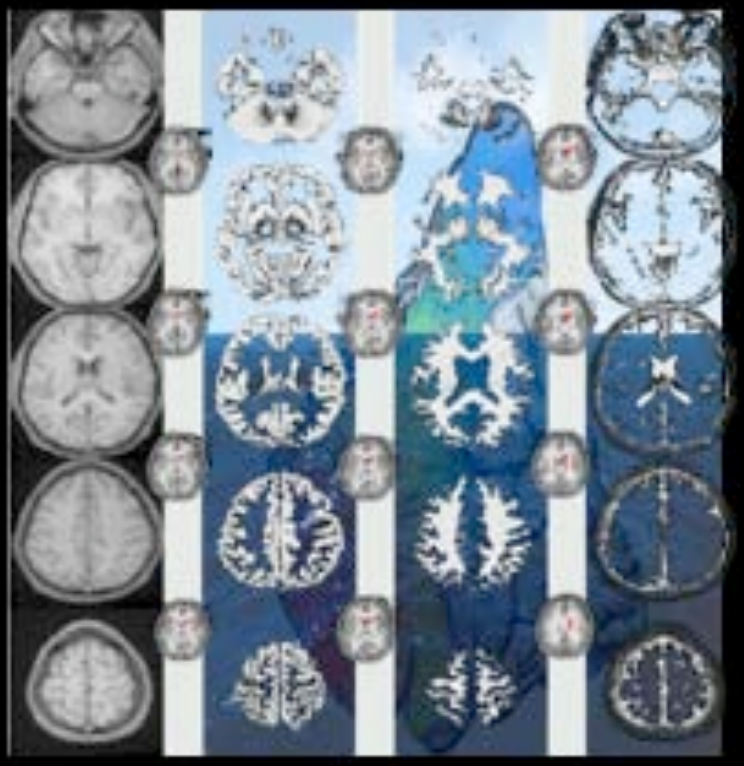
NEUROANATOMY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: VOXEL-BASED MORPHOMETRY AND REGION OF INTEREST APPROACHES



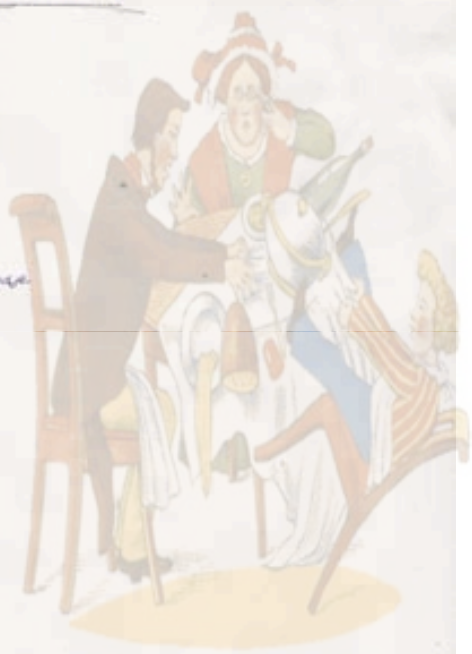
Thesis for a PhD degree in Cognitive Neuroscience
Presented by
SUSANA CARMONA CAÑABATE
and directed by
Óscar Vilarroya Oliver and Antoni Bulbena Vilarrasa
(Universidad Autónoma de Barcelona)

This thesis has been financially supported by a FPU grant (MED: AP2003-0551) from the Ministerio de Educación y Cultura.

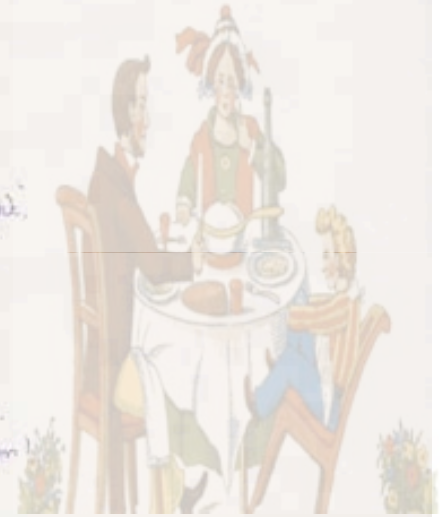
The story of Fidgety Philip

"Let me see if Philip can
Be a little gentleman;
Let me see if he is able
To sit still for once at table:"
Thus spoke, in earnest tone,
The father to his son;
And the mother looked very grave
To see Philip so misbehave.
But Philip he did not mind
His father who was so kind.

He wriggled
And giggled,
And then, I declare,
Swung backward and forward
And tilted his chair,
Just like any rocking horse;-
"Philip! I am getting cross!"



See the naughty restless child
Growing still more rude and wild,
Till his chair falls over quite.
Philip screams with all his might,
Catches at the cloth, but then
That makes matters worse again.
Down upon the ground they fall,
Glasses, bread, knives forks and all.
How Mamma did fret and frown,
When she saw them tumbling down!
And Papa made such a face!
Philip is in sad disgrace.



Where is Philip? where is he?
Fairly covered up, you see!
Cloth and all lying on him;
He has pull'd down all upon him!
What a terrible to do!
Dishes, glasses, smash in two!
Here a knife, and there a fork!
Philip, this is naughty work.
Table all so bare, and ah!
Poor Papa and poor Mamma
Look quite cross, and wonder how
They shall make their dinner now.

by Heinrich Hoffman

A mis padres y a mi hermana

TABLE OF CONTENTS:

SUMMARY

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disease characterized by symptoms of inattention, hyperactivity and impulsivity. Converging data from different studies point to ADHD abnormalities in fronto-striatal circuits. Structural neuroimaging studies partially support fronto-striatal abnormalities and suggest an important role of the cerebellum. However, nearly all these studies are based on the analysis of *apriori* selected regions of interest (known as ROI approaches). Recent studies, using more global approaches, found that ADHD structural abnormalities were not limited to fronto-striatal-cerebellar circuits, but also affect temporal, parietal and cingulate regions.

The aim of the present dissertation is to refine and apply two complementary methods of structural neuroimaging, in order to identify the brain circuits altered in ADHD, as well as to relate them to different clinical ADHD subtypes and to known ADHD neuropsychological deficits. For that purpose, two structural MRI studies will be presented and discussed (Carmona et al. 2005; Tremols et al. 2008). The differential contributions of these studies, which represent a novelty and an improvement of previous ADHD studies, are: a) the application for the first time of voxel-based morphometry analysis to compare ADHD children with non family-related control children; b) the design and application of a new, easy to apply, manual method of caudate nucleus segmentation.

The results confirm previous findings about smaller brain volume in ADHD children, and refine this reduction by attributing it to grey matter (GM) volume. We also confirm abnormalities in fronto-striatal-cerebellar circuits as well as in parietal, cingulate and temporal regions. Specifically, we observed reductions in inferior frontal cortex, dorsal striatum, inferior parietal cortex and posterior cingulate cortex; thus explaining inhibition problems, spatial working memory deficits and visuo-spatial attentional alterations. We also observed GM volume reductions in emotionally driven areas such as orbitofrontal cortex, ventral striatum and middle temporal structures*;* thus accounting for dysfunctional delayed reward and motivational deficits. Interestingly, GM volume reductions, related to emotional processes are more prominent in H-I subtype, more preserved in combined subtypes, and relatively undisrupted in inattentive subtypes, which is in agreement with previous ADHD theories (Castellanos and Tannock 2002). We have also found GM deficits in "sensori-motor" areas (specifically in perirolandic cortex and supplementary motor area), and in the cerebellum. On the one hand, deficits in sensori-motor areas probably reflect problems in fine motor coordination. However, the fact that these reductions are especially prominent in combined and inattentive subtypes brings up the possibility that they may be related to attentional dysfunctions. I hypothesized that deficits in these regions may produce a deficit when integrating and updating information from the external world and, in turn, produce a bias toward internal world focusing, thus, resulting in inattention. On the other hand, cerebellar reductions (which are extensively reported in ADHD literature) seem to be related to all cognitive, affective and sensorimotor deficits. The implication of cerebellum in all these dysfunctions may arise from its role as a modulator of the flow of information between fronto-strital circuits. Finally, our findings are also the first to show caudate head and body differential abnormalities in ADHD, which explain previous heterogeneous results, providing a new and reliable method to study striatal structures.

As a conclusion, GM volume reductions in emotional and cognitive areas support the implication of both *hot* (emotional) and *cool* (cognitive) functions, which agrees with most neuropsychological accounts of ADHD. To our knowledge this is the first time that a neuroanatomical study provides support for the existence of both cognitive and emotional dysfunctions in ADHD children. If these findings are replicated, they will constitute critical evidence for Sonuga-Barke's theory (Sonuga-Barke 2002; Sonuga-Barke 2003) about the dual route model.

LIST OF ABREVIATIONS:

ACC	Anterior Cingulate Cortex
AccN	Accumbens Nucleus
ADHD	Attention Deficit Hyperactivity Disorder
BG	Basal Ganglia
CC	Corpus Callosum
Comb	Combined subtype
CSTC	Cortico-striatal-thalamico-cortical
DA	Dopamine
DAT	Dopamine Transporter
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV Test Revised
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
EF	Executive Functions
FA	Fractional Anisotropy
fMRI	Functional Magnetic Resonance Imaging
FSC	Fronto-striatal circuits
GABA	y-aminobutyric acid
GM	Gray Matter
Gpe	External portion of Globus pallidus
Gpi	Internal portion of Globus pallidus
H-I	Hyperactive-Impulsive subtype
ICD-10	International Classification of Diseases- 10
Innat	Innatentive subtype
IQ	Inteiligence Quotient
MEG	Magnetoencephaloraphy
MPFC	Medial Prefrontal Cortex
MPH	Methylphenidate
MRI	Magnetic Resonace Imaging
MRS	Magnetic Nuclear Spectroscopy
NA	Noradrenaline
OF	Orbitofrontal
OFC	Orbitofrontal cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
ROI	Region of Interest
SMA	Supplementary Motor Area
SNpc	Substantia Nigra pars compacta
SNr	Substantia Nigra pars reticula
SPECT	Single Photon Emision Computed Tomography
TBV	Total Brain Volume
VLPF	Ventro-lateral prefrontal cortex
VTA	Ventral Tegmental Area
WCST	Wisconsin Card Sorting Test
WM	White matter

INTRODUCTION:

Preface

The poem "The Story of Fidgety Philip" (page 3), written by Heinrich Hoffmann in 1846, depicts a child that fails to pay and maintain attention, behaves impulsively and has evident problems of hyperactivity. What Hoffmann was describing then resembles the symptoms observed in children currently diagnosed with Attention Deficit Hyperactivity Disorder (ADHD).

ADHD is among the most common childhood disorders, affecting around 8 to 12% of the worldwide population (Faraone et al. 2003). Popularly, children suffering this disorder are often seen as disobedient, impolite, annoying and poorly educated. However, since the very beginning, scientific findings and clinical observations have highlighted the importance of neurobiological factors in ADHD pathophysiology. In this sense, converging data from different studies point to ADHD abnormalities in fronto-striatal networks produced by dysfunctions in the DA system (Swanson et al. 2007). Structural neuroimaging studies partially support fronto-striatal abnormalities and suggest an important role of the cerebellum in ADHD pathophysiology (Giedd et al. 2001). However nearly all these studies are based on the analysis of *apriori* selected regions of interest (known as ROI approaches) which obviously bias the findings toward previously hypothesized structures.

Recent studies, using more global approaches, found that ADHD structural abnormalities were not limited to fronto-striatal-cerebellar circuits, but also affect temporal, parietal and cingulate regions (Overmeyer et al. 2001; Sowell et al. 2003). This has led some to argue that there is no specific neuroanatomical dysfunction in ADHD. As an alternative, it has been proposed that ADHD results from widespread neurodevelopmental abnormalities that affect the whole brain in a similar fashion (Durston 2003).

The aim of the present dissertation is to refine and apply two complementary methods of structural neuroimaging, in order to identify the brain circuits altered in ADHD, as well as to relate them to different clinical ADHD subtypes and to known ADHD neuropsychological deficits. For that purpose two structural MRI studies will be presented and discussed (see box 1 below). The differential contributions of these studies, which represent a novelty and an improvement on previous ADHD studies, are: a) the application for the first time of an a automatic global-brain neuroimaging analysis to compare ADHD children with non-related control children (study 1); and b) the design and application of a new, easy to apply, manual method of caudate nucleus segmentation (study 2). In addition, these studies represent an important contribution to the neural bases of ADHD because the two samples I used are: a) relatively large; b) familiarly unrelated and c) well-matched for gender, age and laterality.

Box 1: Presented paper.

Study 1:

Global and regional gray matter reductions in ADHD: a voxel-based morphometric study.
Carmona S, Vilarroya O, Bielsa A, Trèmols V, Soliva JC, Rovira M, Tomàs J, Raheb C, Gispert JD, Batlle S, Bulbena A.
Neurosci Lett. 2005 Dec 2; 389(2):88-93.

Study 2:

Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder.
Tremols V, Bielsa A, Soliva JC, Raheb C, Carmona S, Tomas J, Gispert JD, Rovira M, Fauquet J,Tobeña A, Bulbena A, Vilarroya O.
Psychiatry Research: Neuroimaging;163(3) (2008) 270–278
doi:10.1016/j.pscychresns.2007.04.017

The dissertation is organized in the following fashion: the introduction starts by nosologically defining ADHD as well as describing the epidemiological aspects and the history of the illness. This is then followed by a review of the main neurochemical, etiological and neuropsychological findings, which highlight the importance of fronto-striatal circuits as a suitable neuroanatomical base for the disorder. Next, I explain the currently most used ADHD model, known as "dual route model". This model integrates clinical, pharmacological and neuropsychological findings and explains them on the basis of fronto-striatal circuits. This is followed by a comprehensive review of ADHD neuroimaging findings, which partially support the implication of fronto-striatal circuits, but also highlight the importance of other brain regions. After this, I briefly explain the different approaches that have been used to study ADHD neuranatomy in order to stress the importance of combining both procedures. Subsequently, I highlight the general aim of the dissertation as well as the specific aims of each of the papers. Published and unpublished data from study 1 and 2 are then presented. In addition, I also synthesize the main methodological aspects as well as sum up the principal neuranatomical results derived from the studies. Finally, I discuss the results on the base of previous studies in ADHD and healthy population and integrate them within the framework of the dual route model.

