Attention Deficit Hyperactive Disorder (ADHD) - Diagnostic Tools, Treatments, Neurochemistry, Genetics, and Environmental Influences: A Review

Supplementary Materials

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1. Glossary

3' UTR: the untranslated region on the 3’ end of the mRNA strand, which immediately follows the translation termination codon. Regulatory regions within this section of the mRNA strand can influence polyadenylation, translation efficiency, localization, and stability of the mRNA

5' flanking region: is a region of DNA that is adjacent to the 5’ end of a gene. This region contains the promoter, and can also contain enhancers or other protein binding sites. This region of DNA is not transcribed into RNA.

Candidate genes: are genes that are chosen based on a prior knowledge about their biological function to investigate association between genetic variation and phenotypes that could cause different form of disease. The purpose of Candidate Genes studies is to determine which alleles of the genes are more frequent related to a specific disease.

Continuous variation: is the combination of many genes (polygenic inheritance) and could be significantly affected by environment (e.g. the longer the sun exposure, the darker the skin). Height is an example of a characteristic of continuous variation since the traits could vary between an interval. Other characteristic could be skin colour; the more dark genes when compared to fair genes, the darker the skin tone which means that in this case the genes have an additive effect. When plotted, the data will follow a bell shape curve (normal distribution plot) meaning that the phenotypes could range from one extreme to another.

Discontinuous variation: is controlled by alleles of single genes of a very small number of genes and has a few numbers of traits that are easily distinguishable and cannot be measured across a complete range: e.g. either blue or yellow peas or either smooth or wrinkled peas of Mendel. Discontinuous variation is not influenced by the environment and the genes do not have an additive effect. When plotted, the data falls in a couple of discrete histograms.

Genetic linkage: the tendency of genes located close to each other on a chromosome to be inherited together during meiosis. There is a lower chance for genes found in vicinity to be separated onto different chromatids during chromosomal crossover, which means that they are genetically linked.

Genome-Wide Association Studies (GWAS): the opposite of candidate genes, which scans the entire genome for common genetic variation.

Haplotype: There are two meanings for the word haplotype:

1. A combination of alleles at adjacent loci on a chromosome that are inherited together. This type of haplotype may be one locus, several loci, or an entire chromosome depending on the number of recombination events that occur between a given set of loci, if any occurred.

2. A set of single-nucleotide polymorphisms (SNPs) on a single chromosome of a chromosomes pair that are associated statistically.
**Linkage disequilibrium:** the occurrence of some combinations of alleles or genetic markers in a population either more often or less often than would be expected by chance.

**Nonsense-mediated mRNA decay (NMD):** is a surveillance pathway found in all eukaryotes. Its main function is to reduce errors in gene expression by eliminating mRNA transcripts that contain a premature stop codon.

**Orthostatic intolerance:** is the development of symptoms when standing upright which are relieved when sitting back down again. There are many types of orthostatic intolerance. It can be a subcategory of dysautonomia (a disorder of the autonomic nervous system that occurs when an individual stands up).

**Probands:** is the first affected family member who seeks medical attention for a genetic disorder. There can be other subjects and ancestors with the manifested disease, but the proband typically refers to the member seeking medical attention or being studied, even if affected ancestors are known.

**Quantitative trait locus (QTL):** a segment of DNA that is associated with a phenotypic trait and could be found on different chromosomes. The number of QTL shows the variation in the phenotypic trait. The goal of the QTL analysis is to identify whether phenotypic differences are either due to a small number of loci with large effect or due to a large number of loci with a rather small effect e.g. it may tell that the height of a plant is controlled by many loci of small effect or by few loci with a greater effect.

**Restriction enzymes:** enzymes that cut DNA at specific or close to a nucleotide sequence called restriction sites.

**Restriction sites or restriction recognition sites:** are DNA segments, 4 to 8 nucleotides long, usually palindromic which are recognised by restriction enzymes. These restriction enzymes may cut the DNA between two nucleotides from the restriction site or somewhere near.

**SNAP-IV:** is an ADHD rating scale that can be done by parents/guardians and teachers.

**Rs(#):** is an accession number used by researchers and databases to refer to specific SNPs. It stands for Reference SNP cluster ID (refSNP). The number (#) does not have any significant meaning regarding the SNP, it is an association number assigned to that specific SNP.

**Variable number tandem repeats (VNTR):** variation of length of a tandem repeat. A tandem repeat is the adjacent repetition of a short nucleotide sequence. They exist on many chromosomes, and vary from individuals to individuals. They act as an inherited allele, therefore they are often
used for personal or parental identification and are used in genetic and biological research, forensics, and DNA fingerprinting.

Transmission Disequilibrium Test (TDT): is a family-based association test for the presence of a genetic linkage between a genetic marker and a trait. The test will detect genetic linkage only in the presence of genetic association. While genetic association can be caused by population structure, genetic linkage will not be affected, which makes the TDT robust to the presence of population structure.

Variation: the small differences in traits found between individuals of the same species and could be continuous or discontinuous.

2. Attention Deficit Hyperactive Disorder (ADHD)

2.1 Introduction

Attention Deficit Hyperactive Disorder (ADHD) is a heterogeneous behavioral syndrome characterized by the main foundational symptoms of hyperactivity, impulsivity, inattentiveness, difficulty controlling behavior, and difficulty staying focused. While these symptoms tend to cluster together, some people are predominantly hyperactive and impulsive, while others are primarily inattentive [NICE, 2009]. ADHD is one of the most common childhood disorders and can continue through adolescence and adulthood. The symptoms can change and evolve as the individual with ADHD ages. There are two different criteria used for diagnosing ADHD, therefore there are two different criteria for judging and evaluating the severity of the disorder.

The two main diagnostic criteria currently used to identify this disorder are; the International Classification of Mental and Behavioral Disorders 10th Edition (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV). The ICD-10, used in Europe, uses a narrower diagnostic category, which includes only people with more severe symptoms and impairments, while the DSM-IV, used in the United States of America, uses a broader diagnostic basis for the disorder. DSM-IV uses a more inclusive definition with a number of different ADHD subtypes and recognition of comorbidity with other psychological disorders whereas ICD-10 excludes any comorbidity [NICE, 2009].

Symptoms of ADHD are distributed throughout the population and vary in severity. ADHD symptoms can often overlap with symptoms of other related disorders and can be considered comorbid with a number of other disorders. Common coexisting conditions in children with ADHD are disorders of mood, conduct, emotions, motor control, anxiety disorders, and communication. In adults with ADHD the comorbid disorders include personality disorders, bipolar disorder, obsessive compulsive disorder, substance misuse and types of depressive disorders [NICE, 2009]. In order for an individual to be diagnosed with ADHD, the degree of the impairment must translate to difficulties in occupation, education and social situations. Children with moderate
ADHD have symptoms of hyperactivity, impulsivity and/or inattention, or combinations of each or all three and these symptoms are combined with at least moderate impairment in school settings, and multiple domains of social behavior. Children with ADHD typically have troubles regarding homework, schoolwork, safety, common hazards, and forming positive relationships with family and peers. Combined ADHD symptoms corresponds to the ICD-10 diagnosis of hyperkinetic disorder.

2.2 History
The definition of ADHD and hyperactivity disorder is based on the maladaptive high levels of impulsivity, hyperactivity and inattention. Origins of the concept were in the idea that some disturbances of behavior were the result of brain damage or minimal brain dysfunction (MBD). These neurological concepts were reviewed when epidemiological science investigated systematically the causes for behavioral problems in children and adolescence. The controversial brain damage theories were abrogated when the classification of mental disorders emerged in the 1980s in the American Psychiatric Association’s diagnostic scheme, DSM-III, now DSM-IV and the World Health Organization's Classification of Diseases ICD-9, now ICD-10 [NICE, 2009]. North America and Europe classified the illness and called it Hyperkinetic Disorder and more recently ADHD. Both have been extensively investigated biologically and both have genetic and behavioral associations but there is no definitive proof of ADHD being a neurological disease [NICE, 2009], despite extensive evidence reviewed below strongly points in this direction.

2.3 ICD-Hyperkinetic Disorder
In the ICD-10 diagnosis criteria of Hyperkinetic Disorder, patients must exhibit hyperactivity, inattention, and impulsivity in order for a diagnosis. Symptoms should occur before the age of 6 years old and be present in more than one setting. ICD-10 does not diagnose subtypes of ADHD or comorbidity of other disorders along with Hyperkinetic Disorder. According to the ICD-10 criterion, symptoms involving less than the three combined should be alleviated with alternative types of treatment than medication. Hyperkinetic Disorder may exist comorbid with conduct disorder, in which case the diagnosis is Hyperkinetic conduct disorder. The prevalence in school age children with this disorder is estimated to be about 1.5%, compared with an estimated 5.3% for children with ADHD. A psychologist, teacher, and/or parent must observe the symptoms and then the child is referred to a clinician that observes the symptoms of the disorder, then after must also conduct the diagnosis [Tyrer and Silk, 2008]. With regard to adults, discrete usage of the full diagnostic criteria may be inappropriate, because the criteria focus on childhood problems and do not take full account of the developmental changes mentioned in Table 1. Identification of ADHD in adult life have lowered the diagnostic threshold and provide age-appropriate adjustment of the symptoms.
2.4 ADHD DSM-IV

The DSM-IV criterion for ADHD requires the presence of some symptoms of inattention and/or impulsivity and hyperactivity. It is a more broadly defined and more common diagnosis of ADHD. Symptoms should occur at the age of 7 years old and the qualifying symptoms must be present in more than one setting. The diagnosis of ADHD under the DSM-IV criterion is defined as including subtypes of the disorder, primarily inattentive, hyperactive-impulsive or a combined type. Under the DSM-IV criterion, ADHD is commonly associated with several comorbid conditions such as anxiety disorders, depressive disorders, oppositional defiant disorder, conduct disorder, pervasive disorders, tic disorders, and learning disorders. The prevalence of ADHD is about 3%-5%, and in nearly all cases of hyperkinetic disorders an ADHD diagnosis is present [Tyrer and Silk, 2008]. An ADHD diagnosis-evaluation may be initially conducted by a parent, teacher or psychologist. Clinicians must approve the home and school diagnosis in order for patient medications. DSM-IV-TR allows a category of ‘ADHD in partial remission’ for individuals who no longer meet the full criteria; this criterion is particularly relevant for adults with symptoms that may have mild out or dissipated with age but where significant impairments related to the symptoms remain.

In the DSM-IV guideline, ‘ADHD’ is used as an umbrella term when discussing the disorder more broadly. Some of the earlier literature used the term ‘hyperactivity’ for the combination of hyperactive, impulsive and inattentive symptoms. In this guideline ‘hyperactivity’ is restricted to be defined as the combination of symptoms that define overactive behavior. The term ‘ADHD symptoms,’ is used to refer to the combination of hyperactive, impulsive and inattentive symptoms.

ADHD has three subtypes under the DSM-IV criteria:

1. Predominantly hyperactive-impulsive
   - Most symptoms (six or more) are in the hyperactivity-impulsivity categories.
   - Fewer than six symptoms of inattention are present, although inattention may still be present to some degree.

2. Predominantly inattentive
   - The majority of symptoms (six or more) are in the inattention category and fewer than six symptoms of hyperactivity-impulsivity are present, although hyperactivity-impulsivity may still be present to some degree.
   - Children with this subtype are less likely to act out or have difficulties getting along with other children. They may sit quietly, but they are not paying attention to what they are doing. Therefore, the child may be overlooked, and parents and teachers may not notice that he or she has ADHD.

3. Combined hyperactive-impulsive and inattentive
   - Six or more symptoms of inattention and six or more symptoms of hyperactivity-impulsivity are present.
• Most children with ADHD have the combined type.

2.5 Comparing ICD-10 to DSM-IV

DSM-IV and ICD-10 are the most prominent diagnostic classification systems in psychiatry. The two criteria are used for many psychiatric disorders and while ICD-10 is mostly known for its usage in Europe and DSM-IV in the United States, DSM-IV is becoming more popular worldwide. ICD-10 is the most frequently used system worldwide for clinical diagnosis and training, and DSM-IV is the most frequently used system for research, especially in North America [Sørensen et al., 2005].

Table 1, ICD-10 and DSM-IV criteria comparison [Modified table, NICE, 2009, Adapted from ICD-10: Classification of Mental and Behavioral Disorders, 1992]

<table>
<thead>
<tr>
<th>ICD-10 criteria for Attention Deficit Hyperactive Disorder (ADHD)</th>
<th>DSM-IV-TR criteria for Attention Deficit Hyperactive Disorder (ADHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) <strong>Inattention:</strong> At least six symptoms of attention have persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child: Often fails to give close attention to details, or makes careless errors in schoolwork, work or other activities. Often fails to sustain attention in tasks or play activities. Often appears not to listen to what is being said to him or her. Often fails to follow through on instructions or to finish schoolwork, chores or duties in the workplace (not because of oppositional behavior or failure to understand instructions) Is often impaired in organizing tasks and activities Often avoids or strongly dislikes tasks, such as homework, that require sustained mental effort Often loses things necessary for certain tasks and activities, such as school assignments, pencils, books, toys or tools Is often easily distracted by external stimuli Is often forgetful in the course of daily activities</td>
<td>1. Either A or B. A. Inattention – Six or more symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level. Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities. Often has difficulty sustaining attention in tasks or play activities. Often does not seem to listen when spoken to directly. Often does not follow through on instructions; fails to finish schoolwork, chores or workplace duties (not due to oppositional behavior or failure to understand instructions) Often has difficulty organizing tasks and activities Often avoids, dislikes, or is reluctant to do tasks requiring sustained mental effort Often loses things necessary for tasks or activities Is often easily distracted by extraneous stimuli Is often forgetful in daily activities</td>
</tr>
<tr>
<td>B. <strong>Hyperactivity-impulsivity</strong>: Six or more symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level. Hyperactivity Often fidgets with hands or feet or squirms in seat Often leaves seat in classroom or in other situations where remaining seated is expected Often runs or climbs excessively where inappropriate (feelings of restlessness in young people or adults) Often has difficulty playing or engaging in leisure activities quietly Is often ‘on the go’ or often acts as if ‘driven by a motor’ Often talks excessively Impulsivity Often blurts out answers before questions have been completed Often has difficulty awaiting turn Often interrupts or intrudes on others (for example, butts into conversations or games)</td>
<td></td>
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<tr>
<td>2. <strong>Hyperactivity</strong>: At least three symptoms of hyperactivity have persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child: Often fidgets with hands or feet or squirms on seat. Often leaves seat in classroom or in other situations in which remaining seated is expected Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, only feelings of restlessness may be present) Is often unduly noisy in playing or has difficulty in engaging quietly in leisure activities Often exhibits a persistent pattern of excessive motor activity that is not substantially modified</td>
<td></td>
</tr>
<tr>
<td>2. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.</td>
<td></td>
</tr>
<tr>
<td>by social context or demands</td>
<td>3. Impulsivity: At least one of the following symptoms of impulsivity has persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child: Often blurts out answers before questions have been completed Often fails to wait in lines or await turns in games or group situations Often interrupts or intrudes on others (for example, butts into others’ conversations or games) Often talks excessively without appropriate response to social Constraints</td>
</tr>
<tr>
<td>4. Onset of the disorder is no later than the age of 7 years.</td>
<td>4. There must be clear evidence of significant impairment in social, school or work functioning.</td>
</tr>
<tr>
<td>5. Pervasiveness: The criteria should be met for more than a single situation, for example, the combination of inattention and hyperactivity should be present both at home and at school, or at both school and another setting where children are observed, such as a clinic. (Evidence for cross-situationality will ordinarily require information from more than one source; parental reports about classroom behavior, for instance, are unlikely to be sufficient.)</td>
<td>5. The symptoms do not happen only during the course of a pervasive developmental disorder, schizophrenia or other psychotic disorder. The symptoms are not better accounted for by another mental disorder (for example, mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).</td>
</tr>
<tr>
<td>6. The symptoms in 1 and 3 cause clinically significant distress or impairment in social, academic or occupational functioning.</td>
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</table>

The DSM-IV criteria symptoms are divided into two groups, but include subtypes of the disorder. The two DSM-IV criteria groups are: inattentive and hyperactive-impulsive. Six of the nine symptoms in each section must be present for a `combined type (the predominate most common diagnosis of ADHD)` diagnosis of ADHD. If there are insufficient symptoms for a
combined diagnosis then the individual is placed under ADHD-H/I subtypes. Additionally, symptoms must be chronic (present for a minimum of 6 months), maladaptive, functionally impaired across two or more contexts inconsistent with the current developmental level and differentiated from other mental disorders [NICE, 2009]. ICD-10 does not include subtypes for ADHD. They do have other diagnostic material or criteria for symptoms that are similar to the subtypes of ADHD under the DSM-IV criteria, but they are just categorized under separate disorders. ICD-10 ADHD diagnosis must have all three symptoms present and apparent in more than one setting for a diagnosis.

Oppositional defiant disorder and conduct disorder are also diagnoses in the ICD-10 and DSM-IV criteria and need to be differentiated from ADHD. Oppositional defiant disorder refers to persistent, continuous, and frequent disobedience and opposition to authority figures (such as parents, teachers or other adults), characterized by negative, hostile, obstinate, aggressive, incorporative or defiant behavior. The diagnosis should not be made unless these behaviors persist for more than 6 months and are considerably more frequent than normal for a person of the same developmental age. Conduct disorder represents more severe behavioral problems: a persistent pattern of defiant behavior that violates and opposes the societal rules and the rights of others and social institutions. This includes aggression that can take the form of bullying, mobbing, physical aggression towards peers and figures of authority and/or cruelty to animals, destruction of property, pyromania, theft, pathological lying (other than to avoid harm). All these oppositional and conduct disorder problems can be seen in some children with ADHD, but they are not essential features and should not be used as grounds for making the diagnosis of ADHD.

The ICD-10 uses a different nomenclature which consists of the same symptoms described as a group of hyperkinetic disorders of childhood, and inattention, hyperactivity and impulsivity must all be present together. As there are no subtypes in the ICD-10, all individuals must be and may only be categorized under the combined type diagnosis. Additionally, the research diagnostic criteria for the ICD-10 provide an even more restricted set of requirement: the symptom counts must be met in more than one context. Furthermore, there are some exclusion criteria: coexisting psychiatric disorders are not allowed under ICD-10, whereas they are acknowledged and considered in the DSM-IV criteria [NICE, 2009].

2.6 Experiments
Extensive research has been put into both systems but differences between the two still remain. A study in Arhus, Denmark evaluated 199 patients ages 8-13 conducting interviews using DSM-IV as well as ICD-10 criteria to score the diagnosis of patients, these interviews resulted in two different diagnoses per patient [Sørensen et al., 2005]. Since the study tested three different types of disorders, ADHD being one of them, a total of 71 children were diagnosed with ADHD according to the DSM-IV criteria and of these, 17 (24%) did not have the disturbance of activity and attention or the attention without hyperactivity according to the ICD-10 criteria. They all had DSM-IV diagnosis of ADHD, but no diagnosis category for ICD-10 criteria. The study concluded that more children are diagnosed with ADHD using the DSM-IV criteria than when using the ICD-10 criteria. Children included in DSM-IV and not ICD-10 belonged to a subtype hyperactive/impulsive,
because ICD-10 does not offer a diagnosis covering this constellation of symptoms [Sørensen et al., 2005]. The children belonging to the subtype reveal a flaw in the ICD-10 criteria, because it overlooks a group of people with the disorder. The DSM-IV showed to include more symptoms and yielded an overall broader definition to the disorder.

Another study was conducted in an elementary school, Sime Budinic Elementary School from Zadar in the Republic of Croatia. The study included all children from 1st grade to 4th grade of this elementary school, aged 7-10 years old, in a total of 409 students, 215 girls and 194 boys [Karlovic et al., 2002]. They evaluated the children with both ICD-10 and DSM-IV criteria and compared the results. The results of this study suggested significant overlapping of cases identified by the ICD-10 and DSM-IV diagnostic systems. The majority of children with diagnosed hyperkinetic disorder also met the criteria for ADHD. However, the results also suggested that the DSM-IV criteria for ADHD identifies a broader group of children than the ICD-10 definition of hyperkinetic disorder. The children who met the criteria for both hyperkinetic disorder (ICD-10) and inattentive/impulsive represented an ADHD combined type or hyperactive type according to DSM-IV. The children had considerable problems with inattention and overactivity but did not display the required six symptoms of inattention or hyperactivity/impulsivity. However, literature on prevalence rates of hyperkinetic disorder or ADHD varies from 3% 20% [Karlovic et al., 2002]. This suggests that differences in prevalence rates were not due to cross-national differences in the rate of behavioral phenomena but due to differences in diagnostic process or conceptualization of these behavioral patterns [Karlovic et al., 2002].

Table 2, modified from Karlovic et al., 2002

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>In countries in which the ICD-10 system is used in the diagnosis of mental disorders, children with significant problems of hyperactivity or inattention but not both may go undiagnosed.</td>
</tr>
<tr>
<td>2.</td>
<td>The children diagnosed as hyperkinetic according to ICD-10 are likely to correspond to the ADHD combined type only but not to the inattentive or hyperactive-impulsive type. Conversely, the results from studies including these three ADHD subtypes will not necessarily apply to children with hyperkinetic disorder.</td>
</tr>
<tr>
<td>3.</td>
<td>As the ICD-10 system is used worldwide for recording morbidity statistics, the recording of prevalence rates for Hyperkinetic Disorder is likely to be deflated in the countries not using DSM-IV for clinical diagnosis</td>
</tr>
</tbody>
</table>

**2.7 Comorbidity of ADHD**

People with ADHD are at risk for comorbidity of other disorder. In table 3, the ADHD comorbidity rates and percentages of individuals in the United States are shown. A comparative table for the ADHD comorbidity rates in Denmark was unattainable.
Table 3. Comorbidities of ADHD, Center for Disease Control, Vital Health and Statistics, 2013

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of children 3-17 years of age ever diagnosed with ADHD</td>
<td>8.4 %</td>
</tr>
<tr>
<td>Percent of boys 3-17 years of age ever diagnosed with ADHD</td>
<td>11.2 %</td>
</tr>
<tr>
<td>Percent of girls 3-17 years of age ever diagnosed with ADHD</td>
<td>5.5 %</td>
</tr>
<tr>
<td>Number of children 3-17 years of age ever diagnosed with ADHD</td>
<td>5.2 Million</td>
</tr>
<tr>
<td>Number of ambulatory care visits with attention deficit disorder as primary diagnosis</td>
<td>7.3 Million</td>
</tr>
<tr>
<td>Percent of Americans with ADHD</td>
<td>1.21 %</td>
</tr>
<tr>
<td>Boys are more than twice as likely to have ADHD</td>
<td></td>
</tr>
<tr>
<td>Children with a poor health status are 3 times more likely to have ADHD</td>
<td></td>
</tr>
<tr>
<td>Percent of ADHD diagnosis increase between 1997 and 2006</td>
<td>3%</td>
</tr>
<tr>
<td>Median age of onset for ADHD</td>
<td>7</td>
</tr>
<tr>
<td>Colorado has the lowest percent of school-aged children with ADHD</td>
<td>5%</td>
</tr>
<tr>
<td>Alabama has the highest percent of school-age children with ADHD</td>
<td>11.1 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnic Background</th>
<th>Percent</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>7.6%</td>
<td>3.6 Million</td>
</tr>
<tr>
<td>Black</td>
<td>7.4%</td>
<td>705,000</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5.1%</td>
<td>602,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family Structure</th>
<th>Percent</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother and Father</td>
<td>5.9%</td>
<td>2.5 Million</td>
</tr>
<tr>
<td>Mother no Father</td>
<td>11.1%</td>
<td>1.6 Million</td>
</tr>
<tr>
<td>Father no Mother</td>
<td>8.6%</td>
<td>226,000</td>
</tr>
<tr>
<td>Neither Mother nor Father</td>
<td>10.7%</td>
<td>219,000</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattentive with Minor Depression / Dysthymia</td>
<td>21 %</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Percentage</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Inattentive with Oppositional Defiance Disorder</td>
<td>21 %</td>
</tr>
<tr>
<td>Inattentive with Generalized Anxiety Disorder</td>
<td>19 %</td>
</tr>
<tr>
<td>Hyperactive with Minor Depression / Dysthymia</td>
<td>42 %</td>
</tr>
<tr>
<td>Hyperactive with Oppositional Defiance Disorder</td>
<td>22 %</td>
</tr>
<tr>
<td>Hyperactive with Generalized Anxiety Disorder</td>
<td>19 %</td>
</tr>
<tr>
<td>Inattentive &amp; Hyperactive with Minor Depression / Dysthymia</td>
<td>50.7 %</td>
</tr>
<tr>
<td>Inattentive &amp; Hyperactive with Oppositional Defiance Disorder</td>
<td>22.7 %</td>
</tr>
<tr>
<td>Inattentive &amp; Hyperactive with Generalized Anxiety Disorder</td>
<td>12.4 %</td>
</tr>
</tbody>
</table>

### 3. Treatments

#### 3.1 Pharmacological Treatments for ADHD

ADHD is regularly treated with both pharmacological and non-pharmacological methods designed for both children and adults. The pharmacological methods to treat the disorder are usually regarded as first line treatment in treating ADHD and mainly consist of stimulant medications. An agent or drug that increases physiological activity is defined as a stimulant. Non-stimulants have also shown to be effective in treating ADHD [Antshel et al., 2011].

