Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by inattentiveness, hyperactivity, and impulsivity [1]. There is a rapidly growing body of research regarding all aspects of ADHD, both in the basic and clinical sciences. The goal of this review is to compound this information, including the anatomy, pathophysiology, and clinical presentations of ADHD.

Background

Introduction

Symptoms of ADHD are classified as either Inattention or Hyperactivity/Impulsivity. Inattention symptoms include carelessness, distractibility, easily sidetracked, disorganization, misplaces necessary items often, and forgetfulness. Hyperactivity symptoms include restlessness, impulsivity, impatience, intrusiveness, inability to play quietly, and excessive talking. Symptoms usually start in childhood and may persist into adulthood if left untreated. The DSM-5 revised the ADHD diagnostic criteria regarding symptoms, age of onset, and symptom exclusivity. The number of symptoms required for diagnosis in either category (inattention or hyperactivity) has been reduced from 6 to 5 for older adolescents/adults. Age of onset has raised the age limit for initial symptom onset from 7 to 12. ADHD is often treated with medication, therapy, or a combination of both to help manage the symptoms and improve daily functioning for affected individuals [1].

Prevalence

The prevalence of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents is an important topic, given that treatment options for this condition are increasing in the U.S. Accurate measurements of ADHD rates across different groups, locations, and regions can help inform decisions made by healthcare providers, policymakers, and public health officials on how best to allocate resources to manage and control this psychiatric disorder [2]. Studies show that the prevalence of ADHD is quite high among children and adolescents. Based on meta-analytical data, it has been estimated that approximately 5% to 10% of school-aged children in the U.S. have been diagnosed with this condition [3]. These rates are not only high but also show a significant degree of geographic variation across different regions and sociodemographic groups [4]. Researchers have also identified "hot spots" or areas with higher prevalence rates of ADHD, as well as "cold spots," or those regions that seem to exhibit lower than average incidence of the disorder. By identifying these patterns, healthcare providers can better target resources to support and improve care for individuals and their families within their geographical jurisdiction, whether this includes medication, psychosocial interventions, or educational supports [2].

Causes

Potential causes of attention-deficit/hyperactivity disorder (ADHD) involve abnormalities in brain structure and function, along with genetic factors [5]. Although the exact cause remains under investigation, new data points to a genetic component. Along with genetic factors, structural and functional defects of the brain are thought to influence the development of ADHD [6]. These abnormalities may include issues with Dopamine levels, white matter tracts, and Prefrontal Cortex functioning [5]. Furthermore, research suggests that exposure to environmental factors such as lead poisoning, prenatal alcohol exposure, and smoking during pregnancy can increase the risk for ADHD in offspring [6]. However, the precise mechanisms underlying these associations remain unclear [5]. In conclusion, ADHD has numerous potential causes rooted in brain abnormalities, genetics, and environmental factors. While the exact etiology remains elusive, ongoing research continues to shed light on this complex disorder.

Risk Factors

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children that has been associated with several risk factors. These risk factors can be categorized into genetic, environmental, socioeconomic, maternal smoking, and low birth weight factors. Genetic factors have been identified as one of the primary causes of ADHD. Studies have shown that individuals with a family history of ADHD are more likely to develop the disorder themselves [7]. Additionally, certain genes have been linked to an increased risk of developing ADHD, such as those involved in Dopamine regulation and synaptic transmission.  Environmental factors also play a significant role in the development of ADHD. Exposure to environmental toxins such as lead, and mercury has been associated with an increased risk of developing the disorder [1]. Furthermore, factors like poor nutrition, exposure to pollution, and traumatic experiences can all contribute to the development of ADHD. Socioeconomic factors, particularly living in disadvantaged conditions or having a low socioeconomic status, have also been linked to an increased risk of developing ADHD [5]. This may be due to stress and unsupportive home environments. Additionally, lower access to healthcare services in underserved areas could hinder the timely diagnosis and treatment of ADHD [2]. Maternal smoking during pregnancy has also been identified as a risk factor for ADHD [1]. Exposure to Nicotine and other chemicals found in tobacco can alter the normal development of the fetal brain, leading to an increased risk of developing ADHD [8]. However, this risk has been shown to be potentially confounded by genetic risk as well. Finally, low birth weight is another risk factor associated with ADHD. Infants small for gestational age have been shown to have three times higher rates of meeting ADHD diagnostic criteria as children [9]. In conclusion, there are several risk factors that contribute to the development of ADHD in children. These include genetic factors, environmental exposures, socioeconomic status, maternal smoking during pregnancy, and low birth weight. By understanding these risk factors, healthcare professionals can work towards developing appropriate preventative and therapeutic strategies for individuals at high risk of developing ADHD.

Comorbidities

Comorbidities are co-occurring conditions that can be present in individuals diagnosed with attention deficit hyperactivity disorder (ADHD). These comorbidities may impact the presentation, prognosis, and treatment of ADHD. Some common comorbidities associated with ADHD include other neuropsychiatric disorders, conduct problems, substance use disorders, mood disorders, and anxiety disorders [10]. The presence of comorbid conditions in patients with ADHD has been found to negatively impact various outcomes, including symptom severity, quality of life, and overall functioning [11]. It is essential to note that comorbidities may require separate or additional treatment interventions beyond those targeting ADHD symptoms. Consequently, proper evaluation, diagnosis, and management of comorbid conditions are crucial for optimal outcomes in patients with ADHD.

Anatomy

Amygdala

The Amygdala, which is located within the limbic system, is a small almond-shaped structure found deep within the brain. It plays a crucial role in regulating emotions, fear responses, and the storage of memories, particularly those associated with negative or traumatic experiences. The Amygdala's diverse structure consists of five major functional groups: basolateral nuclei, cortical-like nuclei, central nuclei, other amygdaloid nuclei, and extended Amygdala. The Amygdala is connected to other parts of the brain involved in emotional regulation, such as the Prefrontal Cortex and the Hypothalamus, allowing it to coordinate its activity with other areas. Understanding the anatomy of the Amygdala can help medical professionals better diagnose, treat, and care for patients with these conditions [12].

Prior studies have shown associations between abnormalities of the Amygdala and irritability [13]. Irritability is associated with several psychiatric disorders, including ADHD [14]. Suk et al took an additional step, exploring the associations of irritability with activation of the Amygdala, and the associations of facial expression processing with activation of the Amygdala. They recruited 59 children with disruptive mood and behavior disorder aged 10-18 with a self-reported Affective Reactivity Index (ARI) of at least 4. Major findings include increased activation in several regions of the brain in response to positive and negative facial expressions (happiness and fear). The regions of the brain were the right Amygdala, right Precuneus, right Cingulate Gyrus, bilateral Cerebellum, right Superior Frontal Gyrus, right Middle Occipital Gyrus, and Middle Temporal Gyrus [13].