1. Attention-deficit/hyperactivity disorder:

1.1. Definition:

Attention-deficit/hyperactivity disorder (ADHD) is a neurdevelopmental disease characterized by hyperactivity, distractibility and poor impulse control (see DSM-IV-TR and ICD-10 diagnostic criteria in appendix 1, A and B respectively).

According to DSM-IV-TR criteria, for a positive ADHD diagnosis at least six symptoms of inattention or six of hyperactivity-impulsivity must be present for more than six months. These symptoms should manifest before the age of seven and must significantly impair one or more lifetime activities such as interpersonal relations, or academic functioning. DSM-IV-TR permits the differentiation of ADHD intro three subtypes: 1) predominantly inattentive; 2) predominantly hyperactive/impulsive; or 3) combined.

This diagnostic can also be applied to the adult population if symptoms are present prior to age seven. When this diagnosis is applied to adults it receives the name of "adult attention-deficit disorder" (AADD). This reflects the different manifestation of the symptoms, especially motor hyperactivity, which is less frequently manifested in adult patients.

The equivalent terminology for ADHD according to ICD-10 is "Hyperkinetic disorder" (HD). Diagnostic criteria of HD are very similar to those of ADHD, although they do not completely overlap. The main difference is that ICD-10 does not include a predominantly inattentive subtype. According to ICD-10 the purely innattentional syndrome constitutes a different disorder.

1.2. Epidemiology:

ADHD is one of the most common childhood psychological disorders, often persisting into adulthood. It affects between 8 to 12 % of children's worldwide population (Faraone et al. 2003) and 3-5% of adult population (Faraone et al. 2006). According to ICD-10 the prevalence of this disorder is only of 1-2% (Swanson et al. 1998), which is very low compared to the one obtained by applying DSM-IV-TR criteria. Some authors have explained these diagnostic divergences as geographically specific distribution of the illness, nevertheless it seems more plausible to think they are caused by the use of diferent diagnostic criteria. There are also important gender differences in the incidence and manifestation of ADHD (Biederman et al. 1999). Specifically, for each girl with ADHD there are 2 to 3 boys with the diagnosis (Biederman et al. 2002b). Concerning subtypes, it was reported that hyperactivity-impulsivity or combined subtypes are more frequently observed in boys, while girls usually present more symptoms of inattentiveness (Biederman et al. 2002b). However, more recently, it has been suggested that gender differences may be produced by referral biases (Biederman et al. 2005).

1.3. History of ADHD:

A time chronogram of the disorder is depicted in box 2. It is important to point out that, since the very beginning, scientific findings and clinical observations have

highlighted the importance of neurobiological factors in ADHD pathophysiology (see box 2: ADHD timeline).

Box 2: ADHD timeline

1846	Physician Heinrich Hoffmann writes "Die Geschichte vom Zappel-Philipp" (The Story of Fidgety Philip). The poem is a description of a boy with similar characteristics to what nowadays is called ADHD.
1902	George Frederic Stills, a British pediatrician, provides the first comprehensive description of ADHD. He describes a child as overactive, aggressive, innatentive and insolent. His description depicts him as having a "defect in moral control". These observations are reported in a series of lectures at the Royal College of Physicians in England. Stills suggests that the behavioral problems are organic rather than educational. He proposes that the disorder is genetically caused or the result of perinatal brain damage.
1918	After World War I, many children suffered encephalitis. It is noted that the behaviour of encephalitic children is similar to the one described by Stills. This prompts the consideration that the cause of these problems might be brain injury rather that genetic transmission. Children with these behavioral problems are labeled as "brain damaged". Later, the terminology changes to "minimal brain damage" given the high functioning of some of the children.
1934	E. Kahn and L.H. Cohen propose a syndrome called "organic drivenness" to describe the problems of post encephalitic survivors.
1937	Charles Bradley reports that stimulant medication is helpful for reducing hyperactive and impulsive behavior as well as improving concentration and motivation.
1957	The stimulant Methylphenidate (Ritalin) is introduced for treatment.
1960	Stella Chase describes "Hyperactive Child Syndrome". Chase discerns the syndrome hyperactivity from that of brain damage. She highlights other possible causes such as poor parental schedules or environmental toxins.
1962	Due to the existence of the behavioral problems without any empirical measure of brain damage, S.D. Clements and J.D. Peters introduce the terminology of "Mild Brain Dysfunction" as a substitute of "Minimal Brain Damage". The same year, Ronald MacKeith highlights the need to redefine the term "Minimal Brain Dysfunction" because it is too inclusive and heterogeneous.
1968	DSM-II introduces the concept "Hyperkinetic Reaction of Childhood", emphasizing hyperactivity as the core feature of the disorder.
1970s	A series of publications by Virginia Douglas defend attention deficits as being the core dysfunction of the disorder instead of hyperactivity. These publications constitute the main influence for the DSM-III (see below).
1977	ICD-9 includes "Hyperkinetic syndrome of childhood". This disorder is characterized by "short attention span and distractibility".
1980	DSM-III re-categorizes the disorder as Attention Deficit Disorder, with or without Hyperactivity. The classification takes into account three basic features: inattention, impulsiveness and hyperactivity.
1987	The DSM-III R revises the previous edition and includes a category of "Undifferentiated Attention Deficit Disorder" which excludes hyperactivity and impulsivity.
1992	ICD-10 updates the diagnostic, defining the current criteria for "Hyperkinetic Disorder".
1994	DSM-IV describes three ADHD subtypes: inattentive, hyperactive-impulsive and combined.
1996	Francisco Xavier Castellanos found that ADHD children have smaller total brain volume that control children. Other groups have extensively replicated this result.
1997	Russel A. Barkley proposes that inhibition control is the precursor of ADHD dysfunctions.
2002	Edmund Sonuga-Barke proposes the "Dual route model". This model postulates the implication of, at least, two distinct pathways in ADHD pathophysiology: the associative fronto-striatal circuit, which may underlay deficits in executive functions; and the limbic fronto-striatal circuit, which would be related to motivational deficits.

1.4. Neurochemical accounts of ADHD

There is confluent evidence of a dopamine (DA) dysfunction in ADHD (Swanson et al. 2007). The most supported hypothesis point to DA hypofunction. This hypothesis is mainly grounded in pharmacological studies. Psychostimulants, especially those that inhibit the dopamine transporter and therefore raise the amount of extracellular DA (such as methylphenidate (MPH)[1]), ameliorate motivational, cognitive and motor ADHD symptoms (Russell 2003; Sagvolden and Sergeant 1998). As an additional support of the hypodopaminergic hypothesis, reduced levels of DA have been reported to mimic some of the ADHD symptoms (Luthman et al. 1997; Masuo et al. 2002; Masuo et al. 2004).

As an alternative to the hypodopaminergic theory, other hypotheses have been suggested. It has been proposed that there is a dysregulation in DA transmission between the PFC and the striatum (Solanto 2002). In particular, it has been hypothesized that the hypodopaminergic state in the PFC might be the cause of typical ADHD cognitive deficits. As a compensatory mechanism, low DA levels in PFC might also be responsible for the hyperdopaminergic state in the striatum, which, in turn, would cause hyperactivity symptoms. Other theories suggest that abnormal interactions between DA hypofunction and glutamate release of cortical afferents to the striatum underlie ADHD neurochemistry (Russell 2003).

In addition, it is known that MPH not only inhibits the dopamine transporter (DAT), but also the monoamine vesicle transporter (VMAT2). This vesicle influences dopamine, but also noradrenaline (NA) [2] and serotonin (5-HT) transmission (Russell 2003). Therefore, other hypothesis concerning abnormalities of the serotonergic and noradrenergic systems are also being studied. Moreover, drugs that selectively inhibit noradrenergic re-uptake have been proved to be efficient for ADHD treatment (Michelson et al. 2001).

1.5. Etiology of ADHD:

ADHD seems to be associated with genetic and environmental factors as well as interactions between the two.

1.5.1. Environmental factors:

Complications during pregnancy and delivery, as well as low socio-economic status are the main environmental factors implicated in the development of ADHD.

Multiple studies found a direct relationship between ADHD symptoms/diagnosis and the amount of tobacco that the mother smoked during gestation (Kotimaa et al. 2003; Mick et al. 2002). Also, fetus exposure to other environmental toxins, such as lead, polichlorinated bipheniyls (PCBs), marijuana or alcohol, increases the risk of ADHD. In particular, it has been reported that marijuana and alcohol affects attentional skills, whilst lead and PCB's have a more generalized negative effect on brain development (Williams and Ross 2007).

[1] Psychostimulant drug. It presumably works by blocking the reuptake of DA in the striatum.

[2] NA originates principally in locus coeruleus and innervates the cerebral cortex, hippocampus, spinal cord and cerebellum.

Delivery complications, prematurity, and more specifically low birth weight, have also been related to symptoms of hyperactivity (Pinto-Martin et al. 2004). Fetal stress or hypoxia has also been reported as risk factors for ADHD (Zappitelli et al. 2001). The basal ganglia and the middle temporal lobe structures are especially sensitive to damage when there is a lack of oxygen in the brain (Daval et al. 2004; Toft 1999). Interestingly, these very regions have been found to be altered not only in ADHD children (Daval et al. 2004), but also in premature (Perlman 2001) and low birth weight neonates (Abernethy et al. 2002).

With regard to low socio-economical status, epidemiological (Pineda et al. 1999) and clinical studies (Biederman et al. 2002a) show that ADHD children are more likely to belong to low social classes than normal control children. This association may be modulated by other variables more related to poor child rearing, such as educational environment (parent schedules, school, friends, etc.) or even food quality (Fanjiang and Kleinman 2007). Unfortunately, it is difficult to clarify if these variables play a role as etiological factors, maintenance factors or both.

Although there is a possible relationship between social class, smoking habits during pregnancy and giving birth to low-weight babies (Langley et al. 2007; Stein et al. 1987), most of the studies have observed that the predictive effect of each of the factors persist despite covarying for the effect of the others (Mick et al. 2002; Pineda et al. 1999).

Other environmental factors, such as head injuries or long-term marijuana use, may cause a person to present ADHD-like symptoms but not to meet ADHD diagnostic criteria. Therefore they are not typically considered as etiological factors.

1.5.2. Genetic factors:

Family, twin and adoption studies of ADHD suggest that it may be one of the most heritable psychiatric diseases with an estimated heritability of 76% (Faraone et al. 2005).

The hypothesis of dopamine dysfunction in ADHD is widely supported by animal, molecular and neuroimaging studies (Russell 2003). Given this strong evidence of DA dysfunctions, the majority of genetic studies have focused on dopaminergic genes. Polymorphisms in the dopamine D4 receptor (DRD4), the dopamine transporter (DAT) and Beta-hydroxilase (DBH) have been associated with ADHD (Faraone et al. 2005; Heijtz et al. 2007; Russell 2003). Moreover, each of these genetic structures seems to be related to different processes as well as differences in brain morphology. For example, the 7-repeated allele of DRD4 has been reported to predict commission error in a task of sustained attention (Kieling et al. 2006), while DBH has been related to the temporal resolution of spatial attention (Bellgrove et al. 2006). What is more, the combination of genetic risk, as measured by DAT and DRD4 gene polymorphisms, has been found to partially account for the IQ (intelligence quotient) level, suggesting additive effects for dysfunctional dopaminergic state (Mill et al. 2006). Interestingly, Durston et al (Durston et al. 2005) found a relation between DAT 10R/10R genotype and the volume of caudate nucleus and between DRD4 and prefrontal gray matter (GM) volume.

Despite the obvious importance of dopaminergic genes, other genetic studies have recently focused on the noradrenergic and serotonergic systems (Faraone et al. 2005). This line of research is still in an incipient stage as compared to the above-mentioned studies. The results seem promising, however, given the effect of MPH on NA and 5-HT, as previously mentioned in section 1.4. See table 1 for details about genetic factors.

Another interesting candidate gene is FADS2 (Brookes et al. 2006). This gene codifies for the Fatty Accid Desaturase 2, a protein known to modulate dopaminergic transmission and, thus, influence cognition and behavior. This opens up an interesting line of research.

