IJHSR
ijhighschoolresearch.org
REVIEW ARTICLE

# DNA Methylation's Role in the Working Memory Deficits of Attention-deficit/hyperactivity disorder (ADHD)

Hibah Faisal

SICAS DHA, Phase 2 DHA, Lahore, Punjab, 54792, Pakistan; hibahfaisal17@gmail.com

ABSTRACT: The addition of a mere chemical group to our DNA components can change the way our brains think and operate. In recent years, in an attempt to unlock more truths behind the complicated Attention-deficit /hyperactivity disorder (ADHD), research has expanded to the epigenetic factors causing it. These are factors influenced by the environment that affect gene expression and silencing. This paper focuses on the specific influence of DNA methylation (DNAm) in causing the working memory deficits by which ADHD is often characterized. It attempts to establish a direct correlation between the two and provide a holistic view of potential pathways of DNAm that affect working memory. This information can be crucial in understanding the importance of these sites as biomarkers and their utility in regulating ADHD.

KEYWORDS: Biomedical Health Sciences, Molecular Biology of Disease, Attention-deficit /hyperactivity disorder, Epigenetics, DNA Methylation, Working Memory.

## Introduction

The question of how our environment affects us has been vastly explored by researchers. However, the link between our environment, genes, memory, and Attention-deficit /hyperactivity disorder (ADHD) remains complicated and vague. How does a biological process link an environmental factor to a psychological one? Can a single chemical group explain this?

ADHD is one of many common neurodevelopmental disorders prevalent in children, with 11.3% of children aged 12-17 being diagnosed in the United States as of 2022.[1] It is usually characterized by symptoms such as inattention, hyperactivity, and impulsivity - with one evident trait being working memory deficits.[2] While there are multiple models of working memory, Alan Baddeley, on a basic level, defines working memory as the ability to hold and manipulate information over short periods of time.[3] It is important for tasks such as problem-solving, decision-making, and maintaining focus - overall affecting our language, reasoning, and learning. Deficits in working memory have been linked to language and learning impairments, hyperactivity, and even diseases other than ADHD such as schizophrenia.[4] Before we discuss these, it is important to understand how working memory functions and what these 'deficits' look like. Building on Baddeley's model,[3] research into working memory has streamlined the functions of its main components which can be seen in Figure 1: the central executive which coordinates cognitive processes, consisting of the episodic buffer, which integrates and links information to long-term memory; the phonological loop, which handles auditory information; and the visuospatial sketchpad, responsible for visual and spatial data.

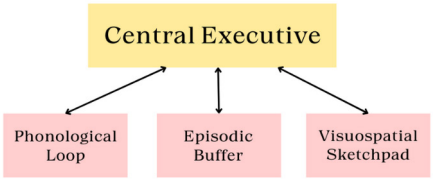


**Figure 1:** Baddeley's Working Memory Model. It breaks down working memory into three core subsystems: the phonological loop, the visuospatial sketchpad, and the episodic buffer - all coordinated by the central executive. (Created by the author).

While Figure 1 briefs us on the neurological backgrounds of working memory, the answer to the previously posed question stems from the field of epigenetics. Traditional research has identified genes associated with ADHD.[5,6] Recent research has gone into 'epigenetic' factors (factors influencing gene expression) affecting ADHD, particularly DNA Methylation (DNAm) that regulates gene expression.[7] DNAm is the addition of a methyl group to DNA that often results in the repression of gene activity.[8] It plays a crucial role in brain development by regulating gene expression in different cognitive processes. In contrast to genetic factors, epigenetic factors (like DNAm) can be influenced by the environment. This alludes to a link between genetic predisposition and environmental factors causing ADHD. However, the particular link of DNAm to evident ADHD traits such as working memory is underexplored.

