EPIGENETICS OF HUMAN COGNITIVE PERFORMANCE

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ABSTRACT

This article has as its objects of study the epigenetic factors involved in the expression of human cognition and seeks to offer a compilation of scientific knowledge about the epigenetic aspects associated with cognitive manifestation. In the meantime, a literature review was carried out with the collection of 21 articles produced between 2018 and 2024, which present as main findings the facts that, from epigenetic modifications, caused by environmental factors, in the patterns of methylation, acetylation, histones, and miRNA expression, impacts on individual intellectual expression are observed that may be directly or indirectly related to these epigenetic mechanisms or to neurological pathologies such as Alzheimer's. Therefore, with the understanding of these cognitive factors, there is the core for research on therapies aimed at cognitive maintenance with aging.

Keywords: Neurogenetics. Epigenetics. Cognition.

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INTRODUCTION

Epigenetics, understood as the study of hereditary modifications in gene expression that do not involve changes in the DNA sequence, has emerged as a fundamental field in understanding the biological processes that modulate human cognitive development. As we progress in investigating the complex mechanisms that govern brain function, epigenetics proves to be a crucial element in elucidating how environmental, behavioral, and social factors interact with the genetic basis to influence cognition.

Epigenetic influences affect critical neurobiological processes, such as neuroplasticity, which allows the nervous system to reorganize its connections in response to experiences. Epigenetic modifications, including DNA methylation and histone acetylation/deacetylation, are essential in regulating gene expression related to cognitive functions such as memory, attention, and learning. Exogenous factors, such as stress, diet, physical activity, and pollutants, can induce epigenetic changes that impact the central nervous system (HARMAN and MARTÍN, 2020). Understanding these interactions is crucial to developing effective interventions that address the various facets of cognitive development.

Critical periods of development, such as childhood and adolescence, are particularly vulnerable to epigenetic influences. During these phases, the brain is in a state of high plasticity, where lived experiences can induce lasting effects.

In addition, other studies raise questions about childhood adversities, such as care deprivation, unfavorable environments, and chronic stress, tend to result in methylation patterns that impact long-term cognitive ability (OH and JERMAN, 2018). Children exposed to adverse conditions often have epigenetic alterations that affect the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and emotional response, leading to difficulties not only in learning, but also in the formation of social bonds and the regulation of behaviors. Research on the impact of childhood adversity on epigenetics suggests that traumatic experiences can leave lasting marks on the epigenetic profile, perpetuating a cycle of disadvantage that can span generations.

In the context of human aging, factors such as loneliness and mental health have often been associated with epigenetic changes that affect cognition (BOWIRRAT and ELMAN, 2023). Studies indicate that loneliness can induce a chronic inflammatory state which, in turn, alters the DNA methylation pattern, negatively impacting cognitive functions in elderly populations. The combination of these factors highlights the complexity of the interaction between aging, mental health, and epigenetics, underscoring the need for integrated approaches to promote healthy aging.

The study is justified by the need to understand the mechanisms of cognitive performance and its modulation. Identifying modifiable factors is essential for preventive and therapeutic interventions, especially in the face of increasing cognitive disorders. Potential contributions include new clinical paradigms to reverse or mitigate negative effects of epigenetic alterations and inform public policies that promote healthy environments, focusing on vulnerable populations such as at-risk children and the elderly.

