropeptide Y has also been shown to be associated with better performance in highly

resilient populations, such as Special Forces soldiers (Morgan et al., 2000). The endocannabinoid system (the target of the psychoactive components of marijuana, e.g., cannabidiol and tetrahydrocannabinol) is also perturbed by stress and trauma in humans and animal models (Hill et al., 2013; Hill, Hunter, & McEwen, 2009; Morena, Patel, Bains, & Hill, 2016). The neuropeptide oxytocin, which is involved in social attachment, has been shown to improve prefrontal cortical activity in combat-exposed veterans (Eidelman-Rothman et al., 2015). The neurotransmitter glutamate is perhaps one of the most significant targets for understanding stress and stress resilience at the neurochemical level, as it has been identified as having a significant role in both fear learning and stress-induced brain plasticity in a large number of studies and models (Popoli, Yan, McEwen, & Sanacora, 2011; Riaza Bermudo-Soriano, Perez-Rodriguez, Vaquero-Lorenzo, & Baca-Garcia, 2012). Most significantly for humans, the drug ketamine, which blocks the N-methyl-D-aspartate class of glutamate receptors, has been shown to be a rapidly effective antidepressant that may also have utility in the treatment of PTSD (Feder et al., 2014; Murrough et al., 2013).

Genetic and epigenetic factors in resilience. Given that human biology is determined to a large extent by genes, it should be unsurprising that variations in a number of genes contribute to vulnerability and resilience. The best studied of these susceptibility/resilience alleles is the long polymorphic repeat in the promoter of the serotonin transporter, which occurs in both long and short variants in humans. The serotonin transporter 5-HTT is the primary target of SSRIs like fluoxetine (Prozac), and people who have one or more short polymorphisms in the gene are more prone to develop anxiety, alcohol abuse, depression, and suicide, particularly when exposed to adversity and developmental trauma (Anguelova, Benkelfat, & Turecki, 2003; Kuzelova, Ptacek, & Macek, 2010; Uher & McGuffin, 2008). The val/met polymorphism in the BDNF gene is also implicated in susceptibility and resilience to psychiatric disorders like depression and to stress vulnerability in adult life, with met carriers generally being susceptible and val carriers showing a more resilient phenotype (Casey et al., 2009; Gunnar et al., 2012). BDNF and 5-HTT polymorphisms have been shown to interact to promote resilience or susceptibility, particularly with regard to early life stress (Ignacio, Reus, Abelaira, & Quevedo, 2014). It is worth noting that in the context of developmental stress there is some evidence that the met allele may promote resilience (Gunnar et al., 2012), likely by reducing the capacity of the developing brain to make maladaptive changes in response to a highly stressful environment. Polymorphisms in genes governing the function of the stress axis have also been implicated in resilience and susceptibility to stress-related mental disorders. The best established of these are polymorphisms in the FKBP5 gene, which codes for a protein that controls the trafficking of the GR, a major target of the stress hormone cortisol. Polymorphisms in the FKBP5 gene can induce vulnerability to PTSD in those with a history of childhood trauma (Klengel & Binder, 2015b). A similar sort of gene–environment interaction exists between trauma, low social

support, and the 5-HTTLPR (5-HT transporter, long polymorphic repeat) mentioned previously (Kilpatrick et al., 2007). This sort of gene-by-environment interaction speaks to the nature of resilience and vulnerability as an emergent property of the interactions of our biology with the environment. Epigenetic mechanisms also play a role, as epigenetic modifications of the FKBP5 gene have been shown to modify risk for PTSD in populations with a history of exposure to childhood adversity (Klengel & Binder, 2015a). Indeed, the global landscape of DNA methylation appears to be significantly different in PTSD patients exposed to child abuse as compared to those with no such history (Mehta & Binder, 2012).

