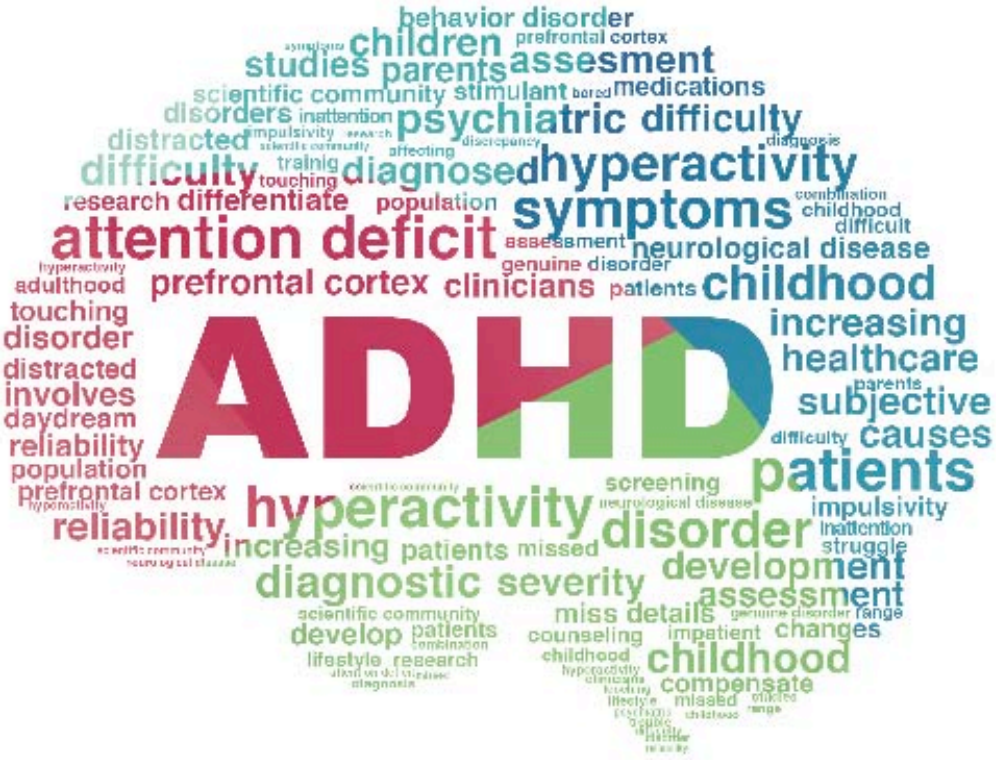
Universitat Autònoma de Barcelona

Neurofunctional Markers of Reward and Timing Processing in Adult Attention Deficit and Hyperactiviy Disorder: **an fMRI Study.**



Doctoral Thesis

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Barcelona 2013

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Barcelona, 2013

The present thesis was supported by a grant of the Ministerio de Ciencia e Innovación, number SAF200910901.

“When it is obvious that the goals cannot be reached,

don't adjust the goals, adjust the action steps.”

Confucius

Para Dani, mi amiga, hermana.

Por creer en mi,

y acompañarme cada día.

Agradecimientos

Creo que este trabajo no hubiera sido posible sin la ayuda de tantas personas que de distintas formas, han sido parte de mi vida durante los últimos años.

A Oscar, mi director, siempre te estaré agradecida por la oportunidad que mas dado de ser parte de este gran equipo y familia que para mi ha llegado a ser la URNC. Gracias por tanta paciencia, ayuda y los ánimos siempre que los necesité. Pero sobre todo, gracias por la confianza que has tenido en mi siempre, que me ha permitdo crecer profesional y personalmente.

A Toni, también director de mi tesis, y de quién he aprendido tanto de TDAH. Te agradezco por toda tu guía, apoyo y dedicación al poyecto.

Susanna, que siempre con paciencia y cariño me ha enseñado tanto desde el comienzo, y con quién siempre he podido contar, como tutora, colega y como amiga. Y en especial, te agradezco muchísimo tu guía y ayuda con los análisis de esta tesis.

Elseline, por transmitirme, además de sus conocimeintos, esa pasión por la ciencia que que hoy realmente he llegado a tener! Gracias por enseñarme tantísimo y por todo el cariño y confianza que me has tenido.

Pepus, mi amigo del alma, gracias por tantos momentos…te agradezco por estar siempre a mi lado, en las buenas y en las malas.

Ana, gracias por tu amistad, tus consejos y los buenos momentos durante tantos años.

Dani Bergé, con quién siempre he podido contar, gracias por estar siempre ahí y sobre todo por tu ayuda con los famosísimos ROIs!

Jordi Fauquet, muchísimas gracias por tu ayuda y consejos metodológicos y estadísticos, no solo para mi tesis, también con todos los proyectos.

Vic, gracias gracias por los cafecitos, por tus palabras, y por siempre estar y ser vos! Gracias por llenarme siempre de esa pasión que siempre tenés!

Chaly...gracias por tu amistad, cariño, apoyo desde que llegaste a la URNC. Pero sobre todo, por todo lo vivido y lo que me has enseñado.

Lara, gracias por una amistad tan linda, y por estar ahí siempre.

Laura, creo que por siempre estaré en deuda contigo por tu apoyo durante los ultimos meses! De verdad gracias noieta…

Nuria, gracias por tu amistad y apoyo tantas veces…con restings, con tesis y con la vida!

Lorena, siempre con tu alegría y le mejor actitud! Gracias por tu amistad!

Lili, Fran, Mireia, Nuria M., Dani G. Gracias por su cariño, confianza y por todos los buenos momentos que me habeis dado! Espero que todavía continuar con todos proyectos tan bonitos que tenemos.

Jo, gracias por llenar la URNC de la mejor actitud, y tu apoyo desde siempre.

Magda, gracias por todo tu esfuerzo, carreras y compañia!

Coloma, por tu dedicación y apoyo!

Ale, Rosa, Rodrigo: Gracias por su confianza en mi, y espero que sigamos adelante con el proyecto!

Adolf Tobeña, por su guía desde el comienzo y su interés en mi trabajo.

Sandra, gracias por tu ayuda en todo momento que lo he necesitado.

A todos en CRC, Claudia, Dolors, Sergi, Xavi, Isa, Alba, Jaume: Les agradezco muchísmo su apoyo durante estos años…realmente ha sido un placer trabajar con vosotros.

A la Fundació IMIM, mi agradecimiento por la ayuda para la impresión de este trabajo. También a todos en el Servei de Recerca y de Informática por su interés y ayuda durante estos años.

Finalmente, a toda mi familia, por creer en mi y apoyarme en cada paso. Mile, Adri, Andre, gracias por siempre estar conmigo en todo momento! Ma, gracias por tu cariño y por tu fé en mi, pero sobre todo por tus enseñanzas. Pa, gracias por tus consejos de cada día y tu apoyo y cariño incondicionales, sos el mejor ejemplo a seguir.

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ABBREVIATIONS:

5HT: Serotonin

5-HTR1B: 5-hydroxytryptamine receptor 1B

5-HTR2: Serotonin receptor 2A

5-HTTLPR: Serotonin-transporter-linked polymorphic region

ADD: Attention Deficit Disorder

ADHD: Attention Deficit Hyperactivity Disorder

ADHD RS: ADHD Rating Scale

ADRA1C: Alpha adrenergic receptor 1C

ADRA2A : Alpha adrenergic recpetor 2

ARSS: Adult self report scale

BDNF: Brain-derived neuropthrophic factor

CAARS: Conners adult ADHD scale

CAADID: Conners adult ADHD diagnostic interview for DSM-IV

CHRNA4: Cholinergic receptor, nicotinic, alpha 4 (Neuronal)

CLOCK: Circadian Locomotor Output Cycles Kaput

CNS: Central nervous system

COMT: Catechol-O-methyltransferase

CPT: Continuos performance test

D1: Dopamine receptor 1

D2: Dopamine receptor 2

DA: Dopamine

DAT1: Dopamine active transporter 1 gene

DBH: Dopamine beta hydroxylase gene

DDC : Dopa decarboxylase gene

DLPFC: Dorsolateral Prefrontal cortex

DMN: Default mode network

DRD1: Dopamine receptor D1

DRD2: Dopamine receptor D2

DRD3: Dopamine receptor D3

DRD4: Dopamine receptor D4

DRD5: Dopamine receptor D5

DSM: Diagnostic and statistical manual of mental disorders

EEG: Electroencephalography

EF: Executive functions

fMRI: Functional magnetic resonance imaging

GM: Gray matter

GRIN1: Glutamate receptor, ionotropic, N-methyl D-aspartate 1

GWAS: Genome wide association studies

MAOA: Monoamine oxidase A

MAOB: Monoamine oxidase B

MBD: Mild brain dysfunction

NA: Noradrenaline

NET: Norepinehrine transporter

NET1: Norepinephrine transporter

nNOS: Nitric oxide synthase

nNOS1: NOS1 nitric oxide synthase

PET: Positron emission tomography

PFC: Prefrontal cortex

PCG: Precentral gyrus

SCID I/II: Structured clinical interview for DSM axis I and II

SLC6A2: Solute carrier family 6 (neurotransmitter transporter, noradrenalin) member 2

SLC6A3: Solute carrier family 6 (neurotransmitter transporter, noradrenalin) member 3

SNAP-25: Synaptosomal-associated protein 25

SNP: Single nucleotide polymorphism

TH: Tyrosine hydroxylase

TPH: Tryptophan hydroxylase

TVA: Tegmental ventral area

VNTR: Variable numer of tandem repeats

WAIS: Weschler adult intelligence scale

WHO: World health organization

WURS: Wender Utah rating scale

1. ABSTRACT

ADHD, conceived as one of the most prevalent childhood psychiatric disorders, is characterized by inattention, hyperactivity and impulsivity symptoms and estimate to affect 5% of worldwide population. Until recently, symptoms were thought to ameliorate with age. However, a recent 10 year follow-up study indicated that 35% of paediatric patients still meet criteria and it's been estimated that affects between 3 and 7% of adult population. Even thought the exact neurobiological substrate of ADHD still unclear, genetic, preclinical and clinical studies point to dopaminergic and/or noradrenergic alterations. Neural activity and grey matter volume decreases in dopamine related regions also corroborate such deficits.

Adults diagnosed with this disorder are likely to neuropsychological deficits involving working memory, attention and inhibitory control. The multiple pathway model proposed by Sonuga-Barke implicates at least two relatively independent but not mutually exclusive endophenotypes; those involving an executive functioning disruption such as inhibition control, and those more related with motivational system abnormalities, basically reward anticipation. Therefore, this model explains neuropsychological heterogeneity of ADHD in terms of dissociable cognitive and motivational deficits, each affecting some but not other patients. Importantly, it is been suggested that temporal processing might constitute a third dissociable neuropsychological component of ADHD. Recently, timing processing deficits are being studied in ADHD, and, furthermore, such abnormalities have been related with impulsiveness, a core symptom of ADHD.

In spite of the influence that motivational and timing processes might have on cognitive functioning, only a few studies have focused on the neural substrate underpinning the

motivational and timing systems and, specifically, their role in the pathophysiology of ADHD.

Therefore, we analyzed functional magnetic resonance images (fMRI) of 20 un-medicated, combined, adult ADHD subjects and 25 healthy controls. Date sets were used to identify and compare the brain activation during a reward/time discrimination paradigm. The paradigm also included distractors during the task, in order to evaluate attention processes. Our results from the Regions of interest (ROIs) analysis indicated decreased brain activation in left and right cerebellum during the reward/time estimation time task in ADHD patients as compared to the control group. The cerebellum is key area of structural and functional abnormalities in ADHD, and, recently it has been implicated as one important mediator in time discrimination. Furthermore, whole brain analysis indicated decreased brain activity in right superior temporal gyrus, right left cerebellum, right fusiform gyrus, right Heschl´s gyrus and left occipital middle gyrus in ADHD group as compared to controls. The opposite contrast showed increased activation levels in right frontal inferior gyrus and left superior parietal gyrus in the patients group. Additionally, ROIs analysis also showed reduced activity in relation to the distractor stimulus in the ADHD group in left dorsolateral prefrontal cortex and the left precentral gyrus. The whole-brain analysis also showed a cluster of reduced activity located in the left post central gyrus, left inferior temporal gyrus and left inferior frontal gyrus. In the opposite contrast, we observed increased brain activity in the right orbitofrontal cortex in the ADHD group. Our results provide evidence that temporal processes, in addition to cognitive (i.e., attention) and motivational/emotional domains, might be a third dissociable neuropsychological component that affects ADHD.

2. INTRODUCTION

2.1 Definition

Attention-Deficit Hyperactivity Disorder (ADHD) is a developmental disorder, defined as age-inappropriate levels of hyperactivity, impulsivity and inattention, according to the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR (APA, 2004). It can result in desadaptative behaviors and may produce important alterations in different vital areas. Attention deficit can be defined as an individual's inability to maintain attention during a determined period of time, hyperactivity as an excessive motor activity and impulsivity as the inability to inhibit a conduct.

According to the DSM-IV (APA, 2004) an individual will be given an ADHD diagnose if six or more symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with the developmental level, and six or more of the symptoms of hyperactivity-impulsivity have persisted for a minimum of 6 months in a maladaptive way, also inconsistent with the correspondent developmental level. Additionally, an ADHD diagnose will be given if Hyperactivity - impulsive or inattentive symptoms were present before the age of 7 years and in two or more settings (for instant at school, work or home). There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning and it should not be a consequence of other mental disorders or medical condition (see Table 1).

According to these criteria, three types of ADHD may be identified:

a. Predominantly Inattentive Type: Inattention criteria are met but Hyperactive-Impulsive criteria not met for the past six months.

b. Predominantly Hyperactive-Impulsive Type: Hyperactive-impulsive criteria are met but inattentive criteria not met for the past six months.

c. Combined Type: if both criteria (Inattentive and Hyperactive-Impulsive) are met for the past 6 months.

Traditionally, ADHD has been conceptualized as a childhood disorder, and therefore the majority of research has focused on children with ADHD. However, recent studies have shown the persistence of behavioral symptoms in adulthood, pointing to the chronicity of ADHD into adulthood (Cubillo & Rubia, 2010).

Table 1. DSM-IV-TR diagnostic criteria for ADHD

A. Either 1 or 2:

1. **Six or more of the following symptoms of inattention have been present for at least 6 months to a point that is inappropriate for developmental level:**

   Inattention

   1. Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
   2. Often has trouble keeping attention on tasks or play activities.
   3. Often does not seem to listen when spoken to directly.
   4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
   5. Often has trouble organizing activities.
   6. Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework).
   7. Often loses things needed for tasks and activities (e.g. toys, school assignments, pencils, books, or tools).
   8. Is often easily distracted.
   9. Is often forgetful in daily
   10. activities.

2. **Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for developmental level:**

   Hyperactivity

   1. Often fidgets with hands or feet or squirms in seat when sitting still is expected.
   2. Often gets up from seat when remaining in seat is expected.
   3. Often excessively runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless).
   4. Often has trouble playing or doing leisure activities quietly.
   5. Is often "on the go" or often acts as if "driven by a motor".
   6. Often talks excessively.

   Impulsivity

   7. Often blurts out answers before questions have been finished.
   8. Often has trouble waiting one's turn.
   9. Often interrupts or intrudes on others (e.g., butts into conversations or games).

B. Some symptoms that cause impairment were present before age 7 years
C. Some impairment from the symptoms is present in two or more settings (e.g. at school/work and at home).
D. There must be clear evidence of clinically significant impairment in social, school, or work functioning.
E. 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 (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

2.2. Historic Introduction of Adult Attention Deficit and Hiperactivity Disorder

ADHD is a behavioral condition that is characterized by hyperactive, inattentive and impulsive behavior. While stories of restive and undisciplined children are as old as humanity itself, reports of behavioral disorders with ADHD-like symptoms have been recorded since the 1700s. Since that time, ADHD has been known as mental restlessness, a defect in moral control, minimal brain damage, hyperkinetic reaction of childhood and ADD.

The first example of a disorder that appears to be similar to ADHD was given by Sir Alexander Crichton in 1798. In his book “An inquiry into the nature and origin of mental derangement” he described a "mental restlessness" that seems very similar to the inattentive subtype of ADHD. He depicted the characteristics of this disorder, including inattentiveness and restlessness in children, which he called "the fidgets." His characterization of the disorder as ‘‘the incapacity of attending with a necessary degree of constancy to any one object’’ is consistent with the second symptom of criterion A1, Inattention (Chrichton, 1978).

In 1844, the German physician Heinrich Hoffmann created some illustrated children’s stories including “Fidgety Phil”, which is conceived nowadays as a popular allegory for children with ADHD. In the story of Fidgety Phil, Hoffmann illustrates a family conflict at dinner caused by the fidgety behavior of the son and culminating in his falling over together with the food on the table (Herzog, Herzog-Hoinkis & Siefert, 1995). Another story in Hoffmann’s ‘‘Struwwelpeter’’ is that of ‘‘Johnny Look-in-the-air’’, which was added in the 5th edition in 1847 (Seidler, 2004). In this story, Hoffmann depicts a boy

showing significant symptoms of inattention. Johnny was always ‘‘looking at the sky and the clouds that floated by’’ (Hoffmann, 1848) and was therefore ‘‘often easily distracted by extraneous stimuli’. Some authors are convinced that the stories of Johnny Look-in-the-air and Fidgety Phil are early descriptions of ADHD (Burd & Kerbeshian, 1988; Kopf, 2006; Thome & Jacobs 2004).

However, the Goulstonian Lectures of Sir George Frederic Still in 1902 are considered by many authors as the scientific starting point of the history of ADHD (Barkley, 2006; Conners, 2000; Palmer & Finger 2001; Rafalovich, 2001; Rothenberger & Neumärker, 2005). In 1902, Still, an english pediatrician, described 43 children who had serious problems with sustained attention and self-regulation, were often aggressive, defiant, and resistant to discipline, excessively emotional or passionate and showed little inhibitory volition, and also showed serious problems with sustained attention and could not learn from the consequences of their actions; though their intellect was normal. Dr. Still believed the unacceptable behaviors were caused by a "defect in moral control." He proposed that this defect was a genetic tendency toward moral deviation or the result of an injury at birth. This demonstration of a connection between brain damage and deviant behavior is considered highly influential regarding the further conceptualization of ADHD (Lange, Reichl, Lange, Tucha & Tucha, 2010).

In 1908, Tredgold observed a correlation between early brain damage, caused by birth defect or perinatal anoxia, and subsequent behavior problems or learning difficulties (Rothenberger & Neumärker, 2005). This was confirmed by the encephalitis lethargica epidemic spread in 1917 (Conners, 2000; Rafalovich, 2001). Many of the affected

children who survived encephalitis, subsequently showed abnormal behavior and was described as "postencephalitic behavior disorder" (Barkley 2006a; Rothenberger & Neumärker 2005). Observed features included a significant change in personality, emotional instability, cognitive deficits, learning difficulties, sleep reversals, tics, depression, and poor motor control (Conners 2000; Kessler 1980; Rothenberger & Neumärker 2005). This assumption of a causal connection between brain damage and symptoms of hyperactivity and distractibility was important to the further conceptualization of ADHD (Rafalovich 2001; Rothenberger and Neumärker 2005). During 1932, the German physicians Franz Kramer and Hans Pollnow, reported "On a hyperkinetic disease of infancy" on which the most characteristic symptom of affected children was a marked motor restlessness. The main symptoms of the "hyperkinetic disease" as described by Kramer and Pollnow are very similar to the current concept of ADHD (Lange et al., 2010).

Another important moment in ADHDs' history took place in 1937, when Charles Bradley reported a positive effect of stimulant medication (benzadrine) in children with various behavior disorders. He observed that it caused a striking improvement in behavior and school performance in some of the children (Brown, 1998; Gross 1995). Bradley started a systematic trial in 30 children and observed remarkable alterations in behavior (Bradley, 1937).

By that time, the notion of a physiological explanation of behavior disorders was remarkable (Rothenberger & Neumärker 2005). This led to the concept of "brain damage" (Kessler, 1980) and the idea that hyperactivity in children may be caused by

damage to the brain (Barkley, 2006a). Under the influence of the work of Strauss and Lehtinen (1947) and Strauss and Kephart (1955), it became general practice to infer brain damage solely from behavioral signs (Barkley 2006a; Ross & Ross 1976). In particular, they considered the symptom of hyperactivity as a sufficient diagnostic sign of underlying brain damage (Ross & Ross 1976). However, Clements and Peters (1962) later incorporated the concept of "minimal brain dysfunction" in order to separate the previous concept from its purely organic etiology. Hyperactivity was related to a certain brain dysfunction, though it did not consisted of brain damage it self. Additionally, environmental factors were included as important aspects of the condition's etiology (Ramos-Quiroga, 2009).

Nevertheless, minimal brain dysfunction was also criticized as too heterogeneous and was later to be replaced by multiple more specific and descriptive labels (hyperactivity, learning disability, language disorders) (Barkley 2006a; Rothenberger & Neumärker 2005). In this context, "hyperactivity the most striking item" and already stated in 1957 by Laufer, Denhoff and Solomons. Their idea of a "hyperkinetic impulse disorder" (Laufer et al. 1957) was continued in the 1960s, and the concept of a hyperactivity syndrome was generated (Barkley, 2006). In 1968, a definition of the concept of hyperactivity was incorporated in the official diagnostic nomenclature, i.e. the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) (Barkley, 2006a; Volkmar, 2003). The concept was labeled "Hyperkinetic Reaction of Childhood" (American Psychiatric Association, 1968).

In the 1970s, the predominant focus on hyperactivity was shifted toward an emphasis on the attention deficit in affected children (Rothenberger & Neumärker, 2005).

Virginia Douglas' (1972) work was very influential and initiated a complete change in the conceptualization of the disorder. With the publication of DSM-III in 1980 (APA, 1980) it was renamed "Attention Deficit Disorder (ADD) (with or without hyperactivity)" (Ramos-Quiroga, 2009). DSM-III considered hyperactivity as no longer an essential diagnostic criterion for the disorder and that the syndrome occurred in two types "with or without hyperactivity" (Conners, 2000). Deficits in attention and impulse control were, however, considered significant symptoms in establishing a diagnosis (Barkley, 2006a). In 1987, the DSM-III-R (APA, 1987) removed the concept of two subtypes and renamed the disorder "Attention deficit-Hyperactivity Disorder" (ADHD). The symptoms of inattention, impulsivity, and hyperactivity were combined into a single list of symptoms with a single cutoff score. However, with the DSM-IV (APA, 1994) ADHD was subdivided into three subtypes, i.e. a predominantly inattentive type, a predominantly hyperactive-impulsive type, and a combined type with symptoms of both dimensions. This categorization has been maintained in the DSM-IV-TR (APA, 2000). The definition of ADHD has therefore not been changed. Nevertheless, a new edition of the DSM is in progress. Critics have called for a validation of ADHD in adults (Fischer & Barkley, 2007; McGough & Barkley, 2004). Since the DSM-IV field trials for ADHD included only children and adolescents up to the age of 17 (Lahey, Applegate, McBurnett, Biederman & Greenhill, 1994) the utility of the DSM-IV criteria in the diagnosis of adults with ADHD has been challenged (Fischer & Barkley 2007).

Even though several authors, including Barkley (2006a), considered that it was Still who pointed to ADHD's persistence into adulthood, as it was consider a chronic disorder, the first studies on Adult with ADHD are only dated since 1960s.

By that time, the disorder was known as Minimal Brain Damage or Dysfunction (MBD) and its likely existence in adults was beginning to be considered because of the publication of several early follow-up studies demonstrating the persistence of symptoms of hyperactivity/MBD into adulthood in many cases (Mendelson, Johnson, & Stewart, 1971; Menkes, Rowe, & Menkes, 1967). Additionally, another source was the publication of research showing that the parents of hyperactive children were likely to have been hyperactive themselves and to suffer in adulthood from sociopathy, hysteria, and alcoholism (Cantwell, 1975; Morrison & Stewart, 1971). Later papers would further confirm this familial association of hyperactivity in which the biological parents of such children also showed attention, impulse control and activity level alterations (Alberts-Corush, Firestone & Goodman, 1986). These suggest that children with ADHD symptoms were likely to have parents with ADHD symptoms, therefore implying that ADHD could exist in adults.Another important evidence implying the existence of ADHD in adults were the published studies on adult patient samples that were believed to have hyperactivity or MBD. The first one appears to be Harticollis et al. (1968), who focused on the results of neuropsychological and psychiatric assessments of 15 adolescent and young adult patients (ages 15–25) seen at the Menninger Clinic. Their neuropsychological performance suggested evidence of MDB or moderate brain damage and their behavioral profile suggested many of the symptoms that Still initially identified in his own child cases, particularly impulsiveness, hyperactivity, concreteness, mood lability, proneness to aggressive behavior and depression. Some cases appeared to have this behavior uniformly or consistently since childhood.

A year later, Quitkin and Klein (1969) described two behavioral syndromes in adults that may be related to MBD. The authors studied 105 patients at the Hillside Hospital in Glen Oaks, New York, for behavioral signs of “organicity” (brain damage). They were studying behavioral

syndromes that might be considered soft neurological signs of central nervous system (CNS) impairment, as well as the results of electroencephalogram (EEG), psychological testing, and history that might differentiate these patients from other types of adult psychopathology. They selected cases that had a childhood history that suggested CNS damage, including early hyperactive and impulsive behavior they believed may be reflecting brain damage. These cases were further sorted into three groups based on current behavioral profiles: socially awkward and withdrawn behavior (*N* = 12), impulsive and destructive behavior (*N* = 19), and a "borderline" group that did not fit neatly into these other two groups (*N* = 11). Results indicated that an early history of hyperactive–impulsive–inattentive behavior was highly predictive of placement in the adult impulsive–destructive group, implying a persistent course of this behavioral pattern from childhood to adulthood. Of the 19 patients in the impulsive–destructive group, 17 had received a clinical diagnosis of Character Disorder (primarily emotionally unstable types) as compared to only five in the socially awkward group (which were of the schizoid and passive dependent types).

These results were in conflict with the widely belief that hyperactive–impulsive behavior tended to wane in adolescence. However, the authors argued that some of these children continued into young adulthood with this specific behavioral syndrome. Quitkin and Klein (1969) also took issue with Harticollis' psychoanalytic hypothesis that demanding and perfectionistic child rearing by parents might be related with this syndrome given that their impulsive–destructive patients did not uniformly experience such an upbringing. Aiming to keep Still's original position that family environment could not account for this syndrome, the authors hypothesized "that such parents would intensify the difficulty, but are not necessary to the formation of the impulsive–

destructive syndrome" (Hartcollis, 1968). Treatment involving educational procedures, as well as phenothiazine medication, became the treatment of choice.

The first paper focused specifically on adult cases defined as MBD, was Shelley and Reister (1972) work. These authors described 16 cases seen at an Air Force training base psychiatric clinic (ages 18-23) because of difficulties coping with their military basic training. These patients were described as having marked difficulties concentrating, being emotionally labile, fearing their loss of impulse control, and showing marked irritability as well as anxiety and self-depreciation. Problems with poor motor skills and sluggish reaction or response timing were noteworthy. While EEG and neurological exams were normal for gross findings of hard neurological signs, all showed evidence of "soft" signs of "neurointegrative disturbances" such as motor clumsiness, poor balance, confused laterality, and poor coordination. Psychological testing also revealed evidence of perceptual-motor problems and motor incoordination and timing. On clinical history, 14 of the 16 cases reported difficulties with temper tantrums and low frustration tolerance as children, with 12 (75%) reporting behavior consistent with hyperkinetic behavior syndrome, among other early behavioral symptoms. Later on, these problems with motor development and coordination have been well documented in children with ADHD (Barkley, 2006).

