Resilience, Stress, and the Neurobiology of Aging

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The aging of the world’s populations represents one of the most remarkable success stories in medicine and of humankind, but it is also a source of various challenges. Getting older can be stressful because of multiple losses (eg, interpersonal, financial) and a decline in health, independence, and cognitive and functional abilities.

Worldwide, human life expectancy has increased steadily for nearly 200 years and this trend is expected to continue. In every decade of the past century, life expectancy increased by about 2 years. This increase was driven in the first decades by improvements in sanitation, housing, and education. A steady decline in early and midlife mortality was mostly the result of our ability to prevent and treat infections. The increase in life expectancy in the latter half of the century was almost entirely attributable to a decline in late-life mortality secondary to medical advances and improved socioeconomic conditions.1

Many older adults are living longer with chronic illnesses yet are making the best of their later years. As George E. Vaillant2 pointed out in his book Aging Well, “The major factors involved in negative personality change at midlife are the same factors that caused negative aging at 70: bad habits, bad marriage, maladaptive defenses, and disease.”

The benefits of a positive outlook

Empirical evidence now supports the long-held belief that positive emotions are good for one’s health. Fredrickson’s “broaden-and-build theory” shows how positive emotions contribute to psychological and physical well-being through more effective coping.3,4 It is a natural drive to seek personal happiness and fulfillment regardless of age. Successful aging is associated with a positive psychological outlook in later years, general well-being, and happiness.2,5-7

With global trends in population aging, many nations are developing and implementing healthy aging policies to promote quality of life and additional years of health.7 One direction is to improve resilience to stress. Depp and Jeste6 have defined resilience as “the ability to maintain biological and psychological homeostasis under stress. It may vary with context, time, age, gender, and cultural origin. Inquiry into resilience has evolved from descriptions of resilient qualities to uncovering the process of resilient adaptation. In older adults, resilience has been studied mostly in the context of successful aging (eg, in centenarians) or in the context of recovery from injury or illness.” The question remains whether resilience can be operationalized and taught to older stressed individuals and whether any
interventions exist that boost resilience to stress and life’s adversities.

CHECKPOINTS

- Human responsiveness to stress may be attenuated by learned or adaptive skills, retraining, or increased resilience to future stress
- Physiological mediators such as adrenaline from the adrenal medulla, glucocorticoids from the adrenal cortex, and cytokines from the cells of the immune system act on receptors in various tissues and organs to produce effects that are adaptive to stress in the short run but can be damaging if the mediators are not shut off when no longer needed
- Prospective determinants of resilience for future studies include neuroendocrine, immunological, neural, genetic, temperamental, and environmental influences.

Stress and aging

Selye\(^8\) coined the term “stress” to define the alarm reaction, the stage of resistance, and the stage of exhaustion in animals and in humans. Only when the subject is overwhelmed or derailed does the stress response system begin to cause disease.\(^9\) Exposure to stress can be characterized in several ways: duration (acute, chronic), responsiveness (adaptive, hyperadaptive, nonresponsive), and severity (mild, moderate, extreme).\(^10\)

Human responsiveness to stress may be attenuated by learned or adaptive skills, retraining, or indifference to future stress. The hypothalamic-pituitary-adrenal axis can be up regulated by a stressful experience, with increased amounts of circulating glucocorticoids, catecholamines, serotonin, and cytokines. These acute responses can lead to pathological changes that may be amplified by the aging of the brain.\(^10\)

The adaptive physiological response to acute stress that involves internal milieu adjustment to change in the environment was initially described by Sterling and Eyer.\(^11\) McEwen\(^12\) extended this definition to include the concept of a set point that changes because of the process of maintaining homeostasis in the body that is mediated by the neuroendocrine, autonomic nervous, and immune systems. Allostasis is the term used to describe this process of “maintaining stability through change.”

Physiological mediators such as adrenaline from the adrenal medulla, glucocorticoids from the adrenal cortex, and cytokines from the cells of the immune system act on receptors in various tissues and organs to produce effects that are adaptive in the short run. If the mediators are not shut off when no longer needed, they can lead to deleterious effects of chronic stress, including receptor desensitization and tissue damage.

