RESEARCH PAPER

ADHD and Bioinformatics: A Comprehensive Review of Emerging Computational Approaches in Understanding and Managing Attention- Deficient/ Hyperactivity Disorder

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ABSTRACT
Attention-Deficit/Hyperactivity Disorder (ADHD) is a complex and heterogeneous neurodevelopmental disorder, regulated by genetic, epigenetic, neurobiological, environmental, and metabolic factors. Clinical diagnosis based on symptoms-based approach has been essential. However, this approach fails in achieving a deep understanding of the underlying molecular mechanisms of ADHD. Advances in bioinformatics and multi-omics approach have greatly influenced ADHD research through genomic, transcriptomic, proteomic, metabolomic, metagenomic, and epigenetic analysis related to disease progression. The purpose of this review is to underscore the role of computational biology, systems biology, artificial intelligence (AI), and machine learning (ML) within the domain of ADHD research. Multiple susceptibility loci involved in neurotransmitter signaling and neurodevelopmental processes have been identified in genomics studies. Transcriptomic and proteomic analysis have identified immune-inflammatory process and synaptic dysfunction in patients with ADHD. The relationship between gut-brain axis, microbiota dysbiosis, and metabolic disorders has been highlighted in metabolomic and metagenomic studies. AI-based computer models have exhibited significant potential for prediction, diagnosis, and personalized psychiatry. However, there are numerous challenges that should be overcome soon such as data heterogeneity, reproducibility, translatability, and biomarker standardization problems. The future perspectives of ADHD research might include multi-omics and computational methods.
Keywords: ADHD, Bioinformatics, Transcriptomics, Neuroinflammation, Artificial Intelligence, Multiomics.

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INTRODUCTION

Attention-Deficit/Hyperactivity Disorder is considered to be one of the most widespread and complex neurodevelopmental disorders, and this disorder is characterized by serious symptoms of inattention, hyperactivity, and impulsivity that are developmentally inappropriate for the individual. Despite the fact that ADHD was recognized as childhood disorder at first, it has been shown that ADHD can develop into a lifelong condition since its symptoms persist in adolescence and adulthood [1]. In the whole world, the prevalence rate of ADHD fluctuates from 5-7% among children and 2-5% among adults. As per the clinical criteria, there are three kinds of ADHD, predominantly inattentive type, predominantly hyperactive-impulsive type, and combined type.

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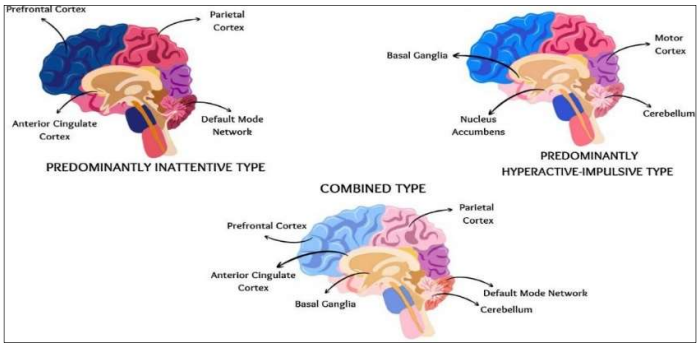

Figure 1: Representation of ADHD as per clinical criteria, there are three types of ADHD

The predominantly inattentive type is characterized by symptoms such as distractibility, forgetfulness, poor organizational skills, and difficulties in concentrating on something. On the other hand, patients with the predominantly hyperactive-impulsive type and the combined type are characterized by high levels of motor activities, impulsiveness, restlessness, and inability to remain still. Patients with the combined subtype are characterized by inattentiveness and hyperactivity-impulsiveness. However, the combined subtype is more prevalent compared to other subtypes. Attention-Deficit/Hyperactivity Disorder (ADHD) is no longer viewed as a simple genetic problem but rather as a complicated interaction among the following factors like, genetics, neurobiology, environment, and epigenetics. Evidence from twin and family studies has revealed the high heritability of ADHD, ranging from 70 percent to 80 percent. This indicates that there is a high genetic predisposition for developing ADHD [2,3]. However, ADHD does not follow the laws of Mendelian inheritance, being classified as a polygenic disorder. In particular, the genes that might contribute to ADHD are those connected with the process of dopaminergic neurotransmission and are represented by SLC6A3 (DAT1), DRD4, and DRD5 genes. These genes are responsible for the reuptake of dopamine and neurotransmission. Abnormalities in dopaminergic circuitry have been reported to cause the development of attention deficit, poor executive function, and problems with reward, which are all the features of ADHD patients [4-6]. At the same time, there are other genes, such as SNAP25 and brain-derived neurotrophic factor (BDNF), that affect synaptic vesicles and neurotransmission. Apart from that, the disruption in neuronal migration, synaptic formation, and brain connectivity implied by the genes ASTN2 and other noncoding RNAs, like LINC00461, may significantly influence ADHD. This information proves that ADHD cannot be regarded as only a gene-related problem but from the standpoint of systems biology [7].

Also, environmental factors have been proven very significant for identifying alterations in the risk of having ADHD, especially throughout brain developmental periods. Prenatal maternal stress, maternal smoking during pregnancy, prenatal alcohol exposure, and environmental toxins during pregnancy have been associated with higher risk for developing ADHD [8,9]. In addition, other postnatal factors like insomnia, stress and trauma can worsen ADHD symptoms and contribute to the disorder's development. Environmental factors are believed to influence ADHD through induction of epigenetic changes, which lead to genetic modification, but without changing DNA structure. ADHD is associated with abnormalities in brain structures responsible for attention regulation, executive functions, behavior regulation, and impulse regulation. Imaging studies have found alterations in frontostriatal circuits, prefrontal cortex, basal ganglia, cerebellum, and default mode network, playing a major role in cognition and behavior regulation. Imbalance in neurotransmitters like dopamine and norepinephrine causes dysfunction in inter-network communication and further contributes to ADHD development. It should be noted that new studies prove that the pathophysiology of the disorder is not limited to neurotransmitter imbalance but includes also neuroinflammation, metabolism disturbance, and disruption of the gut-brain axis. Several studies now suggest that ADHD is a neurodevelopmental disorder with a possible onset in childhood and is linked to delayed cortical maturation, synapse pruning problems, and network disconnection lasting into adulthood [10]. ADHD has come to be viewed in recent times as a lifelong neurodevelopmental condition where symptoms vary depending on the developmental stage of an individual. In children and adolescents, ADHD is diagnosed based on the severity of hyperactivity, impulsivity, and inattentiveness, which make it difficult for a child to function well in class and among peers. Children with ADHD exhibit behaviours such as fidgeting, inability to wait turns, interrupting others while they speak, lack of attention during structured tasks, and losing crucial items.