The following year, Pontius (1973) summarized the clinical observations of more than 100 adult cases of MBD. Many cases of adult MBD showed hyperactive and impulsive behavior and this author proposed that this might be related with frontal lobe and caudate dysfunction. Such dysfunction would lead to "a planning inability, goals

achievement difficulties, keeping such ideas in mind and to follow it through in actions under the constructive guidance of such planning" (Pontius, 1973). Later on, adults with MBD showed deficits indicative of dysfunction in this brain network. Such observations would prove quite prophetic. Two decades later, research demonstrated reduced size in the prefrontal–caudate network in children with ADHD (Castellanos, Giedd, Marsh, Hamburger & Vatuzis, 1996; Filipek, Semrud-Clikeman, Steingard, Renshaw & Kennedy, 1997). By that time, ADHD theories argued that neuropsychological deficits associated with it involved executive functions, such as planning, the control of working memory, rule-governed behavior, response fluency and flexibility (Barkley, 1997).

Later on, Morrison and Minkoff (1975) proposed that adult patients with explosive personality disorder or episodic dyscontrol syndrome might be the adult outcome of the hyperactive child syndrome. By 1976, Mann and Greenspan (1976) proposed that adults having MBD constituted a distinct diagnostic entity (adult brain dysfunction). They believed that MBD adults shared a basic impairment in attention, and that they were also likely to manifest problems with hyperactivity, impulsiveness, depression, and anxiety. They recommended the use of Leon Eisenberg's (1973) behavior questionnaire for hyperactive child syndrome as part of the diagnostic workup. This rating scale was actually developed by C. Keith Conners, who later become a mainstay of the evaluation of hyperactive children (Barkley, 1981). Mann and Greenspan (1976) also found that these symptoms were responsive to antidepressant medication (imipramine) or stimulants, echoing the same suggestion made by Hans Huessy (1974) about antidepressants and stimulants as useful medications for the treatment of these

hyperkinetic or MBD adults. About that time, the first real scientific evaluation of the efficacy of stimulants with adults having MBD was conducted by Wood, Reimherr, Wender, and Johnson (1976). They used a double-blind, placebo-controlled method to assess response to methylphenidate in 11 of 15 adults with MBD followed by an open trial of pemoline (another stimulant), as well as the antidepressants imipramine and amitriptyline. The authors found that 8 of the 11patients tested on methylphenidate had a favorable response and 10 of 15 showed a positive response to either the stimulants or antidepressants. Others in this decade and into the next would also make the case for the

existence of an adult equivalent of childhood hyperkinesis or MBD and the efficacy of using stimulants and antidepressants for its management (Gomez, Janowsky, Zetin, Huey, & Clopton, 1981; Mann & Greenspan, 1976; Packer, 1978; Pontius, 1973; Rybak, 1977; Shelley & Reister, 1972).

ater on, Gomez et al. (1981) reported 100 adult psychiatric patients of which 32% showed signs of childhood hyperactivity, attention deficits, and impulsivity; as compared to a 4% of the control group. Additionally, 20% also had symptoms consistent with adult hyperkinetic syndrome compared to none of their control group. The highest incidences of these symptoms were found in cases traditionally diagnosed as character disorder (47% had childhood and current signs of hyperkinetic syndrome).

Another important event is the development of diagnostic criteria for ADHD in adults. Paul Wender offered explicit criteria for the manner in which the diagnosis of ADHD in adults should be made. At the time, the clinical opinion was that children outgrew the disorder. Wender (1995) recognized that diagnostic criteria proposed for the syndrome

of childhood hyperactivity, as in DSM-II, (APA, 1968) or the later Attention Deficit Disorder, as in DSM-III, (APA, 1980), were not developmentally appropriate for adult patients. While both recognized that ADHD might be a residual condition in some adult, the widespread of its existence in adults was not recognized at the time nor was explicit criteria provided for doing so. Based on his empirical work, Wender (1995) developed an approach for diagnosis of ADHD in adults. These diagnostic guidelines, known as the "Utah criteria," required a retrospective childhood diagnosis, ongoing difficulties with inattentiveness and hyperactivity, and at least two of the following 5 symptoms: mood lability, irritability and hot temper, impaired stress tolerance, disorganization and impulsivity. Wender also developed a self-completed rating scale, the Wender Utah Rating Scale (WURS), to aid in the retrospective diagnosis of childhood ADHD (Ward, Wender, & Reimherr, 1993). These stipulations (childhood diagnosis, careful elucidation of current symptoms and the use of family informants) have become standard practice for many clinicians and investigators.

However, the Utah criteria have diverged further and further from current clinical conceptualizations of ADHD (McGough & Barkley, 2004). By design, the Utah criteria include only individuals with lifelong inattention and hyperactivity, and therefore exclude patients with the predominately inattentive ADHD subtype. Additionally, symptoms of irritability and hot temper were included in early conceptions of childhood ADHD, have proved to be semi-independent of ADHD symptoms, with different associated impairments, and closely associated with problems in the social environment. Therefore, with different developmental outcomes than do the symptoms of ADHD (Hinshaw, 1987; Loeber, Burke, Lahey, Winters, & Zera, 2000). This creates an

automatic confound of ADHD with oppositional defiant disorder, conduct disorder, and possibly the mixed mood dysphoric form of bipolar disorder. Likewise, the inclusion of symptoms of mood lability without further clarification may further confound the delineation of this disorder from other mood disorders in adulthood. Additionally, the Utah criteria exclude the diagnosis of ADHD with coexisting major depression, psychosis, or severe personality disorder, but studies indicate that a significant minority

of children and adults with ADHD are likely to have major depression or dysthymia (20-27%) and personality disorders (11-24%) by adulthood (Barkley, 2006; Fischer, Barkley, Fletcher &Smallish, 2002; Murphy & Barkley, 1996a). Moreover, adults who self-refer to clinics may have even higher rates of anxiety disorders and depression than do children with ADHD followed to adulthood (Murphy & Barkley, 1996b; Shekim, Asarnow, Hess, Zauha, & Wheeler, 1990). A further problem was the initial lack of adequate norms for adults on the WURS, so as to more precisely determine an empirically based cutoff score for developmental deviance of symptoms than those based on clinical experience.

For these reasons, the Utah criteria have declined in use among investigators and clinicians in favor of more current DSM-IV criteria. For instance, later and better-constructed scales with adult norms such as those developed by Conners, Erhardt, and Sparrow (1998), others that were more aligned with the DSM symptoms, designed by Brown (1996) and those developed by Barkley & Murphy (1998; 2006b) that offered DSM based scales as alternatives to the WURS for clinical practice.

During the 90's, several clinical attention programs and research were also being developed in Europe regarding adult ADHD. Norway was the first country that created a national center specialized in the diagnostic and treatment of adults with ADHD. At the present, any mental health center in this country is capacitated to diagnose and treat adults with ADHD. In The Netherlands there was also an important increase in adult ADHD knowledge, mostly related to the work of the psychiatrist Sandra Kooij, therefore a national network of specialist in the disorder was created by that time (Kooij, 2006). Something similar happened in Germany, since several health professionals were developing interest in adult ADHD. The most relevant contribution was the research work performed by Krause, Krause and Trott (1998; 1999) focused in the incipient neuroimaging field. By the year 2002, Spain also developed the Adult ADHD Integral Program, in the Vall d'Hebrón Hospital in Barcelona. All this contributed in the creation of the European Adult ADHD Network (www.adult – adhd.net), as well as in other research collaborations, including European and American countries, focused in both the genetic and clinical study of adult ADHD.

Another relevant moment in the history of adults with ADHD was the development of a nonstimulant medication, atomoxetine. Spencer, Biederman, Wilens, Prince and Hatch (1998), using a double-blind placebo controlled design, demonstrated that atomoxetine was well tolerated and significantly more effective than placebo in reducing clinical symptoms of ADHD. These initial findings led to large multi-site trials of atomoxetine in adult ADHD, evaluating more than 536 adults with ADHD and that also proved the drug to be efficacious for ADHD management in adults (Michelson, Adler, Spencer, Reimherr & West, 2003). These studies are the largest ever done in evaluating a

medication for adults with ADHD. Later, stimulants such as methylphenidate and mixed amphetamine salts would eventually be studied more thoroughly as well for adults with ADHD (Spencer, Biederman, Wilens, Doyle & Surman, 2005; Spencer, Biederman, Wilens, Faraone and Prince, 2001). New delivery systems have also been recently developed that permit greater sustained therapeutic action across the day than did immediate release preparations.

However, in spite of the increasing research and knowledge in the topic, the Diagnostic and Statistical Manual of Mental Disorders (DSM) continues to focus on ADHD as a childhood disorder. Even though the DSM-IV Text Revision (TR) acknowledges symptoms that persist into adulthood, the criteria were developed and validated using mostly male children and adolescents. Importantly, the development of the up-coming DSM-V provides a great opportunity to revisit the criteria for adult ADHD, based on the growing body of new research in adult ADHD.

2.3 Epidemiology

ADHD is consider one of the most frequent childhood onset psychiatric disorder adn epedemiological data showed a wide heterogenity, indicating a prevalence range from 8 to 12% in scholar ages (Faraone, Sergeant, Gillberg & Biederman, 2003). Polanczyk,de Lima , Horta, Biederman & JRohde (2007) indicated a pediatric world prevalence of 5.2% in this disorder.

Until recently, ADHD was thought to decline in adolescence, when a remission of the symptoms took place. However, nowadays it is known that two thirds of ADHD children will continue presenting symptoms in the adult age. According to the criteria of the DSM-IV-TR, 15 % will maintain the complete diagnosis and 50 % will do so partially (APA, 2004).

Globally, symptom`s persistence have been observed in up to 65% of cases (Kooij, Bejerot, Blackwell, Caci, & Carpentier, 2010), with a prevalence of 3–4% of the adult population (Pliszka, 2003). However, the unclear validity of DSM-IV diagnostic criteria for this condition can lead to reduced prevalence rates by underestimation of the prevalence of adult ADHD.

Therefore, epidemiological data on adult populations have been less available. More recently, the National Comorbidity Survey Replication estimated prevalence and correlates of clinician-assessed adult ADHD, with a probability subsample (N=3,199) of 18-44-year-old respondents. The estimated prevalence of current adult ADHD was 4,4% (Kessler, Adler & Barkley, 2006).

These results are homogeneous with the 3,4% obtained in the study performed by the OMS (Fayyad, de Graaf & Kessler, 2007). A total of 11,442 subjects, aged form 18-44 years old, and recluted from Germany, Belgium, Colombia, Spain, EE.UU, France, Italy, Líbano and México participated in the study. The range of prevalence of the disorder was between 1,2-7.3%, but interestingly, the prevalence in the more developed countries was of 4.2%, a very similar result to the one obtained by the NCS-R.

Additionally, a recent metanalysis on ADHD prevalence in adulthood had been published, on which a media of 2,5% in the general population is indicated (Simon, Czobor, Balint, Mészaros & Bitter, 2009). Nevertheless, the authors concluded that this prevalence might be some how conservative, since the DSM-IV-TR criteria tend to infra-estimate ADHD's diagnose in adulthood.

Regarding gender distribution, adult ADHD is more frequent in males than females, even though with a lower proportion than the observed in childhood. In adults, the observed proportion male-female is 1,6 (Fayyad et al. 2007; Kessler et al. 2006), while in children varies between 3:1 and 9:1 (Staller & Faraone, 2006). In non-clinical pediatric samples, prevalence has been estimated to be 2,45 times more frequent in males than females (Polanczyk et al., 2007).

The influence of ethnic and socioeconomic characteristics en adult ADHD has been less studied (Polanczyk & Rohde, 2007). The study performed by the OMS indicated that less educational level have been associated with patients with ADHD as compared to healthy subjects (Fayyad et al. 2007). Additionally, higher frequency of this disorder was observed in white-not hispanic than in hispanic and africanamerican participants, according to the NCS-R (Kessler et al. 2006).

2.4 Clinical aspects of Adult ADHD

2.4.1 Clinical manifestations in adulthood

Manifestations that characteristically appear in adults with ADHD are difficulty in following directions, remembering information, concentrating, organizing tasks, or completing work within time limits. If these difficulties are not managed appropriately, they can cause associated behavioural, emotional, social, vocational and academic problems (Biederman et al., 2008a).

For instance, academic impairments are very common in adults with ADHD. They probably had a history of poorer educational performance and been underachievers, had more frequents school disciplinary problems and had repeated a grade or dropped out of school more often. Work difficulties have also been related with adult ADHD, therefore these patients are very likely to change employers frequently and perform poorly, as well as showing less job satisfaction and fewer occupational achievements.

Social impairments have also been associated with adulthood ADHD, frequently related to impulsiveness symptoms. Adults with ADHD tend to have driving violations such as being cited for speeding, having their license suspended, and being involved in more crashes. They usually rate themselves and others as using poorer driving habits

Relationships difficulties are also very frequent on these patients; they have more marital problems and multiple marriages. Therefore, a higher incidence of separation and divorce has been established. (Biederman et al., 2008a).

Another problem in the social field is the use of illegal substances, which adults with ADHD are likely to suffer. Smoking cigarettes is also more frequent on this population. Self-report psychological maladjustment is also very common. Importantly, much of this functional impairment diminishes with remission of the disorder and can be mitigated by appropriate pharmacological and/or psychological treatment.

2.4.2 Comorbidity

Comorbidity with other psychiatric disorders is frequent is both children and adult with ADHD (Fayyad et al. 2007). A myriad of comorbid conditions such as impulse-control/personality, anxiety, mood, substance use, learning, and sleep disorders overlap with adult ADHD. Furthermore, a number of such conditions have symptoms that can mimic those of ADHD including hyperactivity, impulsivity, inattention, and disruption of circadian rhythms adding to the complexity of recognition and diagnosis of ADHD in adults.

The profile of comorbid disorders in ADHD is practically the same through life, but there is a higher frequency of personality disorders and substance use in adulthood (Biederman, Faraone, Spencer. Wilens, & Normans, 1993). In adults with ADHD, is very common the presence of use of substances disorder, antisocial personality dirsorder, affective disorders and anxiety disorders (Biederman, et al. 1993; Birnbaum, Kessler, Lower, Secnik, & Greenberg, 2005; Downey, Stelson, Pomerleau, & Giordani, 1997; Fayyad et al. 2007; Kessler et al. 2006; Kessler, Adler, Barkley, Biederman & Conners 2005; McGough, Smalley, McCracken , Yang, & Del'Homme 2005; Miller,

Nigg, & Faraone, 2007; Murphy, Barkley & Bush, 2002; Secnik, Swensen & Lage, 2005; Sobanski et al., 2008; Weiss, Hetchman, Milroy, & Perlman 1985).

Miller et al. (2007) evaluated 152 adults with ADHD and 211 healthy subjects. A comorbidity evaluation was performed using the SCID I y II. The results indicated a

57% frequency for use substance disorder, 53% for affective disorders, 30% for anxiety disorders and antisocial personality disorder appeared to have an11% comorbidity. The authors observed significant differences in the frequency of these disorders in comparison to the control group. As for personality disorders, specifically, ADHD patients showed a higher prevalence for cluster B disorders (21,9-20,3%) y C (23,4-20,3%) (Miller et al., 2007).

There is also evidence that indicates comorbidity between ADHD and bipolar I disorder, which has been documented in clinical and epidemiological studies, including children and adults, and in diagnosed ADHD and bipolar I patient samples (Wozniak et al., 2010).

Interestingly, it has been observed a comorbidity pattern for to each ADHD subtype. The first study to evaluate this pattern observed that patients with combined subtype presented a higher frequency of use substance disorder, dissocial disorder and oppositional defiant disorder as compared to inattentive subtype (Millestein, Wilens, Biederman & Spencer, 1997). Moreover, McGonough et al. (2005) also indicated that

adults with combined and impulsive-hyperactive ADHD showed higher comorbidity with substance use disorder than adults with inattentive subtype. Sprafkin, Gadow , Weiss , Schneider and Nolan (2007) observed as well that oppositional defiant disorder, dissocial disorder and substance use disorder were more present in subjects with hyperactivity-impulsivity symptoms than inattentive participants. ADHD adults with inattentive subtype presented minor clinical risk than hyperactivity subjects.

2.4.3 Pharmacology

Stimulants (methylphenidate and dexamphetamine) are first choice medication treatments for ADHD in children and adults, based on an extensive and still growing research (Banaschewski, et al., 2006). Atomoxetine is usually considered the second line treatment, followed by other non-stimulants like bupropion, guanfacine, modafinil and tricyclic antidepressents, based on efficacy outcomes in controlled studies in different age groups (Adler et al., 2009).

Stimulants are effective in about 70% of patients with ADHD in controlled studies (Biederman & Faraone, 2006; Spencer et al., 2005). These agents are thought to block reuptake of norepinephrine and dopamine into the presynaptic neuron, thereby increasing extraneuronal catecholamines (Fone & Nutt 2005; Arnsten, 2006). A recent European study of adults with ADHD showed the effectiveness of methylphenidate over a period of six months, in the longest double blind placebo controlled trial to date (Rosler, Fischer, Ammer, Ose, & Retz, 2009). Stimulant treatment improves the symptoms and impairing behaviours associated with ADHD, and may also be effective on related problems such as low self-esteem, anger outbursts, mood swings, cognitive

problems and social and family functioning (Bouffard, Hetchman, Minde, & Iaboni-Kassab, 2003; Kooij, et al., 2004).

Types of stimulants

In the United States, more than ten different stimulant preparations have been developed for treatment of ADHD, the most recent being long acting formulations of oros-methylphenidate, mixed amphetamine salts, dexmethylphenidate and lis-dexamphetamine (Biederman et al., 2006; Madaan et al, 2008; Weisler et al., 2006). These improvements were necessary because of the very short half-life leading to relatively short duration of symptom control from immediate release methylphenidate (two to four hours) and dexamphetamine (three to five hours). The requirement for a longer duration of activity in adults requires repetitive dosing with immediate release stimulants, of between three to four doses in most cases, and more often in others, to avoid rebound symptoms and for adequate control of ADHD symptoms during the day and evening (Kooij et al., 2004). Compliance to such frequent dosing regimens is however poor in ADHD patients due to forgetfulness, inattentiveness and self-organisation problems, leading to daily instability by frequent rebound symptoms and ineffectiveness of the treatment (Kooij et al., 2004; Ramos-Quiroga, Daigre, Valero, Bosch, Gómez-Barros, Nogueira, Palomar, Roncero & Casas, 2008). Therefore, long-lasting, formulations are preferred for reasons of adherence to treatment, for the protection against abuse, to avoid rebound symptoms, for safer driving, and to provide cover throughout the day without the need for multiple dosing.

Second line pharmacotherapeutic treatments

For adults with ADHD who do not respond to stimulant therapy or who have a condition in which a stimulant is contraindicated, the non-stimulant atomoxetine that is licensed for child and adult ADHD in the USA is an appropriate alternative (Rostain et al., 2008). Atomoxetine has an effect size of around 0.4 in adults (Faraone & Biederman, 2005) a duration of action of 24 hours, and no abuse potential (Kollins, et al., 2008). Atomoxetine may be indicated in patients with comorbid substance use disorders, emotional dysregulation or social anxiety (Adler et al., 2009). Other choices comprise medications like long acting bupropion, modafinil and guanfacine, that have all been investigated in ADHD (Wilens et al., 2005; Biederman, Makris, Valera et al., 2008; Reimherr, Hedges, Strong, Marchant, & Williams, 2005). Tricyclic antidepressants like Desipramine, an imipramine metabolite, has been shown to be effective in adults with ADHD (Wilens et al, 1996). However, these medications must be considered fourth line agents due to their side effects, limited value in treating the symptoms of inattention and relatively low effect size compared to stimulants in the treatment of ADHD (Popper, 1997).

However, it is important to high light the fact that now a days, most clinicians and experts recommend multimodal treatment, comprising of pharmacotherapy psychoeducation, coaching and/or cognitive behavioural therapy; and ideally involving the adult patient's partner, family or close friends.

2.5 Etiology

Both genetic and environmental etiologies have been proposed to account for the behavioral and neuropsychological characteristic of ADHD. This disorder has been conceived as a complex condition with a polygenic base, on which the contribution of several minor effect genes may influence in the expression of the disorder and also interact with environmental factors (Comings et al., 2000; Thapar, Langley, Owen, & O'Donovan , 2007). For this reason, the combination functional polymorphic variants in a certain number of genes might create susceptibility to the disorder that would not be expressed in all enviroments (Bayes et al.., 2005). Therefore, it has become increasingly clear that ADHD might result from the interplay of genetic and environmental risk factors, as dopamine dysfunction as the primary cause of ADHD (Tripp and Wickens). The dopamine dysfunction theory will be detail in following sections.

Genetic Bases for Adult ADHD

Heritability

Genetic research on ADHD started with the finding that hyperactivity tends to aggregate in families. Family studies have detected higher frequency of ADHD in families with an affected member than in families without any ADHD members (Ramos, 2009). Specifically, several studies suggest that the risk for ADHD may be greater among the first-degree relatives of probands with ADHD (Faraone & Doyle, 2000) and, moreover, this tendency increases when the patient's condition persists into adolescence and adulthood, in comparison to the relatives of probands with ADHD that remits before adulthood (Franke et al., 2012).

Additionally, twin studies estimated ADHDs' heritability to be around 50–80% in monozygotic twins and 30-40% in dizygotic twins (Ramos-Quiroga, Ribases-Haro, Bosch-Munso , Cormand-Rifá, & Casas, M. 2007; Thapar et al., 2007b). Longitudinal twin studies show that the continuity of symptoms from childhood through to adolescence is predominantly due to common genetic influences.

Adoption studies found that ADHD is transmitted mostly to biological relatives. Sprich, Biederman, Crawford, Mundy, & Faraone (2000) observed that 6% of adoptive parents of ADHD children, as compared to 18% in biological parents and 3% in controls; which strongly implicates genetic factors as the main causal influences on familial risk for the disorder.

Interestingly, a higher heritability has been described for hyperactivity-impulsivity symptoms than for inattentive (McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007). In conclusion, all mentioned findings suggest that for both child and adult ADHD the disorder is best perceived as the impairing extreme of a quantitative trait (Larsson, Lichtenstein & Larsson, 2006).

Molecular Genetics

For the last years, there has been an important increase of studies focused on the specific identification of genetic polymorphisms, or genetic loci, implicated in ADHD. Most of these studies are based on clinically assessed patients. The majority of studies examined polymorphisms in dopaminergic and serotonergic genes, focusing

predominantly on the dopamine transporter (SLC6A3/DAT1) and the dopamine receptor D4 (DRD4), both asoosciated with ADHD) (Albayrak , Friedel, Schimmelmann, Hinney & Hebebrand).Therefore, different methods are used for these purposes, mostly association and linkage studies, (Ramos, 2009).

Association studies are used for the analysis of polymorphisms in candidate genes, in chromosome regions of interest (genomic segments identified *apriori* through genetic linkage studies) or even in the whole genome. These studies require a previous knowledge of the biological bases of the disorder and this may implicated certain difficulties. However, technological advances have developed the Genome-Wide Association Studies (GWAS), which identify genetic risk factors through the analysis of millions of SNPs that covers most of the human genome, and without a previous hypothesis of the pathologic underlying mechanisms (Albayrak et al., 2008). In ADHD studies, at first studies were mostly focused on the dopaminergic system, specifically, the gen of the dopamine transporter (DAT1) and the (DRD4), due to their implication in the action mechanism of psychostimulants drugs commonly prescribed for ADHD (La Hoste et al., 2006). However, further genes have also been studied (DRD5, DRD3, DRD2, DRD1, TH, DDC, COMT, DBH, 5-HTTLPR, 5-HTR1B, 5-HTR2A, SNAP-25, TPH, MAOA, MAOB, NET1, ADRA1C, ADRA2A, CHRNA47, CHRNA4, BDNF, GRIN1, 2AD) as well as other possible implicated neurotransmission systems (Dorval et al., 2007; Xu, Mill, Zhou, Brookes, Chen, & 2007). So far, ADHD studies have not found specific single nucleotide polymorphism (SNP) at the required significance level (Lasky-Su et al., 2008a; Lasky-Su et al., 2008b; Neale & Faraone 2008, Sonuga-Barke, et al., 2008). However, technique is considered promising in order to improve our

knowledge on ADHD genetics, but more homogenous samples of ADHD patients are needed.

As for linkage studies, the objective is to identify genetic *loci* in susceptible families, mostly with affected children. This way it is possible to study specific chromosome regions associated with the disorder and extrapole the genes they include. As well as association studies, this technique may be focused in *a priori* regions or genes or the whole genome (Ramos, 2009). A recent metanalysis on linkage studies on ADHD, indicated a pronounced association with the locus 16q23 (Zhou et al., 2008b).

Specifically, a neuroimage-genetic study found that the 7repetition allele of the variable number of tandem repeats (VNTR) of the 3 axon of the DRD4 gene might be associated with grey matter (GM) volume decreases in dorsolateral prefrontal cortex (dlPFC) and the cerebellum in adults with ADHD (Monuteaux et al., 2008). Additionally, further research has related several neuropsychological tasks and lower intellectual capacities with polymorphisms of the gene DAT1 (Barkley, Smith, Fischer e& Navia, 2006; Boonstra, et al., 2008; Mill et al., 2006).

Other receptors' genes and dopaminergic enzymes have also been studied. The D5 receptor showed a significant correlation with the DRD5 gene, mostly in male-patients with inattentive symptoms or combined (Johansson et al., 2008). In further studies, the Catechol-O-Metiltransferance (COMT) gene and the noradrenaline transporter (SLC6A2 o NET1) are related with symptoms severity in an specific combination of 2

haplotypes of the COMT and SLC6A2, but not individually (Retz et al., 2008). Another study that used haplotypes found that several polymorphisms of the COMT gene are related to hyperactivity-impuslsivity symptoms (Halelland, Lundervold, Halmoy, Haavik & Johansson, 2009).

The CLOCK gene has also been related to ADHD. This gene regulates the circadian clock and a study with adults with ADHD relates it with the SNP polymorphism rs1801260 (Kissling et al., 2008). Finally, the gene of the neuronal nitric oxide synthase (nNOS) has been related to the impulsive disorders such as ADHD. The short allele of the VNTR in the nNOS1 gene was related as well with the presence of ADHD, and, using evoked potentials, the effect of this allele was correlated with decrease activation in the anterior cingulated cortex while performing a CPT task, suggesting prefrontal medial alteration on these subjects (Reif et al., 2009).

Environmental Factors

For the last years, there has been an increase interest in reduce ADHDs heterogeneity. Therefore, the study of the interaction genes-environment has become an important focus for research. The reciprocal relation between genes and environment might attenuate the risk that a certain disorder, associated to a specific gene, might express in particular environmental conditions (Rutter, Moffitt & Caspi, 2006). Environmental factors associated with ADHD are mostly prenatal factors such as alcohol exposure, nicotine, drugs, arterial hypertension and mother stress during the pregnancy, as well as underweight at birth.

Specifically, there is evidence that suggests a possible interaction between prenatal exposure to nicotine (Becker, El-Faddagh, Schmidt, Esser, & Laucht, 2008;) and alcohol (Brookes et al., 2006), finding an interaction between dopaminergic genes polymorphisms and augmentation in ADHDs' symptoms.

Additionally, family environment has also been associated to greater genetic risk in ADHD (Propper, Willoughby, Halpern, Carbone & Cox, 2007; Sonuga-Barke et al., 2008). Even though not conclusive, there has been observed certain correlation between vital stress factors and ADHD symptoms, specifically with the 5-HTT gene (Muller, Mandelli, Serretti, DeYoung, & De Luca., 2008; Retz et al., 2008a). No relation has been observed between the COMT and NET genes (Retz et al., 2008b). Finally, vital stressors and psicosocial adversity have also been associated with the DAT1 gene. In a study performed by Laucht, Skowronek, Becker, Schimidt, & Esser (2007) adolescents who lived in more adverse environments, and, also presented VNTR polymorphisms of this gene, shown higher inattention and hyperactivity punctuations.

Neurochemical Basis

Even though the neurobiological mechanisms underlying ADHD are still unclear, a great number of studies suggest that dopaminergic and noradrenergic dysfunction might be related to the physiopathology of this disorder, due to their implication in fronto-striatal circuit's modulation (Del Campo, Chamberlain, Sahakian & Robbins, 2011). Dopamine (DA) and Noradrenaline (NA) are known for their important role in

prefrontal related executive functions (EF) appropriate functioning, which are known to be affected in ADHD patients. Recently, literature suggests a decline in dopamine levels is associated with adult ADHD. Additionally, adults with this disorder showed a blunted response to the drug methylphenidate, which acts by increasing dopamine level.

