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IS ATTENTION DEFICIT HYPERACTIVE DISORDER - A NEUROGENETIC DISORDER

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ABSTRACT: An overview of the neurodevelopmental disorder ADHD (attention deficit hyperactivity disorder), its consequences, and details on the brain regions impacted by ADHD are the driving forces behind this review. The hereditary basis of ADHD has been investigated. Throughout the investigation, numerous reviews and research publications were compared and examined. The themes covered in this article are (a) ADHD as well as its symptoms (b) the complexity of the brain regions affected in ADHD patients (c) and (d) linkage analysis for researching the genes of ADHD. The brain's structure, development, and functioning will alter, according to review analysis results. The main brain areas involved include the cerebellum, parietal, Prefrontal and frontal lobes. According to the study, the thickness of the cerebellum will diminish, and the anterior striatal region will be most negatively impacted. There isn't much proof that ADHD is inherited, although a few experts have suggested that there may be a connection between siblings' ADHD and their DNA. For a complete understanding of the condition, a great deal more research must be conducted. The review's study reveals the genetic interplay that occurs in ADHD patients as well as the impact of the disorder on the brain's functional and structural changes. The paper also discusses drugs and techniques for treating ADHD. However, ADHD cannot be cured; all that can be done is treat the symptoms.

INTRODUCTION: A condition known as a neurodevelopmental disorder affects how the brain grows and develops. Among these are speech and language impairments, which impact a person's capacity to speak, ADHD (attention deficit hyperactivity disorder), and others. There is still no known cause for several disorders, including Tourette syndrome (involuntary sounds and movements known as Tics), fragile X syndrome (inherited developmental condition), schizophrenia (severe chronic behavioral disorder), and autism (difficulty in social interactions, communication, and learning) [1].

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Genetic variables, environmental pollutants like lead, lethal exposure to smoking, alcohol, and recreational drugs, preterm birth, low birth weight, and other risk factors can all contribute to the development of these disorders. ADHD is the neurodevelopmental disorder that is most common [2]. Before the age of seven, children with ADHD are typically diagnosed, and some go on to develop it into adulthood [3]. Children with ADHD act impulsively, struggle to focus, and are hyperactive.

Some of the symptoms of ADHD include impulsivity, disarray, trouble prioritizing, poor time management, difficulty focusing and trouble multitasking, impulsive behavior or sleeplessness, poor planning, a low threshold for frustration, frequent mood swings, difficulties going through and performing projects, a short fuse, and difficulty managing stress [4]. Because each patient experiences it differently, so does their course of treatment. ADHD is divided into three categories

by the Diagnostic and Statistical Manual (DSM-5) of the American Psychiatric Association: Mostly impulsive, predominantly hyperactive and primarily inattentive [5]. Predominantly inattentive: The child displays a sequence of inattention symptoms, such as failing to pay close attention to the details or making simple errors in schoolwork, having trouble focusing on tasks, not listening when others are speaking, having trouble listening to instructions, having trouble trying to organize tasks and activities, being easily distracted, and forgetting to complete daily chores. Predominantly Hyperactive: The child exhibits symptoms that include fidgeting with their hands or legs, difficulty sitting still, constant motion, talking excessively, difficulties playing, difficulty waiting, and interrupting other people's talk frequently [6].

Pathophysiology of ADHD: Although the pathogenesis of ADHD is unclear, psychoactive medication and noradrenergic tricyclics are employed to treat it, leading researchers to hypothesize that attention-related brain regions suffer from neuronal transmission deficiencies [7, 8]. By smoothing the release and operation of the dopamine or noradrenaline neurotransmitters, these medications help to lessen the symptoms of ADHD. As a result, impaired neuronal transmission may be related to the etiology and signs of ADHD. Decreased dopamine activity is observed in people with ADHD, and Positive electron transmission (PET) scans have been used to detect the amount of dopamine concentration in the brain [9]. The frontal and prefrontal cortex are the main brain areas involved, though the cerebellum and parietal lobe may also be. Using magnetic resonance, these structural regions have been found. Since studies have shown that the brains of ADHD sufferers differ from normal brains in terms of development, function, and structure, magnetic resonance imaging (MRI) has been utilized to identify these anatomical regions. Children with ADHD also exhibit deformation in the basal ganglia nuclei [10]. The purpose of the project is to educate people on ADHD and to understand better its causes, how they affect brain function, and various methods for managing its symptoms.

