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Editorial

Decoding the Cerebellum's Contribution to Aging and Cognitive Declines

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Recently, an international consensus paper compellingly argues for the critical need to understand how both normal and pathological aging impacts the structure and function of the cerebellum.[1] With rising life expectancy and a growing aging population, clarifying the effects of aging on this key brain region is imperative. The cerebellum is increasingly recognized for its broad involvement in motor control, cognition, emotion regulation, and other domains that commonly decline with age. As such, there is major momentum in the field to fully characterize cerebellar changes across the lifespan and their consequences.[2] A prevalent theme throughout is that substantial structural and functional alterations occur in the cerebellum with normal aging that manifest through behavioral changes.[3] Neuroimaging reveals overall reductions in cerebellar volume, with certain posterior areas more vulnerable.[4] Connectivity between the cerebellum and cerebral cortex also declines. The heterogeneous pattern of cerebellar atrophy likely contributes to the typical age-related motor and cognitive impairments that emerge. An ongoing debate examined is whether these changes are detrimental or compensatory for maintaining performance into old age.[5]

Consensus is reached that the long-held view of the cerebellum being unaffected in Alzheimer's disease is no longer tenable.[6] Robust evidence now demonstrates that cerebellar gray matter loss and beta-amyloid deposition occur, especially in posterior regions, and this contributes uniquely to cognitive impairment apart from hippocampal and cortical contributions.[7] Intriguing questions are raised about how early-life experiences might influence susceptibility to Alzheimer's disease pathology in the cerebellum later in adulthood. Additional work to relate cerebellar dysfunction to the heterogeneity in Alzheimer's disease phenotypes and timing of onset will be important. For motor function, the cerebellum is recognized as critical for predictive timing. Despite overall cerebellar volume loss with aging, increased posterior cerebellar activation on functional imaging in older adults implies neural scaffolding helps preserve task performance.[3] Deterioration of networks underlying processing speed could relate to slowed cognitive performance with age. Intriguingly, musicians who practice intensively across their life show preserved cerebellar structure and function compared to non-musicians, suggesting musical training confers advantages.[8] Interventions to stimulate compensatory scaffolding or target vulnerable areas could aid in maintaining function.

Current theories explaining age-related cognitive changes focus heavily on cortical regions like the prefrontal cortex, while overlooking the role of the cerebellum. However, emerging research shows that the cerebellum displays significant structural, functional, and connective declines in aging. In the aging process, cerebellum acts as critical neural scaffolding that supports and buffers cortical functioning. Through internal model processing, the cerebellum enables automatic behaviors and thoughts, freeing up frontal resources.[9] Cerebellar deficits in aging reduce this compensatory capacity, requiring cortex to work harder to maintain performance. This manifests as overactivation of cortical regions, at the cost of lower efficiency and processing speed. Thus, loss of cerebellar integrity in aging may drive key effects like increased bilateral recruitment. Hence, it is critically important to incorporate the cerebellum to comprehensively understand cognitive aging - it plays a major role in compensation that has been overlooked. Declining cerebellar functioning fundamentally contributes to slower processing and altered brain activation patterns via disrupted cerebellar-cortical interactions.[10] Cerebellum has been reported to involve in the pathophysiology across different types of dementia. It notes that historically the cerebellum has been overlooked, but patterns of atrophy and connectivity changes suggest it contributes to cognitive symptoms in diseases like Alzheimer's and frontotemporal dementia. There seem to be some disease-specific atrophy patterns, with overlap in crus I/II but more anterior lobe involvement in frontotemporal dementia and motor diseases. Atrophy correlates with cognitive performance in some studies. Intriguingly, cerebellar differences emerge in mild cognitive impairment or even presymptomatic mutation carriers, before diagnoses. This suggests a possible compensatory role early on. Thus, the cerebellum may not just passively undergo downstream changes, but actively modulate subcortical-cortical circuits relevant to dementia progression.[11] Cerebellar measures could aid differential diagnosis and prognosis of neurodegenerative conditions if better incorporated into clinical practice. Overall, previous assumptions about cerebellar invulnerability to dementia are challenged, instead, cerebellum is an important player in neurocognitive disorders.