Aging can contribute to poor responsivity to stress because of reduced resilience.\(^13\) Accumulation of wear and tear caused by daily experiences and major life stressors can interact with genetic constitution and predisposing early life experiences to produce individual differences in the age-related diseases.\(^10,13,14\)

Immunity, inflammation, and aging

The plasma concentrations of inflammatory mediators, such as cytokines and acute phase proteins, increase with aging, which results in low-grade inflammation. These changes lead to increased obesity and adiposity; a decrease in production of sex steroids; subclinical infections; and chronic aging-related disorders, such as cardiovascular disease and arthritis. Furthermore, aging is associated with a dysregulated cytokine response following stimulation.\(^15\)

Several inflammatory mediators, such as tumor necrosis factor-α and interleukin-6 (IL-6), have the potential to induce and/or aggravate risk factors in age-associated pathology. Inflammatory mediators are also strong predictors of mortality independent of other known risk factors in elderly cohorts. For example, a proinflammatory factor IL-6 has been linked with Alzheimer disease, osteoporosis, rheumatoid arthritis, cardiovascular disease, and some forms of cancer, and it has been prospectively associated with general disability and mortality in large population-based studies.\(^16-21\)

Neural circuitry and resilience
Brain imaging promotes understanding of brain regulation of positive emotions and resilience. The brain circuitry that is involved in emotional regulation includes several areas of the prefrontal cortex (PFC), amygdala, hippocampus, and anterior cingulate. The PFC plays a crucial role in the anticipation of future affective consequences of action as well as in the persistence of emotion. There are several different functional divisions of the PFC, including the dorsolateral, ventromedial, and orbital sectors. Each of these regions plays a different role in emotional regulation. The amygdala appears to be crucial for learning new stimulus-threat contingencies and to be important in the expression of cue-specific fear. Tonic activation and phasic reactivity in this circuit play an important role in governing different aspects of anxiety. Asymmetries within the PFC and activation of the amygdala are responsible for individual differences in affective style. Plasticity in this circuitry has implications for cultivating positive affect and resilience.

**Resilience and aging**
A coherent pattern of individual characteristics associated with resilience and successful adaptation has emerged. Salient characteristics include commitment, dynamism, humor in the face of adversity, patience, optimism, faith, and altruism. There are emotional and cognitive aspects of resilience that can be innate or learned. The innate affective or emotional styles that are likely to influence resilience refer to the individual styles of affect regulation, which are usually a part of personality structure (eg, optimism or pessimism), or social intelligence. Temperament appears to be one of the determinants of resilience that is, at least, partially heritable. Protective temperamental factors include sociability, intelligence, social competence, internal locus of control, warmth and closeness of affectional ties, and active emotional support within the family network or within religious groups. As such, resilience may represent an important target for treatment and prevention of anxiety, depression, and abnormal stress reactions in aging persons (Figure).

**Well-being and aging**
A sense of well-being is an important characteristic of successful aging. Ryff and colleagues described 2 types of well-being: eudaimonic and hedonic. The aristotelian concept of eudaimonic well-being addresses ideas of self-development and self-acceptance, personal growth, positive relationships, and purposeful engagement. Hedonic well-being is concerned with positive feelings, such as happiness and contentment. A sense of ill-being refers to all negative affect states, such as depression and anxiety. Different biological markers, including neuroendocrine (cortisol, epinephrine, norepinephrine), immune (IL-6, vaccine antibody response), cardiovascular (blood pressure, waist-hip ratio, cholesterol, glycosylated hemoglobin), sleep (duration/latency of rapid eye movement), and neural circuitry (cerebral asymmetry), are associated with the states of well-being or ill-being. The question remains whether resilience is responsible for the differences.

**Psychotherapeutic and psychopharmacological approaches**
Little research exists on preventive strategies to enhance resilience to stress in older adults. There are a few examples of the cognitive-behavioral therapy approach to resilience and well-being in younger adults. The resiliency training program is a 5-day progressive program that provides experiences for participants to enhance personal resilience. Select aspects of resilience that improve as a result of the intervention include self-esteem, locus of control, purpose in life, and interpersonal relations. Fava and colleagues used well-being therapy (a short-term psychotherapeutic strategy) to improve symptoms of anxiety and depression in younger adults. Well-being therapy is based on a multidimensional model that encompasses environmental mastery, personal growth, purpose in life, autonomy, self-acceptance, and positive relations with others. It has been used as a relapse-preventive strategy in mood disorders and in treatment-resistant patients. Complementary and alternative interventions can also help treat or prevent stress-related disorders. Mind-body interventions, such as tai chi and meditation, have also been noted to modulate the
immune response. These interventions can normalize immune and endocrine response to stress and depression. Relaxation and stress reduction can change the immune system by decreasing negative emotions. These interventions may influence immunity by providing people with more social contact or helping them develop better coping strategies.