MATERIALS AND METHODS: This review was based on a wide range of research and review articles that were published in the databases PubMed, Scholars, Medline, Elsevier, and Psych info databases. Data were gathered, examined, and reported based on those findings. Most of the information we gathered concerned kids with ADHD.

DISCUSSION: Depending on the developmental stage of the kid, the design process entails meticulous neuronal growth, placement, and arrangement into functional brain connections, growth of myelin around neurons, and pruning of unnecessary neural circuits [11]. The areas of the human brain are depicted in **Fig. 1** [12].

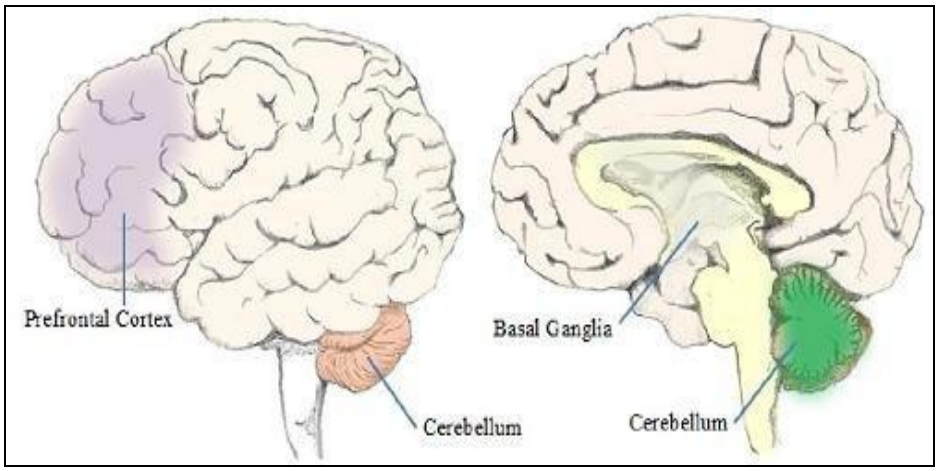

FIG. 1: CEREBELLUM, BASAL GANGLIA, AND PREFRONTAL CORTEX PARTS OF THE HUMAN BRAIN ARE SHOWN IN AN ILLUSTRATION. Source: George, Neuropsychopharmacology.

Basal Prefrontal Cortex: Fig. 2 illustrates how the prefrontal basal cortex, which regulates emotional responses like judgments, and the basal ganglia, which controls impulsive behavior, prevent unnecessary automatic responses to inputs [13-14].

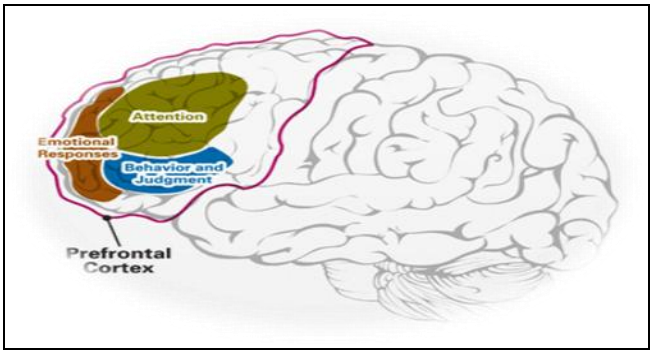

FIG. 2: EFFECTS OF ADHD ON THE PREFRONTAL CORTEX. Source: Jzholliman, Neurodiversity.

For the brain to operate effectively, information must be processed and shared across neural networks; however, neurotransmitter communication between the basal ganglia and the prefrontal cortex is abnormally low in brains associated with ADHD. Dopamine interacts with potent neurotransmitters to control mood and is closely associated with different parts of the brain. Low dopamine levels will impact the functioning of the brains associated with ADHD, or it may seek out alternative treatments such as serotonin transporter gene polymorphism. Lack of awareness, reduced working memory performance, difficulty concentrating, difficulty accomplishing tasks, and inability to avoid superfluous activities are all symptoms of prefrontal cortex dysfunction [15]. According to a study by Shvarzman *et al.*, deformations were observed in basal ganglia nuclei in children with ADHD. The severity of symptoms increases with more obvious deformations.