The pharmacological treatment methods are also described as either disorder oriented or target symptom oriented. The disorder oriented method treats the core psychiatric disorder and the target symptom oriented method treats or mediates individual targets such as aggression, irrespective of the core psychiatric condition [Patel and Barzman, 2013]. Hence, the disorder oriented method is suggested as first line treatment method because it is effective in treating ADHD and decreases impulsivity as well as aggression.

#### 3.1.1 Stimulants

Attention Deficit Hyperactivity Disorder or ADHD is regularly treated with stimulants, which are known to be one of the most commonly prescribed classes of psychotropic drugs and mostly remain the first choice of medication management among patients with ADHD [Antshel et al., 2011].

Stimulants work by affecting how the brain controls impulses and regulates attention and behavior. They carry out the work process by influencing the availability of neurotransmitters. These stimulants provide a number of delivery mechanisms for physicians to choose from, such as in liquid, sprinkle, tablet and capsule or patch form. Physicians have access to these stimulants from active isomer, from mixtures of active and less active isomers or as a prodrug that is activated by
metabolism. These stimulants also exist as immediate release, intermediate release or as extended release formulations [Antshel et al., 2011].

The pharmacological approaches that are used in treating ADHD generally consist of stimulant medication such as Methylphenidate, Dexamethylphenidate, Mixed Amphetamine Salts and Lis dexamphetamine dimesylate (LDX) and non-stimulant medications such as Atomoxetine, Clonidine and Guanfacine are shown in the table below.

Table 4: Showing the different types of Stimulants, modified from [Antshel et al., 2011]

<table>
<thead>
<tr>
<th>Stimulant</th>
<th>Brand name</th>
<th>Daily dosage</th>
<th>Duration</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methylphenidate (Short acting/Immediate release)</strong></td>
<td>Ritalin, Methylin and Desoxyn</td>
<td>Two to three times daily. Starting with 5-18 mg or dosage can be increased until positive effects peak of negative side effects develop</td>
<td>3-6 hours</td>
<td>Appetite suppression, delay of sleep onset, abdominal pain, headache, rebound irritability, tics (motor, vocal), jitteriness</td>
</tr>
<tr>
<td><strong>Methylphenidate (Intermediate acting)</strong></td>
<td>Metadate ER, Metadate CD, Methylin ER, Ritalin LA, Ritalin SR</td>
<td>Once or twice daily</td>
<td>3-8 hours</td>
<td>Same side effects</td>
</tr>
<tr>
<td><strong>Methylphenidate (Long lasting/Extended release)</strong></td>
<td>Concerta, Daytrana Patch</td>
<td>Once daily (Patch left on for 9 hours)</td>
<td>8-12 hours</td>
<td>Same side effects</td>
</tr>
<tr>
<td><strong>Dexamethylphenidate (Short acting)</strong></td>
<td>Focalin</td>
<td>Two to three times daily. Initial dose is half of that of the immediate-release MPH</td>
<td>4-5 hours</td>
<td>Same side effects</td>
</tr>
<tr>
<td><strong>Dexamethylphenidate (Long lasting/Extended release)</strong></td>
<td>Focalin XR</td>
<td>Once daily</td>
<td>8-12 hours</td>
<td>Same side effects</td>
</tr>
<tr>
<td>Dexamphetamine or AMP mixed salts (Short acting/Immediate release)</td>
<td>Dexedrine, DextroStat, Adderall</td>
<td>Two to three times daily. Initial dose is half of that of the immediate-release MPH</td>
<td>4-6 hours</td>
<td>Same side effects</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Dexamphetamine or AMP mixed salts (Intermediate acting)</td>
<td>Dexedrine spansule</td>
<td>Once or twice daily</td>
<td>6-10 hours</td>
<td>Same side effects</td>
</tr>
<tr>
<td>Dexamphetamine or AMP mixed salts (Long lasting/Extended release)</td>
<td>Adderall-XR</td>
<td>Once daily</td>
<td>8-12 hours</td>
<td>Same side effects</td>
</tr>
<tr>
<td>Lisdexamfetamine (Prodrug/Inactive Amphetamine)</td>
<td>Vyvanse</td>
<td>Once daily. Initial dose is 4 times the Immediate-release MPH</td>
<td>8-12 hours</td>
<td>Same side effects</td>
</tr>
</tbody>
</table>

These stimulant medications are at present approved for the treatment of ADHD by the U.S. Food and Drug Administration (FDA). Methylphenidate, dexamfetamine and lisdexamfetamine are specified in many European countries for treating both children (Aged 6 years and over) and adolescents with ADHD. In the United Kingdom, lisdexamfetamine and methylphenidate are currently approved for the treatment of ADHD in children (Aged 6 years and over) [ADHD Institute, 2014a].

Concerta XL®, Equasym XL®, Medikinet®, Medikinet XL®, Ritalin® and Ritalin LA® are ADHD medication containing the active ingredient methylphenidate. These products are licensed by the European Medicines Agency (EMA) for the treatment of ADHD [ADHD Institute, 2014a]. Equasym XL® contains the active compound methylphenidate hydrochloride and can be purchased in Denmark, Finland, France, Germany, Netherlands, Republic of Ireland, Iceland, Norway, Sweden and United Kingdom [Shire, 2014].

Ritalin® and Ritalin LA® contain the active ingredient methylphenidate hydrochloride and are approved for the treatment of ADHD in children. Ritalin® is available in over 70 countries and was first marketed during the 1950s. Ritalin LA® comes in an extended release form and is available in over 30 countries [Novartis, 2014]. Focalin XR contains the active ingredient dexamfetamine hydrochloride and is indicated for adults with ADHD.

The mechanism of action for dexamfetamine is that it blocks the reuptake of DA (DA) and Noradrenaline (NA) into the presynaptic neuron and enhances the amount of these two monoamines in the extraneuronal space [Alkermes, 2013]. Focalin XR is available in Switzerland and in the U.S. Focalin contains the active d-enantiomer of methylphenidate, thus only half the dose of Ritalin® is required [Novartis, 2014]. Elvanse and Vyvanse contain the active ingredient
lisdexamfetamine. Vyvanse is available in Canada, Germany and in the United Kingdom whereas Vyvanse is available in Canada, Brazil and in the U.S. [Shire, 2014].

These stimulants are derivatives or products of either methylphenidate or amphetamine, both of which act by enhancing the neurotransmission of DA and to a lesser extent, enhance NA [Vaughan et al., 2011]. There are arrays of choices for both the methylphenidate and amphetamine derivatives, which allow physicians to modify the duration of medication efficacy better throughout the day to the requirements of the individual, as shown in the table above [Antshel et al., 2011]. Methylphenidate has been available since the 1950s and has been the leading and frequently used medication for treating ADHD in the United Kingdom since the 1980s [Parker, 2013]. This stimulant drug is regarded as first line treatment in the psychopharmacological treatment of adults with ADHD and has shown to be effective in most children with ADHD.

The mechanism of action for methylphenidate is thought to block the reuptake of the neurotransmitter DA, and possibly NA, into presynaptic neurons by blocking DA transporter (DAT) or carrier proteins, hence increasing extracellular levels of DA in the extraneuronal space as shown in the image below. The stimulant drug acts at the brain stem arousal system and the cerebral cortex, where it increases sympathomimetic activity in the central nervous system (CNS) [DrugBank, 2013b]. Methylphenidate, Dexamfetamine and Lis dexamphetamine are central nervous system (CNS) stimulants [Parker, 2013].

![Mechanism of action for methylphenidate](image-url)

Figure 1: Mechanism of action for methylphenidate [ADHD Institute, 2014b], accessed March 28th 2014
Osmotic release oral system (OROS) methylphenidate, a long acting methylphenidate, reduces ADHD symptoms during the day because the drug has been designed to have 12 hour duration of effect, allowing a person to have a single daily dose. According to some studies, this drug has also been shown to be as effective as the immediate release formulation of methylphenidate, which is taken 3 times a day [YJ et al., 2012].

This type of methylphenidate comes in the form of a tablet and once the tablet is ingested, the osmotic pressure of the water entering the tablet shoves or pushes the active drug through the small opening or holes in the tablet. Dexmethylphenidate is synthesized in the form of capsules that can be opened and mixed with food [Antshel et al., 2011].

Amphetamine (AMP) is characterized as a mind altering drug with psychedelic like effects. The drug is capable of speeding up the central nervous system or (CNS) to increase neural activity in the brain. Amphetamines are also termed as the derivatives of phenyl ethylamine which are chemically related to the monoamine neurotransmitters. The misuse of this drug is considered to be a result from its euphoria inducing effects.

Amphetamine-like stimulants are commonly used in treating ADHD, PTSD, narcolepsy and rarely treatment resistant depression or extreme obesity. They are generally considered as the second choice when a person with ADHD does not improve with methylphenidate.

ADHD is thought to be caused by deficient levels of two neurotransmitters, DA and NA in the brain. These two neurotransmitters play an important role in controlling impulses and memory. Amphetamine stimulants work by increasing the level of the neurotransmitters DA, which
is commonly associated with pleasure, movement and attention, and NA, which is involved in energy and alertness. Amphetamines stimulate the release of NA from central adrenergic receptors and at higher doses they cause release of DA, thus allowing people diagnosed with ADHD to focus for longer periods of time and helps them remain calm [DrugBank, 2013a]. Amphetamines can act as a direct agonist on central 5-HT receptors and can inhibit monoamine oxidase (MAO) and the stimulant drug interacts with vesicular monoamine transporter (VMAT) enzymes to increase the release of DA and 5-HT receptors from the vesicles [DrugBank, 2013a].

Amphetamine or Dexamphetamine is a potent psychostimulant and is often recommended for treatment refractory ADHD. This stimulant drug is regarded as a third line treatment option by the U.S. National Institute for Health and Care Excellence (NICE) when methylphenidate and atomoxetine (Non-stimulant) fail [Parker, 2013]. Dexedrine contains the active ingredient dexamphetamine. The drug enhances attention and decreases impulsiveness in patients with ADHD and is also indicated in narcolepsy. Dexedrine is approved for the treatment of ADHD in children (Aged 6 years and over).

The exact mechanism of action for Dexamphetamine is not known. However the drug may enhance the release of monoamines (DA, NA, and 5-HT) from their vesicular storage sites within the presynaptic nerve terminals [Clarks, 2012]. Dexamphetamine also enables the release of cytoplasmic presynaptic monoamines by inducing reverse transporter exchange; for example, the exchange of intracellular monoamines for extracellular amphetamine. The drug may also have some direct agonist actions on central 5-HT receptors [Clarks, 2012]. Dexamphetamine weakly inhibits monoamine oxidase (MAO) causing an increase in presynaptic monoamine levels as shown in the image below.

The vesicular monoamine transporter (VMAT) is a transport protein which is incorporated in the membrane of synaptic vesicles of presynaptic neurons. This transport protein mainly transports monoamine neurotransmitters including, DA, Serotonin, NA, adrenaline, and Histamine into the vesicles where the neurotransmitters are released into synapses to reach postsynaptic receptors [Modified from Wikipedia.org]. Dexamphetamine is only available in an immediate release formulation where multiple dosing is daily required.
Figure 4: Mechanism of action for dexamphetamine [ADHD Institute, 2014c], accessed April 1st 2014

Figure 5: The molecular structure of dexamphetamine can be seen in the image [Helmenstine, 2014], accessed April 1st 2014

Lisdexamphetamine is a psychostimulant prodrug of the phenethylamine and amphetamine chemical family. The molecular structure of this stimulant drug consists of dexamphetamine attached to Lysine as shown in the image below. Lisdexamphetamine is an inactive prodrug of dexamphetamine which is converted into dexamphetamine itself in the body taking responsibility for its activity. The drug is termed as prodrug because it is inactive when consumed and becomes converted to its active form through hydrolysis of the amide bond.
Figure 6: The molecular structure of Lis dexamphetamine [Wiki Commons, 2008], accessed April 1st 2014

The mechanism of action for Lis dexamphetamine is described in terms of amphetamines which are thought to block the reuptake of the neurotransmitters, DA and NA in the presynaptic neuron, thus increasing the release of monoamines in the extra neuronal space [DrugBank, 2013a]. The drug is only licensed for treating ADHD in children at the age of 6 years old or over and is only recommended when methylphenidate is clinically insufficient. The drug also became recently licensed in the United Kingdom to be used in the treatment. Patients that have difficulties in swallowing capsules can easily dissolve the contents of this drug in water and the stimulant drug can also be swallowed as a liquid [Parker, 2013].

An array of extended release formulations for many stimulant medications has been brought to the market that allows patients to take their medications only once daily rather than taking multiple dosing daily. This also has had a great influence on the treatment as earlier the requirements for frequent doses often presented a practical blockade to use the medication effectively [Parker, 2013]. Long acting stimulants usually have duration of 8 to 12 hours and can be used just once daily. This benefits children who are unwilling or unable to take multiple dosing daily. Below are some examples of long acting stimulants.

Adderall XR

![Immediate release Delayed release](image)

beads (50%) beads (50%)
Stimulants are known to increase blood pressure, heart rate and body temperature and cause delay of sleep onset and appetite suppression. There are some concerns over these stimulant medications for being misused and abused because when these stimulant medications are abused, they can cause starvation and repeated abuse of these stimulants can lead to aggression and paranoia among patients. Some studies also show rare but serious cardiovascular complications or side effects, including stroke that mainly occur when stimulant medications are used. Another major concern is addiction to stimulant medications for any individual taking these drugs without medical supervision. One of the main causes to why addiction occurs depends on the doses other than those prescribed by a doctor. This can induce a rapid rise in in DA in the brain [NIH, 2014]. However non-stimulant medications have proven to be effective in treating ADHD.

### 3.1.2 Non-stimulants & Blood pressure medications

Some children are not able to tolerate or respond to stimulant medications due to their side effects that include; loss of appetite, trouble sleeping, hence several non-stimulant medications have been used instead to treat ADHD. The non-stimulant medications which have been approved by the Food and Drug Administration (FDA) for the treatment of ADHD include the selective NA reuptake inhibitors (SNRI), Atomoxetine and the Alpha 2 Agonists, Guanfacine (Long acting form) and Clonidine (Long acting form) as shown in the table below [Antshel et al., 2011].
Table 5: Showing the different types of Non-stimulants, modified from [Antshel et al., 2011]

<table>
<thead>
<tr>
<th>Non-stimulant</th>
<th>Brand name</th>
<th>Daily dosage</th>
<th>Duration</th>
<th>Common Effects</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNRI</strong></td>
<td>Atomoxetine (Strattera)</td>
<td>Once or twice daily. Initial 0.5 mg/Kg; Increase to 1.2-1.8 mg/Kg</td>
<td>18-24 Hours</td>
<td>Sedation, GI irritability, palpitations, sweating, increased suicidal thoughts.</td>
<td></td>
</tr>
<tr>
<td><strong>Alpha 2 Agonist Clonidine</strong></td>
<td>IR Clonidine (Catapres)</td>
<td>Initial dose 0.05-0.1 mg at night; titrate to max 0.4 mg/ per day</td>
<td>3-6 hours</td>
<td>Sedation, Low blood pressure, rebound Hypertension</td>
<td></td>
</tr>
<tr>
<td><strong>Alpha 2 Agonist Clonidine</strong></td>
<td>ER Clonidine (Kapvay)</td>
<td>Once daily. Initial 0.1 mg qhs; titrate to max 0.4 mg qhs</td>
<td>12-24 hours</td>
<td>Same side effects</td>
<td></td>
</tr>
<tr>
<td><strong>Alpha 2 Agonist Clonidine</strong></td>
<td>Clonidine patch (catapres TDS)</td>
<td>Initial TTS-1 up to TTS-3</td>
<td>1-5 days</td>
<td>Same side effects</td>
<td></td>
</tr>
<tr>
<td><strong>Alpha 2 Agonist Guanfacine</strong></td>
<td>IR Guanfacine (Tenex)</td>
<td>Twice daily. Initial 1 mg daily; titrate as needed up to 4 mg MDD</td>
<td>12-24 hours</td>
<td>Same side effects</td>
<td></td>
</tr>
<tr>
<td><strong>Alpha 2 Agonist Guanfacine</strong></td>
<td>ER guanfacine (Intuniv)</td>
<td>Once daily. Initial 1 mg; up to 4 mg</td>
<td>~24 Hour</td>
<td>Same side effects</td>
<td></td>
</tr>
</tbody>
</table>

Both clonidine and guanfacine have been approved by the FDA for the combination and co-administration with stimulant medications [Antshel et al., 2011]. The α-2 adrenergic agonists, clonidine and guanfacine have some beneficial effects in ADHD patients. However, they are not used as first-line treatment options due to their side effects that are related with their actions within the brain.

Clonidine, an imidazole derivative with α-adrenergic agonist properties, blocks the release of NA from the central catecholaminergic nerve terminals and has been found to be effective in treating ADHD, tics and aggression, predominantly in children [Wilens, 2006]. Similar
to clonidine, guanfacine is an alpha-adrenergic agonist but with a few advantages, as it has an extended excretion half-life and is less sedating and hypotensive than clonidine. Studies have shown guanfacine to be helpful in the treatment of ADHD among children, since the drug is capable of reducing hyperactivity and decreases irritability [Patel and Barzman, 2013]. Sedation, low blood pressure and rebound hypertension are common side effects which diminish over time [Antshel et al., 2011].

Centrally acting α-2 adrenoceptor agonists have shown to be effective in the treatment of hypertension. Alpha adrenergic agonists are categorized as sympathomimetic agents that selectively stimulate alpha adrenergic receptors. Sympathomimetic agents or drugs are able to copy the effects of transmitter substances of the sympathetic nervous system such as adrenaline, NA, and DA.

Atomoxetine also known as Strattera is a noradrenaline reuptake inhibitor and is regarded as the first non-stimulant medication proving its effectiveness. The drug was licensed for treating ADHD in both children and adults, though it is recommended by the U.S. National Institute for Health and Care Excellence (NICE) as a second line treatment option when first line treatment options such as the stimulant methylphenidate fails [Parker, 2013].

![Molecular structure of atomoxetine](image)

Figure 8: The molecular structure of atomoxetine is presented below [Wikipedia, 2014], accessed April 7th 2014

Strattera was first marketed in the United Kingdom in July 2004 and has been available in the U.S. since July 2002 [MHRA, n.d.]. The drug is recognized to cause some serious side effects such as liver damage and suicidal behaviors and in 2005, the Committee for Safety of Medicines (CMS) issued guidance following reports of severe hepatic disorders related with atomoxetine (Strattera) [Parker, 2013].

All pharmacological agents or drugs used to treat ADHD act on DA and/or Noradrenaline (NA) neurotransmitters either as agonists or as reuptake inhibitors. The exact role of DA and NA status in ADHD still remains unknown [Parker, 2013]. Atomoxetine is a selective and potent blocker of the presynaptic Noradrenaline transporter (NAT) and has minimal affinity for other neurotransmitter transporters or for noradrenergic receptors [ADHD Institute, 2014a]. This non-stimulant drug through inhibition of the presynaptic Noradrenaline transporter (NAT) increases the activity of NA as shown below [ADHD Institute, 2014a].
Atomoxetine is metabolized by CYP2D6, a member of the CYP superfamily of proteins, which is expressed in the liver as shown in the image below. These enzymes play an important role in the metabolism of xenobiotics.

Figure 9: Mechanism of action for atomoxetine [ADHD Institute, 2014] accessed April 7th 2014

Figure 10: The image shows the structure of CYP2D6 [Wikipedia, 2006], accessed April 7th 2014
The enzyme, CYP2D6 is responsible for the metabolism and elimination of many used drugs. Higher levels of atomoxetine are present in people that are poor/slow metabolizers of drugs, metabolized by CYP2D6 and thereby are at greater risk of harmful effects, compared with people with a functional enzyme. Therefore lower doses of atomoxetine should be prescribed or recommended to people that are poor CYP2D6 metabolizers [Parker, 2013].

3.1.3 Antidepressants

Antidepressants are considered to be not as effective as stimulants in the treatment of ADHD. However, they are usually used for treating depression and ADHD in children whose response to stimulant medication has been inadequate. These drugs have a positive effect on all three major mechanisms of ADHD which include; inattention, impulsivity and hyperactivity. They are also used as an alternative treatment option for children who experience negative side effects such as insomnia from stimulant medication.

Bupropion (Wellbutrin), an antidepressant, is an alternative treatment option for ADHD when abuse of a stimulant is a problem or if stimulant medication is not effective. Bupropion is a NA-DA reuptake inhibitor (NDRI), a drug that mainly acts as a reuptake inhibitor for the neurotransmitters NA and DA by blocking the action of the DA transporter (DAT) and Noradrenergic transporter (NAT). This process thus increases the extracellular concentration of the two neurotransmitters and this also results in the increase in adrenergic and Dopaminergic neurotransmission.

Bupropion is commonly used to treat depression and is also used as a part of a support program to help individuals quit smoking. This drug may also be beneficial to prevent disorders such as Seasonal Affective Disorder (SAD), also known as winter depression [Ogbru, 2014a]. These antidepressants are shown in the table below.

Table 6: Showing the different types of Antidepressants, modified from [Antshel et al., 2011]

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Brand name, (Formulation and Generic name)</th>
<th>Daily dosage</th>
<th>Duration</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NDRI</strong></td>
<td>Bupropion</td>
<td>Two to three times daily. Initial: Lesser of 3 mg/Kg/d or 150 mg; Maximum: Lesser of 6 mg/Kg/d or 450 mg; No singled does greater than 150 mg</td>
<td>8-12 hours</td>
<td>Insomnia, loss of appetite, irritability, anticholinergic (dry mouth, GI etc.), decreased seizure threshold</td>
</tr>
<tr>
<td><strong>NDRI</strong></td>
<td>IR (Wellbutrin)</td>
<td></td>
<td></td>
<td>Same side effects</td>
</tr>
<tr>
<td>NDRI</td>
<td>ER (Wellbutrin SR)</td>
<td>Twice daily</td>
<td>12-24 hours</td>
<td>Same side effects</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>NDRI</td>
<td>(Wellbutrin XL)</td>
<td>Once daily</td>
<td>24 hours</td>
<td>Same side effects</td>
</tr>
<tr>
<td>SNRI’s</td>
<td>Imipramine (Tofranil)</td>
<td>Initial: 1 mg/Kg/d; Maximum: Lesser of 4 mg/Kg/d or 200 mg; One to two times daily; obtain baseline EKG; Monitor serum levels</td>
<td>12-24 hours</td>
<td>Sedation, Cardiac increase heart rate, arrhythmias, anticholinergic (dry mouth, GI, etc.), blurry vision</td>
</tr>
</tbody>
</table>

Tricyclic antidepressants (TCA) inhibit the reuptake of NA, however not DA and are effective in reducing symptoms of ADHD. These antidepressants are very effective in treating the behavioral aspects of ADHD than the cognitive shortages, since they have a positive effect on the major components of ADHD which include; hyperactivity and impulsivity. However these drugs provide insignificant benefits on attention. Imipramine (Tofranil) has been used since the 1950s and the drug is effective in treating depression like disorders [Ogbru, 2014b]. TCAs have quinidine like effects on the heart and if an overdose is used these antidepressants can cause ventricular arrhythmias.