Table 1 Genetic Factors: Based on Faraone's review (Faraone et al. 2005)

SYSTEM	GENE	RELATION TO ADHD
Dopaminergic	Dopamine D4 receptor DRD4	▪ A repeated polymorphism produces blunted response to dopamine. ▪ Expressed in cortical areas (PFC) ▪ Extensively related to ADHD ▪ Subjects with short alleles performed worst on continuous performance test.
	Dopamine D5 receptor DRD5	▪ 148-bp allele related to ADHD specially inattentive and combined subtypes.
	Dopamine D2 receptor DRD2	▪ Non-congruent results regarding its implication in ADHD ▪ Positive results are probably influenced by the presence of Tourette comorbidily in the ADHD group
	Dopamine D3 receptor DRD3	▪ Expressed in ventral striatum (accumbens nuclei) ▪ Non-congruent results regarding its implication in ADHD ▪ Associated with impulsivity and violence
	Dopamine Transporter Gene DAT,SLC6A3	▪ Target for stimulant medication ▪ Knockout mice for this gene present hyperactivity and deficits in inhibitory behavior
	Dopamine-beta-hydroxylase DBH	(Enzyme that converts dopamine to noradrenaline) ▪ Taq1 polymorphism has been significantly associated to ADHD
	Tyrosine Hydroxylase TH	▪ Althought it plays a role in the synthesis of dopamine, there are no congruent results regarding its implication in ADHD
	Catechol-O-Methyltransferase COMT	(Catalyzes the degradation of Dopamine, noradrenaline and epinephrine) ▪ Initially thought to be related only to male cases. ▪ Non-congruent results regarding its implication in ADHD
	Monoamine Oxidase A MAO-A	(Enzyme that modulates the levels of noradrenaline, dopamine and serotonin) ▪ It has been related to commission errors during attentional tasks ▪ Non-congruent results regarding its implication in ADHD
Noradrenergic	Noradrenergic receptors ADRA2A, 2C and 1C	▪ Related to a broad range of psychiatric symptoms: Som has reported that G allele associated with ADHD (specially inattentive and combined subtype) and oppositional defiant or conduct disorder symptoms ▪ Non-congruent results regarding its implication in ADHD
	Noradrenaline Transporter SCL6A2	▪ Thought to be involved because drugs that block this transported are efficacious as ADHD treatment ▪ Non-congruent results regarding its implication in ADHD
Serotoninergic	Serotonin Receptors HTR1B and HTR2A	▪ There seems to be an association between HTR1B gene and ADHD, ▪ Results concerning HTR2A are not congruent.
	Serotonin Transporter 5-HTT; SLC6A4	▪ Related to different psychiatric disorders ▪ Interactive effects with environmental variables such as parental alcohol abuse.
	Tryptophan Hydroxylase TPH	▪ Has been related to aggression and impulsivity ▪ Non-congruent results regarding its implication in ADHD
Other	Acetylcholine Receptors: CHRNA4 and CHRNA7	▪ No congruent results about its implication in ADHD. ▪ Positive result may be probably mediated by the presence of Tourette Comorbidily in the ADHD group
	Glutamate Receptors GRIN2A	(Codes for a subunit of N-methyl-D-aspartate (NMDA)) ▪ Implicated in cognition. ▪ No congruent results concerning its implication in ADHD
	Synaptosomal-Associated Protein 25 SNAP-25	▪ Reduced SNAP-25 expression leads to striatal dopamine and serotonin deficiencies. ▪ It has been related to hyperactivity.

This table identifies genetic polymorphisms that have been related to ADHD. It provides the gene that contains them as well as the neurotransmitter system to which the gene belongs. Only genes from the yellow cells have been consistently implicated in ADHD according to a recent review (Faraone et al. 2005)

1.5.3. Environment-Gene Interacctions

In ADHD, as in nearly all mental disorders, important interactions between genes and environmental factors have been reported. For example, Kahn et al (Kahn et al. 2003) studied the relation between DAT gene alleles and smoking during pregnancy. He found that the presence of a minor allele of DAT exerts a protective effect against the risk produced by maternal smoking. Another study (Jacobson et al. 2006) focused on the mother's genetic polymorphism of the enzyme alcohol dehydrogenase (ADH1B), —involved in the catalyzation of alcohol —and the risk of ADHD for the fetus. The authors report that ADH1B*3 allele exerts a protective effect on the fetus probably by increasing the alcohol metabolism of the mother.

1.5.4. Etiology and phenotypes:

There is an increasing interest in taking into account ADHD phenotype and comorbidity when studying the effect of environmental and genetic factors. Recent research concerning environmental factors has observed that: lower social class and maternal smoking during pregnancy predicts severity of hyperactivity/impulsivity symptoms but bear no relation with inattention (Langley et al. 2007). This study also showed that these two factors were related to Conduct Disorder comorbidity.

Regarding genetic account for ADHD heterogeneity, it has been reported that dopamine D5 receptor (DRD5) specifically influenced inattentive and combined subtype (Lowe et al. 2004). In addition, a MspI polymorphism of the adrenergic alpha2a receptor gene (ADRA2a) was found to be related to inattention (Schmitz et al. 2006), whilst DRD3 polymorphism heterozygosity affects impulsivity scores (Faraone et al. 2005; Retz et al. 2003).

1.5.5. Summary:

To sum up, genetic factors, especially those related to DA, play an important part in ADHD disorder. However, the effects are complex and seem to be mediated by the accumulative effects of various interacting genes, with each other and with the environment. The multiple combinations of interactions are in accordance with the different manifestations of the disorder, as well as the high comorbidity[3] with other disorders such as Conduct Disorder, Anxiety or Tourette syndrome.

[3] For a review about ADHD comorbidity see Artigas-Pallares 2003
Artigas-Pallares, J. [Comorbidity in attention deficit hyperactivity disorder]. *Rev Neurol* (2003) 36 Suppl 1:S68-78.

1.6. Neuropsychology of ADHD:

There are a wide range of studies on neuropsychological deficits in ADHD, and, at the moment, the most consistent finding is that ADHD patients present high inter/intra subject variability in neuropsychological tasks (Castellanos et al. 2006). This is probably due to the fact that ADHD diagnostic is currently based on a complex set of clinical descriptors. Therefore, ADHD neuropsychological intervariability may be a consequence of current diagnostic procedures, which allow for heterogeneous clinical profiles. Furthermore, it is possible that some of the neurospychological dysfunctions might actually be the result of the illness rather than the cause of the disorder.

From a neuropsychological perspective, ADHD generally affects two basic domains: executive functions (high-order cognitive functions such as strategy planning, set shifting, sustained attention, response inhibition or working memory) and motivation (reward management, see section 1.6.2)[4].

1.6.1. Executive Functions (EF):

Lesions to the frontal lobe often induce deficits in executive functions including a wide-range of top-down processes such as behavioral planification, performance monitoring or inhibition control. The behavior of patients with frontal lobe damage sometimes resembles some of the symptoms manifested by ADHD patients. These similarities suggest that a key feature of ADHD might actually be deficits in EF produced by frontal lobe abnormalities. According to a recent review (Nigg 2005) the EF that better distinguish between control and ADHD children are sustained attention, inhibition control and working memory (see also table 2).

Table 2: Neuropsychological deficits in ADHD

Task	Effect size
Spatial Working Memory (spatial span)	0.75
Sustained attention (CPT d-prime)	0.72
Inhibition (Stop Task Response Suppression)	0.61
Set shifting (Trail B Time)	0.55
Planning (Tower-like test)	0.51
Verbal Working Memory (digit span)	0.51
Set shifting (WCST Perseverative errors)	0.35
Inhibition (Stroop Interference)	0.25
"Inhibition" (Posner Covert Visual-Spatial Orienting)	0.20
Full Scale IQ	0.61

This table summarizes the findings of Nigg (Nigg 2005). Effect size is based on Cohen's d index, which is defined as the difference between the two means (ADHD and control children) divided by the pooled standard deviation for these means. Here I list the tasks with the largest effect size. Note further that full scale intelligence quotient (IQ) is included.

[4] Some authors have also proposed other neuropsychological approaches such as those based on "self regulation" or "energetic" models (see Berger for an extensive explanation).
Berger, A., Kofman, O., Livneh, U., et al. Multidisciplinary perspectives on attention and the development of self-regulation. *Prog Neurobiol* (2007) 82(5):256-86.

Attention:
In 1972, Douglas (Douglas 1972) cited by (Stefanatos and Baron 2007) highlighted deficits in sustained attention as the core neuropsychological disturbance in ADHD. Attention can be conceptualized as a complex process that involves multiples abilities such as focusing, ignoring distractions and remaining alert (Stefanatos and Baron 2007). Sustained attention deficits could account for clinical disturbances such as academic difficulties produced by poor focusing, distractibility or forgetfulness. Currently, the most common task used to measure attention is the Continuous Performance Task (CPT). This task infers inattention from errors of omission (for an extensive explanation see appendix 2 about neuropsychological tasks). Various studies have reported that ADHD children commit more omissions errors than controls (Berwid et al. 2005). Moreover, impaired performance correlates with ADHD symptoms (Anderson et al. 2006). Inattention is, however, a difficult process to conceptualize. Omission errors in CPT task can be produced by deficits in other domains such as poor working memory or lack of motivation for the task.

Inhibition:
Barkley (Barkley 1997) proposed that deficits in inhibition control were the main dysfunction in ADHD. According to this theory, disruptions in other processes (attention, working memory, and even motivation) are secondary to poor inhibitory control. Inhibitory control refers to the capacity to stop behavior or suppress its initiation. It is a key process to restrain environmentally guided behavior. Deficits in this process could explain ADHD clinical manifestations such as interrupting others or exasperation when waiting turns. But, according to Barkley's theory inhibition deficiencies could also be the cause of attention deficits (children fail to be focused on a task due to problems in inhibiting potential distracters) and hyperactivity (child behavior is guided by environmental cues or self stimulating motor behavior that failed to be repressed). Neuropsychological indices of poor inhibition control are provided principally by the Stop signal task (SST), Go/No-go task and Stroop-like tasks (see appendix 2). There are a large number of studies supporting the idea that ADHD individuals display deficits in these tasks (Rubia et al. 2007a). However, Rodhes' study (Rhodes et al. 2005), with the larger naïve-ADHD sample, found no differences between groups in response inhibition indices. Thus, the inhibiton control hypothesis is still being questioned (Castellanos et al. 2006).

Working Memory:
Deney and Rapaport, in 2001 (Denney and Rapport 2001) suggested that the primary neuropsychological disturbance in ADHD was an impairment in working memory, and that problems of desinhibition and impulsivity were secondary to this central working memory dysfunction. Working memory can be defined as the capacity to maintain information online, and it is essential in order to keep performing goal directed behaviors despite possible interferences. Without working memory our mind could not work for the pursuit of a purpose and would be freely guided by environmental stimuli. This situation would produce inattention, impulsivity and hyperactivity. Measure of working memory deficits are provided, among others, by digit span (verbal working memory) and by spatial span or Tower-like tests (spatial working memory), (see also appendix 2). Recent meta-analysis reported larger deficits for spatial than for verbal working memory in ADHD (Martinussen et al. 2005). Moreover, spatial working memory seems to be the neuropsychological measure that more precisely discriminates ADHD from control subjects (Nigg 2005;

Nigg and Casey 2005) (see table 2). However, Castellanos (Castellanos et al. 2006) highlights the need of performing a better control of potential confounds when measuring working memory (such attention, motivation, general intelligence, etc).

Finally, regarding EF, Nigg (Nigg 2005) meta-analysis manifested that only from 35 to 50% of ADHD-combined children have deficits in EF, which means that more than 50% or of ADHD children do not have EF deficits.

1.6.2. Motivation:

Given that ADHD symptoms cannot be fully explained by deficits in EF, Sonuga has proposed the incorporation of an additional hypothesis involving motivation[5] and reward processes (Sonuga-Barke 2002; Sonuga-Barke 2003).

The motivational hypothesis has been based on temporal discounting models. The temporal discounting construct reflects the psychological effect by which the perceived value of a reward of a given reinforcement is subjectively reduced by the passing of time. It has been found that ADHD children are over-responsive to recent or immediate reward, but under-responsive to delayed rewards (Tripp and Alsop 1999). Increased temporal discounting effect in ADHD has been suggested to be the base of impulsivity symptoms (Green et al. 1996). In parallel, Kuntsi (Kuntsi et al. 2001), recovered the concept of "Delay Aversion" proposed by Sonuga-Barke in 1992 (Sonuga-Barke and Taylor 1992), and showed that impulsive children prefer immediacy of reward because they have aversion for all kind of delays (pre and post reward). In addition, Solanto (Solanto et al. 2001) showed that inhibition deficits were uncorrelated with the tendency to choose smaller-short term rewards.

Much of the literature reports dysfunctional reward system in ADHD in the sense that rewards lose their reinforcing power as they become distant in time from the action or the cue (Sagvolden et al. 2005). Luman et al 2005 (Luman et al. 2005) examined a large amount of data collected from different studies in which ADHD children were compared to control participants on tasks involving rewards and punishment. Half of the studies reviewed by Luman showed that ADHD and control children differ with regard to the effect of reward contingencies on performance. Specifically, the effect of reinforcement is more prominent in ADHD: they prefer immediate over delayed rewards and seem less psychophysiologically sensitive to reinforcement than controls. Household, school and clinical observations support abnormalities in motivational/reward processes. A child with ADHD diagnosis might be unable to pay attention for more than five minutes in a math class (delayed reward if any) whereas stay focused on a video game for hours (frequent reward delivering). Additionally, novelty also has been observed to play an important role in ADHD performance. A deterioration of performance has been found in later phases of a task, when interest due to novelty has decreased (Toplak et al. 2005). Therefore, novelty and reward, both functions ascribed to DA systems seem to be key aspects in ADHD behavior[6].

[5] Motivation can be defined as a reason or a set of reasons for engaging a behavior.

[6] Dysfunctional DA system in ADHD is extensively supported by pharmacological, genetic and molecular studies. DA has been extensively related to novelty and learning, both the processes necessary for signaling reward and motivating our behavior. Moreover, there is a solid data about over-shouting on DA neurons in ventral striatum when seeing cues that predict the presence of rewards, and hyporesponsivity in these neurons if the predicted reward is not presented

One of the neuropsychological tasks used to measure reward and motivational processes is the "Choice delay task" in which children have to choose between small immediate or large delayed rewards (see appendix 2). Regardless if motivational deficits are the central dysfunction of ADHD or not, motivational theories have highlighted very important aspects that can partially explain the high heterogeneity of results in neuropsychological test, for example the slow down of motivation and, in turn, performance over time (when novelty of stimulation decays), or the effect of what was emphasized in the task instruction (e.i. instructions that emphatize short term reinforcement may improve motivatition and performance in ADHD children much more that those that emphasize delayed reinforcement).

