***Abstract***

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by inattentiveness, hyperactivity, and impulsivity. 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. 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. We will also discuss the research that’s been performed, including their methods and results.

***Background***

***Prevalence***

***Causes (Genetics, Environment, Development Course)***

***Risk Factors (Family History, Prenatal Nicotine Exposure, Fetal Alcohol Syndrome, Prematurity)***

***Complications***

***Comorbidities***

***Treatment***

***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 [Neuroanatomy Amygdala, StatPearls]. 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. Damage to the amygdala has been linked to several mental health disorders, including post-traumatic stress disorder (PTSD) and depression [tsvetkov2015]. Understanding the anatomy of the amygdala can help medical professionals better diagnose, treat, and care for patients with these conditions.

Prior studies have shown associations between abnormalities of the amygdala and irritability. Irritability is associated with several psychiatric disorders, including ADHD. 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. [[suk2023.pdf]]

The study 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. The nucleus accumbens showed a positive correlation bewteen irritability and greater functional connectivity with the left posterior middle temporal gyrus and precuneus. [[mukherjee2022]]

***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 [Neuroanatomy Basal Ganglia, StatPearls].

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. [[tang2019.pdf]]

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. [[shvarzman2022.pdf]]

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. [[cascone2023.pdf]]

***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. [Neuroanatomy Caudate, StatPearls]

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. [[greven2015.pdf]]

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. [[dang2016.pdf]]

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. [[yang2017.pdf]]

The study 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. [[damiani2020.pdf]]

The study aimed to understand how changes in glutamate and GABA levels in the caudate nucleus and nucleus accumbens occur during attention control tasks. ADHD adults aged 31-51 years old were recruited for MPRAGE T1-weighted imaging and MRS scans while performing attention control tasks. During these tasks, smaller increases in glutamate and GABA were seen in ADHD patients compared to those without ADHD. These smaller increases also were found to positively correlate with worsening performance in the attention control tasks for ADHD patients. [[mamiya2022.pdf]]

***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. [Neuroanatomy Cerebellum, StatPearls].

This study 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. [[goetz2017.pdf]]

This study 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. [[wu2022.pdf]]

***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, 31, 32, 33, 23, 26, 29, and 30 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. [[wadekane2022]] and [[StatPearls]]

The study 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. [[bauer2016.pdf]]

The current study 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. [[bonath2016.pdf]]

The aim of this study was to investigate 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. [[fernandez-jaen2016.pdf]]

This study 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 parent-based, 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. [[zhan2017.pdf]]

The study 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. The findings suggest that ADHD children over-activated these regions to compensate for the increased attention demands. [[baytunca2021.pdf]]

***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. [[Statpearls]]

This study 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. [[luders2016.pdf]]

This study 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. [[el-hadad2021.pdf]]

This review discusses that decreased growth rates in the premotor, motor, sensory, and parietal regions of the corpus callosum of ADHD patients. Children with decreased rostral corpus callosum volume were found to have increased impulsivity and hyperactivity. [[dupont2023.pdf]]

***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. The basal ganglia encapsulate and split 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. Inhibitory input (GABAergic) is taken from several structures, including the substantia nigra and ventral pallidum. 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. [[StatPearls, maybe find Dupont or Agaolikum]]

In this study, the researchers 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 gyrus and middle frontal gyrus. They also found that ADHD males with comorbid depression showed decreased GPe FC with the occipital cortex. [[dupont2022.pdf]]

***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. 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 and control social behaviors. [[Statpearls]]

The study 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. [[nickel2017.pdf]]

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. [[StatPearls]]

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). 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. [[ma2011.pdf]]

Middle Frontal Gyrus

Nucleus Accumbens

Pituitary

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. [[StatPearls]]

The study aimed to examine the association between focal stroke lesions in children and ADHD/ADHD traits. 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. Of the patients with ADHD/ADHD traits, the densest area of overlapping lesions was in the posterior ventral putamen. Of the remaining patients (no ADHD/ADHD traits), none of them had lesions in the posterior ventral putamen. They found that those with lesions in this region were more likely to have ADHD. [[max2002.pdf]]

The aim of this study is to investigate differences in putamen volumes among ADHD combined subtype male children with psychopathic traits and controls. Using past MRI scans, the putamens in both groups are analyzed but no local volume differences were found. However, a reversal of symmetry in the putamen is discovered in which children with ADHD tend to have smaller left relative to right putamens compared to their control counterparts who have smaller right relative to left putamens. [[wellington2006.pdf]]

The study aimed to explore differences in putamen functional connectivity between medication-naïve ADHD children and typically developing children. Using seed-based correlation analyses in resting-state fMRI data, it was found in the controls (TD children) that there was positive putamen functional connectivity with the bilateral sensorimotor areas, prefrontal cortex, insula, superior temporal gyrus, and subcortical regions. Negative putamen functional connectivity was observed in the bilateral parietal and occipital cortices. Negative putamen FC was also seen in the frontal and middle temporal cortices and cerebellum. 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. [[cao2009.pdf]]

In this study, researchers investigated a specific genetic variant, rs945270 (reported to affect putamen volume), linked with increased symptoms of attention-deficit/hyperactivity disorder (ADHD) in 14-year-old adolescents. They used a large sample size of 1834 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 bilateral (right more than left) putamen activity during reward anticipation. Right putamen activation negatively correlated with ADHD symptoms. [[xu2017.pdf]]

***Pathophysiology***

***Genetics***