Children with ADHD who use stimulants have considerable outward deformations among all basal ganglia nuclei compared to those who are not taking medication. According to the study, children with ADHD have structural dysregulation within their basal ganglia circuitry, and stimulants may help those kids' basal ganglia morphology return to normal [16].

Fronto- Striatal Region: Fronto-striatal networks play a major role in ADHD. ADHD-related behavioral dysfunction is brought on by dysregulated functional communications [17].

Fig. 3 illustrates how the inferior longitudinal fasciculus, superior longitudinal fasciculus, corpus callosum, anterior corona radiata, cingulum, corticospinal tract and cerebellum of children with ADHD have impaired white matter integrity, which contributes to the dysfunctional communication in the frontal striatum [18].

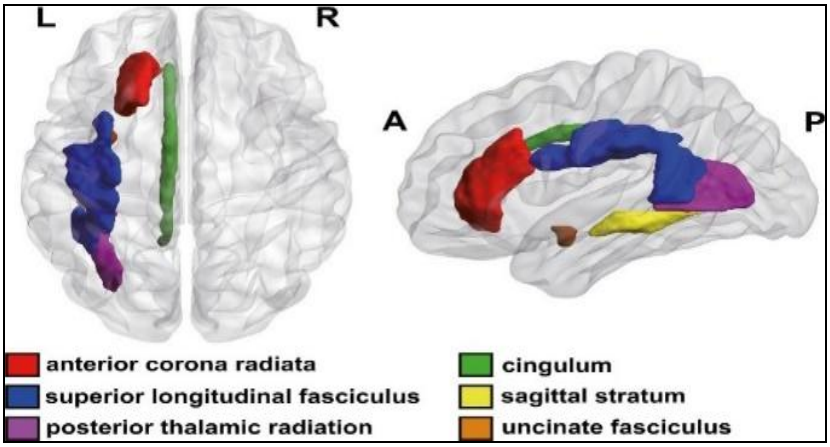

FIG. 3: REGIONS OF FRONTO-STRIATAL NETWORKS. Source: Jia-Yong Wu *et al.*, CNS Neuroscience and Therapeutics.

The striatum as well as its connections, changed in children with ADHD and these changes were linked to symptoms of impulsivity and hyperactivity. The size of basal ganglia regions may well be linked to symptoms of hyperactivity and impulsivity that lessen over time and may go away in adulthood [19]. Despite indications that front striatal dysfunction could be the primary aetiology of ADHD, structural and functional changes have been seen in areas outside of the front striatal circuitry, most notably in the cerebellum and parietal lobes, according to a review of studies by Yerys *et al* [20]. Comparatively, Drechsler MV *et al.* reported the structural and functional brain results in ADHD individuals. It indicates that there isn't universal agreement on the changed anatomical or

functional MRI results of the brain in ADHD kids. Researchers conclude that, even though MRI imaging results can shed light on the neuropathophysiology of a disease, the problem is not clearly defined structurally or functionally from a neuroradiologic standpoint [21].

Cerebellum: Studies on structural neuroimaging indicate that abnormalities in the cerebellum are frequently observed, and a combination of fixed and progressive neuroanatomic impairments defines ADHD. The various cerebellar functions are shown in **Fig. 4** [22-23]. According to a study on the functional and structural neuroanatomy of ADHD, there have been volume reductions in the entire cerebral mass, including the cerebellum, corpus callosum, basal ganglia (striatum), cerebral dorsal anterior cingulate cortex, and prefrontal cortex. Hypoactivation of the frontal cortex, basal ganglia (striatum) and dorsal anterior cingulate cortex have also been reported [24-25].