TCAs are helpful in treating ADHD in both children and adults and these antidepressants are comparatively of low-cost but due to their unpleasant side effects, these antidepressant medications are not considered as a first line treatment option.

### 3.2 Non-pharmacological Treatments for ADHD

A variety of non-pharmacological treatment options or therapies have been used for children and adults with ADHD. These non-pharmacological treatment options include behavioral therapy which comprises of behavioral interventions and cognitive behavioral therapy (CBT), educational approaches, counseling, support groups, parent/teacher training and changes to diet and lifestyle as shown in the image below [ADHD Institute, 2014].
Figure 11: Non-pharmacological therapies for ADHD [ADHD Institute, 2014b], accessed May 21st 2014

3.2.1 Behavioral therapy

Behavioral therapy, also known as behavior modification, has shown to be an effective treatment option for children with ADHD. This kind of therapy involves reinforcing wanted or desired behaviors through reward and praise, thus reducing problematic behaviors by setting boundaries and consequences.

Behavioral therapy can be divided into behavioral interventions and cognitive behavioral therapy. This kind of therapy is not destined to treat inattention or impulsivity. However, it has shown to help with some of the behavior problems that come along with ADHD, such as not obeying rules or not getting along with other people [Husney et al., 2012].

Behavioral interventions comprise of teaching parents and teachers’ tactics in order to handle a child’s troublemaking behavior and be able to address problematic behavioral habits at home or at school and this are stated to be a key part of treating ADHD in children [ADHD Institute, 2014c]. Behavioral interventions normally consist of tested procedures or a set of tested procedures that are aimed to provide parents with tactics or strategies in order to improve family
interactions and their child’s ability to manage his or her behavior, since ADHD often causes children and adolescents to react impulsively and makes it challenging for them to learn and to comply with rules. Therefore, many children and adolescents with ADHD need behavioral therapy in order to interact appropriately with other people [HealthyChildren, 2013].

Parent-led behavioral interventions or parent training are programs/procedures that are designed to train parents in order to effectively manage and shape their child’s behavior. These type of programs focus in turning parents into their child’s personal therapist by teaching them how to retain positive behaviors, regulate which behaviors can be ignored and know when and how to set and impose rules for their children [HealthyChildren, 2013]. One of the main aspects of these programs is to create a healthy bond between the parents and their child. From these programs parents learn strategies in order to help their child avoid behavior problems before they happen and the programs also teach parents to create a system of reward and consequences depending on their child’s behavior. This type of behavioral training session is generally held in an office, often attended by both the parents and their child. These weekly sessions can last for several weeks or months depending on the child’s response to the therapy.

Teacher-led behavioral interventions consist of managing educational activities. Studies have shown that teacher-led interventions for children with ADHD have great beneficial effects on conduct problems, for example giving a child effective commands [Robert et al., 2011].

Cognitive behavioral therapy (CBT) is a particular type of behavioral or talking therapy where negative patterns of thought, feelings and behaviors of an individual are challenged in order to change undesirable behavior patterns. This kind of therapy can help individuals manage their problems by changing the way they think about themselves and behave [NHS Choices, 2012]. However this kind of therapy can’t eliminate problems but can help individuals manage them in a positive way. CBT is effective in treating anxiety disorders and has shown to be as useful as antidepressants for some individuals [Duckworth and Freedman, 2012]. This type of behavioral therapy has also been shown to be helpful in treating depression, ADHD, post-traumatic stress disorder (PTSD) and drug misuse. CBT helps improve an individual’s state of mind on a daily basis and unlike other types of talking therapy, CBT mainly deals with an individual’s current problem rather than dealing with his or her past issues [NHS Choices, 2012].

Parents with the help of a cognitive behavioral therapist can set up a behavioral modification plan of rewards and consequences for their children at home and at school in order to shape their child’s behavior [Block and Smith, 2013]. CBT can make a difference for children with ADHD and help them cope with their symptoms and with the way they behave at home, school or with their friends and families. Parents regularly attend sessions with their child, where the main focus is to get the child to open up and express his or her experiences, feelings and typical behaviors. The therapist can then identify the difficulties the child is going through and can suggest ways to overcome them. A session normally lasts for one hour and takes place twice weekly and individuals with disorders such as ADHD need between 6 and 20 sessions on average, though this can vary greatly from individual to individual [Rutherford, 2014].

A controlled study showed that CBT could be a favorable intervention in order to treat the core symptoms of ADHD in children, though there are other studies suggesting that CBT may only be effective when provided in combination with medication for the treatment of ADHD
Impulsive behavior and hyperactivity diminishes in adult ADHD however attention problems are persistent. Comorbid conditions in adults include mood and anxiety disorders as well as sleep problems. CBT is continued into adulthood, where therapists work directly with their patients instead of being coordinated through parents. Therapists work with their patients in order to improve their attention, memory, time management and planning skills and a complete evaluation regarding their progress is notified to them if they show positive signs along the treatment.

Recent studies have demonstrated that combined parent training and social skills training (SST) procedures have stronger and comprehensive treatment effects when treating the disorder. The National Institute for Health and Clinical Excellence (NICE) guideline recommended in 2009 that interventions consisting of CBT or SST sessions plus parent training are more likely to be beneficial together than any other treatment option for treating ADHD [Young et al., 2009]. SST, developed in the early 1970s, is a form of behavior therapy with the main aim of improving a child’s social skill and teaching them to behave in an adequate manner [Young et al., 2009]. This type of behavior therapy can be used by teachers, therapists or other professionals in order to help individuals with mood disorders, anxiety disorders and personality disorders. SST is usually provided individually or in a group set up once or twice a week.

By teaching patients how to cope with their symptoms, non-pharmacological treatment options can improve the patient’s ability to cope with ADHD symptoms effectively and for these therapies to work, it is compulsory for patients to adapt to their treatment program and is also essential for therapists to monitor their patient’s symptoms, changes in their behavior and their emotional state.

3.2.2 Psychoeducation

Psychoeducation is an education about a certain condition that causes psychological stress is termed as psychoeducation [myVMC, 2008]. There are many methods in which people overcome psychological stress and one way is through education oneself about the condition. Once an individual has a better understanding of their condition, they will more likely feel in control of the situation and this in turn lessens the stress associated with their condition. Individuals that obtain knowledge about their condition are more likely to participate in their self-management and this can bring positive social changes and can build their self-esteem [myVMC, 2008].

Psychoeducation aims to provide information to children/adolescents, teachers and their parents about the mental illness. The main purpose of this treatment is to help children and their families understand how the illness affects them, what kind of treatment is effective and general advice is given to both the parent and child to help them improve the child’s academic and behavioral functioning [MDHS, 2014]. This type of treatment helps children/adolescents and their caretakers understand that there are other people with ADHD with similar problems and that there are treatments effective in treating ADHD. This type of education also helps children and their caretakers understand what will take place in the treatment sessions, how long the treatment might
take and also learn what role the parent, therapist and the child will play in the treatment and that they will work as a team on the problems all together [MDHS, 2014].

Psychoeducational can also be group based which can be very effective in treating the disorder because group situations or sessions are considered less intimidating by many patients as opposed to a one-on-one session with a psychologist. These group-based settings enable individuals to meet in a safe environment and gain support and trust of the group which decreases the amount of stress in the situation. In a group based session, individuals share their experiences with each other and what types of therapy or medication have been effective for them. By these means, everyone has a viewpoint of how other people deal with their situations and this adds to the overall learning experience [myVMC, 2008].

Group psychoeducation can also be applied in schools or classrooms as a precautionary measure [myVMC, 2008]. Once school children understand the condition of a fellow classmate with ADHD or any other disorder, they are not going to view him or her differently and will be more willing to help their fellow classmate. Children diagnosed with ADHD might think that other children might view them as different. If a child has an opportunity to explain about his or her condition, where the class can openly discuss the disorder in a safe environment, misperception surrounding the disorder can be reduced and other children might not think of the individual with the disorder differently [myVMC, 2008].

The effectiveness of psychoeducation treatment mainly depends on the individual that has the disorder, whether he or she truly believes in the treatment or not. If individuals do believe in the treatment and try their best in participating in activities, asking general questions about the disorder or the treatment, then psychoeducation is more likely going to benefit them [myVMC, 2008].

3.2.3 Diet and lifestyle changes

Lifestyle changes and modifying a patient’s diet are also suggested as an approach to treat ADHD but there is limited evidence regarding it. However, many children and adults with the disorder have made significant improvement through nutrition changes [Tora, 2008]. Some studies have also revealed that modifying a patient’s diet and lifestyle changes such as exercise can be as effective as drugs in order to treat the disorder [Tora, 2008]. Nutritional diets and lifestyle changes can be considered as an alternative treatment option for ADHD, though there is limited evidence that a high sugar diet can potentially cause ADHD [Sellick, 2012].

One of the dietary interventions includes the Feingold program or diet, which is a food elimination diet where artificial food colors, artificial food flavors, aspartame (NutraSweet, an artificial sweetener) and preservatives are eliminated from processed foods which help decrease hyperactivity in people with ADHD [Sellick, 2012].

Food colors and dyes used in various cosmetics, drinks, yogurt, candies and cookies have been suspected to cause allergic reactions in both children and adults. Children may also develop symptoms of ADHD as a reaction to these additives [Tora, 2008]. Evidence from recent studies has shown that changing the diet of children with ADHD can be beneficial to some of them.
Parents who have tried the Feingold program have also reported an improvement in their child’s behavior and recent studies have shown that the Feingold program can reduce hyperactive symptoms of ADHD when following the diet program [Sellick, 2012]. There is no evidence that food additives cause ADHD. However recent studies show that certain food colors, flavors and preservatives can increase hyperactivity in some children.

A study conducted by the United Kingdom’s Food Standards Agency in 2007 revealed that consumption of foods containing dyes could aggravate hyperactivity in children. After reviewing the scientific evidence, the U.S. FDA concluded that some children with ADHD and other problematic behaviors may be sensitive to food colorings/dyes and other food additives and these chemicals can worsen their symptoms. These chemicals are often added to processed foods or drinks and are used to maintain or improve the appearance of the food [Quinn, 2012].

Food additives that may increase hyperactivity or have an adverse effect on activity in children include; Sodium benzoate, Yellow No. 5 (Tartrazine), Yellow No. 6 (Sunset yellow), Yellow No. 10 (Quinoline yellow, not approved in the U.S.), Red No. 40 (Allura red), Red No. 3 (Carmoisine, not approved in the U.S.) and Red No. 7 (Ponceau 4R, not approved in the U.S.). The European Union has already given approval to place warning labels on foods containing these artificial colors/dyes [Gardner, 2014]. The U.S. FDA requires labeling of Yellow No. 5 (Tartrazine) on food packaging along with other ingredients and since studies to date have not proved a link between food colorings/dyes and hyperactive behavior, many food colorings or additives do not require labeling on food packaging [Huxsahl, 2011].

Iron deficiency is known to cause abnormal Dopaminergic neurotransmission and can thus contribute to the development of ADHD [Sellick, 2012]. Iron is regarded as an essential nutrient for brain development and a lack of iron in the diet can result in the development of iron deficiency anemia which can cause a person to feel constantly weak and tired. A study also showed that children with the most severe iron deficiency are generally inattentive, distractible and suffer from learning disabilities. Therefore it is highly recommended that people not only with ADHD but normal people should also eat a variety of iron rich foods and foods high with Vitamin C [Sellick, 2012].

Nutritional diets programs have shown to be effective in treating ADHD. Recent studies have also shown that daily consumption of Omega-3 and Omega-6 fatty acids can lessen the frequency of ADHD symptoms. Omega-6 fatty acids can be found in mayonnaise, margarine and processed foods, whereas Omega-3 fatty acids are generally found in walnuts and oily fish [Sellick, 2012].

An approach to lifestyle changes can be exercising. This not only keeps a person physically fit but mentally as well [“Lifestyle Changes”, 2013]. People notice improvement in their mood, helps them to sleep better and boosts their energy and strength when exercising regularly and this is because their body releases endorphins into their bloodstream that act as natural painkillers. Regular exercise not only releases endorphins, which improve mood, but also reduces levels of cortisol which is the stress or depression hormone found in the bloodstream [“Lifestyle Changes”, 2013].
Sleep problems are common in people with ADHD as well as in people with depression disorders. Lack of sleep can affect one’s concentration, memory and learning ability [“Lifestyle Changes”, 2013]. Sleep has also a strong effect on mood and it can only amplify the symptoms, if a person with a mental disorder does not get enough sleep [“Lifestyle Changes”, 2013].

Therefore, it is strongly recommended that people without mental disorders should sleep at least 7 to 8 hours each night. Meditation and relaxation methods also help in relaxing one’s body and reducing tension. Recent studies indicate that lifestyle changes can improve mood, reduce stress and lower health problems for people with mental disorders and these studies also suggest that lifestyle changes can improve brain functioning which includes memory and learning [Lifestyle Changes, 2013].

### 4. Areas of the brain affected in ADHD

#### 4.1 Background information about brain areas

The brain consists of the cerebrum, cerebellum, and the brainstem. The Cerebrum consists of the cerebral cortex, the limbic system and the basal ganglia. Cerebellum is also referred to as the little brain sitting below the cerebrum, as shown in figure 2, consisting of layered cortex and controls motor skills and motion. The areas of the brain affected by ADHD are described in this section.
4.1.1 Cerebrum

The Prefrontal Cortex is the front area of the brain that handles complex cognitive behavior, personality expression, decision making, social behavior and sensory alertness. This area of the brain manages thoughts and actions in accordance with internal goals [Andersen et al., 2013]. A disruption in this area or the networking process between this area and other areas in the brain will result in abnormal behavior. There are also frontal lobe dysfunctions that lead to symptoms of impulsivity and attention disorders.

Striatum is a part of the forebrain and is one of the major end stations for DA signals from the basal ganglia system. It receives inputs from the cerebral cortex and is divided by the white matter tract called the internal capsule, into two sections: the caudate nucleus and putamen. This area of the brain controls body movement and coordination, while facilitating balances motivation with functions for examples inhibiting or inducing behavior in social interactions, voluntary movements, and motor functions [Anderson et al., 2013].
Frontal Lobe controls higher mental functions such as motivation, planning, complex thoughts and social interactions, introspective thought, social behavior and speech production and organization [Anderson et al., 2013].

Frontostriatal Circuit is a group of neural pathways that connect the frontal lobe regions of the brain to the basal ganglia, or striatum. These pathways mediate motor, cognitive, and behavioral functions within the brain. They receive inputs from Dopaminergic, serotonergic, noradrenergic and cholinergic cell groups that modulate information processing. The frontostriatal circuit functions in selection and perception of important information, manipulation of information in working memory, planning and organization, behavioral control, adaption to changes and decision making. These circuits are involved in neurodegenerative disorders including ADHD [Definition influenced from wikipedia.org].

The Temporoparietal Junction (TPJ) is an area of the brain in which the temporal and parietal lobes meet. The TPJ incorporates information from the thalamus and the limbic system while also incorporating the visual, auditory and somatosensory systems. The TPJ integrates information from the external environment as well as from the internal body. It collects the information form these areas and processes it [Definition influenced from wikipedia.org]. Damage to the TPJ had been implicated in having detrimental effects on an individual’s ability to make moral based decisions and has also been correlated with out-of-body experiences. It is also linked to disorders like amnesia, Alzheimer’s disease, schizophrenia and ADHD [EPNS, 2012].

The Corpus Callosum also referred to as the colossal commissure, is a group of fibers beneath the cortex in the eutherian brain. It connects the right and left cerebral hemispheres and facilitates inter-hemispheric communication. It is the largest white matter structure in the brain [Definition influenced from wikipedia.org].

4.1.2 Cerebellum
Cerebellum also known as the “little brain” is a region of the brain that facilitates a role in motor control. It is involved in cognitive functions for example; attention and language, and in regulating fear and pleasure responses, but it’s most established functions are movement-related. It contributes to coordination, precision, and accurate timing. The cerebellum also receives sensory inputs of the spinal cord and other areas of the brain, and integrates these inputs to motor movement, equilibrium, posture and motor learning [Anderson et al., 2013].

The Cerebellar Vermis, Latin for worm is located in the medial zone of the cerebellum. The vermis divides the anterior and posterior regions of the cerebellum. It functions in posture and locomotion and receives somatic sensory input from the head and proximal parts via ascending spinal pathways [Definition influenced from wikipedia.org].
4.1.3 White Matter

White Matter is one of the two main components of the central nervous system and consists of glial cells and myelinated axons that transmit signals from one area of the brain to another, in the cerebrum. It is embedded in the brain, partly in the brain stem or the superficial spinal cord and the cerebellum. White matter tissues are essentially composed of lipid tissue and veined with capillaries. It affects how the brain learns, functions and reacts. White matter is comprised of the tissue that messages pass through, between different areas of the nervous system. The white matter is white because of the fatty substance (myelin) that surrounds the nerve fibers (axons). This myelin is found in almost all long nerve fibers, and acts as an electrical insulation. This is important because it allows the messages to pass quickly from place to place. The brain in general (and especially a child's brain) can adapt to white matter damage by finding alternative routes that bypass the damaged white matter areas, and can therefore maintain good connections between the various areas of grey matter.

Unlike grey matter, which peaks in development in a person's twenties, the white matter continues to develop, and peaks in middle age (Sowell et al., 2003). This claim has been disputed in recent years, however. In a study conducted in 2009 by Jan Scholz et al., a Diffusion Tensor Imaging system was used to demonstrate changes in white matter in the brain. The white matter volume changes as a result of learning new motor tasks. Its is the first paper that correlates motor learning with white matter changes. Previously, many researchers had considered this type of learning to be exclusively mediated by dendrites, which are not present in white matter. The authors suggest that electrical activity in axons may regulate myelination in axons. Similarly, the cause may be gross changes in the diameter or packing density of the axon [Scholz et al., 2009].

There are three different kinds of tracts, or bundles of axons which connect one part of the brain to another and to the spinal cord, within the white matter:

1. Projection tracts extend vertically between higher and lower brain and spinal cord centers, and carry information between the cerebrum and the rest of the body. The cortico spinal tracts, for example, carry motor signals from the cerebrum to the brainstem and spinal cord. Other projection tracts carry signals upward to the cerebral cortex. Superior to the brainstem, such tracts form a broad, dense sheet called the internal capsule between the thalamus and basal nuclei, then radiate in a diverging, fanlike array to specific areas of the cortex.

2. Commissural tracts cross from one cerebral hemisphere to the other through bridges called commissures. The great majority of commissural tracts pass through the large corpus callosum. A few tracts pass through the much smaller anterior and posterior commissures. Commissural tracts enable the left and right sides of the cerebrum to communicate with each other.

3. Association tracts connect different regions within the same hemisphere of the brain. Long association fibers connect different lobes of a hemisphere to each other whereas short association fibers connect different lobes within a single lobe. Among their roles, association tracts link perceptual and memory centers of the brain.
4.1.4 Grey Matter
The other main component of the nervous system, Grey Matter, is composed of neurons, neuropile (dendrites and myelinated and unmyelinated axons), glial cells, and capillaries, and is primarily associated with processing information and cognition. It is found in the cerebral cortex, cerebellum, the thalamus, hypothalamus; subthalamus, basal ganglia-putamen, globus pallidus, cerebellar nuclei, and spinal grey matter. Grey matter undergoes developmental changes and growth throughout childhood and into early adulthood. Grey matter can be analogized as the motherboard, while white matter would be the wiring that hooks up the motherboard. The grey matter includes regions of the brain involved in muscle control, sensory perception such as seeing and hearing, memory, emotions, speech, decision making, and self-control. While 20% of all oxygen taken in by the body goes to the brain, 95% of that goes specifically into the grey matter.

4.1.5 Basal Ganglia
The Basal Ganglia is a group of nuclei that is largely correlated with the cerebral cortex, thalamus and the brain stem. It functions by controlling the voluntary motor movements. Voluntary motor movements include: procedural learning, routine behaviors or “habits,” eye movements, emotion, cognition, arousal, and is correlated with the Dopaminergic mechanisms. The basal ganglia form a forebrain system that retains signals from a large part of the neocortex, then redistributes these cortical inputs both with respect to one another and with respect to inputs from the limbic system, it then focuses the inputs of this redistributed, integrated signals into particular regions of the frontal lobes and brain stem involved in aspects of motor planning and motor memory. The neostriatum or striatum are composed of caudate and putamen, in which all inputs to the basal ganglia are transported through.

The medial to the putamen is the globus pallidus (GP) which is comprised of two pathways, the direct and indirect, which convey information to the thalamus. These pathways have opposite effects on motor activity. In the direct pathway, the striatal cells project directly to GP-internal, increasing the excitatory drive of the thalamus to the cortex using neurotransmitter glutamate. When activated, the cortical projections excite striatal neurons, thus activating the striatal cell, which in turn, uses the inhibitory neurotransmitter GABA. The resulting effect is inhibition of the Thalamus, resulting in an increased Ventral-anterior-ventral lateral thalamic complex (VA/VL) neurons and increase of activity.

The indirect pathway decreases the excitatory drive from thalamus to cortex. The difference between the direct pathway and indirect pathway is that the direct pathway induces motor activity and the indirect suppresses or decreases motor activity.

DA is produced by cells in the pars compacta of the substantia nigra (SNc) and nigrostriatal axon terminals release DA into the striatum. DA has an excitatory effect on cells in the striatum that are a part of the direct pathway, via D1 receptors, and has an inhibitory effect on striatal cells within
the indirect pathway, via D2 receptors. Therefore, DA induces motor activity via the direct pathway and inhibitory effects via the indirect pathway.

4.2 Brain areas affected in individuals with ADHD

There are endless amounts of neuroimaging evidence that exist and suggest the presence of structural abnormalities in the brains of children with ADHD. Some of the initial investigations that were influenced by preliminary theoretical models of ADHD and clinical observations, emphasized significant differences in the frontostriatal circuitry of children with ADHD. It has since become apparent that other regions of the brain may exhibit morphological alterations, including areas of the cerebellum and temporoparietal lobes, basal ganglia (described later in this section) and corpus callosum. The first meta-analysis of Magnetic Resonance Imaging scans (MRI) structural findings in ADHD children demonstrated that the brain regions showing the largest volumetric reductions, in ADHD vs controls, included the posterior inferior cerebellar vermis, the splenium of the corpus callosum, the right caudate, and the total and right cerebral volume [EPNS, 2012].

Because several studies did not record the medication status of the subjects, the authors could not rule out the possibility that medication status might have influenced ADHD brain volumes. The limited number of studies included in the meta-analysis did not allow the authors to perform more powerful quantitative and qualitative analyses of other brain regions. In the Journal of Pediatric Neurology meta-analysis, the selected studies were based on the regions-of-interest (ROI) approach, with an undue concentration on relatively few and more easily measurable cerebral structures (e.g. areas of the caudate nucleus, corpus callosum, putamen, amygdala, hippocampus, etc.) [EPNS, 2012]. A subsequent meta-analysis of voxel-based morphometric (VBM) studies, which are free from the previous bias, found that only right putamen volume loss was significant across studies, although the conclusions of the report should not be considered as definitive, given that only seven studies were included. The most recent VBM meta-analysis, which used the newer meta-analytic technique of signed differential mapping, found that individuals with ADHD had a significant global reduction in grey matter volumes, most prominently in the right lentiform nucleus and extending to the caudate nucleus. Increasing age and stimulant treatment were associated with more normal values in this region [EPNS, 2012].

Another recent VBM study in young adults (with an average age of 20 years) found that individuals with ADHD had less grey matter in the right inferior frontal gyrus, which correlated with poorer outcomes in measures of processing speed, controlled impulsivity, response inhibition and response variability, compared with matched controls [EPNS, 2012].