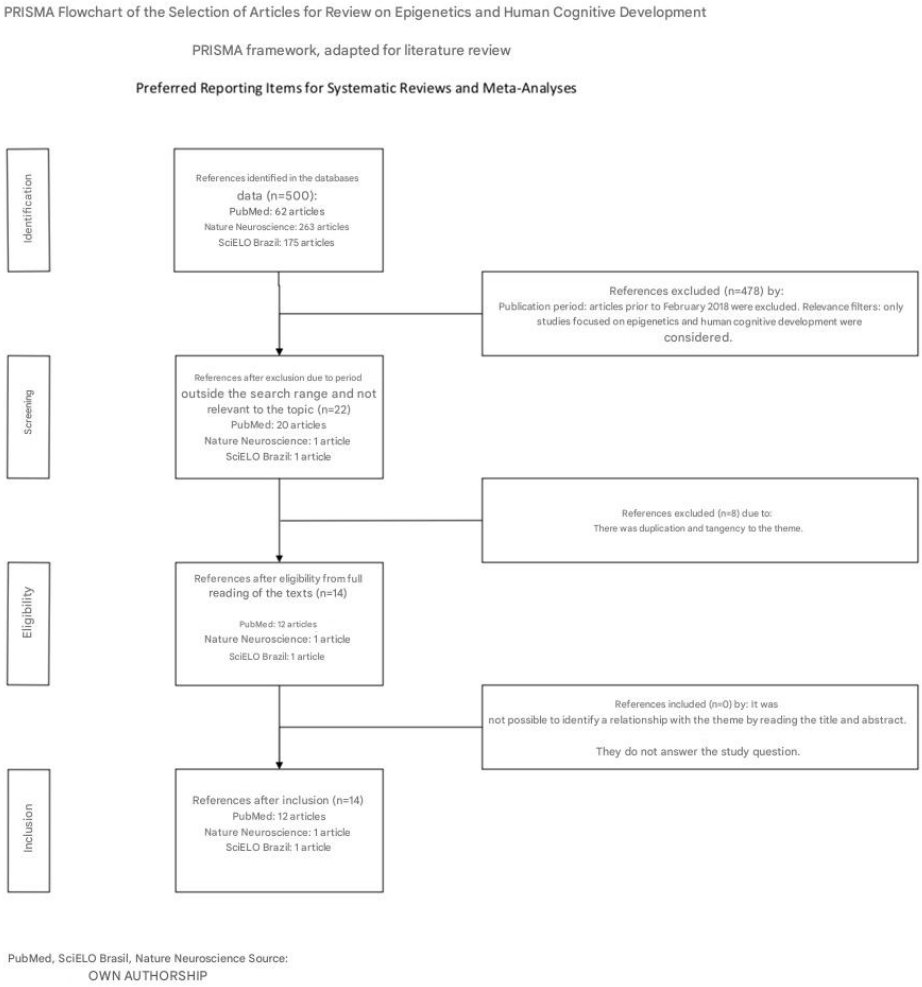
METHODOLOGY

Understanding the theme of epigenetic mechanisms is of paramount importance to investigate the development of human cognition at different levels and in varying intensity. As a result, due to the expressive availability of studies, which serve as support for researchers, those exposed on epigenetics requested an in-depth search in digital supports of technical and methodological rigor. Thus, searches were carried out that could effectively contribute to an answer to the theme "Epigenetics of human cognitive performance", based on the full reading of the selected materials with full inclusion and exclusion criteria, in order to review such recent contents in the field of science, with clear and objective files, for an adequate organization of the key points and main discussions, moving towards the writing of the article in the form of a literature review.

Based on the appropriate design, the scientific bases for the research were then defined, namely: PUBMED, SCIELO BRASIL and NATURE NEUROSCIENCE. This search was mostly guided by recent articles, in evident and renowned sources of knowledge propagation that corroborate the veracity of the information and generate reliability in the study. Thus, the studies that were analyzed are included in the period from February 2018 to August 2024, indicating an exclusion criterion for those that precede this interval. Finally, the files of each stage of each of the analyzed productions were of paramount relevance for the absorption of the content and direction for the writing of the article itself, obeying the specificities of each topic.

In following this plan, the search terms "epigenetic", "cognitive development" were used. To aid the research, Boolean terms were added, namely: AND and OR. With this, the research was carried out and a total of 500 studies were found in all data sources, and initially, only 22 of them were considered adequate for review. In the PUBMED data source, 62 results were found, and 20 results were chosen. On the NATURE SCIENCE platform, 263 studies were identified, and only 1 was considered viable to complement the study, as well as in SCIELO BRASIL, which found 175 articles, but only 1 was added to the review. After the stricter application of the flowchart, duplicity and tangency to the theme were

found, which caused the exclusion of 8 articles, thus leaving a total of 14 works, 12 from PUBMED, 1 from NATURE SCIENCE and 1 from SCIELO BRASIL. Among these texts are scientific articles, dissertations, reports and literature reviews.