Hassani, O. K., Cromwell, H. C., and Schultz, W. Influence of expectation of different rewards on behavior-related neuronal activity in the striatum. *J Neurophysiol* (2001) 85(6):2477-89, Schultz, W. Reward signaling by dopamine neurons. *Neuroscientist* (2001) 7(4):293-302, Schultz, W., Dayan, P., and Montague, P. R. A neural substrate of prediction and reward. *Science* (1997) 275(5306):1593-9.

2. Integrative model of ADHD:

As described in the previous section, neither EF nor motivational theories by themselves can fully account for the clinical and neuropsychological deficits of ADHD. Recently, a new theory has been developed, based on the integration of both domains: EF and motivational aspects. This theory is known as "The dual route model". Although it is not the only ADHD pathophysiology model, it is currently, in my opinion, the one that best accounts for clinical and neurobiological ADHD findings.

2.1 The dual pathway model:

Sonuga-Barke (Sonuga-Barke 2002) proposed the implication of, at least, two distinct pathways in ADHD pathophisiology: the associative fronto-striatal circuit, related to EF deficits; and the limbic fronto-striatal circuit, involved in differences in subjective-reward value and motivational performance (for a comprehensive description about fronto-striatal circuits see appendix 3). This dual model received support after Haber reviews (Haber 2003) on the spiraling flow of information from limbic to associative and to sensorimotor circuits. Haber offered an anatomical explanation of how motivation can influence EF, which, in turn, can affect a great many types of behavior. Thus, ADHD neuropsychological and clinical problems can be produced by deficits in EF, by deficits in motivational processes or by both. In fact, it has been reported that, when are taken into account response on delay aversion (Choose Delay Task) and EF (specifically inhibition: Stop task) the results correctly classified nearly 90% of the ADHD children (Solanto et al. 2001).

The dual-pathways model categorizes neuropsychological ADHD deficits in two groups: *cool* processes and *hot* processes (also known as *cool* EF and *hot* EF). The *cool* processes refer to "top-down" cognitive control over behavior. They are very similar to the above-described EF, including sustained attention, working memory and inhibition control. Brain regions involved in these processes overlap with those of the associative FSC, that is: frontal regions (DLPFC and VLPFC) and dorsal striatum (mainly the head of caudate nucleus). Mesocortical and nigrostriatal DA pathways modulate *cool* processes. By contrast, *hot* processes refer to emotional and motivational aspects, but also to cognitive processes that have an important influence on affective components. They consist of both, "top-down" and "bottom-up" behavioral-control processes, although with a greater weight of bottom-up processes (Kelly et al. 2007). Motivation, time discount, delay aversion and other dysfunctions related to reward system are attributed to deficits in *hot* processes. *Hot* processes are ascribed to limbic cortico-striato-thalamico cortical circuits (OFC, MPFC, ACC, AccN, amigdala and hippocampus), which are highly modulated by DA mesolimbic branches.

2.2. Dual route and phenotypes:

Sonuga-Barke (Sonuga-Barke and Sergeant 2005) proposed that each subtype of ADHD, as defined by DSM-IV-TR, results in different patophysiological manifestations, with different implication of FSC and modulated by different DA branches. Likewise, Castellanos (Castellanos et al. 2006; Castellanos and Tannock 2002) suggested that inattention symptoms might be related to deficits in *cool* processes whereas hyperactivity/impulsivity symptoms would be reflecting

abnormalities in *hot* processes. Moreover, Castellanos proposed that OFC and the ventral striatum could be related to delay aversion and abnormalities in the reward system, whereas DLPFC and dorsal striatum might be implicated in cool processes. Unfortunately, at present, neuroimaging results do not completely support such a clear distinction.

2.3. Summary

Different neuropsychological deficits can lead to similar manifestations, which partially explain the high ADHD inter and intra subject variability. Besides EF, motivational deficits are important to understand ADHD neuropathology and may be mediating high intrasubject variability. Neither EF nor motivational models are individually sufficient to explain clinical and neuropsychological findings in ADHD. Successful goal-directed behavior is likely to require a combination of both, hot and cool systems. *Cool* processes would account for correctly planning and performing behavior in order to achieve the goal, and *hot* would account for setting up and maintaining the incentive value of the goal in order to motivate the behavior towards it. Dual route models help to explain the heterogeneity of the disorder, and have important implications for both clinical practice and research methodology.

3. Neuroimaging in ADHD

A general review of ADHD neuroimaging is offered below. The description focuses on anatomical findings, especially those using Magnetic Resonance Imaging (MRI). I also briefly comment upon Diffussion Tensor Imaging (DTI) and Magnetic Nuclear Spectroscopic (MRS) results. Finally I succinctly report on functional studies, again placing emphasis on functional MRI techniques (fMRI).

3.1. MRI techniques.

MRI techniques are safe and noninvasive. They allow researchers to study anatomical structures of the brain, as well as axonal connections among these structures (using DTI techniques). Furthermore, MRI techniques allow us to analyze chemical composition and integrity of different brain regions (using MRS). MRI has become one of the main options for studying brain functioning (displacing Electroencephalography (EEG), Magnetoencephalography (MEG), Single Photon Emision Computed Tomography (SPECT) and Positron Emission Tomography (PET) technologies) because of the optimal compromise between temporal and spatial resolution (see appendix 4 for a brief description of neuroimaging techniques). Moreover, MRI is especially suitable when studying children, given the lack of ionizing radiation, which not only overcomes ethical problems, but also allows for longitudinal studies.

3.2. Neuroanatomical findings in ADHD children:

The review is based on a search through PUBMED data base (http;www.pubmed.org) using different combinations of the following terms: ADHD, attention deficit hyperactivity disorder, hyperkinetic disorder, magnetic resonance imaging, MRI, neuroimaging, and brain anatomy. Reviews about the issue were examined as a first approach given the enormous number of studies linked to these key terms. Afterwards, each of the original references cited by the reviews, as well as recently published studies, were consulted. Only neuroanatomical studies based on MRI findings are discussed. The initial studies about brain anatomy in ADHD that used Computerized Tomography (CT) are not included in this review. Studies are summarized in table 3.

All the studies used a MRI scanner of 1.5T except the three first studies in the early 90s (Hynd et al. 1993; Hynd et al. 1990; Hynd et al. 1991) that used a MRI scanner of 0.6T. All the studies but two (Overmeyer et al. 2001; Sowell et al. 2003) used manual or automated regions of interest (ROI) techniques. I will talk more extensively about the different techniques in the next section. Briefly, ROI approaches are characterized by the *apriori* selection of the region to study, and, thus, do not provide any information about the rest of the brain. Other procedures, such as those based on voxel based morphometry (Good et al. 2001a; Good et al. 2001b) and surface density (Sowell et al. 2003), allow the study of the brain as a whole, although they require some preprocessing steps (such as normalization) that can distort results (see section 4 for an extensive explanation).

Table 3: List of structural MRI studies in ADHD. Table format based on Durston (Durston 2003)

Author, year and journal	**Designs:** Subjects (n, diagnostic, gender, age), methods and notes	**Results**
Durston, 2004 JAACAP (Durston et al. 2004)	Subjects: 30 ADHD, m, 12.1 30 ADHD-unaffected siblings, m, 11.6 30 Ctrl, m, 10.7 Technique, measures and notes: ROIs: Automatic. Intracraneal and encephalic brain volume, cerebellum, lateral and third ventricle, and PFC (excluding precentral sulcus). Volume.	↓ intracranial but not encephalic brain volume ↓ R cerebellum that do not remain significant after intracranial volume correction ↓ L occipital GM and WM that do not remain significant after intracranial volume correction
Sowell, 2003 Lancet (Sowell et al. 2003)	Subjects: 27 ADHD 16m, 12.3 46 Ctrl, 29m, 12.0 Technique, measures and notes: Computational surface density technique.	↓ inf. portion of DLPFC ↓ ant. portion of R temporal and parietal cortex ↑ GM in temporal post and parietal inferior bil. as well as in R occipital. negative ∝ between R MPFC cortical surface and hyperactivity.
Hill, 2003 Neuropsychol. (Hill et al. 2003)	Subjects: 23 ADHD, 17m, 9.35 23 Ctrl , 16m, 9.36 Technique, measures and notes: ROIs: Manual. Frontal (sup. and inf.), caudate nuclei, CC and cerebellum. Volume. Caudate nucleus was measured in axial sections, and the anterior comisure was established as the inferior limit of caudate.	↓ TBV. ↓ PFC sup. R ↓ cerebellar lobes I-V and VIII-X ↓ smaller splenium of CC No difference in volume or asym of caudate nucleus. Positive ∝ between CPT and R PFC sup. volume *comorbidity: ADHD vs ADHD+ODD. ↓ bil caudate and ↓ splenium.
Kates, 2002 Psychiatry Res(Kates et al. 2002)	Subjects: 13 ADHD m, 9.4 13 TS m, 9.9 13 Ctrl m, 10 Technique, measures and notes: ROI. Manual. Subdivides the frontal lobe into five major modules: prefrontal, premotor, motor (precentral gyrus), anterior cingulate, and deep white matter. Volume.	↓ gray and white matter of the PFC in ADHD as compared to ctrls. After multiple corrections only L PFC tissue remain significant. *Differences did not reach significance when expressed as ratios of TBV
Castellanos, 2002 JAMA (Castellanos et al. 2002)	Subjects: 152 ADHD; 89m; 10.0 139 ctrl; 83 m; 10.5 Technique, measures and notes: ROIs: Automatic methods. Total cerebrum, GM and WM for the 4 major lobes, caudate and cerebellum. Volume. Longitudinal study	↓ total brain in all GM and WM compartments equally, and in the cerebellum ↓ caudate volume normalizes with age ↓ WM volume for previously unmedicated ADHD Negative ∝ between frontal and temporal GM, caudate and cerebellar volumes and attentional problems. *After adjusting for TBV only the difference for the cerebellar volumes remained significant.
Mostofsky, 2002 Biol.Psychiatry (Mostofsky et al. 2002)	Subjects: 12 ADHD; 12 m; 10.1 10 ctrl; 12 m; 10.2 Technique, measures and notes: ROIs: Automatic partelation of frontal GM, WM and CSF. Volume.	↓ frontal lobe volume, frontal white matter L, frontal GM bil. ↓ prefrontal tissue and premotor ↓ WM
Pineda, 2002 J Child Neurol (Pineda et al. 2002)	Subjects: 15 ADHD combined type; 7m; 9.3 15 ADHD inattentive type; 7m; 9.3 15 ctrl; 7m; 9.3 Technique, measures and notes: ROIs: Manual. Head caudat nucleus (3 first coronal sections). Volume. *Groups differ significantly in IQ	Caudate-head L > R all groups. No difference between groups
Castellanos, 2001 Arch Gen Psychiatry (Castellanos et al. 2001)	Subjects: 50 ADHD; fem; 5.3–16.0 50 ctrl; fem; 4.7–15.9 Technique, measures and notes: automated total brain, GM, WM, cerebellum. Manual caudate nucleus, globus pallidus, putamen, vermits & post-inf lobules (VIII-X). Volume.	↓ TBV, frontal L, caudate nucleus R & L, globus pallidus L, cerebellum R, post-inf vermis After correction for verbal IQ only caudate nucleus L and post-inf vermis remain significant
Overmeyer, 2001 Psychol Med (Overmeyer et al. 2001)	Subjects: 18 ADHD (hyperkinetic disorder); 15 m; 8–13 16 siblings (not affected) ctrl; 15 m; 7–14 Technique, measures and notes: VBM. Normalization template made of 5 ctrl brains.	↓ GM in R hemisphere: Med sup frontal gyrus, post cingulate gyrus, retrosplenial cortex, putamen, globus pallidus ↓WM in L hemisphere: Ant to pyramidal tracts, sup to basal ganglia
Overmeyer, 2000Dev Med & Child Neurol (Overmeyer and Taylor 2000)	Subjects: 15 ADHD (hyperkinetic); m; 8–13 15 siblings (non affected); m; 7–14 Technique, measures and notes: ROIs: Manual. CC (7 subdivisions), total brain area. Area.	No differences
Semrud-Clikeman, 2000 JAACAP(Semrud-Clikeman et al. 2000)	Subjects: 10 ADHD; m; 8–17; R 10 ctrl; m; 9–18; R Technique, measures and notes: ROI: Scans and segmentations form Filipek 1997. Volume. Inclusion of RAN, RAS, WCST and Stroop measures.	↓ caudate nucleus head L ↓Ant-sup white matter R Regresion: ∝ caudate nucleus head L volume and CBCL externalizing subscale and caudate asym and "stroop test" ANOVA: ∝ Caudate asym and CBCL internalizing subscale
Pueyo, 2000 Rev Neurol(Pueyo et al. 2000)	Subjects: 11 ADHD, 8m, 14.6 19 Ctrl, 16m, 14.8 Technique, measures and notes: ROIs: Semiatuomatic. Frontal region and caudate nucleus. Volume. * MRI scans results form Mataró 1997	ADHD: R>L caudate, Ctrl: L>R caudate. ↓ R frontal lobe in a ADHD subsample with worst symptomatology as compared to ctrls resulting in L>R frontal lobe asym.