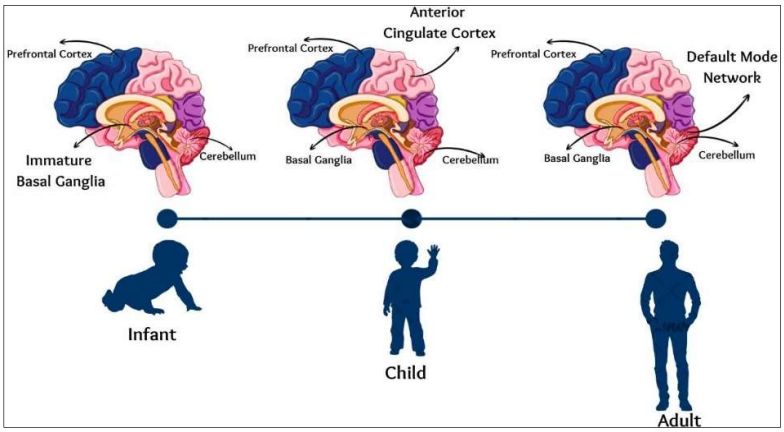

Figure 2: Representation of Brain changes in ADHD across development

The problems are especially prevalent in the primary school age period, whereby academic and social pressures bring out the deficits in attention and self-regulation behaviours. Diagnostic guidelines highlight the importance of identifying early signs of ADHD and stipulate that ADHD signs should have manifested themselves before the age of twelve, without being considered as part of normal development. ADHD is characterized by the presence of hyperactivity, impulsivity, and inattention that are clinically manifested in different ways during childhood and adolescence. The hyperactive and impulsive symptoms in teens diagnosed with ADHD decrease, but their attention, organizational, and forgetting difficulties are more pronounced than those of children suffering from ADHD. In addition, though the symptoms of hyperactivity and impulsivity may not be found in teens with ADHD as opposed to children with ADHD, they might experience planning difficulties, time management issues, poor executive functions, and mood control problems [15]. In adulthood, ADHD continues to be expressed in a manner that suggests a combination of adaptive development and persistent problems associated with neurocognitive functioning. Whereas over hyperactivity in childhood is likely to become less apparent, it becomes replaced by inner restlessness, cognitive hyperactivity, impulsive behaviours, and organizational difficulties [13]. Individuals who are affected by ADHD will be likely to experience problems with job performance, interpersonal relations, managing finances, and setting long-term goals. Studies carried out over long periods of time have suggested that about 40 to 60 percent of people who are diagnosed with ADHD in childhood continue to display signs of ADHD in adulthood [12,14].

The differences seen in the development of ADHD symptoms are linked to changes in the development and organization of the brain and its neural networks. Research in neurodevelopment has shown that the continuous presentation of inattention symptoms is linked to the thinning of the cortex and slower development of the prefrontal areas of the brain, which regulate executive function and attention. Conversely, those who recover from their symptoms have a cortical development pattern that mirrors normal neurodevelopment more closely. This further supports the understanding of ADHD as a neurodevelopmental disorder. Although great strides have been made in comprehending the biology of ADHD, some molecular mechanisms associated with it are still incompletely understood due to its complex etiology and high clinical variability [16,17]. The reductionist paradigm that is traditionally used to address ADHD pathophysiology may be inadequate in the face of such complexity. Therefore, bioinformatic and computational methods have proved to be highly effective tools when examining large sets of genomic, transcriptomic, epigenomic, neuroimaging, and clinical data [11]. Using this type of analysis can reveal abnormal molecular pathways and networks that underlie ADHD and help identify possible biomarkers and therapeutic targets.

OVERVIEW OF PUBLISHED ARTICLES

In the last few decades, there have been many studies done to help understand the genetic, neurobiological, psychological, and environmental underpinnings of Attention-Deficit/ Hyperactivity Disorder (ADHD). Early studies concentrated on the behavioural characteristics of the disorder and dysregulation of neurotransmitters, especially dopamine and norepinephrine systems. Early molecular genetic studies revealed some genes that are responsible for the vulnerability to ADHD, such as SLC6A3 (DAT1), DRD4, and DRD5, which are part of the dopaminergic system and reward pathways [18-21]. These findings were crucial in supporting the hypothesis of the deficiency of dopamine in ADHD patients and helped to understand why stimulants work effectively in treatment by blocking the pathways of catecholamines [22]. However, further studies indicated that it is impossible to explain ADHD through the changes in one neurotransmitter system [23]. The advent of GWAS led to the identification of various genetic loci that influence ADHD susceptibility among big cohorts. Unlike the previous candidate gene strategy, GWAS revealed that there are many common genetic variants with low

penetrance that contribute to the risk of ADHD, thereby collectively affecting the probability of disease manifestation [23,24]. Furthermore, there have been numerous reports of genetic overlap between ADHD and other neuropsychiatric disorders like autism, depression, bipolar disorder and schizophrenia, implicating similar neural and molecular pathways associated with the pathogenesis of these conditions [24]. While genetic studies were ongoing, researchers in the field of neuroimaging made many discoveries concerning brain alterations in ADHD patients. Specifically, it was found that there were brain abnormalities in the prefrontal cortex, basal ganglia, cerebellum, anterior cingulate cortex, and front striatal pathways [25].

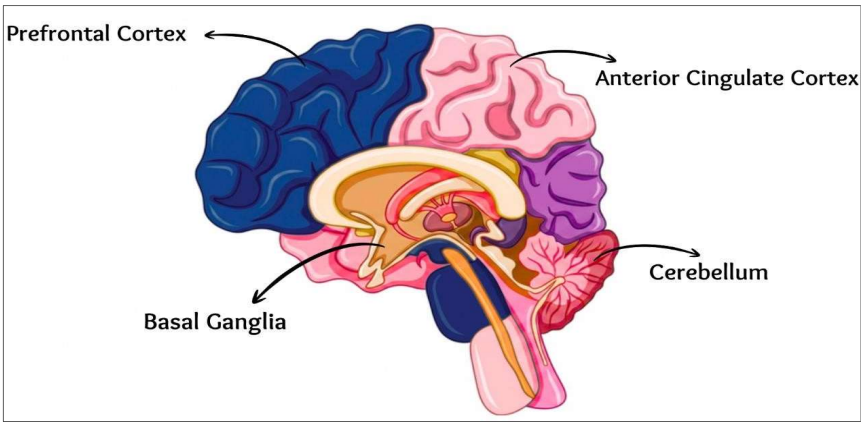

Figure 3: Representation of ADHD, showing Neuroimaging studies that have revealed brain abnormalities in key regions of brain

The above-mentioned brain structures play an important role in such functions as behavioural regulation, executive functioning, and attention processing [25]. Neuroimaging research has shown that those who exhibited signs of ADHD experienced delayed brain maturation and changes in neural connections in comparison to others [25]. This information provided more evidence for the theory about the developmental aspect of ADHD. Further advancements in the study of molecular mechanisms of ADHD have been brought about by transcriptomic and epigenetic research. Transcripts and gene expression studies showed abnormalities in pathways involving synaptic plasticity, neuroinflammation, mitochondrial dysfunction, oxidative stress, and neuronal signaling [26]. Studies on DNA methylation and histone modification as part of the epigenetic analysis indicated that environmental factors may be associated with the development of ADHD through their effects on gene regulation [26]. Moreover, increasing literature has supported the role of non-coding RNAs such as microRNAs and long non-coding RNAs in the development of neurons and synapses for patients with ADHD [26].