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RESULTS

The results of this study highlight a strong connection between epigenetic mechanisms and cognitive development across the lifespan, emphasizing how these molecular changes impact gene expression in brain cells. One of the most relevant processes is DNA methylation, particularly in CpG dinucleotides, since older neuronal cells have higher rates of Egr1 methylation. In addition, with the determination of methyloma, it was found that with aging, there is a displacement of the sites of methylation in the gene bodies and, therefore, hypermethylation of certain areas and hypomethylation of others occur and, consequently, the dysregulation of gene expression responsible for cognitive functions occurs. It is also worth noting that the alterations in DNA methylation patterns depend on the genomic region analyzed, the amount of CpG dinucleotide islands present in

the studied region and the target gene of data collection. It is also essential to highlight that enzymes known as DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, and DNMT3B, are involved in this process and undergo significant modifications as the brain ages, influencing the expression of genes essential for cognitive functions (Harman and Martín, 2019).

It is essential to understand the factors that shape human cognition from childhood onwards due to the intrinsic relationship between childhood IQ and individual health in adult life, given that the cognitive level during the first years of life can influence, at an older age, behavioral choices such as smoking and alcoholism, at an individual socioeconomic level, and at the manifestation of genetic predispositions aimed at intellectual performance (STARR, 2019). In addition, it is observed that individuals exposed to troubled and unstable daily environments during their childhood tend to present changes in physiological and neuropathological mechanisms and, thus, alter their epigenetic ages. Thus, there is a scenario of divergence between the biological age and the epigenetic age of these individuals, who, due to this context, tend to present deficits in their cognitive expressions during adult life (FELT et al., 2023). It is also worth noting that studies have found that, based on the analysis of data collected by Enlow et al, Strathearn et al, and Richards and Wadsworth, individuals exposed to traumatic experiences between 0 and 24 months of life presented deficits in cognitive performance between the ages of 24 and 96 months, that maltreatment in the first years of life has repercussions on individual intellectual performance, and that children who have gone through traumatic events such as death of one of the parents or the divorce of the parents tend to have a lower intellectual performance between 8 and 15 years of age (OH et al., 2018).

Modifications to histones, proteins that help structure DNA, also play a crucial role in regulating genes. With aging, the acetylation of histones in genes linked to memory decreases, compromising their expression. This phenomenon is associated with increased activity of enzymes such as histone deacetylase 2 (HDAC2), which has been linked to a negative impact on memory and brain plasticity (Singh & Thakur, 2018). In addition, oxidative stress has been pointed out as a factor that accelerates brain aging and causes DNA damage, impacting neuronal function (STARR, 2019).

Another relevant point is the performance of microRNAs, which regulate protein synthesis in the brain. Changes in microRNA levels with aging influence the brain's ability to adapt to new stimuli and maintain proper cognitive functions (Mohammed et al., 2019). These microRNAs are related to genes that control neural plasticity and the formation of new synapses, which are vital for memory and learning.