Physical exercise may be an effective intervention for limiting the impact of stress on immunity in chronically stressed older populations. Stress management interventions attempt to alleviate the immune system dysregulation that accompanies psychological stress. Observations from an ongoing study of yoga meditation by family caregivers of patients with dementia have shown that meditation for 25 to 30 minutes can be strikingly beneficial (H. Lavretsky, unpublished data, 2010). Study participants report relief from depression and insomnia and improved coping ability.

**Case vignette**

A 65-year-old African American woman who was caring for her mother with Alzheimer disease and her sister with stroke-related dementia had significant depressive symptoms and distress and scored 12 on the Hamilton Depression Rating Scale (HDRS). Her symptoms began to diminish after she began to meditate daily; after 2 weeks her HDRS score decreased to 1. She reported an increased ability to cope and assess her stressful situation more objectively without the level of anger and resentment that was present before she started meditating. She also learned to allocate time to herself and take part in pleasurable activities. She no longer felt trapped or a victim of the circumstances.

For this stressed caregiver, daily meditation and the recognition of her psychological needs increased her resilience and ability to cope with her life stressors. This woman felt empowered by the idea of wellness, resilience, and self-reliance.

A recently published review of the effect of mindfulness meditation on cellular aging suggests that mindful meditation techniques shift cognitive appraisals from threat to challenge, decrease ruminative thought, reduce stress arousal, and directly increase positive arousal states that affect telomerase activity and telomere length, thereby improving longevity. Further studies are needed because currently there is only preliminary evidence that the use of mind-body techniques such as meditation can be useful in preventing diseases of aging.

Antidepressants have also been shown to promote resilience in patients with posttraumatic stress disorder (PTSD) and in stressed caregivers. Connor and colleagues undertook a 12-week placebo-controlled trial of fluoxetine in civilians with PTSD and reported better efficacy with fluoxetine than with placebo. Pooled results from 2 large, multicenter, randomized, controlled trials of patients with PTSD using extended-release venlafaxine indicated that total Connor-Davidson Resilience scale scores and treatment were significant predictors of both response and remission.

In our randomized placebo-controlled pilot study, 10 mg/d of citalopram improved resilience and decreased levels of depression and distress. This is the first trial of an antidepressant directed toward increasing resilience in a high-risk group of chronically stressed older caregivers. Preliminary results of our study of the complementary use of tai chi to augment treatment response in elderly depressed patients who had a partial response to 10 mg/d of escitalopram show improvement in psychological resilience and a decline in inflammatory markers (ie, C-reactive protein).

**Conclusion**

Research on resilience has shifted the focus of investigation from the illness-based approach to the well-being-oriented approach. A pattern of positive characteristics that could target new interventions to promote successful aging include sound intellectual functioning, the ability to handle emotions, self-esteem, optimism, altruism, humor, and an engaged and active coping style. Prospective biological markers of resilience important for future investigations include neuroendocrine, immunological, neural, genetic, temperamental, and environmental influences. Resilience can be quantified by using standardized assessments in neurobiological and treatment studies. Multimodal assessment of the biological determinants of resilience will help identify targets for intervention to enhance resilience on both individual and cultural levels. Learning to enhance psychological resilience may help overcome health problems and their resulting disabilities. Successful stress reduction and management, particularly among the most vulnerable seniors, can prevent serious mental and physical illness. Integrated modalities to improve resilience and reduce stress in combination with pharmacotherapy and lifestyle changes are likely to improve the overall functioning and well-being of older adults.
References:


44. Davidson JR, Stein DJ, Rothbaum BO, et al. Resilience as a predictor of remission in PTSD patients treated with venlafaxine XR or placebo. Poster presented at: Annual Meeting of the Anxiety Disorders of America; March 23-26, 2006; Miami.