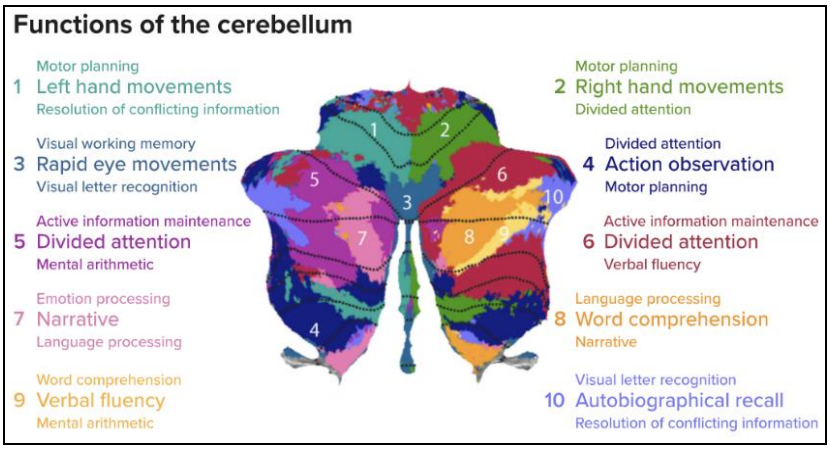

FIG. 4: FUNCTIONS OF CEREBELLUM. Source: M.King *et al*/Nature Neuroscience 2019.

In a study by Rinat *et al.* using the resting state functional MRTI, the connections between the left and right primary and sensory-motor cortices in children with ADHD, DCD (Developmental coordination deficit), were investigated. The study discovered that children with DCD, ADHD, and DCD with ADHD have abnormally strong functional connections within and between the hemispheres between the SM1 and the cerebellum and basal ganglia areas. The study adds to the evidence that suggests common and distinctive brain mechanisms underlie DCD and ADHD [26].

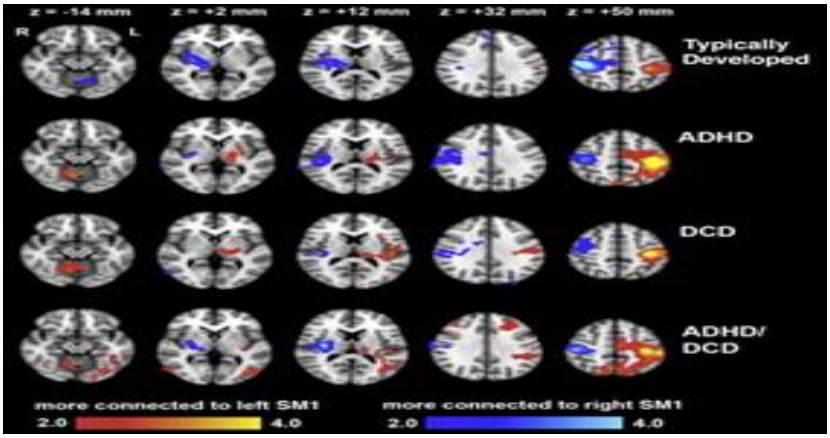

FIG. 5: BRAIN AREAS FOR EACH GROUP SHOWING MORE FUNCTIONAL CONNECTIVITY WITH THE LEFT SM1 THAN THE RIGHT (RED/YELLOW) AND GREATER FUNCTIONAL CONNECTIVITY WITH THE RIGHT SM1 THAN THE LEFT (BLUE/LIGHT BLUE). Source: Kevin *et al.,* NeuroImage: Clinical.

These neural mechanisms include the formation of aberrant motor network connections. It was discovered that there was a substantial correlation between clinical motor function testing and the strength of the functional links between the right SM1 and SM2 in children with DCD and DCD + ADHD (but not ADHD). A comprehensive analysis by Perugi *et al*. raises the possibility that dopamine

and noradrenaline have a dual role in the aetiology of ADHD and its therapy. According to the review, pharmacotherapies for ADHD affect a variety of cognitive functions via the tight interplay of the DA and NA systems in corticostriatal circuitry. The catecholamine levels in the brain are raised by medications used to treat ADHD, such as methylphenidate, dextroamphetamine and atomoxetine. However, the prefrontal cortical and subcortical pathways through which these drugs exert their therapeutic effects are still not completely understood. However, the current level of knowledge focuses on the molecular neuroimaging literature and the functions of dopamine (DA) and noradrenaline in controlling cortico-striatal networks. Recently positron emission tomography research has highlighted the value of assessing DA indicators in striatal subregions controlled by distinct cortical connections at baseline or after drug administration. This strategy makes it possible to identify the neurobiological causes of and cure illness by concentrating on brain circuits [27]. A different study by Martine Hoogman of the Radboud University Medical Centre found that people with ADHD had somewhat smaller brains than those without the condition. Figure 6 depicts the PET scans of patients with ADHD and those without it. According to the study's findings, those with ADHD have distinct brain structures than those without it [28].