It is also important to highlight that several genes are responsible for brain development through the phenotypic expression of processes such as neurulation, neurogenesis, neuronal development, and the development of synapse circuits. In the meantime, genes ARHGAP11B, CROCCP2, DUF1220, FZD8, ZNF558, TMEM14B, TKTL1a, TBC1D3, PPP1R17 and PDGF, NOTCH2NL, CBLN2, EPHA7, FOXP2a, OSTN, PLXNA1, and SRGAP2C (ZHOU et al., 2024) are associated with these neurological processes and, based on this, environmental factors can trigger epigenetic changes that affect the expression of genes related to neurological diseases such as microcephaly and Alzheimer's through gene alteration and increase vulnerability to psychiatric disorders such as anxiety, depression, schizophrenia and bipolar disorder (VAN IJZENDOORN et al. 2010). From this, it was found that, among the epigenetic factors related to depression, changes in DNA methylation rates stand out. In this sense, individuals with a confirmed diagnosis of depression had high methylation rates of nuclear receptor subfamily 3 member 1 of group C (NR3C1) and of the solute 6 member 4 carrier family (SLC6A4) and, thus, showed a dysregulation of the stress response of the hypothalamic-pituitary-adrenal axis in addition to an impairment of gene expression that is responsible for regulating the body's response to stress. In addition, it was observed that in the brains of schizophrenic people there are considerable changes in the methylation levels of genes related to neuronal development and dopamine functionality, which have the effect of effecting the schizophrenic condition. Another relevant epigenetic alteration found in the brains of individuals with this pathology is the modification of histone patterns when comparing the epigenomes of individuals with and without the disease (COLITĂ et al., 2024). It is also worth noting that Alzheimer's, responsible for cognitive decline, has, from oxidative stress, a scenario in which a reduction in DNA methylation can be triggered, as a DNA oxidation scenario occurs, which increases the levels of hydroxymethylation mediated by TET enzymes and interferes in the binding between DNA and DNMTs that synthesize the methyl S-adenosylmethionine donor and, therefore, this change in the DNA methylation pattern favors the development of Alzheimer's disease and thus directly affects memory and cognition. It is also worth noting that oxidative stress is an indirect stimulant to H3K9 methylation through stimulation of SIRT1 action, which protects itself from oxidative stress through its increase in mitophagy and autophagy. Thus, SIRT1 stimulates the action of histone methyltransferase, which causes an increase in H3K9me3 rates. (IONESCU-TUCKER and COTMAN, 2021).

DISCUSSION

The results found by this study emphasize the diverse relationships between genetic, epigenetic and environmental mechanisms and their effects on cognitive performance. Among these relationships are the functions of genes in brain development, the influence between the daily environment experienced during childhood and future cognitive performance, the impacts of aging on intellectual functioning, and the role of neurological diseases in the decline of cognitive activity. From this perspective, a strong scientific basis is noticeable that seeks to prove that cognitive performance depends on several factors to be expressed and, based on this, the main epigenogenic factors aimed at intellectual activity and their effects will be discussed.

Several genes are responsible for brain development through the phenotypic expression of processes such as neurulation, neurogenesis, neuronal development, and the development of synapse circuits. In the meantime, genes are related to these brain processes and the development of neurological diseases such as microcephaly and schizophrenia (ZHOU et al., 2024). Thus, it is evident the role played by genes in the constitution of brain mechanisms such as the synthesis of neurons and synaptic circuit mechanisms and that neurogenetic dysregulation is capable of resulting in neurological disorders such as microcephaly and schizophrenia, which directly affect individual cognitive development.

In addition, it was found that there is a strong relationship between environmental stimuli and cognitive performance in memory processing activities and IQ levels, as external factors are capable of increasing the epigenetic age of young individuals and, thus, alter their neuronal DNA methylation mechanisms (FELT et al., 2023). Based on this, it is possible to infer that the experiences lived during childhood are capable of reflecting on individual cognition even during adult life and, thus, the importance of maintaining a family environment and healthy social interaction for ephebes is highlighted so that they can have an adequate intellectual development.

It is also possible to establish a direct relationship between aging and changes in cognitive performance, given that with the advance of biological age, there is a dysregulation of epigenetic mechanisms such as methylation, acetylation, and histone alterations that can lead to a faulty memory and, consequently, in lower intellectual performance (HERMAN and MARTÍN, 2019).