Recent developments in computational biology and bioinformatics have greatly impacted the study of ADHD because it has helped analyze huge amounts of data from multiple biological dimensions. Contemporary studies often involve an approach that combines genomics, transcriptomics, epigenomics, neuroimaging, and clinical data using systems biology and omics approaches. Bioinformatic techniques, including genome-wide association analysis, pathway enrichment analysis, protein-protein interaction network analysis, machine learning, and artificial intelligence methods, have been used to identify new biomarkers and abnormal signaling pathways for ADHD [27,28]. Not only molecular and computerized techniques but also the impact of the gut-brain axis and dysbiosis of the microbiome on ADHD have drawn increased interest from researchers. A number of recent studies indicate an alteration in the composition of gut bacteria in people with ADHD, including the species known for their involvement in the metabolism of neurotransmitters, immune system regulation, and inflammatory responses [29]. It is assumed that metabolic products of bacteria, short-chain fatty acids, and tryptophan metabolism may exert their influence on behavior regulation via two-way interaction between the gut and central nervous systems [29]. While being an emerging area of research, the study of the microbiome opened up interesting perspectives for ADHD therapy.

As a whole, current literature on ADHD has greatly enhanced the comprehension of ADHD as a biologically intricate and heterogeneous neurodevelopmental condition. Whereas prior literature was mainly concerned with imbalances in neurotransmitters and behaviour, contemporary literature has increasingly favoured an association between ADHD and a host of interlinked genetic, neurodevelopmental, immunological, metabolic, and environmental causes. The application of bioinformatics and systems biology as well as multi-omics approaches is thus crucial in advancing our knowledge of ADHD and finding ways to manage and diagnose the condition using precision medicine.

Table 1. Historical evolution of ADHD research from early neurotransmitter-based theories to modern multi-omics approaches. Highlighting major scientific milestones that contributed to understanding the genetic, neurobiological, and systems-level mechanisms.

Time Period	Research Domain	Key Findings	Contribution
1950s–1980s	Behavioral & Neurotransmitter Research	Dopamine and norepinephrine imbalance associated with ADHD	Established neurochemical basis of ADHD
1980s–1990s	minergic Pathway Studies	Dopamine dysfunction linked with hyperactivity and impulsivity	Supported dopamine-deficit hypothesis
1990s–2000s	Candidate Gene Studies	DRD4, DRD5, and SLC6A3 genes associated with ADHD	Introduced genetic basis of ADHD
2000s	Polygenic Research	ADHD recognized as apolygenic disorder	Showed multiple genes contribute to ADHD
2000s–2018	Neuroimaging Studies	Brain abnormalities in prefrontal cortex and related regions	Linked ADHD with altered brain development
Present Era	Multi-Omics Approaches	Integration of genetic, neural, immune, and environmental factors	Provides systems-level understanding of ADHD

RESEARCH GAP WITH UNSOLVED CHALLENGES

Although considerable advances have been made toward the genetic, neurobiological, and clinical characterization of Attention-Deficit/Hyperactivity Disorder (ADHD), a number of important scientific barriers remain that prevent the development of accurate diagnostic tools and effective treatments for this condition. Perhaps the biggest barrier to current research on ADHD is the tremendous biological and clinical heterogeneity observed in the syndrome. ADHD is characterized by diverse symptom patterns, disease courses, treatment responses, and comorbidity profiles, which make the discovery of common biological markers or identification of a unified disease mechanism challenging [30]. While several genetic, neuroimaging, transcriptional, and behavioural changes have been discovered in ADHD patients, a number of results lack reproducibility between different datasets, indicating that ADHD may encompass various neurodevelopmental syndromes rather than a singular disease [31]. An additional critical issue is the poor reproducibility and validation of proposed biomarkers for ADHD. Several biomarkers relating to neurotransmitter communication, inflammation, neuroimaging measures, metabolic changes, and epigenetics have been proposed. Although very few of those biomarkers have been found to be reproducible in different populations [32,33]. Many research efforts for biomarkers have depended upon small sample sizes and homogeneous groups, consisting mainly of young populations of Caucasian descent, thus limiting the potential of the results from being generalized to other clinically or ethnically different populations [32]. Besides, computational approaches are still at the exploratory stage, lacking adequate experimental validation, longitudinal replication, and clinical application [30]. No reliable molecular biomarker has been identified so far. The analysis of multi-omics datasets is also one of the key unsolved problems in ADHD research. While the analysis of each individual omics approach can shed light on the disease mechanisms, integrating all of these heterogeneous datasets poses significant computational and statistical challenges [30,39]. The different sequencing technologies, preprocessing protocols, methods for batch effect correction, data dimensions, and normalization approaches often lead to contradictory results and poor comparability across studies [30,36]. In some cases, relevant information such as sequencing coverage, quality control protocols, feature selection criteria, and preprocessing procedures may be poorly described, leading to issues with replicability and interpretation of the results [30]. Therefore, the lack of standardized multi-omics integrative frameworks constitutes an important limitation to modeling ADHD pathophysiology.

Several artificial intelligence (AI) and machine learning (ML) methodologies have been proposed as effective means for diagnosing ADHD, subtyping, and identifying biomarkers of ADHD. However, many challenges need to be addressed in terms of their clinical translation [34,35]. Indeed, most AI applications for ADHD show an outstanding predictive power by employing neuroimaging, electroencephalogram (EEG), behavioural measures, or a combination of different techniques still, AI models frequently experience high levels of overfitting, external validation issues, and lack of generalizability due to the inability to predict outcomes in other data sets [34,35]. Another important limitation is that most AI algorithms behave like black boxes, making them unreliable in clinical practice due to poor transparency and lack of interpretability [37]. Yet another neglected aspect of ADHD research involves the relationship of gut brain axis dysfunction, immune communication, and metabolic dysregulation in relation to the development of ADHD. While recent studies have provided evidence that microbiome dysbiosis, neuroinflammation, mitochondrial malfunctioning, and kynurenine pathway dysfunction may be involved in ADHD pathogenesis, present data are inconclusive and lack validation in longitudinal studies [30,40]. Most of the currently available studies focusing on the microbiome are characterized by their small sample size and cross-sectional methodology which makes it impossible to uncover any causality between

abnormality of microflora and appearance of ADHD symptoms. Additionally, connections between environmental, genetic, immunological and neuromorphological aspects of the disease have not been clarified yet and should be researched in a comprehensive longitudinal manner. Finally, studies in ADHD patients have been associated with certain difficulties related to subjectiveness of diagnostic criteria and similarity to other neuropsychiatric diseases. Diagnosis of ADHD is currently based on behavioral test and clinician's observations rather than biological markers which increases the possibility of diagnostic errors, delay and inconsistency [29]. Similarity with other diseases such as autism spectrum disorder, anxiety, depression, bipolar disorder, learning disability, etc. represents another barrier to precise diagnosis and classification of subtypes [28]. In sum, it is clear from all of these outstanding issues that although there have been huge advancements made, there is still much to learn about the biological mechanisms underlying attention deficit hyperactivity disorder. This means that future scientific work must focus on conducting large longitudinal cohort studies, integrating multi-omics data using standardized protocols, developing explainable AI models, and identifying experimentally validated biomarkers which can aid in the diagnosis and treatment of ADHD [30,34,35].