Mukherjee et al aimed to examine the relationship between irritability in ADHD-Combined Presentation and altered functional connectivity. Functional connectivity was measured using Resting-state fMRI of the Amygdala and Nucleus Accumbens in ADHD patients aged 12-23. Irritability was positively correlated with atypical functional connectivity. The Amygdala had greater connectivity with the right Inferior Frontal Gyrus and Caudate/Putamen, and less functional connectivity with the Precuneus [14].

Basal Ganglia

The Basal Ganglia consist of several, adjacent structures deep to the Cerebrum. These structures are the Striatum, Subthalamic Nucleus, and Substantia Nigra. The Striatum contains the Caudate, Nucleus Accumbens, Olfactory Tubercle, and Lenticular Nuclei. The Lenticular Nuclei are the Putamen, Globus Pallidus Externus, and Globus Pallidus Internus [15].

Tang et al investigated the association between Basal Ganglia morphology and motor response control. ADHD children aged 8-12 were evaluated via go/no-go tasks and shape-based morphometric analyses of T1-weighted 3D MPRAGE images using a 3T scanner. The results showed decreased volumes and inward deformation of the Putamen and dorsal Globus Pallidus in male, ADHD children relative to male controls. The same findings were absent in female, ADHD children relative to female controls. There was also a positive correlation between decreased volume/inward deformation of these structures and poorer motor response control [16].

Shvarzman et al used Diffusion Tensor Imaging (DTI) to investigate levels of iron deposition in the Basal Ganglia and their association with ADHD. They recruited ADHD children aged 8-12 for DTI of their brains, and also utilized brain-behavior analyses. They found that ADHD children had reduced iron in the bilateral limbic Striatum. Lower tissue-iron levels in the bilateral limbic Striatum correlated with anxious, depressive, and affective symptom severity [17].

Cascone et al used MRI and fMRI to assess intrinsic dopamine availability in the Basal Ganglia and Thalamus of ADHD children aged 8-12. The ADHD-only participants also underwent a crossover Methylphenidate challenge. They found that increased iron in the Putamen was negatively associated with successful response inhibition regardless of ADHD-status. During their crossover challenge, they also found that higher Putamen and Caudate iron levels positively correlated with better response to Methylphenidate. This was seen in the ADHD children's improved task performance with Methylphenidate [18].

Caudate

The caudate nucleus is a crucial subcortical structure in the brain, located in the striatum of the basal ganglia, lateral to the thalamus. It consists of three parts - the anterior head, body, and tail, which work together with the putamen to contribute to cognitive, emotional, and learning processes. The caudate head is connected to the lateral and medial prefrontal cortices and manages memory acquisition, storage, retrieval, and manipulation. The caudate body and tail modulate learning acquisition. Their neurons primarily consist of GABAergic medium spiny neurons that inhibit other basal ganglia structures [19].

Greven et al conducted a cross-sectional study with the goal of detecting associations with brain structure volume with ADHD. They used brain MRI data from the Dutch NeuroIMAGE sample dataset of ADHD children and adult patients, unaffected siblings, and typically developing control individuals. They were measuring volumes of the whole brain, along with the caudate nucleus, putamen, nucleus accumbens, amygdala, globus pallidus, hippocampus, thalamus, and brainstem. The findings in ADHD patients consisted of a 2.5% decrease in total brain volume of ADHD patients, 3% decrease in total gray matter volume. Unaffected siblings had increased total brain volume relative to ADHD patients, but still decreased total brain volume relative to typically developing controls. Age appeared to be negatively associated with caudate and putamen volumes in typically developing controls. However, in ADHD patients and their unaffected siblings, age had no statistically significant association with caudate/putamen volumes [20].

Dang et al aimed to clarify the relationship between caudate asymmetry and ADHD symptoms. T1-weighted MRI scans of adults aged 18-35 were analyzed for caudate asymmetry. The ADHD score from the Test of Variables of Attention (TOVA) was used to assess attentional problems, while impulsivity, was measured using the Barratt Impulsiveness Scale, a self-report measure. The findings suggest that larger right relative to left caudate volumes correlate with higher attentional impulsiveness and worse ADHD scores on the TOVA [21].

Yang et al examined the dorsal caudate's functional connectivity with other parts of the brain in children with ADHD, using resting-state functional connectivity data from MRI scans. The results showed the dorsal caudate's positive connectivity with prefrontal areas, cingulate cortex, and temporal lobe, as well as its negative connectivity with precuneus, occipital cortices, and cerebellum. A correlation between the left dorsal caudate's connection to the left inferior frontal gyrus and severity of ADHD was also found [23].

Damiani et al aimed to clarify the relationship between subcortical regions and ADHD. Whole-brain voxel-wise resting state functional connectivity (rsFC) was measured via fMRI of ADHD children aged 7 to 18. Total ADHD, Hyperactivity and Inattention scores were collected using the Conners’ Parent Rating Scale Revised, Long Version, in order to evaluate associations between rsFC changes and ADHD. Structures of focus were the caudate, amygdala, putamen, pallidum and hippocampus. The study found that the caudate nucleus showed increased rsFC with the anterior cingulate and right insula. They also found that the increased rsFC of the caudate nucleus positively correlated with ADHD symptomatology [23].

Cerebellum

The cerebellum is an integral part of the human brain involved in vital motor function and balance control. It is in the posterior cranial fossa, posterior to the fourth ventricle. This area can be damaged in humans leading to a loss of controlled muscles movements, difficulty with balance and learning new motor skills [24].

Goetz et al aimed to investigate the relationship between ADHD and cerebellar/balance deficits. The study included ADHD children aged 7-11 that were using the Phyaction Balance Board, and evaluated with an international ataxia rating scale and Conners’ Continuous Performance Test. The results showed that ADHD patients' balancing task performance and sway amplitudes were poorer than the control group [25].

Wu et al aimed to understand the neural mechanisms of emotional dysregulation (ED) in children with ADHD and MDD. Participants included 22 ADHD and 21 MDD patients, all with clinical ED. These patients underwent resting-state functional connectivity analysis, voxel-based morphometry, and diffusion tensor imaging analysis, along with clinical rating scales for ED, ADHD, and MDD. The results showed increased rsFC in the cerebellum and supramarginal gyrus, decreased rsFC in the right supplementary motor area and right lateral parietal area, lower gray matter (GM) volume in the SMG, and both RSFC and GM were correlated with clinical rating scale scores for all patients with ED due to ADHD or MDD [26].