The cerebellum's proposed role in spatial navigation, depression, and epigenetic changes altering gene expression and coordination are also probed.[12] Converging neuroimaging evidence reveals associations between smaller cerebellar gray matter volumes and major depressive disorder. However, how cerebellar white matter hyperintensities might relate to late-life depression requires further human studies.[13] Animal model and neuropathological approaches will help elucidate mechanisms. A few key priorities for the field deserve to be addressed, including actively pursuing cerebellar biomarker development, examining sex differences in cerebellar aging trajectories, delineating the timeline of cerebellar senescence across the lifespan, and incorporating cerebello-thalamo-cortical connectivity into conceptual models. Incorporating the cerebellum will undoubtedly be essential for developing more accurate, multimodal models of both healthy brain aging and pathological conditions like Alzheimer's disease. Particularly, physio-cognitive decline syndrome, a progressive condition with concomitant impairment of mobility and cognition, has been shown to increase the risk of disability, dementia and mortality and the neuroimaging studies confirmed the association with gray matter atrophy in cerebellum, thalamus, hippocampus and amygdala.[14] Utilizing the brain age platform, which is a composite measure that aggregates various neuroimaging features to ascertain biological age, it has been observed that individuals with PCDS are three years older than their robust counterparts in the brain age. Furthermore, mobility impairment has been identified as the primary factor contributing to this age discrepancy, underscoring the significant role of the cerebellum in advanced brain aging.[15] Importantly, clinical trials have demonstrated the reversibility of physio-cognitive decline syndrome that successfully promote healthy aging through multidomain intervention incorporated with chronic condition management.[16-18] The recent study using data of 20 years identified four distinct subtypes of intrinsic capacity decline in older adults and found that each subtype was associated with different age-related outcomes. In this data-driven analysis physio-cognitive decline plus depressive mood has been identified as a specific entity that increased risk for falls and functional limitations.[19]

A previous study found that lower maximum gait speed in older individuals was significantly associated with an increased risk of dementia. This association is likely due to reduced gray matter volume in the hippocampus, insula and cerebellum, and an increase in white matter hyperintensities.[20] Besides, another study found a positive correlation between hemoglobin concentration and gray matter volume in certain brain regions, including the hippocampus and cerebellum, among middle-aged and older adults. This suggests that monitoring hemoglobin levels could be important for preventing neurodegeneration in this population.[21]

Overall, much work remains to unravel how aging impacts cerebellar reserve and compensation. Clinical trials directly targeting the cerebellum could help maintain function longer into old age. Non-invasive stimulation approaches to enhance plasticity represent another promising direction, provided issues with optimizing protocols for the aging brain are addressed through modeling studies. The consensus paper makes a compelling case that the field urgently needs

to fully incorporate the cerebellum to significantly advance comprehension of brain aging.[1] It represents an invaluable reference for ongoing efforts to maximize healthy lifespan by preserving cognitive and motor function into older age. Extending focus beyond cortical structures to include the cerebellum will be vital for generating more accurate, multimodal models of healthy brain aging and neurodegenerative conditions. By providing an authoritative overview of this rapidly evolving field, the recent consensus paper makes a persuasive argument that incorporating the cerebellum will be key for developing interventions to maintain function and elucidating the complex biological phenomenon of cerebellar aging. Significant work remains, but a pivotal step toward the goal of maximizing cognitive and motor function across the lifespan has been initiated.