Berquin, 1998 Neurology (Berquin et al. 1998)	Subjects: 46 ADHD; m; 11.7; R 46 ctrl; m; 11.8; R Technique, measures and notes: ROIs: Manual. Total brain, caudate nuclei, cerebellum, vermis volume & area, ant lobules (I–V), post- sup (VI–VII) & post-inf (VIII–X) lobules. Volume.	↓ total brain and cerebellum (not significant after correcting for total brain) ↓ vermis volume (significant after correcting for total brain and verbal IQ) ↓ post-inf vermis lobules volume and area ADHD: verbal IQ ∝ total brain, post-inf lobules vermis and caudate nucleus R Ctrl: vermis ∝ total brain and caudate nucleus L
Mostofsky, 1998 J Child Neurol (Mostofsky et al. 2002)	Subjects: 12 ADHD; m; 8.2–14.6 23 ctrl; m; 6.6–24.6 Technique, measures and notes: ROIs: Manual. Midsagittal area of intracranial volume, vermis, 4th ventricle. Area *Correction using rations.	↓ post-inf lobules ↓ vermis (VIII–X)/ intracranial ratio
Casey, 1997 JAACAP (Casey et al. 1997)	Subjects: 26 ADHD; m; 5.8–12.8 26 ctrl; m; 6.3–12.7 Technique, measures and notes: ROI: Scans and segmentation from Castellanos 1996. Volume. Inclusion of a task to measure sensory selection, response selection and response execution.	↓ reaction time (RT) and accuracy (acc) for ADHD Sensory selection: ADHD: RT % acc caudate nucleus R. Ctrl: acc on inhibitory trials ∝ prefrontal cortex R Response selection: Ctrl: RT ∝ globus pallidus L Response execution: ADHD: RT ∝ caudate symmetry Ctrl: RT ∝ globus pallidus L Correlations predominantly in R hemisphere
Filipek, 1997 Neurology (Filipek et al. 1997)	Subjects: 15 ADHD; m; 8–18 15 ctrl; m; 8–19; above average IQ Technique, measures and notes: ROIs: Automated cortex, white matter, central gray nuclei, hippocampus, amygdala, caudate nucleus, lateral ventricles. Manual pericallosal subdivisions, ínsula, caudate head (anterior pericallosal) and tail (posterior pericallosal). Volume.	↓ white matter frontal, predominantly R ↓ ant-sup & ant-inf (including caudate head) region, predominantly R ↓ caudate nucleus L head (trend R) ↓ retrocallosal regions (including parietal and occipital) ADHD symmetry in caudate regions as compared to asymmetrical caudate volume in ctrls. In non-responders reversed asym pattern.
Mataró, 1997 Arch Neurol (Mataro et al. 1997)	Subjects: 11 ADHD; 8 m; 19 ctrl; 16 m; Age range: from 14 to 16 Technique, measures and notes: ROI: Semin-automated one slice area of total encephalon and caudate nucleus. Area that mainly include the head of caudate Neuropsyhocoligcal measures	↓ attentional and frontal task ↑R head of caudate nuclei Ctrls: negative ∝ between bil caudate and performance on attention tasks. ADHD: negative ∝ between L caudate and time to solve Tower of Hanoi Task.
Aylward, 1996 J Child Neurol (Aylward et al. 1996)	Subjects: 10 ADHD; m; 11.3 16 ADHD$+TS; m; 11.3 11 ctrl; m; 10.7 Technique, measures and notes: ROIs: Manual. Partial estimate total brain, caudate nucleus, globus pallidus and putamen. Volume	↓ globus pallidus
Baumgardner 1996 Neurology (Baumgardner et al. 1996)	Subjects: 16 TS; 13 m; 12.6 13 ADHD; m; 11.2 21 TS+ADHD; 19 m; 11.3 27 ctrl; 21 m; 10.8 Technique, measures and notes: ROI: 1 slice area intracranial & CC (5 subdivisions). Area.	↓ rostral body of CC (2nd subdivision from ant)
Castellanos, 1996 Arch Gen Psychiatry (Castellanos et al. 1996b)	Subjects: 57 ADHD; m; 5.8–17.8 55 ctrl; m; 5.5–17.8 Technique, measures and notes: Increased sample of Castellanos 1994. ROI: semi-automated total brain, cerebellum, frontal lobe manual caudate nucleus (total), putamen, globus pallidus, hippocampus amygdala, lateral ventricles, area CC and vermis lobules (I–V, VI–VII, VIII–X)	↓ total brain ↓ frontal lobe R, caudate nucleus R and cerebellum (significant after covarying for total brain and verbal IQ) ↓ amygdala (no significant after covarying for total brain and verbal IQ)
Castellanos, 1996 Neurology (Castellanos et al. 1996a)	Subjects: 26 ADHD, m; 6.6–14.4 14 ADHD$TS; m; 7.1–13.8 31 ctrl; m; 6.7–13.9 Technique, measures and notes: ADHD and ctrl group MRI scans results Castellanos 1994 ROI: Semi-automated total brain, ant frontal. Manual caudate nucleus (total), globus pallidus, putamen Volume.	↓Globus pallidus bilaterally in ADHD and ADHD+TS ADHD and ADHD+TS: L>R globus pallidus Ctrl: R>L globus pallidus
Lyoo, 1996 Biol Psychiatry (Lyoo et al. 1996)	Subjects: 51 ADHD; 45 m; 11.7 (clinical diagnosis only) 25 ADHD; 21 m; 12.5 (DISC diagnosis) 28 pat ctrl; 16 m; 12.9 20 pat ctrl; 17 m; 12.2 (DISC screening) Technique, measures and notes: ROIs: total brain, CC, lateral ventricles, cerebellum, brainstem. Volume.	↓ splenium of CC (clinical group) ↓ isthmus of CC (DISC group) ↑ post vent (both)

Castellanos 1994, Am J Psychiatry (Castellanos et al. 1994)	Subjects: 50 ADHD; m; 6.4–19.5 48 ctrl; m; 5.5–17.8 Technique, measures and notes: ROIs: Semi-automated total brain. Manual caudate nucleus (anterior to Monroe foramen). Volume.	↓ TBV ↓caudate nucleus R (resulting in ↓ asym) Ctrl: caudate nucleus ↓ with age ADHD: not
Giedd 1994 Am J Psychiatry (Giedd et al. 1994)	Subjects: 18 ADHD; m; 6.7–15.2 18 ctrl; m; 6.3–15. Technique, measures and notes: ROI; Manual. CC (7subdivisions) total brain area. Area	↓ rostrum and rostral body
Semrud-Clikeman, 1994 JAACAP (Semrud-Clikeman et al. 1994)	Subjects: 15 ADHD; m; 8–18 15 ctrl; m; 8–19 Technique, measures and notes: ROI: CC (7 subdivisions). Area.	↓ splenium
Hynd, 1993 J Child Neurol (Hynd et al. 1993)	Subjects: 11 ADHD; 8m; 11.0 11 ctrl; 6m; 11.1 Technique, measures and notes: ROI; Manual total brain area and caudate nucleus (mainly head). Area.	↓ caudate nucleus L (producing reversed asym, mainly in males)
Hynd, 1991 J Learn Disabil (Hynd et al. 1991)	Subjects: 7 ADHD; 5m; 9.1 10 ctrl; 8m; 11.8 Technique, measures and notes: ROI; Manual 5 subdivisions of CC. Area.	↓ CC, particularly genu & splenium
Hynd, 1990 Arch Neurol (Hynd et al. 1990)	Subjects: 10 ADHD; ?m; 10.1 10 dyslexic; ?m; 9.9 10 ctrl; ?m; 11.8 Technique, measures and notes: ROI; Manual total brain area, width ant/post, length insula/planum temporale. Area.	↓ ant width R

Extant ADHD neuroimaging studies. ADHD= attention deficit hyperactivity disorder; Ctrl= controls; ODD= oppositional defiant disorder; TS= tourette syndrome; m= males; ROI= region of interest; VBM= Voxel Based Morphometry; R= right; L= left; bil= bilateral; inf= inferior; sup= superior; post= posterior; ant= anterior; vent= ventral; med= medial; lat= lateral; PFC= prefrontal cortex; CC= corpus callosum; DLPFC= dorsolateral prefrontal cortex; MPFC= medial prefrontal cortex; GM= gray matter; WM= white matter; CSF= cerebro-spinal fluid; TBV= total brain volume; DISC= diagnostic interview schedule for children; ↑= increased; ↓= decreased; ∝= correlation

3.2.1 Total brain volume and regional abnormalities:

In general, MRI anatomical findings point to total brain volume reductions in ADHD. In addition, specifict reductions has been observed in the fronto-striatal circuit (mainly prefrontal cortex and caudate nuclei), cerebellum and corpus callosum.

TOTAL BRAIN VOLUME:

The vast majority of studies found reduced total brain volume (TBV) in ADHD (Anderson et al. 2002; Castellanos et al. 2001; Castellanos et al. 1996b; Castellanos et al. 2002; Filipek et al. 1997; Hill et al. 2003; Kates et al. 2002; Mostofsky et al. 2002). Especially, Castellanos (Castellanos et al. 2001; Castellanos et al. 1996b) reported that ADHD have 5% small TBV as compared to controls. Some studies have also reported specific GM and WM reductions (Castellanos et al. 2002; Mostofsky et al. 2002). However TBV cannot be used as diagnostic criteria yet. On the one hand, TBV is highly variable among individuals, even when matching for age, gender, height and weight (Giedd et al. 2001) and thus needs big samples in order to see differences. On the other hand, one also has to take in to account that ADHD is a neurodevelopmental disorder. Therefore, reduced GM, WM or TB volumes should not necessarily be takes as a patognomonic sign of ADHD *per se*, but as a reflection

of impaired developmental process such as myelinization[7] and synaptic pruning[8] (Berger et al. 2007; Giedd et al. 2001).

Neuroanatomical research primarly focuses on studying frontal lobe and basal ganglia structures, because clinical, neurochemical and neuropsychological observations suggest fronto-striatal abnormalities.

FRONTAL LOBE:

In line with neuropsychological theories, DLPFC (related to cool processes) and OFC (related to hot processes) are suitable candidates to be involved in ADHD psychopathology. Differences in frontal ROI delimitations make it difficult to compare the measures across studies. However, all the studies measuring at least part of the PFC found reduced volumes in ADHD children (Castellanos et al. 2001; Castellanos et al. 1996b; Castellanos et al. 2002; Durston et al. 2004; Filipek et al. 1997; Hill et al. 2003; Kates et al. 2002). Interestingly, Mostofsky proposed that frontal reductions in ADHD are not only due to reduced prefrontal (DLPF and OFC) but also to smaller premotor areas (Mostofsky et al. 2002). Studies performed by Sowell (Sowell et al. 2003) and Overmeyer (Overmeyer et al. 2001), using more sophisticated computational techniques, also found that frontal lobe was reduced in ADHD children.

BASAL GANGLIA:

Caudate:

The basal ganglia, especially the caudate nucleus, have frequently been thought to play a pivotal role in ADHD psychopathology. The *apriori* implication, plus the fact that the caudate is an easily delimitable region, has made this structure a good candidate in ROI approaches. Nearly all the ROI studies found smaller total or head caudate volumes. While there is no consensus concerning the laterality of this reduction, various studies point to right-caudate-nucleus reductions. These reductions might result in reversed or loss of the caudate asymmetries observed in normal population (in which R>L). Importantly, Castellanos (Castellanos et al. 2002) found that differences in the volume of caudate nuclei disappear with age. This "normalization" of caudate volumes supports the implication of neurodevelopmental and dynamic aspects in the disorder.

[7] Myelinization is a gradual developmental process whereby a protective material called myelin wraps around the axons and therefore increases WM volume. Myelin protects the fiber and the speed of action potential along the axons. Although the bulk of myelinization occurs during the fetal and infancy stages, the process can take up to 10 years to reach completion.

[8] Synaptic pruning is a regulatory process that reduces the overall number of overproduced neurons into more efficient synaptic configurations. Presumable this underlies the GM volume decrease produced during late adolescence in normal populations.

Putamen:
None of the ROI studies looking at the putamen have found difference in volume between ADHD and control subjects. Only one study, that used a VBM approach found a smaller putamen volume in ADHD children as compared to their non-affected sibling (Overmeyer et al. 2001).

Globus pallidus:
The globus pallidus is a difficult structure to measure using automatic or manual ROI techniques. However, most of the ROI studies that compare Gp reported reductions in ADHD children as compared to control children (Aylward et al. 1996; Castellanos et al. 1996a; Castellanos et al. 1996b). In addition, Overmeyer's VBM-study also found smaller Gp in ADHD (Overmeyer et al. 2001). As in the case of caudate nucleus, there is no agreement concerning the laterality of the reduction.

CEREBELLUM:

In 1986 Nasrallah ((Nasrallah et al. 1986) cited by (Hale et al. 2000)) reported cerebellar atrophy in adult ADHD brains. The relevance of these results was called into question because of the history of alcohol abuse in the ADHD sample (Pfefferbaum et al. 1998). At present, there is more solid evidence about the cerebellar implication in ADHD. Specifically, ADHD volume reductions have been found in the posterior inferior lobules and the cerebellar vermis. Moreover, in the largest studIy to date, the only ADHD reduction that remained significant after correcting for total brain volume was the cerebellum, which, interestingly, correlates with attentional problems (Castellanos et al. 2002).

CORPUS CALLOSUM:

As in the case of caudate nuclei, corpus callosum (CC) is a good structure to study using ROI techniques. On the base of prior data, it was suspected that the anterior parts of the CC (the rostrum), that connect both prefrontal hemispheres, were disrupted, thus, reflecting PFC dysfunctions. However, although rostral parts of the CC have been found reduced in ADHD, also posterior parts (known as splenium of CC), that connect temporal and parietal lobes, have been reported to be smaller in ADHD children. Besides CC reductions, ADHD has been consistently associated with decreased WM volume throughout the whole the brain (Castellanos and Acosta 2002; Filipek et al. 1997; Hynd et al. 1991; Mostofsky et al. 2002; Overmeyer et al. 2001). Moreover, it has been suggested that stimulant medication might "normalize" WM deficits (Castellanos et al. 2002).