Furthermore, it has been emphasized that the morphological alterations found in children with ADHD are unlikely to be a phenomenon of the behavioral symptoms, because genetic similarities were found in first-degree relatives to whom also exhibited similar, though attenuated, changes in cortical grey and white matter [EPNS, 2012]. Previously overlooked morphological aspects of cerebral structures, beyond their volume, have also been implicated. Studies that focus on architectural alterations have reported global thinning of the cortex (prominently in the medial and
superior prefrontal and precentral regions), reductions in the density of the dorsolateral prefrontal cortex (along with increases in grey matter in the posterior temporal and inferior parietal regions), reduction in surface area, and decreased cortical folding [EPNS, 2012]. Rather than a decrease in cortical thickness, the latter findings may account for the overall cortical volume previously reported in [EPNS, 2012]. Data from published investigations of cortical anatomy are somewhat conflicting due to methodological differences, but a recent study employing sophisticated computational imaging analysis supports that cortical thinning is a reliable finding in children and adolescents with ADHD. Furthermore, it also appears that the rate of cortical thinning (a process which also occurs normally in development, during later stages of cortical maturation) is correlated with severity of hyperactivity and impulsivity in children with ADHD and those without.

Additionally, studies exploring the shape of brain structures are beginning to report abnormalities in structures scarcely explored in early studies, such as the amygdala (along with a possible compensatory enlargement of the hippocampal head) and the thalamus, therefore providing neurobiological evidence to support the emotional and complex sensorial alterations frequently described in children with ADHD. An additional advance in the field has been the study of abnormalities in the white matter fibers that connect grey matter regions. Recent studies employing diffusion tensor imaging (DTI) are providing quantitative information relating to the structure and architecture of brain white matter fibers, thus overcoming the limitations of earlier studies (e.g. Castellanos et al.) that explored the entire cerebral white matter volume without investigating specific fiber pathways [EPNS, 2012].

Some research involving MRI scans show that children with ADHD had smaller frontal and temporal lobes, which among other functions; control planning and attention, which both are negatively affected in ADHD patients. A study showed that the temporal and inferior parietal cortices showed increased grey matter (up to 24% more) in ADHD patients [CDC, 2014]. Increased amounts of grey matter appeared to contribute to inattention, and a larger frontal lobe induces hyperactivity. Although the children in this study were previously taking stimulant medications, researchers believed that the changes in brain size were not due to the children’s ADHD medications. Another study showed that there is an overall brain shrinkage of 3-4% among children with ADHD [NIH, 2014]. This supported the previous statement that brain size changes were not due to the medications prescribed to the children. The study also found that ADHD medications may aid brain development [NIH, 2014]. Children that did not use medication had even less white matter than those with ADHD who were using medication. White matter aids the connection of different areas of the brain, and those with denser white matter have more developed brains. Despite these findings more research should be done to find the exact differences in normal brains and ADHD brains, as there are some overlapping and conflicting findings in current research.

In hyperkinetic disorders, the excitatory input to Globus Pallidus internal (GP internal) is lost resulting in less inhibition reaching the Ventral Anterior and Ventral lateral nuclei of the thalamus (VA/VL) causing hyperactivity in VA/VL and the motor cortex, resulting in hyperactivity of the motor system. Such imbalances are seen in ADHD where lower levels of DA and lower D1 receptor activity are found in individuals with ADHD.
Figure 13: Globus pallidus, [Wikipedia.org] accessed May 21st 2014

Figure 14: Cortex Cerebri [Wikipedia.org] accessed May 21st 2014

**Brain: Ventral lateral nucleus**

- MNG = [Midline nuclear group](#)
- AN = [Anterior nuclear group](#)
- MD = [Medial dorsal nucleus](#)
- VNG = [Ventral nuclear group](#)
- VA = [Ventral anterior nucleus](#)
- VL = Ventral lateral nucleus
Figure 15: [Thalamic nuclei, Wikipedia.org] accessed may 21st 2014

Table:

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<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>VPL</td>
<td>Ventral posterolateral nucleus</td>
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<tr>
<td>VPM</td>
<td>Ventral posteromedial nucleus</td>
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<tr>
<td>LNG</td>
<td>Lateral nuclear group</td>
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<td>PUL</td>
<td>Pulvinar</td>
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<td>MTh</td>
<td>Metathalamus</td>
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<td>LG</td>
<td>Lateral geniculate nucleus</td>
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<td>MG</td>
<td>Medial geniculate nucleus</td>
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Figure 16: Thalamic nuclei, [Wikipedia.org], accessed May 21st 2014

Underactive basal ganglia generally corresponds to a deficit of DA and a relative excess of serotonin and or GABA whereas overactivity of basal ganglia corresponds to a relative access to DA and a deficit of the neurotransmitters GABA and/or serotonin. The basal ganglia is mediated by the neurotransmitter glutamate which is a cause of hyperactivity. Underactivity of the basal ganglia yields a tendency for ADD and ADHD.

Movement disorders associated with basal ganglia dysfunction comprise a spectrum of abnormalities that range from the Hypokinetic disorder (from which Parkinson's disease, PD, is the best-known-example) to hyperkinetic disorder (exemplified by Huntington's disease and hemiballism) at the other. In addition movement disorders, major mental disorders including schizophrenia and attention deficit hyperactivity disorder (ADHD) have been linked to abnormalities in the basal ganglia and their allied nuclei. Recent evidence indicates that a DA-induced imbalance of basal ganglia neural circuitries may be an important pathophysiological component in ADHD. Hyperactivity of the inhibitory DA (D2) transmission has serious cognitive effects on the brain and is linked to hyperactivity in ADHD. Through this disinhibition, the thalamus exhibits hyperactivity that overstimulates the cortex resulting in dysfunctions of
perception, attention, stimulus distinction, information processing and affective regulation (inducing hallucinations and delusions) and motor disabilities.

Volumetric abnormalities of basal ganglia have been associated with ADHD, especially in boys. Studies using large deformation diffeomorphic metric mapping (LDDMM) have examined the effect ADHD, sex and their interaction on basal ganglia shapes. The basal ganglia (caudate, putamen, globus pallidus) were manually delineated on MRIs from 66 developing children (35 boys) and 47 children (27 boys) with ADHD. LDDMM mappings from 35 developing children were used to generate basal ganglia templates [Qui et al., 2009]. Shape variations of each structure relative to the template were modeled for each subject. The results yielded that boys with ADHD showed significantly smaller basal ganglia volumes compared to developing boys, and LDDMM revealed that the basal ganglia shapes varied widely. Volume compression was seen bilaterally in the caudate head and body and anterior putamen as well as in the left anterior globus pallidus and right ventral putamen. Volume expansion was most identifiable in the posterior putamen. No volume or shape differences were unveiled in girls with ADHD. The conclusions were that the shape compression pattern of basal ganglia in boys with ADHD suggests that ADHD-associated deviations from typical brain development are comprised of multiple frontal-subcortical control loops, including circuits with premotor, coulometer, and prefrontal cortices. Future investigations involving brain-behavior analyses will help to distinguish the task-dependent contributions of these circuits to impaired response control that is typical of ADHD [Qui et al., 2009].

5. Neurochemistry

5.1 Brain Communication

Numerous neurotransmitters contribute to the complex signaling processes in the brain. Serotonin and the catecholamine, noradrenalin, adrenaline and DA all belong to the group of biogenic amines. Both DA and serotonin are synthesized in relatively few neurons located in few structures of the brain. These neurons have axons reaching a large number of brain structures, where they release DA or serotonin into the synaptic cleft. Neurotransmitters can bind specifically to more than several hundred different receptors. Particular neurotransmitters can stimulate postsynaptic cells expressing one receptor while restraining postsynaptic cells expressing a different receptor. Noradrenalin which is synthesized from tyrosine is a stimulating neurotransmitter in the autonomic nervous system and has related functions as a hormone outside the nervous system. DA, also synthesized from tyrosine, and serotonin synthesized from tryptophan, is released at few sites in the brain affecting mood, learning, sleep and attention. These neurotransmitters play a vital role in various nervous system disorders. Attention-deficit/hyperactivity disorder (ADHD) is associated with a lack of DA/noradrenalin in the brain and is treated with drugs increasing the concentrations of these neurotransmitters [Reece et. al. 2010]. Neurotransmitter receptors in postsynaptic neurons can be
There are two major types of receptor channels; ligand-gated ion channels (LGICs) including both ionotropic- and metabotropic receptors, and voltage-gated ion channels (VGICs). Ligand-gated ion channels opens up when a ligand bind to an extracellular part of the channel. Voltage-gated ion channels opens when an action potential reaches voltage-sensing fragments of the voltage-gated channel [Waller et. al. 2010]. It happens within a few milliseconds [Lodish et. al. 2000]. Ligand-gated ion channels include numerous receptors such as nicotinic acetylcholine receptors, 5HT3 receptors (serotonin Na+, K+, Ca++) and glycine receptors (Cl⁻) all consisting of several transmembrane subunits gathering around one central channel. Peptide subunits are organized so the hydrophobic amino acids face the membrane lipid bilayer and the hydrophilic amino acids face the channel. When an agonist bind to a receptor a conformational change results in fast openings of the ion channel. Ligand-gated G-protein-coupled receptors can influence ion channels in two different ways: directly, using G-protein subunits to interact with the channel and
indirectly, using a second messenger system which affects the status of the channel [Waller et. al. 2010].

Figure 18: Shows a typical ligand-gated transmembrane ion channel [Waller et. al. 2010] Accessed April 2\textsuperscript{nd} 2014

Second messengers are molecules generated by ligand-receptor bonding that operates signal transduction. Cyclic adenosine monophosphate (cAMP), 1,4,5-trisphosphate (IP\textsubscript{3}) and diacylglycerol (DAG\textsubscript{1}) are second messengers used by ligand-gated subunits.

Ionotropic receptors are linked directly to ion channels and allow ions to move in and out of the cell. In general, the ions allowed to travel through ionotropic receptors are limited to Na\textsuperscript{+}, K\textsuperscript{+}, Cl\textsuperscript{-} and Ca\textsuperscript{2+}.

Metabotropic receptors do not have ion channels in their structure; they affect ion channels or intracellular signaling by activating G-proteins. These receptors are seven transmembrane monomeric proteins containing a neurotransmitter binding site on its extracellular domain and bind to G-proteins on its intracellular domain. When ligands bind to metabotropic receptors, they activate G-proteins which then either detach from the receptor to interrelate directly with ion channels or it binds with an effector protein for example enzymes forming intracellular messengers that open or close ion channels [Purves et al. 2001]. G-proteins are versatile signaling molecules coupled to ligand-gated receptors. G-protein-coupled receptors regulate the ion channels indirectly [Lodish et. al. 2000]. The N-terminals in G-protein-coupled transmembrane receptors are located on the extracellular side which crosses the membrane seven times resulting in the C-terminals being located on the intracellular side of the cell.
Figure 19: shows a G-protein-coupled receptor (7 transmembrane) [Waller et. al. 2010] Accessed April 2nd 2014

The inner loops typically use a G-protein to engage in coupling to the second messenger system while the outer loops creates the active site for ligand binding. When a suitable agonist bind to the ligand binding site located on the extracellular part of the membrane, it changes the conformation of the receptor activating the g-protein complex.

There are several other types of metabotropic receptors though we did not find examples of those in neurosignaling.
Figure 20: shows how neurotransmitters can affect postsynaptic cell activity through two types of receptor proteins; ionotropic- and metabotropic receptors [Purves et al. 2001] Accessed March 23rd 2014

![Diagram showing action potential](http://www.nature.com/nature/journal/v442/n7102/full/nature04886.html)

Figure 21: [http://www.nature.com/nature/journal/v442/n7102/full/nature04886.html](http://www.nature.com/nature/journal/v442/n7102/full/nature04886.html) accessed May 10th 2014

The resting potential of neurons is typically -60 to -70 mV. Signaling to the neuron can initiate an action potential resulting in depolarization of the cell membrane.

An action potential is normally initiated in the axon hillock, and is responsible for the transfer of information from the soma via the axon to the end plate at the synaptic cleft. For action potentials to keep up the speed of the action potential, some axons are surrounded by myelin sheaths which are interrupted regularly by nodes of Ranvier where the action potential is regenerated. Once the action potential reaches the endplate of the presynaptic cell axon, calcium channels open resulting in fusion of neurotransmitter vesicles with the membrane liberating the transmitter into the synaptic cleft to activate postsynaptic receptors [Kandel, 2000]. In addition, they can stimulate auto-receptors in presynaptic membranes resulting in further release or reduction of the neurotransmitter [Waller et. al. 2010]. Neurotransmitters can either diffuse out of the synaptic cleft, be enzymatically degraded be re-uptaken into the presynaptic neuron. [Reece et. al. 2010].
A neurons' system processes information in three subpopulations of neurons: sensory neurons, interneurons and motor neurons. Sensory receptors are dendrites of sensory neurons able to receive a specific stimulus: exteroceptors include tactile receptors (touch, pain and temperature) and receptors for taste, smell, hearing and vision. Exteroceptors "sense" stimuli from the cardiovascular system and visceral organs. They signal to the autonomic nervous system. Proprioceptors receive input from joints, ligaments, tendons and skeletal muscle. These stimuli create action potentials travelling to the soma of the sensoric nerve's cells located in a sensory ganglia associated with the spinal cord and forward via the axons to different sensory centers of the brain. The input is transferred from the axon to dendrites of other neurons (often interneurons) and further to the motor center, where the signal is transferred to dendrites of motor neurons in motor ganglia. Their axons transfer the signal to e.g. skeletal muscle. Interneurons form local circuits which connect neurons in the brain and are by far the majority of brain neurons. In principle, all other brain functions are similar to the sensory-motor circuit: a stimulus reaches a dendrite, and signaling is initiated to other neurons resulting in happiness, anger, sorrow etc. The greater part of synapses are chemical synapses are chemical synapses but some electrical synapses contain gap junctions in which electrical current can flow from one neuron to another. Neurotransmitters are either synthesized in the presynaptic cytoplasm or transported down the axon. Specific transporters concentrate the neurotransmitters in vesicles. In the vesicle, the neurotransmitter can form a complex with adenosine triphosphate (ATP) causing a reduction in free concentration of the neurotransmitter within the vesicle [Waller et. al. 2010].
Figure 23: illustrates how a nerve impulse is transmitted across a chemical synapse. [Picture: Reece et. al., Campbell Biology, 9th ed. 2010 page 1055] accessed March 3rd 2014

Voltage-gated ion channels comprise several transmembrane proteins crossing the membrane in several loops forming a central pore which is fundamental to the passing of ions and is accountable for the selectivity of the channel for a certain ion. Ion selectivity is decided by the amino acid composition of a tiny fragment of the pore, which differs for every type of ion channel. Voltage-gated channels activity can be altered by drugs, either directly by drugs blocking or binding to activated Na⁺ channels or indirectly through intracellular events. Voltage-gated ion channels include Na⁺, K⁺, Ca ++ and Cl⁻ channels. Both ligand- and voltage-gated ion channels are known to control transport of single ions, however, ions of similar diameter and charge may traverse the channel [Waller et. al. 2010].

Along with ion pumps as for example the Na⁺K⁺ATPase, ion selective channels determine the resting potential, the action potential and the cytosolic concentration of ions. Due to the electrogenicity of Na⁺K⁺ATPase, the charge across the plasma membrane is unbalanced because it carries 3 Na⁺ out of the cell for every 2 K⁺ it carries in, resulting in the cell's interior becoming negative relative to the exterior. Exitable cells in multicellular organisms detecting action potentials play a central role in hormone secretion, nerve conduction, memory and learning among others [Nelson, Cox 2013].
The inner loops typically use a G-protein to engage in coupling to the second messenger system while the outer loops creates the active site for ligand binding. When a suitable agonist bind to the ligand binding site located on the extracellular part of the membrane, it changes the conformation of the receptor activating the g-protein complex.

The increased or decreased release of a neurotransmitter is controlled by presynaptic receptors described as either inhibitory (reduce activity) or excitatory (increase activity). Inhibitory transmitters cause the inside of the cell to increase its negativity by encouraging new impulses in postsynaptic cells to hyperpolarize. An excitatory transmitter causes a threshold to be exceeded or approached by depolarizing the postsynaptic cell. Ligands for presynaptic receptors have two main sources: neurotransmitters that are released from vesicles and can act presynaptically (autoreceptors) and neurotransmitters that are released from additional neurons, normally through axo-axonal synapses which includes another neurotransmitter than the one released by the neuron itself (heteroreceptors) [Waller et. al. 2010].

Autoreceptors are present in any part of presynaptic cell membranes; the axon, dendrites, cell body etc. It is a part of a negative feedback loop in signal transduction and are only sensitive to the hormones and neurotransmitters released by the neuron where they are located. Autoreceptors are generally G-protein-coupled receptors that operate through second messengers. Heteroreceptors are similar to autoreceptors but they are sensitive to hormones and neurotransmitters that are not released by the neuron in which they are located [Bear et. al. 2006]. When a neurotransmitter leaves the postsynaptic receptor it can be broken down enzymatically, diffuse away or be re-uptaken by the presynaptic neuron. Postsynaptic cell responses to neurotransmitters rely on different factors; the type of the neurotransmitter and its the concentration in the synaptic cleft, the types of the chemically sensitive ion channels and the different receptors in the postsynaptic membrane.
**Biosynthesis:**

Both noradrenaline and DA are synthesized from tyrosine (TYR) in the postganglionic neurons (sympathetic nervous system) and the adrenal medulla as seen in the figure below.

![Diagram showing biosynthesis of DA and noradrenaline](image)

Tyr = tyrosine; TH = tyrosine hydroxylase; DD = DOPA decarboxylase; DA = dopamine; DBH = dopamine β-hydroxylase; NE = norepinephrine

Figure 25: Shows the synthesis of DA and noradrenaline as well as the release of Noradrenaline [Klabunde, 2012] accessed May 3rd 2014

Tyr is transported to the nerve axon and is then converted into L-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase. This step is rate-limiting for noradrenaline synthesis. Next L-DOPA is converted into DA through DOPA-decarboxylase. DA synthesis occur in the cytoplasm of nerve cells in the ventral tegmental areas and is the first catecholamine synthesized from DOPA. DA is then transported into vesicles and can be converted into noradrenaline via DA β-hydroxylase [Klabunde, 2012]. The methylation of noradrenaline is catalyzed by phenylethanolamine N-methyltransferase (PNMT) with S-adenosylmethionine (SAMe). As cofactor, PNMT has been detected in both the brain and heart at low levels though it is primarily found in the cytosol of endocrine cells in the adrenal medulla [Modified from Wikipedia, Adrenaline].
Abnormalities in the DA system is believed to be the superior imbalance involved in ADHD disorder even though dysregulation of serotonin (5-HT) and noradrenaline (NE) systems is assumed to play a role too.

Figure 26: shows the synthesis of Tyrosine, DA, Noradrenaline (noradrenaline ) and adrenaline (adrenaline ) [http://en.wikipedia.org/wiki/File:Conversion_of_phenylalanine_and_Tyrosine_to_its_biol...importan_derivatives.png] accessed May 3rd 2014

Figure 27: shows how the different neurotransmitters affect human behavior. [http://www.deplin.com/lifewithdepression-causes] Accessed May 10th 2014
5.2 Dopamine (DA)
DA is a neurotransmitter as well as a hormone and has several important functions in the human brain and body. Symptoms in ADHD patients are normally associated with low levels of DA release. Low levels of DA can cause antisocial behavior, decreased motivation, impaired attention and suppressed sex drive among other deficits. Increased levels of DA can cause insomnia, impatience, aggression, restlessness among others. In the brain, DA functions as a neurotransmitter and it governs motivation, arousal, motor control, reward and cognition among some lower-level functions. There are relatively few dopaminergic neurons but the pathways reach numerous other brain areas and have powerful effects. There are four axonal DA pathways: the nigro-striatal; the mesolimbic; the mesocortical and the tuberoinfundibular. Dopaminergic neurons are present in brain areas such as The substantia nigra (midbrain area) in which important pathways go to striatum, subthalamic nucleus and globus pallidus which play significant roles in motor control. A stable DA flow from the substantia nigra through the pathway is essential for a healthy functioning basal ganglia which is crucial for modulating movement. A significant release of DA is needed for individuals to feel good and do physical activity because movement is connected to DA release. DA is connected to attention and alertness as well and the release of DA boost individual's ability to focus and cognitive understanding [Andersen et. al. 2013]. The Dopaminergic neurons in substantia nigra are darkly pigmented and particularly vulnerable to damage. Another midbrain area in which Dopaminergic neurons are located is the ventral tegmental area. In this area pathways go to the prefrontal cortex and the nucleus accumbens among other areas in which the neurons play a central role in reward and motivation. The nucleus accumbens is considered the part of the striatum most involved in the highest level of motor control as e.g. decision-making along with motivation. [Modified from Wikipedia]
Figure 28: shows DA pathways as well as some DA affected areas in a normal brain
Accessed May 10th 2014

From the ventral tegmental area in the midbrain the mesocortical pathways arises which stimulates various regions of the frontal cortex. This pathway is engaged in a number of aspects of memory and learning. The mesolimbic pathway derives from the ventral tegmental area and stimulates the nucleus accumbens, components of the limbic system and the olfactory tubercle. This pathways is implicated in the influence of motivated behavior. The tuberoinfundibular pathway arises from the arcuate and periventricular nuclei located in the hypothalamus. The projections from this pathway release DA into the perivascular spaces of the capillary plexus of the hypophyseal portal system and is then transported to the anterior pituitary where it inhibits the release of prolactin [Vallone et. al. 2000]. The hypophyseal portal system is a system of blood vessels connecting the hypothalamus and the anterior pituitary with the function of transport and exchange of hormones allowing rapid communication between the glands [Modified from Wikipedia].
Figure 29: shows the main circuits of the basal ganglia [Modified from Wikipedia, Basal Ganglia Circuits] Accessed May 13th 2014

The figure above shows the circuits of the basal ganglia. Each arrow has a + or a - which indicates whether the effect of the pathways are inhibitory or excitatory. Red arrows refer to GABAergic pathways that are inhibitory, green arrows refer to glutamatergic pathways that are excitatory and turquoise arrows refer to Dopaminergic pathways that are inhibitory on indirect pathway and excitatory on direct pathway [Modified from Wikipedia, Basal Ganglia Circuits].

**DA receptors:**

The first evidence of DA (DA) receptors in the central nervous system came in 1972 when the idea that DA stimulates adenylyl cyclase (AC) activity was brought up. Based on biochemical and pharmacological data, the suggestion that there are numerous binding sites for DA surfaced. It was then proposed that DA receptors exist as two separate populations, one which is positively coupled to AC and the other independent of the cAMP-generating system. In 1979, based on observations and data, the classification of D1 and D2 receptors was suggested that the D1 receptor stimulates AC and the D2 receptor is not coupled to this effector. This was confirmed by subsequent studies and the dual receptor concept was the foundation of the DA receptor study for a decade. The three DA receptor subtypes were characterized and named D3, D4 and D5 after gene cloning procedures were introduced [Missale et. al. 1998].

DA receptors belong to the seven transmembrane domain G-protein coupled receptor family. The five DA receptors, D1 through 5, are subdivided into two subfamilies, the D1-like family and the D2-like family. The subdivision is based on their biochemical and pharmacological properties [Vallone et. al. 2000]. The receptors D1 and D5 form the D1-like subfamily due to high sequence homology, they stimulate AC and they have typical D1 pharmacology. D2, D3 and D4 receptors form the D2-like subfamily [Jaber et. al. 1996]. The pharmacological profiles of D1 and D2 receptors are significantly different, both the D3 and D4 receptors bind the hallmark D2-selective ligands through fairly high resemblance while the D5 receptor show the typical ligand-binding D1 receptor characteristics. Additionally, the initial difference between D1 and D2 receptors when it comes to positive and negative coupling to AC (signaling events), applies, also to the D3, D4 and D5 receptors, D5 being coupled to AC stimulation and D3 and D4 inhibiting cAMP formation [Missale et. al. 1998].