Specifically, the most important dopaminergic innervation to the prefrontal cortex (PFC) came from the mesolimbic circuit, constituted by tegmental ventral area (TVA) projections to the PFC, as well as the amygdala and the nucleous accumbens (Volkow, et al., 2009). Several pathologies, including ADHD, have been associated with alterations in dopaminergic release in this circuit. Many studies have focused in the role of DA in the PFC, since D1 dopaminergic receptors are predominant on this region (Fuster, 2008). Additionally, animal studies showed that excessive or escase stimulation of these receptors may cause deterioration of the PFC functioning, specifically, it may cause alterations in the regulation of functions related to working memory and attention (Arnsten & Pliska, 2011). D2 receptors, such as the DRD4 have also shown increase levels in the PFC, which has been associated to the elevated affinity of NA for this receptor (Arnsten & Li, 2005). More recently, a positron emission tomography (PET) study in un-medicated, adult ADHD patients, found decreased levels of DAT and DRD2 and DRD3 receptors in subcortical regions of the left hemisphere, including the nucleous accumbens, caudate and mesencephale (Del Campo et al, 2011).

As for NA, the main afferent circuit to the PFC originates in the Locus Coeruleus. NA receptors α2A are the most abundant in this region (Arnsten & Pliska, 2011). Only a

balanced and adequate stimulation of these receptors might improve the appropriate functioning of attentional, behavioural and emotional processes (Del Campo et al., 2011; Wang et al.,2007). In addition, studies on primates have indicated that blocking this receptors might result in hyperactivity, impulsivity and working memory dysfunction (Arnsten & Li, 2005). Human studies have revealed that poor activity levels of dopamine beta hydroxylase enzyme, which synthesises the NA, showed to be related to attentional difficulties, impulsivity and EF alterations (Arnsten & Pliska, 2011). Together, all these finding seem to point ADHDs' physiopathology as a fronto-striatal circuit dysfunction.

Finally, the serotonergic system has also been implicated in ADHD physiopathology. Recent research has shown that symptoms related to this disorder, predominantly linked to changes in catecholaminergic neurotransmission, are also affected by variation in serotonin-related genes (Zimmermann et al., 2012). The neurotransmitter serotonin (5-HT) has been linked to the neurobiological underpinnings of aggressive behavior by a considerable body of animal research, suggesting that low central nervous system 5-HT activity is associated with aggression and impulsivity (Taub & Vickers., 1994; Angoa-Pérez et al., 2012). Additionally, different studies indicate alterations in cerebrospinal fluid concentration of the 5-hydroxyindoleacetic acid consistently associated with clinical characteristics of ADHD such as hyperactivity, aggression and impulsive behaviors (Castellanos & Acosta, 2004; Spivak, Vered, Yoran-Hegesh, Averbuch, & Mester 1999). Finally, even thought that drugs with serotoninergic activity are not the first choice treatment for ADHD, they might decrease symptoms of this condition (Solanto, 1998).

Positive results have been published on selective serotonin reuptake inhibitors, dual antidepressants, tricycle antidepressants and monoamine oxidase inhibitors (Findling, et al., 2007; Malthotra & Santosh, 1998; Mukaddes & Abali 2004; Popper, 1997; Rubinstein, Malone, Roberts, & Logan, 2006).

2.6 Neuropsychology of Adult ADHD

From a neuropsychological perspective, a considerable amount of deficits are associated with ADHD (Barkley & Murphy, 1998): poor academic performance, learning disorders, subtle cognitive deficits, conduct disorders, antisocial personality disorder, poor social relationships, and a higher incidence of anxiety and depression symptoms, particularly in adulthood (Wilens, Spencer,& Biederman, 2001).

Therefore, neuropsychological studies of ADHD in both adults and children, implicate a broad range of processes. These include executive dysfunctions in inhibitory response and working memory, and also non-executive deficits such as perception, memory and timing. Additionally, alterations in motivational processes have also been described in this population (Sonuga-Barke et al., 2010).

According to Barkley (1999) ADHD's core impairment is response inhibition, related to abnormalities in the prefrontal cortex and connections to other brain regions, mostly to basal ganglia.

Response inhibition is defined by the capacity to delay a prepotent response to an event, to interrupt ongoing responses given feedback about performance, and to inhibit responding to sources of interference when engaged in tasks requiring self-regulation and goal-directed action (Barkley, 1999). See Figure 1.

According to this author, poor response inhibition affects four intermediate executive functions:

a. Working memory: The ability of holding facts in mind while manipulating information; accessing facts stored in long-term memory
b. Self- regulation of affect/motivational arousal: Refers to emotional self -control, social perspective taking, ability to express emotions internally and intrinsic motivation directed at long term-goals.
c. Internalization of speech: Allows formulating rules and plans in order to solve problems. Related to internal reflection, description, questioning and instructing. Also creates internal rules for governing behavior.
d. Reconstitution: Ability to create complex and novel behavior sequences in order to attain future goals (generation of fluency). Involves analysis and synthesis capacity.

Such abnormalities might result in a lack of motor control, fluency and syntax. Therefore, deficits in response inhibition and executive dysfunctioning might lead to impairments in control, timing, persistence, flexibility and goal directed actions. Additionally, problems with sustained attention might result from a limited intrinsic motivation (Barkley, 1999).

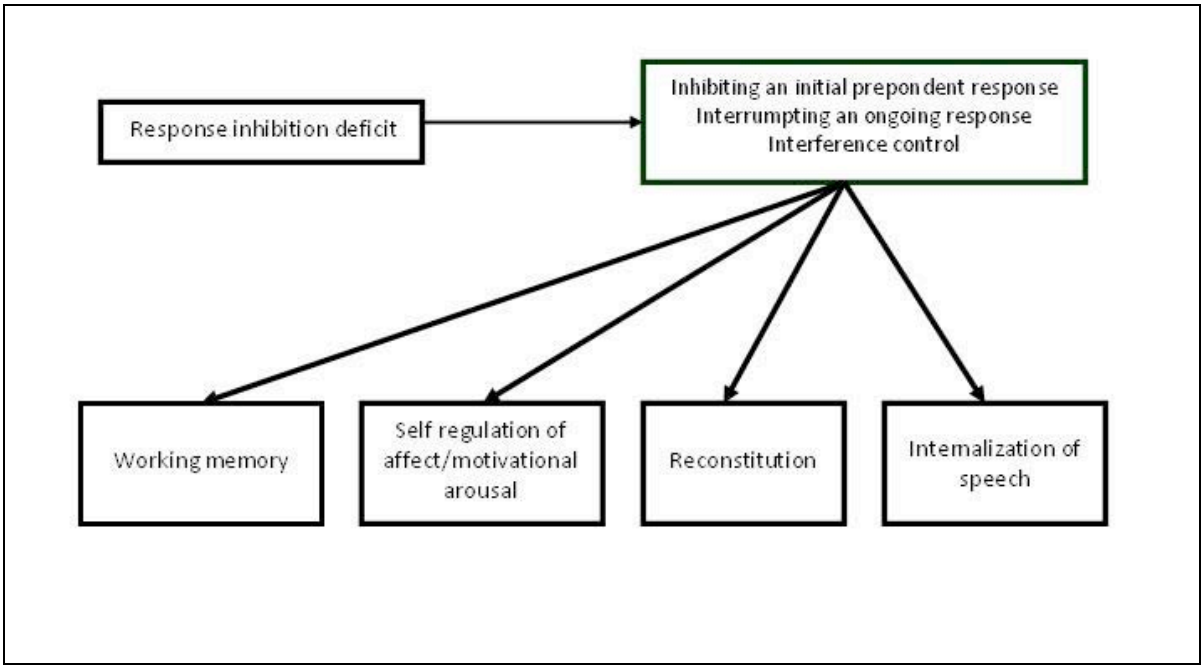


Figure 1. Barkley's model proposes response inhibition as ADHD's core impairment, also affecting other intermediate executive functions.

Accordingly, studies have emphasized on poor behavioural inhibition as the central impairment of the disorder. From a neuropsychological point of view, ADHD's literature indicates deficits in more affective executive functions, known as "hot executive functions" which are mostly involved in behavioural inhibition and motivation. Furthermore, deficits have also been observed in the "cool" aspects of executive functions such as self-regulation, working memory, planning, and cognitive flexibility. Specifically, the "hot executive functions" are associated with ventral and medial regions of the prefrontal cortex (including the anterior cingulated cortex) , namely "hotbrain"; and the "cool executive functions" are associated with the dorsolateral prefrontal cortex and are called "coolbrain" (Sonuga Barke, 2002; 2003).

For this reason, the dual pathway model explains the neuropsychological heterogeneity in ADHD in terms of dissociable cognitive and motivational deficits that affect some but not affect every patient. This model considers the hypothesis of delay aversion (as a motivational aspect) which refers to the tendency to choose a smaller immediate reward rather than wait for a larger delayed reward (Sonuga-Barke, 2002; 2003).

Accordingly, escaping from delay constitutes the most important reinforcement due to the fact that they perceive delay as very unpleasant. Therefore, when ADHD patients are not able to reduce delay, they tend to disconnect and let time passes by directing their attention toward other stimuli or incrementing stimulation level through movement (Albert, López-Martín, Fernández-Jaén & Carretié, 2007).

Therefore, the dual pathway model distinguishes two alterations in independent neural systems: fronto-striatal and mesolimbic systems. However, recent studies point to deficits in temporal processing as a third dissociable neuropsychological component of ADHD (Sonuga-Barke et al., 2010) (Figure 2).

For the last years, convergent data from neuroimaging, neuropsychology, genetics and neurochemical studies consistently point to the involvement of the frontostriatal network as an important contributor to the pathophysiology of ADHD. The frontostriatal network involves the lateral prefrontal cortex, the dorsal anterior cingulate cortex, the caudate nucleus and putamen. In addition, recent literature demonstrates abnormalities affecting other cortical regions and the cerebellum (Edmond V, 2009). Specifically, recent studies indicate sensorimotor deficits and alterations in the

processing of these stimuli (Duerden, Tannock & Dockstader, 2012; Wang et al.,; 2009) as well as timing functions deficits (Sonuga-Barke, Bitsakou & Thompson, 2010). Specifically, timing functions have been related with impulsiveness, as a premature, impatient and delay aversion response pattern that does not consider consequences of one's act, known as poor temporal foresight (Rubia et al., 2001). Additionally, ADHD patients have shown deficits in motor timing, time estimation and temporal foresight (Noreika, Falter & Rubia, 2013; Rubia, Halari, Christakou, & Taylor, 2009a; Toplak, Dockstader & Tannock, 2006).

Concretely, neuropsychological findings indicate that ADHD children are characterized by a limited executive functioning, specifically in tasks that imply both cognitive and motor inhibition, in addition to sustained attention (Rubia et al., 2001; Rubia, Smith & Taylor, 2007; Rubia et al., 2009b). Motivational deficits have also been found (Luman, Oosterlaan & Sergeant, 2005).

Furthermore, such cognitive and motivational limitations are likely to persist even in the adulthood (Biederman et al., 2007). As for adults with ADHD, the most common findings are abnormalities in motor response and interference inhibition (Bekker et al., 2005; Harvey, Epstein & Curry, 2004), working memory (Boonstra et al., 2005; Dige, Maahr, & Backenroth-Ohsako, 2010), and also sustained, selective and flexible attention (Boonstra et al., 2005; Epstein, Conners, Sitarenios & Erhardt, 1998; Malloy-Diniz, Fuentes, Leite, Correa & Bechara, 2007). Additionally, studies on alterations in emotional processes have also been conducted (Malloy-Diniz et al., 2007) as well as on time processing deficits (Sonuga-Barke, 2010).

Accordingly, studies conducted with fMRI – both with children and adults- had focused on the neuroanatomical and functional pathophysiology of the mentioned regions. However, such abnormalities might be related somehow with comorbility and medication (Cubillo and Rubia, 2010). Finally, it is important to mention that there are few neuroimaging studies of adults with this pathology in comparison of those conducted with children.

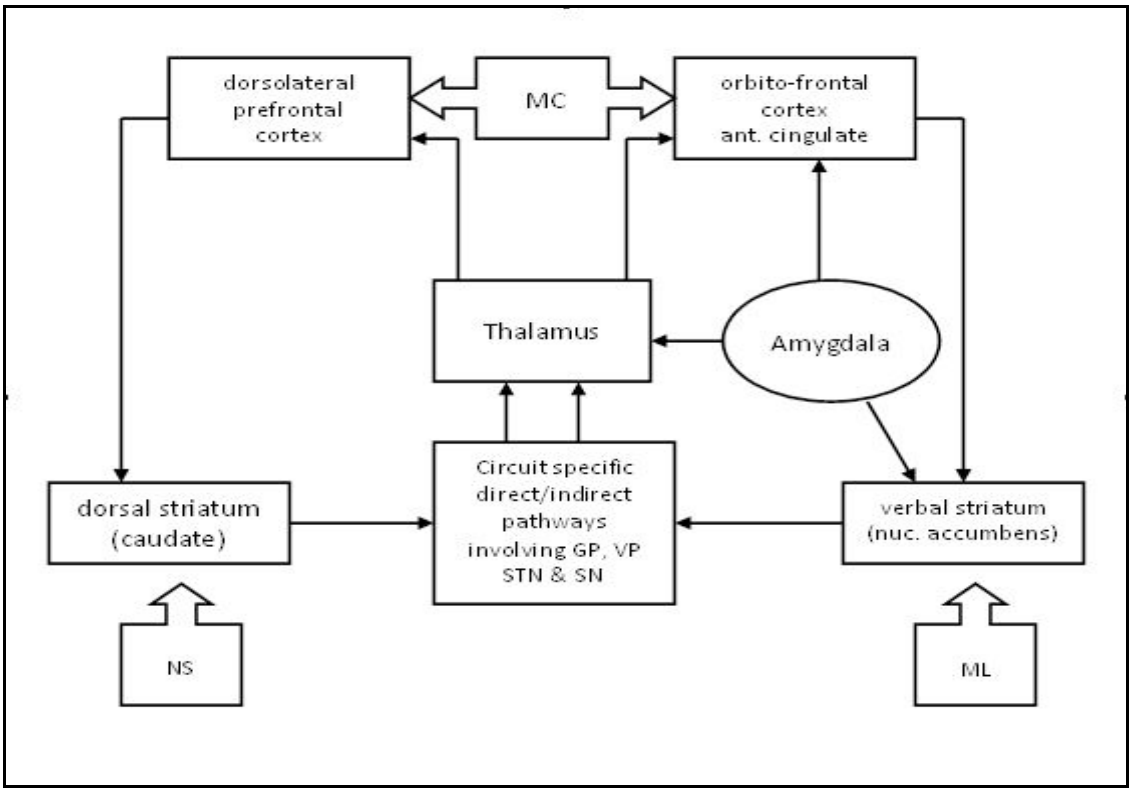


Figure 2. Representation of Sonuga-Barke's dual pathway model, which proposes alterations in both fronto-striatal and mesolimbic systems (adapted from Sonuga-Barke, 2003). MC:, ML:, GP, VP:, STN:, SN:, NS.

2.7 Neuroimaging in Adult ADHD

2.7. Neuroanatomical Findings

The results of structural neuroimaging studies on children with ADHD show grey matter (GM) deficits in frontal areas (Cubillo & Rubia, 2010; McAlonan et al., 2009), basal ganglia (Filipek et al., 1997; Carmona et al., 2009) and cerebellum (Castellanos et al., 2002; Mackie et al., 2007). In addition, volumetric diminutions in parietal, temporal, and occipital regions have also been observed among this population (Castellanos et al., 2002; Tiemeier et al., 2010). Carmona et al. (2009) found GM reductions in the right caudate nucleus among children with ADHD as compared to controls. Such alterations might be related, according to longitudinal studies, with an underdevelopment in the maturation of the cerebral structure, with an average of 3 years (Shaw et al., 2007).

Additionally, our research group observed GM reductions in the caudate nucleus in children with ADHD (Trèmols, et al., 2008; Soliva, et al., 2010a) and furthermore, an alteration between the top and the body of such nucleus was found, which is not present among control subjects. Specifically, patients with ADHD present a smaller right caudal nucleus, principally due to the decrease of the body, but not the top, of this nucleus. The different proportion top/body of the right caudal nucleus has been confirmed as a diagnostic marker of the disorder, with high specificity (95%), which is being automatized and replicated in adult samples (Igual et al., 2011; Igual, Soliva, Escalera, Gimeno, Vilarroya, & Radeva, 2012).

The striatal alterations prevail in other ADHD child samples, according to Frodl and Skokauskas (2012). Moreover, regarding adult ADHD, Montes et al., (2010) found decreased GM volume in the right caudate in adults with ADHD, were no differences were found for gender. Moreover, this discovery is correlated with the intensity of symptoms of ADHD.

Additionally, Frodl and Skokauskas (2012) performed a metanalysis on which less GM volume in children with ADHD was observed, mainly in basal ganglia, including the globus pallidus and the right putamen. Furthremore, structural deficits have also been described in limbic regions, such as the amygdala and the ACC in non-medicated children; all though such alterations seem to decrease as entering the adulthood. However, according to the metanalysis (2012) adult ADHD symptoms persistently were correlated with GM volumetric deficits in the ACC.

Nowadays, although there are few studies involving structural neuroimaging in ADHD adults, GM volumetric reductions in frontal regions, known for their intervention in executive processes, have become evident (Frodl & Skokauskas, 2012; Montes et al., 2010; Depue, Burgess, Bidwell, Willcutt, & Banich, 2010) Hesslinger et al. (2002) showed GM volumetric deficits in the left orbitofrontal cortex in 8 unmedicated ADHD males. The analysis consisted on the selection a priori of this region of interest (ROI). Similarly, Makris et al. (2007) found less total volume of GM in the cortex, anterior cingulate, and in the left superior DLPFC.

reductions in the caudate nucleus, as well as in the anterior cingulate, inferior parietal lobule, putamen, and cerebellum. Similarly, deficits in cortical thickness have been also observed. Makris et al. (2010) found decreased cortical thickness in adults with ADHD in the dorsolateral and orbitofrontal cortex, bilaterally. In addition, reduced cortical thickness was found in the ACC and the PCC, as well as in the temporo-occipito-parietal association area (Depue,et al., 2010).

Recently, Duerden et al. (2012) reported cortical thickness alterations in sensorimotor regions in patients with ADHD and that such alterations do not seem to disappear during adolescence, but to persist in adulthood. Specifically, teenagers with ADHD showed reduced cortical thickness in the supplementary motor area, whereas adult patients presented an increased cortical thickness. The authors (Duerden et al., 2012) also analyzed the possible effect of the age on such diminutions. The results showed a reduced cortical thickness in older control subjects, whilst ADHD subjects presented few changes. These finding suggests that sensorimotor regions might be altered within the ADHD, and that such changes persist until the adulthood.

More recently, Hoekzema et al. (2012a) found differences in the cortical thickness in a sample with both children and adults with ADHD (adults were medicated and non-medicated). Principally, decreased cortical thickness was observed in children in the attentional dorsal circuit, including the inferior and superior cortex, bilateral; as well as the frontal cortex (frontal superior and precentral gyrus, bilateral).

Decreased cortical thickness was also observed in the orbitofrontal cortex and in the medial occipital cortex, bilaterally. However, differences in adults were as strong as in children, including only few deficits in the superior parietal cortex, precentral gyrus and in both superior frontal and precentral cortices. Likewise, increased cortical thickness (although precisely located) was observed in frontal and temporal regions. These results suggest a neuroanatomical profile of the ADHD that involves alterations of the cortical thickness in regions related to attentional processes, which is less pronounced in adults than in children (Makris et al., 2007).

Importantly, our group also observed reduced cortical thickness volume in the ventral striatum in adults with ADHD with previous history of medication, in comparison to non-medicated adults. Furthermore, recent studies show a bare reduction of the ventral striatum (bilateral) in patients after having been treated with metilphenidate. Nevertheless, a volumetric recovering of this structure has been found, in which eventually reaches the same volume as the control subjects. Such pattern of volumetric changes in the ventral striatum is also presented in children with ADHD (Hoekzema et al, 2012b).

The results of our study suggest that alterations in the ventral striatum volume previously observed in patients with ADHD, interestingly might represent a transitory effect involved in the exposition to stimulants, more than in an inner feature of the ADHD (Hoekzema et al., 2012b)

Finally, only two of the aforementioned studies have used ID as technique so as to investigate deficits in white matter in patients suffering ADHD. Makris et al. (2008) found a reduction in the fiber's tract that connects the cingulate with the DLPFC; the right hemisphere, and also in the superior longitudinal fascicle with prefrontal and parietal regions, which are also associated with the executive functioning and attention, respectively Konrad et al. (2010) noticed abnormalities in the structural connectivity of the frontostriatal circuit in adult patients with ADHD. Additionally, the authors also found a direct correlation between the integrity of the white matter and the punctuations of attention and hyperactivity.

2.7.2 Functional Findings

Resting state Functional connectivity

Brain functional connectivity is defined as the temporal dependency of the neuronal activity between cerebral regions anatomically separated. The study of the low-frequency signal in the cerebral activity after having applied the BOLD technique during resting state has revealed patterns of synchronized cortical activity, which has permitted to describe the intrinsic functional architecture of the human brain (Proal, Alvarez-Segura, de la Iglesia-Vayá, Martí-Bonmatí, & Castellanos, 2011).

Originally, Raichle et al. (2001) described a Default Mode Network, DMN, which shows a strong coherency in the spontaneous activity during resting state (functional connectivity) but becomes suppressed during the execution of cognitive tasks that require attention.

Recently, evidence has demonstrated that ADHD is characterized by presenting not only structural and functional frontal, parietal, and other cerebral alterations, but also in the interregional functional connectivity among such cerebral regions, which form neural networks (Cubillo & Rubia, 2010).

Regarding studies conducted among child with ADHD, the existent literature indicates decreased functional connectivity in the fronto-striatal, fronto-parietal, and fronto-cerebellum networks during resting state (Cao et al., 2006).

However, it has also been observed an increase in the interregional connectivity between the anterior cingulate, the striatum and temporocerebellar regions (Yu-Feng et al., 2007; Tian et al, 2006). Additionally, Sun et al. reported minor connectivity between the anterior cingulate cortex and the DMN, including the prefrontal dorsomedial cortex and the posterior cingulate cortex. The results also showed a negative correlation age and functional connectivity in controls, although not in patients. These findings suggest that there might be an abnormal pattern of development in the functional networks between the anterior cingulate and DMN, which might explain ADHD's pathophysiology.

Additionally, a study performed with youth ADHD also described differences in comparison to controls subjects regarding functional connectivity, since an increase in functional connectivity during resting state was found between a ROI that spanned all the anterior cingulate and regions that included the thalamus, cerebellum, insula and the pons, bilateral (Yu-Feng et al., 2007).

According to the consulted bibliography, there is just one study describing functional connectivity during resting in adults with ADHD, conducted by Castellanos et al. (2008)., 2008). The results showed decreased connectivity between anterior and posterior components of DMN, specifically between the ventromedial prefrontal cortex (including the anterior cingulate and the precuneus) and the posterior cingulate. Moreover, the anterior cingulate not only has a relevant role in the DMN, but it is also related to more introspective attention processes (Fransson, 2006).

In addition, Fransson (2006) observed a reorganization of the intrinsic activity (DMN) during attention tasks in healthy individuals. Weissman et al. (Weissman, Roberts, Visscher, & Woldorff, 2006) reported momentaneous reductions in regions related to frontal activity (anterior cingulate cortex) during attention processes, also in healthy subjects. On the other hand, increased activity was also observed in the DMN (posterior cinguluate cortex and precuneus), which suggests alterations in the frontal-DMN connectivity in ADHD subject, and specifically, suppression incapability of the DMN in these patients.

Moreover, Sonuga-Barke & Castellanos (2007) suggested the inhibition interference hypothesis, according to which, the DMN is related to a general activity mostly associated with resting state phases, but, however, it might influence during more directed processes, producing fluctuation periods between a process and the other. Sun et al (Tian et al., 2006) found a disfunction in the connectivity of the anterior-posterior cingulate cortices among children, and the study of Castellanos et al. (2008) confirms

that such changes may persist into adulthood. Therefore, a dysfunction in the frontal-DMN interaction is suggested, as a relevant aspect regarding the pathophysiological mechanisms underpinning ADHD.

Task Positive functional connectivity

Wolf et al. (2009) evaluated ADHD adults and controls during the performance of a three-phase (encoding, delay, and probe) working memory task. The groups did not differ in performance during the task, but they did differed in the patterns of brain activation elicited by the task (task-positive networks for working memory) and in the functional connectivity during the delay phase of the task. The ADHD group showed less functional connectivity for some brain regions (ventral–lateral PFC, anterior cingulate gyrus, superior parietal, and cerebellum) and greater functional connectivity for other brain regions (right PFC and left dorsal anterior cingulate cortex and cuneus), consistent with the hypothesis of ADHD-related dysfunction of the prefrontal–parietal, anterior cingulate, and cerebellar brain regions, based on anatomical and functional imaging studies previously described.

Additionally, Cubillo et al. (2010) observed less functional interregional connectivity in non-medicated adult patients, between inhibition related regions, i.e., right inferior prefrontal cortex, and other regions that included the left inferior prefrontal cortex, the thalamus, the anterior and posterior cingulus, and biltareal temporo-parietal regions. A decrease of the connectivity between the thalamus and the posterior cingulus was also found; both results during the realization of a Stop task.

Both studies found functional connectivity deficts during the realization of cognitive tasks in areas that are well known for being affected in ADHD subjects, children and adults, specifically the inferior prefrontal cortex, the cingulate, striatal regions, as well parietal and cerebellar regions.

To sum up, functional connectivity findings indicate that ADHD's altered mechanisms not only involve volumetric or functional alterations in certain regions, but also could imply a dysfunction in the connections of the areas involved in the physiopathology of the disorder.

Functional Magnetic Resonance Imaging in Adult ADHD: reward/motivation, working memory, response inhibition, attention and time estimation paradigms.

Most functional studies conducted among ADHD adults have focused on the cognitive deficits that characterize this condition. The following section is divided according to the most studied tasks: reward/motivation, working memory, response inhibition, attention and time estimation (see table 2).

Working memory:

In Functional Magnetic Resonance Imaging (fMRI) working memory is probably the aspect regarding ADHD that has been more studied in adults than in children. Above all, the verbal aspect of such function has been well studied. Almost all studies (Wolf et

al., 2009; Valera, Faraone, Biederman, Poldrack & Seidman, 2005) confirm that adults with ADHD show altered patterns of neuronal activity in relation to working memory tasks, even though presenting a similar performance in tasks to the control group.

As mentioned before, Wolf et al. (2009) conducted an fMRI study with ADHD adults using a delay working memory task. The behavioural results did not reflected significant differences between ADHD individuals and the control group, however, differences in neural activation patterns and functional connectivity were observed. Specifically, ADHD subjects showed reduced activation in the left ventrolateral prefrontal cortex, as well as in the cerebellum and occipital regions. Such results, suggest functional deficits in the ventromedial prefrontal cortex and in the cerebellum; accompanied by abnormalities regarding functional connectivity in the same regions and in the anterior cingulate cortex and parietal cortex related to the working memory processing, in ADHD adults.

Hale, Bookheimer, McGough, Phillips & McCracken, 2007 studied working memory using the paradigms of *span*, direct and inverse digits. The ADHD adults and control subjects appear to activate similar neutral networks in order to process the information, nevertheless, differences in the neural activation were observed in some regions. Specifically, in the "span" task of direct digits, ADHD subjects showed increased activation in the right hemisphere –specifically, in the dorsolateral frontal cortex, the inferior frontal cortex, the superior medial parietal lobule, and the precuneus, as well as in the left hemisphere- including the medial cingulate cortex (midbody), in the union of the posterior-occipital temporal lobule and the visual cortex.