OTHER REGIONS:

As with the frontal lobe, Castellanos (Castellanos et al. 2002) found parietal, temporal and occipital lobe volume reduction in ADHD. The reductions in parietal, temporal and occipital areas support the idea of widespread abnormalities due to abnormal brain development in ADHD individuals. In the same line, Durston (Durston et al. 2004) also reported occipital lobe reductions in ADHD children. Moreover,

concerning the two studies that used computational techniques, which allow of whole brain exploration, Sowell (Sowell et al. 2003) found right anterior portions of temporal and parietal cortices reductions in ADHD and Overmeyer (Overmeyer et al. 2001) reported reduced posterior cingulate and retrosplenial cortex in ADHD.

3.2.2 Clinical and pharmacological correlations

In addition to the discrepancies due to methodological techniques, differences in clinical/neuropsychological profiles and/or psychopharmacological response can be modulating neuroanatomical findings in ADHD. Here I garner the most relevant correlations found between these variables and the volume of different brain regions.

Brain regions and clinical/neuropsychological profile:

Neuroanatomical comparisons between ADHD subtypes have not provided congruent results yet. However, studies report interesting correlations between brain anatomy and clinical and neuropsychological variables. For example, hyperactivity and impulsivity measures have been related to reduced rostrum and rostral area of the CC. These results suggest deficits in frontal connections (probably OF and perirolandic areas given the location of the fibers). In addition, Sowell found that right MPF surface negatively correlate with hyperactivity measures (Sowell et al. 2003).

Intelligence quotient score (IQ) has also been related to brain volume. Specifically, Castellanos (Castellanos et al. 2001; Castellanos et al. 1996b) found that total brain and prefrontal volume correlate with IQ in ADHD children. In addition Berquin (Berquin et al. 1998) reported that IQ correlates with TBV, cerebellar vermis and right caudate nucleus in ADHD children.

Caudate nucleus was also found to correlate with increased time response in the executive function task "Tower of Hanoi" (Mataro et al. 1997). Moreover, a significant relationship between reversed caudate asymmetry and measures of inhibition and externalizing behavior has been reported (Semrud-Clikeman et al. 2000).

Interestingly, Casey (Casey et al. 1997) found that PFC, caudate and pallidal volumes correlated with different subprocesses of response inhibition (sensory selection, response selection, and response execution) in the ADHD group but not in the control group. This correlation predominantly involved the right hemisphere, thus supporting the implication of right fronto-striatal dysfunctions in ADHD.

Finally, the only study performed with a female sample found that pallidum, caudate, and prefrontal volumes correlated with measures of ADHD severity and cognitive performance (Castellanos et al. 2001).

Brain regions and psychopharmacological response:

Filipek (Filipek et al. 1997) reported that ADHD subjects that have a good response to stimulant medication had smaller and more symmetric caudate nuclei as well as smaller left anterior-superior cortex, whereas non-responders were characterized by reversal caudate asymmetry and smaller retrocallosal white matter. In addition, Castellanos (Castellanos et al. 2002) found that unmedicated children with ADHD present smaller WM volumes as compared to controls and to medicated ADHD children.

3.2.3. Summary:

On the one hand neuroanatomical findings support fronto-striatal dysfunctions and highlights the importance of cerebellum in ADHD pathopsysiology. On the other

hand, non-ROI approaches suggest that brain may be altered in a more widespread way.

3.3.Diffusion Tensor Imaging in ADHD:

Diffusion tensor imaging (DTI) is a relatively novel technique, that has been applied to the study of different disorders such as multiple sclerosis (Ge et al. 2005), schizophrenia (Kubicki et al. 2005), or OCD (Szeszko et al. 2005). Currently there are only five articles that study ADHD with DTI methods. Only one of the articles performed a case-control comparison. In this study, Ashtari (Ashtari et al. 2005) found that ADHD patients showed lower FA (Fractional Anisotropy) in the right supplementary motor cortex, internal capsule (presumably reflecting frontostriatal conection) and cerebral peduncle, as well as in the left middle cerebellar peduncle, anterior lobe of the cerebellum (at the level of dentate nucleus) and parieto-occipital region. They also reported a significant negative correlation between patients' inattention (as measured by Conners' Innatentive subscale) and FA in the cerebellum.

3.4 Magnetic Resonance Spectroscopy in ADHD:

Spectroscopy has been mainly applied with diagnostic pruposes, such as in the case of tumor pathologies. More recently it is been used to the study of psychiatric disorders. ADHD studies based on MRS are discrepant. In general, results reported that ADHD present increased Glx/Cr ratio[9] in anterior cingulate (Moore et al. 2006) and bilateral frontal lobe (Courvoisie et al. 2004; MacMaster et al. 2003) while decreased NAA/Cr[10] in right frontal lobe (Courvoisie et al. 2004), bilateral lenticular nuclei (Sun et al. 2005) and striatum (Jin et al. 2001).

3.5 Functional neuroimaging in ADHD:

In this section I summarize the main functional neuroimaging findings in ADHD. For a more comprehensive view I refer to the following reviews (Bush et al. 2005; Durston 2003; Hale et al. 2000).

Given that functional neuroimaging studies are guided by neuropsychological theories I have organized this section in a similar way as that used when describing the main neuropsychological findings. Descriptions about brain activity during rest as

[9] Glutamate/glutamine/g-aminobutyric acid (Glx): Glutamate neurotransmitter is the most abundant amino acid in the human brain. Glutamine, the main derivative for glutamate, is thought to be localized in cerebral astrocytes. Elevated levels of the Glx, especially glutamate, are believed to be toxic for neuronal tissue. Creatine/phosphocreatine (Cr): Creatine has been related to cellular homeostasis. The Cr peak is thought to be relatively stable; therefore it is frequently used as a denominator when quantifying different metabolites as ratios.

[10] N-acetyl-aspartate (NA): NA is a potential neuronal marker. It is localized in neurons but not in mature glial cells, CSF, or blood. When this metabolite decreases it could be reflecting diminished neuronal function, or neuronal loss.

well as during the performance of cool and hot cognitive tasks will be summarized. I also briefly mention the effect of drugs (specifically MPH and D-AMPHE[11]) on brain function.

3.5.1. Global metabolism:

In 1990, Zametkin found that global metabolism, as measured by PET studies, was reduced in adult stimulant-naïve ADHD subjects (Zametkin et al. 1990). Posterior findings using the same technique, in adults (Ernst et al. 1998) and adolescent (Ernst et al. 1994a; Zametkin et al. 1993) samples reported that this global metabolism reduction was only observed in female, but not in male ADHD subjects. In addition decreases in global metabolism significantly correlated with increased age therefore adding credence to developmental aspects of the illness (Ernst et al. 1998). However, neither MPH nor D-AMPH have been explicitly reported to affect global metabolism (Ernst et al. 1994b; Matochik et al. 1994; Matochik et al. 1993).

3.5.2. Resting state brain:

Kim (Kim et al. 2002), studying a large drug-naïve children/adolescent sample using SPECT, found that ADHD individuals using SPECT show decreased perfusion in the right lateral prefrontal, middle temporal and cerebellar cortices, but increased perfusion in angular/postcentral and occipital gyri. Also, while some studies support frontal hypoperfusion (Sieg et al. 1995; Zang et al. 2007), others find frontal hyperperfusion in ADHD (Gustafsson et al. 2000). Parietal cortex blood flow has also been reported to be either higher (Sieg et al. 1995) or lower (Gustafsson et al. 2000) during resting state in ADHD. In general, the most consistent results derived from PET and SPECT showed reduced blood flow in temporal cortex (Gustafsson et al. 2000; Kim et al. 2002; Sieg et al. 1995) and in cerebellum (Gustafsson et al. 2000; Kim et al. 2002; Zang et al. 2007) in ADHD.

Recently, a new method for investigating resting-state brain function using fMRI techniques has been developed[12]. Using this method, Zang (Zang et al. 2007) found that, in comparison to control children, ADHD subjects had reduced activity in right inferior frontal cortex and bilateral cerebellum, as well as increased activity in right anterior cingulate, left sensorimotor cortex and bilateral brainstem.

Regarding the effect of MPH over the resting brain, it has been reported that this drug decreases perfusion in perirolandic areas (Lou et al. 1989; Schweitzer et al. 2003) as well as increasing perfusion in cerebellar vermis (Schweitzer et al. 2003) thalamus and temporal cortex (Kim et al. 2001). Striatal activity has been found either enhanced (Schweitzer et al. 2003) or decreased (Kim et al. 2001; Lee et al. 2005; Lou et al. 1989) after MPH administration.

[11] D-AMPHE (Dextroamphetamine) is a psychostimulant/sympathomimetic. It has multiple mechanisms of action, including blocking uptake of adrenergic and DA, stimulating release of monoamines and inhibiting monoamine-oxidase.

[12] This method is based on the studies of low-frequency fluctuations (LFF) that has been extensively used to study functional connectivity. The amplitude of low-frequency fluctuation (ALFF) has been suggested to be an index of regional spontaneous neuronal activity.

3.5.3. Cool functions: Executive functions:

Attention:
A SPECT study found that children with ADHD have decreased perfusion in right striatum and increased perfusion in anterior cingulate cortex when performing a sustained attention task (Lou et al. 1998). Another SPECT study, that used CPT as a task for eliciting sustained attention, found that ADHD children have reduced perfusion in frontal and temporal regions (Amen and Carmichael 1997). This study has been largely criticized because the results are based on visual inspection; however, posterior PET studies support reduced perfusion in fronto-temporal areas during CPT (Ernst et al. 1994a; Zametkin et al. 1993). In addition, reduced perfusion in left frontal regions during CPT has been found to correlate withseverity of ADHD symptoms (Zametkin et al. 1990). Given the intrinsic properties for fMRI principles (need of filtering low frequency changes), it is controversial to use this technique to measure sustained attention. Therefore fMRI have been mainly focused on selective attention instead of sustained attention. Reduced activity in parietal, precuneus and thalamic regions has been observed in ADHD children during selective attentional tasks (Tamm et al. 2006).

Working memory:
Working memory studies support fronto-temporal and cerebellar abnormalities in ADHD subjects as measured by PET techniques. More recently Vance, (Vance et al. 2007a) studied spatial working memory using fMRI. The authors observed brain activity while ADHD and control children performed mental rotation tasks. They found that, compared to control subjects, in ADHD children there is less activation of the right parieto-occipital (cuneus and precuneus) regions, right inferior parietal lobe and right caudate. As in the case of attentional processes, the effect of medication on brain function while performing working memory tasks is not consistent.

Inhibition:
Since Barkley (Barkley 1997) proposed inhibition deficits as the core dysfunction in ADHD, inhibitory control paradigms has become the most analyzed process in neuroimaging studies. Nearly all the studies used the go-nogo task, although others tasks such as *stop signal task* (Pliszka et al. 2006) and a stroop-like task (Bush et al. 1999) have also been used. Langleben et al (Langleben et al. 2001), using a go-nogo task on a SPECT study, found asymmetric perfusion in frontal lobes in ADHD subjects. Specifically the authors reported that left frontal perfusion was bigger than the right in ADHD children with moderate/severe symptomatology, and that there were no differences between right and left perfusion in the group with lower symptomatology. The study thus concluded a reverse asymmetry pattern of frontal perfusion assuming that right frontal perfusion is bigger than left in normal population, but they did not include a control group in their study to test the frontal perfusion pattern in healthy children.

Concerning fMRI go-nogo studies, results are inconsistent. Anterior cingulate activity has been found to be either reduced (Tamm et al. 2004) or increased (Schulz et al. 2004) and the same happens in the case of inferior temporal gyrus (Schulz found reduced activity (Schulz et al. 2004) whereas Tamm found increased (Tamm et al. 2004)). Left caudate nucleus (Durston et al. 2003), precental gyrus, hippocampus and cerebellum (Schulz et al. 2004) have been reported to be hypoactive during go-nogo

performance, whereas different frontal regions have been found to be hyperactive (Schulz et al. 2004) during this task.

There is more agreement concerning failures in ACC activation in ADHD children as measured by different inhibitory tasks. In this sense Rubia (Rubia et al. 1999) designed an fMRI study in which subject performed two tasks: a motor syncronization task and a Stop signal task. During both tasks, reduced activation in ACC was observed in the ADHD group as compared to the control group. Likewise, Bush (Bush et al. 1999) designed a stroop-like task known as Counting stroop[13], to study inhibition processes in ADHD subjects. Bush also found that ADHD subjects failed to activate ACC during interference trials. Interestingly, Pliska also reported reduced activation in the anterior cingulate cortex in the ADHD group during stop signal task, but only after unsuccessful inhibition trials (Pliszka et al. 2006) .

Different studies have been performed in order to study MPH effects over brain function while subjects performed go-nogo task. Results are inconsistent. Studies based on T2-relaxometry[14] found normalization blood flow in putamen (Teicher et al. 2000) and decreased blood flow in cerebellar vermis after MPH (Anderson et al. 2002) when comparing MPH with placebo. Interestingly, Vaida (Vaidya et al. 1998), using a go-nogo fMRI study, found that while MPH increased frontal activity in both groups, striatal activation was increased in the ADHD group but reduced in the control group after MPH administration.