WHY TRADITIONAL APPROACHES ARE INSUFFICIENT

The traditional methodologies that have been employed in research concerning Attention-Deficit/Hyperactivity Disorder (ADHD) have played an important role in identifying and explaining the underlying behavioural disturbances and neurotransmitter dysfunction associated with the condition. However, these methods do not provide adequate knowledge on the biological intricacy and diversity of the disorder [41]. For many years, behavioural analysis along with psychological assessment has served as the primary method of studying and diagnosing ADHD. While these systems have continued to be useful in practice, they tend to be more descriptive rather than explanatory, and they also require subjective information from individuals suffering from this disorder [42]. As a result, diagnosis can vary among different patients, which raises the risk of misdiagnosis, delays in treatment, and confounding the condition with other disorders such as autism spectrum disorder, anxiety disorders, bipolar disorder, and learning disabilities [43].

The first limitation of conventional ADHD research is its reductionism. Past studies often looked into neurotransmitter mechanisms, including dopamine and norepinephrine transmission, in explaining the pathophysiology of ADHD [44]. Despite the fact that dysfunction in the dopaminergic system plays a crucial role in ADHD pathology, increasing evidence indicates that ADHD is more complicated than the interaction between genetic vulnerability and neurodevelopmental mechanisms [45]. Thus, single-gene analysis and isolated mechanism examination are unable to account for the complexity of ADHD. In addition, past studies were limited by their failure to examine the interplay between multiple biological layers, such as genetics, brain imaging, or behavioural aspects of the disease. The traditional methods used in diagnosis and treatment have also been limited by the lack of objective biomarkers that could be used in diagnosing ADHD [46]. In turn, the currently existing methods of diagnosing this disease are based on patient interviews and patient behavior rating but not on any neurobiological factors [43]. It means that there exists a certain amount of subjectivity in diagnosing the illness and the methods used may differ considerably for various populations and age groups. Furthermore, it should be mentioned that symptoms of ADHD differ depending on the age of the person. While hyperactivity decreases with age, other symptoms remain constant [47]. Moreover, there exist certain disadvantages of traditional treatment.

For instance, pharmacologic interventions including stimulants, methylphenidate, and amphetamines are primarily focused on catecholaminergic systems and have proven effective in managing symptoms in the short term [48]. However, there is considerable variation in the responses of patients under treatment, as some individuals have faced side effects, poor efficacy in the long run, and partial relief from symptoms [49]. Additionally, the conventional approach focuses on the management of symptoms without addressing the underlying biological processes that cause the disease. Further, one major drawback of traditional methodology is the inability to manage and analyze huge amounts of biological data generated by technological advances [50]. Modern developments in disciplines like genomics, transcriptomics, epigenomics, metabolomics, neuroimaging, and microbiome research have indicated that complex biology is involved in ADHD, and these data can only be analyzed in combination using a few tools. Traditional methodologies and those involving statistical analysis and hypotheses do not always have adequate processing capabilities to combine these biological data and identify meaningful biological relationships among different genes, metabolic pathways, neural circuits, and environmental stimuli [51].

There are new findings pointing to the existence of abnormalities within the system beyond the imbalance of neurotransmitters in relation to the attention deficit hyperactivity disorder including neuro inflammation, mitochondrial dysfunction, oxidative stress, impairment of energy metabolism and gut-brain axis disruption [45,52]. These findings refute the previous assumptions on ADHD which assume that the cause of ADHD is only a deficiency of dopamine and call for the application of systems biology approaches in analyzing the interaction between different levels of the body.

On the other hand, it is now possible to say that there

have been remarkable developments in the fields of bioinformatics, systems biology, artificial intelligence, and multi-omics studies, which are powerful enough to tackle all the flaws of traditional approaches employed in ADHD studies [50,51]. Through these computing tools, a wide range of analysis can be done on whole-genome data, gene expression data, neuroimaging data, epigenetic data, microbiome data, and clinical data, which may lead to identification of disrupted pathways and networks behind the development of ADHD, as well as biomarkers for this disorder. Together, all these constraints indicate that conventional methods, despite being historically significant, have not been able to provide sufficient insight into the biological intricacies of ADHD. Any further advances in the study of ADHD will necessitate the application of an interdisciplinary approach that takes into consideration computational biology, multi-omics techniques, systems neuroscience, and clinically proven biomarkers.

Table 2. Comparison between traditional and current or emerging approaches in Attention-Deficit/Hyperactivity Disorder research and clinical management

Aspect	Traditional ADHD Approaches	Current & Emerging ADHD Approaches
Diagnosis	Symptom-based and subjective (DSM, behavioral assessment)	Biomarker-driven and precision-based diagnosis
Biological Focus	Mainly dopamine and norepinephrine imbalance	Multi-factorial: genetics, epigenetics, immunity, metabolism, microbiome, neural networks
Research Method	Reductionist, single-pathway studies	Systems biology and multi-omics integration
Data Analysis	Conventional statistical methods	AI, machine learning, and bioinformatics approaches
Biomarkers	No reliable objective biomarkers	Ongoing discovery of molecular and imaging biomarkers
Understanding of ADHD	Considered mainly a neurotransmitter disorder	Recognized as a heterogeneous neurodevelopmental disorder
Treatment Strategy	Generalized symptom management	Personalized and precision medicine approaches
Medications	Mainly stimulants and non-stimulants	Pharmacogenomics-guided targeted therapies
Consideration of Individual Variability	Limited	Includes genetic, environmental, metabolic, and developmental differences
Gut-Brain Axis	Mostly ignored	Active focus on microbiome and neuroimmune interactions
Neuroimaging & Omics Integration	Rarely integrated	Combines genomics, transcriptomics, neuroimaging, and clinical data
Clinical Outcome	Variable efficacy and side effects	Aim for accurate diagnosis and optimized individualized treatment
Future Potential	Limited understanding of disease complexity	Improved biomarker discovery and targeted therapeutic development

BIOINFORMATICS: REVOLUTIONIZING ADHD RESEARCH THROUGH COMPUTATIONAL INSIGHTS

The advent of bioinformatics has marked a shift from symptom-oriented to a data-centric and precise science by making it possible to reveal novel aspects related to ADHD at the level of molecules, genetics, neurobiology, and computation [53]. Contrary to the previous methods which mostly used behavioural assessments and basic molecular analysis techniques, bioinformatics offers sophisticated computational tools for analyzing complex multidimensional datasets resulting from genomic, transcriptomic, epigenomic, neuroimaging, metabolomic, microbial, and artificial intelligence-based studies [54]. The main advantage of bioinformatics in ADHD research is the ability to find genes that cause the disease and biological pathways that are disrupted as a result of it [55]. Using computational methods in GWAS, RNA sequence, and epigenetic data analysis, scientists were able to reveal genes linked to neurotransmitter regulation, neuronal migration, synaptic plasticity, immune signaling, cortical development, and other processes underlying ADHD [56]. Thus, the research on the topic has moved away from studying single genes to studying networks of molecules.

