THIRD OF 4 PARTS

Resilience and mind-body interventions in late-life depression

Enhancing resilience can improve outcomes in patients with late-life depression

Resilience has been defined as the ability to adapt and thrive in the face of adversity, acute stress, or trauma.[1] Originally conceived as an inborn trait characteristic, resilience is now conceptualized as a dynamic, multidimensional capacity influenced by the interactions between internal factors (eg, personality, cognitive capacity, physical health) and environmental resources (eg, social status, financial stability).[2,3] Resilience in older adults (typically defined as age ≥65) can improve the prognosis and outcomes for physical and mental conditions.[4] The construct is closely aligned with "successful aging" and can be fostered in older adults, leading to improved physical and mental health and well-being.[5]

While initially resilience was conceptualized as the opposite of depressive states, recent research has identified resilience in the context of major depressive disorder (MDD) as the net effects of various psychosocial and biological variables that decrease the risk of onset, relapse, or depressive illness severity and increase the probability or speed of recovery.[6] Late-life depression (LLD) in adults age >65 is a common and debilitating disease, often leading to decreased psychological well-being, increased cognitive decline, and excess mortality.[7,8] LLD is associated with several factors, such as cerebrovascular disease, neurodegenerative disease, and inflammation, all of which could contribute to

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Resilience in older adults

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Interventions targeting language might be useful to improve coping in late-life depression

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brain vulnerability and an increased risk of depression.[9] Physical and cognitive engagement, physical activity, and high brain reserve have been shown to confer resilience to affective and cognitive changes in older adults, despite brain vulnerability.[9]

The greatest levels of resilience have been observed in individuals in their fifth decade of life and later,[4,10] with high levels of resilience significantly contributing to longevity[5]; however, little is known about which factors contribute to heterogeneity in resilience characteristics and outcomes.[4] Furthermore, the concept of resilience continues to raise numerous questions, including:

- how resilience should be measured or defined
- what factors promote or deter the development of resilience
- the effects of resilience on various health and psychological outcomes
- which interventions are effective in enhancing resilience in older adults.[4]

In this article, we describe resilience in older adults with LLD, its clinical and neurocognitive correlates, and underlying neurobiological and immunological biomarkers. We also examine resilience-building interventions, such as mind-body therapies (MBTs), that have been shown to enhance resilience by promoting positive perceptions of difficult experiences and challenges.

Clinical and neurocognitive correlates of resilience

Resilience varies substantially among older adults with LLD as well as across the lifespan of an individual.[11] Identifying clinical components and predictors of resilience may usefully inform the development and testing of interventions to prevent and treat LLD.[11] One tool widely used to measure resilience—the self-report Connor-Davidson Resilience Scale (CD-RISC)[12]— has been found to have clinically relevant characteristics.[1,11] Using data from 337 older adults with LLD, Laird et al[11] performed an exploratory factor analysis of the CD-RISC and found a 4-factor model:

- grit
- adaptive coping self-efficacy
- accommodative coping self-efficacy
- spirituality.[1,11]

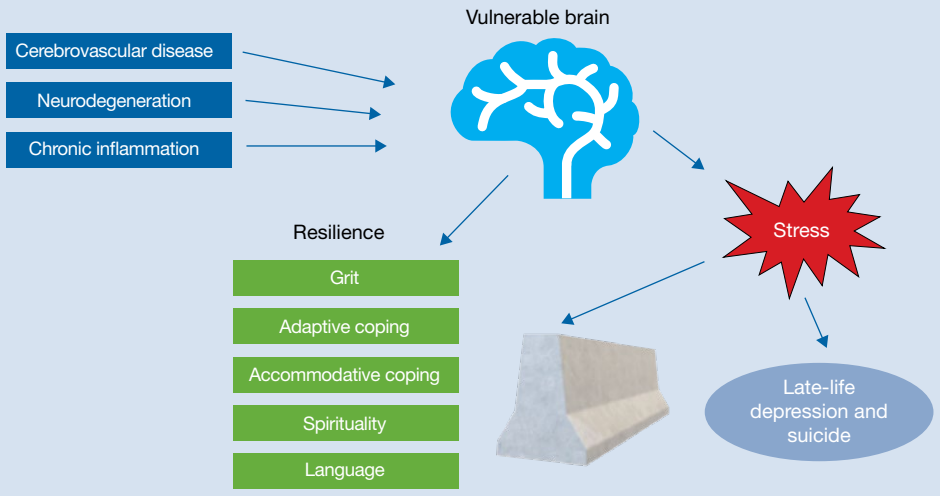
Having a strong sense of purpose and not being easily discouraged by failure were items characteristic of grit.[1,11] The preference to take the lead in problem-solving was typical of items loading on adaptive coping self-efficacy, while accommodative coping self-efficacy measured flexibility, cognitive reframing, a sense of humor, and acceptance in the face of uncontrollable stress.[1,11] Finally, the belief that "things happen for a reason" and that "sometimes fate or God can help me" are characteristics of spirituality.[1,11] Using a multivariate model, the greatest variance in total resilience scores was explained by less depression, less apathy, higher quality of life, non-White race, and, somewhat counterintuitively, greater medical comorbidity.[1,11] Thus, interventions designed to help older adults cultivate grit, active coping, accommodative coping, and spirituality may enhance resilience in LLD.[1,11]

