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LETTER

The role of epigenetics in cognitive aging: mechanisms, interventions, and future directions

Pranab Dev Sharma[a,*], Abdullah Al Noman[b], Himanshu Sharma[c]

[a] *Biotechnology program, Department of Mathematics and Natural Science, BRAC University, Dhaka, Bangladesh.*
[b] *School of Pharmacy, BRAC University, Dhaka, Bangladesh.*
[c] *Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad (UP)-244001, India.*

Abstract

The decline of one's cognitive skills owing to aging along with conditions like Parkinson's and Alzheimer's disease is partly caused by changes in the expression of relevant genes, which do not require the sequence of DNA to be altered. This study looks at the processes of DNA methylation, histone alterations, and non-coding RNAs in cognitive decline, concentrating on their effects on synaptic plasticity, neuroinflammation, and survivability of neurons. New treatment approaches targeting these epigenetic mechanisms, for example, HDAC and DNMT inhibitors, appear to be helpful in reducing cognitive deficits. Changes in one's lifestyle, for example, diet and physical activity, could have an effect on brain functioning and may alter the patterns of gene expression. Having said that, the potential of epigenomic therapeutics is enormous, but there are still limitations in specificity and practical implementation. There is a strong potential in using a personalized approach based on multi-omics and novel artificial intelligence technology to optimize therapeutic approaches to age-related cognitive impairment. Further research needs to be conducted to ensure the safety, accuracy, and effectiveness of the treatment aimed at improving the brain health of the elderly.

Keywords: Cognitive aging, epigenetics, gene expression, synaptic plasticity, neuroinflammation, AI-driven therapeutics

Cognitive decline in aging is a multifaceted process influenced by genetic, environmental, and epigenetic factors. Unlike genetic mutations, epigenetic modifications regulate gene activity dynamically and reversibly, making them attractive targets for therapeutic intervention [1]. This letter uniquely integrates evidence across the spectrum of epigenetic modifications and their implications for cognitive aging. Additionally, we provide useful insights into how artificial intelligence is transforming this field by enabling more precise and personalized approaches. Our analysis indicates that combination approaches targeting multiple epigenetic pathways simultaneously may yield superior outcomes compared to single-target interventions.

* Corresponding author: Pranab Dev Sharma
Mailing address: Biotechnology program, Department of Mathematics and Natural Science, BRAC University, Dhaka, Bangladesh.
Email: pranab.dev.sharma@g.bracu.ac.bd
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Epigenetic changes, such as DNA methylation, histone modifications, and non-coding RNAs, regulate gene activity without altering the DNA sequence. DNA methylation is a crucial epigenetic modification that regulates gene expression by adding methyl groups to cytosine residues, often leading to gene silencing. Studies have demonstrated that hypermethylation of genes involved in synaptic plasticity and memory, such as brain-derived neurotrophic factor (BDNF) and reelin, correlates with cognitive impairment in aging individuals [2]. Furthermore, Histones undergo various modifications, including acetylation (addition of acetyl groups that loosens DNA packaging, enabling gene expression), methylation, and phosphorylation, which influence chromatin structure and gene accessibility. Age-associated reductions in histone acetylation, mediated by increased histone deacetylase (HDAC) activity, are linked to cognitive decline [3]. HDAC inhibitors (HDACi), such as vorinostat and sodium butyrate, have shown promise in preclinical studies for enhancing memory function by restoring histone acetylation levels [4]. Recent studies have introduced selective HDAC2 inhibitors, like JRM-28, that show promise in improving memory and synaptic plasticity while reducing side effects, paving the way for new treatments for neurodegen-

erative diseases [5]. Moreover, Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), regulate post-transcriptional gene expression. Specific miRNAs are involved in modulating neuroinflammation and synaptic plasticity, indicating their potential as therapeutic targets for cognitive aging. For instance, miR-132 and miR-124 have emerged as critical regulators of synaptic function, with age-related decreases correlating with cognitive deficits in human studies [6, 7].

Lifestyle interventions, including regular exercise and polyphenol-rich diets, regulate epigenetic mechanisms, improving neural resilience. For instance, moderate-intensity exercise increases BDNF via histone acetylation [8]. A meta-analysis consistently showed cognitive enhancement [9]. Polyphenol-rich diets, such as those including green tea and curcumin, modulate DNA methylation patterns, enhance neural resilience, and support synaptic plasticity while reducing neuroinflammation [10]. Table 1 summarizes interventions below. The mechanisms of synaptic plasticity, neuroinflammation, and neuronal survival rate are present in Table 2.

Recent advancements in AI-driven approaches are revolutionizing epigenetic research in cognitive aging. Deep learning models, such as in Deep-PGD, identify methylation patterns in the prefrontal cortex predictive of HDAC inhibitor responsiveness [16]. Neural networks integrate multi-omics data (epigenomics, transcriptomics, and proteomics) for personalized cognitive therapies. Machine learning models in distinguishing aging-related epigenetic shifts from Alzheimer's alterations [17]. These innovations promise earlier intervention and enhanced therapeutic precision.

Epigenetic mechanisms play a crucial role in cognitive aging, offering novel targets for therapeutic intervention. Unlike previous reviews that examined isolated mechanisms, our analysis integrates findings across multiple epigenetic pathways and highlights their collective impact on cognitive function. While lifestyle modifications and pharmacological approaches show promise, further research is needed to improve specificity and clinical applicability. AI-driven epigenetics is emerging as a powerful tool for optimizing personalized treatments, potentially revolutionizing cognitive health interventions in aging populations. Our synthesis suggests that combination approaches targeting multiple epigenetic pathways simultaneously, guided by AI-based precision medicine, represent the most promising future direction in this field.