Ad for the inverse *span* condition, firstly, in regard to subjects with ADHD, reduced activation was observed as compared to controls in the left parietal line, in the right supramarginal gyrus and in the union of the posterior temporal lobule and occipital lobule of the right hemisphere. Furthermore, a bilateral hipoactivation of the superior parietal lobules was also observed. These subjects present an increased activation in the right hemisphere- precisely in the superior posterior temporal line, in the Wernicke area, the union angular/occipital and in the medial cingulate cortex as compared to controls.

The following two studies come from the same investigation group. The first one (Valera, Faraone, Biederman, Poldrack, & Siedman, 2005) used the n-back task in order to compare the cerebral activity of ADHD adult subjects with a control group. As well as in the study of Wolf et al. (2009), differences between patients and controls were not observed regarding behavioural data, but there were neural activation differences, since it was reported that ADHD adults showed less activation in the left cerebellum, occipital regions and, furthermore, the patient group presented a tendency towards deceased activation in the right prefrontal cortex.

Additionally, in a study conducted with a bigger sample, the authors report decreased brain activity in ADHD patients in the medial frontal cortex, bilateral, including the anterior cingulate cortex (Valera et al., 2009).

In addition, this study (Valera et al., 2009) compares neural differences regarding gender. Using the N-back task, it was observed decreased activation in prefrontal regions in the ADHD group (including male and female subjects) in comparison with the control group. Regarding gender related differences, ADHD male subjects, as compared to male controls, showed reduced brain activity in the right frontal lobule, temporal lobule, subcortical regions, left occipital lobule and cerebellum. In contrast, differences among ADHD women and controls were not observed. Moreover, negative correlations were found between activity related to working memory and hyperactivity symptoms in male patients and with inattention symptoms in female patients. Such findings point to differences related to neural activity and ADHD symptoms in women and men.

Reward/Motivation

In recent years, the interest in studying the motivational/reward system in ADHD has increased. Until recently, most research in adults has found reward related abnormalities in ADHD subjects. Thus, such differences have been mostly observed in the ventrial striatum (Ströhl, et al., 2008; Carmona et al., 2012) and in the orbitofrontal cortex (Ströhle et al., 2008; Stark et al., 2011; Wilbertz et al., 2012). Furthermore, several studies have found correlations between such alterations and ADHDs' symptom severity (Ströhle et al., Stark et al., 2011).

In order to compare the neural response during reward anticipation and the rewarding moment in adults with ADHD, Ströhle et al. (2008), used a monetary incentive delay (MID). During reward anticipation, a decline of activation in the ventrial striate was observed, whereas increase activation in the orbitofrontal cortex, frontal lateral and bilateral regions, the right caudate and the putamen, was produced during response for the prize. Moreover, reward anticipation activity in the ventral striatum was negatively correlated with self-perception scores of the hyperactivity and impulsivity symptoms.

Additionally, as comparing cerebral activity in a series of elections between two types of economic reward (little reward and immediate, or major reward and delayed) Plichta, et al. (2009) reported that adults with ADHD showed decreased ventral striate and amygdalar activation in relation to immediate reward. In addition, delayed rewards provoked increased activity levels in the caudal nucleus and the amygdala (bilateral). A significant correlation between self-perception punctuations and the activation in the dorsal caudal nucleus and the amygdala was also found during a delayed rewarded task.

Stark et al. (2009) observed reward anticipation in different type of task (monetary reward, punishment avoidance, and oral feedback) in a sample of 31 non-clinical female subjects that presented a behaviour related to ADHD (evaluated by ASRS). In the three conditions, increased brain activation was found in the reward system (accumbens, anterior cingulate cortex, orbitofrontal cortex and amygdala). The most notable increase was observed in relation to the monetary reward, followed by punishment avoidance and, finally, the oral feedback showed the lowest activation. Furthermore, an opposite relation between severity of the behaviour related to ADHD and the activation of the nucleus accumbens was also observed.

In other study, Wilbertz et al. (2012) conducted two monetary reward and non-monetary paradigms in an ADHD group and in a control group.

In both samples, an activation in the ventral and dorsal striate was observed, and in the medial orbitofrontal cortex. Within the condition of monetary reward such activation was higher than within the non-monetary. The difference between samples appeared during the codification of the reward value, this is, involving a motivational change.

It seems that among normal subjects, higher the reward higher the activation in the medial orbitofrontal cortex, whereas among ADHD subjects such relation cannot be observed, which reflects a possible dysfunction in the reward/motivational system, among ADHD subjects.

Finally, our group (Carmona et al., 2012) reported less activity in the bilateral ventral striate in non-medicated ADHD adults, in comparison with controls, during the reward anticipation, using a monetary incentive delay (MID) paradigm. Thus, neural activity observed in the accumbens was negatively correlated with hyperactivity/impulsivity symptoms. These findings suggest the implication of the neural reward network in the physiopathology of adult ADHD.

Motor response inhibition

Besides its relation to circuits that regulate attention and impulsivity, ADHD's pathophysiology is also thought be associated with neural networks that control motor response inhibition. Apparently, such alterations might be present in both children and adults with ADHD. The control motor response inhibition tasks is usually measured with Go / NoGo or Stop tasks, in which subjects have to inhibit motor response to the stimulus Go after the presentation of Stop or NoGo signals (Carmona et al., 2012).

In their review, Schneider, Retz, Coogan, Thome and Rösler (2006) also observed reduced activation in fronto-striatal and attention networks (parietal) in adults with ADHD using a Go / NoGo paradigm, specifically during response inhibition (NoGo condition).

In a study with parents of ADHD children, who were also diagnosed with the disorder, Epstein et al. found underactivations in the bilateral inferior frontal cortex and in the left caudate in patients compared to controls. These results were correlated with attention performance measures of the task. Patients also showed increased activation in the left inferior parietal lobe and the anterior cingulate. Subsequently, in a study by Dibbets, Evers, Hurks, Marchetta and Jolles (2011) patients showed increased activation in the right medial frontal cortex during the Go response, as compared to controls.

Finally, Cubillo et al. (2010) observed in ADHD patients less activation than controls in bilateral inferior and premotor regions, anterior cingulate cortex, striatum, and right thalamus during successful inhibition responses and in right inferior frontal cortex, striatum and bilateral thalamus during failures to inhibit the response.

The results of these studies indicate reduced fronto-striatal activation in adults with ADHD during motor tasks inhibition, consistent with the fMRI results obtained with children with this disorder.

Attention

Despite the importance of attention regarding ADHDs' pathophysiology, there are very few fMRI studies that investigate this function and its alterations.

In one of the first studies, attention was studied using a switch task. Simultaneously, in order to investigate the motor inhibition, a stop task was also used. The performance in ADHD subjects did not differed in a significant way compared to healthy controls. However, adults with ADHD showed decreased activation in the bilateral inferior prefrontal cortex, caudate nucleus and thalamus in both tasks. Also, reduced activity was observed in the left parietal lobe, but only in relation to the switch task. Moreover, it was possible to correlate the severity of behavioural symptoms with more extensive activation (Cubillo et al., 2010).

Additionally, the same group (Cubillo, Halari, Giampietro, Taylor, & Rubia, 2011) used an "oddball" paradigm to compare adult ADHD patients and controls, on which reduced activity in the left lateral prefrontal and dorsolateral cortex was observed.

Finally, on their most recent study, the authors (Cubillo, Halari, Smith, Taylo , & Rubia, 2012) used a sustained attention task in order to study attention related neural activity in adults with ADHD. The patient group showed reduced activation in the lateral fronto-parietal-striatal circuit, particularly in the inferior frontal cortex, striatum, thalamus, insula, the accumbens and in the supplementary motor area. Furthermore, increased activation was observed in the posterior regions of the brain, including the cerebellum, the inferior and posterior parietal cortex and occipital regions.

Timing

While fMRI studies have mostly focused on response inhibition, attention, working memory and reward processing deficits in ADHD; deficits in timing functions have also been observed in patients with this disorder (Noreika et al., 2013; Rubia et al., 2009; Toplak et al., 2006).

Even though a wide range of timing tasks have been used in order to study timing processing deficits, a recent metanalysis of timing functions performed by Weiner, Turkeltaub and Coslett (2010) in healthy adults showed that regions that mediate sub-second and supra-second motor and perceptual timing functions. This might indicate that there are neural networks mediating timing functions across temporal domains and sensory modalities (Weiner et al., 2010). Accordingly, recent studies have implicated certain key areas in timing functions, including the inferior and dorsolateral prefrontal cortex, the cerebellum and the parietal lobes (Rubia et al., 2009a; Rubia & Smith 2004; Weiner et al. 2010). Specifically, lateral prefrontal areas, including the insula, might be a temporal accumulator underlying

motor and perceptual timing functioning; the cerebellum is considered as key regions for temporal prediction and parietal lobes are thought to play an important role for implicit timing and attention to temporal information. The basal ganglia might also be implicated as "Internal clock" mostly by integrating cortical oscillating activity, however they are more active during sub-second timing functions (Coull, Chen, & Merck, 2010; Rubia et al., 2009; Rubia & Smith 2004; Weiner et al., 2010).

Furthermore, in recent studies, adult ADHD patients appear to show brain function abnormalities during timing processing. Specifically, timed and untimed sensorimotor synchronization have been related with decreased activation in typical areas of sub-second sensorimotor: inferior and orbitofrontal cortex, premotor cortex, basal ganglia, insula, parietal lobes and cerebellum (Valera et al., 2010; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2012).

Concretely, there are only 2 studies in an adult ADHD sample, performed by Valera et al. (2010). The first one included a synchronised finger sequencing paradigm and the results indicated decreased brain activation in ADHD patients as compared to controls, including the left inferior and orbitofrontal cortex, bilateral insula, bilateral precentral gyrus, bilateral inferior parietal lobe, left medial and superior temporal cortex and right cerebellum. The second study was an unsynchronised finger sequencing task, on which the ADHD group showed less activation in comparison to controls in regions that included bilateral inferior frontal cortex, right orbitofrontal cortex, right amygdala, left precentral gyrus, left caudate/putamen, left insula and bilateral cerebellum (Valera et al., 2010). However, given the fact that fMRI literature of timing functions in ADHD is relatively small, further research might be needed in order to establish firmer conclusions.

3. OUTLINE, OBJECTIVES AND HYPOTHESIS

3.1 Outline

ADHD, conceived as one of the most prevalent childhood psychiatric disorders, is characterized by inattention, hyperactivity and impulsivity symptoms and estimate to affect 5% of world wide population (Polanczyk et al., 2007). Until recently, symptoms were thought to ameliorate with age. However, in cases most of ADHD children, symptoms appear to persist into adulthood. A recent 10 year follow-up study indicated that 35% of paediatric patients still meeting ADHD diagnostic criteria and it's been estimated that ADHD affects between 3 and 7% of adult population (Kessler et al, 2005).

Even thought the exact neurobiological substrate of ADHD still unclear (Volkow et al., 2007), genetic, preclinical and clinical studies point to dopaminergic and/or noradrenergic alterations (Faraone, Sergeant, Gillberg, & Biederman, 2003). Neural activity and grey matter volume decreases in dopamine related regions also corroborate such deficits (Del Campo et al., 2011).

As ADHD children, adult diagnosed with this disorder also present neuropsychological deficits, mostly involving working memory, attention and inhibitory control. In this direction, the multiple pathway model proposed by Sonuga-Barke (Sonuga-Barke et al., 2010) implicates at least two relatively independent but not mutually exclusive ADHD endophenotypes; those involving an executive functioning disruption such as inhibition control, and those more related with motivational system abnormalities, basically reward anticipation. Executive functions are thought to be mediated by dopaminergic

networks connecting dorsal striatal regions with lateral and dorsolateral prefrontal cortex; while reward processing is thought to be subserved by dopaminergic circuits including the ventral striatum to the orbitofrontal, medial prefontal and cingulate cortex (Habas & Rauch 2010). Therefore, this model explains neuropsychological heterogeneity of of ADHD in terms of dissociable cognitive and motivational deficits, each affecting some but not other patients. Additionally, it is been suggested that temporal processing might constitute a third dissociable neuropsychological component of ADHD (Sonuga-Barke et al., 2010).

However, in spite of the influence that motivational processes might have on cognitive functioning, only a few studies have focused on the neural substrate underpinning the motivational system and, specifically, its role in ADHD pathophysiology. The majority of fMRI studies on ADHD have mostly assessed executive functioning, particularly, response inhibition. Recently, motivational paradigms have been used in ADHD populations in order to study the neural functioning of reward processing (Carmona et al., 2012). Specifically, studies assessing reward anticipation in ADHD indicated decreased recruitment of the ventral striatum (VStr) in both child and adult patients in comparison to healthy subjects (Plichta et al., 2009; Scheres, Milham,. Knutson, & Castellanos, 2007; Strohle et al., 2008). Additionally, almost all of such studies have reported a negative correlation between VStr activation and hyperactive/impulsive symptoms (Scheres et al., 2007; Strohle et al., 2008).

Recently, timing processing deficits have also been studied in ADHD. Timing abilities are critical to the successful management of everyday activities, as well as personal safety. Furthermore, such abnormalities have been related with impulsiveness, a core symptom of ADHD. Concretely, experimental data of youth ADHD have shown less accurate performance than healthy subjects on timing tasks, including paced finger tapping (Rubia, Noorlois, Smith, Gunning, & Sergeant, 2003), duration reproduction (Barkley, Kiplowitz, Anderson, & McMurray, 1997; Meaux & Chelonis, 2003, duration discrimination (Toplak, Rucklidge, Hetherington, John, & Tannock, 2003), verbal time estimation (Smith, Taylor, Warner Rogers, Newman, & Rubis, 2002), and temporal anticipation (Rubia etl., 2003). In fact, one of the most consistent findings in ADHD youth is increased within-subject variability on a range of tasks (as reviewed in (Klein; Wendling, Huettner, Ruder, & Peper, 2006; Leth-Steensen, King Elbaz, & Douglas, 2000), indicating an inability to register responses at evenly timed intervals. This variability has been shown to be related to attention ratings and accordingly, to decrease in response to methylphenidate (Rubia et al., 2003; Baldwin et al., 2004). Thus, an increased knowledge of timing management has important implications in understanding core features of ADHD. Interestingly , some of the most consistent anatomical and functional findings in ADHD have been in areas associated with timing, including frontal, BG, and cerebellar regions (Paloyelis, Mehta; Kuntsi, & Asherson, 2007; Seidman et al., 2006 ; Valera, Faraone, Murray, & Seidman, 2007). To date, only 3 studies have examined timing processing in ADHD adults, using a finger tap task. To our knowledge, there are no studies on time discounting tasks in unmedicated adults with ADHD.

It's been known that medication drugs such as methylphenidate or atomoxetine have proved to influence short and long-term structural and functional functioning in key regions for reward anticipation and attention processes, namely the inferior frontal gyrus and the VStr, the analysis of medication naïve patients is crucial in order to asses how the neurobiological substrate of ADHD is affected in adults with this condition.

Taking all that account, the aim of our study is to elucidate the neural substrate of reward anticipation and timing discounting responses in adults with ADHD who had never received medication for this condition. Using an fMRI time estimation/reward task we will be able to test the hypothesis that abnormalities in motivational system and timing networks contribute to the pathophysiology of ADHD and, furthermore, determine whether both tasks are related to each other, or if they represent independent domains at neural and/or behavioral levels, as proposed by current models (Sonuga-Barke, 2010).

3.2 Objectives

3.2.1 General objective:

The general objective of the study is to identify brain functional alterations related to reward/motivation system and timing processing in adult ADHD patients relative to healthy controls.

3.2.2 Main objectives:

Determine differences in brain functional activity between a group of adult ADHD patients and a control group during an fMRI reward/motivation task.

Identify differences in brain functional activity between a group of adult ADHD patients and a control group during an fMRI time estimation task.

3.2.3 Specific objectives

- Identify behavioural differences in attention ratings and response variability in the task performance between the adult ADHD group and the control group.
- Assess correlations between attention ratings and response variability, and brain functional activity in the both adult ADHD and control groups.
- Identify correlations between the clinical and neuropsychological punctuations and brain functional activity in both groups.

3.3 Hypothesis

Based on previous studies on reward anticipation and time estimations tasks performed on ADHD patients, we predict that, a) relative to control subjects, ADHD unmedicated adults would show decreased basal ganglia (mostly VStr) activation during reward anticipation; as well as reduced activation in the inferior frontal cortex, basal ganglia and cerebellar regions, which are commonly engaged in timing and have been shown to be abnormal in ADHD, in comparison to controls, b) regarding the attention related task, we hypothesize that adults

with ADHD would show increased brain activity in the attention network regions, i.e., parietal superior lobe as well as inferior frontal lobe, c) we hypothesize lower attention ratings and higher response variability in the ADHD adult group in comparison to the control groups and d) we predict that activation levels in the inferior frontal gyrus and the VStr will correlate in a negative manner with ADHD clinical severity punctuations.

4. METHODS

4.1 Participants

Forty adults with combined ADHD and 40 healthy subjects were recruited for the study over a two-year period. Both clinical and control samples included right handed males and females group homogeneous for age and gender (See Table 4). Thirty-five subjects (20 ADHD and 15 controls) were excluded from the analysis due to problems occurring during the paradigm or the images presented too much movement or machine artefact. Sociodemographic data are depicted in Table 1.

A specialized team of psychiatrists and psychologists from Vall d'Hebrón Hospital evaluated all subjects. All patients met criteria for ADHD combined subtype and never received any pharmacological treatment for their condition. Psychiatrists performed ADHD diagnosis according to the criteria of the Diagnostic and Statistical Manual of Mental Diseases, Forth Edition, Test Revised (DSM-IT-TR) (APA, 2004). In order to confirm diagnoses, several instruments were applied, including the Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Conners, Erhardt and Sparrow, 1999), the Wender Utah Rating Scale (WURS) (Ward, 1993), the ADHD Rating Scale (Du Paul, Power, Anastopoulos, & Reid, 1998) and the Conners`Adult ADHD Rating Scale (CAARS) (Conners et al., 1999). Additionally, the mentioned scales also accounted for impulsivity, hyperactivity and/or inattention ratings, important for subtype-diagnostic purposes and further correlational analyses.

Moreover, neuropsychological tests were applied in order to evaluate the subjects' IQ. Such scales included the visual and logic subscales of the Wechsler Memory Scale (Wechsler,2005), the Trail Making Test (TMT) A and B, (Reitan & Wolfson, 1985), and 5 subscales of the Wechsler Adult Intelligence Scale Third Edition (WAIS-III), including the vocabulary test, the arithmetic and digit span tests, the block design test and the symbol search subscale (Wechsler, 2005).

The exclusion criteria included comorbidity with other psychiatric condition or personality disorders, assessed by the Structured Clinical Interview for Axis I (SCID-I) (First, Spitzer, Gibbon & Williams, 2012) and Axis II (First; Gibbon, Spitzer; Williams, & Benjamin, 1997). Subjects with substance use disorder, including the use of tobacco or cannabis within the last 6 months, as well as those with a history of severe drug consumption (cocaine, heroin, synthetic drugs) were also excluded from the study. Finally, according to our exclusion criteria, subjects with an estimated IQ inferior from the standard deviation from the mean were not included.

The study was approved by the Hospital de Vall d`Hebrón Ethics Committee and informed consent was obtained from ADHD patients and healthy subjects before participating in the study.

4.2 MRI and fMRI acquisition parameters

Functional MRI images were obtained in a Phillips 3T scanner equipped with a 8 head-coil. For anatomical reference, a T1-weighted pulse sequence was employed using the following parameters: TR=500 ms, TE=50, matrix 240 x 200, FA=8, slice thickness=1mm. The sequence for functional images was a T2-weighted gradient single shot echo sequence (EPI) with a TR=3,000 ms, TE=35, FA=90, FOV=230 x 230 cm, gap= 1mm and and a matrix size of 76 x 75.

4.4 MRI and fMRI procedure

During the fMRI acquisition all subjects participated in an event-related reward/time estimation fMRI paradigm, similar to the one employed by Jimura, Locke, & Braver (2010).

The functional paradigm was designed using E-Prime Studio (http://www.eprime2.eu/home.htm). During the task, subjects were instructed to watch a red traffic light and to count for how many seconds it was on for. Next when the red light switched to green, used the duration estimated for the red light to make the duration of both light coincide. They did so by pressing a button, which caused the green light to switch to a fixation prompt, thus starting to a new trial. Additionally, subjects were told that in some of the red lights they would see an animal (a bird, a bee or a butterfly) flying above the traffic light. However, they were instructed that they were not supposed to do anything about them, they were only there to add the task some difficulty.

In order to assess reward and motivation, subjects were told that during the first time of the task, they would only see the red and green traffic lights. During the second half on the paradigm, we explained to the subjects that they would see a “euro” cue before the red light, meaning that that trial would be rewarded according to their performance in the estimating task. Upon each trial, the subjects were given feedback indicating how well they did and how much had earned so far. However, not all trials in the second half of the paradigm were rewarded. Instead, the subjects ascertained which trials were rewarded and which were not by the “euro” cue at the beginning of each rewarded trial.

Specifically, each trial begun with a fixation cross that lasted for 1000 ms. In the case of the rewarded trials, a “euro” cue was depicted for 500 ms after the fixation cross. For both rewarded and unrewarded trials, the reed traffic light was presented between 1000- and 6000 ms, randomly, followed by a 1000 ms inter-stimulus fixation cross. Finally, when the target (the green light) was shown its duration depended on the subjects` reaction time (mostly between 1000 and 6000 ms). The target was followed by a variable delay of between 1000 and 3000 ms. In the case of the rewarded trials, subjects were shown a feedback screen indicating the amount lost or gained in the trial as well as total quantity earned up to that point followed by a 1000-3000 ms variable delay. In total, the paradigm lased for 16 minutes. The first not rewarded half of the paradigm consisted of 40 trials and the second half included another 40, divided in 28 rewarded and 12 not rewarded trials. Trials included in the paradigm are illustrated in figure 3.

Because each trial consisted of multiple events, the activity components of interest were extracted from the time course. Specifically, the early trial component included the activity related to the presentation of the reward/not reward cues and the time estimation set, whereas the late trial period basically included the counting task and the response probe. Lastly, the final component included the feedback presentation.

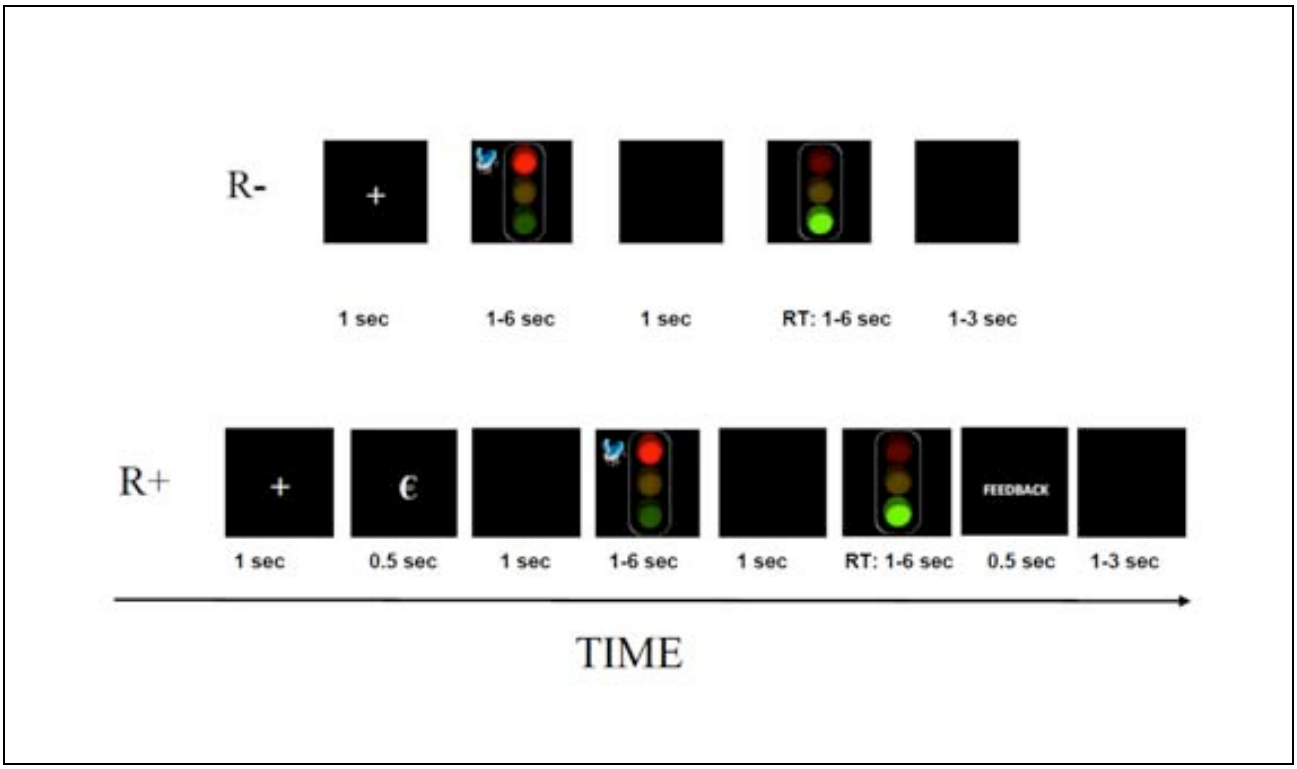


Figure 3. Figure 3 depicts unrewarded and rewarded trials included in the reward/time estimation paradigm we used.

4.5 Study Design

We employed a mixed factorial design, with a single within group factor, on which the one factor was the group (presence or not of ADHD) and two intra factor variables (reward: yes/no and distractor yes/no) in order to determine group related differences regarding the behavioural and neuroimaging data. The presence of ADHD was considered the independent variable (two levels) and the dependent variables included the behavioural performance and Blood-oxygen-level dependence (BOLD) response during the task.

4.6 Statistical Analysis

The statistical analysis aimed to assess differences between the ADHD and the control group in the clinical, behavioural and neuroimaging data. Consequently, several tests were performed in order to evaluate differences in those levels.

4.6.1 Analysis of clinical and behavioral data

Clinical and behavioural data were analyzed with the SPSS 21 (Statistical Package for Social Sciences) (SPSS for Windows Rel 21 SPSS Inc, Chicago IL). A t -student test for two independent samples was employed in order to perform a mean comparison for the quantitative data and a $\chi 2$ -test for the qualitative data.

In order to evaluate behavioral differences between the ADHD and the control group, a repeated-measure analysis was performed including the differential error of the

achieved reaction times (RT) of patients and controls during the time estimation task. The differential error was obtained by subtracting the real time of the stimulus minus the patient's RT. Specifically, the conditions were included for the analyses were: not rewarded trials rewarded trials and distractor trials and not distractor trials.

4.6.2 fMRI Analysis

All time series were converted from Dicom into the statistical parametric mapping (SPM8) format. Image preprocessing and statistical analysis were performed using SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom) and custom software (spm8w, Dartmouth College) implemented in Matlab 7.8 (The Mathworks Inc., USA). First, the anatomical scan was rigid-body transformed to match the first functional volume. In order to correct for between-scan movements, all volumes were realigned to the first volume. Individual translation and rotation movement parameters that exceeded a maximum of 4 mm were excluded from the analysis. Then, functional images were spatially normalized (linear and non-linear transformations) into the Montreal Neurological Institute (MNI) reference system, generating normalization parameters, which were applied to all functional images. A subsequent spatial smoothing with an isotropic Gaussian kernel (12x12x12 mm full-width at half-maximum, FWHM) was applied to increase the signal-to-noise ratio and to compensate for inter-individual differences in the location of corresponding functional areas. All data were high pass filtered (128 s) to remove low frequency noise.