Cingulate Gyrus

The cingulate gyrus and cortex reside within the medial surface of the cerebral hemisphere and are part of the limbic system, playing a crucial role in numerous vital neural circuits which interact with structures such as the reward area of the limbic cortex. The set of Brodmann areas 24, 25, 32, 33, 23, 29, 30, and 31 constitute the cingulate gyrus. This information is important for understanding the anatomy of the brain's limbic system, which plays a critical role in regulating emotions, motivation, and cognitive function [27].

Bauer et al aimed to investigate glutamate levels in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) of adults with ADHD and healthy controls using single-voxel proton MRS on a 3T scanner. Results showed increased ACC glutamate levels in ADHD patients, and a positive correlation between glutamate levels in the ACC and severity of hyperactivity/impulsivity symptoms in ADHD patients [28].

Bonath et al utilized voxel-based morphometry with DARTEL to measure regional gray matter volumes. The Culture Fair Intelligence Test and the d2-test were used to assess selective attention performance. Together these were analyzed to find correlations between gray matter abnormalities and ADHD symptoms. The researchers found that subjects with ADHD exhibited reduced GM volume in the anterior cingulate cortex (ACC), occipital cortex, bilateral hippocampus/amygdala, and widespread regions of the cerebellum in ADHD patients. GM volume in the ACC was negatively associated with test scores of selective inattention [29].

Fernandez-Jaen et al investigated the association between dopamine transporter gene (DAT1) 3´UTR genotype and the cingulate cortical thickness in ADHD patients. Using brain MRIs from 46 ADHD patients homozygous for the 10-repeat allele and 52 ADHD patients with either 0 or 1 copies of the allele, researchers found that the homozygous individuals had increased thickness in the right cingulate gyrus and right Brodmann Area 24 [30].

Zhan et al aimed to examine the subgenual anterior cingulate cortex (sgACC) of children diagnosed with ADHD-combined type (ADHD-C). The ADHD-C patients underwent Diffusion tensor imaging (DTI), resting-state functional MRI (rs-fMRI), and clinical DSM-IV scoring of ADHD symptoms. They found a disconnected functional network between the sgACC, and the occipital lobe and cerebellum. Results also showed disrupted white matter in the subgenual cingulum bundle (sgCB), increased variability of spontaneous brain activity in the sgACC, and higher radial diffusivity in the sgCB. From their analyses, they found a negative correlation between increased clincal scores with sgACC spontaneous brain activity [31].

Baytunca et al examined dynamic regional cerebral blood flow alterations of ADHD children using event-related Arterial spin labeling (ASL) scanning. 17 healthy controls and 20 children with ADHD were scanned on a 3 Tesla MRI scanner during a go/no-go task. The right anterior cingulate cortex, frontopolar cortex, and orbitofrontal cortex (Brodmann Areas 32, 10, 11) activation was increased in ADHD children during the attention task [32].

Corpus Callosum

The corpus callosum is a crucial white matter structure in the brain that connects the left and right hemispheres to facilitate communication between them. Anatomically, it is divided into four parts: rostrum, genu, body, and splenium. It consists of approximately 200 million heavily myelinated nerve fibers. The corpus callosum is pivotal in integrating and transferring sensory, motor, and high-level cognitive signals between the two hemispheres [33].

Luders et al investigated whether there is a link between ADHD symptoms in adults over 60 years old and the thickness of their corpus callosum. Results indicated that in males the thickness of anterior third, anterior/posterior midbody, isthmus, and splenium of the corpus callosum was negatively correlated with inattention and hyperactivity. Females exhibited a positive correlation between the thickness of the rostral body of the corpus callosum and hyperactivity [34].

El-Hadad et al explored the changes in the white matter of the corpus callosum and their association with ADHD symptoms. In a case-control study conducted at Menoufia University Hospitals, researchers recruited ADHD children aged 3-14. Both behavioral and cognitive functions were evaluated by studying brain Diffusion Tensor Imaging (DTI) in correlation with radiological data from both groups. The results showed that the isthmus of the corpus callosum had a mean FA value lower in the ADHD group, indicating reduced white matter consistency [35].

Globus Pallidus

The globus pallidus (GP) is located subcortical and medial to the putamen. It is named after its paleness due to relatively increased myelin, contrasting with the darker appearance of the neighboring structures. White matter encapsulates and splits the GP, into globus pallidus externus (GPe) and globus pallidus internus (GPi). GPe is the lateral subdivision, while GPe is the medial one. It works in tandem with the caudate nucleus and putamen, as these structures provide the majority of the Inhibitory input (GABAergic). The GP is heavily involved in controlling conscious and proprioceptive movements, with GPe acting as a relay for information, while GPi outputs to the thalamus [36].

Dupont et al aimed to investigate associations between functional brain connectivity profiles and sex differences in ADHD adults. Participants underwent structural MRI and rsfMRI on a 3 T full body MR scanner and seed-based connectivity analysis of the external globus pallidus (GPe) was performed. Their results showed that male ADHD patients had decreased functional connectivity compared to female ADHD patients, specifically between GPe, and left middle temporal/right middle frontal gyri. Surprisingly, they also found that female healthy controls had even lower FC than ADHD males, while male healthy controls had even higher FC than ADHD females [37].

Hippocampus

The hippocampus is a key component of the brain that plays a vital role in memory consolidation, decision-making, and other cognitive functions. It is located within the inferior temporal horn of the lateral ventricle. Memory consolidation is a core function of the hippocampus, which is the process of generating long-term memory from short-term memory, which ensures that important information is stored for future use [38]. Its neural circuits enable the storage and retrieval of information related to place, direction, and distance, allowing us to navigate our surroundings efficiently. Furthermore, it integrates various sensory inputs and interacts with other brain regions to regulate emotional responses [39].

Nickel et al aimed to compare amygdala and hippocampus volumes using MRIs of ADHD adults and controls. Clinician-administered diagnostic interviews and self-report scales were also collected. Results showed that there was no significant difference in volume of either region. However, they found hyperactivity in specifically ADHD patients negatively correlated with left amygdala volumes [40].

Hypothalamus

The hypothalamic nuclei are split into the periventricular, medial, and lateral zones, surrounding the mammillary bodies and the third ventricle. It is connected to the cerebral cortex through the medial forebrain bundle, hippocampus through the fornix, amygdala through the stria terminalis, thalamus through the mammillothalamic tract, pituitary through the median eminence, and retina through the retinohypothalamic tract. Through a multitude of direct connections and interplay between the different anatomical areas in this motor hierarchy, the hypothalamus serves as the integrator and modulator of this network, ultimately allowing it to respond adaptively to both internal and external cues in order to maintain homeostasis [41].

