HHS Public Access

Author manuscript

Int Psychogeriatr. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Int Psychogeriatr. 2023 December ; 35(12): 689–691. doi:10.1017/S1041610223000170.

Coexisting Depression and Frailty as an Accelerated Aging Phenotype of Late-Life Depression

Warren D. Taylor, M.D., M.H.Sc.[1,2]

[1]Center for Cognitive Medicine, Department of Psychiatry and Behavioral Science, Vanderbilt University Medical Center, Nashville, TN

[2]Geriatric Research, Education, and Clinical Center, Veterans Affairs Tennessee Valley Health System, Nashville, TN

Conceptualizing late-life depression (LLD) in context of aging provides insights into how the underlying neurobiology of LLD contributes to adverse clinical outcomes. It may be particularly useful to consider LLD in relationship to accelerated aging, or biological aging processes that occur more rapidly or more severely than expected (Christman *et al.*, 2020). This relationship between depression and aging is likely bidirectional: depression may accelerate aging processes, while accelerated aging processes, particularly those involving the brain, may increase the risk for developing new-onset or recurrent depressive episodes (Andreescu *et al.*, 2019; Rutherford *et al.*, 2017). Among the many implications of an 'accelerated aging hypothesis of late-life depression' is the utility of considering LLD as a geriatric syndrome that coexists with and is influenced by other deleterious geriatric syndromes, including frailty.

Frailty is a syndrome characterized by accelerated aging in multiple organ systems, defined by weakness, medical morbidity, decreased physical function, fatiguability, and unintentional weight loss (Fried *et al.*, 2001). Frailty and depression are highly comorbid, with approximately 40% of frail elders having depression and approximately 40% of individuals with LLD exhibiting frailty (Soysal *et al.*, 2017). Such cross-sectional associations are supported by longitudinal studies further demonstrating this reciprocal risk. Depression is associated with worsening trajectories in functional status, including reduced walking speed and hand strength (Lever-van Milligen *et al.*, 2017), and older depressed adults are more likely to develop frailty than nondepressed individuals (2.6 increased hazard) (Chang *et al.*, 2022). Conversely, both pre-frail and frail individuals are at increased risk for depression (1.86 and 2.46 odds, respectively) (Marconcin *et al.*, 2022) and within-person increases in frailty are strongly associated with concomitant worsening depression (Mayerl *et al.*, 2020). However, despite clear epidemiological data supporting reciprocal relationships, the underlying neurobiological mechanisms underlying these relationships are

Correspondence: Warren D. Taylor, MD, MHSc, Vanderbilt University Medical Center, 1601 23rd Avenue South, Nashville, TN 37212, USA, warren.d.taylor@vumc.org, Telephone: (615) 322-1073, Fax: (615) 875-0686.

Description of Author's Role: Dr. Taylor is responsible for the entirety of the manuscript.

Conflict of Interest: None

unclear. It is similarly unclear what interactive effects frailty and depression have on the brain.

The pilot study reported by Shuster and colleagues in *International Psychogeriatrics* (Shuster *et al.*, 2023) begins to address these questions. This study examines structural and microstructural brain differences between older, never-depressed healthy individuals and individuals with comorbid LLD and frailty (defined as either pre-frail or frail). Intriguingly, the authors found group differences only in the white matter microstructure obtained from diffusion tensor imaging (DTI), specifically white matter mean diffusivity (MD). The depressed and frail group exhibited increased MD extending over several white matter tracts involved in inter-hemispheric communication, emotional and cognitive processing. They did not observe group differences in regional subcortical volumes, cortical thickness, or other DTI measures such as fractional anisotropy (FA).

The ultimate significance of this report depends on how we interpret this specific finding and how it guides this area of research. The authors interpret the difference in MD as potentially representing longer-term effects of cytotoxic edema, occurring within the white matter's glial cells and potentially secondary to neuroinflammation. This is a reasonable hypothesis, as MD is sensitive to cellular swelling that restricts diffusion (Schlaug *et al.*, 1997) and increases can occur chronically in context of inflammation or following hypoxia. It is worth noting that, despite the clinical neuroscience research community having substantial experience using MRI-based diffusion imaging, interpretation of DTI results can be challenging. As most cerebral white matter voxels contain multiple fiber groups with varying trajectories, there are substantial limits about the ability for many DTI measures, such as FA, to support definitive conclusions about the underlying white matter microstructure (Figley *et al.*, 2021). However, as MD allows for equal weight across all three axes of the diffusion tensor, MD may be more robust to crossing fibers and be a more reliable marker of how tissues are constraining water diffusion within each voxel (Figley *et al.*, 2021). The increased MD values observed in the identified regions by Shuster and colleagues suggests that, when compared with never-depressed participants, individuals with LLD and frailty exhibit loss of white matter structure in those regions.