At the single subject (first level) analysis, changes in the BOLD response for each subject (i.e., "activation") were assessed by linear combinations of the estimated GLM parameters (beta values), which are displayed by the individual contrast images (percent signal change or effect size). We mainly focused on the BOLD data underlying reward and not rewarded trials as well as distractor and not distractor trials of the paradigm. However, since our purpose was to asses neural differences related to the reward's effect, we only included the early component of each trial, when the activity was most likely related to the presentation of the reward/not cues and the time counting set. Therefore, the analysis was performed by modeling the following conditions: (1) Reward (2) Not reward (3) Distractor and (4) No-distractor. For these conditions, we modeled the onsets and durations of the trials. Then, these conditions were modeled as explanatory variables convolved with a standard hemodynamic response function as implemented in SPM8. Realignment parameters were included as additional regressors in the statistical model.

In addition, both conditions (reward and distractor) were analyzed separately due to the small number of trials that included the presence of both conditions. The rest of the conditions were not analyzed at the second level because we were mainly interested in alterations of the subcortical-cortical reward system, and attention related processing. Subsequently, these contrasts and their variances were submitted to the second-level analysis.

At the second level of analysis, two-sample *t*-tests were conducted to determine activations differences between both groups (ADHD and controls) using the individual contrast images '"reward cue > no-reward cue" and "distractor > no-distractor".

Therefore, aiming to assess possible group differences, we entered the resulting images for the contrast 'reward > no-reward' in a two-sample *t*-test as implemented in SPM8 comparing ADHD patients and healthy subjects. In a similar way, we also entered the images that resulted for the contrast 'distractor>no-distractor' and calculated the two-sample *t*-test between ADHD patients and controls subjects. For all whole-brain analyses, the threshold for statistical significance was set at $P < 0.005$ and family-wise error (FWE) corrected at the voxel level across the whole brain. An additional minimum cluster size criterion of 10 voxels was applied. Finally, identification of anatomic areas was determined using the stereotaxic atlas of Montreal Neurological Institute.

4.5.2.1 Region of interest Analyses (ROIs)

We also performed a standard ROI analysis. First, *apriori* regions extracted from the contrasts reward>no reward were analyzed. These regions included the nucccleus accumbens, caudate, ventral striatum, inferior frontal gyrus and cerebellum since they have been related to reward processes (Carmona et al., 2012) and temporal functioning (Valera et al., 2010). In addition, *apriori* regions were extracted for the contrast distractor > no distractor, including the DLPFC as well as the inferior parietal gyrus the precentral gyrus and the cerebellum, due to their known role in attention processes (). More specifically, standard ROIs were defined by the Human Atlas IBASPM 116 of WFU_Pickatlatlas (http://www.fmri.wfubmc.edu/cms/software#PickAtlas) and then used as a mask in MarsBar to extract the beta values from the contrasts derived from the second-level analyses.

5. RESULTS

5.1 Sociodemographic results

The results of the performed χ2 test indicated no significant differences regarding the gender between the ADHD group and the control group. As for the age and intellectual coefficient (IQ) variables, a two-sample t-test showed that both groups did not present significant differences between them (See table 2 and 3).

Table 2

A χ^2 test was performed to assess gender differences.

ADHD *N*=(20)	Healthy Controls *N*=(25)	χ^2	df	*P* value
(Male:11, Female:9)	(Male:13, Female:12)	0.841	1	0.540

χ^2: Pearson chi-square (statistical value); *N*: population; df: degrees of freedom; *P*: significance value.

Table 3. Two-sample t-test for the variables age and IQ.

	ADHD	Healthy Controls	*T*-value	df	*P*-value
Variable	**Mean (SD)**	**Mean (SD)**			
Age	38.15(5.659)	34.96(7.834)	1.528	43	0.134
Estimated IQ	44.2750(7.16988)	48.1600(8.17736)	-1.671	43	0.102

IQ: Intelligence Quotient; WAIS (Wechsler Adult Intelligence Scale estimated IQ: [(Vocabulary punctuation + Block design punctuations)/2]; SD: standard deviation; *T*-value: statistical value df: degrees of freedom; *P*: significance value.

5.2 Clinical results

In order to evaluate clinical differences between the ADHD patients and the control group, a two sample t-test was performed for all the applied clinical ratings. As expected, the ADHD group obtained statistically higher punctuations in all scales, reflecting more persistent levels of inattentive and hyperactivity/impulsivity symptoms, characteristic of such disorder. These results are consistent with a properly diagnose of both ADHD and control groups that fulfilled inclusion criteria. The clinical data of ADHD patients and control subjects are depicted in table 4. Variables are expressed by their mean and their standard deviation (SD).

Table 4. Clinical data.

	ADHD	**Controls**			
Clinical Ratings	**Mean (SD)**	**Mean (SD)**	***T*-value**	**df**	***P* value**
WURS	55.20 (13.241)	15.28 (10.620)	11.229	43	<0.001
ADHD rating scale	37.45 (6.778)	5.80 (4.848)	18.250	43	<0.001
CAARS					
A) Inattention	40.30 (25.868)	5.88 (5.238)	6.506	43	<0.001
B) Hyperactivity/restlessness	38.90 (24.163)	7.88 (5.449)	6.240	43	<0.001
C) Impulsivity/emotional lab.	40.95 (26.526)	5.00 (4.555)	6.673	43	<0.001
D) Self-concept	30.50 (27.27)	2.80 (2.773)	5.045	43	<0.001
E) DSM-IV inatt	40.55(32.102)	3.36 (3.450)	5.767	43	<0.001
F) DSM-IV hyper-imp	39.80 (4.71)	3.68 (3.037)	6.436	43	<0.001
G) DSM-IV tot	51.90 (25.542)	7.04 (5.496)	8.560	43	<0.001
H) ADHD index	44.45 (27.810)	5.96 (3.888)	6.856	43	<0.001

ADHD (Attention-Deficit/Hyperactivity Disorder); SD: standard deviation; *T*-value: statistical value; df: degrees of freedom; *P* value: significance value; DSM-IV: Diagnostic and Statistical Manual of Mental Diseases, fourth edition TR; CAARS: Conners Adult ADHD Rating Scale self-rating, form: Long);WURS: Wender Utah Rating Scale; emotional lab: emotional lability; DSM-IV inatt: DSM-IV inattentive symptoms; DSM-IV hypper-imp: DSM-IV hyperactive-impulsive symptoms; DSM-IV tot: DSM-IV total ADHD symptoms.

5.3 Behavioural results of the Reward/Time estimation paradigm

Table 5 depicts the means and standard deviations of the different behavioural variables that were studied during the reward/time estimation paradigm in ADHD and control groups. In order to assess for behavioural differences, performance was expressed by the differential error value for each condition (Real Time-Reaction Time).

Table 5. Means and standard deviations corresponding to the reward/time estimation paradigm.

Variable	ADHD	Healthy Controls
	Mean (SD)	Mean (SD)
DifError Reward	560. 97 (259.96)	517.88 (247.71)
DifError No Reward	1478.48 (556.57)	1368.90 (592.63)
DifError Distractor	1012.48 (413.21)	996.83 (415.12)
DifError No distractor	1026.97 (427.92)	889.95 (394.99)
Total Points	21.47 (2.002)	22.28 (2.021)

DifError: differential error value; SD: standard deviation.

Even though the means were very similar between the ADHD group and the control group, the results indicate behavioral/performance differences in the accomplished reaction times (RT) among both groups, as illustrate on table 4. In spite the fact that statistical significance was not achieved, it may be observed a higher differential error in the ADHD group, since they estimated the seconds the red light was on less

accurately than the control group. This might suggest time estimation deficits in this group. Additionally, the results of the multivariate analysis of variance indicated that there were not significant differences between ADHD patients and the healthy group of controls regarding behavioral performance during the paradigm. However, significant differences were observed in the within-subjects analysis in the reward condition, which might indicate that the paradigm was well design but perhaps a more sensitive task may be required to obtain group differences (see Table 6).

Table 6. Multivariate analysis of variance of the behavioral data from the reward/time estimation paradigm.

Between subjects analysis

Variable	F	df	*P* value
DifError Reward Vs No Reward	0.413	1	0.524
DifError Distractor Vs No Distractor	0.413	1	0.524

Within subjects analysis

Variable	F	df	*P* value
DifError Reward Vs No Reward	208.73	1	<0.001
DifError Distractor Vs No Distractor	1.834	1	0.183

Interaction effect

Variable	F	df	*P* value
DifError Reward Vs No Reward	0.295	1	0.590
DifError Distractor Vs No Distractor	3.165	1	0.082

DifError: diferential error value; df: degrees of freedom; SD: standard deviation; *T*-value: statistical value; df: degrees of freedom; *P* value: significance value.

5.4 fMRI results

5.4.1 Region of interest analysis (ROIs)

The results of the performed ROI analysis indicated decreased cerebellar activity in ADHD patients as compared to controls. Specifically, we observed significant differences between ADHD patients and controls in the left cerebellar region IV and the right cerebellar region IX by applying during the reward/time estimation task. As for the rest of the performed ROIs regarding this contrast, we did observed significant differences between groups. See Table 7; figure 4.

Additionally, ROIs analysis also showed reduced activity during the distractor task in the ADHD group in left DLPFC and the left precentral gyrus, as depicted on table 7. However, not significant differences were observed with regard to the additional performed ROIs for this contrast. Results are depicted in table 8 and figure 5.

Table 7. ROIs analysis form the reward>no reward contrast

Region of interest	Center of mass (MNI coordinates)			*t*	*P* value
	x	y	z		
Cerebellar lobe IV (BA19)	-22.5	-60.3	-23.5	2.20	0.01
Cerebellar lobe IX (BA)	10	-50	-47.6	1.96	0.02798

This table shows the results of the performed ROIs in the cerebellum during the reward/time estimation task. Abbreviations: *T*: statistical value; *P*: significance value.

Table 8. ROIs analysis form the distractor>no distractor contrast

Region of interest	Center of mass (MNI coordinates)			*t*	*P* value
	x	y	z		
Dorsolateral Prefrontal Cortex (BA46)	-33.8	31.5	34.1	1.62	0.0279
Left Precentral Gyri (BA3)	-41.5	-11.6	39.8	1.71	0.0468

This table shows the results of the performed ROIs in DLPFC and the precentral gyrus, respectively, during the attention /time estimation task. Abbreviations: *T*: statistical value; *P*: significance value.

5.4.2 Whole-brain analysis

Whole-brain results revealed reduced activation in the patient group during reward/estimation task in various brain regions, including which included the left and right cerebellum, right supplementary motor area, left rolandic opper gyrus, right Heschl's gyrus, right precunueus and left middle occipital gyrus. Brain activation patterns for this contrast are illustrated on figure 6.

In the opposite contrast, ADHD patients showed increased activation levels in right frontal inferior gyrus and left superior parietal gyrus than the control group (See table 9).

As for the attention task (distractor>no distractor) we also detected in the ADHD group a cluster of reduced activity located in the left post central gyrus, left inferior temporal gyrus and left inferior frontal gyrus, as compared to the control group. In the opposite contrast, we observed increased brain activity in the right orbitofrontal cortex in the patients group. See table 10.

Table 9. Whole-brain analysis from the reward> noreward contrast

Brain Region	Center of mass (MNI coordinates) x	y	z	Cluster size (mm^3)	*t*	*P* value
ADHD<Control						
Left cerebellum (BA 19)	- 33	-63	-18	245	3.52	0.001
Right cerebellum (BA 19)	6	-57	-45	62	3.23	0.001
	15	-39	-48			
Right supplementary motor	12	-15	63	148	5.68	0.001
Area (BA 6)						
Left rolandic opperculum (BA 48)	-51	-24	15	18	3.45	0.001
Right Heschl's Gyrus (BA18)	45	-18	9	25	3.29	0.001
Right Precuneus (AB 30)	12	-51	12	37	3.07	0.002
Left middle occipital gyrus (BA18)	-27	-84	6	22	2.97	0.002
ADHD>Control						
Right frontal inferior gyrus (BA48)	30	24	27	78	3.47	0.001
Left superior parietal gyrus (BA1)	-21	-45	81	32	3.10	0.002

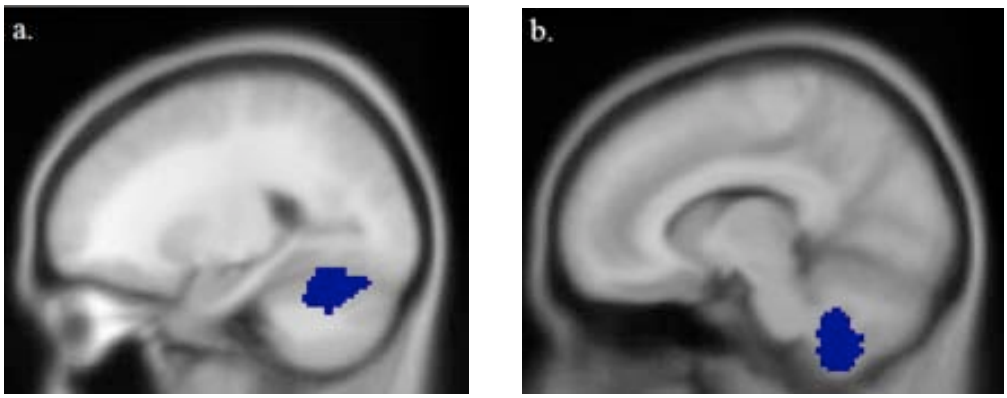
This table shows the results of the performed ROIs in the cerebellum during the reward/time estimation task. Abbreviations: *T*: statistical value; *P*: significance value.

Table 10. Whole-brain analysis from the distractor> no distractor contrast

Region of interest	Center of mass (MNI coordinates)			Cluster size (mm^3)	*t*	*P* value
	x	y	z			
ADHD<Control						
Left Postcentral Gyrus (BA48)	-57	-18	33	52	3.90	$p < 0.001$
Left Postcentral Gyrus (BA4)	-48	-18	45		2.83	0.002
Left Superior temporal Gyrus (BA20)	-45	-9	-36	52	3.47	0.002
Left inferior frontal Gyrus (BA48)	-39	15	24	86	3.28	0.001
	-48	18	24		3.13	0.001
ADHD>Control						
Right orbitofrontal cortex (BA11)	12	57	-21	22	3.34	0.001

This table shows the results of the whole-brain analysis associated with the reward/time estimation task. Abbreviations: BA: Brodmann area; *T*: statistical value; *P*: significance value.

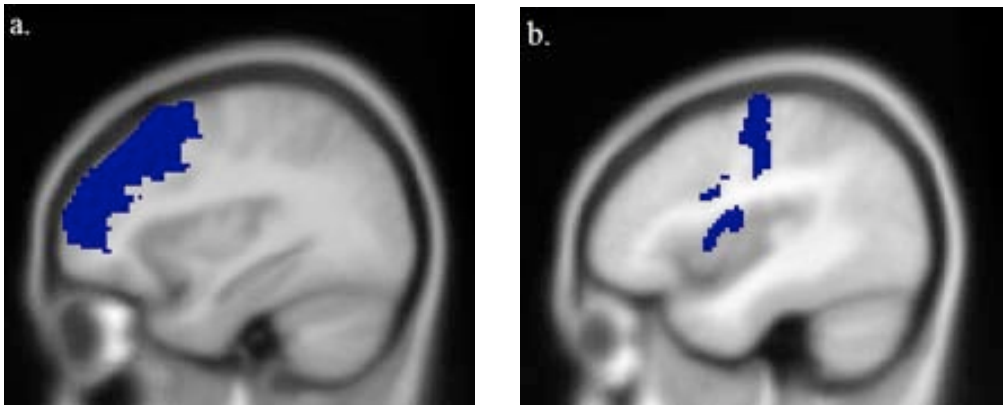
Figure 4. Figure 4 shows reduced cerebellar activity in the ADHD group associated with the performance of the reward/time estimation task.



a. **Standard ROI of the left cerebellar lobe IV**

b. **Standard ROI of the right cerebellum lobe I**

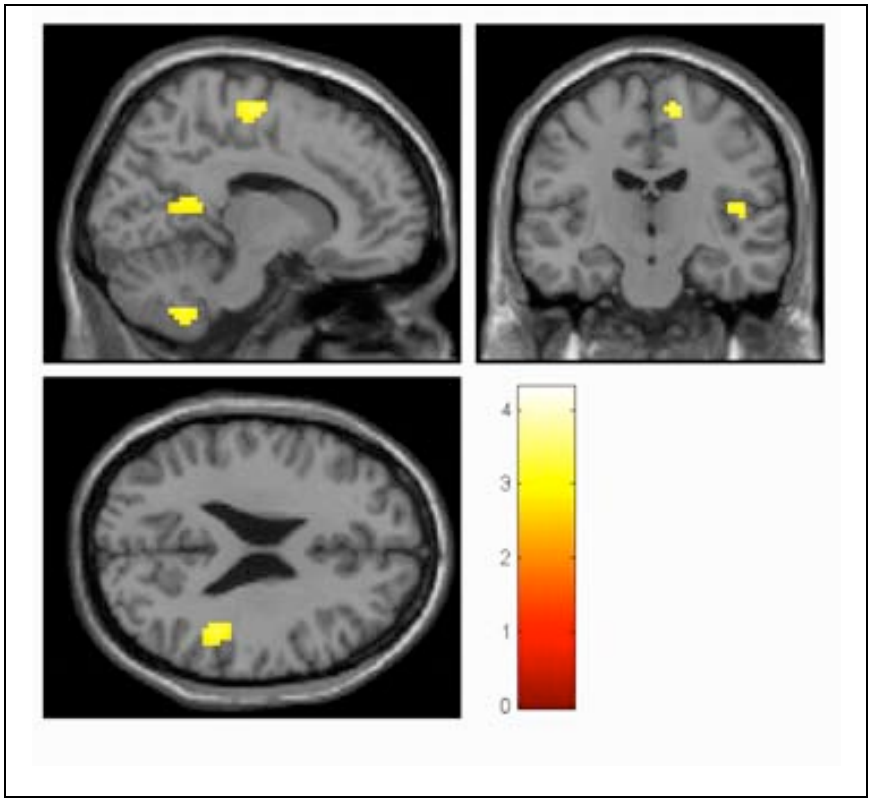
Figure 5. Decreased activity in the ADHD group associated with performance during the attention/time estimation task.



a. **Standard ROI of the left DLPFC**

b. **Standard ROI of the left precental gyrus**

Figure 6. Figure 6 shows decreased whole-brain activity in the ADHD group in comparison to the controls during the reward /time estimation task.



6. DISCUSSION

The main objective of this study has been to identify alterations in brain function related to the reward/motivation system and timing processing in adult ADHD. Therefore, 20 ADHD patients and 25 controls participated in an event-related reward/time estimation fMRI paradigm. With the aim of evaluating group related differences regarding the behavioural and neuroimaging data, we applied a mixed factorial mixed design with single within group factor, on which the one factor was the group (presence or not of ADHD) and two intra factor variables (reward: yes/no and distractor yes/no). In addition, all the applied clinical scales and ratings were analysed.

Based on previous findings that point to frontostriatal and cerebellar deficits in ADHD, (Noreika et al, 2013) we hypothesized that patients would show decreased ventral striatum and caudate activation during reward anticipation and also reduced activation in basal ganglia and cerebellum during timing related responses. As for the distractor/no distractor contrasts, we predict increased activity on the default mode network areas, and decreased level of activation in attention related regions. Additionally, we predict lower attention ratings and higher response variability in the ADHD adult group in comparison to the control groups.

Interestingly, our study yielded important new insights regarding the neural substrate underpinning ADHD in adults. The primary results indicated decreased brain activation in left and right cerebellum during reward anticipation/time estimation task in the ADHD group as compared to the control group. However, no differences were detected in left/right caudate regions, left/right nucleus accumbens regions and left/right inferior

frontal regions. Furthermore, whole brain analysis indicated decreased brain activity in the ADHD group as compared to the control group in right superior temporal gyrus, right and left cerebellum, right heschl's gyrus and left occipital middle gyrus. The opposite contrast indicated increased brain activation in the right frontal inferior gyrus and left superior parietal gyrus in ADHD in comparison to control subjects. At a behavioural level, we did not found any significant differences between the ADHD and the control group in the achieved performance when comparing the reward vs no reward conditions.

Regarding the distractor condition, the extracted apriori ROIs included the middle, inferior and superior frontal gyri, the accumbens, the caudate and the cerebellum. The results indicated decreased brain activity in the left precentral gyrus and left middle frontal gyrus in the ADHD group. The whole brain analysis indicated reduced brain activity in the left post central gyrus, left temporal gyrus and left inferior frontal gyrus in the ADHD group in comparison to the control group. By contrast, increased brain activity was detected in the right superior frontal gyrus in ADHD patients. The behavioural analysis for the distractor vs no distractor conditions did not indicate significant differences among groups.

It is relatively well established that both reward and attention related neural mechanisms might be core components in ADHD's physiopathology (Durston et al., 2007). Most fMRI studies have focused on cognitive impairments involving working memory, attention and inhibitory control. In addition, motivational system abnormalities have

been observed and related to dysfunctions in the neural functioning of reward anticipation processes. However, recent studies suggest a third possible component in the pathophysiology of ADHD, involving timing functioning deficits (Hart et al., 2012; Valera et al., 2010).

As proposed by Sonuga-Barke (2010) deficits in different neurobiological pathways may independently lead to symptoms in ADHD. This multiple pathway model might involve at least three independent pathways: a dorsal frontostriatal pathway involved in cognitive control, a ventral frontostriatal pathway involved in reward processing and a frontocerebellar pathway related to temporal processing (Durston et al., 2007).

Recently, dysfunctional temporal processing have been argued to play an important role in impulsiveness, a core symptom of ADHD, that is defined as a premature (i.e., badly timed), impatient and delay averse (for ADHD patients, the duration of time seems subjectively more intolerable) response pattern that does not consider the consequences of future acts Rubia et al., 2009a). Observational and experimental data on ADHD have also accounted for widespread time related deficits in these patients (Valera et al., 2010). Specifically, people with impulsive disorders typically show cognitive deficits in all temporal processing domains, including motor timing, perceptual timing and temporal foresight (Noreika et al., 2013). Such alterations may represent an important aspect that might help understanding ADHD patients' inability to adjust to environmental timing demands. For instance, it has been observed that these individuals usually present difficulties in daily life aspects such as punctuality, planning, and memory. Thus, ADHD subjects are known for choosing immediate smaller rewards

over delayed larger ones, and presenting premature responses (Barkley, 1999; Rubia et al., 2009a). Taken together, all these impulsive related behaviors tipically observed in ADHD might indicate timing disturbances as part of the disorders`pathophysiology. Our results indicate that cerebellar deficits in ADHD might be related to temporal processing abnormalities that might affect cognitive performance among these patients as compared to healthy subjects.

This abnormal activation pattern has been observed while performing the reward task. As predicted, ADHD adults presented decreased brain activity than controls in both hemispheric-cerebellar regions. Recent literature has indicated that ADHD might be a neurodevelopment disorder involving the frontostriatal pathway and connections with the cerebellum and parietal lobe (Rubia et al., 2009a). Additionally, recent neuropsychological and neuroimaging studies have identified the cerebellum as a third region involved in ADHD's patophysiology, since several studies show reduced activation (Valera et al.,2010; 2005; Durston et al., 2007) and decreased volume (Castellanos, 1997; Berquin et al., 1998) of the cerebellum in ADHD patients.

Recently, cerebellar functions have been studied more carefully. It has been observed that this structure is massively interconnected with the cerebral cortex and that it receives information from widespread cortical areas, including regions of the frontal, parietal, temporal, and occipital lobes (Strick, Dum, & Fiez, 2009). Anatomically, the cerebellum (latin for little brain) is formed by a tightly folded and corrugated layer of cortex, with white matter underneath, several deep nuclei embedded in the white matter, and a fluid-filled ventricle in the middle (Edwards, Newman, & Bismark., 2008).

Like the cerebral cortex, it is also divided in lobes, including the flocculonodular lobe, the anterior lobe (rostral to the "primary fissure"), and the posterior lobe (dorsal to the "primary fissure"). The latter two can be further divided into the midline cerebellar vermis and lateral cerebellar hemispheres.

As for its' functional anatomy, the cerebellum can be divided into different regions based on functional connectivity with sensorimotor or prefrontal and parietal cortices. For instance, lobules IV to VI have shown multiple loops with frontal regions, including projections with motor cortex (Strick et al., 2009). In addition, lobule IX has been related to several functional tasks including sensation (Hui et al., 2005), motor synchronization (Jantzen et al., 2004), working memory (Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997) and perception of change in stimulus timing (Liu, Lachamp, Liu, Savtchouk, & Sun., 2008). Therefore, it is possible that lobule VI–crus I contribute in estimating the valence of salient, emotional cues and selecting appropriate behavioral responses (Habas et al., 2009). Additionally, lobules VI and VIIA are sensitive to verbal working-memory load, suggesting the cerebellum processes input from prefrontal working-memory systems (Desmond et al., 1997). Collectively, this suggests that cerebellar damage may disrupt the maintenance of intervals in working memory during time reproduction.

Additionally, it is been suggested that the cerebellar cortex is not functionally homogeneous (Strcik et al., 2009). It might contains localized regions that are interconnected with specific motor or nonmotor areas of the cerebral cortex and this map of function in the cerebellar cortex is likely to be as rich and complex as that in the cerebral cortex (Kelly & Strick 2003).

Consequently, global dysfunction of the cerebellar cortex can cause wide-ranging effects on behavior (Schmahmann, 2004). For instance, dysfunction of a specific portion of the cerebellum can lead to determined deficits, which may be motor or nonmotor depending on the concrete site of the cerebellar abnormality occur. Specifically, this output to nonmotor areas of the cerebral cortex is thought to originate specifically from a ventral portion of the cerebellar dentate and this nonmotor region of the dentate is recognized by several molecular markers.

Moreover, studies with patients that suffered from cerebellar injuries have shown that, in addition to motor coordination deficits, cerebellar lesions may cause cognitive difficulties such as producing and perceiving time intervals (Ivry & Keele 1989). Furthermore, studies with cerebellar lesions patients, have also shown cognitive and behavior alterations such as difficulties in the administration of the time, difficulties in sustaining attention, difficulties in dealing with abstract concepts, impulsivity, and difficulties in production and organization, very similar to those found in ADHD (Baldacre et al. 2012).

Specifically, it has been suggested that recurrent networks in the cerebellum allow fine discriminations in different spatiotemporal patterns of input to the cerebellar cortex (de Solages et al. 2008). With the loss of precise timing information and control, motor commands and internal cognitive states may no longer be appropriately selected and sequenced at a fine level. Thus, an affected individual may become less motorically coordinated and might exhibit problems with task-shifting and other forms of executive

control (Strick et al. 2009). This suggests that there might be a frontocerebellar circuit/substrate underlying timing processing engaged for movement control (Valera et al., 2010).

As mentioned before, the cerebellum has been known as a key area of structural and functional abnormalities in ADHD, and, recently, it has been implicated as one important mediator in time discrimination (Smith, Taylor, Brammer, Halari, & Rubia, 2008). Specifically, it has been suggested as being important for stimulus expectancy and detection, which is dependent on events timing (Rubia et al., 2007) since patients with ADHD are impaired in target detection and discrimination, by showing more errors and slower and more variable response (Banaschewski et al., 2003). Cerebellar implication in timing aspects may be sustained by the fact that neuroimaging studies in both healthy subjects and ADHD patients account for evidence of shared underlying neural mechanisms of different timing functions. For instance, in healthy adults, the frontal premotor areas, basal ganglia, cerebellum, and parietal lobes appear to be involved in different temporal domains including motor and perceptual timing (Wiener, Turkeltaub, & Coslett, 2010).

Timing abilities involve the capacity to accurately process and act on temporal information. Therefore, our perception of time is related to several processes that help structure actions and enable anticipation of events. Classic theories of timing (Gibbon, Church, & Meck, 1984; Killeen & Fetterman, 1988; Zakay & Block, 1996) have used a clock metaphor to describe a timekeeping mechanism, which conceives time through

the accumulation of pulses. This timekeeper's functioning depends upon attention, which controls the starting and stopping of pulses, this way enabling anticipation of events. Once the representation of time is formulated, it is routed to working memory. An abnormal temporal processing may be due to a disruption in one or more of these processes (Harrington, Lee, Boyd, Rapcsak, & Knight, 2004).