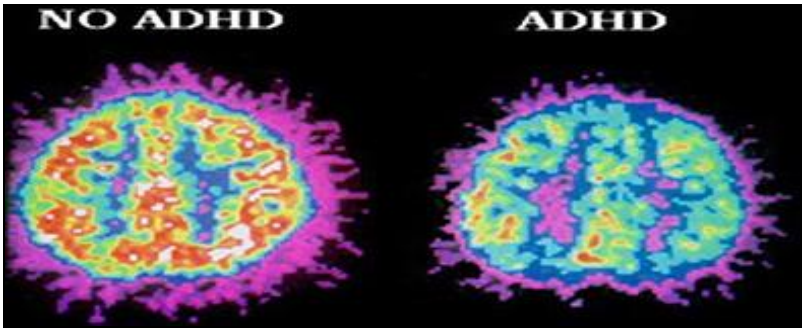

FIG. 6: A PET SCAN DEMONSTRATING THE DIFFERENCE BETWEEN A BRAIN WITH ADHD AND ONE THAT DOES NOT. Source: Healthy Gamer GG.

Regarding causation, there are several theories. Regarding causation, there are several theories. Although the actual aetiology of ADHD is unknown, factors like genetics, environmental factors and issues with the central nervous system's development may contribute, as seen in **Fig. 7.**

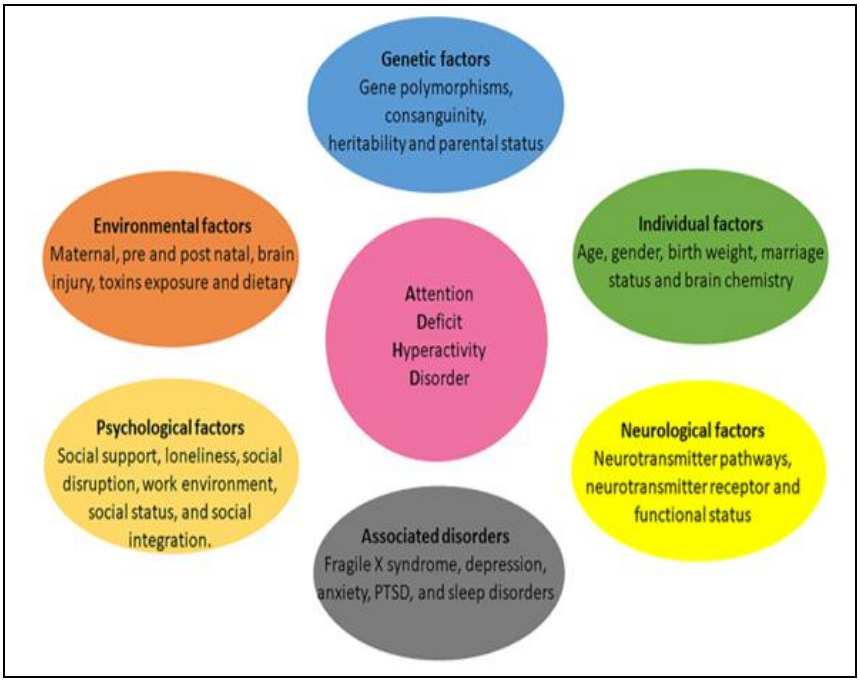

FIG. 7: CAUSES OF ADHD

TABLE 1: ANALYSIS OF HERITABILITY AND NON-SHARED ENVIRONMENT IN BROAD ADHD AND STRICT ADHD BY SEX

Diagnosis	Male		Female	
	Heritability	Non-shared environment	Heritability	Non-shared environment
Broad ADHD diagnosis	0.62 (0.54-0.71)	0.38 (0.29-0.46)	0.55 (0.46-0.64)	0.45 (0.36-0.54)
Strict ADHD diagnosis	0.65 (0.53-0.76)	0.35 (0.24-0.47)	0.53 (0.30-0.77)	0.47 (0.23-0.70)