Bioinformatics technology has been extremely useful in the area of biomarker identification and disease prediction as well [57]. With the help of various machine learning tools, protein-protein interaction maps, and multilayered omics integration methods, scientists are able to pinpoint molecular markers which are correlated with Attention-Deficit Hyperactivity Disorder (ADHD) diagnosis, symptomology, treatment efficacy, and various types of the condition [58]. In this way, it might be possible to lessen the reliance on behavioural diagnoses and develop objective diagnostics based on biomarkers in the future. Artificial intelligence techniques are increasingly utilized for neuroimaging and electroencephalogram analysis purposes. Bioinformatics also brings another crucial benefit in the development of precision medicine for ADHD treatment [59,60]. The differences in biological and clinical parameters among individuals suffering from ADHD contribute to the variation in their treatments. The application of bioinformatics makes it possible to combine various sources of information (genetic, transcriptomic, epigenetic, microbiomics, and clinical) to

understand the uniqueness of an individual's biology. Additionally, bioinformatics has helped to unravel the connection between other possible pathways and ADHD. Some of the possible connections established by bioinformatics are related to processes like neuroinflammation, oxidative stress, mitochondrial dysfunction, and dysfunction of the gut-brain axis. It has been discovered that the microbiome analysis via bioinformatics techniques shows variations among microbial species that are involved in neurotransmitter synthesis and immune responses. However, it is necessary to emphasize that bioinformatics can help in ensuring reproducibility, scalability, and international collaboration within the sphere of attention deficit hyperactivity disorder. Using open-access databases and computerized repositories makes it possible for researchers from other countries to be able to obtain information about genomics, transcriptomics, brain imaging, and clinical data to use for additional research and comparisons. In general, bioinformatics has become an indispensable tool in modern studies of attention deficit hyperactivity disorder because of its capability to integrate biological information, identify relationships at the molecular level, discover biomarkers, and help personalize the approach to medicine. With the development of computational tools, bioinformatics is likely to become even more prominent in the future treatment of ADHD [61,62].

Table 3. Major databases, repositories, and bioinformatics tools commonly used in modern Attention-Deficit/Hyperactivity Disorder and neuropsychiatric research

Database / Tool	Description	Official Link
National Center for Biotechnology Information Sequence Read Archive (SRA)	Repository for raw sequencing and RNA-Seq datasets	https://www.ncbi.nlm.nih.gov/
Gene Expression Omnibus (GEO)	Public database for gene expression and transcriptomic datasets	https://www.ncbi.nlm.nih.gov/geo/
ENCODE Project Consortium	Functional genomics and epigenomics resource	https://www.encodeproject.org/
GTEx Consortium	Tissue-specific gene expression database	https://gtexportal.org/home/
PsychENCODE Consortium	Multi-omics resource for neuropsychiatric disorders	https://www.psychencode.org/
QIIME 2	Tool for microbiome and 16S rRNA analysis	https://usegalaxy.eu/root?tool_id=qiime2_coretoolsimport
STRING	Protein-protein interaction and pathway analysis database	https://string-db.org/
Cytoscape	Biological network construction and visualization tool	https://cytoscape.org/
g:Profiler	Functional enrichment and pathway analysis platform	https://biit.cs.ut.ee/gprofiler/gost
KEGG	Biological pathway and metabolic network database	https://www.genome.jp/kegg/
Reactome	Curated molecular pathway resource	https://reactome.org/
DGIdb	Drug-gene interaction and therapeutic target resource	https://dgidb.org/
miRDB	miRNA target prediction resource	https://mirdb.org/
ADHD-200 Consortium	Public MRI/fMRI datasets for ADHD research	http://fcon_1000.projects.nitrc.org/indi/adhd200/

GENOMICS APPROACH

The recent technological improvements in genomics have made it possible to advance the understanding of the etiology of Attention-Deficit/Hyperactivity Disorder (ADHD) using the technique for the discovery of numerous genomic variations, susceptibility regions, and biological pathways involved in the development of this condition [63]. In contrast to the past candidate gene studies, which focused mainly on a limited number of neurotransmitter-related genes, the recent genomics technologies, such as GWAS, WGS, WES, and CNV, have provided considerable insight into the polygenicity of ADHD [64]. According to current research findings, ADHD can be considered a disorder associated with several genetic mutations affecting neuronal communication, synaptogenesis, cortical development, neurotransmission, and neurodevelopment [65]. The advent of genomics in ADHD research has enabled the study of disease susceptibility and biological diversity at a systems level. The first key advantage of using genomics in the study of ADHD includes the possibility of detecting new disease-related genomic loci in large groups of people, along with finding common genetic grounds for ADHD and other psychopathologies, like autism spectrum disorder, schizophrenia, depression, and bipolar disorder [66]. Some significant genes related to ADHD include SLC6A3, DRD4, SNAP25, FOXP2, DUSP6, and SEMA6D. All of these genes affect neuronal communications and brain development [67]. In addition, polygenic risk scoring (PRS) studies helped

researchers to calculate overall genetic risk factors and to study links between ADHD risk alleles and behavioural characteristics. These discoveries proved the theory that ADHD is one of the most heterogeneous neurodevelopmental disorders, based on several biological mechanisms rather than a particular reason.

Demontis *et al*. in 2019 considered the most important genomic studies, which was conducted on ADHD [68]. By conducting the genome-wide association study with more than 20,000 ADHD cases and almost 35,000 controls, the scientists were able to reveal the first genome-wide significant ADHD-risk loci. Furthermore, the variants found in the study were related to the activity of genes that are involved in synaptic functions, neurodevelopment, and dopamine signaling pathways. Most importantly, the case study revealed high genetic correlations of ADHD with such characteristics as educational attainment, obesity, smoking, and major depressive disorder, thus proving the great interconnectedness of the condition in terms of biology and clinical implications [68]. Hence, the significance of genomics approach in discovering novel molecular mechanisms was once again demonstrated by this study. Genomics meta-studies have later provided even more ADHD loci and increased genomics significance in biomarker discovery and precision medicine [69].

TRANSCRIPTOMICS APPROACH

Transcriptomics has also been discovered as one more significant modern approach for studying ADHD because it allows the study of gene expression patterns related to the progression of ADHD, neurodevelopmental disorders, and neuronal signal transmission processes [70]. While genomics identifies genetic variations contributing to the development of the condition, transcriptomics focuses on the behaviour of the genes in particular biological states. The use of RNA-Seq, microarray, and single-cell transcriptomics enables identification of DEGs, altered pathways, transcription networks, and cellular responses associated with ADHD [71]. Transcriptomic analysis has demonstrated the presence of deregulated signaling pathways in patients suffering from ADHD [72]. Bioinformatics pipelines that include FastQC, HISAT2, STAR, featureCounts, DESeq2, and edgeR have made it possible to perform large-scale transcriptomic analysis for identifying disease-related biomarkers [73]. Moreover, the integration of transcriptomics with pathway enrichment, protein interaction, and machine learning has enabled an increased understanding of the biological functions related to ADHD manifestations and differential treatments.