Interestingly, as in previous studies (Valera et al. 2010; Rubia et al 2009a) our ADHD patients failed to activate cerebellar regions VI and IX in the same level as healthy individuals during a time discrimination task. Therefore, cortico-cerebellar network might be disrupted in ADHD, since deficits are found in cerebellar areas as well as in cerebral regions, including frontal, parietal and basal ganglia. These findings are line with recent studies indicating that cerebellar regions might be specifically connected with sensorimotor or prefrontal and parietal cortices (Valera et al., 2010) as well by cerebellar damage studies that indicate cognitive deficit similar to those observed in ADHD (Baldacara et al., 2012). We consider that ADHD might be characterized by inefficient frontocerebellar recruitment that might result in neural dysfunctioning in timing related tasks. We suggest that abnormalities in this region may represent a harder capacity for these patients to internally represent the passage of time and to appropriately discriminate it.

Finally, a recent perspective suggests that cerebellar activation reflects the use of sensorimotor imagery, such as imagined speech. Specifically, representations and processes that would be engaged during actual movement are co-opted to provide internal representations that assist cognition. In the motor domain, several studies have

shown that the cerebellum activates when subjects imagine making a movement, such as a finger tap (Hanakawa, Dimyan, & Hallett, 2008). Similarly, the cerebellum is active when subjects are instructed to imagine producing simple speech utterances (Ackermann, Wildgruber, Daum & Grodd, 1998). These findings raise the possibility that the cerebellum will be recruited whenever subjects engage in inner speech—which implies one's internal (imagined) voice to represent, maintain, and organize relevant information and conscious thoughts. Humans exhibit a strong tendency to engage in verbal coding and recoding, and thus internal speech-based representations may be important for a wide array of tasks that do not explicitly require speech or language processing. Beyond inner speech per se, recent findings suggest that conceptual knowledge of the world may rest, in part, upon internally driven activation of perceptual and motor representations (embodied cognition) (Barsalou 1999). Interestingly, self-directed speech has been observed to be an impaired and immature area regarding ADHD`s neuropsychology since it might involve formulating rules and plans to solve problems as well as internal reflection, description, questioning, instructing and it is related with the creation of internal rules in order to govern behavior. Evidence suggests ADHD youngsters to be less compliant with verbal commands and to develop inner speech at a later age (Barkley, 1999). Thereby, since our patients were instructed to silently count the specific time intervals, implicated areas in imagined speech might be recruited. Interestingly, our results indicate that patients were not able to recruit the proper activation level as the controls did, reflecting that inner speech might be a disturbed cognitive area in ADHD that could be related to cerebellar functioning deficits.

However, even though we observed decreased brain activation in right and left cerebellum in ADHD patients during the time estimation task, it was interesting that no significant differences were found in the nucleus accumbens and/or frontal regions, since the time discounting task involved rewarded as well as unrewarded stimulus. In addition to confirming the cerebellum's role in timing processing events and its possible dysfunctioning as part of ADHD´s pathophysiology; these findings might implicate several aspects: a) the lack of accumbens and frontal abnormalities could be explained by the fact that the temporal discrimination task might represent a possible masking effect on the reward condition, b) typically observed alterations in the basal ganglia are thought to mitigate with age, c) cerebellar alteration seemed to persist in to adulthood, d) medication status and e) the time units implemented in the task and f) different ages in previous findings.

First, our results indicated that, even in the event of a rewarded task, time estimation processing may be a preponderant, superior mechanism in ADHD, thus altered in this disorder. This might elucidate a possible masking effect on which neural activity related to the reward condition became mitigated due to a superior neural requirement for the time discrimination task. Second, follow up studies on children and adolescents with ADHD have shown that volumetric alterations in the basal ganglia, concretely in the right caudate, typically found in this disorder, tend to mitigate with age, while cerebellar alterations were observed to persist in adulthood; regardless of medication (Proal et al., 2011). Third, since our study was carried out in an un-medicated ADHD sample, this could also be related with the fact that we did not observed further activity differences

in the basal ganglia, in contrast to previous studies in adult ADHD (Valera et al., 2010). Fourthly, another important aspect is that other fMRI studies in ADHD have used sub-second paradigms, and there is evidence that supra-second and sub-second timing may account for different neural mechanisms (Valera et. al, 2010). This problem has been exacerbated by failures to demonstrate impairments across different measures of timing, which would strengthen the relationship between localized brain dysfunctions and deficient timekeeping operations (Harrington et al., 2004). Lastly, even though the outcomes of this study are consistent with those of Durston et al. (2007) and Smith et al. (2008) regarding cerebellar underactivations during time expectancy and duration discriminations tasks, it is important to point out that the present results differed in that we did not find brain activity differences in frontal regions, including the inferior frontal gyrus. However, such studies dealt with young ADHD patients, on contrast to our study, which used adults. This suggests that further research is needed in all age groups in order to obtain converging evidence that might improve the present knowledge on the neural substrate underlying timing processing dysfunctions in ADHD.

Finally, the whole brain analyses also indicate several areas that showed decreased activity in the ADHD patients as compared control subjects. These included the left cerebellum 6 and right cerebellum 9 (same indicated in ROIs analyses) right supplementary motor area, left rolandic opper gyrus, right Heschl's gyrus , right precunueus and left middle occipital gyrus. As mentioned before, the cerebellum is thought to play an important role in temporal functioning (Valera et al.,2010; Noreika et al. 2013). Another interesting finding is the underactivation found in the right

supplementary motor area in ADHD patients, which have been related to non-motor perceptual timing task, such as duration discrimination in both sub-second and supra-second levels (Smith, Taylor, Lidzba, & Rubia, 2003; Teki, Grube, & Griffiths, 2011; Weiner et al., 2010) and also appears to present an abnormal recruitment in ADHD (Rubia et al., 2009a; Smith et al., 2008; Valera et al., 2010; Vloet et al., 2010). In addition, Heschl's gyrus has been associated with inner speech (Dierks et al., 1999). Importantly, this executive function has been shown to be dysfunctional in ADHD (Barkley, 1999) which could explain the decreased activation we found in ADHD in comparison to controls in relation to a task that implicate internal speech functioning, reflecting patients' neural deficiencies in activating this area. Another interesting finding was the decreased activation pattern we observed in the right precuneus. The posterior cingulate/precuneus is thought to mediate visual–spatial attention to reward (Small et al., 2003) and delay gratification (Wittmann, Leland, & Paulus, 2007). It was found to be reduced in ADHD children during rewarded attention trials (Rubia et al., 2009b) therefore reflecting reduced attention representation of the delayed reward option. Consistently with such findings, we observed reduced activation on patients in the precuneus. This could be related to the fact that our task not only involved attention allocation, but also implicate the reward system, widely known for its deficits regarding ADHD's neural and neuropsychological mechanisms. Therefore, our patients might be reflecting difficulties in allocate the attention during the reward condition. The left rolandic operculum gyrus and the left middle occipital gyrus also presented decreased brain activity in ADHD patients as compared to controls. However, further research is needed in order to elucidate the role these regions might play regarding ADHD's neural abnormalities.

By contrast, ADHD patients displayed increased activation levels in right frontal inferior gyrus and left superior parietal gyrus than controls. Inferior prefrontal activation is thought to mediate related functions of sustained attention, inhibition and working memory (Rubia, Smith, Bramer, Toone, & Taylor, 2005; Rubia et al., 2009b). Additionally, inferior parietal regions are important for allocating attention to time, imagery and quantity representations, thus contribute to inter-temporal choice in their role as magnitude comparators of both time and reward (Sandrini et al., 2004). Since ADHD patients are known for their attention difficulties, an increased activation in attention associated areas could indicate that ADHD patients might require an extra loading in order to perform the task. Therefore, an increased level of activity was recruited in areas related with attention processes, such as frontal inferior gyrus and superior parietal gyrus, are very likely to act as a compensatory mechanism to perform the task adequately.

Therefore, we suggest that cerebellar underactivation in these patients might be related to timing functions, such as the adjustment of behavior to specific durations, the ability to perceive and estimate the passage of time and the ability to consider future consequences. However, further research with more sensitive tasks might be elucidating, since our task did not reflect behavioral differences between groups. In the within subjects tests we did observed significant differences, implicating that the paradigm in deed was well structured, since subjects achieved different performances, regardless of the group. Even though neural abnormalities were detected, perhaps more sensitive tasks such as millisecond estimating task (our durations included relatively

long stimulus intervals, i.e., from 1 second to 6 seconds) may reflect more accurately behavioral disturbances related to timing possessing in ADHD.

As for the results of the ROI analysis in the distractor>no distractor contras, it was interesting that we observed decreased activation levels in left DLPFC and the left precentral gyrus in ADHD patients as compared to controls, once more reflecting that these patients might present difficulties in recruiting cognitive related regions.

It has been known that the DLPFC plays an important role in executive functioning including working memory (Barbey, Colom, & Grafman, 2013), sustained attention (Banich et al., 2009), and endogenous shift of attention to time (Coull et al., 2010). Interestingly, several cognitive functions mediated by DLPFC are known to be closely linked with timing functioning, particularly working memory and attention (Pouthas & Perbal, 2004). For instance, attention to time is critical to an adequate estimation or in adjusting motor responses to external stimuli (Wiener et al., 2010). Working memory is necessary to hold temporal information online, an aspect that is crucial for further reproduction of temporal time intervals or for inter-temporal decision making (Dutke, 2005; Hinson, Jameson &Whitney, 2003).

Furthermore, working memory and timing processing may function within connected neural mechanisms. Theories of timing (Gibbon et al., 1984; Killeen & Fetterman, 1988; Zakay & Block, 1996) use a clock metaphor to describe a timekeeping mechanism, which represents time through the accumulation of pulses.

The operation of the timekeeper depends upon attention, which controls the starting and stopping of pulses, thereby enabling anticipation of events. Once a representation of time is formulated, it is routed to working memory. Impaired temporal processing can therefore be due to a disruption in one or more of these processes (Harrington et al., 2004).

Moreover, frontal regions, in particular the DLPFC, are known to be involved in perceptual timing, most common in supra-second intervals (Basso, Nichelli, Wharton, Peterson, & Grafman, 2003; Lewis & Miall, 2003; Jech, Dusek, Wackermann & Vymazal, 2005). Therefore, it might be possible that relatively long durations may require an increased DLPFC functioning, since working memory and attention are further needed in time perception tasks. In our findings, we observed that ADHD patients fail in activating prefrontal regions such as the DLPFC and precental gyrus, implicated in executive and, more specifically, timing functioning (Noreika et al., 2013).

Furthermore, substantial literature provides evidence of ADHD-related dysfunction in multiple neuronal systems involved in cognitive functioning, including prefrontal deficits (Cortese et al., 2012). Additionally, as mentioned before, there is also growing evidence of timing processing deficits in ADHD and that it might be related to an abnormal recruitment of prefrontal regions such as the precentral gyrus and DLPFC and its' interconnections. In addition to the supplementary motor area and anterior congulate

cortex, the DLPFC and the precentral gyrus have been strongly related with timing domains including duration discrimination at both sub and supra-second levels. (Christakou et al., 2013; Rubia et al., 2009a; Smith et al., 2008; Valera et al., 2010; Vloet et al., 2010). Even in non-motor time estimation tasks, frontal regions have been involved in both motor and nonmotor timing tasks, which may indicate a neural underpinning mechanism shared in different timing functions (Valera et al., 2010).

Therefore, it is not surprising that ADHD patients showed a reduced recruitment of key areas involved in both executive and timing functioning, i.e., the dlPFC and precentral gyrus. Due to the presence of the distractor, which added more difficulties to the task, and hence an increased cognitive load, especially with regard to working memory, attention and timing. This might suggests that the allocation of attentional resources needed for temporal processing are more vulnerable in ADHD patients than in healthy individuals. Barkley, Koplowitz, Anderson and McMurray (1997) found that distraction during a duration reproduction task increased the magnitude of performance errors in children with ADHD but not among healthy controls. In addition, impaired activity levels have also been found in the left fronto-parietal as working memory demands exceed the capacity of adults with ADHD as compared to controls subjects (Ko et al, 2013).

Consequently, ADHD patients were unable to attain the same frontal functioning as the healthy individuals when a distraction stimulus was presented, reflecting functional brain abnormalities in key areas implicated in cognitive functioning, more than in temporal functioning. This might explain why cerebellar underactivations were not found when analyzing brain activity during the presence of a distractor stimulus, which required greater attention allocation.

As previously mentioned, primary motor areas (precentral gyrus) have been related to internal movement's generation since it has been implicated in both motor and non-motor tasks, (Valera et al., 2010) as well as in sub and supra-second timing processes (Wiener et al., 2010). Failure to activate the premotor regions as strongly as controls during the time estimation paradigm, might reflect ADHD difficulties in generating internal sensorimotor at required rates, as needed in counting for several seconds, according to the instructions that were given to all subjects. Counting may also required an important working memory loading, since it also might implicate internal speech functioning. This cognitive domain has also shown to be dysfunctional in ADHD (Barkley, 1999). Therefore, a temporal discrimination task with an additional distractor factor might represent increased difficulties for ADHD patients in the recruitment of implicated areas for performing the counting task. This is consistent with the underactivated prefrontal areas our ADHD patients showed in comparison to control subjects. Even though behavioral differences were not observed, probably because of a lack of sensitivity regarding the task, neural abnormalities were observed thereby reflecting blunted mechanisms in prefrontal regions activity in ADHD patients during working memory and temporal related processes.

As mentioned before, the DLPFC have been established as a key region in distinct cognitive contexts which also appears to be impaired in ADHD. Abnormal patterns of activation might indicate executive dysfunction in ADHD patients probably related with higher needed attention levels in respond to the distractor, and it might also indicate difficulties for ADHD individuals in engaging frontocerebelar circuits crucial for an adequate performance in tasks (Valera et al., 2010), following the notion that this area subserves several cognitive domains, according to its connections with other cortical and subcortical areas (Cubillo et al.,2012; Rubia, 2011). Considering the increased attention loading due to the distractor, our results indicate that ADHD adults might be characterized by difficulties in allocating extra-cognitive resources when needed, since they did not where able to recruit implicated regions as controls did. Even thought our analysis of the behavioral data did not reflect performance differences between patients and controls, the observed deficits in brain activation may indicate the effects of the distraction in attention levels, by reflecting mayor difficulties in the recruitment of cognitive implicated regions.

Furthermore, the whole brain analysis for the distractor context indicated reduced brain activity in the left post central gyrus, left inferior temporal gyrus and left inferior frontal gyrus in the ADHD group in comparison to the control group. As mentioned above, decreased activation levels the post central gyrus/inferior frontal gyrus might reflect ADHD difficulties in generating internal sensorimotor representations at required rates in comparison to controls. As mentioned above, there is increasing evidence of timing processing deficits in ADHD and that it might be related to an abnormal recruitment of

prefrontal regions such as the precentral/inferior frontal gyri. These regions have been strongly associated with timing domains including duration discrimination at both sub and supra-second levels. (Christakou et al., 2013; Rubia et al.,2009a; Smith et al.,2002; 2008; Valera et al.,2010; Vloet et al.,2010). Additionally, as for the inferior temporal gyrus, it is thought to be related to visual perception (Onitsuka et al., 2004). Therefore, a decreased activation in this area in the ADHD patients might represent difficulties in visual perception/integration of figures, i.e. foreground objects as the distractor, in ADHD individuals as compared to healthy subjects. Nevertheless, it is our thought that perception related deficits should be considering for future restudies regarding ADHD underpinning neural mechanisms.

In the opposite contrast, we observed increased brain activity in the right orbitofrontal cortex in the ADHD patients. Specifically, this region has been related to impulsivity and altered orbitofrontal functioning in ADHD has also been reported in studies investigating the effect of reward on executive functioning (Cubillo et al., 2011; Dibbets et al., 2011). However, in the distractor context, a specific attribution of orbitofrontal abnormalities to either anticipatory or consumatory processes is difficult since the focus on this context is the effect of attention rather than a reward processing alone. Moreover, some uncertainties remain with respect to the direction of orbitofrontal alterations in ADHD, for some studies found a hypoactivation whereas others a hyperactivation (Wilbertz et al., 2012). Concretely, the latter is our case, thereby we consider that these interpretations might remain speculative and should be considered for future research on ADHD.

Another interesting finding, as mentioned before, is that cerebellar alterations were not found in the distractor context. This could indicate that distraction had a significant effect on ADHD patients as compared to controls, reflecting the difficulties that ADHD individuals have in filtering irrelevant information, since the subjects were instructed to ignore the distractor. Therefore, an extra cognitive allocation needed for performing a specific attention task might require a stronger recruitment of prefrontal regions (i.e. DLPFC and PCG) than cerebellar recruitment, probably more related to the estimation task. Our results may confirm cognitive deficits that characterize ADHD subjects, as they seem to have more complications than controls in maintaining attention in a specific task (counting) as instructed. They were easily distracted and thereby, it is possible the role of prefontal regions was more detected than cerebellar involvement.

Finally, there were no significant relationships between the CAARS inattention and impulsivity scales and the cerebellar, DLPFC and the precentral gyrus ROIs. This could imply that temporal dysfunctions may not be associated with all ADHD symptoms. However, such alterations might as well represent core features of ADHD, but independently of inattentive and hyperactive symptoms. Perhaps a more precise measure of symptom severity would have shown a relationship. Future studies designed to address such questions using other ADHD rating scales could be revealing.

To summarize, there is a number of important aspects to these findings. Mainly, our results confirm the cerebellum as an altered neural substrate implicated in ADHD pathophysiology that might as well be related to abnormal timing processing and e

xecutive functioning. Additionally, several important assets of our study include the following: no medication and comorbidity effects, a considerable sample size and the novelty of our study's design (no previous studies have implemented this task and there are few studies with un-medicated adult ADHD samples).

It is known that long-term medication involving methylphenidate have proved to meliorate impulsive behaviour in ADHD, which might result in the improvement of timing related deficits in these patients (Noreika et al., 2013). Therefore studying neural responses to reward anticipation and timing discounting in patients who had never received medication might improve understanding of the neural substrate underpinning the pathophysiology of ADHD. Another important aspect on these results is that any comorbidity with other psychiatric disorder was excluded from the study, which ensures that our results could not be related to other condition's effect.

Additionally, our sample size may represent a considerable number as compared to similar studies involving adult ADHD, which included fewer patients. Finally, even though there is substantial evidence of time related deficits in youth ADHD patients, to our knowledge, only two studies have investigate timing functioning in adults with ADHD and both are performed by the same research group (Valera et al., 2010). Therefore the importance of our study, which aims to improve the actual understanding of the abnormal timing substrate that seems to characterize adults with ADHD.

In conclusion, taken together, all these results implicate the cerebellum and DLPFC as dysfunctional regions that might lead to timing and executive dysfunctions strongly observed in ADHD. Furthermore, in light of these results, we suggest that ADHD is more likely to involve a variety of brain regions or circuits rather than being limited to certain key nodes or regions. Specifically, this circuit might involve fronto-striato-parietal networks, as well as cerebellar areas (Hart et al., 2013). Therefore, an increased understanding of response variability and timing functioning might provide important implications for treatment and knowledge of core features of ADHD that seem to persist into adulthood (Valera et al., 2010). For these reasons, anatomical and neural alterations involving such regions, and, more important, the connections/circuits between them, are thought to play an important role in the neural dysfunction characterising ADHD individuals.

These findings are in line with a conception of ADHD neural dysfunction as reflecting altered functioning within a set of brain regions, which may form functional circuits. Recently, it is been suggested that timing processing might represent a third component in ADHD's neuropsychological dissociable pathway (Sonuga-Barke et al., 2010). ADHD have been conceived as an heterogeneous condition, with different individuals affected in different level in the different affected domains. Therefore, our results extend the conception the dual pathway model of ADHD heterogeneity, since we provide evidence that temporal processes might be a third dissociable neuropsychological domain that affects ADHD, most likely to involve specific neural mechanisms that could be the core underpinning diverse problems observed in ADHD (Sonuga-Barke et al., 2010).

LIMITATIONS:

Regarding our results and conclusions, a number of limitations need to be considered. First, the task employed reflected seems not to be sensitive enough to detect the behavioural mechanism underpinning timing or motivational related deficits. Most likely that a more sensitive test, for instance a subsecond task or perhaps a more elaborated cognitive paradigm such as those similar to the Stroop test, might reflect more regarding ADHD's neural abnormalities as well as the affected behavioural performance. Secondly, several functional data sets had to be excluded from the study because of artefacts effects, probably because of patients' movement inside the scanner. This might represent a limitation for our study because perhaps that the patients that move the most (and were discarded) are likely to be the ones with higher symptomatology. Therefore, we lost important endophenotypes that best represent ADHD's neural abnormal substrate.

7.REFERENCES

Ackermann, H., Wildgruber, D., Daum, I. & Grodd, W. (1998). Does the cerebellum contribute to cognitive aspects of speech production? A functional magnetic resonance imaging (fMRI) study in humans. Neuroscience, 247, 187–90.

Adler LA, Liebowitz M, Kronenberger W, Qiao M, Rubin R, Hollandbeck, M.,… Durell T. (2009) Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder. Depression and Anxiety. 26(3):212-21.

Albayrak O, Friedel S, Schimmelmann BG, Hinney A, & Hebebrand J. (2008). Genetic aspects in attention-deficit/hyperactivity disorder. Journal of Neural Transmision.,2008;115: 305–315.

Albert, J., López-Martín, S., Fernández-Jaén, A., & Carretié, L. (2007). Emotional alterations in attention deficit hyperactivity disorder: existing data and open questions. Revista de neurologia, 47(1), 39-45.

Alberts-Corush, J., Firestone, P. & Goodman, J. T. (1986). Attention and impulsivity characteristics of the biological and adoptive parents of hyperactive and normal control children. American Journal of Orthopsychiatry, 56 (3), 413-23.

American Psychiatric Association. (1968). Diagnostic and statistical manual of mental disorders (DSM-II) (2nd ed.). Washington DC: Author.

American Psychiatric Association. (1980). Diagnostic and statistical manual of mental disorders (DSM-III)(3rd ed.). Washington DC: Author.

American Psychiatric Association. (1987). Diagnostic and statistical manual of mental disorders (DSM-III-R) (3rd ed. rev.). Washington DC: Author.

American Psychiatry Association. (1994). Diagnostic and statistical manual of mental disorders (DSM-IV) (4th ed.). Washington DC: Author.

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (DSM-IV-R)(4th ed.). Text revision. Washington DC: Author.

Angoa-Pérez, M., Kane, M. J., Briggs, D. I., Sykes, C. E., Shah, M. M., Francescutti, D. M., ... & Kuhn, D. M. (2012). Genetic depletion of brain 5HT reveals a common molecular pathway mediating compulsivity and impulsivity. Journal of neurochemistry, 121(6), 974-984.

Arnsten, A.F. (2006). Stimulants: Therapeutic actions in ADHD. Neuropscychopharmology, 31(11), 2376-83.

Arnsten, A.F., & Pliszka, S.R. (2011). Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacology, biochemistry and behaviour, 99, 211-216.

Arnsten, A. F., & Li, B. M. (2005). Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biological psychiatry, 57(11), 1377-1384.

Baldaçara, L., Borgio, J. G. F., Araújo, C., Nery-Fernandes, F., Lacerda, A. L. T., & Moraes, W. A. D. S. (2012). Relationship between structural abnormalities in the cerebellum and dementia, posttraumatic stress disorder and bipolar disorder. Dementia e neuropsychologia, 6(4).

Baldwin, R. L., Chelonis, J. J., Flake, R. A., Edwards, M. C., Feild, C. R., Meaux, J. B., & Paule, M. G. (2004). Effect of methylphenidate on time perception in children with attention-deficit/hyperactivity disorder. Experimental and clinical psychopharmacology, 12(1), 57.

Banaschewski, T., Becker, K., Scherag, S., Franke, B. & Coghill, D. (2010). Molecular genetics of attention-deficit/hyperactivity disorder: an overview. European Child & Adolescent Psychiatry, 19(3), 237-257.

Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E. & Rothenberger, A. (2003). Association of ADHD and conduct disorder-brain electrical evidence for the existence of a distinct subtype. Journal of Child Psychology and Psychiatry, 44(3), 356-357.

Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., …Taylor E. (2006) Long-acting medications for the hyperkinetic disorders: a systematic review and European treatment guideline. European Child and Adolescent Psychiatry, 15(8): 476-95.

Banich, M.T., Burgess, G.C., Depue, B.E., Ruzic, L., Bidwell, L.C., Hitt-Laustsen, S., et al. (2009). The neural basis of sustained and transient attentional control in young adults with ADHD. Neuropsychologia, 47(14), 3095-104.

Barbey, A.K., Colom, R. & Grafman, J. (2013). Dorsolateral prefrontal contributions to human intelligence. Neuropsychologia, 51(7), 1361-1369.

Barkley, R. A., Koplowitz, S., Anderson, T., & McMurray, M. B. (1997). Sense of time in children with ADHD: Effects of duration, distraction, and stimulant medication. JOURNAL-INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY, 3, 359-369.

Barkley, R. A., Murphy, K. R., & Bush, T. (2001). Time perception and reproduction in young adults with attention deficit hyperactivity disorder. Neuropsychology, 15(3), 351.

arkley, R.A. (2006). The relevance of the Still lectures to attention-deficit/hyperactivity disorder: a commentary. Journal of Attention Disorders, 10, 137–140.

Barkley, R. (2006). Attention-Deficit Hyperactivity Disorder: A handbook for diagnosis and treatment, 3ª. Ed. New York, NY: The Guilford Press.

Barkley, R. (1999). Response inhibition in attention-deficit hyperactivity disorder. Mental Retardation and Developmental Disabilities Research Review, 5(3), 177-184.

Barkley, R., & Murphy, K. (1998). Attention-Deficit Hyperactivity Disorder: A Clinical Workbook. Secon Ed. The Guilford Press.

Barkley, R. A., Smith, K. M., Fischer, M., & Navia, B. (2006). An examination of the behavioral and neuropsychological correlates of three ADHD candidate gene polymorphisms (DRD4 7+, DBH TaqI A2, and DAT1 40 bp VNTR) in hyperactive and normal children followed to adulthood. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 141(5), 487-498.

Barsalou, L.W. (1999). Perceptual symbol systems. Behavioral and Brain Functions, 22, 577-609.

Basso, G., Nichelli, P., Wharton, C.M., Peterson, M. & Grafman, J. (2003). Distributed neural systems for temporal production: a functional MRI study. Brain Res Bull, 59(5), 405-11.

Bayes, M., Ramos-Quiroga, J.A., Cormand, B., Hervas-Zúñiga, A., del Campo, M., Duran-Tauleria, E., Estivill, X. (2005). Large-scale genotyping in research into autism spectrum disorders and attention deficit hyperactivity disorder. Revista de neurologia, 40, 187-90.

Becker, K., El-Faddagh, M., Schmidt, M.H, Esser, G., & Laucht, M. (2008). Interaction of Dopamine Transporter Genotype with Prenatal Smoke Exposure on ADHD Symptoms. Journal of Pediatrics , 152(2),263-9.

Bekker, E. M., Overtoom, C. C., Kooij, J. J., Buitelaar, J. K., Verbaten, M. N., & Kenemans, J. L. (2005). Disentangling deficits in adults with attention-deficit/hyperactivity disorder. Archives of general psychiatry, 62(10), 1129.

Bekker, E.M., Overtoom, C.C., Kooij, J.J, Buitelaar, J.K., Verbaten, M.N., & Kenemans, J.L. (2005). Disentangling deficits in adults with attention-deficit/hyperactivity disorder. Archive of General Psychiatry, 62(10),1129-36.

Berquin, P. C., Giedd, J. N., Jacobsen, L. K., Hamburger, S. D., Krain, A. L., Rapoport, J. L., & Castellanos, F. X. (1998). Cerebellum in attention-deficit hyperactivity disorder A morphometric MRI study. Neurology, 50(4), 1087-1093.