Genetics: Geneticaetiology received the majority of attention in this review. But it's also crucial to keep in mind that ADHD might possibly have other causes. The scientific paper on genes and heredity is known as genetics. A section of DNA called a gene that includes instructions for creating one or more molecules that support bodily function. A branch of behavioral genetics known as "psychiatric genetics" investigates how genes contribute to the development of mental diseases [29]. The fundamental tenet is that if genetic variables play a role in an illness, gene sharing will result in a similar risk of the condition. A better knowledge of psychiatric diseases and improved treatment strategies based on genetic factors are both aided by psychiatric genetics. Family, twins, and adoption studies constitute the foundation for genetic condition research. Family studies make understanding if a disease or trait runs in the family easier. In the case of studies, a family member's medical history is gathered to see whether a particular illness increases the likelihood that it will be passed on to other family members. This might be influenced by environmental or genetic factors [30]. According to a study by Faraone *et al*., ADHD has a high heritability of 74% [31].

Family studies discuss how a person's relationships with their families, communities, cultures, organizations, and society affect them. Twin studies are carried out to determine how much of an individual's variation in a trait results from their genes versus their environment. These studies aid in learning complex concepts and lower the risk of developing certain diseases. To properly investigate twins, the traditional twin study design must be used. Fraternal twins and identical twins share roughly half of their genes in common, whereas identical twins and fraternal twins share all of their genes. As a result, any increased resemblance between fraternal twins should be due to genes rather than environmental factors [32]. In their study, Bhang et al. looked at 16,366 Swedish twins. Based on their symptoms, the evidence indicates that the extreme and sub-threshold variations of DSM-IV ADHD have a strong hereditary relationship [33]. **Table 1** provides explanations of the study's findings. According to a study by Florence Levy, MD and colleagues, ADHD is a behaviour that differs genetically across the entire population. The study contends that shared familial environmental influences and non-additive genetic variation are not supported by the data [34]. Adoption studies can measure the proportion of a trait's change that is caused by genetic and environmental factors. By comparing the phenotypic similarities of adoptees with their innate and foster parents, or with their non-biological siblings, the common biological or environmental impacts can be determined. In other instances, the disease may manifest in the child before it does, explaining how the biological parents are to blame [35]. According to a study conducted by Emmerik *et al.*, natural relatives of quasi-ADHD children are more likely to have the disorder than adopted relatives of fostered ADHD children. The risk of ADHD in foster parent's relatives was comparable to that in control children's relatives [36].

According to studies, 76% of ADHD cases are heritable. The candidate genes that most consistently code for the structures and enzymes associated with monoamine neurotransmission are those whose complicated genetics of ADHD include multiple interacting genes. ADHD may be linked to a gene that produces dopamine, a neurotransmitter with the capacity to keep regular and continuous attention. Catecholamines play a substantial role in prefrontal-dependent executive skills being deficient in ADHD patients through neuromodulation of fronto-striato-cerebellar circuits, making them an important target for the pharmacological treatment of ADHD. Even so, there is a lack of understanding of the neurological pathways driving ADHD and its treatment [37]. In a study by Merwood Chen *et al.,* data from 894 subjects with DSM-IV-diagnosed ADHD phenotypes and 1135 of their siblings (siblings) were analyzed. The patients' ages ranged from 5 to 17 years. Males make up 87% of those with

ADHD, as opposed to 52% of siblings. Compared to siblings of controls, the study indicated that siblings of ADHD probands had a nine-fold higher risk of developing ADHD. The study's findings explain how DSM-IV combined probands demonstrate a similar association to dimensional ADHD symptom scores across siblings. This supports the primary criterion of quantitative trait locus mapping of ADHD.