It is essential to understand the fact that dysregulations in brain epigenetic mechanisms lead to damage to neurological functions and, in this bias, there is a scenario conducive to the development of diseases that have the effect of reducing the cognitive

performance of individuals affected by these maladjustments (PEEDICAYIL, 2024). Based on this, given the role of the study of epigenetics in understanding how environmental factors can interfere with gene expression and, therefore, the development of pathologies (COLITĂ et al., 2024), some of the clinical conditions that are related to lower intellectual performance will be addressed. In light of this, Porto et al found that depression can affect individual cognition by promoting a reduction in memory and attention in those affected by this condition (PORTO et al., 2002). Based on this, it was contacted by Colită et al that, among the epigenetic factors aimed at depression, changes in DNA methylation rates stand out and, therefore, there is a scenario conducive to the development of depression and, consequently, to the reduction of intellectual performance (COLITĂ et al., 2024). Regarding bipolar disorder, it has a decline in cognitive activity as a clinical characteristic (MONTEJO et al., 2022). Based on this fact, it is worth noting that the increase in methylation levels in the gene whose function is to encode the dopamine D2 receptor is a prominent epigenetic factor for the occurrence of bipolar disorder and, therefore, there is a decrease in the full reception of dopamine, a reality that has the effect of an instability in individual mood (COLITĂ et al., 2024). With this, one of the epigenetic causes for the occurrence of bipolar disorder is emphasized, a clinical condition that must be understood due to its reflexes in the cognitive sphere.

It is also important to highlight the influences that schizophrenia exerts on cognition, since reduced intellectual performance is characteristic of this disease (MCCUTCHEON et al., 2023). From this perspective, it is observed that in individuals diagnosed with schizophrenia there are alterations in methylation patterns and histone modifications in their brains (COLITĂ et al., 2024). Therefore, the presence of epigenetic modifications that originate psychic pathologies responsible for reducing the cognitive performance of individuals affected by them is clear. Alzheimer's is a neurodegenerative disease that presents, in most confirmed cases, a symptomatic picture characterized by memory lapses and, consequently, a reduction in intellectual performance (KNOPMAN et al., 2021). In the meantime, this clinical condition has a great influence on its development of oxidative stress from physiological aging and, as a result, epigenetic modifications occur that influence cognitive expression (IONESCU-TUCKER and COTMAN, 2021). Therefore, it is evident that these oxidative factors must be scientifically understood in order to be adequately combated in order to avoid a neurodegenerative condition that affects individual cognition.

As this is a literature review, this study was carried out based on the collection of articles whose themes are focused on neurodevelopment, epigenetics and neurogenetics. However, it is important to emphasize that, given the considerable scope of research

focused on genetic factors responsible for human cognition, this study has as its main limitation the fact that it was not possible to address all the research focused on this field, but rather the articles that were judged as most relevant by its authors.

Therefore, in order to review the knowledge related to the epigenetics of cognitive performance, the authors selected the scientific articles judged as more relevant and more coherent to the discussion of this theme and, therefore, other studies focused on this area were not addressed, a fact that can be considered negative and limiting to the study because it may not have analyzed data that are also relevant, however, not found in the data collection for the writing of this article.

From the presentation and discussion of the data emphasized in this article, it is possible to establish that the study of epigenetic mechanisms aimed at human cognition is essential for the understanding of intellectual functioning and, therefore, based on this understanding, it may be possible to develop therapeutic measures for the treatment of neurological diseases that result in cognitive decline. Thus, based on the neurogenetic bases made by this study, it is expected that in the future, they will be used to deepen scientific knowledge about cognition and to develop therapeutic ways to maintain it during all stages of life. In addition, based on what has been discussed in this article, it is possible to observe how several factors, ranging from the genes responsible for neurogenesis to oxidative stress arising from old age, are responsible for the expression of human cognition and intellectuality and that these are the result of several neurogenetic processes and, therefore, this article is fundamental for the compilation of these data through a systematic review to offer an overview of the factors epigenetic responsible for cognition. Thus, this study may serve as a basis for further studies aimed at understanding intellectuality and aimed at developing clinical techniques that ensure, for all age groups, the effective fight against cognitive decline originating from a range of neurodegenerative diseases such as Alzheimer's disease.