DA functions seem to be mediate primarily by D2-like receptors. The DA receptor family is expressed in distinct areas of the brain that overlap. D1 receptors are plentiful and extensive in areas that receive Dopaminergic innervations such as the striatum, hypothalamus and the limbic system. D2 receptors are also extensive in these areas and in the pituitary gland as well. D3 and D4 receptors are located in the limbic system [Howell, 2014].

The transmembrane domains of all DA receptors have a high sequence homology. The members of the D1-like subfamily share a substantial overall homology, 78% for D1 and D5, though the D2-like subfamily has a less significant overall homology of 46% for D2 and D3 and 53% for D2 and D4. Various conserved amino acids exist in DA binding sites [Jaber, 1996].
Signal transduction pathways:
DA receptors activate numerous signal transduction pathways. The main effects mediated by DA are the modulation of signaling $\text{Ca}^{2+}$ and activation as well as inhibition of the cAMP pathway [Valloné et al. 2000].

Adenylyl cyclase
D1-like receptors are positive regulators of cAMP levels. It has been indicated that the D5 receptors activates adenylyl cyclase (AC) causing an increase in cAMP in response to agonist. D1 receptor stimulated AC has been recognized in various Dopaminergic areas of the brain as for example in the striatum, the olfactory tubercle and the nucleus accumbens [Missale et al. 1998].

Calcium channels
D1-like receptors modulate intracellular calcium levels using various mechanisms. One of these is by stimulating phosphatidylinositol (PI) hydrolysis through phospholipase C (PLC) that results in the production of Inositol 1,4,5-trisphosphate (IP$_3$) and diacylglycerol (DAG), mobilizing intracellular calcium stores. Studies show a conflict to whether or not D1-like receptors are actually capable of stimulating PI hydrolysis though D1-like receptor agonists cause PI metabolism to increase in several brain regions. The D1 receptor also affects the calcium channels' activity in which D1 agonists raise the calcium currents via protein kinase A (PKA) inhibitors. PKA, also known as cAMP-dependent protein kinase is an enzyme family with various functions such as regulation of lipid, sugar and glycogen metabolism and its activity depends on cellular cAMP levels. Additionally, D1 agonists in rat striatal neurons are known to reduce calcium current by P- and N-type calcium channels [Missale et al. 1998]. P- and N-type calcium channels both belong to high voltage-gated calcium channels. P-type calcium channels are high voltage activated and are most often found in the cerebellum. N-type calcium channels are also high voltage activated but are found all over the brain and in the peripheral nervous system. Overall D1-like receptors regulate calcium via various mechanisms [Modified from Wikipedia voltage-dependent calcium channels].

D2-like receptors can alter intracellular calcium levels through stimulation of PI hydrolysis. In the pituitary, D2 receptors inhibit PI metabolism. Studies show, in the cell lines tested, that neither D3 nor D4 receptors produce an increase in PI hydrolysis. Additionally, D2-like receptors can cause intracellular calcium levels to decrease through inhibition of inward calcium currents. Akin to D1-like receptors, D2-like receptors appear to change intracellular calcium levels via multiple mechanisms while D3 and D4 receptors only seem to inhibit calcium currents [Missale et al. 1998].
Potassium channels

DA receptors influence potassium channels' activity. Regarding D1-like receptors, this has not been well documented. D1-like agonists increase potassium efflux through a cAMP-independent mechanism. D2-like receptors increase the outward potassium currents causing hyperpolarization. It seems that G-protein mechanisms modulate the activation of potassium currents [Missale et. al. 1998].

5.3 Noradrenaline (norepinephrine)

Noradrenaline is a catecholamine which acts as a hormone as well as a neurotransmitter. It is distributed in hippocampus, Locus Ceruleus, cerebral cortex, hypothalamus, thalamus, amygdala and nucleus of the stria terminals. As a stress hormone it influences areas of the brain which control responding and attention actions. In the brain noradrenaline is a messenger that triggers arousal, the fight response, fear and sex which increases the heart rate and activates the release of glucose increasing blood flow to skeletal muscles [Heneka et. al. 2010]. When the neurotransmitter system activates, it exerts various effects for instance arousal and alertness on large regions of the brain. When noradrenaline is needed, it activates the process of sensory information and thereby motivates the different areas of the brain responsible for reasoning. Noradrenaline is significant to preserving as well as increasing overall arousal, alertness, memory storage after emotion intense events and as mentioned earlier it triggers fight response and fear [Suellen May 2010]. Noradrenaline targets the class of G-protein-coupled adrenergic receptors present in various cells and when a catecholamine binds to the receptor it typically stimulates the sympathetic nervous system [Modified from Wikipedia]. Noradrenaline is released by the sympathetic nervous system and is then converted into adrenaline in the adrenal glands as part of the fight or flight response [Koch 2010b]. In another part of the nervous system noradrenaline is concerned with symptoms of depression. Noradrenaline is released from noradrenergic neurons into the sympathetic -and central nervous system as neurotransmitters and released as a hormone into the blood from adrenal medulla. Binding to adrenergic receptors, carrying out the actions of noradrenaline and when operating as a drug it increases the blood pressure by means of increasing vascular tone (vasodilatory capacity) through activation of α-adrenergic receptors [Heneka et. al. 2010]

A stressful event causes physiological changes in the brain which causes noradrenaline to be released when the Locus Ceruleus is activated, where most norepinephrine pathways origins. From Locus Ceruleus, the noradrenergic neurons project bilaterally along separate pathways such as, the spinal cord and cerebral cortex, to several locations [Suellen May 2010]. In the Locus Ceruleus, one single noradrenaline producing neuron has the capability to innervate tissue in wide-ranging regions since they have branching axons that stimulate the brain stem, cerebellum, and spinal cord on top of amygdala and hypothalamus among others [Koch 2010a].
5.4 Adrenaline (Epinephrine)

Adrenaline is a neurotransmitter and a hormone that acts on almost every body tissue. Adrenaline release is triggered by stresses such as noise, threat, bright lights and excitement all of which are processed in the central nervous system. The actions of adrenaline depends on the tissue expression and tissue type of the adrenergic receptors it binds to. Adrenaline binds to all adrenergic receptors and triggers various metabolic changes because it is a nonselective agonist of every adrenergic receptors which include subtypes such as α1, α2, β1, β2 and β3.

When binding to α-adrenergic receptors, adrenaline inhibits insulin secretion as well as stimulates glycogenolysis in the muscle and liver and cause an increase in blood glucose and fatty acid β-oxidation.

The adrenal medulla is the major contributor to circulating adrenaline, it contributes over 90% of the total amount. Adrenaline has a β2-adrenergic receptor mediated effect on the airway and metabolism due to the fact that there are no direct neural link between the sympathetic ganglia and the airway. As a central neurotransmitter adrenaline is significant.

The synthesis of adrenaline precursors is stimulated by the sympathetic nervous system and ACTH by an increase in tyrosine hydroxylase and DA β-hydroxylase activity both of which are involved in catecholamine synthesis. ACTH also releases cortisol by stimulating the adrenal cortex which enhances adrenaline synthesis because of an increase in the PNMT expression in chromaffin cells. Splanchnic nerve of the sympathetic nervous system to the adrenal medulla stimulate adrenaline release. Acetylcholine released by preganglionic sympathetic fibers of splanchnic nerves operates on nicotinic acetylcholine receptors which cause depolarization. Adrenaline is then released into the bloodstream. Among other catecholamines, adrenaline does not put forth negative feedback with the goal to down regulate its own synthesis which is unlike most other hormones. Reuptake into nerve terminal endings, metabolism by monoamine oxidase and catechol-O-methyl transferase terminate its action [Modified from Wikipedia].

5.5 Serotonin

Serotonin (5-hydroxytryptophan, 5-HT) plays a central role in aggression, mood, sexuality, sleep, body temperature, appetite and the modulation of anger. Serotonergic neurons are primarily located in nine clusters most of them in the raphe nuclei of the pons, the midbrain and medulla. In the dorsal and medial raphe nuclei, two of the most important clusters are found. The neurons found in the medial raphe nuclei project to dentate gyrus while the neurons found in the dorsal raphe nuclei project to the basal ganglia. Axons of serotonergic neurons of both the dorsal and medial raphe nuclei are send to the cerebral cortex [Gilmore et al. n.d.]. Serotonin neurons found in the raphe nuclei are the main source of the release of serotonin in the brain. The raphe nuclei are distributed in pairs down the reticular formation (the core of the brain stem) running from the lower medulla oblongata all the way through the pons and into the midbrain [Koch 2010a].

Serotonin signaling has a powerful influence on the transmission of for example DA and noradrenaline. Serotonergic neuron axons project to both the brain and the spinal cord, where they virtually influence every neuron's activity. This implies that serotonergic neurons play an essential role in behavior. The capacity human beings have to organize their lives as well as relating
to others rely deeply on the serotonergic system's functional integrity. Serotonergic neurons make up a small amount of all the neurons in the brain but the serotonin receptors on target neurons are extremely varied. In mammalian brains, fourteen types of receptors have been found, acting in various ways in different places.

Serotonin stimulates the entire brain. The spinal cord, the cerebellum's deep nuclei and cortex are the end station of the axons of serotonergic neurons in the lower raphe nuclei. In the Higher Raphe nuclei, the neuron's axons terminate in three different places: I) the cingulate cortex, that includes the cingulum which is a region of association fibers that connect the hippocampus and the corpus callosum, II) the neocortex and III) the subcortical nuclei that includes the thalami; the corpus straia that includes the nucleus accumbens; the hypothalamus, amygdala and the hippocampus [Koch 2010a].

The monoamine transporter used for 5-HT is SERT which is located on the presynaptic neuron. A 2006 study proposed a new monoamine transporter, PMAT, that possibly account for a considerable proportion of 5-HT clearance. PMAT has been classified as a low-affinity transporter which contrasts the high-affinity SERT. Though PMAT has lower serotonergic affinity, it has higher transport capacity than SERT. In addition, serotonin can signal via a non-receptor mechanism known as serotonylation wherein it modifies proteins [Modified from Wikipedia, Serotonin].


Except from the 5-HT<sub>3</sub> receptor which is a ligand-gated ion channel, all serotonin receptors are seven transmembrane G-protein-coupled receptors, activators of intracellular second messenger cascades. These receptors are coupled to several intracellular functions by intracellular domains though the functions of the extracellular domains are uncertain. Six classes of G-protein-
coupled 5-HT receptors are found in mammals, namely 5-HT\textsubscript{1}, 5-HT\textsubscript{2}, 5-HT\textsubscript{4}, 5-HT\textsubscript{5}, 5-HT\textsubscript{6} and 5-HT\textsubscript{7}. In addition, these six classes are divided into subclasses; the 5-HT\textsubscript{1} receptor class holds 5-HT\textsubscript{1A}, 5-HT\textsubscript{1B}, 5-HT\textsubscript{1D}, 5-HT\textsubscript{1E} and 5-HT\textsubscript{1F}; the 5-HT\textsubscript{2} receptor class holds 5-HT\textsubscript{2A}, 5-HT\textsubscript{2B} and 5-HT\textsubscript{2C} receptors. In general the 5-HT\textsubscript{4}, 5-HT\textsubscript{6} and 5-HT\textsubscript{7} classes do not have subclasses and alternative mRNA splicing provides sequence diversity. The 5-HT\textsubscript{5} receptor class holds 5-HT\textsubscript{5A} and 5-HT\textsubscript{5B} subclasses [Roth 2006].

The subtype 1A receptor is extensively expressed all over the brain. The highest density is found in the medial temporal cortex (raphe nuclei and the pituitary gland) and in the hippocampus while lower levels are found in the pre-frontal cortex. Low denseness of the serotonin subtype 1A is found in the basal ganglia [CNS Forum1, 2014].

![Brain Diagram](http://www.cnsforum.com/educationalresources/imagebank/serotonergic/hrl_rept_sys_sn1a_dist) accessed May 7\textsuperscript{th} 2014

5-HT\textsubscript{2} receptors can be found several places in the brain due to wide distribution; the substantia nigra, amygdala, choroid plexus, cerebral cortex, hypothalamus, hippocampus, substantia innominata and parts of the basal ganglia [CNS Forum2, 2014].
Figure 34: shows the distribution of the serotonin 5HT2 receptor in the brain. [http://www.cnsforum.com/educationalresources/imagebank/serotonergic/rcpt_sys_sn2_dist] accessed May 7th 2014

The ligand-gated ion channel, the 5-HT3 receptor, controls the release of DA. High levels of the 5-HT3 receptor is found in the human brainstem, especially in the postrema which controls vomiting and the nucleus tractus solitarius (located in the medulla oblongata) which is a sequence of nuclei that forms grey matter. Lower density of the 5-HT3 receptor is found in the cerebral cortex, the limbic system and hippocampus [CNS Forum3 2014].
The receptor subtype 5-HT₄ is coupled to G-proteins which regulates neurotransmission by stimulating intracellular messenger adenylate cyclase. High levels of expression of the 5-HT₄ receptor is found in the striato-nigral system, the substantia nigra, the lenticular nucleus and notably in the caudate nucleus. Lower density of the 5-HT₄ receptor is found in the frontal cortex and hippocampus [CNS Forum4, 2014].

Like the 5-HT₄ receptor subtype, 5-HT₆ and 5-HT₇ subtypes are coupled to G-proteins which regulates neurotransmission by stimulating adenylate cyclase. High levels of expression of the 5-HT₆ receptor is found in the nucleus accumbens, hippocampus, the olfactory tubercle, dentate gyrus and the corpus striatum. Lower density of the 5-HT₆ receptor is found in the amygdala and the cerebellum. Rat studies propose that the 5-HT₇ receptor can be found in various places in the brain due to its broad distribution, human tissue shows levels in the thalamus [CNS Forum5, 2014].
Figure 37: shows the distribution of serotonin 5HT\textsubscript{6} and 5-HT\textsubscript{7} receptors in the brain. [http://www.cnsforum.com/educationalresources/imagebank/serotonergic/5ht6_5ht7_dist] accessed May 7th 2014

Serotonin is synthesized from tryptophan in serotonergic neurons in the raphe nuclei. Tryptophan hydroxylase produces 5-hydroxytryptophan (5-HTP). To produce serotonin, 5-HTP is then decarboxylated by aromatic L-amino acid decarboxylase. Next serotonin is stored in synaptic vesicles and placed at nerve terminals waiting for action potential. When releasing serotonin into the synaptic cleft, serotonergic receptors in the post-synaptic neurons are activated [Gilmore\textsuperscript{A} et. al. n.d.]. See figure below.
6. Genetics of ADHD

ADHD is one of the most investigated neurological disorders, however, researchers are in disagreement concerning the genetic mutations and neurochemical imbalances involved in the development of the disorder. The contradicting results can perhaps be explained by the smaller sampling, population diversity (ethnicity) with different allele frequency or not having a relevant control with experimental groups during the research. Despite the contradictions, it is agreed that many genes are involved in the development of ADHD, each gene contributing with a small effect to the symptomatology of the disorder. There is no single known cause for the development of ADHD, however, research of family and twin studies found that the heritability to be 76%, making it among the most heritable of psychiatric disorders [Cornish and Wilding, 2010].

The most studied genes are those that regulate the DA, serotonin and noradrenalin systems from which the DA system was the focus point. The different kind of genes investigated are genes encoding for neurotransmitters release and reuptake, genes that encode proteins involved in release and those encoding for enzymes that synthesize and recycle them. In table 7 the most often associated genes with ADHD can be found along with the number of studies which have been conducted concerning its association, both showing significant or nonsignificant results.

Research has also been interested in finding candidate genes for attention. Common factors, such as psychosis, mood dysregulation, and cognitive impairment are found in many neurodevelopmental disorders, transcending the diagnostic categories. Some of these disorders are Autism Spectrum Disorder, Major Depression Disorder, Schizophrenia, and Bipolar Disorder. Questions arise concerning if there are common genes coding for these symptoms, and if boundaries between the syndromes are needed, such as if they are distinct disorders that have overlapping origins or if they are different variations of one disorder.

Males are three times more diagnosed with ADHD than females. Several motives are believed to lead to this discrepancy. ADHD in girls is mainly manifested as the inattentive subtype than the combined subtype like in boys which leads to more obvious and problematic symptoms. It is also shown that girls internalize these symptoms making the diagnostic even more difficult. However, it is hypothesized that these factors alone cannot entirely explain the 3:1 frequency therefore, genetics and neurochemical differences are taken into consideration. Estrogen is believed to play a protective role in girls, making them less prone to develop ADHD while evidence for at least four risk genes that might have sexually dimorphic effects (phenotypic difference between males and females).

Table 7, Top Genes connected with ADHD, showing the number of studies (significant, non-significant and trend) as of February 26th, 2014. Significant: \[ P < 1 \times 10^{-4} \], Non-significant: \[ 1 \times 10^{-3} \], Trend: \[ 1 \times 10^{-3} < P < 1 \times 10^{-2} \]. Modified from http://adhd.psych.ac.cn/topGene.do.
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<tr>
<td>MAOA monoamine oxidase A</td>
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**MISC**

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### 6.1 Dopaminergic genes

The most studied genes are those that regulate the DA, serotonin and noradrenaline systems from which the DA system was the focus point. The different kind of genes investigated are genes encoding for neurotransmitters release and reuptake, genes that encode proteins involved in release and those encoding for enzymes that synthesise and recycle them.

#### 6.1.1 The Dopamine Transporter DAT1

As mentioned before, basal ganglia are situated at the base of the forebrain and are the main part of the brain that is in charge of motor activity, emotions and reward. There are two main classes of diseases as a result of malfunctioning of basal ganglia, the motor related like Parkinson and Huntington disease and mental disorders like schizophrenia, bipolar disorder and ADHD believed to be due to reduced extracellular DA levels.

The main neurotransmitter that regulates basal ganglia activity is DA and an optimum DA extracellular concentration is kept through the release mechanism but also by the reuptake mechanism of the plasma membrane DA transporter DAT. DAT is a part of the NA-/Cl- dependent transporter group that also includes serotonin and NA transporters together with other neurotransmitter carriers. DAT is expressed mainly in the striatum and nucleus accumbens. It is assumed that the main regulation of the levels of DA found in the synapse is through the removal of the neurotransmitter by DAT and, therefore, it is the primary target of psychostimulants like amphetamine, methamphetamine, cocaine and in the ADHD case, methylphenidate. If DAT is unable to bring back the DA in the presynaptic neuron for metabolization, the DA will remain longer in the synapse having, as effect, an increase in the extracellular levels of DA [Gainetdinov, 2008].

An important way to investigate the mechanism of the dopamine system and the relevant pharmacological drugs like methylphenidate is to create mice that are genetically modified to have abnormal DAT functioning. Furthermore, based on these gene modifications, the ADHD condition
can be induced in mice which provides an invaluable method to test pharmacological treatments. Even though a rodent brain is not as complex as the human brain and the ADHD symptoms like impulsivity and inattention can be only partially induced, the genetically modified mice still remain the most widely used method [Gainetdinov, 2008]. It is also an effective method of observing long-term effects over an organism's life span, like a mouse, whereas in humans observation could take up to 50+ years.

Several kinds of mutant mice were developed regarding the level of DAT expression with the most popular model being the DAT knockout mice (DAT-KO) where all DAT genes are completely turned off. Useful insights were also obtained by using DAT knock down mice (DAT-KD) in which the degree of DA expression is severely reduced, DAT siRNA treated mice in which the DAT expression is moderately decreased, the over expressing mice which had moderately higher levels of DAT and the mice with marked increase in DAT expression called BAC-transgenic DAT over expressing mice [Gainetdinov, 2010].

The knockout mice, in which the DAT gene was completely unexpressed had an overall level of extracellular DA, 5 times higher than normal with a markedly 300 times increase in the time the DA spent in the synapse, while the DA levels in the presynaptic neurons decreased 20 times and DA release was decreased four times. This suggests that even if the DA levels are higher in the synapse, the DA release is diminished because the storage vesicles are depleted and the DA release is mainly dependent on the synthesis rate [Gainetdinov et al., 1998; Jones et al., 1998]. The mode of DA transmission in DAT-KO mice is described as “volume transmission” because DA molecules can cover a long and wide distance and are able to affect a large number of postsynaptic receptors [Jones et al., 1998]. Even though the DA release and the DA stored in the vesicle in the presynaptic neurons are decreased and suggest “hyperdopaminergia”, the overall levels of DA in the synapse are highly increased, therefore, it is decided that the DAT-KO mice manifest “hyperdopaminergia” instead, which leads to extreme hyperactivity [Gainetdinov and Caron, 2003]. Furthermore, they had deficits in learning and memory tests while cognitive tests showed a strong impaired behavioral inhibition.

A more subtle version of DAT dysfunction, DAT heterozygous mice that have around 50% reduction in DAT expression and two times increase in the extracellular DAT, do not display signs of hyperactivity. In the case of mild deficiency in DAT expression achieved by injecting small interfering RNA (siRNA) in substantia nigra, a 40% decrease in DA transporter levels was observed and no signs of hyperactivity were monitored. When DAT is mildly around 30% over expressed, no signs of ADHD symptoms were observed but instead hypoactivity was displayed. In the case of a high over expression of DAT using bacterial artificial chromosome lead to a three-times increase in DAT in the presynaptic neurons with a 40% decrease in the DA release in the synapse. The conclusion from the experimental evidence of genetically modified mice is that a decrease in DAT expression is the cause of ADHD symptoms which supports the clinical observations.

Rats that had the DAT1 turned off or deleted providing an in vivo model for a high deregulation of the DA system. These “knocked out” mice developed two features similar with ADHD: hyperactivity and reduced inhibitory behaviours. [Cornish and Wilding, 2010]. The gene is located on the short arm of chromosome 5 and it is also the gene that is deleted in another syndrome characterised by hyperactivity called Cri-du-chat [Cornish and Bramble, 2002].
In ADHD, this gene has a 40 base pairs variable number tandem repeat (VNTR) in the 3’ untranslated region and VNTR polymorphism is not silenced because it has been shown to affect the expression of the transporter by identifying higher levels of messenger RNA (mRNA) which did not get translated. It is still debatable if it is possible that this polymorphism, found in the untranslated region, can cause such significant alterations in the expression and function of DAT [Gainetdinov, 2010].

Brain imaging studies do not agree regarding the DAT expression in ADHD. Initial observations pointed out to a significant increase in DAT expression in ADHD patients, with a down regulation of DAT expression when methylphenidate was administered [Dougherty et al., 1999]. Sceptical to these findings, other studies found instead, a high decrease in DAT levels in several brain areas [Volkow et al., 2007; Volkow et al., 2010]. Of great importance, is the evidence found in a wide range of experimental methods, especially using drugs, either decreasing or increasing the levels of DA. They showed that an increased DA level in basal ganglia lead to psychomotor stimulation, hyperactivity, euphoria and reward [Carlsson et al., 2001; Gainetdinov et al., 2002].

There are 3 to 13 VNTR alleles but the most common alleles are 9 and 10 VNTR with some small variations in different populations [Kang et al, 1999] and it is the genotype that is homozygous for the 10 tandem repeat alleles that confers the higher risk of inheriting ADHD, the heterozygous 9/10 alleles and the homozygous 9 results in a lower susceptibility for the condition [Cornish and Wilding, 2010]. Even though there has been extensive research focusing on this gene, the results obtained were mixed. Some investigations reproduce the result that homozygous for the 10 tandem repeat allele have a higher chance of developing ADHD while other studies found no correlation. These results could be explained by a smaller sampling, chance, population diversity etc.

A study that investigated the amount of DAT in vivo in ADHD adults concluded that there is on average 70% more DAT in these subjects than in healthy controls, building evidence on the hypodopaminergic condition hypothesis in the disorder [Dougherty et al., 1999].

6.1.2 Dopamine D4 receptor gene DRD4
The DRD4 gene was not as widely studied as compared DAT1 gene even though stronger evidence was found in relation with ADHD. The D4 receptor gene is found on the shorter arm of chromosome 11 and ten different alleles were identified from 2 to 11 VNTR 48 base pair repeats (16 amino acids) located in the third exon of the gene. Strong findings point to a higher risk of developing ADHD if the 7 repeat allele is inherited but more studies showed that ethnic groups have associations with different alleles of this polymorphism [Misener and Barr, 2009].