Additionally, it demonstrates that there are no threshold effects on the sibling risk for ADHD and that the recurrence risk ratio is 9.0 [38]. According to molecular genetic studies, the genetics of ADHD is complicated. To identify the chromosomal areas that give rise to the genes for ADHD, a study was carried out. To determine whether chromosomal areas are shared more frequently than expected among ADHD patients, this study looks at several DNA markers from across the genome. According to the study's findings, relatives of probands with ADHD have a greater incidence of the disorder than relatives of controls. Additionally, it states that the incidence rate of the first relatives is 4-9%, putting ADHD at a higher risk than schizophrenia but lower than rheumatoid arthritis [39].

The polygenetic nature of ADHD, according to a study by Liuyan Zhang *et al.*, suggests that several genes are jointly responsible for the disease's onset. However, the dopaminergic and serotonergic system's genes, such as DRD4, SLC6A3 and DBH, are thought to be linked to ADHD susceptibility [40]. Studies on genomic DNA copy number variations in ADHD have recently come to light. This aided in finding uncommon or significant deletions or duplications in ADHD patients [41]. In a study, SNPs C-759T and G-697C in the HTR2C region were investigated in relation to ADHD. The researchers were led by Xu, X., Wolraich, *et al*. In this study, 180 DSM-IV ADHD combined subtype probands with DNA from both parents and just the mother was used. According to the study's findings, the G-697C polymorphism is more frequently transmitted to ADHD probands than the C-759T polymorphism. It offers proof that the development of ADHD may be influenced by the G-allele of the G-697C HTR2C polymorphism [42]. However, a case-controlled investigation by S. Luo *et al*. on genetic studies of genes associated with dopamine in adult ADHD patients indicates that there is no correlation between the genes (dopamine transporter SLC6A3 (DAT 1) and dopamine receptor D4 (DRD4)) and ADHD [43]. ADHD cannot be diagnosed with a specific test. There are specific criteria for diagnosing ADHD, according to the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition. People with ADHD have a consistent pattern of impulsivity and inattention that affects their functioning and development. The age of the patient, the age group, and the amount of time from the onset of the symptoms are considered while making a diagnosis [44]. Neurodevelopmental diseases can cause minor abnormalities in the structure and function of the brain, which can be detected by imaging techniques including X-rays and MRIs (T1-weighted anatomical imaging). Diffusion-tensor imaging (DTI), a relatively new technique for assessing the microstructure of the brain, measures the motion of water molecules in the white matter using scalar parameters [45]. However, these instruments can only be used to determine how the brain is structured, how it works and how it is growing.

Treatment is needed since Polanczyk, de Crisafulli *et al.* estimate that 5.29% of school-age children have ADHD [46]. The usage of stimulant medications is the most effective treatment for the symptoms of ADHD [47]. Even though there is no single treatment for ADHD, prevention, medication, and counseling can relieve symptoms. You can use either the drug or therapy alone, but combining the two will result in much greater management. General practitioners can oversee treatment under the direction of pediatricians or psychiatrists [48]. We will examine the existing approaches to treating ADHD in our study. There are both pharmaceutical and non-pharmacological treatments for ADHD, according to a study [49] by Chung *et al.* The pharmacological method of treatment uses stimulant drugs like methylphenidate and dexmethylphenidate. Clonidine and atomoxetine, which are not stimulants, also work well.

Although these stimulant and non-stimulant drugs are approved for usage in North America, they are not favoured abroad. Studies demonstrate that taking methylphenidate once daily helps to lessen the symptoms of ADHD [50, 51]. According to other research, using stimulants during adolescence can help lessen various psychiatric problems [52]. When

stimulant drugs are taken daily, there are side effects such as decreased appetite and difficulty falling asleep, but the - 2- agonists created provide the best benefits in ADHD [53, 54]. Patients are advised to undertake routine electrocardiography monitoring before and during the administration of stimulant drugs to prevent major side effects such as blood pressure and heart rate increases. According to studies, stimulant drugs are more effective than non-stimulant ones [55]. Stimulants, non-stimulants and behavioural therapy are all ADHD drugs that have received FDA approval to treat the condition's symptoms. You can utilize stimulants that contain amphetamine, methylphenidate, or both. In ADHD-afflicted hyperactive children, they have a reduced effect. They raise dopamine levels, linked to motivation, focus and movement in the brain. Atomoxetine, guanfacine and clonidine are the three non-stimulants that are employed. For kids who cannot take stimulants, these non-stimulants are an alternative to stimulants. Children aged 6 and older are the target audience for these drugs' safety and efficacy tests [56].