Resilience may also be positively associated with cognitive functioning and could be neuroprotective in LLD.[13] Laird et al[13] investigated associations between baseline resilience and several domains of neurocognitive functioning in 288 older adults with LLD. Several positive associations were found between measured language performance and total resilience, active coping, and accommodative coping.[13] Additionally, total resilience and accommodative coping were significantly associated with a lower self-reported frequency of forgetfulness, a subjective measure of memory used in this study.[13] Together, these results suggest that interventions targeting language might be useful to improve coping in LLD.[13] Another interesting finding was that the resilience subdomain of spirituality was negatively associated with memory, language, and executive functioning performance.[13] A distinction must be made between religious attendance (eg, regular attendance at religious institutions) vs religious beliefs, which may account for the previously reported associations between spirituality and improved cognition.[13]

Self-reported resilience may also predict greater responsivity to antidepressant

Figure

Vulnerability and resilience factors in late-life depression



Factors contributing to late-life depression (LLD), such as cerebrovascular disease, neurodegenerative disease, and chronic inflammation, can lead to a vulnerable brain that is at risk for major depressive disorder. Clinical and neurocognitive resilience factors, such as grit, adaptive coping, accommodative coping, spirituality, and language, can protect vulnerable brains from developing LLD.

Source: Adapted from reference 9

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Self-reported resilience may predict greater responsivity to antidepressants in older adults with late-life depression

medication in patients with LLD.[14] Older adults with LLD and greater self-reported baseline resilience were more likely to experience improvement or remission from depression with antidepressant treatment.[14] This is congruent with conceptualizations of resilience as "the ability to adapt to and recover from stress."[14,15] Of the 4 identified resilience factors (grit, adaptive coping, accommodative coping, and spirituality), it appears that accommodative coping predicts LLD treatment response and remission.[14] The unique ability to accommodate is associated with better mental health outcomes in the face of uncontrollable stress.[14,16-18] Older adults appear to engage in more accommodative coping due to frequent uncontrollable stress and aging-related physiological changes (eg, sleep changes, chronic pain, declining cognition). This could make accommodative coping especially important in this population.[14,19]

The ***Figure***, adapted from Weisenbach et al,[9] exhibits factors that contribute to LLD, including cerebrovascular disease, neurodegeneration, and chronic inflammation, all of which can lead to a vulnerable aging brain that is at higher risk for depression, particularly within the context of stress. Clinical and neurocognitive factors associated with resilience can help buffer vulnerable brains from developing depression.

Neurobiological biomarkers of resilience in LLD

Psychobiological consequences can add to existing risk factors and bidirectionally interact to increase health risks, including LLD.[6] Stress is the primary factor in examining resilience, whether through protective measures or its adverse effects on biological and psychological systems. Resilience is often seen as adaptive maintenance of homeostasis in the face of stress.[6] Stress and resilience were examined over multiple studies through the lens of several biomarkers, including gross

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The neurobiology underlying resilience involves brain networks associated with stress response, negative affect, and emotional control

anatomical features, stress response (endocrine, immune, and inflammatory), and cardiovascular indicators.

Gross anatomical indicators: Findings from neuroimaging

The neurobiology underlying psychological resilience involves brain networks associated with stress response, negative affect, and emotional control.[19] Increased amygdala reactivity and amygdala frontal connectivity are often implicated in neurobiological models of resilience.[20] Leaver et al[20] correlated psychological resilience measures with amygdala function in 48 depressed vs nondepressed individuals using functional magnetic resonance imaging. Specifically, they targeted the basolateral, centromedial, and superficial nuclei groups of the amygdala while comparing the 2 groups based on resilience scores (CD-RISC), depressive symptom severity, and depression status.[20] A significant correlation was identified between resilience and connectivity between the superficial group of amygdala nuclei and the ventral default mode network (VDMN).[20] High levels of psychological resilience were associated with lower basal amygdala activity and decreased connectivity between amygdala nuclei and the VDMN.[20] Additionally, lower depressive symptoms were associated with higher connectivity between the amygdalae and the dorsal frontal networks.[20] These results suggest a complex relationship between amygdala activity, dorsal frontal regions, resilience, and LLD.[20]