Biederman, J., Spencer, T. J., Wilens, T. E., Weisler, R. H., Read, S. C., & Tulloch, S. J. (2005). Long-term safety and effectiveness of mixed amphetamine salts extended release in adults with ADHD. CNS spectrums,10(12 Suppl 20), 16-25.

Biederman, J., Makris, N., Valera, E. M., Monuteaux, M. C., Goldstein, J. M., Buka, S., ... & Seidman, L. J. (2008). Towards further understanding of the co-morbidity between attention deficit hyperactivity disorder and bipolar disorder: a MRI study of brain volumes. Psychological Medicine, 38(7), 1045-1056.

Biederman, J., & Faraone, S. V. (2006). The effects of attention-deficit/hyperactivity disorder on employment and household income. The Medscape Journa, of Medicine, 8(3),12.

Biederman, J., Faraone, S. V., Spencer, T.,, Wilens, T., Norman, D., Lapey, K.A., et al. (1993). Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry, 150(12), 1792-8.

Biederman, J., Petty, C. R., Fried, R., Doyle, A. E., Spencer, T., Seidman, L. J., Gross, L., Poetzl, K. and Faraone, S. V. (2007). Stability of executive function deficits into young adult years: a prospective longitudinal follow-up study of grown up males with ADHD. Acta Psychiatrica Scandinavica, 116: 129–136.

Biederman, J.; Petty, C.R., Fried, R., Kaiser, R., Dolan, C.R., Schoenfeld, S., Doyle, A.E., Seidman, L.J. & Faraone, S.V. (2008a). Educational and Occupational

Underattainment in Adults With Attention-Deficit/Hyperactivity Disorder: A Controlled Study. Journal of Clinical Psychiatry, .69, No. 8, 1217-1222.

Biederman, J.; Seidman, L.J., Petty, C.R., Fried, R., Doyle, A.E., Cohen, D.R., Kenealy , D.C. & Faraone, S.V. (2008b). Effects of Stimulant Medication on Neuropsychological Functioning in Young Adults With Attention Deficit/Hyperactivity Disorder. Journal of Clinical Psychiatry,69. 7, pp. 1150-1156.

Birnbaum, H. G., Kessler, R. C., Lowe, S. W., Secnik, K., Greenberg, P.E., Leong, S.A., et al. (2005). Costs of attention deficit-hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000. Current Medical Research and Opinion, 21(2),195-206.

Boonstra, A. M., Kooij, J. J., Buitelaar, J. K., Oosterlaan, J., Sergeant, J. A., Heister, J. G. A. M., & Franke, B. (2008). An exploratory study of the relationship between four candidate genes and neurocognitive performance in adult ADHD. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(3), 397-402.

Boonstra, A. M., Oosterlaan, J., Sergeant, J. A., & Buitelaar, J.K. (2005). Executive functioning in adult ADHD: a meta-analytic review. Psychological Medicine, 35(8),1097-108.

Bouffard, R., Hechtman, L., Minde, K., & Iaboni-Kassab, F. (2003). The efficacy of 2 different dosages of methylphenidate in treating adults with attention-deficit hyperactivity disorder. Canadian Journal of Psychiatry, 48(8),546-54.

Bradley, C. (1937). The behavior of children receiving benzedrine. American Journal of Psychiatry, 94, 577-585.

Brookes, K., Xu, X., Chen, W., et al. The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. Molecular Psychiatry (2006a) 11(10):934-53.

Brookes, K. J., Mill, J., Guindalini, C., Curran, S., Xu, X., Knight, J., ... & Asherson, P. (2006). A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. Archives of General Psychiatry, 63(1), 74.

Brown, W.A. (1998). Charles Bradley, M.D., 1902–1979. American Journal of Psychiatry, 155, 968.

Burd, L. & Kerbeshian, J. (1998). Historical roots of ADHD. Journal of the American Academy of Child and Adolescence Psychiatry, 27:262.

Cantwell, D. P. (1972). Psychiatric illness in the families of hyperactive children. Archives of General Psychiatry, 27(3), 414-7.

Cao, Q., Zang, Y., Sun, L., Sui, M., Long, X., Zou, Q., & Wang, Y. (2006). Abnormal neural activity in children with attention deficit hyperactivity disorder: a resting-state functional magnetic resonance imaging study. NeuroReport, 17(10), 1033-1036.

Carmona, S., Proal, E., Hoekzema, E. A., Gispert, J. D., Picado, M., Moreno, I., ... & Vilarroya, O. (2009). Ventro-striatal reductions underpin symptoms of hyperactivity

and impulsivity in attention-deficit/hyperactivity disorder.Biological psychiatry, 66(10), 972-977.

Carmona, S., Hoekzema, E., Ramos-Quiroga, J. A., Richarte, V., Canals, C., Bosch, R., ... & Vilarroya, O. (2012). Response inhibition and reward anticipation in medication-naïve adults with attention-deficit/hyperactivity disorder: A within-subject case-control neuroimaging study. Human brain mapping, 33(10), 2350-2361.

Castellanos, F.X. & Acosta, M.T. (2004) The neuroanatomy of attention deficit/hyperactivity disorder. Revista de neurología, 38: 131–136.

Castellanos, F.X. (1997). Toward a pathophysiology of attentiondeficit/hyperactivity disorder. Clinical Pediatrics, 36, 381-393.

Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., ... & Rapoport, J. L. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA: the journal of the American Medical Association, 288(14), 1740-1748.

Castellanos, F. X., Margulies, D. S., Kelly, C., Uddin, L. Q., Ghaffari, M., Kirsch, A., ... & Milham, M. P. (2008). Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biological psychiatry, 63(3), 332-337.

Christakou, A., Murphy, C.M., Chantiluke, K., Cubillo, A.I., Smith, A.B., Giampietro V., et al. (2013).Disorder-specific functional abnormalities during sustained attention in youth with Attention Deficit Hyperactivity Disorder (ADHD) and with autism. Molecular Psychiatry, 18(2), 236-44.

Clements, S.D. & Peters, J.E. (1962). Minimal brain dysfunctions in the school-age child. Diagnosis and treatment. Archives of General Psychiatry, 6, 185–197.

Comings, D. E., Gade-Andavolu, R., Gonzalez, N., Wu, S., Muhleman, D., Blake, H., ... & MacMurray, J. P. (2000). Multivariate analysis of associations of 42 genes in ADHD, ODD and conduct disorder. Clinical genetics, 58(1), 31-40

Conners, C. K., Erhardt, D., & Sparrow, E. (1999). Conners' Adult ADHD Rating Scales:(CAARS). Toronto: MHS.

Conners, C.K. (2000). Attention-deficit/hyperactivity disorder: historical development and overview. Journal of Attention Disorders, 3, 173-191.

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., & Castellanos, F. X. (2012). Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. American Journal of Psychiatry, 169(10), 1038-1055.

Coull, J. T., Cheng, R. K., & Meck, W. H. (2010). Neuroanatomical and neurochemical substrates of timing. Neuropsychopharmacology, 36(1), 3-25.

Crichton, A. (2008). An inquiry into the nature and origin of mental derangement: On attention and its diseases. (Original work published 1798). Journal of Attention Disorders, 12, 200-204.

Cubillo, A., & Rubia, K. (2010). Structural and functional brain imaging in adult attention-deficit/hyperactivity disorder. Expert Review of Neurotherapeuthics, 10(4),603-620.

Cubillo, A., Halari, R., Giampietro, V., Taylor, E. & Rubia, K. (2011). Fronto-striatal underactivation during interference inhibition and attention allocation in grown up children with attention deficit/hyperactivity disorder and persistent symptoms. Psychiatry Research, 193(1), 17-27.

Cubillo, A., Halari, R., Smith, A., Taylor, E. & Rubia, K. (2012). Fronto-corticaland fronto-subcortical brain abnormalities in children and adults with ADHD: A review and evidence for fronto-striatal dysfunctions in adults with ADHD followed up from childhood during motivation and attention. Cortex, 48, 194-215.

Cubillo, A., Halari, R., Ecker, C., Giampietro, V., Taylor, E., & Rubia, K. (2010). Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood Attention-Deficit Hyperactivity Disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching. Journal of psychiatric research, 44(10), 629-639.

de Graaf, R., Kessler, R. C., Fayyad, J., ten Have, M., Alonso, J., Angermeyer, M., ... & Posada-Villa, J. (2008). The prevalence and effects of adult attention-deficit/hyperactivity disorder (ADHD) on the performance of workers: results from the WHO World Mental Health Survey Initiative.Occupational and environmental medicine, 65(12), 835-842.

De Solages, C., Szapiro, G., Brunel, N., Hakim, V., Isope, P. et al. (2008). High-frequency organization and synchrony of activity in the Purkinje cell layer of the cerebellum. Neuron, 58, 775-8.

del Campo, N., Chamberlain, S. R., Sahakian, B. J., & Robbins, T. W. (2011). The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. Biological psychiatry, 69(12), e145-e157.

Depue, B.E., Burgess, G.C., Bidwell, L.C., Willcutt, E.G., & Banich, M.T. (2010). Behavioral performance predicts grey matter reductions in the right inferior frontal gyrus in young adults with combined type ADHD. Psychiatry Research, 182(3),231-237.

Depue, B.E., Burgess, G.C., Willcutt, E.G., Ruzic, L., & Banich, M.T. (2010). Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: evidence from deficits in individuals with ADHD. Neuropsychologia, 48(13),3909-3917.

Desmond, J.E., Gabrieli, J.D.E., Wagner, A.D., Ginier, B.L. & Glover, G.H. (1997). Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functional MRI. Journal of Neuroscience, 17, 9675-9685.

Dibbets, P., Evers, L., Hurks, P., Marchetta, N. & Jolles, J. (2011). Differences in feedback-and inhibition-related neural activity in adult ADHD. Brain Cognition, 70(1), 73-83.

Dierks, T., Linden, D. E., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., & Singer, W. (1999). Activation of Heschl's gyrus during auditory hallucinations. Neuron, 22(3), 615-621.

Dige, N., Maahr, E., & Backenroth-Ohsako, G. (2010). Reduced capacity in a dichotic memory test for adult patients with ADHD. Journal of Attention Disorders. 13(6),677-83.

Dorval, K. M., Wigg, K. G., Crosbie, J., Tannock, R., Kennedy, J.L., Ickowicz, A.,…Barr, CL. (2007). Association of the glutamate receptor subunit gene GRIN2B with attention-deficit/hyperactivity disorder. Genes, Brain and Behaviour, 6(5), 444-52.

Douglas, V.I. (1972). Stop, look and listen: the problem of sustained attention and impulse control in hyperactive and normal children. Canadian Journal of Behavioral Science, 4, 259-282.

Downey, K. K., Stelson, F. W., Pomerleau, O. F., & Giordani, B. (1997). Adult attention deficit hyperactivity disorder: psychological test profiles in a clinical population. Journal of Nervous and Mental Disease, 185(1),32-8.

Duerden, E., Tannock, R., & Dockstader, C. (2012). Altered cortical morphology in sensorimotor processing regions in adolescents and adults with attetion-deficit/hyperactivity disorder. Brain research, 1445,82-91.

DuPaul, G. J., Power, T. J., Anastopoulos, A. D., & Reid, R. (1998). ADHD Rating Scale—IV: Checklists, norms, and clinical interpretation. Guilford Press.

Durston, S., Davidson, M. C., Mulder, M.J., Spicer, J.A., Galvan, A., Tottenham, N.,… & Casey, B.J. (2007). Neural and behavioral correlates of expectancy violations in

attention-deficit hyperactivity disorder. Journal of Child Psychology and Psychiatry, 48, 881-889.

Dutke, S. (2005). Remembered duration: working memory and the reproduction of intervals. Attention, Perception and Psychophysics, 67(8), 1404-13.

Edwards, C.R., Newman, S. & Bismark, A. (2008). Cerebellum volume and eyeblink conditioning in schizophrenia. Psychiatry Research, 162 (3), 185-194.

Epstein, J. N., Casey, B. J., Tonev, S. T., Davidson, M. C., Reiss, A. L., Garrett, A., ... & Spicer, J. (2007). ADHD-and medication-related brain activation effects in concordantly affected parent–child dyads with ADHD.Journal of Child Psychology and Psychiatry, 48(9), 899-913

Epstein, J. N., Conners, C. K., Sitarenios, G., & Erhardt, D. (1998). Continuous performance test results of adults with attention deficit hyperactivity disorder.The Clinical Neuropsychologist, 12(2), 155-168.

Faraone, S. V., & Doyle, A. E. (2000). Genetic influences on attention deficit hyperactivity disorder. Currents Psychiatry Reports, 2(2),143-6.

Faraone SV, Sergeant J, Gillberg C, Biederman J. (2003): The worldwide prevalence of ADHD: Is it an american condition? World Psychiatry. 2:104–113.

Faraone, S.V., & Biederman, J. (2005): What is the prevalence of adult attention deficit/hyperactivity disorder? Results of a population screen of 1019 adults. Journal of Attention Disorders, 9(2), 384 -391.

Fayyad, J., De Graaf, R., Kessler, R., Alonso, J., Angermeyer, M., Demyttenaere, K., ... & Jin, R. (2007). Cross–national prevalence and correlates of adult attention–deficit hyperactivity disorder. The British Journal of Psychiatry, 190(5), 402-409.

Filipek, P.A., Semrud-Clikeman, M., Steingard, R.J., Renshaw, P.F., Kennedy, D.N., & Biederman, J. (1997). Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology, 48 (3),5 89-601.

Findling, R. L., Greenhill, L. L., McNamara, N. K., Demeter, C. A., Kotler, L. A., O'Riordan, M. A., ... & Reed, M. D. (2007). Venlafaxine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder. Journal of child and adolescent psychopharmacology, 17(4), 433-445.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (2012). Structured Clinical Interview for DSM-IVo Axis I Disorders (SCID-I), Clinician Version, Administration Booklet. American Psychiatric Pub.

First, M. B., Gibbon, M., Spitzer, R. L., Williams, J. B. W., & Benjamin, L. S. (1997). User's guide for the structured clinical interview for DSM-IV Axis II personality disorders. New York State Psychiatric Institute, Biometrics Research, New York.

Fischer, M. & Barkley, R.A. (2007). The persistence of ADHD into adulthood: (once again) it depends on whom you ask. Attention Deficit and Hyperactivity Disorder, 15, 7-16.

Fone, K.C.F., & Nutt, D.J. (2005). Stimulants: use and abuse in the treatment of attention deficit hyperactivity disorder. Current Opinion in Pharmacology, 5,87–93.

Franke, B., Faraone, S.V., Asherson, P., Buitelaar, J., Bau, C.H., Ramos-Quiroga, J.A.,…Reif, A. . (2012). The genetics of attention deficit/hyperactivity disorder in adults, a review. Molecular Psychiatry, 17, 960-87.

Fransson, P. (2006). How default is the default mode of brain function?: Further evidence from intrinsic BOLD signal fluctuations. Neuropsychologia, 44(14), 2836-2845.

Frodl, T. & Skokauskas N. (2012). Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatrica Scandinava, 125(2), 114-26.

Fuster, J. (2008). The Prefrontal Cortex (4ª. Ed.). London, UK: Academic Press.

Gibbon, J., Church, R.M. & Meck, W.H. (1984). Scalar timing in memory. Annals of the New York Academy of Sciences, 423, 52-77.

Gross, M.D. (1995). Origin of stimulant use for treatment of attention deficit disorder. Americal Journal of Psychiatry, 152, 298-299.

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C. F., Menon, V., & Grecious, M.D. (2009). Distinct cerebellar contributions to intrinsic connectivity networks. The Journal of Neuroscience, 29(26), 8586-94.

Haber, S. N., & Rauch, S. L. (2010). Neurocircuitry: a window into the networks underlying neuropsychiatric disease. Neuropsychopharmacology, 35(1), 1-3.

Hale, T. S., Bookheimer, S., McGough, J.J., Phillips, J.M., & McCracken, J.T. (2007). Atypical brain activation during simple and complex levels of processing in adult ADHD: an fMRI study. Journal of Attention disorders, 11(2), 125-139.

Halleland, H., Lundervold, A. J., Halmøy, A., Haavik, J., & Johansson, S. (2009). Association between Catechol O-methyltransferase (COMT) haplotypes and severity of hyperactivity symptoms in Adults. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 150(3), 403-410.

Hanakawa, T., Dimyan, M.A. & Hallett, M. (2008). Motor planning, imagery, and execution in a distributed motor network: a time-course study with functional MRI. Cerebral Cortex, 18, 2775-88.

Harrington, D.L., Lee, R.R., Boyd, L.A., Rapcsak, S.Z. & Knight, R.T. (2004). Does the representation of time depend on the cerebellum? Effect of cerebellar stroke. Brain, 127, 561-74.

Hart, H., Radua, J., Mataix-Cols, D., & Rubia, K. (2012). Meta-analysis of fMRI studies of timing in Attention Deficit Hyperactivity Disorder (ADHD).Neuroscience & Biobehavioral Reviews.

Hart, H., Radua, J., Nakao, T., Mataix-Cols, D., & Rubia, K. (2013). Meta-analysis of Functional Magnetic Resonance Imaging Studies of Inhibition and Attention in Attention-deficit/Hyperactivity DisorderExploring Task-Specific, Stimulant Medication, and Age EffectsADHD Functional MR Imaging Studies Meta-analysis. JAMA psychiatry, 70(2), 185-198.

Harticollis, P. (1968). The syndrome of minimal dysfunction in young adult patients. Bulletin of the Menninger Clinic, 32, 102-114.

Harvey, A.S., Epstein, J.N. & Curry, J.F. (2004). Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychology, 18(3), 485-503.

Hesslinger, B., Tebartz van Elst, L., Thiel, T., Haegele, K., Hennig, J., & Ebert, D. (2002). Frontoorbital volume reductions in adult patients with attention deficit hyperactivity disorder. Neuroscience letters, 328(3), 319-321.

Herzog, G.H., Herzog-Hoinkis, M., Siefert, H. & Hoffmann, H. (1995). Leben und Werk in Texten und Bildern. Frankfurt am Main/Leipzig: Insel-Verlag.

Hinson, J.M., Jameson, T.L. & Whitney, P. (2003). Impulsive desition making and working memory. Journal of Experimental Psychology: Learning, Memory and Cognition, 29(2), 298-306.

Hui, K.K.S., Liu, J., Marina, O., Napadow, V., Haselgrove, C., Kwong, K.K. et al. (2005). The integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST 36as evidenced by fMRI. NeuroImage, 27, 479-496.

Hoekzema, E., Carmona, S., Ramos-Quiroga, J. A., Canals, C., Moreno, A., Fernández, V. R., ... & Vilarroya, O. (2012a). Stimulant drugs trigger transient volumetric changes in the human ventral striatum. Brain Structure and Function, 1-12.

Hoekzema, E., Carmona, S., Ramos-Quiroga, J. A., Fernández, V. R., Picado, M., Bosch, R., ... & Vilarroya, O. (2012). Laminar thickness alterations in the fronto-parietal cortical mantle of patients with attention-deficit/hyperactivity disorder. PloS one, 7(12), e48286.

Hoffmann, H. (1948). Der Struwwelpeter. Oder lustige Geschichten und drollige Bilder für Kinder von 3 bis 6 Jahren. Loewes, Stuttgart: Frankfurter Originalausgabe.

Igual, L., Soliva, J.C., Escalera, S., Gimeno, R., Vilarroya, O., & Radeva, P. (2012). Automatic brain caudate nuclei segmentation and classification in diagnostic of Attention-Deficit/Hyperactivity Disorder. Computer Medical Imaging and Graphics. 36(8), 591-600.

Igual, L., Soliva, J. C., Hernández-Vela, A., Escalera, S., Jiménez, X., Vilarroya, O., & Radeva, P. (2011). A fully-automatic caudate nucleus segmentation of brain MRI: Application in volumetric analysis of pediatric attention-deficit/hyperactivity disorder. Biomedical engineering online, 10(1), 1-23.

Ivry, R.B. & Keele, S.W. (1989). Timing functions of the cerebellum. Journal of Cognitive Neuroscience, 1, 136-52.

Jantzen, K.J., Steinberg, F.L. & Kelso, J.A. (2004). Brain networks underlying human timing behavior are influenced by prior context. Proceedings of the National Academy os Sciences of the United States of America, 101, 6815-6820.

Jech, R., Dusek, P., Wackermann, J. & Vymazal, J. (2005). Time perception in functional brain imaging. Casopis Lekaru Ceskych, 144(10), 678-84.

Jimura, K., Locke, H. S., & Braver, T. S. (2010). Prefrontal cortex mediation of cognitive enhancement in rewarding motivational contexts. Proceedings of the National Academy of Sciences, 107(19), 8871-8876.

Johansson, S., Halleland, H., Halmøy, A., Jacobsen, K. K., Landaas, E. T., Dramsdahl, M., ... & Haavik, J. (2008). Genetic analyses of dopamine related genes in adult ADHD patients suggest an association with the DRD5-microsatellite repeat, but not with DRD4 or SLC6A3 VNTRs. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(8), 1470-1475.

Kelly, R.M. & Strick, P.L. (2000). Rabies as a transneuronal tracer of circuits in the central nervous system. Journal of Neuroscience Methods, 103, 63-71.

Kessler, J.W. (1980). History of minimal brain dysfunctions. In: Rie HE, Rie ED (Ed.) Handbook of minimal brain dysfunctions: a critical view (pp. 18-51). New York: Wiley.

Kessler, R. C., Adler, L., Barkley, R., Biedermann, J., Conners, C.K., Demler, O., et al. (2006). The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. American Journal of Psychiatry, 163(4), 716-23.

Kessler, R. C., Adler, L. A., Barkley, R., Biederman, J., Conners, C. K., Faraone, S. V., ... & Zaslavsky, A. M. (2005). Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. Biological psychiatry, 57(11), 1442-1451.

Killeen, P.R. & Fetterman, J.G. (1988). A behavioral theory of timing. Psychological Review, 95, 274-95.

Kissling, C., Retz, W., Wiemann, S., Coogan, A. N., Clement, R. M., Hünnerkopf, R., ... & Thome, J. (2008). A polymorphism at the 3′-untranslated region of the CLOCK gene is associated with adult attention-deficit hyperactivity disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(3), 333-338.

Ko, C. H., Yen, J. Y., Yen, C. F., Chen, C. S., Lin, W. C., Wang, P. W., & Liu, G. C. (2013). Brain activation deficit in increased-load working memory tasks among adults with ADHD using fMRI. European archives of psychiatry and clinical neuroscience, 1-13.

Konrad, A., Dielentheis, T. F., El Masri, D., Bayerl, M., Fehr, C., Gesierich, T., ... & Winterer, G. (2010). Disturbed structural connectivity is related to inattention and impulsivity in adult attention deficit hyperactivity disorder. European Journal of Neuroscience, 31(5), 912-919.

Köpf, G. 2006.ICD-10 literarisch. Wiesbaden: Deutscher Universitäts-Verlag.

Kollins, S. H., Anastopoulos, A. D., Lachiewicz, A. M., FitzGerald, D., Morrissey-Kane, E., Garrett, M. E… & Ashley-Koch, A. E. (2008). SNPs in dopamine D2 receptor gene (DRD2) and norepinephrine transporter gene (NET) are associated with continuous performance task (CPT) phenotypes in ADHD children and their families. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(8), 1580-1588.

Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Burgué M, Carpentier PJ, et al. (2010). European consensus statement on diagnosis and treatment of adult ADHD: the European Network Adult ADHD. BMC Psychiatry. 19: 67.

Kooij, J. J. S., Burger, H., Boonstra, A. M., Van der Linden, P. D., Kalma, L. E., & Buitelaar, J. K. (2004). Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. Psychological medicine, 34(6), 973-982.

Klein, C., Wendling, K., Huettner, P., Ruder, H., & Peper, M. (2006). Intra-subject variability in attention-deficit hyperactivity disorder. Biological psychiatry, 60(10), 1088-1097.

Johansson, S., Halleland, H., Halmøy, A., Jacobsen, K. K., Landaas, E. T., Dramsdahl, M., ... & Haavik, J. (2008). Genetic analyses of dopamine related genes in adult ADHD patients suggest an association with the DRD5-microsatellite repeat, but not with DRD4 or SLC6A3 VNTRs. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(8), 1470-1475.

LaHoste, G. J., Swanson, J., Wigal, S. B., Glabe, C., Wigal, T., King, N., & Kennedy, J. L. (1996). Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Molecular psychiatry, 1(2), 121-124

Lange, K., Reichl, S., Lange, K., Tucha, L. & Tucha O. (2010). The history of attention deficit hyperactivity disorder. Attention Deficit and Hyperactivity Disorders, 2, http://link.springer.com/journal/12402/2/4/page/1241-255.

Lahey, B. B., Applegate, B., McBurnett, K., & Biederman, J. (1994). DMS-IV field trials for attention deficit hyperactivity disorder in children and adolescents. The American Journal of Psychiatry.

Larsson, H., Lichtenstein, P. & Larsson, J.O. (2006). Genetic contributions to thedevelopment of ADHD subtypes from childhood to adolescence. Journal of the American Academy of Child and Adolescent Psychiatry, 45(8), 973-981.

Lasky-Su, J., Anney, R.J., Neale, B.M., Franke, B., Zhou, K., Maller, J.B.,…Faraone S.V. (2008a). Genome-wide association scan of the time to onset of attention deficit hyperactivity disorder. American Journal of Medical Genetics, 147B, 1355-1358.

Lasky-Su, J., Neale, B. M., Franke, B., Anney, R. J., Zhou, K., Maller, J. B., ... & Faraone, S. V. (2008). Genome-wide association scan of quantitative traits for attention deficit hyperactivity disorder identifies novel associations and confirms candidate gene associations. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(8), 1345-1354.

Laucht, M., Skowronek, M. H., Becker, K., Schmidt, M. H., Esser, G., Schulze, T. G., & Rietschel, M. (2007). Interacting effects of the dopamine transporter gene and psychosocial adversity on attention-deficit/hyperactivity disorder symptoms among 15-year-olds from a high-risk community sample. Archives of General Psychiatry, 64(5), 585.

Laufer, M.W., Denhoff, E. & Solomons, G. (1957). Hyperkinetic impulse disorder in children's behavior problems. Psychosomatic Medicine, 19, 38-49.

Leth-Steensen, C., King Elbaz, Z., & Douglas, V. I. (2000). Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. Acta psychologica, 104(2), 167-190.

Lewis, P.A. & Miall, R.C. (2003). Brain activation patterns during measurement of sub- and supra-second intervals. Neuropsychologia, 41(12), 1583-92.

Liu, S.J., Lachamp, P., Liu, Y., Savtchouk, I. & Sun, L. (2008). Long-term synaptic plasticity in cerebellar stellate cells. Cerebellum, 7(4), 559-62.

Luman, M., Oosterlaan, J., & Sergeant, J. A. (2005). The impact of reinforcement contingencies on AD/HD: a review and theoretical appraisal. Clinical psychology review, 25(2), 183-213.

Ma, C.L., Arnsten, A.F., & Li, B.M. (2005). Locomotor hyperactivity induced by blockade of prefrontal cortical α2-adrenoceptors in monkeys. Biological Psychiatry, 57(2),192-195.

Mackie, S., Shaw, P., Lenroot, R., Pierson, R., Greenstein, D., Nugent, T., ... & Rapoport, J. (2007). Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. American Journal of Psychiatry, 164(4), 647-655.

Makris, N., Biederman, J., Valera, E. M., Bush, G., Kaiser, J., Kennedy, D. N., ... & Seidman, L. J. (2007). Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. Cerebral Cortex, 17(6), 1364-1375.

Makris, N., Seidman, L. J., Valera, E. M., Biederman, J., Monuteaux, M. C., Kennedy, D. N., ... & Faraone, S. V. (2010). Anterior Cingulate Volumetric Alterations in Treatment-Naïve Adults With ADHD A Pilot Study. Journal of attention disorders, 13(4), 407-413.

Madaan, V., Daughton, J., Lubberstedt, B., Mattai, A., Vaughan, B.S., Kratochvil, C.J. (2008). Assesing the efficacy of treatments for ADHD: overview of methodological issues. CNS Drugs, 22(4), 275-90.