The 48 base pairs VNTR polymorphism is located in the third intracellular loop of the receptor and has been shown to influence the affinity of the receptor for DA [Misener and Barr, 2009]. These studies also pointed out that the 7 repeat VNTR has a slightly decreased sensitivity for DA than the 4 repeat VNTR allele, which may suggest that this 48 base pairs polymorphism might be the factor that induces functional change that contributes to the ADHD symptoms [Asghari et al., 1994]. This means that the 7 repeat allele leads to ADHD because of a hypodopaminergic signalling
induced by a lower binding of DA to the related receptor. This difference in receptors DA affinity is not related to the length of the VNTR alleles. There is no relation between the number of repeats in the alleles and susceptibility for ADHD meaning that while the 7 VNTR allele has a lower affinity for DA and the 4 VNTR a higher one it has been shown that the “longest 10 VNTR” allele is slightly more sensitive to dopamine than the 2 VNTR version [Jovanovic et al., 1999].

The frequency of the VNTR alleles is different across populations. The 7 repeat allele is found in 48% of Amerindians while in only 1.9% of East and South Asians [Chang et al., 1996] while differences in the base pair sequence between the repeat was also identified [Lichter et al., 1993]. The difference of alleles frequency in ethnic populations may influence the power to detect the DRD4 alleles association with ADHD which means that a very accurate controls have to be used. Furthermore, the ethnicity of the samples has to be taken into consideration when researching for this gene. In Asian populations the 2 repeat allele is the most common one which can only be found in Caucasian in a very low frequency and substitutes for the susceptibility of the 7 VNTR allele which suggests that mainly this 2 repeat allele is responsible for ADHD in Asian populations [Brookes et al., 2005a]. A study with a small number of Chinese subjects found a connection between ADHD [Leung et al., 2005] and this allele but other studies did not find any association [Brookes et al., 2005b; Qian et al., 2004].

Other DRD4 polymorphisms that may contribute to ADHD

- In the first exon of the gene: a 13 and a 21 bp deletion and a 12 bp repeat
- In the promoter region: 120 bp repeat, a 27 bp deletion and several SNPs such as -616C/G, -521C/T and -376C/T

The 120 bp repeat variant has been shown to have a lower transcription rate compared to the short allele which means that the DRD4 gene for this polymorphism does not get expressed as much as the short allele. This could lead to a lower number of D4 receptors in the postsynaptic neurons. It is believed that the long variant allele is more likely to be inherited by children suffering from ADHD [D’Souza et al., 2004]. While a couple of other studies have found a correlation between this 2 repeat allele and ADHD, other clinical and population trials did not. In one study even a connection with the short allele was seen [Misener and Barr, 2009].

6.1.3 Dopamine D5 receptor gene DRD5

The DRD5 gene is located on the chromosome 4 and the 148 bp polymorphism located 18.5 kilobases (kb)5’ of the DRD5 gene. An analysis based on 14 independent samples has strongly supported a 75% association between and the inattentive subtype even though the sample was relatively small the correlation probability is too high to be overlooked but also for the combination-type. It is also stated that this finding requires additional research [Lowe et al., 2004].

6.1.4 Dopamine receptors D1, D2 and D3

From these three DA receptors D1, D2 and D3, studied for association in ADHD, only the DRD1 gene was found to have a correlation with the disorder. D1 receptors are mainly found in brain
regions involved in ADHD namely prefrontal cortex and striatum [Missale et al., 1998]. Significant evidence between 4 markers haplotype in DRD1 and families with ADHD was identified but only for the inattentive subtype of ADHD [Misener et al., 2004] while another study supported these results with a significantly higher frequency of 2 of the 4 markers investigated by the previous study [Bobb et al., 2005]. Two more family-studies found no association with the DRD1 gene but these results could be due to a small sample size or simply because they investigated individual markers instead of a haplotype of markers [Kirley et al., 2002].

6.1.5 Dopamine beta hydroxylase DBH

Dopamine beta hydroxylase is the enzyme that catalyses the production of noradrenaline from DA and it is encoded by the DBH gene. DBH inhibits tyrosine-hydroxylase’s activity (the enzyme that converts L-DOPA to DA) which reduces the production of DA. DBH is found in the brain in the catecholamines vesicles and it is released together with neurotransmitters and other vesicular contents during the synaptic vesicle fusion and its enzymatic activity is measured in plasma or serum [Lewis et al., 1992].

It has been shown that animals with decreased DBH in the serum, had reduced production of noradrenaline from DA and as affect, the tyrosine-hydroxylase’s activity failed to down regulate the DA synthesis which resulted in hyperactivity, aggression and self-stimulation. Therefore, it has been suggested that DBH contributes to ADHD by a hyperdopaminergic signalling. The DBH gene is found on chromosome 9, it has around 23 kb and contains 12 exons that encode for 603 amino acids protein [Kobayashi et al., 1989].

One of the polymorphisms investigated was C-1021T in which the substitution of C with T positioned in the promoter area 1021 bp upstream of the translational start site. Homozygous individuals for the TT allele were found to lead to lower levels of DBH in plasma membrane with 4 out of 8 subjects displaying very low DHB levels being homozygous for the T allele. Following studies on African American, European American and Japanese populations agreed upon the strong correlation between the TT genotype and low levels of DBH [Zabetian et al. 2001].

Another polymorphism 5'ins/del that consists of a 19 bp insertion/deletion approximately 4.7 kb away from the 5’transcriptional start site is associated with plasma DBH activity in the way that the deletion leads to a decrease expression of DBH while the insertion will have increased DBH expression [Cubells et al., 2000].

The G444A polymorphism found in exon 2 can influence the DBH levels as well. Studies conducted on European American patients suffering from mood and anxiety disorders showed that the 444A allele induces lower plasma DBH activity while 444G allele increases this enzyme’s activity [Cubells et al. 1998]. This polymorphism only substitutes the third codon of glutamine Glu, therefore without changing the primary structure. The alteration in DBH could be explained by the position of G444A polymorphism which is situated at the boundary of exon 2 with intron 2 that can affect the mRNA splicing into the mature mRNA which can further on affect the DBH as mentioned above [Kobayashi et al., 1989]. A slight increase in the transmission of 444A allele was observed in ADHD patients but not statistically significant.
6.1.6 Dopa Decarboxylase
Dopa decarboxylase is an enzyme that catalyses the formation of L-dopa from tyrosine. The dopa decarboxylase gene encoding for this protein is found on chromosome 7, it is formed from 15 exons made up of 85 kb. The expression of the DDC gene is controlled by two promoters, therefore mutations in the coding or promoter regions may affect the function of the gene or the amount the enzyme is being produced. A study analysed a 4-bp insertion/deletion in exon 1 for possible association with ADHD and came to the conclusion that there is a slight increase in transmission in ADHD cases [Hawi et al., 2001].

The levels of dopamine decarboxylase were investigated in a study conducted on children with ADHD and it was found that the levels were increased by 48% in the midbrain compared to the control group. These results suggest an abnormality in the DA system but it is not known what could trigger this increase in dopamine decarboxylase [Ernst et al., 1999].

6.2 Serotonergic Genes
Evidence suggests that there is a complex link between serotonergic genes (and therefore mechanisms) and the development of ADHD, especially in the 5-Hydroxytryptamine transporter gene (5-HTT), a serotonin transporter gene, and HTR1B, a serotonin receptor gene [Cornish and Wilding, 2010]. In addition to playing the role of a neurotransmitter in a mature nervous system, serotonin also has an important function during development. Serotonin is involved in the formation and differentiation of neurons along with the organization and migration of the neurons to appropriate position and the arrangement of the synapses between the neurons [Halmoy et al., 2010]. Abnormalities within the serotonin system are linked to the pathogenesis of a range of psychiatric disorders including suicidal behaviour, depression, and alcoholism. A growing amount of evidence suggests that serotonergic input may affect DA's influence on attention. The link between serotonin and DA is well established. Animal studies show an interaction between the DA system and the serotonin transporter genes, such as the 5-HTT, playing an inhibitory role in the DA reward system. Other studies demonstrate that DA release in the prefrontal cortex and the striatum midbrain can be regulated by serotonin, mainly the HTR1B receptor. Activation of the 5-HT1B receptor increases striatal DA release, which is associated with enhanced locomotors and motor activity, an effect that is blocked by a 5-HT1B antagonist [Kranzler et al., 2002]. The central infusion of 5-HTT can increase the inhibitory effect of DA on neurons of the ventral tegmental area of the brain, the origin of the dopaminergic cell bodies of the mesocorticolimbic dopamine system. Additional mice studies suggest that mice lacking the HTR1B gene have a higher probability of showing hyperactive and impulsive behaviour which can be associated with ADHD. These findings suggest that mutations within the serotonergic genes may be an important factor in the development of ADHD.

Of the serotonergic genes, the serotonin transporter genes (SLC6A/5-HTT/SERT) and its genetic variants, 5-HTTLPR, are often studied. However, negative and conflicting results, even in large-scaled meta-analysis, are often found. Two genes, Tryptophane hydroxylase (TPH) 1 and 2 (TPH1 and TPH2), coding for the isoenzymes involved in the biosynthesis of serotonin has been a focus in previous studies. Research suggests that alterations in these genes or enzymes in pregnant
females could result in birth defects [Halmoy et al., 2010]. A recent study of 1636 patients and 1923 controls investigated the two TPH genes [Franke et al., 2012]. Evidence found an association with TPH1 and ADHD, however not TPH2. Additionally a study investigated 19 serotonergic genes. It was found that there was an association of aADHD (adult ADHD) with single markers or haplotypes (combinations of alleles at the same loci that are inherited together) in monoamine oxidase B (MAOB), dopa decarboxylase (DDC) and HTR2A. HTR2A was also found to be associated with aADHD in two additional studies. However the mutations found to be involved in these studies differed.

6.2.1 Serotonin Transporter Gene (SLC6A4/5-HTT)

SLC6A4/5-HTT is a gene that encodes for the serotonin transporter (SERT). This gene is one of the most extensively studied genes within the field of psychiatry, including many ADHD studies. The serotonin transporter is responsible for the reuptake of serotonin into the presynaptic neuron, playing a key role in the amount of serotonin available in the synapses and serotonin turnover. This is strongly associated with impulsive behaviour [Cornish and Wilding, 2010]. 5-HTT is located on the short arm of chromosome 17 (image 1) at p11.2 and has two alleles, the short (S) and the long (L) allele. This gene can have a gene-linked polymorphic promoter region with a 44-base pair insertion-deletion, known as SERTPR [Thomas and Ellingrod, 2009; Cornish and Wilding, 2010]. Insertion-deletion mutations can create reading-frame shifts of the mRNA. It has a long (L) variation of a 16 repeat sequence and a short (S) variation of a 14-repeat sequence. The S alleles has been associated with lower levels of transcription, and leading to lower expression. The L allele, L5-HTTLPR, and the homozygous long/long (L/L)-genotype, has been associated with rapid serotonin reuptake. Studies have found that the L allele results in higher serotonin transporter mRNA transcription. The alterations of the 5-HTTLPR can result in changed expression of the SERT protein and changed concentrations of extracellular serotonin in the brain. It has also been found to be associated with changes in the brain structure, one study finding less grey matter in the perigenual anterior cingulate cortex and amygdale for the short allele carriers compared to subjects with the long/long genotype [Pezawas et al., 2005].

Image 39: Chromosome 17, the 5-HTT gene is located at p11.2 [Wikipedia]

In addition to the S and L alleles of the SERTPR, SLC6A4 also contains a variable number of tandem repeats (VNTR) polymorphism called STin2, within its second intron [Thomas and Ellingrod, 2009]. A mutation within an intron (usually is a base substitution) can create an alternative splicing site which competes with the normal splice sites during RNA processing. This creates a proportion of mature messenger RNA that is not spliced correctly to remove intron sections. There are 3 variations of the STin2 consisting of 9, 10 and 12 repeats. These are known as STin2.9, STin2.10, and STin2.12. The rate of serotonin reuptake is lower among individuals who are homozygous for STin2.12 than those who are heterozygous which means that STin2.12 could increase serotonergic signalling. The STin2.10 allele in some reports has been labelled as the "bad" allele, in terms with its relationship to suicide and depression treatment response ["STin2", 2012].

The rs25531 gene, found on chromosome 17 position -28564346, has two variations: the G and the A allele [Carasos and Lennon, 2011]. The A allele is in phase with the short form of 5-
HTTLR and has shown to result in lower levels of serotonin, resulting in slightly less happy individuals whom would benefit from more support from family. The rs25531 G allele polymorphism is almost always in phase with the long (L) allele of the 5-HTTLPR gene, one of the most common studied variations in this region. The (L) long allele could be associated with lower levels of serotonin, and has been shown to be associated with increased ADHD severity [Franke et al., 2012]. Rs25531 has been studied to see if an association was found between it and Obsessive Compulsive Disorder (OCD), mood disorders after traumatic brain injuries (TBI), blushing (considered a prime pathophysiological marker of social anxiety disorders), and suicidal attempts in depressed individuals, however no associations was found. This allele has been associated with individuals less sensitivity to pain. The rs140700 allele has been associated with ADHD (P=0.00084) in a study conducted by Landaas et al. [2010]. 448 patients and 580 controls in discovery sample, 1894 patients and 1977 controls in meta-analysis [Franke et al., 2012]. Only the S allele was found to be associated with aADHD at P=0.06 in replication.

6.2.2 Serotonin Receptor Genes
The serotonin receptor 1A (HTR1A) gene has in a study by Jacob et al., of 123 cases with aADHD (and 83 patients suffering from personality disorders), been found to be associated with a decreased risk of anxious-fearful cluster C personality disorders in adult ADHD (P=0.016) [Franke et al., 2012]. HTR1A acts on the central nervous system, where it regulates neuronal inhibition and controls behaviour, such as sleep, feeding, thermoregulation, aggression, anxiety. The HTR2A gene encodes for the serotonin 2A receptor, a receptor type that plays an important role in agitation, insomnia, and sexual dysfunction [Thomas and Ellingrod, 2009]. Many single-nucleotide polymorphisms (SNPs) have been identified within this gene, the frequent studied being T102C (a SNP also known as rs6313) and -1438G/A which found the C/C genotype of T102C is in perfect linkage disequilibrium with the G/G genotype of 1438G/A located upstream in the promoter region [Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. In a study of 132 tagged-SNPs an association with combined subtype of aADHD and children (lowest P=0.0036, or 1.63) [Ribases et al., 2011]. A study of the T102C polymorphism with 203 healthy subjects assessed with Adult ADHD Self-Report Scales (ASRS) for aADHD symptoms. It was found that the association of the C allele with hyperactivity and impulsivity (P=0.020) and total ASRS scale (P=0.042), highest scores were in the T/T genotype [Reutre et al., 2006]. A regression analysis which took out life events and personality into account of 110 cases of the rs6314 (His452Tyr), found no effects of the gene on ADHD severity [Müller et al., 2008; Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012].

This mutation is an SNP that results in the creation of a Tyrosine amino acid instead of the normal Histidine due to the first base in the codon being a thymine (T allele) instead of the normal cytosine (C allele). The C/C genotype is the most common.

HTR3A codes for the serotonin 3A receptor. This receptor plays an important role in gastrointestinal mechanisms, and when normal expression of the gene is disrupted plays an role in adverse effects such as diarrhoea, nausea, and vomiting. Several variants have been found. The C195T SNP has not shown to be involved in any functional changes while the C178T (also known
as Pro16SER) the SNP results in a higher expression of the serotonin 3A receptor [Thomas and Ellingrod, 2009].

The serotonin 1B receptor gene, HTR1B, is located on the long arm of chromosome 6q13 [Cornish and Wilding, 2010]. Upon this gene the relatively common and widely studied G861C polymorphism, the G allele, is found. Three genetic studies have found an association between this gene and inattention in ADHD (Hawi et al., 2002; Quist et al., 2003; Smoller et al., 2006), however one other study found no association (Mill et al., 2005).

The Postsynaptic serotonin 3B receptor is encoded by the HTR3B gene. Mutations such as the Tyr129Ser and the 100-102AAG insertion-deletion have been identified [Thomas and Ellingrod, 2009; Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. The AAG insertion-deletion variant is hypothesized to alter the structure and translational efficiency of mRNA. The AAG deletion has been associated with vomiting due to chemotherapy, which may be due to a decrease in the receptor translation resulting in fewer receptors. The effect of the Tyr129Ser is not well characterized.

Serotonin 2C receptor gene (HTR2C), located on the X chromosome, has also been studied in its association with ADHD. In a study of 488 Han Chinese, the relationship between the C-759T and G-697C polymorphism of the HTR2C gene was investigated [Li et al., 2006; Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. Using Transmission Disequilibrium Test (TDT), it was found that the C allele, the G allele, and the haplotype (set of SNPs on a chromosome statistically associated) C/G were greatly over-transmitted to affected probands. The haplotype C/C and T/C were under-transmitted. The families were divided into three subtypes according to the diagnosis of probands. The G allele and C/G were significantly over-transmitted to ADHD-C (combined) probands, while the T/C was under-transmitted to those individuals. No biased transmission of any allele or haplotype was found for probands with ADHD-I (inattentive). This suggest that there are different subtypes of ADHD which have different genetic background.

### 6.2.3 Tryptophan Hydroxylase Gene (TPH)

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme responsible for catalyzing the synthesis of serotonin from tryptophan. An increased function of this enzyme could raise serotonin levels [Thomas and Ellingrod, 2009]. Studies have been conducted on the TPH1 and TPH2 (chromosome 12) to find relation with ADHD. No association with TPH1 and aADHD was found in the study, no Gene x Environment effect [Franke et al., 2012; Johansson et al., 2008]. Rs17794760 was found to have insignificant effect on TPH1 (the ancestral allele Guanine changed to Adenine within an intron on chromosome 11 in the TPH1 gene). Molecular studies have reported findings of significant associations between markers mapped to TPH2 and the multiple psychiatric conditions including ADHD. A study of four SNPs located in the fifth intron of the TPH2 (rs1843809, rs1386493, rs1386488, and rs1386496) concluded no association between the markers and ADHD in an UK sample [Sheehan et al., 2007]. While in an Irish sample rs1843809 (Guanine to Thymine intron SNP) and rs1386493 (Guanine to Adenine intron SNP) were reported to be associated with ADHD [Sheehan et al., 2007; Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. Rs1843809 and rs1386493 results in a nonsense-mediated mRNA decay
(NMD). This is a surveillance pathway that mainly functions to reduce errors in gene expression by eliminating mRNA transcripts that contain a premature stop codon. It was concluded in the Sheehan et al. study that a larger sample size is needed clarify if there is an association between TPH2 and ADHD. In a study by Sizoo et al. [2010] it was found that possession of the G allele of TPH2 rs1843809 and the L allele of 5-HTTLPR was less frequent in ADHD (P=0.041) compared with Autism Spectrum Disorder (ASD) (P=0.04) patients [Franke et al., 2012]. In 2010 the single largest ADHD genetic study of 6 SNP's on TPH1 and TPH2, with 3,559 participants concluded that there was not consistent evidence for a substantial effect of common genetic variants on persistent ADHD [Johansson et al., 2010].

6.3 Noradrenaline and Adrenergic Genes

Noradrenaline (NA), also known as noradrenalin or 4,5-β-trihydroxy phenethyamine is a hormone and neurotransmitter synthesized from DA. One of its main roles is to affect the heart, an increase in NA from the sympathetic nervous system results in an increase in the heart contractions. NA's frontal B1 and alpha-2a receptors play an essential role in differentiation of focused attention versus inhibition of distractions while paying attention [Hunt, 2006]. It is also essential in executing functions involving reasoning, learning, and problem solving. It is believed that patients with predominantly inattentive ADHD have mutations to their NA transporter gene (SLC6A2), which affects the levels of NA in their brains.

6.3.1 The Noradrenergic Transporter Gene SLC6A2

The noradrenergic transporter gene (SLC6A2), which is the focus of research concerning the noradrenergic genes related to ADHD, is located on chromosome 16 locus 16q12.2 [Gizer et al., 2009]. It is highly expressed in the frontal lobe and the protein for which it codes is highly involved in the reuptake of DA and NA. The gene is encoded by 14 exons, made of 617 amino acids with 12 membrane-spanning domains. SNPs of SLC6A2, have been linked to ADHD, psychiatric disorders, postural tachycardia, and orthostatic intolerance. Specifically rs3785143 (Cytosine to Thymine SNP) and rs11568324 (Cytosine to Thymine SNP) have been associated with ADHD, however only ALA457Pro (Guanine to Cytosine SNP in the first codon base) has been confirmed directly to be associated with ADHD and orthostatic intolerance 2 [Gizer et al., 2009; Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. Rs3785143 and rs11568324 have been further supported in its association with ADHD in two additional studies Kim et al. [2008] and Xu et al., [2008]. In total thirteen SLC6A2 SNPs have been discovered. Studies are finding conflicting results, many of them finding an association with the gene and ADHD, however, disagreeing on the SNPs. In a study by Retz et al., subjects were genotyped for three SLC6A2 SNPs: rs5569, rs998424, and rs2242447 [Retz et al., 2008; Franke et al., 2012]. It was found that there was association with ADHD, however, there was no gene x environment interaction with psychosocial adversity in childhood. Nominal association was found with ADHD scores of combination of two haplotypes (SNP's) of SLC6A4 and Catehol-O-Methyltransferase gene (COMT). In a review, by Gizer et al., two SNPs of SLC6A4 which had been tested for association with ADHD in a sufficient number of studies were
chosen for the meta-analysis. The rs5569 (Guanine to Adenine SNP, also known as Thr429Thr) found on exon 9 was concluded to have no significant association with ADHD, a no 'risk' allele was indicated. The results of the meta-analysis were nonsignificant [Gizer et al., 2009; Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. The Second SNP of the gene SLC6A4, rs2242447 (Cytosine to Thymine SNP, found in intron 13), was also concluded to have no significant association with ADHD. There are still compelling reasons for future studies to investigate this gene in relation to ADHD. Though these results did prove to be not significant, associations have been found linking the gene with ADHD. However, due to lack of consistency in the SNPs genotyped across the studies, the results could be evaluated in the meta-analysis [Gizer et al., 2009].

A common, functional A/T SNP (rs28384840) found -3081 upstream to the transcription initiation site has been identified and associated with ADHD in a study by Kim et al., [2006] [Gizer et al., 2009]. The SNP is located within a sequence which is critical for cell-type-specific promoter function of the SLC6A2 gene. The T allele of this SNP reduces the promoter function relative to the A allele. Reduced promoter function results in reduced transcription rate, and therefore lower expression of the gene.

6.3.2 Adrenergic α-2A-receptor genes (ADRA2A and ADRA2C)
Additional studies have tested for association of the Adrenergic α-2A-receptor genes (ADRA2A and ADRA2C), however, no evidence was found of their involvement in adult ADHD [Franke et al., 2012]. Presynaptic inhibitory alpha-adrenergic receptors are involved in regulating the release of NA through a negative feedback mechanism. When alpha2-adrenergic receptor activity is increased, it suggests that there is a diminished NA release and activity, while a decrease in alpha2-adrenergic activity suggests an increase in NA functioning. It is suggested by evidence that the involvement of a disturbance in the NA activity in the pathophysiology of cADHD includes the finding that 23 ADHD boys usually have lower levels of alpha2-receptor binding in platelets than in controls [Hunt, 2006].