Ma et al investigated the association between the hypothalamus–pituitary–adrenal (HPA) axis and ADHD in non-stress states. Participants were male children with ADHD aged 6 to 14. ADHD was delineated into three sub-groups: ADHD-predominantly inattention type (ADHD-I), ADHD-predominantly hyperactive impulsive type (ADHD-HI), and ADHD-combined type (ADHD-C). The levels of cortisol and adrenocorticotropin hormone (ACTH) were evaluated per morning (8:00 am). and ADHD patients overall showed decreased cortisol relative to the control group. The ADHD-HI group specifically showed even further decreased cortisol relative to the other two groups (ADHD-I and ADHD-C). No associations regarding ACTH were found [42].

Middle Frontal Gyrus

The middle frontal gyrus (MFG), part of the prefrontal cortex, plays an essential role in human cognitive function, facilitating attention, working memory, and language processing. It is located lateral to the superior frontal gyrus and medial to the inferior frontal gyrus. Various functional magnetic resonance imaging (fMRI) studies have shown that this region is actively involved in attentional processes [43].

Tafazoli et al explores the middle frontal gyrus levels of major metabolites in children diagnosed with attention deficit hyperactivity disorder (ADHD). The results indicate decreased metabolite levels, including Cr (creatine and phosphocreatine), in ADHD subjects particularly in the right MFG. Cr was positively correlated with performance on attention tests and decreases in this metabolite may be associated with either ADHD or pharmacological treatment of these individuals with methylphenidate [44].

Nucleus Accumbens

The nucleus accumbens (NAc) is a crucial part of the basal ganglia, located in the ventral portion of the striatum. It receives direct input from various brain regions such as the amygdala, hippocampus, thalamus, and prefrontal cortex through excitatory glutamatergic projections. Additionally, it also receives indirect dopaminergic inputs from the substantia nigra pars compacta. The NAc is a key component in modulating emotional responses, reward processing, and motor function [45].

In the study discussed earlier, Mukherjee et al found that the Nucleus Accumbens showed a positive correlation between irritability and greater functional connectivity with the left Posterior Middle Temporal Gyrus and Precuneus [14].

Pituitary

The Pituitary Gland is located inside the sella turcica of the sphenoid bone and is divided into the anterior lobe and posterior lobe. The pituitary gland produces hormones that regulate various physiological processes, such as growth, metabolism, reproduction, and sleep cycles. It also regulates the release of adrenocortical hormones such as cortisol which modulates the response to stress [46].

West et al aimed to investigate if the different ADHD subtypes of inattentive (ADHD-I) and combined (ADHD-C) showed distinct cortisol reactivity responses to a psychosocial stressor compared with typically developing children. Participants studied include 52 children with ADHD-C, 23 children with ADHD-I, and 25 healthy control subjects. Stress was measured by comparing cortisol responses after a public speaking task. ADHD-I showed higher cortisol responsivity, while those with ADHD-C displayed blunted cortisol responses. Hyperactivity symptoms were linked to lower cortisol responsivity to stress. These findings suggest that low cortisol responsivity to stress might be a neurobiological marker for ADHD-C [47].

Fairchild et al aimed to understand if hyperactive/impulsive or combined type attention-deficit hyperactivity disorder (ADHD) has reduced basal cortisol secretion or cortisol hyporeactivity. Children with ADHD and comorbid oppositional defiant disorder demonstrated decreased basal cortisol and a decreased cortisol awakening responsivity. However, some studies reporting normal cortisol responses and others showing blunted cortisol responses in non-comorbid ADHD [48].

Putamen

The putamen, located in the basal ganglia's dorsal portion, works in a complex cortico-basal ganglia network. It is responsible for integrating distinct functional channels and directing coordinated actions, adjusted according to external and internal stimuli. The putamen and globus pallidus make up the lentiform nucleus. It also combines with the caudate nucleus to form the striatum, which is part of the basal ganglia. Its roles include modulating learning, motor control, speech articulation, reward cognitive processes and addiction [49].

Max et al aimed to examine the association between focal stroke lesions in children and ADHD/ADHD traits, however it's important to note that sample size of this study was understandably very small, with main results derived from 13 children. Participants underwent psychiatric assessments including the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) and brain MRIs. There was a trend showing increased presence of ADHD/ADHD traits in children with putamen lesions, with the densest overlapping region of the collective lesions being the posterior ventral putamen [50].

Cao et al aimed to explore differences in putamen functional connectivity between medication-naïve ADHD children and typically developing children. ADHD children relative to controls had, increased left putamen FC with the right globus pallidus/thalamus, decreased left putamen positive FC with the right frontal and limbic regions, decreased left putamen negative FC with the right cerebellum and right temporal lobe, and decreased right putamen negative FC with the left cerebellum and right precuneus [51].

Xu et al investigated a specific genetic variant, rs945270 (reported to affect putamen volume), linked with increased symptoms of attention-deficit/hyperactivity disorder (ADHD). They used a large sample size of 1834, 14-year-old children and analyzed ADHD symptoms via their Strengths and Difficulties Questionnaire (SDQ). They also analyzed the Region-of-interest (ROI) analyses of putamen activation by functional magnetic resonance imaging (fMRI) using the Stop Signal (SST, for assessing response inhibition) and monetary incentive delay (MID, for assessing reward sensitivity) tasks. They found that the C-allele at rs945270 was negatively correlated with symptom scores, especially hyperactivity. However, in males, the c-allele was negative correlated with putamen activity during successful response inhibition, regardless of ADHD symptoms. In females, the c-allele was positive correlated with right putamen activity during reward anticipation [53].

Striatum

The striatum is a subcortical structure within the basal ganglia, consisting primarily of GABAergic projection neurons (SPNs) that receive glutamatergic inputs from various regions of the cerebral cortex, thalamus, and limbic system. Cortico-/thalamo-striatal projections carry these signals, and these signals are essential for controlling motor, procedural, and reinforcement-based behaviors in mammals [54].

Volkow et al conducted a prospective study of the association of localized dopamine increases and long-term clinical response to treatment with stimulant medications like methylphenidate in patients diagnosed with ADHD. Using positron emission tomography, researchers found that dopamine increases in the ventral striatum were associated with reductions in symptoms of inattention during long-term methylphenidate treatment. The study also showed that increased dopamine in the temporal and prefrontal cortices led to improved ADHD symptoms [55].

Hulst et al aimed to examine changes in performance and fMRI activity during the anticipation of reward in children with ADHD symptoms, regardless of a primary diagnosis of ADHD. A total of 76 boys, aged 8–12 years were involved. This included 27 typically developing children and 49 boys who displayed symptoms of ADHD. Of those displaying symptoms 24 had a diagnosis of adhd and 25 had a diagnosis of ASD with ADHD symptoms. They used event-related fMRI to assess performance and ventral striatum activation during reward anticipation. The results showed that children with ADHD symptoms, regardless of diagnosis, had reduced ventral striatum activity during reward anticipation. There was a positive relationship between parent-rated sensitivity to reward and greater anticipatory ventral striatum activity in children with ADHD symptoms. However, no quantitative correlation was found between ventral striatum activity and ADHD symptom severity [56].