3.5.4. Hot functions: Reward/motivation:

There is little work concerning reward/motivational brain functions in ADHD. Here I summarize two neuroimaging studies that test the hypotheses of abnormal brain reward/motivational brain systems in ADHD. On the one hand Ernst (Ernst et al. 2003) offers an indirect measure of motivational effects over behavior using a gambling decision-making task. During this task, brain activity was measured with H20 PET. The authors reported abnormal activation in ACC and VLPFC regions. On the other hand, Scheres directly measure brain-reward systems using Knutson paradigms (Knutson et al. 2001a; Knutson et al. 2001b; Knutson et al. 2000). Specifically, in Scheres' study, subjects were presented with three different cues: one that signaled a potentially rewarded response, another signaled an unrewarded response, and a third that signals no response requirement. In reward trials, participants had to respond to a target while it was on screen in order to obtain the reward. In the non-rewarding trials, there was no reward regardless of the response, and in the non-response trials, participants were required to refrain from responding. There were different reward magnitudes: 20c, 1$ and 5$. The authors reported reduced ventral striatal activation during reward anticipation trials that became more reduced as the reward magnitude increased. Interestingly, the reduction in ventral striatum activity correlated with hyperactive/impulsivity symptoms but not with inattentive symptoms. Until date no studies have directly measured medication effect on brain reward/motivational systems in ADHD subjects.

[13] Unlike the original, this task is ideal for fMRI because it does not require that subjects talk while being scanned. During this task subjects report by button-press the number of words that appear on the screen. Words are specially designed to create interference (word "three" written two times) or be neutral (animal names written X times). See also appendix 3 about neuropsychological tasks.

[14] Steady state measure of blood volume.

3.5.5. Summary:

Functional neuroimaging results point to reduced global metabolism in ADHD women but not in men. In addition, during resting state there seems to be a reduced perfusion in temporal cortex and cerebellum. Concerning cool functions, activity in fronto-striatal-cerebellar circuits, temporal and parietal areas seems to be reduced in ADHD children during attentional and working memory tasks. Regarding inhibition paradigms, studies have highlighted the role of ACC in ADHD pathophisiology. Specifically it has been reported that ADHD subjects fail to activate ACC during intrinsic conflict situations (inhibition of a preponderant response) and error signaling. Recently a new-interesting line of research about hot brain functions has been developed. Although more studies are warranted in order to better understand reward/motivational brain dysfunctions in ADHD, the results are promising and point to failures in ventral striatal activity. The effect of medication on ADHD brain function is very inconsistent and not yet clear.

Finally, it is important to mention that, although this section focuses on SPECT, PET and fMRI studies, EEG and MEG have also provided interesting results, such as increased rolandic spikes (Becker and Holtmann 2006) and diminished activity in limbic regions during cognitive tasks (Mulas et al. 2006) in ADHD children.

4. Analysis techniques for structural MRI data: Voxel based morphometry (VBM) and Regions of Interest (ROI) approaches

In line with the recent introduction of novel neuroimaging techniques, different analytic approaches have been developed in order to study brain structure and function. As a simplification, these techniques can be divided in two groups: those that use a confirmatory approach, namely Region of Interest (ROI), and those that use a more exploratory approach, such as for example voxel based morphometric (VBM) techniques. Below I explain these two methodologies, as well as the advantages and disadvantatges of each one in the context of neuroanatomical analysis.

4.1. Region of Interest (ROI)

ROI is the traditional method for studying MRI neuroanatomy. Basically it consists of the following steps: (see also figure 1).

1) *Apriori* selection of the region/regions to study on the base of previous literature.
2) Selection of the slices that contain this region and the plane/planes (axial, coronal or sagital) in which the region is more easily identified.
3) Manual delimitation and filling in the region of interest across the different slices. More recent versions of these ROI methods used semi-automatic or fully automatic delimitation of the region/regions of interest.
4) Recount of the voxels that have been marked as pertaining to the region of interest
5) Multiplication the number of voxels ascribed to that region by the size of the voxel in each of the three dimensions (x, y, z)[15]. This gives us an approximation of the volume of the region we are interested in. Some studies, specially the first ones, offer information about the area instead of volume of a region, which basically means that the delimitation of the ROI was done in a single slice.
6) Finally the volume of the region/regions is included as a variable in a statistical model.

There are different softwares to perform ROI delimitations, among them the most famous one is MRIcro (www.mricro.com) .

[15] In order to obtain reliable information about the volume of the regions, it is important to acquire 3D images. This type of acquisition is characterized by having no gap between slices, thus avoiding loss of information in any of the three axes of space (x, y and z).

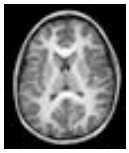
Figure 1: Exemplification of a region of interest (ROI) analysis

Example applied to ADHD neuroanatomy:

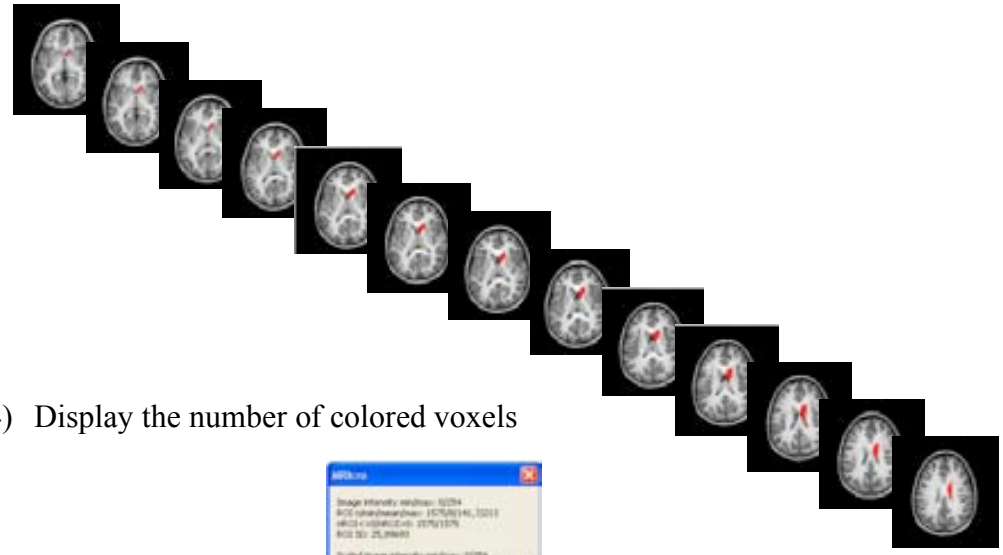
1) Clinical, pharmacological, animal and neuropsychological studies have highlighted the role of caudate nucleus in ADHD pathophysiology.

REGION OF INTEREST= CAUDATE NUCLEUS

2) Caudate nucleus is easily identified in axial slices.

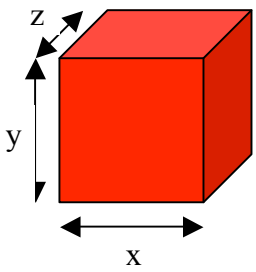


3) Drawing the regions of interest.



4) Display the number of colored voxels

5) Multiply the number of voxels by the dimensions of the voxel.



4.2. Voxel Based Morphometry (VBM)

Voxel based Morphometry (VBM) is an automatic approach that offers the possibility of studying the brain as a whole (without needing to select an *apriori* region of interest) (Good et al. 2001a; Good et al. 2001b). Nowadays it has become one of the most used methods for analyzing structural images. Statistical Parametric Mapping (SPM) (http://www.fil.ion.ucl.ac.uk/spm/) is the software most commonly used to perform VBM analysis.

Below I summarize the main steps for performing a VBM analysis. I focus my description specifically on the latter version of this procedure, the optimized voxel-based morphometry (OVBM) approach, in which the normalization process is notably improved. The steps to perform an OVBM study are the following: (see also figure 2)

A. Visual inspection of the images: Given that it is a fully automatic method it is essential to perform a visual inspection of the quality of the images. Scans with low contrast, intensity inhomogeneities, aliasing, movement or blood artifacts should be corrected or discarded.
B. Creation of study specific templates for the whole brain and the different tissues (GM, WM and CSF). In order to do this, the customized templates, based on all our subjects 3D images, should be:
   B.1. Spatially normalized[16] by non-linearly registering each of subjects to the standard T1-MRI template.
   B.2. Segmented[17] into GM, WM and CSF portions.
   B.3. Smoothed[18] with an isotropic Gaussian kernel normally of 8 mm full width at half maximum (FWHM).
C. Application of the OVBM algorithm.
   C.1. Segmentation of the original 3D images. This step allows the calculation of TBV, GM, WM, and CSF global volumes in milliliters.
   C.2. Normalization of the segmented GM and WM images according to their corresponding tissues template (GM of WM depending on the aim of the specific analysis) thus preventing any contribution of non-tissue voxels and achieving optimal spatial normalization. This is done in two steps:
      C.2.1. Determination of the parameters that better describes the deformation of the segmented images in order to be adjusted to the specific-tissue template.

[16] Normalize: Corregister each image to a standardized template. Given that different brains do not mach perfectly this registration is flexible and non-linear.
[17] Segment: Section the image into the different brain tissues: GM, WM and CSF. This process is based on the combination of the voxel intensity and the localization of the voxel.
[18] Smooth: Blur the intensity of each voxel so that it represents a mean of itself and its neighbors. The blurring is performed with a kind of filter known as Gaussian kernel. The number of voxels selected to perform the average is known as full width at half maximum (FWHM).

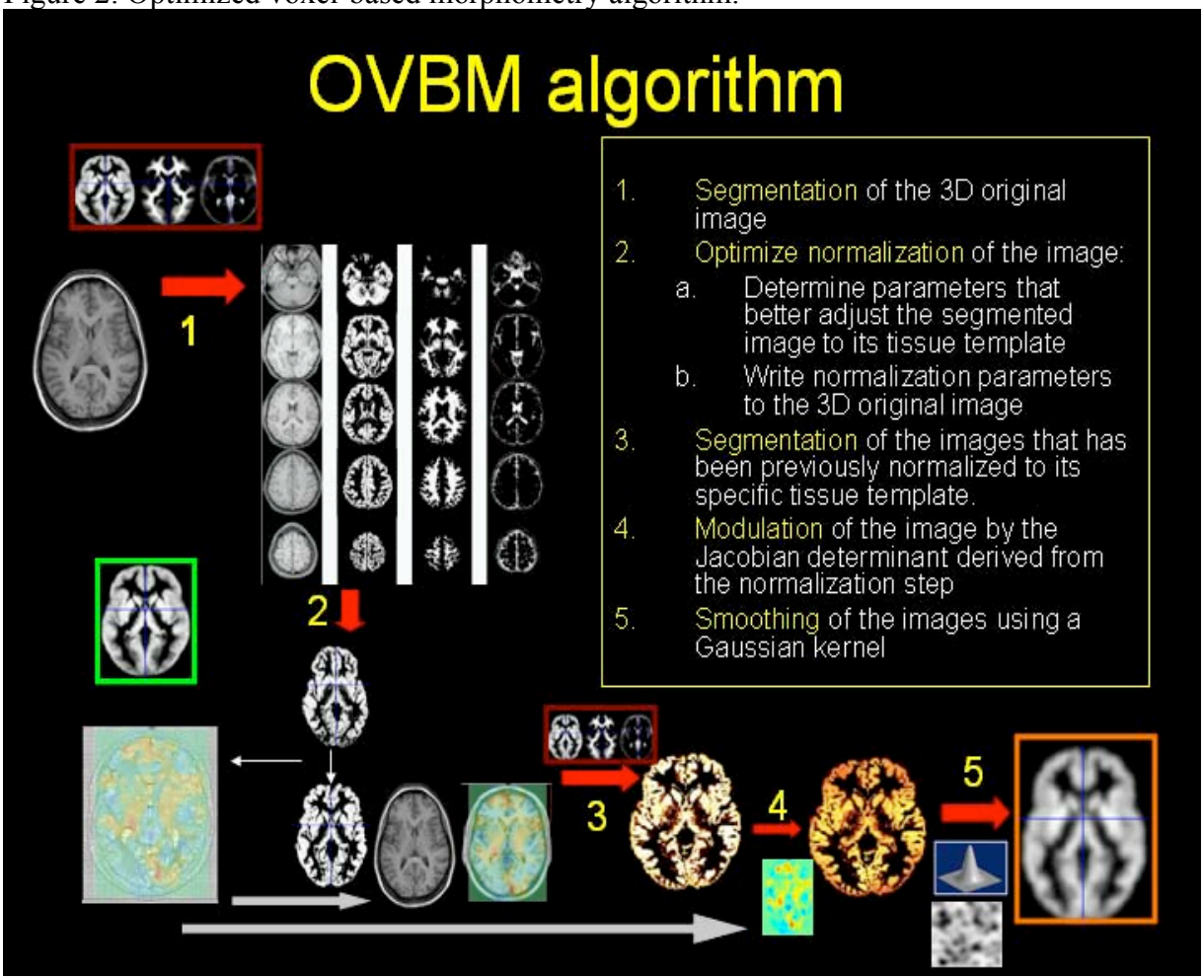
C.2.2. Application of the above mentioned parameters, known as normalization parameters, to the original 3D images.

C.3. Segmentation of the spatially normalized images to reject remaining non-tissue voxels (scalp, skull or venous sinuses).

C.4. Modulation of the images by the Jacobian determinants derived from their spatial normalization step. This introduces intensity changes in the GM/WM images according to the variation in volumes that the normalization process produced. The Jacobian-modulated GM step allows making inferences about differences in volumes rather than concentrations.

C.5. Smoothing with an adequate Gaussian kernel so that each voxel represents a mean of itself and its neighbors. Theoretically the number of voxel selected to perform this average (FWHM of the Gaussian kernel) should be in accordance to the number of voxels of the region/regions in which we hypothesize to find differences.

Figure 2: Optimized voxel-based morphometry algorithm.