Despite being a small modification, uncovering this link can have a significant impact. This connects back to ADHD diagnosis. According to a study,[9] several difficulties come with



DOI: 10.36838/v7i3.1

ADHD's behavioral diagnosis right now - that only top-tier experts can see through. The most important including its nonspecific symptoms (i.e. symptoms like inattention etc. are common childhood behaviors), its comorbidity with other disorders (such as speech impairments), and its variability across individuals (various mixtures of symptoms can be present between different people with ADHD) as well as between different stages of someone's life. Although research into biological pathways and the consequence diagnosis of ADHD is undergoing, it is not yet specific enough for clinical use.[9] That is where exploring this link between DNAm and ADHD traits becomes significant as DNAm patterns can serve as 'biomarkers' - biological molecules that indicate disease or abnormality in an individual.[9] These biomarkers can help make diagnosis more specific and accurate. Specifically exploring working memory in relation to this is significant. Studies establish working memory as a core component in causing functional outcomes in ADHD,[10] hence this specific cognitive function seems like a relevant area to focus on when trying to streamline a direct pathway in how DNAm results in the pathogenesis of ADHD.

Overall, this review aims to investigate the epigenetic mechanisms such as DNAm that cause working memory deficits in ADHD. Through synthesizing recent studies, it will aim to create a specific correlation between the two, exploring potential gene locations for DNAm in relation to working memory. To do this, it will first frame the cognitive functions affected by DNAm that are also utilized in ADHD. Then, closely examine working memory deficits in ADHD, outlining the main genetic and environmental causes present in current research. Finally, it will establish the following links between ADHD working memory deficits and DNAm: (i) DNAm affects dopamine regulation which disrupts working memory (ii) DNAm affects synaptic plasticity which impacts working memory function. Conclusively, the paper will discuss the implications of these findings for the development of biomarkers and targeted therapies for ADHD.

## Discussion

***Examining the Neurological Basis of Working Memory Deficits in ADHD:***

Understanding the association of working memory deficits with ADHD relies on two observations relevant to this paper: (i) working memory is important for certain cognitive functions - such as problem-solving, etc, and (ii) these cognitive functions are impaired in ADHD, leading to the disorder's characteristic symptom.

Referring to the first observation, our working memory affects our reasoning, comprehension, and learning. This is proven by studies showing deficits in working memory being the cause of learning disabilities and other dysfunctions.[4,10] One study links this to errors in these individuals while accessing phonological representations, a core pathway within the phonological loop, which is central to working memory function.[2] Also, capacity limits in attentional control exacerbate these issues, as individuals may struggle to prioritize or sustain focus on auditory tasks. These limitations manifest in difficulties with tasks requiring sustained focus. These can be considered manifestations of working memory deficits which will become significant when analyzing studies done on ADHD patients later on.

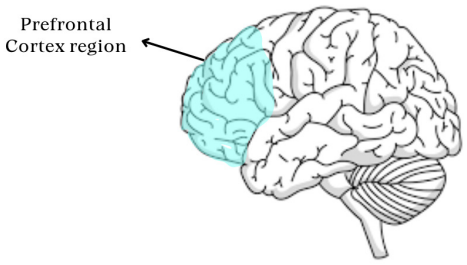


**Figure 2:** The Prefrontal Cortex Region is located at the front of the brain's frontal lobe. It is essential for high-order cognitive functions such as decision-making, attention regulation, and working memory – all involved in ADHD. (Created by the author).

Going into the neurological background, studies have shown that these functions of working memory are based in the brain's prefrontal cortex through processes such as PET Scans, analyzing subjects with prefrontal damage, and tests including working memory-related tasks and tracking brain activity. The prefrontal cortex is a region in the frontal lobe of our brains, refer to Figure 2, with a wide variety of functions - usually related to executive function.[11] This fact becomes relevant as we move onto the second observation, on these working memory impairments being present in ADHD patients. Older studies using neuroimaging techniques have demonstrated that individuals with ADHD often exhibit reduced activity in the prefrontal cortex during tasks requiring working memory. More recent studies have highlighted specific ADHD-related cognitive functions that are not fully operative due to working memory deficits. For instance, Kofler and his team[2] analyzed the response of children with and without ADHD to working memory tasks looking to test if working memory deficits resulted in organizational problems - a core symptom of ADHD. They concluded that impaired working memory processes affect children's ability to sustain attention and maintain consistent task engagement - overall causing organizational problems.