Several possible mechanisms could both explain the observed neuroimaging findings and contribute to the bidirectional relationship between depression and frailty. This inflammation hypothesis proposed by Shuster and colleagues is reasonable as pro-inflammatory markers are associated with both LLD and frailty, as well as DTI measures of subcortical white matter integrity (Aronica *et al.*, 2022). However, there are alternative hypotheses. For example, higher vascular burden is associated with LLD, frailty, and white matter pathology (Stewart, 2019; Taylor *et al.*, 2013). Similarly, LLD can promote sedentary behavior and isolation, or be a result of chronic pain or physical disabilities. Thus, depression may contribute to muscle atrophy, deconditioning, and frailty (Brown *et al.*, 2022; Taylor *et al.*, 2022). Notably, the contributing factors considered in these alternative hypotheses are themselves associated with increased inflammation, further supporting potential common shared pathways for the bidirectional relationship between depression and frailty.

Geriatric syndromes and accelerated aging processes such as LLD and frailty do not occur in isolation. It is important to consider not only the interrelationship between depression and frailty, but also how these syndromes are related to or may influence other negative aging outcomes. Previous work published in *International Psychogeriatrics* demonstrates that depression not only increases the risk of developing frailty (Chang *et al.*, 2022), but comorbid depression and frailty also independently and interactively increase mortality risk, particularly in the pre-frail population (Ruiz-Grao *et al.*, 2021). Other studies published in *International Psychogeriatrics* additionally demonstrate that frailty increases the risk for developing cognitive decline and dementia (Wallace *et al.*, 2021), a relationship that may be mediated by poor sleep quality (Kaur *et al.*, 2019).

Cumulatively, the broader literature supports a bidirectional scientific model wherein medical illnesses common in aging, such as hypertension, diabetes, and musculoskeletal pain syndromes have deleterious effects that are at least partially mediated by pro-inflammatory processes. These processes contribute to physical frailty and disability, also increasing the allostatic load in the brain resulting in regional atrophy, loss of white matter microstructure, and increased neuropathology that may be characterized as accelerated aging (Andreescu *et al.*, 2019; Christman *et al.*, 2020). These changes then increase vulnerability for developing depression and cognitive impairment. Such neuropathology may in turn hasten physical decline and worsen frailty. This may be mediated by discrete cognitive deficits common in LLD, such as difficulty with initiation of activities, loss of interest, apathy and motivational disturbances, and decreased willingness to expend effort (Taylor *et al.*, 2022). In context of medical infirmity, this could hasten sarcopenia, deconditioning, and frailty. It may also contribute to increased mortality.

While this *International Psychogeriatrics* report (Shuster *et al.*, 2023) advances our understanding of this model, its cross-sectional nature limits our ability to make causal inferences. Aging is a dynamic process and examining within-subject trajectories of change is an informative, powerful approach. Other limitations that should be considered when interpreting these data, include the smaller sample size that, as noted by the authors, reduces statistical power and increases risk for type II errors. Additionally, frailty was defined using a clinical assessment questionnaire, and future work may benefit from objective, direct measures of function, such as grip strength or gait speed. Finally, while the report characterizes neuroimaging findings in a depressed-frail phenotype, the study did not include non-frail depressed individuals or frail but never-depressed individuals. Thus independent or overlapping contributions of depression and frailty on the neuroimaging findings cannot be disentangled.

Limitations aside, this pilot study from Shuster and colleagues provides a solid direction for future work in this clinically relevant area. It will be critical to disentangle both common and unique mechanistic pathways underlying the reciprocal relationship between depression and frailty. This should be examined broadly, including neuroimaging measures but also biological measures of immune system function and inflammation, measures of medical morbidity and vascular function, and potentially other established markers of accelerated aging, including telomere length. It also should include environmental assessments and measures of physical function, as well as measures of lifestyle factors

including physical activity. As noted in their report, future work would benefit from larger samples and longitudinal designs, as well as a wider range of participants, including non-frail individuals with LLD, or frail but never-depressed participants. Ultimately this work should provide mechanistic targets suitable for intervention, which could include anti-inflammatory approaches or movement-based interventions designed to slow or reduce frailty and improve physical condition.