Chen et al aimed to explore differences in dorsal striatum functional connectivity (FC) between men and women with attention deficit hyperactivity disorder (ADHD). The researchers used resting state fMRI data of adult participants curated from the Human Connectome Project. They performed seed-based correlations for caudate and lentiform nucleus (LN) FC and examined associations between ADHD symptom severity, inattention, and hyperactivity and specific patterns of dorsal striatum connectivity. In men, inattention was negatively correlated with LN FC with the right superior frontal gyrus. In women, inattention was negatively correlated with caudate FC with the right inferior parietal gyrus and positively correlated with LN FC with the left inferior frontal gyrus. Also in women, hyperactivity was positively associated with LN FC with a cluster in the dorsal anterior cingulate cortex and supplementary motor area [57].

Substantia Nigra

The substantia nigra (SN) is an essential part of the midbrain, playing a crucial role in regulating motor control and reward functions through its involvement in the basal ganglia. The SN consists of two regions, pars compacta (SNpc) and pars reticulata (SNpr). The SNpc contains dopaminergic neurons while the SNpr has gamma-aminobutyric acid-containing (GABAergic) neurons. SN projections to the putamen make up the nigrostriatal pathway. SN dopaminergic neural projections travel through the medial forebrain bundle and form connections with other regions of the brain, affecting a wide range of functions including cognitive, emotional, and motor control [58].

Tomasi et al aimed to investigate the maturation of dopaminergic (DA) pathways from over time and explore any differences in healthy children, children with ADHD, and young adults. The researchers used a total of 1420 “resting-state” functional scans of children and adults to examine changes in connectivity patterns between the ventral tegmental area (VTA) and substantia nigra (SN) in relation to age. They found that functional connectivity matures significantly over time and varies by age group. Age-related increases of the VTA FC were found with limbic regions and default mode network. Age-related decreases of the SN FC were found with motor and medial temporal cortices. ADHD children had greater VTA FC in amygdala, left parahippocampus, right globus pallidus, left thalamus, and right insula, and greater SN FC in amygdala and insula than TDC. ADHD children had stronger VTA FC in thalamus, subthalamic nucleus, globus pallidus and stronger SN FC in left amygdala and insula than TDC. In ADHD children, age-related VTA FC increases in superior frontal/precentral gyri, ACC, inferior OFC, and insula, and age-related SN FC decreases in precentral gyrus, paracentral lobe, and lingual gyrus [59].

The cross-sectional, analytical study measured size and echogenicity of the substantia nigra using TCS to determine an association between these and ADHD. Participants included 34 ADHD and 34 healthy individuals aged 6–12 years. Results showed increased SN hyper-echogenicity and decreased thalamic nuclei hypo-echogenicity in ADHD children. Typically developing children with a family history of ADHD showed similar results for ADHD children [60].

Thalamus

The thalamus is a central structure of the diencephalon composed of mostly gray matter. It connects with the contralateral thalamus through the interthalamic adhesion. It is bounded laterally by the internal capsule and anterolaterally by the caudate head. Each thalamic side can be divided into three groups: lateral, medial, and anterior nuclei. These are split by the internal medullary lamina [61]. In addition to anatomic grouping, these nuclei can also be categorized based on function. There are three categories: Relay (lateral nuclear group, medial nuclear group, and anterior nuclear group), Reticular, and Intralaminar nuclei. Relay nuclei projections target specific cortical areas and the nuclei have been split into lateral nuclear group (ventral posterolateral, ventral posteromedial, and lateral geniculate nuclei), medial nuclear group (medial and pars paramediana) and anterior nuclear group [62].

Li et al aimed to examine the neurobiological basis of inattentiveness in ADHD by analyzing functional MRI data from children and young adolescents with the disorder. The objective was to investigate cortico-pulvinar functional pathways during sustained attention and their association symptoms of inattentiveness. The method used to conduct the study involved analyzing visual attention task-based fMRI data from 22 ADHD children and 22 controls. Results indicated that subjects with ADHD exhibited reduced pulvinar activations bilaterally, decreased bilateral pulvinar FC with the right prefrontal regions, and increased right pulvinar FC with the bilateral occipital regions. Additionally, the left pulvinar activation magnitude had a negative correlation with the DSM-IV inattentive index for the ADHD group [63].

Fu et al conducted a cross-sectional analysis that investigated neuroanatomical alterations related to ADHD diagnosis and subtype, focusing on subjects without comorbidity. 121 children with uncomorbid ADHD (54 iADHD and 67 cADHD) were analyzed using T1-weighted structural MRI images from the ADHD-200 database. Regional GM increase of the right thalamus and precentral gyrus was found to be linked only to the inattentive subtype. The right thalamus volume positively correlated with inattentive severity in iADHD [64].

Physiology

In ADHD research, it is widely accepted that multiple neurotransmitters are involved, such as serotonin, acetylcholine, glutamate, and opioids. However, the most studied pathways are dopaminergic and noradrenergic ones. Patients with ADHD usually experience reduced brain size in areas like the prefrontal cortex, corpus callosum, cerebellar vermis, caudate nucleus, and globus pallidus. In addition, research has discovered genetic polymorphisms related to the D4 and D5 receptors and the dopamine transporter (DAT), which have been found to cause dysfunctions in the dopaminergic system [65].

Dopamine

Dopamine is a chemical messenger or neurotransmitter in the brain that plays an essential role in regulating functions such as motivation, cognitive function, and motor control. In ADHD, there is believed to be a deficiency of dopamine transmission due to several factors: genetic predisposition, environmental exposure, and/or prenatal developmental issues. This theory explains the efﬁcacy of methylphenidate (MPH) and dextroamphetamine in treating ADHD symptoms because they help normalize dopamine levels, thereby reducing hyperactivity and improving attention span. The role of dopamine in ADHD is supported by various lines of evidence, including the efﬁcacy of psychostimulant drugs, genetic predisposition, environmental factors, and the recent increase in research investigating the involvement of dopamine receptors.