Understanding what affects the prefrontal lobe or other areas associated with working memory to cause ADHD in the first place, recent research suggests that a mix of genetic and environmental factors contribute. This is the idea that forms the foundation of this paper - epigenetic factors, specifically DNAm cause these deficits. Establishing the link between this and the known neurological basis of working memory deficits in ADHD, i.e. the prefrontal cortex, requires us to know more about DNAm in relation to the cognitive processes described above.

***DNAm and Cognitive Function: Causes of DNAm, Pathways Affected, and Link to ADHD:***

DNAm involves the addition of a methyl group to cytosine bases in the DNA, usually at regions called CpG sites. These chemical modifications can act like switches, turning specific genes on or off depending on the methylation pattern. As explained above, DNAm is an epigenetic process that responds

DOI: 10.36838/v7i3.1

to environmental factors - directly impacting gene expression related to cognitive functions. This section will explore how DNAm influences pathways involved in neurotransmitter regulation and synaptic plasticity (pathways that allow neurons to communicate with each other), particularly focusing on dopamine signaling and other neurotrophic factors.

To be able to understand how DNAm affects us, it is necessary to know what causes these chemical 'methyl' groups to change our gene expression in the first place. Studies show that during critical periods of brain development, especially prenatal periods, environmental factors such as prenatal exposure to toxins (e.g., tobacco smoke, heavy metals) or stress can lead to aberrant DNAm patterns.[12,13]

Going into detail, Moore explains the basic mechanisms for DNAm,[8] involving the addition of a methyl group to cytosine (a base in our DNA), to form 5-methylcytosine (5mC), as demonstrated in Figure 3 below. This suppression occurs because the methyl groups either physically block transcription factors - proteins that activate genes - from binding to the DNA, or they recruit proteins that condense the DNA structure, making it less accessible for transcription. Moore explains that research shows methylation and demethylation occur even in our neurons, which are non-dividing (no change in genes passed down). This suggests that methylation is about more than just regulating gene expression but also about adapting it to external stimuli, these adaptations affect synaptic plasticity and cognitive function.

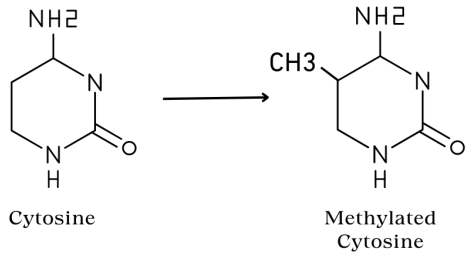


**Figure 3:** Basic DNA Methylation - the addition of a methyl group to cytosine, forming 5-methylcytosine (5mC). This modification can repress gene activity by blocking transcription factor binding or recruiting proteins that compact DNA, making it less accessible. In neurons, DNAm is important since it adapts gene expression in response to external stimuli, influencing synaptic plasticity and cognitive functions. (Created by the author).

Research has identified pathways impacted by DNAm that affect cognitive function. The two most relevant pathways to ADHD that will be discussed here are (i) dopamine regulation and (ii) neurotrophic signaling pathway.