ADRA2A, located at 10q23-q25, is hypothesized to influence attentional processes and some aspects of executive control, and therefore, is an interesting candidate gene for ADHD [Gizer et al., 2009]. Studies have found an association between this gene and the inattentive symptom of ADHD. Three SNPs have been thoroughly studied for association to the disorder, rs1800544 (Guanine to Cytosine SNP located in the promoter region), rs1800545 (Guanine to Adenine SNP), and rs553668 (Adenine to Guanine SNP) [Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. In the meta-analysis review by Giver et al, rs1800544’s G allele was concluded to be a 'high-risk' allele, based on previous studies, while the results of the meta-analysis were non-significant. Research has also suggested that a significant interaction effect of maltreatment and the ADRA2A genotype on the behavioural functioning of 15 year old boys in relation to the rs1800544 polymorphism [Kiiv et al., 2010]. Boys with the C/C genotype and a higher score of maltreatment displayed more overactive behaviour and concentrating difficulties than boys with the C/C genotype and low maltreatment score. They also had a higher rating of inattentive symptoms, measured by the SNAP-IV. Among the boys with low maltreatment score, those with the C/C genotype demonstrated less
overactivity than those with a G allele. In girls, those with a G allele did not differ from the C/C genotype, however, in maltreated girls with the G/G genotype, aggression and inattention symptoms were lower, and the score of aggressive behaviour was also lower in comparison to the maltreated girls with the C/C genotype. This data suggests that family environmental factors may act together with the ADRA2A genotype to increase the expression of hyperactivity and inattentiveness in adolescents [Kiiv et al., 2010]. In previous studies rs1800545 had not been found to be associated with ADHD. The T allele of rs553668 was originally considered a "high-risk" allele, however the results have not been found across other studies.

6.3.3 Adrenaline
Activation of adrenaline receptors on the cranial vagus nerve has shown to increase the release of central noradrenaline, which has been shown to enhance memory formation [Croft, 2011]. In patients with ADHD, reduced urinary adrenaline levels have been found, while contrary findings have been found in patients with anxiety or PTSD. ADHD is often comorbid with anxiety, resulting in an increased risk of accident and injury. Further research is needed to fully understand the connection between adrenaline and ADHD.

6.4 Catecholaminas degradation enzymes

6.4.1 Monoamine Oxidase (MAO)
Monoamine Oxidase (MAO) is a group of enzymes that catalyse the oxidation of monoamines. They are substrates for the action of several monoamine oxidase inhibitor drugs which makes them very important in pharmacology. Imbalance of MAO in the body, either lower or higher levels, have been related with schizophrenia, depression, attention deficit disorder substance abuse and migraines. Moderate inhibition of MAO activity, in humans, has been shown to lead to mood elevation, motor hyperactivity and hyperreflexia. The genes encoding for MAO-A and MAO-B are located on the short arm of the chromosome X and have around 70% similarity, they are made up of 15 exons and are identical in the exon-intron organization. Having in mind that ADHD is at least 3 times more frequent in boys than in girls, it makes sense to hypothesize that genes located on the X chromosome might have a contribution in ADHD. These two enzymes differ in the substrates they bind in the brain: MAOA mainly metabolizes serotonin and NA while MAOB preferentially metabolizes dopamine [Cornish and Wilding, 2010].

The first polymorphism studied for the MAO genes was the microsatellite DXS7 which contains a varying number of 2-bp repeats. A study on 72 ADHD children and their parents showed a significant correlation of the 157-bp allele with a frequency of 0.59 with a second common allele of 0.31 [Jiang et al. 2000]. Another test supports this finding by an association of the dinucleotide repeat (CA) for MAO for a probability of less than 0.05 [Lowe et al., 2001]. A UK research on a sample of ADHD families showed trends for association to the 122-bp allele, but not to the 114 bp allele of the MAOA (CA) polymorphism [Payton et al., 2001].
Other two MAOA polymorphisms were found to interfere with the normal transcriptional activity: an exon 8 SNP (941T/G) and a 5’ region 30-bp VNTR located 1.2 kb upstream the MAOA gene. The MAOA exon 8 polymorphism (941T/G) with the 941T being associated with low activity of the degradation of monoamines, while the 941G is related with an increased degradation of monoamines. The T/G substitution is made on the third base of a triplet codon and encodes for the same amino acid which means that the protein primary structure is not changed. The increased or decreased effect in the MAO activity comes from the presence or absence of restriction enzymes sites [Hotamisliligil and Breakefield 1999].

The second polymorphism mentioned above has at least 5 alleles (2, 3, 3.5, 4 and 5 repeats) of a 30-bp repeat located 1.2 kb upstream of the MAOA gene. The 3.5 and 4 repeats alleles were found to induce a 2-10 times higher transcription rate than the 3 and 5 repeats [Sabol et al., 1998]. A later study found a higher transcriptional activity correlated with the longer alleles, suggesting that the longer alleles (3.5, 4 and 5) induce more transcription [Deckert et al., 1999]. But even though another study on Israeli families found a significant association between ADHD and with the longer 4 and 5 repeat alleles [Manor et al., 2002b]. A research in Indian population associated the 3-repeat allele of this polymorphism with a lower transcriptional activity in males [Das et al., 2006]. It is suggested that these differences in function might be caused by variants in the nucleotide sequence which was observed within this polymorphism [Das et al., 2006].

Association of ADHD with alleles that induce high activity (increased monoamine degradation) of MAOA, namely exon 8 941G and promoter VNTR 4 and 5 repeat alleles, is found over several studies that support a hypodopaminergic state contributing to ADHD [Levy and Swanson, 2001]. For MAOB gene only one study was published that found an association with ADHD. Four polymorphisms showed strong correlation with ADHD from which two polymorphisms were newly discovered. The A>G in intron 13 and C>T in the 3’UTR had previously been investigated while 2327T>C and 2327T>C in exon 15 were completely new variants [Wang et al., 2008].

6.4.2 Catechol-O-Methyltransferase (COMT)

COMT is one of the enzymes that has as a function with the inactivation of catecholamines like DA, adrenaline and NA by attaching a methyl group to these neurotransmitters. The majority of research related with ADHD is focus on a single polymorphism called Val158Met. It is a single nucleotide polymorphism (SNP) in the COMT gene and it is a substitution of G with A which changes Valine with Methionine at codon 158. The A or Met allele is associated with a lower enzymatic activity. Some studies found a correlation with ADHD, mainly the inattention subtype [Eisenberg et al. 1999], and once the sample size was bigger the results failed to be replicated [Misener et al., 2004].

6.5 Others
6.5.1 Nicotinic acetylcholine receptor 4 (CHRNA4)
Evidence suggests that there may be a relationship between the nicotinic neurotransmitter system and ADHD symptoms. This suggestion comes from research where nicotine administration is shown to improve attention and working memory in adults with ADHD. Also, nicotinic agonist have shown to reduce the severity of ADHD symptoms [Gizer et al., 2009]. Giving this evidence, researchers have begun to examine the link between the nicotinergic system (specifically the nicotine receptors) and ADHD. The nicotinic acetylcholine receptor subunit alpha-4 gene (CHRNA4) is involved in the coding of ligand-gated ion channels that mediate fast signal transmission at synapses. The gene is found at 20q13.33, and is highly expressed in the frontal lobe. There has been contradicting results concerning the connection of the CHRNA4 gene and ADHD, however, collecting evidence is starting to support the link. A study by Todd et al., found that two single nucleotide polymorphism (SNPs rs2273506 and rs6090384) located at a 5' intron, were associated with severe inattention problems [Todd et la., 2003; Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. The locations of these polymorphisms is theorized to affect the pre-mRNA stability or splicing. Rs2273506 is either a Cytosine to Adenine or Cytosine to Guanine SNP that results in Leu63Leu, meaning the coded amino acid was not changed. Rs6090384 results in a base substitutions of Thymine to Cytosine.

Research by the Vanderbilt University Medical Center has noted that combined ADHD patients have an altered choline transporter gene. Choline is the precursor to acetylcholine, formed by the breakdown of acetylcholine. It influences neural communication, similarly like NA and DA [Stannard, 2010]

6.5.2 Brain Derived Neurotrophic Factor gene (BDNF)
The Brain Derived Neurotrophic Factor (BDNF) gene is found at 11p14.1. It codes for a protein that goes by the same name. This protein is a member of the neurotropin family of growth factors which acts on certain neurons of the central and peripheral nervous system [Gizer et al., 2009 ]. It supports the survival of existing neurons, and encourages the growth and differentiation of new neurons and synapses. It is mainly found in the hippocampus, cortex, and basal forebrain. BDNF is shown to influence reward pathways in the brain where it modulates the response to DA by enhancing the effects of stimulants on the dopaminergic pathways. This makes it an interesting candidate gene for ADHD.

A common polymorphisms studied is the rs6265 (Val66Met) found in codon 66 [Gizer et al., 2009; Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. This SNP in the gene is where adenine and guanine alleles vary, resulting in a variation between the amino acid valine and methionine. The more common G allele encodes the valine, while the A allele encodes Met. This is shown to influence the intracellular tracing and activity-dependent secretion of BDNF in the brain. The G/G genotype is the most common/normal, A/G is believed to impair motor skills learning, and the homozygous A/A genotype has shown to result in increased depression resistance, impaired motor skills learning, and contribute to introverted personality type [McHungen et al., 2010; Cariaso and Lennon, 2011]. A study has shown that the presence of this BDNF polymorphism is associated within the brains motor system functions, altered short-term plasticity,
and a greater error in short-term motor learning. Subjects who were involved in a driving-based motor learning task showed that those with the polymorphic genotype showed greater error during short-term learning and poorer retention over 4 days, relative to subjects without the polymorphism [McHugon et al., 2010]. Research suggests that the G allele resulting in the Valine amino acid is a high 'risk' allele. However, present meta-analysis does not support the association between the Val66Met polymorphism in the BDNF gene and the development of ADHD.

6.5.3 Phenylethylamine PEA
PEA (phenylethylamine) is an excitatory neurotransmitter. It is found that levels of PEA tend to be lower in patients with ADHD [Croft, 2011]. Studies that tested urine levels of PEA in subjects with ADHD during treatment with stimulants (methylphenidate or dextroamphetamine), found that the levels of PEA were increased. Additionally, studies have also shown that the efficacy of the treatment correlated positively with the degree to which urinary PEA increased.

6.5.4 SNAP-25 Gene
The synaptosomal-associated gene, SNAP-25, is located on the short arm of chromosome 20 at p11.2 [Cornish and Wilding, 2010]. SNAP-25 codes for a protein that is essential for axonal growth, synaptic plasticity, and neurotransmitter release. This gene is outside of the major neurotransmitter system, however, due to its function and possible etiological role in ADHD it has also become a focus of research. In an animal study, by Hess et al. in 1992, of the coloboma mouse strain, which has been bred to lack one copy of the SNAP-25 gene, the mice displayed hyperactive behaviour [Gizer et al., 2009]. Seven SNP's related to SNAP-25 have been mapped [Gizer et al., 2009]. These polymorphisms are rs362987 (Adenine to Cytosine SNP) found in intron 4, rs363006 (Adenine to Cytosine SNP) found in intron 6, rs3746544 (Guanine to Thymine SNP) found in the 3' URT, rs1051312 (Thymine to Cytosine SNP) also located in the 3' URT, rs1889189 (Thymine to Cytosine SNP) located in the 5' flanking region, rs6039806 (Cytosine to Adenine SNP) found in intron 2, and rs8636 (Thymine to Cytosine SNP) located in the 3' URT [Gizer et al., 2009; Cariaso and Lennon, 2011; Ensembl, 2014; Zhang et al., 2012]. In a study of the SNAP-25 gene, involving different SNP's, it was found that variations in the SNAP-25 gene alone does not affect the phenotype, however, it may nevertheless lead to the development of a clinical ADHD picture in combination with other genetic factors [Pazvantoglu et al., 2013]. The same study also suggested that a combination of NET1 (rs2242447) and Snap-25 (rs3746544) is a risk factor for ADHD. It suggested that problems associated with the noradrenergic and serotonergic system and SNAP-25 may play a role in combination with one another or alone, in the pathophysiological mechanisms of ADHD [Pazvantoglu et al., 2013]. The 3' URT is an untranslated section of mRNA that can influence polyadenylation, translation efficiency, localization, and stability of the mRNA. Polymorphisms within this region can therefore, influence the translation of the mRNA leading to increased/decreased translation rate, and therefore an increase/decrease in the product. While a polymorphism found in the 5' flanking region can influence the creating of mRNAs, since it is the site of the promoter for transcription of a gene. The last three SNP's yielded non-significant results
in the review, though significant heterogeneity as found in the effect sizes across studies for the polymorphism rs6039806. The A allele of rs363006 was identified as having an association with ADHD, while the meta-analysis were found to be non-significant. Rs363006 provided negative results in both. Rs3746544 in previous had not reported a significant association with ADHD, and was therefore, not designated a risk allele. However the results of the meta-analysis by Gizer et al. provided significant association between ADHD and the T allele. Two polymorphisms have in 2010 been mapped at 1065 and 1069, and have been found to be associated with ADHD. However, recent studies have struggled to replicate their findings in its entirety [Cornish and Wilding, 2010].

7. Interviews

7.1 Patients

7.1.1 Caroline Jackson
* Pseudonym

Personal interview. April 3rd 2014 (ADHD)

When and how (teacher/parent/self/doctor) were you diagnosed?
I was diagnosed the summer after my first year at college. I had been highly active in high school as a competitive show jumper (horses) so I was used to being physically exhausted (I’d ride roughly 4-5 hrs a day) before starting my work. I thrived in school because I was studying topics that interested me and thrived in general because I had a highly active lifestyle. When I went to college everything started out really well – there were so many new things, so I was constantly busy. However, when everything began to settle down and I was only riding twice a week, staying focused became harder. Exams seemed almost impossible to study for as I couldn’t retain information without some sort of deadline looming over me and I would pull all-nighters on a regular basis to write my papers. I needed the adrenaline rush to get my work done. I knew that I was smart so I couldn’t quite understand why learning had become increasingly hard and I know that I was acting differently than usual. I would have to go on incredibly long walks to tire out my brain and to think – I think at my highest level while moving and I was constantly anxious. When I got back to New York I sought out a professional and was quickly diagnosed.

Which type of ADHD do you have?
I have combined ADHD but can also fall under ADD as, being female, my hyperactivity tends to mask itself under a feeling restlessness instead of the physical manifestation of restlessness while sitting, etc.

Do you have co-morbidity - other disorders along side?
I’m pretty healthy though I’ve had two major knee surgeries and now, in retrospect, understand why my recovery was slightly rougher than expected. People with ADHD tend to have more of an addictive personality and are prone towards depression. (Women, in particular, internalize everything and try to compensate and cover up the physical manifestations of ADHD by becoming slightly OCD, incredibly good prevaricators, etc.) The pain meds, therefore, really messed with my head and I had a rough few weeks before I simply refused to take them.

Have you been a part of the Feingold (Diet where you remove artificial food colors) program?
Nope. I’ve never heard of it actually.

Have you ever done psychotherapy or behavioral treatment?
No, I’ve learned to compensate pretty well throughout the years on my own. I did have the initial testing along with IQ tests, etc.

What kind of medication are you taking? How often do you take it? Doses?
I was on Concerta at 27mg when for about a year but, with riding, the increased heartbeat was dangerous. I then switched to Adderall but have since stopped, as I much prefer having a clear head. I don’t enjoy having my brain “slowed down” simply so others can follow.

Side effects from medication?
Slower thought process. Less abrupt and direct in my manner but I couldn’t function at the same level of intelligence.

Medication in combination with psychotherapy or behavioral treatment?
No - see question 5

What happens if you don't take your medication?
When I first stopped (when I arrived in Denmark) I felt like I needed a million cups of coffee to wake me up. I still am a caffeine (coffee and tea) addict but now my head isn’t so completely fuzzy at first.

Do you have any difficulties in general due to ADHD?
I don’t like messy foods. One of my symptoms is slight OCD in certain departments and if something becomes too messy or frustrating to eat – I don’t care if it’s the best thing in the world – I have to stop. I also have a tendency to avoid speaking publically – Since my adrenaline rush can’t subside like it does “normally,” I have a tendency to shake and talk incredibly fast, etc. I absolutely hate to be in situations where embarrassment is involved – even if it’s watching someone on television. I also have the usual symptoms: talks too much, slightly anxious, caffeine addict, a bit of a control freak but I still maintain good grades and try to be a perfectionist if at all possible.

Do you have family members with ADHD? and if so - who - mom/dad/siblings etc.?
Yes, my twin brother.

7.1.2 Gavin Jackson
* Pseudonym
Personal interview. April 3rd 2014 (ADHD)

When and how (teacher/parent/self/doctor) were you diagnosed?
Don't remember - at a very young age. Probably by teachers? And/or doctors as in the N.Y. private school system you are constantly being tested

Which type of ADHD do you have?
ADHD-PI (Predominately Inattentive)

Do you have co-morbidity - other diseases along side?
ADHD is not a disease its a Neurodevelopmental disorder, that is the final D in ADHD. No I don't have any diseases alongside ADHD, I do however also have Dyslexia which is classified as a learning disability.

Have you been a part of the Feingold (Diet where you remove artificial food colors) program?
No.

Have you ever done psychotherapy or behavioral treatment?
No, I have ADHD-PI (predominantly inattentive) not ADHD-PHI (predominantly hyperactive-impulsive).

What kind of medication are you taking? How often do you take it? Doses?
Concerta once a day.

Side effects from medication?
Loss of appetite as concerta is a steroid.

Medication in combination with psychotherapy or behavioral treatment?
No.

What happens if you don't take your medication?
Don't get the benefits i.e. no negative effects, just no positive ones.

Do you have any difficulties in general and food due to ADHD?
No, just loss of appetite.

Do you have family members with ADHD? and if so - who - mom/dad/siblings etc.?
My twin sister (Caroline Jackson).

**7.1.3 Andrew Gill**
*Pseudonym*

Personal interview. April 3rd 2014 (ADD)

**When and how (teacher/parent/self/doctor) were you diagnosed?**
I was diagnosed at the age of 8 through a standard ADD test administered by a psychologist.

**Which type of ADHD do you have?**
I was not given specifics just attention deficit disorder.

**Do you have co-morbidity - other disorders along side?**
Yes, would rather not get into that.

**Have you been a part of the Feingold (Diet where you remove artificial food colors) program?**
No.

**Have you ever done psychotherapy or behavioral treatment?**
Yes I did some one on one with a psychologist but it was no help.

**What kind of medication are you taking? How often do you take it? Doses?**
I am currently not taking any ADD medication.

**Side effects from medication?**
Not applicable.

**Medication in combination with psychotherapy or behavioral treatment?**
No help from therapy whatsoever.

**What happens if you don't take your medication?**
N/A.

**Do you have any difficulties in general due to ADHD?**
ADD medication makes you lose hunger appetite.

**Do you have family members with ADHD? And if so - who - mom/dad/siblings etc.?**
No family member has ADD.
When and how (teacher/parent/self/doctor) were you diagnosed?
I was diagnosed in 2005 by a doctor.

Which type of ADHD do you have?
I don't know about types but I have adult ADD. No hyperactivity.

Do you have co-morbidity - other disorders along side?
None.

Have you been a part of the Feingold (Diet where you remove artificial food colors) program?
No. That's really hard in the US to do. And very expensive.

Have you ever done psychotherapy or behavioral treatment?
No.

What kind of medication are you taking? How often do you take it? Doses?
20mg Vyvanse. I only take it when I need it. Usually work days.

Side effects from medication?
I get very tense in my jaws.

Medication in combination with psychotherapy or behavioral treatment?
No.

What happens if you don't take your medication?
Literally nothing- I'm pretty unproductive and super distracted off my medication.

Do you have any difficulties in general due to ADHD?
No just being able to focus to complete tasks and getting overwhelmed if there seems to be too much involved in completing some tasks.

Do you have family members with ADHD? and if so - who - mom/dad/siblings etc.?
I am the only one diagnosed among my siblings but I feel very sure both of my brothers are. My daughter is as well and is also in Vyvanse 20mg.
7.1.5 Nadja Mona Olsen
* Pseudonym

Personal interview. April 3rd 2014 (ADHD)

When and how (teacher/parent/self/doctor) were you diagnosed?
I was diagnosed in January 2014. My boyfriend suggested I should go to the doctor because he suspected I had ADHD. I went to a doctor who sent me to a psychiatrist.

Which type of ADHD do you have?
Combined hyperactive-impulsive and inattentive.

Do you have co-morbidity - other disorders along side?
No, I don't have comorbidity diseases but I have been struggling with diagnoses such as depression, bulimia, insomnia, social anxiety and panic disorder.

Have you been a part of the Feingold (Diet where you remove artificial food colors) program?
No but I eat as natural as I can and I have always tried to do so for other reasons. When that's said, my symptoms do get worse when I eat candy or drink soda.

Have you ever done psychotherapy or behavioral treatment?
Lots! I am currently doing body therapy (massage/ acupuncture/ relaxation) at least once a week. But I started that way before I got my diagnosis - it has shown to be efficient and a big help that I've worked with myself, especially after I got my diagnosis.

What kind of medication are you taking? How often do you take it? Doses?
Medikinet. 15 mg a day, sometimes more if needed.

Side effects from medication?
Haven't had any.

Medication in combination with psychotherapy or behavioral treatment?
No.

What happens if you don't take your medication?
I just started it not too long ago. I have to admit that I have more energy and focus than I used to. I usually get tired, confused, extremely impatient and skimpy with things when I don't take my medication.

Do you have any difficulties in general due to ADHD?
In general, I often "change" friendships because I'm an "in the moment" person and impulsive and I therefore, forget to maintain contact. I forget that I should text someone because I'm so busy with the one thing that catches my focus at a given time. It's extremely hard for me to finish my school work because I have to focus for a longer time and because I have to finish it. If I have to prepare...
something where I feel others expect more than I can give them or I don't know how to give it to them, I get really stressed and sad, I cry, yell at the people who are closest to me and my stomach hurts. I often get "fired" from jobs because I lack overview or because I get stressed too quickly. I had a nervous breakdown when I was 22 due to a night job and stress and I have now learned that I should go to bed between 1am and 2am the latest otherwise my entire upcoming week will be ruined. Due to the fact that my disease wasn't diagnosed during childhood I often felt like people didn't understand me and I sometimes have a tendency to be insecure if certain situations remind me of my childhood.

Food: I prefer not to eat sugars and other foods with "bad" carbs because I become restless and extra hyperactive inside which often result in a quicker tendency to become explosively angry or sad but I am almost used to it by now and so are my friends. But mostly I eat veggies and nuts, sometimes meat and other proteins.

**Do you have family members with ADHD? and if so - who - mom/dad/siblings etc.?**
Yes - my little sister has ADD - she is the only one in the family who is diagnosed but I think my mother has something as well.

7.1.6Samantha Riggs
* Pseudonym
Personal interview. April 3rd 2014 (ADHD)

**When and how (teacher/parent/self/doctor) were you diagnosed?**
Most of my teachers in elementary school picked up on it but it wasn’t large enough of an issue to affect my learning capabilities so my parents decided to let me cope with it without medical attention—but it was something that forced me to work harder than the other students, especially when it came to focusing. Finally, towards the end of high school, I was officially diagnosed by my therapist but I still did not agree to take the medication because I did not want to gain a tolerance.

**Which type of ADHD do you have?**
Combined ADHD: both inattentiveness and hyperactivity.

**Do you have co-morbidity - other disorders along side?**
Anxiety.

**Have you been a part of the Feingold (Diet where you remove artificial food colors) program?**
No.

**Have you ever done psychotherapy or behavioral treatment?**
Behavioral treatment with my therapist.

**What kind of medication are you taking? how often do you take it? Doses?**
I do not take any medication. I have tried psychostimulants.
**Side effects from medication?**
No negative. Helped my focus drastically but my dad, being a doctor, usually does not let me get too attached to medications because there is a high dependence rate on most forms of ADHD medication so my dad didn't want me to rely on medication because he wants me to be able to function without it. He believes I will learn to adjust myself without medication aids.

**Medicine in combination with psychotherapy or behavioral treatment?**
Behavioral treatment.

**What happens if you don't take your medication?**
When I wasn’t on it, my focus is horrible and I am very anxious and energetic. Usually cannot get work done until I am fully alone with absolutely no distractions. It can be very, very difficult to get something done even as simple as one homework assignment.

**Do you have any difficulties in general and to food due to ADHD?**
I do not have difficulties with food due to ADHD just attention and anxiety.