Studies on non-pharmacological therapies include omega-fatty acid supplements, neurofeedback, behavioral therapy, and parent or child training. When compared to an attention skills control condition, neurofeedback significantly reduces the symptoms of ADHD, according to a study done by researchers utilizing it as the primary and primary evaluation method [57]. Another study that used neurofeedback as its main method revealed that, when compared to the controls, ADHD symptoms had significantly improved. The average stimulant medication dose was also increased for the control group patients [58]. A study that focused mostly on behavioral therapy found that depression and anxiety have improved. The study involved taking control group ratings on the depression and anxiety scales. The study's participants in the 3-to-12-month age range were assessed. The study also notes that conduct disorder in children has improved more than other behavioral disorders [59]. Research results for the kid or parent training, studies with 120 participants using behavioral interventions such as organization skills, interpersonal skills, paying attention in class, parenting practices, sleep hygiene, and parent-teacherbehavioral teaching, helped parents learn how to deal with their emotional responses, but that the majority of programs had been designed to help parents manage specific behaviors in their own ADHD children [60]. A study comparing behaviorally-based interpersonal training skills for the patient and parental groups to group therapy found a substantial difference in ADHD grading rubric IV at 6 months compared to non-pharmacologic treatment with children or parent training [61].

Another study with 57 participants compared conventional drug therapy with behavioral therapy for kids together with parent and teacher training. The results showed that after 20 weeks of follow-up, there had been noticeable improvements in the combined visual and auditory continuous performance. A large amount of focus was seen [62]. When researchers conducted a study using 1130 patients as participants wherein essential fatty acid supplements were assessed by comparing with a placebo in 7 trials, they used dietary supplements containing omega fatty acids as the principal interventions. Four trials demonstrated the active role of omega-3 by itself. Omega-3 and omega-6 combinations were visible in two trials. One trace only displayed omega-6. Ages 6 to 18 were involved in the study, which lasted six months and seven weeks [63, 64, 65].

RESULTS: According to the study's findings, ADHD is a neurodevelopmental condition affecting children and adults in some situations. Although the cause of ADHD is uncertain, numerous studies are continuously being done to understand the condition better. According to numerous researchers, scientists, psychiatrists and medical professionals, ADHD is brought on by genetic, environmental, low birth weight and pregnancy-related issues. Even though the disorder's pathophysiology is not fully known, researchers explain that children with ADHD will have alterations in the brain's structure, growth and function compared to children without the condition. The prefrontal basal cortex, the frontostriatal region, and the cerebellum are the brain's three most damaged areas. Numerous investigations have shown that the frontostriatal region is more severely impacted than other regions. A few research also explains that children with ADHD have structural and functional changes

in the frontostriatal circuitry's extraneural regions, primarily the cerebellum and parietal lobes. The volume of the cerebellum has decreased, according to another research. Our analysis concentrated on inherited ADHD. Siblings of people with ADHD had a higher risk of developing ADHD, according to research comparing it to family, twin, and adoption studies.

Additionally, the study shows that biologically adopted relatives have a higher risk of ADHD than adoptive relatives. There is, however, little solid proof that inherited factors contribute to ADHD. Additionally, research demonstrates conflicting opinions about the relationship between certain chromosomal regions, genes, and ADHD. It is essential to address the hereditary complexity of ADHD as a result. The study also offers information on how ADHD is treated.

Along with the therapy, the treatment also comprises pharmacological and non-pharmacological procedures. Behavioral therapy, parent training in behavior control and dietary supplements are all included in the treatment. Our study also discusses the stimulant and non-stimulant drugs used for therapy that the FDA has licensed. Stimulants are the most popular and well-known ADHD treatments, according to our data.

CONCLUSION: Our research has found that ADHD is a hereditary illness that primarily affects children. It may persist throughout adulthood in some circumstances. ADHD patients exhibit significant effects on many brain regions. Both structural and functional changes could occur. Since there is no complete cure for ADHD, the symptoms can be treated with stimulants, non-stimulants, or in some circumstances, treatment. We conclude that to detect and treat the disease, this study area necessitates extensive research and exposure.

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