Vlasova et al[21] further addressed the multifactorial character of psychological resilience. The associations between the 4 factors of resilience and the regional integrity of white matter in older adults with LLD were examined using diffusion-weighted MRI.[21] Grit was found to be associated with greater white matter integrity in the genu of the corpus callosum and cingulum bundle in LLD.[21] There was also a positive association between grit and fractional anisotropy (FA) in the callosal region connecting the prefrontal cortex and FA in the cingulum fibers.[21] However, results regarding the FA in the cingulum fibers did not survive correction for multiple comparisons and should be considered with caution, pending further research.[21]

Stress response biomarkers of resilience

Stress response biomarkers include endocrine, immune, and inflammatory indices. Stress has been identified as a factor in inflammatory responses. Stress-related overstimulation of the HPA axis may increase the risk of LLD.[22] Numerous studies have demonstrated an association between increased levels of peripheral proinflammatory cytokines and depressive symptoms in older adults.[23] Interleukin-6 (IL-6) has been increasingly linked with depressive symptoms and poor memory performance in older adults.[9] There also appears to be an interaction of inflammatory and vascular processes predisposing to LLD, as increased levels of IL-6 and C-reactive protein have been associated with higher white matter pathology.[9] Additionally, proinflammatory cytokines impact monoamine neurotransmitter pathways, leading to a reduction in tryptophan and serotonin synthesis, disruption of glucocorticoid receptors, and a decrease in hippocampal neurotrophic support.[9] Alexopoulos et al[24] further explain that a prolonged CNS immune response can affect emotional and cognitive network functions related to LLD and has a role in the etiology of depressive symptoms in older adults.

Cardiovascular comorbidity and autonomic nervous system dysfunction

Many studies have revealed evidence of a bidirectional association between cardiovascular disease and depression.[25] Dysregulation of the autonomic nervous system (ANS) is an underlying mechanism that could explain the link between cardiovascular risk and MDD via heart rate variability (HRV), though research examining age-related capacities provide conflicting data.[25,26] HRV is a surrogate index of resting cardiac vagal outflow that represents the ability of the ANS to adapt to psychological, social, and physical environmental changes.[27] Higher overall HRV is associated with greater self-regulating capacity, including behavioral, cognitive, and emotional control.[28] Additionally, higher HRV may serve as a biomarker of resilience to the development of stress-related disorders such as MDD. Recent studies have shown

an overall reduction in HRV in older adults with LLD.[29] When high- and low-frequency HRV were investigated separately, only low-frequency HRV was significantly reduced in patients with depression.[29] One explanation is that older adults with depression have impaired or reduced baroreflex sensitivity and gain, which is often associated with an increased risk of mortality following cardiac events.[30] More research is needed to examine the complex processes required to better characterize the correlation between resilience in cardiovascular disease and autonomic dysfunction.

The ***Box***[6,31,32] describes the relationship between markers of cellular health and resilience.

Mind-body therapies

There is increasing interest in improving older adults' physical and emotional well-being while promoting resilience through stress-reducing lifestyle interventions such as MBTs.[33] Because MBTs are often considered a natural and safer option compared to conventional medicine, these interventions are rapidly gaining popularity in the United States.[33,34] According to a 2017 National Health Survey, there were 5% to 10% increases in the use of yoga, meditation, and chiropractic care from 2012 to 2017, with growing evidence supporting MBTs as minimally invasive, cost-effective approaches for managing stress and neurocognitive disorders.[35] In contrast to pharmacologic approaches, MBTs can be used to train individuals to self-regulate in the face of adversity and stress, thus increasing their resilience.

MBTs can be divided into mindful movement exercises and meditative practices. Mindful movement exercises include yoga, tai chi, and qigong. Meditative practices that do not include movement include progressive relaxation, mindfulness, meditation, and acceptance therapies. On average, both mindful movement exercise (eg, yoga) and multicomponent mindfulness-based interventions (eg, mindfulness-based cognitive therapy, mindfulness-based stress reduction [MBSR], and mindfulness-based relapse prevention) can be as effective as other active treatments for psychiatric disorders such as MDD, anxiety, and substance use disorders.[36,37] MBSR specifically has been shown to increase empathy, self-control, self-compassion, relationship quality, mindfulness, and spirituality as well as decrease rumination in healthy older adults.[38] This suggests that MBSR can help strengthen the 4 factors of resilience.