DRD1, or the Dopamine Receptor D1 gene, has been implicated in the pathophysiology of Attention-Deficit Hyperactivity Disorder (ADHD). Recent studies on individuals diagnosed with ADHD have found an initial association between this genetic variation and symptoms of hyperactivity and attention deficits. This correlation may lead to future research and development of targeted treatment options for ADHD, focusing on the specific role of DRD1 in patients experiencing these symptoms. Ribases et al aimed to evaluate the contribution of DRD1, DRD2, DRD3, DRD4, DRD5, DAT1, TH, DBH and COMT to attention-deficit hyperactivity disorder (ADHD). They conducted a case-control study of genotyped 533 ADHD patients and 533 sex-matched unrelated controls. Only one of the tested DRD1 SNPs were correlated with ADHD in children (rs265977). A two-marker haplotype (rs863126–rs265977) was specifically associated with childhood combined-type ADHD. The latter analysis was replicated in an independent sample of German families with combined-type ADHD children, which found the haplotype rs835541–rs863126 to be associated with cADHD [66]. Yokokura et al aimed to investigate the roles of dopamine D1 receptors (D1Rs) and microglial activation in attention-deficit/hyperactivity disorder (ADHD), using positron emission tomography (PET). Twenty-four ADHD individuals underwent PET measurements for D1Rs and activated microglia. The ADHD group showed reduced anterior cingulate cortex (ACC) D1R, while increased microglial activation was found in the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC). This reduction in D1R correlated with severity of hyperactivity in ADHD individuals, while increased microglial activation correlated with processing speed/attentional deficits specifically in the ADHD group [67].

The DRD2 gene, which encodes the dopamine receptor D2, has been extensively studied in relation to attention deficit hyperactivity disorder (ADHD). Moro et al investigated the association between Taq1A polymorphism and ADHD in children. DRD2-Taq1A gene polymorphism was genotyped in 50 ADHD patients and 50 controls. Phenotype distributions of A1 allele were positively correlated with ADHD, as did the heterozygous A1A2 genotype. In addition, ADHD cases showed lower distribution of the homozygous A2A2 genotype [68]. Safavi et al aimed to examine changes in two specific polymorphisms, rs2283265 and rs27072, within the dopamine receptor D2 (DRD2) and dopamine transporter gene (SLC6A3), respectively, in ADHD patients. The methods employed involved a descriptive-analytical study with 100 ADHD patients and 100 controls to analyze rs2283265 and rs27072 polymorphisms. The GG genotypes of both polymorphisms, rs2283265 (DRD2) and rs27072 (SLC6A3), were positively correlated with ADHD [69].

DRD3, also known as the Dopamine receptor 3 gene, plays a significant role in the etiology of ADHD (attention deficit hyperactivity disorder) symptomatology. The overall role of DRD3 in ADHD (Attention-Deficit/Hyperactivity Disorder) appears to be related to its the Catechol-O-Methyltransferase (COMT) gene [70]. Fageera et al aimed to investigate the role of candidate genes, such as DRD3 (Ser-9-Gly), in ADHD using a comprehensive approach. This included combining dimensional behavioural analysis with pharmaco-dynamic evaluation and association/linkage testing. The researchers evaluated children with ADHD at baseline observation followed by methylphenidate administration or placebo, each for one week. They assessed various quantitative behavioural and cognitive dimensions. By combining family-based (FBAT) and quantitative trait genetic analyses with nuclear families, they found the T allele was associated with poorer teacher-rated behavioral scores during the MPH week in boys. The results provide convergent evidence for DRD3 (Ser-9-Gly)'s role in ADHD and its modulation of behavior, including response to pharmacological probes [71]. Two years later, Fageera et al aimed to examine the joint effect of two functional variants in DRD3 and COMT on ADHD behaviors. Methods included assessing 362 children with ADHD by parents and teachers during a baseline evaluation, followed by one week each of MPH and placebo administered in a double-blind crossover design. Results showed statistically significant association between DRD3 and COMT genotypes and Conners’-Teachers scores. COMT Met/Met genotype had lower scores without MPH, suggesting that stratifying children according to their COMT genotypes helped detect statistically significant effects of DRD3 genotype [70].

DRD4 plays a complex and noteworthy role in the development and diagnosis of attention-deficit hyperactivity disorder (ADHD) in children. Chang et al aimed to investigate the link between organophosphate pesticides (OPs), attention-deficit/hyperactivity disorder (ADHD) in children, and their association with oxidative stress and genetic polymorphisms. The research involved 93 children diagnosed with ADHD and 112 control children from North Taiwan. They collected the serum samples of both groups to analyze six dialkyl phosphate (DAP) metabolites of OPs and oxidative stress biomarkers. Additionally, they identified the genotype variations of dopamine receptor D4 gene (DRD4) in the children with ADHD. The results revealed that children with ADHD had significantly higher dimethylphosphate (DMP) levels than control children. Furthermore, those carrying DRD4 GA/AA genotypes were less likely to have ADHD compared to DRD4 GG carriers. The estimated value of the AP (the influence of gene-environment interaction on ADHD risk) was found to be 0.59, which indicated that nearly 60% of ADHD cases in DMP-exposed children with the DRD4 GG genotype were attributed to this. The study showed that DRD4 GG children who had been exposed to high DMP and had high HNE-MA levels had an increased risk of developing ADHD [72]. This study aimed to explore the association between dopamine receptor D4 (DRD4) methylation and phthalate exposure on continuous performance test (CPT) variables in children with Attention-Deficit Hyperactivity Disorder (ADHD). The researchers analyzed urine samples to assess mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-n-butyl phthalate (MBP) levels. They also examined the methylation status of CpG sites in DRD4. The results showed a significant interaction effect between CpG26 and CpG28 methylation combined with the MEHHP level when assessing omission errors [73]. Qian et al aimed to investigate the interaction of regulating dopamine D4 receptor (DRD4) on functional brain activity during resting state in ADHD children by measuring regional homogeneity (ReHo) and functional connectivity (FC). Resting-state fMRI data was analyzed from 49 children with ADHD. DRD4 2R allele carriers had decreased ReHo in the bilateral posterior cerebellar lobes, but increased ReHo in the left angular gyrus. The study also found that DRD4 2R allele carriers showed decreased FC of multiple brain structures towards the left angular gyrus. These structures were the left striatum, right inferior frontal gyrus, and cerebellar lobes. Additionally, it was found that some structures had increased FC, such as the left superior frontal gyrus, medial frontal gyrus, and rectus gyrus [74]. Palaniyappan et al explored the effects of 7-repeat (7R) 'risk' allele polymorphism of the DRD4 gene on cortical thickness and gyrification in children with attention deficit/hyperactivity disorder (ADHD). Participants included 49 children aged 9–15 years, half of whom had ADHD. Reduced inferior frontal gyrification was observed in ADHD patients who carried the DRD4 7R allele [75]. Chen et al investigated how specific gene variants might be linked to differences in brain function among children diagnosed with ADHD, a neuropsychiatric disorder. The study focused on the dopamine D4 receptor gene (DRD4) and its relationship with resting-state functional MRI images of 49 children with ADHD and 37 healthy controls. The researchers employed two analytical approaches to examine the effects of DRD4 genotype on brain network connectivity. They measured "degrees of centrality" (DC), which is a parameter that captures functional relationships between brain structures. Significant diagnosis-by-genotype DC interactions were observed in the left inferior temporal gyrus (ITG), bilateral middle temporal gyrus (MTG), left superior parietal gyrus (SPG), and right middle frontal gyrus (MFG) [76].