On the first point, dopamine is a neurotransmitter that regulates and helps modulate various cognitive functions such as reward processing and focus.[14,15] Studies show that individuals with ADHD tend to have dopamine dysfunction.[16] In fact, they explain that dopamine dysregulation has been linked to the pathogenesis of ADHD. This makes sense considering the role of dopamine in modulating cognitive functions such as focus that are affected in ADHD. Genes involved in the dopamine regulation pathway, such as DAT1 (dopamine transporter) and DRD4 (dopamine receptor), have been shown to undergo DNAm changes in individuals with ADHD. According to a study done by Tonelli on DAT1,[17] DNAm changes can alter the availability of dopamine in the synaptic cleft, potentially leading to the cognitive deficits observed in ADHD. Another important factor is that dopamine has been shown to specifically be released into the prefrontal cortex where it is assumed to regulate neural circuits that affect certain cognitive functions.[15] Research has also shown that many dopamine receptors (e.g. D1) are present in the prefrontal cortex.[18]

Secondly, DNAm has been shown to impact our neurotrophic signaling pathway. It can repress the expression of Brain-Derived Neurotrophic Factor (BDNF),[19] which is a protein that plays an important role in neural plasticity.[20] Neural plasticity refers to the brain's ability to adapt to various changes throughout our lives, the part of this affected by BDNF is synaptic plasticity - which refers to the strengthening and weakening of neural connections over time.[21] Synaptic plasticity has been shown to affect the encoding and retrieval of memory - especially in the prefrontal cortex, impacting working memory specifically.[22] This shows us that these two pathways influenced by DNAm impact working memory and may relate to ADHD.

***Linking DNAm and Working Memory Deficits in ADHD:***

So far, it has been established that (i) working memory deficits are a defining feature of ADHD, affecting cognitive abilities e.g. problem-solving, decision-making, etc. (ii) DNAm is an epigenetic process that modifies gene expression, influencing cognitive functions and potentially contributing to ADHD-related deficits and, (iii) DNAm affects genes related to dopamine regulation (e.g., DAT1, DRD4), and the synaptic plasticity in the neurotrophic pathway.

People with ADHD are typically associated with dopamine imbalances due to a lack of proper dopamine regulation.[16] Before, the role of dopamine in regulating neural circuits in the prefrontal cortex, which is heavily linked to working memory function, was established. Since dopamine is so heavily interlinked with both DNAm and working memory - it seems reasonable to conclude that methylation on specific dopamine-related genes such as DAT1, can lead to imbalances in dopamine levels in the prefrontal cortex. This imbalance disrupts the pathways required for effective working memory, causing the deficits observed in ADHD.

Shang highlights that deficits might not arise only from dopamine level alterations but also from the downstream effects on synaptic plasticity.[23] Since DNAm disrupts neurotrophic pathways that play an important role in synaptic plasticity and hence working memory, it also seems reasonable to conclude that this results in the pathogenesis of the working memory deficits seen in ADHD.

## ■ Conclusion

Conclusively, this research explores the relationship between DNAm and working memory deficits in ADHD to highlight the significant role of epigenetic factors in cognitive impairments. Epigenetic factors such as DNAm can occur in pathways related to dopamine regulation and synaptic plasticity - this can be on, for example, dopamine receptor genes


DOI: 10.36838/v7i3.1

or BDNF promoter genes. Since both these genes are linked to working memory pathways and brain areas that function in working memory, i.e. the prefrontal cortex, the paper concludes that DNAm has a significant role in the working memory deficits in ADHD. Gaining understanding of how DNAm affects our brain function is important for guiding practice medicinal approaches through identifying biomarkers. These could help diagnose and develop targeted therapies for ADHD when in clinical use.[17] DNAm at specific sites in the promoter regions of neurotrophic genes, like DAT1, can indicate disruptions in neurotrophic pathways and ADHD in general. This knowledge could also inform the development of novel pharmacological treatments targeting epigenetic pathways, such as DNAm inhibitors or enhancers.