Immunity, inflammation, and resilience. It has long been known that the immune system is regulated by the glucocorticoids released by the HPA stress axis. Under normal conditions, glucocorticoids can block the secretion of proinflammatory cytokines like interleukin-6 (Silverman, Pearce, Biron, & Miller, 2005). However, in situations where the stress axis is chronically dysregulated, the capacity to block proinflammatory cytokine production can be reduced and inflammation can increase (Bekhbat, Rowson, & Neigh, 2017). Thus, chronic stress—which itself decreases the energetic resources available for resilience—causes increased activation of the immune system, which further depletes resources and contributes to a variety of disease states in a vicious cycle. Elevated inflammatory markers are associated not only with mental disorders like depression and PTSD (Mitchell & Goldstein, 2014) but also with medical diseases like cancer and atherosclerosis (Li et al., 2017). Therefore, interventions that can reduce stress, as well as those that reduce inflammation, have the capacity to disrupt the cycle of stress, immune dysregulation, and disease that undermines resilience and promotes susceptibility to further insult. The capacity of even acute moderate exercise to reduce levels of inflammatory markers likely underlies its positive effects on mood and resilience (Dimitrov, Hulteng, & Hong, 2017; Ironson, Banerjee, Fitch, & Krause, 2017). Similarly, recent work has provided some evidence that meditation can reduce both stress and immune activation (Black & Slavich, 2016; Kurth, Cherbuin, & Luders, 2017). Interventions such as meditation and moderate exercise are a promising area of research for promoting resilience in clinical populations. Inflammation remains relatively underexplored from the resilience perspective in preclinical models, but that appears to be changing (Bilbo, Smith, & Schwarz, 2012; Schwarz & Bilbo, 2012).

Developmental and psychosocial factors in resilience. In addition to the biological factors identified previously, a number of psychosocial factors also contribute to resilience. In children, resilience is increased by positive relations to caregivers, strong social support, and systems that support meaningful interpretations of adversity, such as religion (Horn et al., 2016; Masten, 2001; Werner, 2012). Cognitive factors also play a role in children as they do in adults, as intelligence, good executive function and emotional regulation, motivation to achieve, and mastery are all associated with higher resilience (Horn et al., 2016; Sapienza & Masten, 2011; Wu

et al., 2013). In adults, positive outlook, emotional regulatory capacity, social support, and adaptive coping strategies are all associated with increased resilience (Boyce & Chesterman, 1990; Southwick & Charney, 2012). Active coping both at the time of trauma and while reexperiencing it promotes resilience, as opposed to avoidant or emotionally oriented coping strategies (LeDoux & Gorman, 2001; Murray, Merritt, & Grey, 2016; Silver, Holman, McIntosh, Poulin, & Gil-Rivas, 2002; Thabet, 2017). Humor also is associated with resilient responses in a number of populations (Sliter, 2013), though gallows humor is associated with worse outcomes than other varieties (Craun & Bourke, 2015). As mentioned above, exercise promotes resilience as well, likely through a number of mechanisms that include increased neuroplasticity, reduced inflammation, physical hardiness, and feelings of mastery or self-esteem (Behrman & Ebmeier, 2014; Ding, Vaynman, Souda, Whitelegge, & Gomez-Pinilla, 2006; Erickson & Kramer, 2009; Mueller, 2007; Stewart & Yuen, 2011). The complexity of the effects of exercise is an example of the generally interrelated quality of the factors that promote resilience. The practice of exercise has clear biological effects (e.g., improved cardiovascular function), but it also relates to psychological traits such active coping, mastery, and positive motivation (which help individuals to successfully engage in a program of exercise) in a self-reinforcing fashion.

Building Resilience

Research in social work and other disciplines has validated a number of interventions for promoting resilience, although linking these interventions to underlying neurobiology is a project that remains in its early stages. Most theoretical models of resilience recognize that the trait arises from a reduction in risk along with an increase in either buffering or compensatory adaptations. In this context it is important to recognize that although stress and trauma substantially contribute to the risk factor, the absence of adversity does not necessarily contribute to resilience to future insults. Indeed, exposure to controllable stressors is a major contributor to building resilience, and it has been argued that healthy caregiver–child interaction is structured in such a way that the child is supported in confronting increasingly challenging tasks and learning how to adapt to such challenges on the way to becoming an independent adult (DiCorcia & Tronick, 2011). Similar processes are involved in exposure therapies for PTSD and phobias, and in these cases the neurobiology is well delineated, though the developmental neurobiology of resilience remains less well defined.