DRD5 (dopamine receptor D5) is a gene that encodes the dopamine receptor D5 protein, which plays an important role in regulating various neurotransmitters involved in cognitive processes, emotional responses, and behavioral activities. Recent studies have focused on investigating the relationship between the DRD5 polymorphism (CA)n repeat located on chromosome 18 (where n can vary from 2 to 9 repeats), and attention-deficit/hyperactivity disorder (ADHD). Maitra et al aimed to investigate the contribution of DRD5 gene variants in the symptoms of ADHD, focusing on brain regions with high receptor expression and examining 22 exonic variants. Among these variants, rs6283 'C' and rs113828117 'A' exhibited higher occurrence in families with ADHD probands. Several haplotypes also showed biased occurrence in the probands. The research further reveals significant differences in genotypic frequencies between early and late onset groups, with the latter exhibiting higher hyperactivity scores. Based on these findings, the authors suggest that the age of ADHD onset may be affected by DRD5 variants, necessitating further investigation into the role of DRD5 in the disease etiology [77]. Klein et al aimed to examine the association between a specific genetic variant, the variable number tandem repeat polymorphism upstream of DRD5 gene (ADHD-associated VNTR), and adult ADHD. To do this, they utilized the International Multicentre persistent ADHD CollaboraTion (IMpACT) project's database. After gathering information from N=6979 participants, comprised of 3344 cases and 3635 healthy individuals, the study analyzed whether common DRD5 alleles were associated with adult ADHD risk or symptom counts. The findings suggest that none of the tested alleles had significant associations with these outcomes in adults [78].

Norepinephrine

Norepinephrine (NE) plays an essential role in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). Increased levels of NE have been observed in individuals with ADHD, contributing to dysregulation in neurotransmitter function. This dysregulation is thought to be significant in the pathophysiology of ADHD.

Hohmann et al investigated how variants in a gene encoding for the norepinephrine transporter (NET, SLC6A2), specifically rs3785157 and rs28386840 are associated with diagnosis and development of ADHD. Participants included children followed from age 4 to 15 years old in Germany. Diagnostic interviews were used to assess the rate of ADHD lifetime diagnosis, while the Child Behavior Checklist (CBCL) was administered at ages 8 and 15 for externalizing behavioral analyses, and a continuous performance task (CPT) exam was carried out to analyze omission errors. The study found that homozygous carriers of certain gene variants were positively correlated with developing ADHD and CBCL externalizing behavior scales. Heterozygous rs3785157 children were negatively correlated with CPT omission errors [79].

Sigurdardottir aimed to examine the effects of single nucleotide polymorphisms (SNPs) within the NET gene on norepinephrine transporter (NET) non-displaceable binding potential (BPND). 20 adult patients with ADHD and 20 healthy controls underwent PET scans using the radioligand (S, S)- [18F]FMeNER-D2. Linear mixed models analyses showed significant genetic differences in cerebellar and thalamic NET BPND between patients with ADHD and healthy controls. ADHD patients carrying the major alleles for both rs28386840 and rs2242446 had higher NET BPND in the thalamus than controls carrying the major alleles. Healthy controls carrying the major alleles for rs15534 and rs40615 had higher NET BPND in the cerebellum than ADHD patients carrying the major alleles. For the major allele in both rs15534 and rs40615, CAARS hyperactivity/impulsivity was positively associated with cerebellar NET BPND. For the minor allele group of both, CAARS hyperactivity/impulsivity was negatively associated with cerebellar NET BPND [80].

Cetin et al investigated the relationship between ADHD and NET1 gene, CES1 metabolism and ADRA2A adrenergic pathway. Participants included 114 ADHD children and 83 controls. CES1 gene Gly143Glu polymorphism (rs71647871) homozygous GG Genotype was found in all patients of the Turkish population studied. NET1 G1287A polymorphism (rs5569) was not associated with ADHD, while ADRA2A C1291G polymorphism (rs1800544) was associated with an increased risk for ADHD, particularly in males. The risk of individuals carrying NET1 G1287A AA genotype having concurrent Oppositional Defiant Disorder diagnosis was lower than those with other genotypes. Moreover, those who carried the AA genotype had higher initial attention deficit score compared to others (p=0.045) [81].

Huang et al aimed to investigate the effect of methylphenidate (MPH) in treating ADHD-diagnosed Taiwanese children and its association with the ADRA2A gene -1291C/G single nucleotide polymorphism (SNP). The subjects were given MPH for 4 weeks, and their response was evaluated by Swanson, Nolan and Pelham version IV total scores. Out of the 59 participants, 74.6% responded positively to the treatment. Interestingly, binary logistic regression analysis showed that GG homozygotes had greater responsivity to MPH treatment. [82]

Shang et al aimed to investigate if the norepinephrine transporter gene (SLC6A2) affected intrinsic brain activity in children with ADHD. Additionally, the study wanted to see if these gene-brain modulations were related to visual memory and attention. The researchers found that children with ADHD had lower ReHo and DC (which stands for Regional Homogeneity and Degree Centrality) in certain areas of their brains compared to typically developing children. Interestingly, they also found that a specific haplotype, or combination of genetic variants, was associated with right precentral and postcentral gyri increased DC. Furthermore, there were interactions between the TG haplotype and ADHD status in certain brain areas. When examining these specific ADHD-TG group participants, researchers found correlations between intrinsic brain activity (measured by ReHo) and visual memory and attention tasks. This suggests that the SLC6A2 gene may play a role in modulating intrinsic brain activity and affecting visual memory and attention in children with ADHD who have this specific haplotype [83].

Sigurdardottir et al also investigated whether abnormalities exist in norepinephrine transporter (NET) promoter DNA methylation in attention deficit hyperactivity disorder (ADHD). It was found that "region 1" of the NET promoter was hypermethylated in ADHD patients compared to controls, suggesting an epigenetic dysregulation in ADHD. Methylation at specific cytosine-phosphate-guanine (CpG) sites was negatively correlated with NET distribution in the thalamus, locus coeruleus, and the raphe nuclei [84].

Ulke et al aimed to investigate whether central NET availability is altered in adult ADHD patients compared to healthy controls, using positron emission tomography-magnetic resonance imaging (PET-MRI) and a ROI approach. The results showed that fronto-parietal-thalamic-cerebellar regions had significantly reduced NET availability in ADHD patients compared to healthy controls [85].