Future studies perhaps could aim to map specific DNAm patterns/regions linked to ADHD and working memory deficits, focusing on longitudinal research to observe how DNAm changes over time and influences symptom progression or response to treatment. More research into the specific lifestyle characteristics prompting harmful epigenetic changes and the duration of their effect, including their potential transgenerational impact, could help highlight modifiable risk factors alongside highlighting preventative strategies to mitigate the risk of ADHD. Beyond clinical settings, these findings could drive public health policies, potentially emphasizing early screening programs or promoting environments that minimize adverse epigenetic effects, such as reducing prenatal exposure to toxins or increasing access to mental health resources to reduce stress that can genetically impact generations.

## Acknowledgments

The author thanks her mentors, Dr. Hannah Tarder-Stoll and Monika Rybak for their guidance throughout the research project.

## References

1. Reuben, C. Attention-Deficit/Hyperactivity Disorder in Children Ages 5–17 Years: United States, 2020–2022. 2024, No. 499.
2. Kofler, M. J.; Sarver, D. E.; Harmon, S. L.; Moltisanti, A.; Aduen, P. A.; Soto, E. F.; Ferretti, N. Working Memory and Organizational Skills Problems in ADHD. *J. Child Psychol. Psychiatry* 2018, *59* (1), 57–67. https://doi.org/10.1111/jcpp.12773.
3. Baddeley, A. Working Memory. *Comptes Rendus Académie Sci. - Ser .III - Sci. Vie* 1998, *321* (2), 167–173. https://doi.org/10.1016/S0764-4469(97)89817-4.
4. Salamé, P.; Danion, J.-M.; Peretti, S.; Cuervo, C. The State of Functioning of Working Memory in Schizophrenia. *Schizophr. Res.* 1998, *30* (1), 11–29. https://doi.org/10.1016/S0920-9964(97)00107-2.
5. Li, Z.; Chang, S.; Zhang, L.; Gao, L.; Wang, J. Molecular Genetic Studies of ADHD and Its Candidate Genes: A Review. *Psychiatry Res.* 2014, *219* (1), 10–24. https://doi.org/10.1016/j.psychres.2014.05.005.
6. Dark, C.; Homman-Ludiye, J.; Bryson-Richardson, R. J. The Role of ADHD Associated Genes in Neurodevelopment. *Dev. Biol.* 2018, *438* (2), 69–83. https://doi.org/10.1016/j.ydbio.2018.03.023
7. Ibrahim, O.; Sutherland, H. G.; Haupt, L. M.; Griffiths, L. R. An Emerging Role for Epigenetic Factors in Relation to Executive Function. Brief. *Funct. Genomics* 2018, *17* (3), 170–180. https://doi.org/10.1093/bfgp/elx032.
8. Moore, L. D.; Le, T.; Fan, G. DNA Methylation and Its Basic Function. *Neuropsychopharmacology* 2013, *38* (1), 23–38. https://doi.org/10.1038/npp.2012.112.
9. Cecil, C. A. M.; Nigg, J. T. Epigenetics and ADHD: Reflections on Current Knowledge, Research Priorities and Translational Potential. *Mol. Diagn. Ther. 2022, 26* (6), 581–606. https://doi.org/10.1007/s40291-022-00609-y.
10. Kofler, M. J.; Rapport, M. D.; Bolden, J.; Sarver, D. E.; Raiker, J. S. ADHD and Working Memory: The Impact of Central Executive Deficits and Exceeding Storage/Rehearsal Capacity on Observed Inattentive Behavior. *J. Abnorm. Child Psychol.* 2010, *38* (2), 149–161. https://doi.org/10.1007/s10802-009-9357-6.