Hess *et al*., conducted transcriptomic study, illustrating the growing importance of the RNA-Seq method in ADHD research. In their investigation, scientists explored transcriptomic profiles in ADHD and observed considerable disruption in immune system and neuronal signaling pathways. The results have shown changes in the expression levels of genes implicated in inflammation, synaptic signaling, neurotransmission, and brain circuits, indicating that ADHD is characterized not only by dopamine dysfunction but also by other factors [74]. Most importantly, this work has offered evidence for the involvement of immunological and neuroinflammatory mechanisms in the development of ADHD. It is important to refer to some other transcriptomics research aimed at finding biomarkers and predicting the response of patients with ADHD to therapy using RNA sequencing in peripheral blood samples [75]. Specifically, genes involved in functions related to mitochondria, oxidative stress, circadian rhythm, and neurotransmitters were found to be differently expressed in subjects suffering from ADHD compared to control groups. It is obvious that there may be an important role of transcriptomic approaches in finding markers and designing personalized therapy in the future. In summary, it is quite clear from the above review of current research that gene expression profiling is important for ADHD pathophysiology.

PROTEOMICS APPROACH

The use of proteomics has proven to be vital in current research studies on Attention-Deficit/ Hyperactivity Disorder (ADHD) because it allows researchers to study protein biology at a high-throughput level and identify proteins involved in specific processes and molecular interactions relevant to the disease [76]. Genomics and Transcriptomics have already provided information about the genetic and transcriptional processes related to ADHD. However, proteomics can give insights into the actual functional proteins involved in those physiological processes [77]. Proteins are, after all, the end products of gene expression, and hence studying them will help understand the biological mechanisms behind ADHD. New developments in mass spectrometry, liquid chromatography, tandem mass spectrometry (LC-MS/MS), protein microarrays, and proteomics informatics have allowed scientists to detect differentially regulated proteins and signaling pathways that have gone awry in individuals with ADHD [78]. The proteomics approach has shown alterations in proteins linked to dopamine signaling, mitochondrial dysfunction, inflammation, synaptic communication, cytoskeleton dynamics, and reactive oxygen species regulation [79]. Informatic software such as STRING, Cytoscape, UniProt, Proteome Discoverer, and MaxQuant are often used for protein determination, pathway enrichment, protein-protein interaction (PPIs), and the identification of novel biomarkers [80].

Park *et al*., conducted their studies using proteomic profiling of proteins in people suffering from ADHD. In their study, researchers were able to identify several proteins responsible for various functions such as immune signaling, oxidative stress pathways, and neuron development that exhibited dysregulation in people suffering from ADHD [81]. This implies that proteomics can offer useful insights about molecular functional

changes that cannot be obtained using genomics. Another significant proteomic study investigated alterations in cerebrospinal fluid (CSF) and serum protein related to the severity of ADHD symptoms [82]. In the research, researchers identified proteins associated with neurotransmitter metabolism, neuroinflammation, energy metabolism, and mitochondrial dysfunction in ADHD patients.

METABOLOMICS APPROACH

Metabolomics has emerged as yet another important new method that has been applied to ADHD studies due to its ability to provide an extensive study of the metabolites generated in cell metabolism [83]. This method contrasts with genomics and transcriptomics, since while the former two mainly focus on the study of genetic inheritance and gene expression, metabolomics helps examine current biochemical processes taking place in a biological organism [84]. As metabolites are directly affected by genes, proteins, the environment, dietary intake, microflora, and other physiological factors, they are especially relevant to ADHD. Metabolomics research in recent times has helped reveal metabolic disorders in relation to neurotransmitter metabolism, amino acid metabolism, lipids metabolism, oxidative stress responses, mitochondrial energetics, and inflammatory pathways in patients with ADHD [85]. Metabolomics computations together with MS, NMR, and machine learning algorithms have allowed scientists to discover potential biomarkers that could help diagnose, evaluate symptoms, measure cognitive impairment and therapeutic outcomes for people with ADHD [86]. Bioinformatics resources like Metabo Analyst, KEGG, HMDB, and pathway enrichment tools are frequently used for metabolomics analyses, including metabolite identification, pathway mapping, biomarker discovery, and pathway function inference [87].

Anand *et al*. showed significant differences in amino acids, fatty acid, and oxidative stress-related metabolites [88]. Abnormalities in tryptophan and catecholamine metabolism imply that neurotransmitter imbalance and mitochondrial dysfunction play critical roles in ADHD development. The results obtained from this study indicate that metabolomics can provide valuable information about the biochemical mechanisms underlying the behavioural and cognitive problems associated with ADHD. Another metabolomics study conducted recently used machine learning along with metabolomics profiling to develop biomarkers that can be used to diagnose ADHD [89]. The study found metabolite markers related to neurotransmitter biosynthesis, lipid metabolism, and inflammation processes, which accurately discriminated between ADHD subjects and normal subjects. Significantly, the study emphasized how the use of metabolomics coupled with artificial intelligence and multi-omics approaches could lead to the development of diagnostic and treatment biomarkers. Overall, recent metabolomics studies have clearly pointed to the significance of metabolic pathways in ADHD research.

METAGENOMICS APPROACH

Metagenomics research has lately demonstrated its great potential in studying the relationship between ADHD and the gut microbiome by providing possibilities for investigating the gut microbiome-nervous system connection through the use of the microbiota-gut-brain axis [90]. Numerous studies have discovered the role of gut microbiota concerning brain function, neurotransmission production, immune response regulation, metabolic processes, and neuroinflammation, all factors that have a direct relationship with ADHD pathogenesis [91]. Different from traditional approaches to microbial research, metagenomics sequencing allows researchers to conduct extensive microbial research without isolating microorganisms in the lab setting [92]. Advances in shotgun metagenomics, 16S rRNA gene sequencing, microbial pathway studies, and computational methods for profiling the microbiome have provided opportunities to discover specific bacteria and pathways responsible for ADHD [93]. Changes in the levels of specific genera, which produce or influence the production of neurotransmitters, SCFAs, inflammatory factors, and tryptophan metabolism, have been described [94]. There are multiple bioinformatics tools such as QIIME 2, PICRUSt2, MetaPhlAn, and HUMAnN that can be applied for microbial species analysis, diversity analysis, and function prediction for the analyzed datasets [95]. Such computational methods allow advancing beyond bacterial species classification to their function investigation.