Harstad et al analyzed electronic health records of preschool-age children with ADHD treated across seven outpatient developmental-behavioral pediatric practices in the US. They found that improvement was reported in 66% of children who received α2-adrenergic agonists and 78% of those who received stimulants. Adverse effects were also documented, with daytime sleepiness being more common among those receiving α2-adrenergic agonists, while moodiness/irritability, appetite suppression, and difficulty sleeping were reported more frequently in the group receiving stimulants [86].

Serotonin

Serotonin (5-HT) involvement has been implicated in Attention-Deficit-Hyperactivity-Disorder (ADHD) via orbitofrontal-striatal circuitry. This neurotransmitter is involved in hyperactivity and impulsivity of ADHD, but perhaps not with inattention. Genetic variants like SLC6A4, SERT, and 5-HTT may increase risk of ADHD due to serotonin deficit. However, more research is needed to fully understand the complex relationship between serotonin and ADHD [87].

Park et al investigated if Serotonin transporter gene (SLC6A4) methylation is associated with ADHD. The study finds that SLC6A4 promoter methylation is positively correlated with worse hyperactive-impulsive symptoms. Additionally, there is a negative correlation between SLC6A4 methylation levels and right occipito-temporal cortical thickness [88].

Perroud et al investigated the relationship of childhood maltreatment with serotonin 3A receptor (5-HT3AR) methylation and its association with clinical severity outcomes. Participants included 346 bipolar, borderline personality, and adult attention deficit hyperactivity disorders patients. Clinical scoring and DNA methylation status of eight 5-HT3AR gene CpGs was collected. They found that higher severity of bipolar, borderline personality, and adult attention deficit hyperactivity disorders was associated with higher rates of childhood maltreatment. This effect was mediated by two 5-HT3AR CpGs. Higher CpG2 and CpG4 methylation was positively correlated with history of suicide attempt, prior hospitalization, and substance dependence. However, lower CpG5 methylation was positively correlated with those three variables [89].

Wang et al aimed to investigate the cumulative effect of genetic polymorphisms within the dopamine, norepinephrine, and serotonin neurotransmitter pathways on ADHD susceptibility in Chinese children. Methods included a case-control study with 168 ADHD patients and 233 controls recruited. Classification and regression tree (CART) analysis and logistic regression models were utilized. Results indicated that combined ADRA2A rs553668GG/GA and SLC6A4 rs6354 GG/GT genotypes had a 6.15-fold increased risk of ADHD, compared to combined ADRA2A rs553668 AA and ANKK1 rs1800497 AA genotypes. The unfavorable alleles of ADRA2A rs553668 G, DRD2 rs1124491 G and SLC6A4 rs6354 G showed cumulative effects on ADHD [90].

Glutamate

Glutamate is a major excitatory neurotransmitter involved in cognitive functions including learning and memory. Glutamatergic neurons play a critical role in modulating the activity of other neuronal systems, such as the noradrenergic, dopaminergic, and serotonergic systems, which are also implicated in ADHD. The role of glutamate, an important neurotransmitter in learning and memory, has been implicated in the pathology of ADHD as it influences executive functions.

Zhang et al investigated whether group III mGluR gene variations, particularly GRM4, GRM7, and GRM8, are associated with attention-deficit/hyperactivity disorder (ADHD) in the Chinese Han population. It found that GRM4 rs1906953 T was associated with a reduced risk of ADHD, while GRM7 rs9826579 C was associated with an increased risk. Functional assays were conducted to further understand these associations. The results revealed the association of GRM4 rs1906953 and GRM7 rs9826579 with ADHD, as well as the impact of rs1906953 on transcriptional activity of GRM4 [91].

Zhang et al also aimed to comprehensively explore the relationship between genetic variations within GRIN2A, GRIN2B, GRIK1, GRIK4, GRID2, and ADHD. Genotyping was performed with the Sequenom MassARRAY system in a two-stage case–control study using ADHD symptoms assessment with Swanson, Nolan, and Pelham version IV scale and Integrated Visual and Auditory Continuous Performance Test. The study found that GRID2 rs1385405 showed a significant association with ADHD risk in the codominant model (OR = 2.208, 95% CI = [1.387, 3.515]) in the first stage and in the codominant model (OR = 1.874, 95% CI = [1.225, 2.869]) and recessive model (OR = 1.906, 95% CI = [1.265, 2.873]) in the second stage. GRID2 rs1385405 was also found to relate to inattention and hyperactivity symptom. The study concluded that their data provided evidence for the participation of GRID2 variants in conferring the risk of ADHD [92].

Chatterjee et al aims to investigate the role of glutamate (Glu) in attention deficit hyperactivity disorder (ADHD) by analyzing genetic variations, Glu levels, and expression of Glu receptors in eastern Indian ADHD probands. They have focused on ADHD because of its negative impact on scholastic achievement and peer relationships, and the pivotal role of Glu in learning and memory. They hypothesize that down-regulation of the glutamatergic system may affect ADHD etiology and treatment efficacy.  The methods employed by the researchers involve collecting peripheral blood samples with informed consent for genetic variant, Glu level, and GluR expression analysis. The subjects were treated with methylphenidate or atomoxetine, allowing for the assessment of post-therapeutic improvement in ADHD trait scores based on different GluR genotypes.  Two specific Glu receptor variants, GRM7 rs3749380 "T" and GRIA1 rs2195450 "C", were found to be associated with ADHD (P ≤ 0.05). Additionally, a few other GluR genetic variants were found to be significantly associated with higher trait severity, low IQ, lower plasma Glu levels, down-regulated GluR mRNA expression, and poor response to medications [93].

GABA

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system, while glutamate acts as an excitatory neurotransmitter. Studies have shown that GABA is involved in the neurophysiology of attention deficit hyperactivity disorder (ADHD).

Ende et al aimed to investigate the relationship between glutamate and GABA levels in the anterior cingulate cortex (ACC) of female patients with Borderline Personality Disorder (BPD), Attention-Deficit/Hyperactivity Disorder (ADHD), and healthy controls. It found that both patient groups had higher scores on self-reported impulsivity, anger, and aggression compared to the healthy controls. The study also showed that GABA levels in ACC were significantly lower in ADHD than in healthy controls, while there was a positive relationship between glutamate levels and impulsivity, and a negative correlation between GABA levels and aggression [94].

Puts et al aimed to measure the concentrations of GABA and glutamate in cortical and subcortical regions of unmedicated children with ADHD using Magnetic Resonance Spectroscopy at high field strength (7T) while also assessing their behavioral inhibitory control. The study found that children with ADHD had poorer inhibitory control and significantly reduced GABA/Cr in the striatum, but not in other regions. No significant differences were found for Glu/Cr levels or correlations with behavioral manifestations of ADHD. The primary finding was a reduction in striatal GABA levels in unmedicated children with ADHD at 7T [95].

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