CONCLUSION

It was highlighted in the review that DNA methylation and histone modifications, which are some of the epigenetic mechanisms, play essential roles in the development and maintenance of cognitive functions during life. Under this bias, the regulation of processes, such as neuroplasticity, memory, and learning, is carried out through DNA methylation, mediated by DNMTs, which undergoes changes with aging, which mainly affects gene expression in crucial regions, such as the prefrontal cortex and the hippocampus. In addition, histone modifications and HDAC activity, specifically HDAC2, were associated

with memory decline and reduced gene expression in older individuals. Furthermore, microRNAs are essential regulators of protein production and brain adaptation to new stimuli and changes in their levels is directly related to the impact on neuronal plasticity.

It has also been observed that external factors, such as obesity and oxidative stress, are negative influencers of epigenetic regulation, as they can accelerate cognitive decline. In this sense, some evidence cited in the article indicates that therapeutic interventions, such as the inhibition of HDACs, the use of antioxidants, and the modulation of microRNAs, have great potential to reverse these epigenetic modifications and restore cognitive functions, creating ways to prevent and treat neurodegenerative diseases, such as Alzheimer's.

There are several limitations to the study, even though the findings presented provide a detailed insight into the influence of epigenetic factors on cognition. In principle, most of the studies observed are based on animal models, which may limit the generalization of studies to humans, since animal and human systems have different complexities. In addition, small samples are usually used in DNA methylation analysis studies and histone modifications, reducing the statistical robustness and reliability of the results.

Another limitation is that the influence of multifactorial factors, such as diet, stress, and lifestyle, which interact in a complex way with epigenetic modifications, is not yet fully understood, introducing uncertainties about the extent and specificity of these effects. Finally, most research studies epigenetic modifications at specific stages of life, such as child development and aging, which leaves gaps in how these changes accumulate and interact during adulthood.

In the review, important points are analyzed both in the practical and theoretical spheres. In the practical field, detailed knowledge of the influence of epigenetic factors on cognition can bring new ways to prevent the effects of aging and neurodegenerative diseases. As an example, therapies directed to the modulation of enzymes such as HDACs and DNMTs, as well as the regulation of microRNAs, can be developed, in order to restore cognitive function and promote neuroplasticity. It is also noticeable that there is the possibility of reversing epigenetic alterations through HDAC inhibitors and antioxidants, thus opening new hopes for preventive and therapeutic treatments in elderly populations or those at risk of cognitive decline.

On the other hand, from a theoretical point of view, during the review it becomes clear that epigenetics plays a central role in the interaction between exogenous factors and gene expression, which shapes brain function and cognition. Thus, in the study, the

theoretical basis on brain plasticity is expanded, making it evident how lifelong experiences, such as stress, diet, and exposure to substances, can influence cognitive performance. Similarly, the relationship between epigenetics and factors, such as oxidative stress and obesity, contributes to a more integrated understanding of the conditions that favor or harm brain health.

Thus, the need for interdisciplinary approaches, which combine molecular biology, neuroscience, psychology and public health, is noticeable, in order to develop programs and policies that promote cognitive well-being during life.

For future studies, it is recommended that they focus on expanding the use of human models, either through advanced cell culture techniques, such as brain organoids, or through clinical studies, which will examine epigenetic modifications at different stages of life. This change would contribute to the improvement of the translation of preclinical findings to clinical practice.

In addition, it is essential that longitudinal studies that follow epigenetic changes over time in diverse populations are carried out. With this change, the understanding of how epigenetic factors accumulate, interact and affect cognitive development during the individual's life would be better understood.

Therefore, epigenetics not only provides information about how the environment shapes gene expression, but also contributes to the development of new approaches to prevention and treatment of neurodegenerative diseases of cognitive declines associated with aging. Thus, continuous research and the development of interventions based on these mechanisms have the potential to improve quality of life and well-being in vulnerable populations.

In conclusion, it is imperative that scientists, health professionals, and policymakers recognize the importance of these findings and work together to transform theoretical knowledge into practical actions that benefit society as a whole. Epigenetics, with its modulation and reversal possibilities, represents a promising frontier for promoting healthy and sustainable cognitive development across generations.

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