Aarts *et al*. showed that there were major changes in the composition of the gut microorganisms in patients with ADHD [96]. They observed an increase in the number of Bifidobacterium bacteria which have been involved in dopamine biosynthesis. Notably, this research offered data concerning the ways in which microbial metabolism can influence the brain's reward mechanisms via the manipulation of the dopaminergic system [96]. Noteworthy is the metagenomic analysis performed to elucidate the role of dysbiosis and inflammatory pathways of gut microbiota in the pathogenesis of ADHD [97]. The study revealed alterations in the levels of microbial taxa associated with immune response, neurotransmission, and gut permeability. Additionally, the connection between gut microbiota and clinical manifestations of ADHD was established, suggesting that these microbes may be used as biomarkers of this disorder. Modern multilevel analyses have provided additional evidence that gut microbes interact with metabolic processes, immune reactions, and neurochemical signaling pathways in ADHD [98].

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING APPROACH

Artificial Intelligence (AI) and Machine Learning (ML) have played an important role in the field of ADHD studies owing to the ability of these techniques to analyze

huge and complex data sets rapidly and precisely [99]. The conventional statistical methods have found it hard to manage big data sets in genomics, neuroimaging, transcriptomics, behavior, and clinical fields simultaneously. On the contrary, AI and ML can identify hidden patterns, biomarkers, non-linear correlations, and disease signatures at various biological levels [100]. Machine learning algorithms such as SVM, RF, CNN, DNN, gradient boosting, and ensemble learning are getting more common in the ADHD studies [101]. These machine learning methods are very effective in handling the data sets that are generated through MRI, fMRI, EEG, genetics, transcriptomics, metabolomics, and behavioral experiments. The artificial intelligence techniques have exhibited enormous potential in distinguishing the patients of ADHD from normal individuals and predicting the severity of symptoms, disease subtypes, and improving the diagnosis accuracy [102].

Furthermore, deep learning algorithms have the potential to utilize multi-modal data sets in order to find biologically meaningful information that cannot be found using conventional methods. The major example of the case study carried out by the ADHD-200 Consortium shows the importance of using machine learning in the classification of ADHD [103].

Through the analysis of resting state fMRI images, which were collected from several international centers, researchers used the machine learning approach and found the distinctive brain connectivity pattern associated with ADHD. The study proved the feasibility of using the neuroimaging approach with the help of AI technology for ADHD classification [103].

Deep learning algorithms were used by Cao *et al*. to predict multimodal neuroimaging and behavioral data [104]. The researchers succeeded in identifying certain patterns in neural activity associated with executive dysfunction, impulsivity, and attention problems characteristic for patients with ADHD. It was demonstrated that AI algorithms were more effective in terms of prediction of ADHD in comparison to clinical assessment [104]. In addition, recently there were many studies which combined genomics, transcriptomics, and neuroimaging data and demonstrated great potential for precision psychiatry [105]. Nonetheless, despite all these achievements, there are still many challenges related to the application of AI and machine learning techniques for the research of ADHD. Many studies suffer from such limitations as small sample size, heterogeneity of data, overfitting, lack of external validation, and low interpretability of models [106]. Ethical aspects such as protection of patient data and reproduction of results should also be considered. Nevertheless, AI and machine learning are very strong tools which have huge potential for revolutionizing the research of ADHD in computational psychiatry.

EPIGENETIC APPROACH

The usage of epigenetics became one of the main and effective approaches in studying ADHD, since epigenetics provides information about environmental factors' impact on gene expression process without any modifications of DNA structure [107]. Therefore, considering that ADHD is a complex disease which is affected by such factors as genetics, prenatal issues, environment, nutrition, toxins and social aspects, using epigenetics approach can provide biological proof of the connection between genes and environment [108]. Epigenetics includes such processes as DNA methylation, histones modifications, chromatin remodeling, and microRNAs and other noncoding RNAs modulation. Due to the recent technologies of methylation arrays, ChIP-Seq, bisulfite sequencing and epigenomics study, it becomes possible to detect epigenetic markers of ADHD [109]. The methylation alterations were detected in genes responsible for the modulation of dopaminergic pathway, neurogenesis, synaptogenesis, stress response, and immune system regulations [110]. The commonly used computational approaches, like ENCODE, MethBank, EWAS Atlas, GEO, methylation profiling pipelines, are used in order to study global methylation and related regulatory pathways of ADHD [111]. The role of environmental conditions in influencing ADHD development has been clarified significantly by these methodologies.

Walton *et al*. conducted a study where the role of DNA methylation related to ADHD traits in children was evaluated [112]. The research found variations in methylation sites in genes involved in the development of neurons, neurotransmission, and cognition. Most importantly, the study showed that exposure to environments during pregnancy and early development may cause vulnerability to ADHD by epigenetic regulatory processes. The results of this study have clearly shown that ADHD is not only genetic but is also environmentally influenced at the molecular level. Another important epigenetics research focused on the alteration in microRNA expression that is related to ADHD [113]. There were a few microRNAs found to be upregulated or downregulated, which affect synaptic transmission, brain plasticity, inflammatory responses, and the dopaminergic system. This study proposed the possibility that non-coding RNAs can be used as markers for ADHD diagnostic purposes. In addition, some epigenome-wide association studies (EWAS) revealed associations between the severity of ADHD symptoms and methylation markers related to stress reactions, immune system activation, and corticogenesis [114].

PATHWAY AND NETWORK ANALYSES APPROACH

Pathway and network analyses have taken greater significance in the field of ADHD research since they allow for the investigation of complex interactions between molecules, proteins, metabolites, signaling pathways, and cellular functions in terms of genes, as

opposed to studying each individual molecule [115]. The fact that ADHD is seen as a neurodevelopmental disorder based on systems biology, and involves interconnected pathways related to neurotransmission, synaptic plasticity, neuroinflammation, immune response, metabolic function, oxidative stress, and neuronal differentiation [116], highlights the limitations of reductionism. Advances in the field of systems biology, PPI studies, gene co-expression, and pathway enrichment analysis have led to more accurate identification of biologically significant modules involved in ADHD [117]. Several computational software packages, including STRING, Cytoscape, GeneMANIA, KEGG, and Reactome, are extensively used for finding hub genes, pathways, molecular interactions, and biological functions related to ADHD [118]. Poelmans *et al*. explored the molecular interaction networks that contribute to the development of attention deficit hyperactivity disorder (ADHD) [119]. Genetic association, protein-protein interactions, and pathway analysis were used to discover dysregulated pathways contributing to neurotransmission, synaptic vesicle transport, neural migration, and neurogenesis. Notably, the study highlighted the presence of functional networks of ADHD-related genes working together instead of working alone, thereby lending support to the theory that ADHD is a disease of systems biology [119]. One other major network-based study analyzed the interactions of proteins and hubs of genes from transcriptomic data related to ADHD [120]. The key hub genes that were identified included those involved in the transport of dopamine, inflammation response, cellular communication, and mitochondrial functions. Pathway enrichment analysis indicated dysregulation in several biological pathways including synaptic transmission, oxidative stress, and immune responses. This demonstrates the importance of pathway and network analyses in biomarker discovery, subtyping of diseases, and identifying new drug targets. The integration of genomic, transcriptomic, metabolomic, and microbiome data into biological networks has recently been explored to improve the knowledge on ADHD [121]. Together, these analyses have revolutionized ADHD research because they have enabled large-scale studies of interlinked molecular networks involved in the disease process. They help to understand the complexities of biology, identify disease-related pathways, and provide a basis for the emergence of integrative precision psychiatry.