Developmental interventions. Building resilience begins in childhood, or even before birth. Interventions that increase parental coping skills should, in turn, increase the capacities of children to grow and flourish successfully. Childhood adversity has an impact on brain structure and function across the lifespan (Hackman & Farah, 2009; Teicher et al., 2016), and the ACE literature has established the epidemiological risks associated with high adversity quite well with regard to the burden

of both medical and mental illness (Anda et al., 2010). A number of factors have been shown to promote resilience in early life, including positive relationships with caregivers and peers, consistent parenting, social frameworks that promote meaning, intelligence, high emotional self-regulation, and self-efficacy or mastery, many of which are potentially modifiable with clinical or family-centered interventions (Horn et al., 2016; Traub & Boynton-Jarrett, 2017). Early childhood interventions have demonstrated efficacy with regard to a number of social and economic endpoints, but they have not yet seen common implementation (Shonkoff & Fisher, 2013). Although the effect sizes in these studies is often moderate and a number of challenges exist to their broader implementation (Fisher, 2016), these interventions nonetheless have the potential to reduce the risk of mental and medical disorders in a large percentage of the population. This is an important consideration given that the ACE literature clearly identifies childhood adversity as a major challenge to public health.

Family dynamics between caregivers and children contribute to both resilience and susceptibility across the lifespan. The intellectual genealogy of the project of understanding susceptibility and resilience dates back to Freud's identification of the family as the source of many of the conflicts that lead to mental disorders in later life. However, empirical research into resilience and susceptibility during development properly began in the 1960s. Early researchers such as Patterson identified intrafamilial relationships as the most important predictors of disruptive behavior in children. Disruptive behavior is broadly important in the present context as it is predictive of a variety of negative outcomes, such as peer rejection and delinquency (Patterson, DeBaryshe, & Ramsey, 1989), and can deplete resilience. Disruptive behavior was found to be most likely in families with patterns of harsh, unevenly applied discipline and low levels of caregiver warmth and support (Reid, Patterson, & Snyder, 2002). Another significant observation was that in such families, negative interactions between caregivers and children increased over time as both parties made more punitive efforts to control the behavior of the other (Capaldi & Patterson, 1994; Fisher, 2016; Patterson, Reid, & Dishion, 1992). The complex interactions between a caregiver's experiences and resources and the temperament and needs of the child likely contribute to both resilience and susceptibility, and this complexity highlights the importance of understanding resilience as an emergent property arising from dynamic social, biological, and psychological interactions over time (Halfon et al., 2014; Pastorelli et al., 2016; Tronick & Hunter, 2016).

Some of the first evidence-based interventions to promote resilience and reduce dysfunction emerged from the work mentioned previously, beginning with Parent Management Training Oregon (Patterson, Chamberlin, & Reid, 1982), which evolved into Treatment Foster Care Oregon (TCFO) and related approaches that focused on interventions in a foster-care environment, where children are at much higher risk of adversity having already lost one set of caregivers and facing potential rejection

from foster parents. TCFO includes both parenting interventions and group interventions (e.g., playgroups) for the children. The TCFO approach led to improved outcomes in a number of measures, including a reduced likelihood of rejection by caregivers and improved cognitive outcomes (Fisher, 2016). The work also helped build on other research showing that abnormalities in the HPA axis were associated with childhood adversity in a number of contexts (Fisher, Gunnar, Dozier, Bruce, & Pears, 2006; Gunnar & Fisher, 2006). A randomized clinical trial of the TCFO approach demonstrated that the intervention normalized morning cortisol levels (a measure of HPA function) in fostered children, who also demonstrated improvements in attachment-related behaviors (Fisher, Stoolmiller, Gunnar, & Burraston, 2007). The approach also has been show to improve signatures of brain activity in an executive task (Bruce, McDermott, Fisher, & Fox, 2009). Other programs focused on improving the quality and sensitivity of parenting, such as the Attachment and Biobehavioral Catch-up intervention, have also shown a positive impact on avoidant behavior and cortisol secretion (Bernard, Hostinar, & Dozier, 2015; Dozier et al., 2009).