**Do you have family members with ADHD ? and if so - who - mom/dad/siblings etc.?**
Just 1st cousins.

**7.1.7 Astrid Hansen**
* Pseudonym
Personal Interview, April 29th 2014. ADD

**When and how (teacher/parent/self/doctor) were you diagnosed?**
I was officially diagnosed in 2003, during my junior year of high school. I was doing poorly in school, mostly math and science classes. I could not focus, I had low self-confidence, and math and science were my bad subjects. I had a 2.7 grade-average in school at the time when my mom decided to scheduled an appointment with a private psychiatrist to evaluate me for the problems i had been facing in school. I took a 3 hour test or so, maybe it was a little longer, or a little shorter, but it was a test filled with all kinds of problems that tested my attention. I had to repeat numbers, forwards and backwards. I had to look at color schemes and detect patterns. I also had to look at sets of pictures that had slight differences and was supposed to determine the differences between the two pictures. There were all types of tests and exercises. At the end of the test, they looked at the results and I was later diagnosed with ADD. The doctor did not ask to speak to my teachers or anything, just diagnosed me.

**Which type of ADHD do you have?**
ADD I do not have ADHD, but I have impulsivity problems so that was just a symptom I dealt with, but it is milder with medication.
Do you have co-morbidity - other disorders alongside?
Panic disorder, panic attacks, depression, Depression in grad school but symptoms of low self-esteem left after medication.

Have you been a part of the Feingold (Diet where you remove artificial food colors) program?
No, maybe I should try it.

Have you ever done psychotherapy or behavioral treatment?
I have weekly therapy session. I am weighed each visit and talk about anxiety management, being anxious and other personal problems. My personal therapist is not specifically there to treat ADHD, it is just personal things that helps me, but they are aware of my diagnosis and medications. I have had therapy on and off since high school. I was pretty depressed and stressed in college and sought out more help through therapy but now it is just a weekly personal choice. We work on ways of dealing with stress and anxiety.

What kind of medication are you taking? How often do you take it? Doses?
I take Ritalin now at 10 mg/3X day. I have tried almost all medications for ADD and I just switched from Adderall back to Ritalin, it was cheaper and Ritalin is what I prefer. Adderall is more like a drug. I feel like I am actually on something whereas with Ritalin, it helps me focus but is not as intense. I feel like my body gets easily addicted to Adderall, for example, when I am coming down, I want another pill to maintain the high or the good feeling. I have experienced sleep problems, feeling more druggy along with other more intense feeling on Adderall, where on the other hand Ritalin is more manageable. Ritalin is not as addictive, no drug rush. Adderall comedown gives the impulse to take more.

Side effects from medication?
Hmm, so far I have mentioned sleep problems, obviously appetite suppressant, so I am not so hungry. Which is usually a good thing. People think, wow any kind of appetite suppressant is good, so I won't get fat. But of course it is a problem, I have learned to make sure to eat and remind myself to eat. But on Ritalin, it is not as apparent as on Adderall. On Adderall, I will not be hungry at all. The sleep was a big problem, if I thought I'd have a productive night and take an Adderall, then I'd just be up all night. But Ritalin doesn't give me the same problems. I can sleep on Ritalin and eat on Ritalin. I have also gotten a bone spur in my jaw, it is from jaw clenching. It is not noticeable, but still kind of freaky. The doctors said it is not a problem unless it bothers me or hurts me. But about the sleep thing, it is my own fault. I should know when to take my medication, and I know that if I take one before bed time, I will be up all night, so I should know when to take it and when not to take it. Dependency-adderall. When I was taking Adderall I was taking 20mg of Adderall 3X day. When I am off meds I get really tired, when I was off Adderall I slept for 3 weeks and ate everything. I was just so tired and soooo hungry. It still happens when I am off Ritalin. I am just very very tired.

Medication in combination with psychotherapy or behavioral treatment?
Yes. I take meds and have therapy, but it is not psychotherapy or specific to ADHD.

**What happens if you don’t take your medication?**
I think I answered that before, but I also get a Placebo effect. If I don’t have it around and know I’ll need it, I might get anxious and then when I take it I feel relaxed knowing that, “this is happening now,” so I know I will be prepared to get my work done etc.

**Do you have any difficulties in general to ADHD?**
I don’t see it as difficulties, I think I am more in touch with my creative side. I don’t see it as a handicap, I see it as something else. Like I have a lot of creativity in me that is being expressed so I really think that it could be because of my ADD? Maybe. I just don't see it as a bad thing.

**Do you have family members with ADHD? And if so - who - mom/dad/siblings etc.?**
Yes. My dad has ADD or maybe ADHD. He has it way more severe than I do. He was diagnosed the same time as me and he is extremely impulsive. Like, very very very impulsive. That is how I am here! But he went in to the psychiatrist around the same time as I did and got diagnosed, yes.

**Anything else you wish to share? Anything I have missed that you think is relevant to this topic?**
No, I think you covered it all. Thanks

7.1.8 Natalie Lloyd
* Pseudonym
Personal interview, may 4th 2014

**When and how (teacher/parent/self/doctor) were you diagnosed?**
When I was in college, at 20 years old I was having a hard time focusing on projects for work and school. I met with a doctor, I attended a seminar, they took blood tests, gave me a quiz, observed behavior, spoke with my mom about my childhood because adult Adhd is usually present during early development but not diagnosed, then we talked about medications. I tried Ritalin but it made me shaky so I switched to slow release Adderall which did not cause shakiness.

**Which type of ADHD do you have?**
Combination type hypo and hyper. Sometimes I get really energetic and can't focus and sometimes my thoughts are cloudy and disorganized.

**Do you have co-morbidity - other diseases alongside?**
No

**Have you been a part of the Feingold (Diet where you remove artificial food colors) program?**
No
Have you ever done psychotherapy or behavioral treatment?
No but I see my doctor every three months to discuss the medication and evaluate if it needs to change before she writes me a new rx

What kind of medication are you taking? How often do you take it? Doses?
20 mg extended release adderall. I take it as needed and I discussed this with my doctor because I didn't want to become addicted to the medication. Usually I don't take it on the weekends but during the weekdays if I find myself getting frustrated with my inability to focus then I will take one 20mg pill in the morning.

Side effects from medication?
If taken on an empty stomach it can cause an upset stomach. Sometimes it suppresses my appetite.

Medicine in combination with psychotherapy or behavioral treatment?
I use behavioral techniques my mom taught me when I was younger. Sometimes physical activity helps and writing sticky notes and reminders to help me not forget things.

What happens if you don't take your medication?
Nothing really. I get frustrated and impatient with myself. I usually only rely on the medication when I cannot focus on my own.

Do you have any difficulties in general and food due to ADHD?
I can’t drink coffee after i take my medication or will make me feel nauseous. I usually try to eat a little something shortly after I take my pill and drink a lot of water.

Do you have family members with ADHD? And if so - who - mom/dad/siblings etc.?
Yes, my mom and brother

7.2 Professionals

7.2.1 Michaela Sorina (psychologist)
Personal interview, may 6th 2014

Where do you draw the line between symptoms resulting from “bad parenting” and ADHD diagnosis?
For me, this is kind of subjective because my oldest nephew was thought to have ADHD when he was about 5 or 6 by his teacher. He would act out, talk out, not focus, etc. but I truly feel like his case could have easily been misdiagnosed because you know my brother, I love him, but he’s probably one of the worst parents in life when it comes to showing the “proper” love/affect/discipline to his kids. And that goes back to our parents and our upbringing. I don’t
think there really is a set true line in which to draw your diagnosis from because each case is so different from the next.

The DSM is retarded. The way it is written is vague and often leads to misdiagnosis because of how certain behaviors are interpreted across doctors. I wish I had the right notebooks, but I think I left them all at my ex’s house. The DSM is written by a committee of psychologists and psychiatrists and is updated every so often. I think the newest version came out last year or comes out this year. But in being so, the DSM is kind of biased, like depending on who is on the board and who has donated what. I think according to the DSM it also says if you’re a caffeine drinker, you would be considered to have a “mental disorder.” Not that you are “crazy” but that you have a “disorder” implying something is wrong with you. So how they word things are very awkward.

What are the differences (pros and cons) of a self-diagnosis, teacher-diagnosis, parent-diagnosis?
Pretty much self-explanatory. A combo of teacher, parent, and doctor diagnosis is best when determining whether or not a child has ADHD/ADD since you would get different perspectives of the child’s behaviors in different environments.

Medication. Most doctors nowadays are relying heavily on prescription drugs, hence the crazy high rates of over medication. Vinnie actually has ADHD and his complaints about the drugs are pretty consistent with other users of Ritalin. Like feeling lethargic. Your body and your mind is there, but you just seem to be out of it. He didn’t like it at all, he actually stopped taking it in high school and didn’t tell his parents he stopped. He smokes weed to calm his mind down and focus on videos and what not. (don’t tell him I told you lol) Also cognitive behavioral therapy helps but most effective treatment is medication for sure.

Mmm, not too sure how the funding works. I’m sure its pretty complicated considering how sharky insurance companies are. Some parents notice symptoms of ADHD really early on and some symptoms develop more gradually over time (impulsivity, hyperactivity, inability to focus, etc.) so I think just depending on how severe would be more appropriate of a time. Definitely by 6 or 7, I think a child’s mind has developed enough to comprehend their obstacles if they’re that much of a distraction.

For the most part they are safe. The only time it gets hairy is when medication is combined with other substances and medications. Each person is different so just with any medication, it is best to find the right dosages or combo of dosages for the individual.

I believe in more medication free treatments which is why I went into psychology rather than psychiatry. I think psychiatrists get easily pushed around and persuaded by drug companies to prescribe their medications and because of insurance purposes or lack of health care for people, health care professionals are moving further away from “care” business and more about being cash cows. Like being limit to only a certain amount of sessions before having to diagnose patients. My dad, for example, takes a bazillion pills for his PTSD, probably about 10 in the morning and the same at night. Imagine how much those pills would cost if he didn’t have the VA taking care of his medical? Its ridiculous. And he’s become so dependent on those drugs over the last 25 years, you can seriously see the difference if he’s “off his meds.” But again, on a case by
case level each treatment may require one over the other or taking amphetamines short term. It just depends.

I don’t know the exact statistics on this is just know that like 1 in 5 or something individuals diagnosed with ADHD as children end up having those symptoms carrying on into adulthood.

7.2.2 Nana Jensen* (psychologist)

* Pseudonym
Personal interview, April 28th

Job Title
Psychologists, Practical Psychology, Employed for Copenhagen Kommune, Børne og Ungdomsforvaltning, works with children and adolescents between ages of 0-18 years. Employment covers all public and private school institutions within Copenhagen Commune and focuses on the welfare and pedagogical education field.

Interview:

What diagnosis criteria do you work with?
I work with ICD-10, but I am a psychologist and when I receive information about a child the diagnosis has already been given or if I believe a child has a certain disorder I refer them to the psychiatrist to be further evaluated and then a potential diagnosis will be made in the future through the psychiatrist.

Where do you draw the line between symptoms resulting from “bad parenting” and ADHD diagnosis?
It is important to be sensitive with a diagnosis and make sure symptoms are in all or more than one setting. A lot of the time the children have a debatable symptom or symptoms that could look like ADHD but then when I observe them in other settings, the symptoms dissipate. Also when a child is having a problem in one school subject, and not the others, this is not a concern of ADHD, it is just a natural thing in children. Some kids have difficulties in school and school settings, but this does not mean they necessarily have ADHD. Also sometimes teachers and or parents have a hunch that a child has ADHD but when I or a colleague observes them, it gives an objective opinion. So, the opinion of the child’s condition is not one sided. A lot of male patients get diagnosis and from teachers it is more difficult to deal with boys because they are often already hyperactive, and with an ADHD diagnosis on top of the already active behavior, it can be difficult to deal with.

Are young children being misdiagnosed?
I think it is easy to be diagnosed with ADHD if you are only following the ICD-10 manual. Therefore, it is extremely essential to really look into the symptoms. There are a lot of behaviors that overlap with “bad” behavior of normal kids. I look at the way children work in school settings with as much as an unbiased opinion as possible. So, I follow a certain criteria for the disorder and
then try to come up with alternative treatments before I send the child to a psychiatrist for further evaluation. Maybe parents and teachers have heard the word “ADHD” so much that they begin to throw it around a lot. They may think that a child that is slower in school, hyperactive, or easily distracted has ADHD but then it is my job to work as a detective to see what the problem is. Then if I truly believe the problem is a disorder, then the next step is for the psychiatrist to diagnose the child.

**What do you believe to be the pros & cons of each ICD-10/DSM-IV criteria?**
No comment.

**What are the differences (pros and cons) of a self-diagnosis, teacher-diagnosis, parent-diagnosis?**
As mentioned before, the psychiatrist has the final say in the matter. So, maybe in other places a parent, a teacher or a individual can diagnose themselves but it is my job in the younger children’s school setting to determine if they need to see a psychiatrist or if the problem can be alleviated by alterations in the school or lifestyle of the child. Sometimes the children have good inputs to solve the problem. Sometimes the school system is the problem. The system needs to be filled with predicted breaks and change in curriculum.

**What are the different types of treatment for ADHD?**
Behavioral therapy, behavioral cognitive therapy- Where you work focus on new solutions to a problem.

  Solution focus therapy- Learning strategies to deal with hyperactivity. Breathing therapy- breathing exercises for when the child feels hyperactivity coming on.

  Psychotherapy- I have not worked with this but I know that some people do it.

  My colleagues and I talk with teachers at the schools about what they can do to improve the situation and how they can change their teaching style, break schedule and curriculum to better the environment for children.

**Which are most popular, effective, etc?**
It is always important, that you explore all options and not just take medications. At my job we work with changing the surroundings first and see if there are improvements, then combination of alternative treatments or therapy with light medication and finally medication is the last resort. We feel that adults are best equipped for change, so having the teachers change for the children is the best.

**How do budgets affect treatment for ADHD?**
Since we can (financially) employ psychologists to work with children at public schools, there are maybe different goals for the children than if there is not enough money to pay for employing psychologists.

**At what age is it appropriate to tell a child that they have been diagnosed with ADHD?**
Start to try to the children as early as possible. Talk on the children´s level. It is important for the identity of the child to tell them that they have the disorder. Do not put too much responsibility on the child. Just make them aware of differences in all children. It is important to tell the child that the symptoms are quantitative not qualitative. We all have problems, they just have certain ones magnified. Some of the parents have ADHD. We use the Biopsychosocial Model identify the severity of the symptoms.

**Are the medications recommended for ADHD safe for children? Long-term side effects, loss of appetite, insomnia, and brain development, addiction?**
In my own opinion, medication is the last resort. I have not worked with the children long enough to see any types of bad side effects.

**How effective are medication free treatments vs pharmacological treatments?**
Note sure. Change environment. Change the lessons, group therapy, than individual therapy. Alternative is always best, but then a combination of therapy and low medication, then last resort - medication. If you just have ADHD, and no other diagnoses, then it is easier to deal with without medication.

**ADHD in males vs females adults vs children?**
Many times the males have the hyperactive or are accused of having ADHD, there is now, just recently a bigger focus on the quiet girls, but the most focus goes to the hyperactive symptoms.
All problems in school, are they at school and at home and other situations? The important thing is that it is the symptoms are apparent in more than one setting or in all settings.

**7.2.3 Rachel Gordon (Psychiatrist)**
Personal interview, April 16th 2014

**What diagnosis criteria do you work with?**
I use the DSM IV and am beginning to use the DSM V in my work. I currently work at Kaiser Permanente and this medical HMO uses the DSM IV and will begin to use V in the fall.

**Where do you draw the line between “bad parenting” and ADHD diagnosis?**
It is a pretty clear line. I wouldn’t say the two are related at all and bad parenting looks VERY different than a child who has ADD or ADHD. Most of my child clients who have ADD/ADHD have wonderful, caring and involved parents who are very concerned about their children. ADHD is a genetic neurobiological disorder and will rarely (if ever) be caused by “bad parenting” or environmental factors alone. A child with ADHD will be unresponsive to or act out with parents who set clear limits and consequences just as much as they might with permissive parents. Their symptom picture is usually very consistent, but the families they come from are not. This leads me to believe that the family system and the parenting style have little to do with the cause of ADHD. (But ADHD is highly genetic and very often children with ADHD have one parent who also has it,
which of course does affect parenting style). Parents of children with ADHD are tired, confused and frustrated. They can’t figure out why their child isn’t living up to his/her “potential” or why they seem “lazy”. By the time the child has come in for therapy, the parents and/or teacher have identified a problem and know something needs to be addressed. Having said that, there are parenting styles that do not help children with ADHD. These styles can actually makes ADHD symptoms worse. For example, children with ADHD need structure and routine. A household that is inconsistent and chaotic with no set morning and evening routines would be difficult for a child with ADHD.

**What do you believe to be the pros & cons of each ICD-10/DSM-IV criteria?**
The DSM-IV criteria are actually pretty accurate. Almost everyone I have worked with who has ADD or ADHD has the symptoms described in the DSM-IV. It is important that the symptoms have occurred since childhood and the DSM makes this clear. If they did not, then it is not ADD. Since this is a neurological disorder, it would be around since birth. It is also important that the DSM highlights that these behaviors must be somehow developmentally inappropriate. It is important that we are not just diagnosing a kid for being a kid. This is one area that things get confusing. When diagnosing a seven year for ADHD, how much of what you’re seeing is because your client is seven and how much is actually not age appropriate? Also, anxiety looks a lot like inattention when kids are young, so how do we distinguish these? I would say these are some of the limitations of diagnosing so young. Sometimes kids grow out of behaviors that seem like ADD, sometimes it is really anxiety and sometimes it really is ADD. Of all the DSM disorders and criteria, I think the ADD section is actually pretty good and really resonates with clients. One con though is marking anyone at a young age of course.

**What are the differences or results to Self-diagnosis, teacher-diagnosis, with respect to medication?**
I don’t know how clients might react differently depending on who diagnoses them. I haven’t ever talked to anyone about that. But, it is my understanding that only a mental health professional like a therapist (i.e. an MSW, MFT, PsyD or PhD) or a psychiatrist (M.D.) can give an official diagnosis. A teacher might notice particular behaviors and let a parent know, who then might take their kid to a mental health person. Or a parent might notice the behavior and then just take the kid in. Also, most kids do not know what their symptoms mean and would not connect the dots that they may have ADD until they are in high school. So, kids younger than around 13/14 would not be coming in on their own according usually. I imagine it is most empowering when a person feels that something is off and brings themselves in to be tested and diagnosed. This just means there is the fullest amount of consent, motivation and engagement in the treatment. Having parents bring you in is probably second best because then the parents are showing advocacy and support for their child. If the parents and teacher are on the same page, that is good. I can imagine that there have been times that the teacher says the child has ADD and the parents dismiss this, which can cause tension and be a real shame. But honestly, as long as the child/teen feels supported by everyone involved in the treatment, I kind of doubt that it really matters who the initial person is who brought up the issue.
At what age is it appropriate to tell a child that they have been diagnosed with ADHD?
I think it is almost always appropriate to tell an adult client their diagnosis in general. People usually feel a sense of relief and new understanding and explanation for their experience. It also leads to rich and important conversations between clinician and client about how treatment should look. This is of course a general statement and each case is different. Children present a few considerations, however. The main consideration with sharing a diagnosis with a child is their developmental and cognitive abilities to understand what it is you’re even talking about. Children under 10 (ish) probably will not understand what a formal diagnosis means. But this does not mean you cannot talk about it. You can talk about their diagnosis in terms of their experience. For example, a child with an anxiety disorder might better understand you talking about “how they feel nervous all the time” in place of more clinical language. I think telling a child they have ADHD is one of the easier diagnosis to share. ADHD has become so common in our discourse about children. It is not stigmatized in the same way many other mental health issues are. People know what it is. People know that it is not a choice and that the individual is not to blame for her/his condition. Most of the time kids feel very relieved to know they have ADHD. Children with ADHD often have experienced a long list of unexplained failures. They cannot do what the other kids can do and they know it. Because of this, undiagnosed ADHD can cause severe blows to self-esteem. It is much better for the child (and their parents) to know that they have a learning disability so that the child can understand they are not the problem but rather they have a problem with attention. This also greatly helps parents and teachers from blaming their children and/or students for being lazy or unmotivated. ADHD/ADD can cause others to feel that the person is lazy, unmotivated, not living up to their potential, not listening and not trying hard enough. Once everyone knows the child has ADD, these painful accusations can go away. I have a seven year old client with ADHD and he knows he has a problem with attention and that he has to take a pill for it right now. This is much better than the shame he was carrying with him up until recently.

Are the medications recommended for ADHD safe for children? Long-term side effects, loss of appetite, insomnia, and brain development, addiction?
According to the FDA etc. they are safe for children. The truth is we really don’t know much about medication at all but children get put on medication all the time and do quite well. We do not know the long term side effects be not enough children have been on medication as kids and then grown up. The short term side effects include a huge range of fun: being too tired, not being able to sleep, not having an appetite, zoning out, feeling “like a zombie”, feeling “not like myself”, having flat affect, anxiety, irritability, weight gain, weight loss, hyperfocus, becoming less social. Additionally, coming off ADHD medication can be hard on kids. Some kids get emotional, cranky and difficult to handle when their medication wears off at the end of the day. And for some kids, they are totally fine. As of now there are no known addictive properties to ADHD medication (again we don’t really know). I have never heard of this. In my experience, one thing I have seen kids get “addicted to” is the performance they have while on the medication. Some kids get very upset when asked to change their medication (usually because they are having some other negative side effect) be they fear that they will lose their ability to succeed without it. Additionally, sometimes kids believe that
it is the pill that makes them behave better and do well and do not give themselves any credit for their accomplishments. Therapy should address this if it is happening.

**How effective are medication free treatments vs pharmacological treatments?**

Because ADHD is a neurological condition medication really is effective in treatment. I am NOT a big medication proponent. I really think we have no idea what we are doing when it comes to medication BUT with ADHD it really does seem to help. Medication free treatment is mostly behavioral. Therapy would consist of teaching and practicing organizational skills, study skills, time management skills and setting up consistent schedules and routines for the client. Some therapists use cell phones and computers to create schedule reminders for clients in addition to use old school methods like planners, to-do lists, calendars etc. While these types of skills are very helpful, the medication can target things like focusing on school work, increasing reading retention, school performance and test performance. These are things that behavioral interventions would have a harder time addressing. Medication can target the stuff that really affects a kids self-esteem. However, the decision to go on mediation should be one that is approached with lots of care and conversation. There are great pros to medication: increased school performance, increase self-esteem, increase peer acceptance, decreased likelihood of substance abuse (Teens with untreated ADD are some of the highest teen drug and alcohol abusers.) And there are cons like side effects. The family should constantly be re-evaluating whether their child should remain on medication and the goal should always be to learn enough behaviors and skills so that medication is not necessary into adulthood. The bottom line is medication can have tough side effects for a child but no medication can often have even more difficult effects on their sense of self.

**ADHD in males vs females adults vs children?**

I don’t have any hard data on demographic prevalence of ADHD in boys v girls etc. I am sure you can find that online or something. One thing I do know though is that ADHD looks different in boys than girls. Girls usually have the Inattentive type or just ADD. Many girls who have ADD are quiet and seem to “daydream” a lot. They are not expressing their symptoms through acting up or impulsive behaviors as many boys do. For this reason, girls with ADD often are not diagnosed or treated. Boys usually have ADHD and have behaviors that are more impulsive, hyperactive and all over the place. Boys have a harder time sitting still and it is much harder to manage and to miss. This is why boys usually are the ones who are diagnosed. Also, most adults have ADD even if they had ADHD as children. Adults learn to control the impulsive and less socially acceptable behavior and so usually just “zone out” and “daydream” as adults. People with ADD/ADHD often respond to it by either becoming very rigid and anxious or by being very chill and “go with the flow”. These are both personality strategies to deal with the symptoms of ADD.
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Diagnostic Overlap, Table modified from Karlovic et al., 2002

Diagnostic Overlap Diagram, Figure X, showing the DSM-IV diagnosis criteria and overlap, NICE, 2009


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