Malthotra, S. & Santosh, P.J. (1998). An open clinical trial of buspirone in children with attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 37(4),364-37.

Malloy-Diniz, L., Fuentes, D., Leite, W. B., Correa, H., & Bechara, A. (2007). Impulsive behavior in adults with attention deficit/hyperactivity disorder: characterization of attentional, motor and cognitive impulsiveness. Journal of the International Neuropsychological Society, 13(04), 693-698.

McAlonan, G. M., Cheung, V., Chua, S. E., Oosterlaan, J., Hung, S. F., Tang, C. P., ... & Leung, P. W. (2009). Age-related grey matter volume correlates of response inhibition and shifting in attention-deficit hyperactivity disorder. The British Journal of Psychiatry, 194(2), 123-129.

McGough, J.J. & Barkley, R.A. (2004). Diagnostic controversies in adult attention deficit hyperactivity disorder. Americal Journal of Psychiatry, 161, 1948-1956.

McGough, J. J., Smalley, S. L., McCracken, J. T., Yang, M., Del'Homme, M., Lynn, D. E., & Loo, S. (2005). Psychiatric comorbidity in adult attention deficit hyperactivity disorder: findings from multiplex families. American Journal of Psychiatry, 162(9), 1621-1627.

McLoughlin, G., Ronald, A., Kuntsi, J., Asherson, P., & Plomin, R. (2007). Genetic support for the dual nature of attention deficit hyperactivity disorder: substantial genetic overlap between the inattentive and hyperactive-impulsive components. Journal of Abnormal Child Psychology, 35(6),999-1008.

Meaux, J. B., & Chelonis, J. J. (2003). Time perception differences in children with and without ADHD. Journal of pediatric health care, 17(2), 64-71.

Mendelson, W. B., Johnson, N. & Stewart, M. A. (1971). Hyperactive children as teenagers: a follow-up study. Journal of Mental and Nervous Disease, 153, 273-9.

Menkes, M. M., Rowe, J. S. & Menkes, J. H. (1967). A twenty-five year follow-up study on the hyperkinetic child with minimal brain dysfunction. Pediatrics, 39(3), 393-9.

Mill, J., Caspi, A., Williams, B. S., Craig, I., Taylor, A., Polo-Tomas, M., ... & Moffitt, T. E. (2006). Prediction of heterogeneity in intelligence and adult prognosis by genetic polymorphisms in the dopamine system among children with attention-deficit/hyperactivity disorder: evidence from 2 birth cohorts. Archives of General Psychiatry, 63(4), 462.

Miller, T. W., Nigg, J. T., & Faraone, S. V. (2007). Axis I and II comorbidity in adults with ADHD. Journal of Abnormal Psychology, 116(3),519-28.

Millestein, R. B., Wilens, T.E, Biederman, J., Spencer, T.J. (1997). Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD, Journal of Attention Disorders, 2(3),159-166.

Montes, L. G. A., Ricardo-Garcell, J., De La Torre, L. B., Alcántara, H. P., García, R. B. M., Fernández-Bouzas, A., & Acosta, D. Á. (2010). Clinical correlations of grey matter reductions in the caudate nucleus of adults with attention deficit hyperactivity disorder. Journal of psychiatry & neuroscience: JPN, 35(4), 238.

Monuteaux, M. C., Seidman, L. J., Faraone, S. V., Makris, N., Spencer, T., Valera, E., ... & Biederman, J. (2008). A preliminary study of dopamine D4 receptor genotype and structural brain alterations in adults with ADHD. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(8), 1436-1441.

Morrison, J. R. & Stewart, M. A. (1971). A family study of the hyperactive child syndrome. Biological Psychiatry, 3(3), 189-95.

Mukaddes, N. M., & Abali, O. (2004). Venlafaxine in children and adolescents with attention deficit hyperactivity disorder. Psychiatry and Clinical Neuroscience, 58(1),92-5.

Müller, D. J., Mandelli, L., Serretti, A., DeYoung, C. G., De Luca, V., Sicard, T., ... & Kennedy, J. L. (2008). Serotonin transporter gene and adverse life events in adult ADHD. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(8), 1461-1469.

Murphy, K. R., Barkley, R. A., & Bush, T. (2002). Young adults with attention deficit hyperactivity disorder: subtype differences in comorbidity, educational, and clinical history. Journal of Nervous and Mental Disorders, 190(3),147-57.

Neale, B. M., & Faraone, S. V. (2008). Perspective on the genetics of attention deficit/hyperactivity disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(8), 1334-1336.

Noreika, V., Falter, C.M., Rubia, K. (2013). Timing deficits in attention-deficit/hyperactivity disorder (ADHD): evidence from neurocognitive and neuroimaging studies.Neuropsychologia, 51(2):235-66.

Onitsuka, T., Shenton, M. E., Salisbury, D. F., Dickey, C. C., Kasai, K., Toner, S. K., ... & McCarley, R. W. (2004). Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. The American journal of psychiatry, 161(9), 1603.

Palmer, E. & Finger, S. (1798). An early description of ADHD (Inattentive Subtype): Dr Alexander Crichton and `Mental Restlessness'. Journal of Child Psycholgy and Psychiatry, 6, 66–73.

Paloyelis, Y., Mehta, M. A., Kuntsi, J., & Asherson, P. (2007). Functional MRI in ADHD: a systematic literature review. Expert review of neurotherapeutics, 7(10), 1337-1356.

Plichta, M. M., Vasic, N., Wolf, R. C., Lesch, K. P., Brummer, D., Jacob, C., ... & Grön, G. (2009). Neural hyporesponsiveness and hyperresponsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder. Biological psychiatry, 65(1), 7-14.

Pliszka SR. (2003). Psychiatric comorbidities in children with attention deficit hyperactivity disorder: implications for management. Pediatric Drugs. 5: 741-50.

Pontius, A. A. (1973). Dysfunction patterns analogous to frontal lobe system and caudate nucleus syndromes in some groups of minimal brain dysfunction. Journal of the American Medical Women's Association, 26(6), 285-92.

Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Amercian Journal of Psychiatry., 164(6):942-8.

Popper, C. W. (1997). Antidepressants in the treatment of attention-deficit/hyperactivity disorder. Discussion. The Journal of clinical psychiatry. Supplement, 58(14), 14-31

Pouthas, V. & Perbal, S. (2004). Time perception depends on accurate clock mechanisms as well as unimpaired attention and memory processes. Acta Neurobiologiae Experimentals, 64(3), 367-85.

Proal, E., Reiss, P. T., Klein, R. G., Mannuzza, S., Gotimer, K., Ramos-Olazagasti, M. A., ... & Castellanos, F. X. (2011). Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. Archives of general psychiatry, 68(11), 1122.

Proal, E., Álvarez-Segura, M., de la Iglesia-Vayá, M., Martí-Bonmatí, L., & Castellanos, F. X. (2011). Actividad funcional cerebral en estado de reposo: redes en conexión. Rev Neurol, 52(Supl 1), S3-10.

Propper, C., Willoughby, M., Halpern, C. T., Carbone, M. A., & Cox, M. (2007). Parenting quality, DRD4, and the prediction of externalizing and internalizing behaviors in early childhood. Developmental Psychobiology, 49(6), 619-632

Quitkin, F. & Klein, D. F. (1969). Two behavioral syndromes in young adults related to possible minimal brain dysfunction. Journal of Psychiatr Research, 7(2), 131-42.

Rafalovich, A. (2001). The conceptual history of attention deficit hyperactivity disorder: idiocy, imbecility, encephalitis and the child deviant. Deviant Behaviour, 22, 93-115.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. Proceedings of the National Academy of Sciences, 98(2), 676-682.

Ramos-Quiroga JA, Ribasés-Haro M, Bosch-Munsó R, Cormand-Rifà B, & Casas M. (2007). Genetic advances in attention deficit hyperactivity disorder. Revista de neurología. ;44, S51.

Ramos-Quiroga, J. A., Bosch, R., Castells, X., Valero, S., Nogueira, M., Gomez, N., ... & Casas, M. (2008). Effect of switching drug formulations from immediate-release to extended-release OROS Methylphenidate. CNS drugs,22(7), 603-611.

Ramos-Quiroga, J.A. (2009). Genetic factors, Evaluation and Pharmacological Treatment. (Doctoral dissertation). Universidad Autónoma de Barcelona, Barcelona, Spain.

Reif, A., Jacob, C. P., Rujescu, D., Herterich, S., Lang, S., Gutknecht, L., ... & Lesch, K. P. (2009). Influence of functional variant of neuronal nitric oxide synthase on impulsive behaviors in humans. Archives of general psychiatry, 66(1), 41.

Reimherr FW, Hedges DW, Strong RE, Marchant BK, Williams ED. (2005). Bupropion SR in adults with ADHD: a short-term, placebo-controlled trial. Neuropsychiatr Dis Treat. 1(3):245-51.

Reitan, R.M. & Wolfson, D. (1985). The Halstead-Reitan neuropsychological test battery: Therapy and clinical interpretation. Tucson, AZ: Neuropsychological Press.

Retz-Junginger, P., Sobanski, E., Alm, B., Retz, W., & Rösler, M. (2008). Age and gender aspects of attention-deficit hyperactivity disorder. Der Nervenarzt, 79(7), 809.

Retz, W., Freitag, C. M., Retz-Junginger, P., Wenzler, D., Schneider, M., Kissling, C., ... & Rösler, M. (2008). A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: interaction with adverse childhood environment. Psychiatry research, 158(2), 123-131.

Retz, W., Rösler, M., Kissling, C., Wiemann, S., Hünnerkopf, R., Coogan, A., ... & Freitag, C. (2008). Norepinephrine transporter and catecholamine-O-methyltransferase gene variants and attention-deficit/hyperactivity disorder symptoms in adults. Journal of neural transmission, 115(2), 323-329.

Rösler, M., Fischer, R., Ammer, R., Ose, C., & Retz, W. (2009). A randomised, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/hyperactivity disorder. European archives of psychiatry and clinical neuroscience, 259(2), 120-129.

Ross, D.M. & Ross, S.A. (1976). Hyperactivity: research, theory and action. New York: Wiley.

Rostain AL. (2008). Attention-deficit/hyperactivity disorder in adults: evidence-based recommendations for Management. Postgraduate Medical Journal120(3):27-38.

Rothenberger, A. & Neumärker, K.J. (2005). Wissenschaftsgeschichte der ADHS. Steinkopff, Darmstadt: Kramer-Pollnow im Spiegel der Zeit.

Rubinstein, S., Malone, M. A., Roberts, W., & Logan, W. J. (2006). Placebo-controlled study examining effects of selegiline in children with attention-deficit/hyperactivity disorder. Journal of Child & Adolescent Psychopharmacology, 16(4), 404-415.

Rubia K, Taylor E, Smith A, Oksanen H, Overmeyer S, & Nweman, S. (2001). Neuropsychological analyses of impulsiveness in childhood hyperactivity. The British Journal of Psychiatry, 179:138–43.

Rubia, K., Noorloos, J., Smith, A., Gunning, B., & Sergeant, J. (2003). Motor timing deficits in community and clinical boys with hyperactive behavior: the effect of methylphenidate on motor timing. Journal of abnormal child psychology, 31(3), 301-313.

Rubia, K., & Smith, A. (2004). The neural correlates of cognitive time management: a review. Acta neurobiologiae experimentalis, 64(3), 329-340.

Rubia, K., Smith, A. B., Brammer, M. J., Toone, B., & Taylor, E. (2005). Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. American Journal of Psychiatry, 162(6), 1067-1075.

Rubia, K., Smith, A. & Taylor, E. (2007). Performance of children with attention deficit hyperactivity disorder (ADHD) on a test battery of impulsiveness. Child Neuropsychology, 13, 276-304.

Rubia, K., Halari, R., Christakou, A. & Taylor. E. (2009a). Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention deficit hyperactivity disorder during temporal processes and normalization with methylphenidate. Philosophical Transactions of the Royal Society, 364, 1919-1931.

Rubia, K., Smith, A., Halari, R., Matsukura, F., Mohammad, M., Taylor, E., & Brammer, M. (2009b). Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. American Journal of Psychiatry, 166(1), 83-94.

Rubia, K., Halari, R., Cubillo, A., Mohammad, A.-M., Brammer, M. & Taylor, E. (2011). Methylphenidatenormalisesfronto-striatalunderactivationduring interference inhibition inmedication-naiveboys. Neuropsychopharmacology, 36(8), 1575-1586.

Rubinstein S, Malone MA, Roberts W, Logan WJ. (2006). Placebo-controlled study examining effects of selegiline in children with attention-deficit/hyperactivity disorder. Journal of Child and Adolescent Psychopharmacolog, 16(4):404-15.

Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene–environment interplay and psychopathology: multiple varieties but real effects. Journal of Child Psychology and Psychiatry, 47(3-4), 226-261.

Sandrini, M., Rossini, P. M. & Miniussi, C. (2004). The differential involvement of inferior parietal lobule in number comparison: a rTMS study. Neuropsychologia 42, 1902-1909.

Scheres, A., Milham, M. P., Knutson, B., & Castellanos, F. X. (2007). Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. Biological psychiatry, 61(5), 720-724.

Schneider, M., Retz, W., Coogan, A., Thome, J., & Rösler, M. (2006). Anatomical and functional brain imaging in adult attention-deficit/hyperactivity disorder (ADHD)—a neurological view. European archives of psychiatry and clinical neuroscience, 256(1), i32-i41.

Schmahmann, J. D. (2004). Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. The Journal of Neuropsychiatry and Clinical Neurosciences, 16(3), 367-378.

Secnik K, Swensen A, Lage MJ. (2005). Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. Pharmacoeconomics. 23(1):93-102.

Seidler, E. (2004). “Zappelphilipp” und ADHS. Von der Unart zur Krankheit. Deutsches Ärzteblatt, 101, A239-A243.

Seidman, L. J., Biederman, J., Liang, L., Valera, E. M., Monuteaux, M. C., Brown, A., ... & Makris, N. (2011). Gray matter alterations in adults with attention-deficit/hyperactivity disorder identified by voxel based morphometry. Biological psychiatry, 69(9), 857-866.

Seidman, L. J., Valera, E. M., Makris, N., Monuteaux, M. C., Boriel, D. L., Kelkar, K., ... & Biederman, J. (2006). Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. Biological Psychiatry, 60(10), 1071-1080.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., ... & Rapoport, J. L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proceedings of the National Academy of Sciences, 104(49), 19649-19654.

Shelley, E. M. & Riester, A. (1972). Syndrome of minimal brain damage in young adults. Diseases of the Nervous Systtem, 33(5), 335-8.

Small, D.M., Gitelman, D.R., Gregory, M.D., Nobre, A.C., Parrish, T.B. & Mesulam, M.M. (2003). The posterior cingulate and medial prefrontal cortex mediate the anticipatory allocation of spatial attention. Neuroimage 18(3), 633-641.

Smith, A., Taylor, E., Warner Rogers, J., Newman, S., & Rubia, K. (2002). Evidence for a pure time perception deficit in children with ADHD. Journal of Child Psychology and Psychiatry, 43(4), 529-542.

Smith, A., Taylor, E., Lidzba, K. & Rubia, K. (2003). A right hemispheric frontocerebellar network for time discrimination of several hundreds of milliseconds. Neuroimage, 20, 344-350.

Smith, A.B., Taylor, E., Brammer, M., Halari, R. & Rubia, K. (2008). Reduced activation in right lateral prefrontal cortex and anterior cingulate gyrus in medication-naïve adolescents with attention deficit hyperactivity disorder during time discrimination. Journal of Child Psychology and Psychiatry, 49(9), 977-985.

Smith, A., Cubillo, A., Barrett, N., Giampietro, V., Simmons, A., Brammer, M., & Rubia, K. (2002). Differential neurofunctional effects of methylphenidate and atomox-etine in boys with attention deficit hyperactivity disorder during time perception. Biological Psychiatry, in press.

Simon V, Czobor P, Bálint S, Mészáros A, Bitter I. (2009). Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. British Journal of Psychiatry. 194(3):204-11.

Sobanski E, Brüggemann D, Alm B, Kern S, Philipsen A, Schmalzried H., …, Rietschel, M. (2008). Subtype differences in adults with attention-deficit/hyperactivity disorder (ADHD) with regard to ADHD-symptoms, psychiatric comorbidity and psychosocial adjustment. The European Journal of Psychiatry, 23(2):142-9.

Solanto, M.V. (1998). Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behavioural brain research. 94(1):127-52.

Soliva, J. C., Fauquet, J., Bielsa, A., Rovira, M., Carmona, S., Ramos-Quiroga, J. A., ... & Vilarroya, O. (2010). Quantitative MR analysis of caudate abnormalities in pediatric ADHD: Proposal for a diagnostic test. Psychiatry Research: Neuroimaging, 182(3), 238-243.

Sonuga-Barke, E.J. (2002). Psychological heterogeneity in AD/HD- a dual pathway model of behaviour and cognition. Behavioural Brain Research, 130(1-2), 29-36.

Sonuga-Barke, E.J. (2003). The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. Neuroscience and Biobehavioural Reviews, 27(7), 593-604.

Sonuga-Barke, E.J. & Castellanos, F.X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neuroscience & Biobehavioural Reviews. 977-86.

Sonuga-Barke, E. J., Lasky-Su, J., Neale, B. M., Oades, R., Chen, W., Franke, B., ... & Faraone, S. V. (2008). Does parental expressed emotion moderate genetic effects in

ADHD? An exploration using a genome wide association scan. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(8), 1359-1368.

Sonuga-Barke, E.J. (2010). Disambiguating inhibitory dysfunction in attention-deficit/hyperactivity disorder: toward the decomposition of developmental brain phenotypes. Biological Psychiatry, 67(7), 599-601.

Sonuga-Barke, E., Bitsakou, P., & Thompson, M. (2010). Beyond the dual pathway model: evidence for the dissociation of timing, inhibitory, and delay-related impairments in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child & Adolescent Psychiatry, 49(4), 345-355.

Spencer, T., Biederman, J., Wilens, T., Doyle, R., Surman, C., Prince, J., ... & Faraone, S. (2005). A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. Biological psychiatry, 57(5), 456-463.

Spivak, B., Vered, Y., Yoran-Hegesh, R., Averbuch, E., Mester, R., Graf, E., & Weizman, A. (1999). Circulatory levels of catecholamines, serotonin and lipids in attention deficit hyperactivity diiorder. Acta Psychiatrica Scandinavica, 99(4), 300-304.

Sprafkin J, Gadow KD, Weiss MD, Schneider J, Nolan EE. (2007). Psychiatric comorbidity in ADHD symptom subtypes in clinic and community adults. Journal of Attention Disorders, 11(2):114-24.

Sprich, S., Biederman, J., Crawford, M. H., Mundy, E., & Faraone, S. (2000). Adoptive and biological families of children and adolescents with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry, 39(11), 1432-1143.

Staller J, Faraone SV. (2006). Attention-deficit hyperactivity disorder in girls: epidemiology and management. CNS Drugs. 20(2):107-23.

Stark, R., Bauer, E., Merz, C. J., Zimmermann, M., Reuter, M., Plichta, M. M., ... & Herrmann, M. J. (2011). ADHD related behaviors are associated with brain activation in the reward system. Neuropsychologia, 49(3), 426-434.

Strauss, A.A. & Kephart, N.C. (1955). Psychopathology and education of the brain-injured child. Volume II. Progress in theory and clinic. New York: Grune & Stratton.

Strauss, A.A. & Lehtinen, L.E. (1947). Psychopathology and education of the brain-injured child. New York: Grune & Stratton.

Strick, P.L., Dum, R.P. & Fiez, J.A. (2009). Cerebellum and nonmotor function. Annual Review of Neuroscience, 32, 413-434.

Ströhle, A., Stoy, M., Wrase, J., Schwarzer, S., Schlagenhauf, F., Huss, M., ... & Heinz, A. (2008). Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. Neuroimage, 39(3), 966-972.

Taub, D. M., & Vickers, J. (1994). Low CSF 5-HIAA concentrations and severe aggression and impaired impulse control in nonhuman primates. American Journal of Psychiatry, 151(1), 0.

Teki, S., Grube, M. & Griffiths, T.D. (2011). A unified model of time perception accounts for duration-based and beat-based timing mechanisms. Frontiers in Integrative Neuroscience, 5, 90.

Thapar, A., Langley, K., Owen, MJ., & O'Donovan MC. (2007a). Advances in genetic findings on attention deficit hyperactivity disorder. Psychological Medicine, 37 (12):1681-92.

Thapar, A., Langley, K., Asherson, P., & Gill, M. (2007b). Gene–environment interplay in attention-deficit hyperactivity disorder and the importance of a developmental perspective. The British Journal of Psychiatry, 190(1), 1-3.

Thome, J. & Jacobs, K. (2004). Attention deficit hyperactivity disorder (ADHD) in a 19th century children's book. European Psychiatry, 19, 303-306.

Tian, L., Jiang, T., Wang, Y., Zang, Y., He, Y., Liang, M., ... & Zhuo, Y. (2006). Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neuroscience letters, 400(1), 39-43.

Tiemeier, H., Lenroot, R. K., Greenstein, D. K., Tran, L., Pierson, R., & Giedd, J. N. (2010). Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. Neuroimage, 49(1), 63-70.

Toplak, M. E., Dockstader, C., & Tannock, R. (2006). Temporal information processing in ADHD: findings to date and new methods. Journal of neuroscience methods, 151(1), 15-29.

Wang L, et al. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. Neuroimage. 31(2):496-504.

Tiemeier H, et al. (2010). Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. Neuroimage. 49(1):63-70.

Toplak, M. E., Dockstader, C., & Tannock, R. (2006). Temporal information processing in ADHD: findings to date and new methods. Journal of neuroscience methods, 151(1), 15-29.

Toplak, M. E., Rucklidge, J. J., Hetherington, R., John, S. C. F., & Tannock, R. (2003). Time perception deficits in attention-deficit/hyperactivity disorder and comorbid reading difficulties in child and adolescent samples. Journal of Child Psychology and Psychiatry, 44(6), 888-903.

Tripp, G., & Wickens, J. R. (2009). Neurobiology of ADHD. Neuropharmacology, 57(7), 579-589.

Tremols, V., Bielsa, A., Soliva, J. C., Raheb, C., Carmona, S., Tomas, J., ... & Vilarroya, O. (2008). Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder. Psychiatry Research: Neuroimaging, 163(3), 270-278.

Valera, E. M., Faraone, S. V., Biederman, J., Poldrack, R. A., & Seidman, L. J. (2005). Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. Biological Psychiatry, 57(5), 439-447.

Valera, E. M., Faraone, S. V., Murray, K. E., & Seidman, L. J. (2007). Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biological psychiatry, 61(12), 1361-1369.

Valera, E. M., ... & Seidman, L. J. (2008). Attention and executive systems abnormalities in adults with childhood ADHD: A DT-MRI study of connections. Cerebral Cortex, 18(5), 1210-1220.

Valera EM., et al. (2009). Sex differences in the functional neuroanatomy of working memory in adults with ADHD. American Journal of Psychiatry. 167(1):86-94.

Valera, E. M., Spencer, R., Zeffiro, T. A., Makris, N., Spencer, T. J., Faraone, S. V., ... & Seidman, L. J. (2010). Neural substrates of impaired sensorimotor timing in adult attention-deficit/hyperactivity disorder. Biological psychiatry, 68(4), 359-367.

Vloet, T.D., Gilsbach, S., Neufang, S., Fink, G.R., Herpertz-Dahlmann, B. & Konrad, K. (2010). Neural mechanisms of interference control and time discrimination in attention-deficit/hyperactivity disorder. Journal of the American Acadademy of Child and Adolescence Psychiatry, 94(4), 356-67.

Volkmar, F.R. (2003). Changing perspectives on ADHD. American Journal of Psychiatry, 160, 1025-1027.

Volkow, N. D., Wang, G. J., Kollins, S. H., Wigal, T. L., Newcorn, J. H., Telang, F., ... & Swanson, J. M. (2009). Evaluating dopamine reward pathway in ADHD. JAMA: the journal of the American Medical Association, 302(10), 1084-1091.

Wang M., Ramos, B.P., Paspalas, C.D., Shu, Y., Simen, A.,Duque A., …Arnsten, A.F. (2007). Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. Cell. 129(2):397-410.

Wang, L., Zhu, C., He, Y., Zang, Y., Cao, Q., Zhang, H., ... & Wang, Y. (2009). Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Human brain mapping, 30(2), 638-649

Ward, M. F. (1993). The Wender Utah Rating Scale: An Aid in the Retrospective. Am J Psychiatry, 1(50), 885.

Wechsler, D.A. (1987). Wechsler Memory Scale–revised. New York: Psychological Corporation.

Wechsler, D. A. (2005). Escala Wechsler de Inteligencia para adultos (WAIS- III). Madrid: Ediciones TEA.

Wiener, M., Turkeltaub, P. & Coslett, H.B. (2010). The image of time: A voxel-wise meta-analysis. NeuroImage 49(2), 1728-1740.

Weisler, R. H. (2007). Review of long-acting stimulants in the treatment of attention deficit hyperactivity disorder.

Weiss, G., Hechtman, L., Milroy, T., & Perlman, T. (1985). Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. Journal of the American Academy of Child Psychiatry,24(2), 211-220.

Weissman, D. H., Roberts, K. C., Visscher, K. M., & Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. Nature neuroscience, 9(7), 971-978.

Wilens, T. E., Biederman, J., Prince, J., Spencer, T. J., Faraone, S. V., Warburton, R., ... & Geller, D. (1996). Six-week, double-blind, placebo-controlled study of desipramine for adult attention deficit hyperactivity disorder.American Journal of Psychiatry, 153(9), 1147-1153.

Wilens, T. E., Spencer, T. J., & Biederman, J. (2001). A review of the pharmacotherapy of adults with attention-deficit/hyperactivity disorder. Journal of attention disorders, 5(4), 189-202.

Wilens, T., MCBurnett, K., Stein, M., Lerner, M., Spencer, T., & Wolraich, M. (2005). ADHD treatment with once-daily OROS methylphenidate: final results from a long-

term open-label study. Journal of the American Academy of Child & Adolescent Psychiatry, 44(10), 1015-1023.

Wittmann, M., Leland, D. S. & Paulus, M. P. (2007). Time and decision making: differential contribution of the posterior insular cortex and the striatum during a delay discounting task. Experimental Brain Research, 179(4), 643-653.

Wilbertz, G., Tebartz van Elst, L., Delgado, M. R., Maier, S., Feige, B., Philipsen, A., & Blechert, J. (2012). Orbitofrontal reward sensitivity and impulsivity in adult attention deficit hyperactivity disorder. Neuroimage, 60(1), 353-361.

Wolf, R. C., Plichta, M. M., Sambataro, F., Fallgatter, A. J., Jacob, C., Lesch, K. P., ... & Vasic, N. (2009). Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. Human brain mapping, 30(7), 2252-2266.

Wozniak, J., Faraone, S.V., Mick, E., Monuteaux, M., Coville, A., & Biederman, J. (2010). A controlled family study of children with DSM-IV bipolar I disorder and psychiatric comorbidity. Psychological Medicine, 40:1079–1088.

Xu, X., Mill, J., Zhou, K., Brookes, K., Chen, C. K., & Asherson, P. (2007). Family-based association study between brain-derived neurotrophic factor gene polymorphisms and attention deficit hyperactivity disorder in UK and Taiwanese samples. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144(1), 83-86.

Zakay, D., & Block, R. A. (1996). The role of attention in time estimation processes. Advances in psychology, 115, 143-164.

Zimmermann, M., Grabemann, M., Mette, C., Abdel-Hamid, M., Ueckermann, J., Kraemer, M., ... & Zepf, F. D. (2012). The effects of acute tryptophan depletion on reactive aggression in adults with attention-deficit/hyperactivity disorder (ADHD) and healthy controls. PloS one, 7(3), e32023.

Zhou, K., Dempfle, A., Arcos-Burgos, M., Bakker, S. C., Banaschewski, T., Biederman, J., ... & Lewis, C. M. (2008). Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147(8), 1392-1398.