Funding Source:

Dr. Taylor is supported by NIMH grants R01 MH123662 and R01 MH121620

REFERENCES

Andreescu C, et al. (2019). Disruption of Neural Homeostasis as a Model of Relapse and Recurrence in Late-Life Depression. American Journal of Geriatric Psychiatry, 27, 1316–1330.

Aronica R, Enrico P, Squarcina L, Brambilla P and Delvecchio G (2022). Association between Diffusion Tensor Imaging, inflammation and immunological alterations in unipolar and bipolar depression: A review. Neuroscience and Biobehavioral Reviews, 143, 104922. [PubMed: 36272579]

Brown PJ, et al. (2022). Frailty and Depression in Late Life: A High-Risk Comorbidity With Distinctive Clinical Presentation and Poor Antidepressant Response. Journals of Gerontology. Series A: Biological Sciences and Medical Sciences, 77, 1055–1062. [PubMed: 34758065]

Chang CC, et al. (2022). Assessment of incident frailty hazard associated with depressive symptoms in a Taiwanese longitudinal study. International Psychogeriatrics, 34, 61–70. [PubMed: 34275507]

Christman S, et al. (2020). Accelerated brain aging predicts impaired cognitive performance and greater disability in geriatric but not midlife adult depression. Translational Psychiatry, 10, 317. [PubMed: 32948749]

Figley CR, Uddin MN, Wong K, Kornelsen J, Puig J and Figley TD (2021). Potential Pitfalls of Using Fractional Anisotropy, Axial Diffusivity, and Radial Diffusivity as Biomarkers of Cerebral White Matter Microstructure. Frontiers in Neuroscience, 15, 799576. [PubMed: 35095400]

Fried LP, et al. (2001). Frailty in older adults: evidence for a phenotype. Journals of Gerontology. Series A: Biological Sciences and Medical Sciences, 56, M146–156. [PubMed: 11253156]

Kaur S, et al. (2019). Sleep quality mediates the relationship between frailty and cognitive dysfunction in non-demented middle aged to older adults. International Psychogeriatrics, 31, 779–788. [PubMed: 31006402]

Lever-van Milligen BA, Lamers F, Smit JH and Penninx BW (2017). Six-year trajectory of objective physical function in persons with depressive and anxiety disorders. Depress Anxiety, 34, 188–197. [PubMed: 27701790]

Marconcin P, et al. (2022). Prevalence of Frailty and Its Association with Depressive Symptoms among European Older Adults from 17 Countries: A 5-Year Longitudinal Study. International Journal of Environmental Research and Public Health, 19.

Mayerl H, Stolz E and Freidl W (2020). Frailty and depression: Reciprocal influences or common causes? Soc Sci Med, 263, 113273. [PubMed: 32810695]

Ruiz-Grao MC, Sanchez-Jurado PM, Molina-Alarcon M, Hernandez-Martinez A, Avendano Cespedes A and Abizanda P (2021). Frailty, depression risk, and 10-year mortality in older adults: the FRADEA study. International Psychogeriatrics, 33, 803–812. [PubMed: 33077009]

Rutherford BR, Taylor WD, Brown PJ, Sneed JR and Roose SP (2017). Biological Aging and the Future of Geriatric Psychiatry. Journals of Gerontology. Series A: Biological Sciences and Medical Sciences, 72, 343–352. [PubMed: 27994004]

Schlaug G, Siewert B, Benfield A, Edelman RR and Warach S (1997). Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke. Neurology, 49, 113–119. [PubMed: 9222178]

Shuster E, et al. (2023). Neuroimaging features of depression-frail phenotype in older adults: a pilot study. Int Psychogeriatrics.

Soysal P, et al. (2017). Relationship between depression and frailty in older adults: A systematic review and meta-analysis. Ageing Res Rev, 36, 78–87. [PubMed: 28366616]

Stewart R (2019). Cardiovascular Disease and Frailty: What Are the Mechanistic Links? Clinical Chemistry, 65, 80–86. [PubMed: 30504259]

Taylor WD, Aizenstein HJ and Alexopoulos GS (2013). The vascular depression hypothesis: mechanisms linking vascular disease with depression. Molecular Psychiatry, 18, 963–974. [PubMed: 23439482]

Taylor WD, et al. (2022). Influences of dopaminergic system dysfunction on late-life depression. Molecular Psychiatry, 27, 180–191. [PubMed: 34404915]

Wallace L, Hunter S, Theou O, Fleming J, Rockwood K and Brayne C (2021). Frailty and neuropathology in relation to dementia status: the Cambridge City over-75s Cohort study. International Psychogeriatrics, 33, 1035–1043. [PubMed: 33586645]