Research has also begun to evaluate the neurobiological mechanisms by which meditative therapies enhance resilience in mental health disorders, and several promising mechanistic domains (neural, hormonal, immune, cellular, and cardiovascular) have been identified.[39] The physical yoga discipline includes asanas (postures), pranayama (breathing techniques), and dhyana (meditation). With the inclusion of mindfulness training, yoga involves the practice of meditation as well as the dynamic combination of proprioceptive and interoceptive awareness, resulting in both attention and profound focus.[40] Dedicated yoga practice allows an individual to develop skills to withdraw the senses (pratyahara), concentrate the mind

Box

Cellular health and resilience

Among the biomarkers of resilience, telomere length and telomerase activity serve as biomarkers of biological aging that can differ from the chronological age and mark successful anti-aging, stress-reducing strategies.[31] Telomerase, the cellular enzyme that regulates the health of cells when they reproduce (preserving the telomeres, repetitive DNA strands at the ends of chromosomes), is associated with overall cell health and cellular biological age.[31] When telomerase is reduced, the telomeres in a cell are clipped, causing the cells to age more rapidly as the telomeres get shorter through the process of cellular reproduction.[31] Psychological stress may play a significant role in telomerase production and subsequent telomere length.[32] Lavretsky et al[32] evaluated the effect of brief daily yogic meditation on depressive symptoms and immune cell telomerase activity in a family of dementia caregivers with mild depressive symptoms. Brief daily meditation practice led to significant lower levels of depressive symptoms that was accompanied by an increase in telomerase activity, suggesting improvement in stress-induced cellular aging.[6,32]

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Dysregulation of the autonomic nervous system could explain the link between cardiovascular risk and MDD via heart rate variability

Related Resources

- Lavretsky H. *Resilience and Aging: Research and Practice*. Johns Hopkins University Press; 2014.
- Lavretsky H, Sajatovic M, Reynolds CF, eds. *Complementary and Integrative Therapies for Mental Health and Aging*. Oxford University Press; 2016.
- Eyre HA, Berk M, Lavretsky H, et al, eds. *Convergence Mental Health: A Transdisciplinary Approach to Innovation*. Oxford University Press; 2021.
- UCLA Jane & Terry Semel Institute for Neuroscience & Human Behavior. Late-life Depression, Stress, and Wellness Research Program. https://www.semel.ucla.edu/latelife

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Growing evidence supports mind-body therapies as cost-effective approaches for managing stress and neurocognitive disorders

(dharana), and establish unwavering awareness (dhyana).[41] The physical and cognitive benefits associated with yoga and mindfulness may be due to mechanisms including pranayama and activation of the parasympathetic nervous system; meditative or contemplative practices; increased body perception; stronger functional connectivity within the basal ganglia; or neuroplastic effects of increased grey matter volume and amygdala with regional enlargement.[41] The new learning aspect of yoga practice may contribute to enhancing or improving various aspects of cognition, although the mechanisms are yet to be clarified.

Continued research in this area will promote the integration of MBTs into mainstream clinical practice and help alleviate the increased chronic health burden of an aging population. In the face of the COVID-19 pandemic, public interest in improving resilience and mental health[42] can be supported by MBTs that can improve coping with the stress of the pandemic and enhance critical organ function (eg, lungs, heart, brain).[43,44] As a result of these limitations, many resources and health care services have used telehealth and virtual platforms to adapt to these challenges and continue offering MBTs.[45]

Enhancing resilience to improve clinical outcomes

Increasing our understanding of clinical, neurocognitive, and neurobiological markers of resilience in older adults with and without depression could inform the development of interventions that treat and prevent mood and cognitive disorders of aging. Furthermore, stress reduction, decreased inflammation, and improved emotional regulation may have direct neuroplastic effects on the brain, leading to greater resilience. Complementary use of MBTs combined with standard antidepressant treatment may allow for additional improvement in clinical outcomes of LLD, including resilience, quality of life, general health, and cognitive function. Additional research testing the efficacy of those interventions designed to improve resilience in older adults with mood and mental disorders is needed.

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Bottom Line

Identifying the clinical, neurocognitive, and neurobiological biomarkers of resilience in late-life depression could aid in the development of targeted interventions that treat and prevent mood and cognitive disorders of aging. Mind-body interventions can help boost resilience and improve outcomes in geriatric patients with mood and cognitive disorders.

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