School-based interventions have been shown to have a positive impact on resilience—defined as lower levels of PTSD or depressive symptoms—in populations of children exposed to warfare. School programs have the benefit of enhancing natural systems of social support around the child, and some explicitly aim to encourage children to seek support and succor from their peers (Jordans, Pigott, & Tol, 2016). Other interventions include stress inoculation training, which focuses on teaching adaptive coping strategies prior to stress exposure. These interventions have been associated with lower symptom levels and better adaptive coping (Diab, Punamäki, Palosaari, & Qouta, 2013; Wolmer, Hamiel, Barchas, Slone, & Laor, 2011; Wolmer, Hamiel, & Laor, 2011). The Child and Family Traumatic Stress Intervention is a brief, early intervention for trauma-exposed children referred by the police or other emergency services. The intervention comprises four sessions and is designed to improve caregiver or parent emotional support, and to improve communication between the traumatized child and caregivers. The approach has been shown to reduce the presence of PTSD symptoms 3 months later (Berkowitz, Stover, & Marans, 2011).

Adult interventions. For adults, a number of interventions have been created to boost resilience in groups likely to face trauma in the course of their working lives (e.g., soldiers and firefighters). These approaches often involve training in job-specific skills to enhance the sense of control under stress as well as improve relaxation, mindfulness, and other more general stress-management approaches (M. J. Friedman, Keane, & Resick, 2014; Whealin, Ruzek, & Southwick, 2008). Relaxation techniques may help to normalize HPA axis activity, and many of these approaches appear to work, in part, by enhancing coping self-efficacy (or self-perceived adaptive coping), which has been shown to lead to more positive outcomes after trauma (Hobfoll et al., 2007). The U.S. and other western militaries have developed a num-

ber of training interventions explicitly aimed at enhancing resilience by targeting those traits common to resilient individuals. The Comprehensive Soldier Fitness program, which is applied both before and after combat deployments, is built around increasing personal strengths, positive emotion, and the creation of meaning around the challenges of a soldier's duties in wartime (Cornum, Matthews, & Seligman, 2011; Fertout et al., 2011; Mulligan, Fear, Jones, Wessely, & Greenberg, 2011). One such intervention has been shown to enhance hardiness and social cognition in a randomized clinical trial (Cacioppo et al., 2015). Other work examining rates of PTSD in combat-deployed units in Afghanistan has identified good leadership, unit cohesion, and good morale as potentially protective factors against PTSD, which fits evidence that being able to attach meaning and having a clear adaptive coping strategy promotes resilience (Hunt, Wessely, Jones, Rona, & Greenberg, 2014). Similar observations demonstrate that longer combat deployment times are associated with reduced resilience, a finding that has recently led the U.S. military to reduce combat deployments from 12 to 9 months (Hunt et al., 2014; Office of the Surgeon Multi-National Force–Iraq & Office of the Surgeon General, U.S. Army Medical Command, 2008). Hardiness training has some similarities to the military approaches and has been applied to populations outside of high-stress professions (e.g., college students); it has been shown to reduce PTSD symptoms and buffer the effects of more common stressors. Hardiness training aims to enhance the capacity to reframe stressors more positively as challenges and opportunities for growth (M. J. Friedman et al., 2014; Kobasa, Maddi, & Kahn, 1982; Maddi, 2007).

Mindfulness or meditation-based approaches also appear to have some benefit in promoting resilience in a number of contexts (Rees, 2011; Thompson, Arnkoff, & Glass, 2011), including some specifically oriented toward social workers (Trowbridge & Mische Lawson, 2016). Meditation and cognitive–behavioral therapy have been shown to help normalize stress responses and recruit neuro-plastic mechanisms in a positive, stress-resistant direction (Davidson & McEwen, 2012; Rosenkranz et al., 2016). Meditation also has the capacity to enhance cognitive resilience by enhancing positive emotion, cognitive flexibility, and perspective taking (Dahl, Lutz, & Davidson, 2015). In individuals with high ACE levels, higher levels of mindfulness are associated with fewer adverse health outcomes (Whitaker et al., 2014). It is worth noting that mindfulness has bidirectional effects, as mindfulness in caregivers (e.g., teachers) improves the quality of relationships and reduces the level of conflict (Becker, Gallagher, & Whitaker, 2017).