REFERENCES

1. Arleo A, Bareš M, Bernard JA, et al. Consensus paper: Cerebellum and ageing. *Cerebellum.* Published online July 10, 2023. doi:10.1007/s12311-023-01577-7.
2. Chen LK. Cognitive impairments and physical frailty: Two sides of the same coin? *Aging Med Healthc.* 2021;**12**(1):1-3. doi:10.33879/amh.121.2021.03018.
3. Filip P, Gallea C, Lehéricy S, Lungu O, Bareš M. Neural scaffolding as the foundation for stable performance of aging cerebellum. *Cerebellum.* 2019;**18**(3):500-10. doi:10.1007/s12311-019-01015-7.
4. Han S, An Y, Carass A, Prince JL, Resnick SM. Longitudinal analysis of regional cerebellum volumes during normal aging. *Neuroimage.* 2020;**220**:117062. doi:10.1016/j.neuroimage.2020.117062.
5. Beuriat PA, Cristofori I, Gordon B, Grafman J. The shifting role of the cerebellum in executive, emotional and social processing across the lifespan. *Behav Brain Funct.* 2022;**18**(1):6. doi:10.1186/s12993-022-00193-5.
6. Tromp D, Dufour A, Lithfous S, Pebayle T, Després O. Episodic memory in normal aging and Alzheimer disease: Insights from imaging and behavioral studies. *Ageing Res Rev.* 2015;**24**(Pt B):232-62. doi:10.1016/j.arr.2015.08.006.
7. Trejo-Lopez JA, Yachnis AT, Prokop S. Neuropathology of Alzheimer's Disease. *Neurotherapeutics.* 2022;**19**(1):173-85. doi:10.1007/s13311-021-01146-y.
8. Yamashita M, Ohsawa C, Suzuki M, et al. Neural advantages of older musicians involve the cerebellum: Implications for healthy aging through lifelong musical instrument training. *Front Hum Neurosci.* 2022;**15**:784026. doi:10.3389/fnhum.2021.784026.
9. Shen C, Chen QS, Zuo CT, Liu FT, Wang J. The frontal and cerebellar metabolism related to cognitive dysfunction in multiple system atrophy. *Front Aging Neurosci.* 2022;**14**:788166. doi:10.3389/fnagi.2022.788166.
10. Bernard JA. Don't forget the little brain: A framework for incorporating the cerebellum into the understanding of cognitive aging. *Neurosci Biobehav Rev.* 2022;**137**:104639. doi:10.1016/j.neubiorev.2022.104639.
11. Devita M, Alberti F, Fagnani M, et al. Novel insights into the relationship between cerebellum and dementia: A narrative review as a toolkit for clinicians. *Ageing Res Rev.* 2021;**70**:101389. doi:10.1016/j.arr.2021.101389.
12. Horvath S, Mah V, Lu AT, et al. The cerebellum ages slowly according to the epigenetic clock. *Aging (Albany NY).* 2015;**7**(5):294-306. doi:10.18632/aging.100742.
13. Lin C, Huang CM, Karim HT, et al. Greater white matter hyperintensities and the association with executive function in suicide attempters with late-life depression. *Neurobiol Aging.* 2021;**103**:60-7. doi:10.1016/j.neurobiolaging.2020.12.016.
14. Liu LK, Chou KH, Hsu CH, et al. Cerebellar-limbic neurocircuit is the novel biosignature of physio-cognitive decline syndrome. *Aging (Albany NY).* 2020;**12**(24):25319-25336. doi:10.18632/aging.104135.
15. Kuo CY, Lee PL, Peng LN, et al. Advanced brain age in community-dwelling population with combined physical and cognitive impairments. *Neurobiol Aging.* 2023;**130**:114-23. doi:10.1016/j.neurobiolaging.2023.06.017.
16. Lee WJ, Peng LN, Lin MH, Lin CH, Chen LK. Clinical efficacy of multidomain interventions among multimorbid older people stratified by the status of physio-cognitive declines: A secondary analysis from the randomized controlled trial for healthy aging. *J Nutr Health Aging.* 2022;**26**(10):909-17. doi:10.1007/s12603-022-1843-3.
17. Liang CK, Lee WJ, Hwang AC, et al. Efficacy of multidomain intervention against physio-cognitive decline syndrome: A cluster-randomized trial. *Arch Gerontol Geriatr.* 2021;**95**:104392. doi:10.1016/j.archger.2021.104392.
18. Ozcan Gulsen E, Gulsen C, Soke F, Sayan M, Tunca Yilmaz O. The effect of dual-task on manual dexterity and functional mobility in community-dwelling older adults. *Aging Med Healthc.* 2022;**13**(4):149-54. doi:10.33879/amh.134.2021.06036.
19. Meng LC, Chuang HM, Lu WH, et al. Multi-trajectories of intrinsic capacity decline and their impact on age-related outcomes: A 20-year national longitudinal cohort study. *Aging Dis.* Published online November 21, 2023. doi:10.14336/AD.2023.1115-1.
20. Tajimi T, Furuta Y, Hirabayashi N, et al. Association of gait speed with regional brain volumes and risk of dementia in older Japanese: The Hisayama study. *Arch Gerontol Geriatr.* 2023;**106**:104883. doi:10.1016/j.archger.2022.104883.
21. Chen WL, Nishita Y, Nakamura A, et al. Hemoglobin concentration is associated with the hippocampal volume in community-dwelling adults. *Arch Gerontol Geriatr.* 2022;**101**:104668.