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Editorial Comment: Stress and Late-Life Depression

Christopher C. Abbott, M.D., M.S., **Mohamad Khafaja, M.D.**

Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque, NM.

Preclinical models of acute stress (forced swim test, tail suspension test), neuroimaging, and postmortem investigations have provided invaluable information on the neurobiology of stress on the brain. Stress and depression result in neuronal atrophy and volume loss within prefrontal cortices and hippocampal regions, decreased neuronal and glial proliferation, and decreased expression of brain derived neurotrophic factor.[1] Stress- and depression-related disrupted connectivity between cortical and limbic regions is associated with aberrant feedback loops, endocrine abnormalities, and increased inflammatory markers. Other brain regions such as the amygdala and the subcallosal cingulate cortex become overactive. These neurobiologic changes are associated with the duration and severity of the depressed episode. Other age-related changes in neuronal loss and synaptic inefficiency may further increase susceptibility to depression in late life. The relationship between stress, aging, and depression is thus compelling but complex.

In this issue of the journal, Schaakxs et al.[2] examine the relationship between age and a wide variety of depression risk factors (socioeconomic status, life stressors, personality, social functioning, lifestyle, and health). They used a large database (N =2215) to test the “ontime, off-time” hypothesis, which posits that risk factors occurring during ages with the lowest occurrence would be most associated with depression. This cross-sectional investigation focused on individual with current depression (defined as last 6 months) and healthy comparisons. The older age range had the highest occurrence of depression risk factors. The results were mixed but provided some support for the “ontime, off-time” hypothesis. Risk factors such as chronic disease and increased body mass index, which occurred most frequently in older ages, had the strongest association with depression in younger ages. In contrast, other depression risk factors such as reduced social functioning and recent negative life events remained constant throughout the life span.

Pertinent to late-life depression, other depression-specific variables (number of depressive episodes, depression subtype) also influence the relationship between psychosocial stressors and depression. Recurrent depressive episodes throughout the life span may be associated with a “kindling” model, which posits that the role of psychosocial precipitants or stressors will diminish with progressive depressive episodes.[3] Stressful life events are strongly associated with initial depressive episodes, and this relationship attenuates with the increased number of depressed episodes. At a certain threshold, stressful life events are no

Send correspondence and reprint requests to Christopher C. Abbott, Department of Psychiatry, Center for Psychiatric Research MSC11 6035, University of New Mexico School of Medicine, 1101 Yale Blvd NE, Albuquerque, NM 87131. cabbott@salud.unm.edu.

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longer associated with depression. Thus, older individuals that have numerous depressed episodes will have a weak relationship between psychosocial stressors and risk of depression. Similarly, the age at onset for depression may influence the relationship between stress and depression risk. Although not definitive, late-onset depression (defined as depression onset after 50–60 years of age) may have a stronger neurobiologic basis, possibly related to cerebrovascular disease and weaken the relationship with psychosocial stressors.[4] Schaakxs et al. did not assess the relationship between risk factors, number of depressive episodes, or age at depression onset, but their results may be interpreted in this context. The relationship between risk factors (pain, chronic disease burden) and depression in younger age may be related to stronger relationship between stressor and depression onset, which would be consistent with reduced impact from kindling and late-onset depression.

Specific depression subtypes may also be associated with differential depression risk in the context of psychosocial stressors. Historically, exogenous (reactive) and endogenous (nonreactive) depression subtypes were differentiated based on the perception of the presence or absence of a causal psychosocial precipitant. Regardless, this distinction failed to inform treatment or prognosis for depressive episodes and is no longer used. In contrast, depressive episode with melancholic features is defined phenomenologically with nonreactive mood and psychomotor disturbance.[5,6] Melancholic features also differ from nonmelancholic depression with an older age at onset and increased occurrence in older age. In addition, many individuals with melancholic features describe depression occurring “out of the blue” and contextually disproportionate to any antecedent stressors. Recent debate has focused on whether melancholia represents a unique syndrome or a depression subtype, which is beyond the scope of this commentary. However, the current investigation may have included respondents with melancholic features, which may have influenced the associations between depressive risk factors and risk of depression in the older cohorts.

Compensatory mechanism may also mitigate the impact of psychosocial stressors in late life. These mechanisms include psychological coping mechanisms, physical activity, brain reserve, and support systems.[7] Top-down processing, which describes the interaction between a stimulus (stressor) and expectations, can assist at-risk individuals in contextualizing a specific stressor. In addition, support systems with similar demographics facing familiar stressors (bereavement in late life) may also provide protection against depression. This compensatory mechanism may not be present when late-life stressors happen earlier in life or “off-time.” In the Schaakxs et al. investigation, several risk factors that were most prevalent in late life were associated with increased risk of depression in young adulthood. These results support the “on-time/off-time” hypothesis and may reflect a loss of compensatory mechanisms. This important investigation thus offers a novel perspective of risk factors for depression and may inform targeted interventions to at-risk populations (increased social support for younger adults with numerous chronic diseases).

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