Table 4. Summary of major findings and conflicting observations across multi-omics studies in Attention-Deficit/Hyperactivity Disorder research.

Research Area	Study Findings	Contradictory Findings	Possible Reason for Conflict
Genomics	Several GWAS studies identified strong ADHD-associated loci linked to dopaminergic and neurodevelopmental genes [125]	Some studies reported limited reproducibility of candidate genes across populations [126]	Ethnic variability, polygenic complexity, sample heterogeneity
Transcriptomics	RNA-Seq studies identified immune and neuronal dysregulation pathways [127]	Other studies detected differentially expressed genes with minimal overlap	Tissue source differences, sequencing pipelines, cohort variation
Proteomics	Increased inflammatory and oxidative stress proteins observed in ADHD [128]	Some studies reported weak or inconsistent protein biomarker associations	Variations in sample type, medication exposure, proteomic methods
Metabolomics	Altered tryptophan metabolism and mitochondrial dysfunction identified [129]	Certain metabolomic studies failed to reproduce consistent metabolite signatures	Dietary influences, environmental factors, metabolic variability
Metagenomics	Reduced microbial diversity and altered gut-brain pathways reported [131]	Some investigations found no major microbiome differences [138]	Geographic variation, diet, antibiotics, sequencing methodology
Epigenetics	DNA methylation changes linked with neurodevelopmental genes [132]	Other studies showed inconsistent methylation signatures across cohorts [133]	Tissue specificity, age-dependent changes, environmental exposure
Neuroimaging + AI	Machine learning models showed high ADHD prediction accuracy [135]	External validation studies demonstrated reduced reproducibility [136]	Overfitting, small datasets, lack of standardization
Biomarker Discovery	Multi-omics studies proposed candidate biomarkers for ADHD diagnosis [140]	No universally validated biomarker currently exists	Biological heterogeneity and limited longitudinal validation

DISCUSSION

The Attention-Deficit/Hyperactivity Disorder (ADHD) is now more understood to be a very heterogeneous neurodevelopmental condition, which involves

interaction between genetics, epigenetics, neurotransmitter imbalance, immunology, metabolism, environment, and gut brain interaction disorders [122]. While the conventional approach based on symptoms has done well in the diagnosis of ADHD, the recent findings made using advanced techniques in bioinformatics show that the etiopathogenesis of the ADHD cannot be accounted for through a single biological pathway [123]. Genomic, Transcriptomic, Proteomic, Metabolomic, Metagenomic, Epigenetic, and Artificial Intelligence technologies have increased our knowledge about ADHD. Genomic research has conclusively shown that ADHD is highly heritable through both common and rare genetic variations linked to neurodevelopment, neurotransmission, dopaminergic function, and corticogenesis [124]. GWAS studies have found several ADHD-risk genetic loci and shown that there is substantial overlap between ADHD and other psychiatric conditions like autism spectrum disorder, depression, schizophrenia, and bipolar disorder [125]. However, although it is well-established that ADHD is a polygenic condition, many of the individual genetic factors have only a modest biological impact, which makes it difficult to translate them into useful biomarkers. Studies involving transcriptomics and proteomics have yielded further information on the functional impacts of genetic predisposition for ADHD [127]. Some of the identified biochemical pathways include neuroinflammation, oxidative stress, mitochondrial dysfunction, synaptic plasticity, neurotransmitter metabolism, and immune function. It is notable that transcriptomics and proteomics have indicated that ADHD may be more than the presence of a dysfunction related to the dopaminergic system and may represent a systemic dysregulation process [128]. Although, it is not uncommon for there to be discrepancies between different studies, as a result of factors such as tissue source, sequencing methods, analysis approach, number of subjects, and clinical characteristics.

Moreover, investigations into metabolomics and metagenomics have enhanced the understanding of ADHD as a system disorder driven by metabolic and microbial factors [129]. Metabolic anomalies in the processing of amino acids, tryptophan metabolism, fatty acid metabolism, mitochondria, and gut microbial diversity have shown an impact on ADHD manifestations and cognitive impairment [130]. Recent research on gut microbiota imbalance and microbiota-gut-brain interactions shows a possible role of microbial metabolites in regulating neurotransmitters and neuroinflammation [131]. However, significant individual variability in gut microbes has hampered reproducibility in metagenomic studies.

Epigenetic research has further emphasized the influence of the environment in the pathogenesis of ADHD [132]. Disruptions in the process of DNA methylation, histone modifications, and non-coding RNA expression have been associated with exposure during pregnancy, stress response, neurodevelopmental processes, and neurotransmission disruptions [133]. This finding adds strength to the hypothesis that ADHD is the product of an interaction between genetics and the environment. Nevertheless, epigenetic patterns are extremely organ-specific and responsive to changes in the environment; this makes the detection of uniform epigenetic patterns challenging. The use of artificial intelligence and machine learning approaches has made significant strides in being able to integrate complex biological and clinical data [134].

Machine-learning approaches have demonstrated immense potential in the categorization of ADHD, biomarker discovery, neuroimaging analysis, and predicting drug responses [135]. Deep learning models that use data from genomics, neuroimaging, EEG, transcriptomics, and behavioral studies might find their place in precision psychiatry and personalized therapy in the future. However, problems like overfitting, bias, lack of interpretability, poor external validation, and lack of diversity of datasets prevent such models from clinical practice [136]. Another crucial issue highlighted by current research on ADHD is the presence of contradictions in scientific works conducted on this matter. Diversities in characteristics of patients, co-morbidities, sequencing platforms, sample handling procedures, bioinformatics software, statistical thresholds, and degree of environmental exposure result in contradictory results [137]. Thus, there can be both increased and decreased amounts of certain bacteria in the gut microbiome of people diagnosed with ADHD [138].

The different regulation of the gene expression in two distinct groups of patients is often possible to demonstrate by means of transcriptomic and epigenomic analyses. However, the major progress in the study of the molecular mechanisms of the heterogeneity of ADHD was achieved owing to the creation of numerous approaches in bioinformatics and systems biology [139]. The approaches, which make it possible to combine the data gained through the use of genomics, transcriptomics, proteomics, metabolomics, microbiome analysis, epigenomics, neuroimaging and clinical researches, can provide more biological information than the analysis of separate omics approaches can give [140].

To conclude, the results of scientific investigations demonstrate that ADHD should not be treated as a disease of behavioral regulation disorders and dysfunctioning of the dopaminergic system; rather, it is a neurological disorder with a number of biological mechanisms interacting with each other and influenced by environmental factors. Future developments in the fields of computational biology, omics technologies, artificial intelligence and network medicine are likely to have a great impact on the diagnostics and personalized treatment of ADHD.

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