11. Chafee, M. V.; Heilbronner, S. R. Prefrontal Cortex. *Curr. Biol.* 2022, *32* (8), R346–R351. https://doi.org/10.1016/j.cub.2022.02.071.
12. Yusuf Ali, A.; Inyang, B.; Koshy, F. S.; George, K.; Poudel, P.; Chalasani, R.; Goonathilake, M. R.; Waqar, S.; George, S.; Jean-Baptiste, W.; Mohammed, L. Elements That Influence the Development of Attention Deficit Hyperactivity Disorder (ADHD) in Children. *Cureus* 2022. https://doi.org/10.7759/cureus.27835.
13. Guo, J.; Riley, K. W.; Durham, T.; Margolis, A. E.; Wang, S.; Perera, F.; Herbstman, J. B. Association Studies of Environmental Exposures, DNA Methylation and Children's Cognitive, Behavioral, and Mental Health Problems. *Front. Genet.* 2022, *13*, 871820. https://doi.org/10.3389/fgene.2022.871820.
14. Iversen, S. D.; Iversen, L. L. Dopamine: 50 Years in Perspective. *Trends Neurosci.* 2007, *30* (5), 188–193. https://doi.org/10.1016/j.tins.2007.03.002.
15. Juárez Olguín, H.; Calderón Guzmán, D.; Hernández García, E.; Barragán Mejía, G. The Role of Dopamine and Its Dysfunction as a Consequence of Oxidative Stress. *Oxid. Med. Cell. Longev.* 2016, *2016* (1), 9730467. https://doi.org/10.1155/2016/9730467.
16. Wu, J.; Xiao, H.; Sun, H.; Zou, L.-Q. Role of Dopamine Receptors in ADHD: A Systematic Meta-Analysis. Mol. *Neurobiol. 2012, 45* (3), 605–620. https://doi.org/10.1007/s12035-012-8278-5.
17. Tonelli, E.; Pascale, E.; Troianiello, M.; D'Addario, C.; Adriani, W. DAT1 Gene Methylation as an Epigenetic Biomarker in Attention Deficit Hyperactivity Disorder: A Commentary. *Front. Genet.* 2020, *11*, 444. https://doi.org/10.3389/fgene.2020.00444.
18. Seamans, J. K.; Yang, C. R. The Principal Features and Mechanisms of Dopamine Modulation in the Prefrontal Cortex. Prog. *Neurobiol.* 2004, *74* (1), 1–58. https://doi.org/10.1016/j.pneurobio.2004.05.006.
19. Yang, G.; Song, Y.; Zhou, X.; Deng, Y.; Liu, T.; Weng, G.; Yu, D.; Pan, S. DNA Methyltransferase 3, a Target of microRNA-29c, Contributes to Neuronal Proliferation by Regulating the Expression of Brain-Derived Neurotrophic Factor. *Mol. Med. Rep.* 2015, *12* (1), 1435–1442. https://doi.org/10.3892/mmr.2015.3531.
20. Bathina, S.; Das, U. N. Brain-Derived Neurotrophic Factor and Its Clinical Implications. *Arch. Med. Sci.* 2015, *6*, 1164–1178. https://doi.org/10.5114/aoms.2015.56342.
21. Stampanoni Bassi, M.; Iezzi, E.; Gilio, L.; Centonze, D.; Buttari, F. Synaptic Plasticity Shapes Brain Connectivity: Implications for Network Topology. *Int. J. Mol. Sci.* 2019, *20* (24), 6193. https://doi.org/10.3390/ijms20246193.
22. Takeuchi, T.; Duszkiewicz, A. J.; Morris, R. G. M. The Synaptic Plasticity and Memory Hypothesis: Encoding, Storage and Persistence. *Philos. Trans. R. Soc. B Biol. Sci.* 2014, *369* (1633), 20130288. https://doi.org/10.1098/rstb.2013.0288.
23. Shang, C.-Y.; Gau, S. S.-F. Association between the DAT1 Gene and Spatial Working Memory in Attention Deficit Hyperactivity Disorder. *Int. J. Neuropsychopharmacol. 2014, 17* (01), 9–21. https://doi.org/10.1017/S1461145713000783.

## Author

Hibah, a senior at SICAS DHA, is drawn to the unknown in biology, with a curiosity that might one day lead to a PhD.



DOI: 10.36838/v7i3.1