As discussed earlier, exercise training has long been associated with increased resilience (see, e.g., Kobasa, Maddi, & Puccetti, 1982). Exercise training has demonstrable effects on the HPA axis, cognitive function, and anxiety (Reul et al., 2015), which promote a resilient phenotype. In addition to the inflammation reduction mentioned previously, exercise promotes neural plasticity by increasing levels of neurotrophic factors like BDNF. These plastic changes are also linked to improve-

ments in cognition and resilience (Baek, 2016; Silverman & Deuster, 2014). Most significantly from the neuroscience perspective, aerobic exercise is linked to increased volume in brain regions like the prefrontal cortex and hippocampus, whose volumes are typically decreased in individuals with a history of chronic stress or trauma (Erickson, Leckie, & Weinstein, 2014; Erickson et al., 2011; Hayes, Hayes, Cadden, & Verfaellie, 2013). Given that these brain areas are responsible for some of the cognitive traits of resilience, such as emotional regulation and cognitive flexibility, the value of aerobic exercise as a resilience-building intervention is clear.

Although we have described a number of interventions that appear to have efficacy for promoting resilience to some extent, it is important to note that research validating these approaches from a mechanistic, neuroscience perspective remains limited. For example, whereas exercise is well validated—perhaps because it is easy to study both animal models and humans—more complex longitudinal interventions are less well studied. This is partially due to the general resistance of funding agencies to support multidecadal intervention research, but also due to the limitations in cross-disciplinary communication between researchers in social work, social and developmental psychology, and mechanistically minded neuroscientists.

Conclusions and Future Directions

Social work researchers have led the way in developing models and interventions to promote and understand resilience, but our understanding of the neurobiology underlying resilient phenotypes remains limited, particularly with regard to resilience to developmental adversity. We know much more about what can go wrong than how the brain can be tuned or prepared to make things go right even in the face of substantial trauma.

What has emerged is a consilience between neuroscience and social work with regard to both clinical and preclinical resilience research that shows that reducing early life stress exposure, increasing social support, and providing tools to improve stress coping (either individually or in combination) can result in increased resilience. It is also clear that resilience has neurobiological correlates in those brain regions like the hippocampus and prefrontal cortex that support complex cognition, sociality, and successful coping. Interventions, education, and some psychopharmacological approaches that increase function in these regions will in turn contribute to resilience. Other brain regions, such as the amygdala, tend to be hyperreactive in vulnerable people; thus, interventions that reduce amygdala activity, such as exposure therapy for PTSD, are likely to promote resilience. Social workers can promote resilience in early development through prenatal maternal education, family-centered therapy, and by intervening to prevent child abuse. Support for adult caregivers—in terms of mental health interventions, parenting education, and social and economic support to increase their available resources—will improve the resilience of both the caregivers and the children (or dependent adults)

in their care. In adult populations, interventions that increase social support—as well as practices such as meditation and exercise that support healthy brain plasticity—will have protective effects. Also important across developmental stages is the reduction in number and severity of stressors, whether economic, social, medical, or otherwise. Treatment of mental disorders both with medication and talk therapies should be encouraged; however, because the severity of symptoms is often embedded in a client's overall context, psychiatric treatment should not be the only source of support considered.

Although the insights we have described are important, significant gaps remain in our understanding of resilience. Whereas the life-course approach to human disease has led to increased research focused on the relevance of early life to later health, comparatively little attention has been paid to developmental stages like adolescence, when many mental disorders first emerge, or middle age, when many chronic medical conditions make their first appearance. Resilience research would do well to fill in these gaps and develop age-appropriate interventions that are sensitive to individual life histories.

Experimental research is most easily done when only one variable is manipulated. However, both clinical intuition and the body of research we have presented here suggest that resilience is a complex phenomenon and that many interventions show some utility. A useful avenue for future research would be to examine how integrating multiple interventions might improve clinical outcomes. Social workers are uniquely suited to organizing such a multimodal research program given their position in coordinating different networks and types of support and treatment for their clients.

By more closely examining molecular, anatomical, and physiological mechanisms of resilience, we may be more able to prevent the negative impacts of trauma when they occur and treat those pathologies that do emerge. Awareness of how resilience and susceptibility express themselves in terms of cognitive capacities and brain function will help clinicians to understand how to work with the biological limitations and capacities of their clients. Conversely, neuroscientists need to seek more input from clinicians in order to better inform models of resilience and trauma that have too often been driven by mechanistic studies in model organisms rather than direct human experience. Resilience research in the neurosciences remains in its early stages, and there is substantial cause for optimism that a cross-disciplinary, neuroscience-informed approach will have a substantial impact on our capacity to build resilience in both individuals and communities.

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