Table 1. Specific empirical evidence for each intervention.

Intervention	Mechanism	Empirical evidence	Reference
HDAC inhibitors	Histone acetylation, enhancing gene expression	Vorinostat improved memory in preclinical models	[11]
DNMT inhibitors	DNA methylation reduction, reactivating genes	5-azacytidine restored neuroprotective gene expression	[12]
Polyphenol-rich diet	BDNF promoter methylation modulation	Clinical trial showed reduced BDNF methylation	[10]
Regular exercise	Increased BDNF levels via epigenetic regulation	Meta-analysis demonstrated cognitive benefits	[9]

Table 2. Key epigenetic mechanisms affecting cognitive function.

Mechanism	Biological impact	Implications	Reference
Synaptic plasticity	Strengthening or weaking of synapses	Essential foe learning and memory	[13]
Neuroinflammation	Activation of immune cells causing neural damage	Connected with cognitive decline in neurodegenerative diseases	[14]
Neuronal survival rate	Rate of neuron viability under stress	Influences neuroplasticity and recovery	[15]

Declarations

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References

1. Gonzales MM, Garbarino VR, Pollet E, Palavicini JP, Kellogg DL, Jr., Kraig E, *et al*. Biological aging processes underlying cognitive decline and neurodegenerative disease. *J Clin Invest*, 2022, 132(10): 158453. [Crossref]
2. Ju LS, Jia M, Sun J, Sun XR, Zhang H, Ji MH, *et al*. Hypermethylation of hippocampal synaptic plasticity-related genes is involved in neonatal sevoflurane exposure-induced cognitive impairments in rats. *Neurotox Res*, 2016, 29(2): 243-255. [Crossref]
3. Park J, Lee K, Kim K, & Yi SJ. The role of histone modifications: from neurodevelopment to neurodiseases. *Signal Transduct Target Ther*, 2022, 7(1): 217-227. [Crossref]
4. Vecsey CG, Hawk JD, Lattal KM, Stein JM, Fabian SA, Attner MA, *et al*. Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB:CBP-dependent transcriptional activation. *J Neurosci*, 2007, 27(23):

6128-6140. [Crossref]
5. Rahman AFMT, Bulbule S, Belayet JB, Benko A, Gottschalk CG, Frick DN, *et al*. JRM-28, a novel HDAC2 inhibitor, upregulates plasticity-associated proteins in hippocampal neurons and enhances morphological plasticity via activation of creb: implications for Alzheimer's disease. *Cells*, 2024, 13(23): 1964-1974.
6. Sun Y, Luo ZM, Guo XM, Su DF, & Liu X. An updated role of microRNA-124 in central nervous system disorders: a review. *Front Cell Neurosci*, 2015, 9: 193-203. [Crossref]
7. Hansen KF, Karelina K, Sakamoto K, Wayman GA, Impey S, & Obrietan K. miRNA-132: a dynamic regulator of cognitive capacity. *Brain Struct Funct*, 2013, 218(3): 817-831. [Crossref]
8. Kukla-Bartoszek M, & Głombik K. Train and reprogram your brain: effects of physical exercise at different stages of life on brain functions saved in epigenetic modifications. *Int J Mol Sci*, 2024, 25(22): 12043.
9. Hoang LN, Lee H, & Lee SJ. Improving cognitive impairment through chronic consumption of natural compounds/extracts: a systematic review and meta-analysis of randomized controlled trials. *Front Aging Neurosci*, 2024, 16: 1531278. [Crossref]
10. Yaskolka Meir A, Keller M, Hoffmann A, Rinott E, Tsaban G, Kaplan A, *et al*. The effect of polyphenols on DNA methylation-assessed biological age attenuation: the DIRECT PLUS randomized controlled trial. *BMC Med*, 2023, 21(1): 364-374. [Crossref]
11. Gao Y, Aljazi MB, Wu Y, & He J. Vorinostat, a histone deacetylase inhibitor, ameliorates the sociability and cognitive memory in an Ash1L-deletion-induced ASD/ID mouse model. *Neurosci Lett*, 2021, 764: 136241. [Crossref]
12. Pan Y, Daito T, Sasaki Y, Chung YH, Xing X, Pondugula S, *et al*. Inhibition of DNA methyltransferases blocks mutant huntingtin-induced neurotoxicity. *Sci Rep*, 2016, 6: 31022. [Crossref]
13. Oyovwi MO, Ogenma UT, & Onyenweny A. Exploring the impact of exercise-induced BDNF on neuroplasticity in neurodegenerative and neuropsychiatric conditions. *Mol Biol Rep*, 2025, 52(1): 140-150. [Crossref]
14. Grabska-Kobyłecka I, Szpakowski P, Król A, Książek-Winiarek D, Kobyłecki A, Głąbiński A, *et al*. Polyphenols and their impact on the prevention of neurodegenerative diseases and development. *Nutrients*, 2023, 15(15): 3454-3465. [Crossref]
15. Romero Garavito A, Díaz Martínez V, Juárez Cortés E, Negrete Díaz JV, & Montilla Rodríguez LM. Impact of physical exercise on the regulation of brain-derived neurotrophic factor in people with neurodegenerative diseases. *Front Neurol*, 2024, 15: 1505879. [Crossref]
16. Teragawa S, Wang L, & Liu Y. DeepPGD: a deep learning model for DNA methylation prediction using temporal convolution, BiLSTM, and attention mechanism. *Int J Mol Sci*, 2024, 25(15): 8146-8156. [Crossref]
17. Tanaka M. From serendipity to precision: integrating AI, multi-omics, and human-specific models for personalized neuropsychiatric care. *Biomedicines*, 2025, 13(1): 167-178. [Crossref]

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