4.3. Advantages and disadvantages of VBM.

VBM allows rapid voxel by voxel comparisons of the whole gray and white matter compartments, therefore, there is no need of a priori selection of ROIs. With ROI methods we can only extract conclusions about the region being studied but know nothing about other regions. The main advantage of VBM is that it allows less time consuming exploratory approaches. In addition, VBM is a more objective and replicable measure, because it not influenced by inter/intrarater variability. However, despite all of the above-mentioned advantages, VBM also has disadvantages as compared to ROI approaches. For example, manual delimitation of a region by a neuroanatomist is more valid, and less susceptible to errors or image artifacts, than automatic analysis performed by software. The main criticism of VBM is that it needs to deform and smooth the images in order to perform valid comparisons (see also table 4). Therefore, VBM, instead of displacing traditional ROI techniques has become a useful complement.

Table 4: Advantages and disadvantages of ROI and VBM techniques.

Region of Interest (ROI)	Voxel Based Morphometry (VBM)
Manual or semi-automatic - Very time-consuming. - Human expert delimitation has more credibility.	Fully automatic - Less time consuming. Easier to analyze bigger samples. - More consistency, no human bias.
Measure images in their original space: - It does not need to deform the images. More anatomically valid. - Images do not need to be smoothed.	Manipulation of the images: - Deformation of the images during the normalization step. - Images need smoothing in order to make reliable comparisons.
Measures and differences are based on landmarks.	Measures and differences are based on Voxel-average.
Only susceptible to artifacts that affect the region of interest.	Very susceptible to artifacts.
Confirmatory hypothesis - It is guided/supported by previous research. - It does not allow for inferences about other regions.	Exploratory hypothesis - It allows the analysis of the whole brain. - Increase multiple comparison error.

AIMS:

The present dissertation was aimed to refine and apply two complementary methods of structural neuroimaging, in order to identify the brain circuits altered in ADHD, as well as to relate them to different clinical ADHD subtypes and to known ADHD neuropsychological deficits. For that purpose two structural MRI studies will be presented and discussed:

Study 1:
- *Global and regional gray matter reduction in ADHD: A voxel-based morphometric study*.
- Aim: To apply, for the first time, an optimized voxel-based morphometry analysis to compare the brains of ADHD children with those of non family-related control children.

Study 2:
- *Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder*.
- Aim: To study caudate nuclei volumes in ADHD applying a manual ROI analysis. In addition we aimed to test a new, easy to apply, manual method of caudate nucleus segmentation.

METHODS AND RESULTS:

This thesis consists of 2 studies. Each study resulted in a publication. In this section, I present the two papers. Following each of the papers, a set of "Unpublished analyses/results" is also provided in order to complement and extend the published papers. These additional data are aimed at analyzing differences between ADHD subtypes, as well as to check if the differences reported in the original papers are still valid when comparing only the male subsample. With this in mind, I performed:
a) within ADHD subtype comparisons for the whole sample (males and females); b) between group comparisons (ADHD vs. Controls) only for the male subsample; and c) within ADHD subtype comparison only for the male sample.

Finally, at the end of this section, a diagram describing the main aspects of each of the studies is also presented.

1. Study 1:

1.1. Paper 1: Global and regional gray matter reduction in ADHD: A voxel-based morphometric study

Available online at www.sciencedirect.com
SCIENCE DIRECT
Neuroscience Letters 389 (2005) 88–93
Neuroscience Letters
www.elsevier.com/locate/neulet

Global and regional gray matter reductions in ADHD: A voxel-based morphometric study

S. Carmona [a], O. Vilarroya [a,*], A. Bielsa [c], V. Trèmols [b], J.C. Soliva [d], M. Rovira [d], J. Tomàs [c], C. Raheb [c], J.D. Gispert [f], S. Batlle [c], A. Bulbena [e]

[a] *Unitat de Recerca en Neurociencia Cognitiva, Departament de Psiquiatria i Medicina Legal, Universitat Autonoma de Barcelona, Campus de Bellaterra, Barcelona, Spain*
[b] *Departament de Pediatria, USP Institut Universitari Dexeus, Barcelona, Spain*
[c] *Servei de Psiquiatria, Hospital Vall d'Hebron, Barcelona, Spain*
[d] *CRC Corporacio Sanitaria, Barcelona, Spain*
[e] *Institut d'Atenció Psiquiàtrica, IMAS, Spain*
[f] *Institut d'Alta Tecnologia – Parc de Recerca Biomèdica de Barcelona, Spain*

Received 3 May 2005; received in revised form 10 July 2005; accepted 11 July 2005

Abstract

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder characterized by inattentiveness, motor hyperactivity and impulsivity. According to neuroimaging data, the neural substrate underlying ADHD seems to involve fronto-striatal circuits and the cerebellum. However, there are important discrepancies between various studies, probably due to the use of different techniques. The aim of this study is to examine cerebral gray (GM) and white (WM) matter abnormalities in a group of ADHD children using a voxel-based morphometry protocol. The sample consisted of 25 children/adolescents with DSM-IV TR diagnosis of ADHD (medicated, aged 6–16 years) who were compared with 25 healthy volunteer children/adolescents. ADHD brains on an average showed a global volume decrease of 5.4% as compared to controls. Additionally, there were regionally specific effects in the left fronto-parietal areas (left motor, premotor and somatosensory cortex), left cingulate cortex (anterior/middle/posterior cingulate), parietal lobe (precuneus bilaterally), temporal cortices (right middle temporal gyrus, left parahippocampal gyrus), and the cerebellum (bilateral posterior). There were no differences in WM volume between ADHD children and control subjects. The results are consistent with previous studies that used different techniques, and may represent a possible neural basis for some of the motor and attentional deficits commonly found in ADHD.

Keywords: Attention deficit hyperactivity disorder; ADHD; Developmental disorder; Neuroimaging; Optimized voxel based morphometry; Structural brain abnormalities

The neural basis of attention deficit and hyperactivity disorder (ADHD) remains unclear. Converging data suggest that ADHD symptoms may be secondary to abnormalities in the right fronto-striatal-cerebellar circuits [5,21,28]. Structural and functional neuroimaging techniques have recently been used to map ADHD brains. According to ADHD studies [10,16,21,31], the MRI findings that are most replicated in ADHD children are smaller total brain volumes, smaller cerebellum, abnormalities in prefrontal cortex and in caudate nuclei, and a smaller rostrum of the corpus callosum. So far, however, the studies have not provided consistent findings concerning global and regional structural brain abnormalities [7,31].

Some of these inconsistencies may stem from differences in the methodology used to explore ADHD brains. The development of new and more refined methods, such as the voxel-based morphometry protocol, provides a more sensitive means of revealing both subtle and/or gross structural abnormalities in ADHD brains. Voxel-based morphometry is an automated method of examining structural MR images of the brain [3,47] based upon the statistical parametric map-

* Corresponding author.
E-mail address: oscar.vilarroya@uab.es (O. Vilarroya).

0304-3940/$ – see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2005.07.020

Table 1
ADHD group comorbidities

Type	Percent
Symptomatic	
Anxiety	42.9
Depresion	9.5
Simple phobia	14.3
Tics	23.8
Obsessions	28.6
Nigthmares	14.3
Insomnia	28.7
Diagnostic	
Babbling	15
Dislalia	5

ping (SPM) techniques originally designed for the analysis of functional images [19]. This method has the advantage of examining the brain as a whole, as well as examining differences in cerebral gray (GM) and white (WM) matter.

In this study, our aim is to apply a voxel-based morphometry analysis with an optimization of the spatial segmentation and normalization (OVBM) for comparing a group of ADHD children with a control group in order to find global and regional differences in cerebral gray and white matter. To our knowledge, this is the first time that an OVBM has been used to study ADHD brains.

The study sample consisted of two groups. The experimental group included 25 children (21 boys and 4 girls) who were diagnosed with ADHD according to the DSM-IV TR criteria. The control group consisted of 25 children (21 boys and 4 girls) with no history of ADHD. The patients were recruited from the "Servei de Paidopsiquiatria" at the "Vall d'Hebron" Materno-Infantil Hospital. None of the ADHD children had other diagnostic comorbidities. Symptomatic comorbidity is listed in Table 1. Controls were selected from the Traumatology Department using a convenience sampling. These patients have suffered minor physical trauma. Controls were selected using a convenience sampling matching for age, gender, laterality and estimated IQ. Exclusion criteria for the sample were comorbidity of any other psychiatric disorder (including negativism or oppositional disorder), evidence of neurological disorders, perinatal anoxia, and a WISC-R full-scale IQ below 80. In the control group two psychologists excluded ADHD diagnosis using a semiestructured interview with parents or rating of a IQ lower than 80 (estimated by Block Design and Vocabulary subtest of the WISC-R). All the children had the parental acceptance to participate in the study. The demographic and clinical data are summarized in Table 2.

The brain images were obtained with a 1.5 T Signa General Electric scanner, with an axial 3D (SGE-T1 3D with a 256 × 256 matrix and 2-mm interval, RT = 13.2 ms, ET = 4.2 ms, flip angle 15°, slice plane = axial). The image processing consisted, first, of a visual inspection of the images using MRIcro's (version 1.37; http://www.mricro.com). We then employed the Statistical Parametrical Mapping 2 (SPM2) to create a sample-specific template for the whole brain and the different tissues (GM, WM and CSF), and to apply an optimized voxel-based morphometry script [23,24] with the following stages:

1. GM, WM and CSF segmentation of T1 3D images using the brain-volume template that we previously created.
2. Calculation of total brain volumes and GM, WM and CSF partial volumes.
3. Normalization of GM and WM images to their corresponding template (GM or WM template depending on the aim of the analysis).
4. Segmentation of the previously normalized images.

Table 2

	ADHD				Control
	Inattentive	Hyperactive–impulsive	Combined	Total	
n	5	5	15	25	25
Boys	5	5	11	21	21
Girls	0	0	4	4	4
Age (mean)	11.63 (S.D.: 2.04)	10.29 (S.D.: 2.91)	10.7 (S.D.: 3.39)	10.82 (S.D.: 3)	11.18 (S.D.: 3.21)
Laterality[a]					
R	3	4	10	17	17
L	1	0	2	3	2
C.D.	1	1	3	5	6
Methylphenidate medication (mean dose: mg/kg)					
	0.59 (S.D.: 0.083)	0.65 (S.D.: 0.064)	0.63 (S.D.: 0.037)	0.62 (S.D.: 0.57)	
Conners' rating (hyperactivity)					
T	19.1 (S.D.: 6.4)	15.25 (S.D.: 3.18)	18.37 (S.D.: 2.53)	14.6 (S.D.: 6.2)	
P	14.5 (S.D.: 6.4)	11.2 (S.D.: 1.06)	12.71 (S.D.: 1.62)	13.03 (S.D.: 3.6)	

R: right-handed; L: left-handed; C.D.: cross-dominance, Comb.: combined subtype; I–H: impulsive–hyperactive subtype; Inatt.: Inattention subtype; mg/kg: methylphenidate milligrams per kilogram, P: parents; T: teacher.

[a] Laterally measured with a battery that includes Piaget's Test, Head's Test and Nadine Galifrast–Granjon's Test.

	Mean (S.D.) (cc)		Statistical power (cc)	Mean difference	p	Reduction (%)	CI %
	TDAH ($n=25$)	Controls ($n=25$)					
GM	744.39 (50.44)	784.55 (45.15)		40.16	0.005	5.2	1.6–8.6
WM	335.22 (50.00)	358.15 (43.19)	37.8	22.93	0.089		
CSF	258.08 (28.14)	271.64 (25.16)	21.6	13.56	0.079		
Total	1137.49 (108.37)	1414.35 (89.36)		76.86	0.009	5.4	1.4–14.8

S.D.: standard deviation; cc: cubic centimeters; n: number of subjects; CI: confidence interval.

5. Modulation of the intensity levels in the normalized and segmented images with the Jacobian of the deformation field, thus conveying volumetric information to the image intensity levels.
6. Smoothing of the modulated image with a Gaussian kernel of 12 mm × 12 mm × 12 mm FWHM, according to the matched filter theorem.

To study global volumetric measures (quantitative differences in total brain volume, GM, WM and CSF segment volumes), we used SPSS 11.5 and performed for the comparison of the means comparison t-test for independent samples (threshold of $p<0.05$) given that the normal rule was preserved for all the variables in both groups (ADHD and Control). Regarding regional morphometric analysis (qualitative differences in GM and WM volumes), smoothed GM and WM images were analyzed voxel-by-voxel using an analysis of covariance in which global activity and age were included as nuisance covariates. ADHD subtypes were coded as different groups. This model allows performing comparisons between not only control group and ADHD group but also ADHD subtypes. Non-sphericity correction was used. GM and WM results were at a threshold of $p<0.005$ (FDR-corrected) and only clusters of above 10 voxels were analyzed. Finally we tested the statistical power of our analysis of global effects (for those effects that did not reach statistical significance) using a p value of $\alpha<0.05$ and a power level of $1-\beta=0.8$.

The comparison of the mean of global volumetric measures (Table 3) showed that the subjects in the ADHD group had 5.4% (from 1.4 to 14.8%) smaller total brain volume ($p=0.009$). Additionally, they showed a 5.2% (from 1.6 to 8.6%) decrease in GM volume ($p=0.005$) in comparison with healthy controls. Differences in other measures did not reach significance given the statistical power of our design.

Fig. 1 and Table 4 show the results of the OVBM analysis. As compared to controls, ADHD brains presented a reduction in GM segment in cortical regions as well as in the cerebellum. We did not detect any regions of increased GM in the ADHD group in comparison with the control group and any difference in WM between the groups.

Specifically, we found less GM volume in ADHD children in frontal lobe: left dorsolateral prefrontal cortex (rolandic operculum), perirolandic areas including somatosensory, motor and premotor cortices and orbitofrontal cortex (bilateral rectal gyrus, bilateral frontal superior and right frontal inferior); cingulate cortex: left anterior, middle and posterior gyrus; parietal lobe: bilateral precuneus; temporal lobe: right

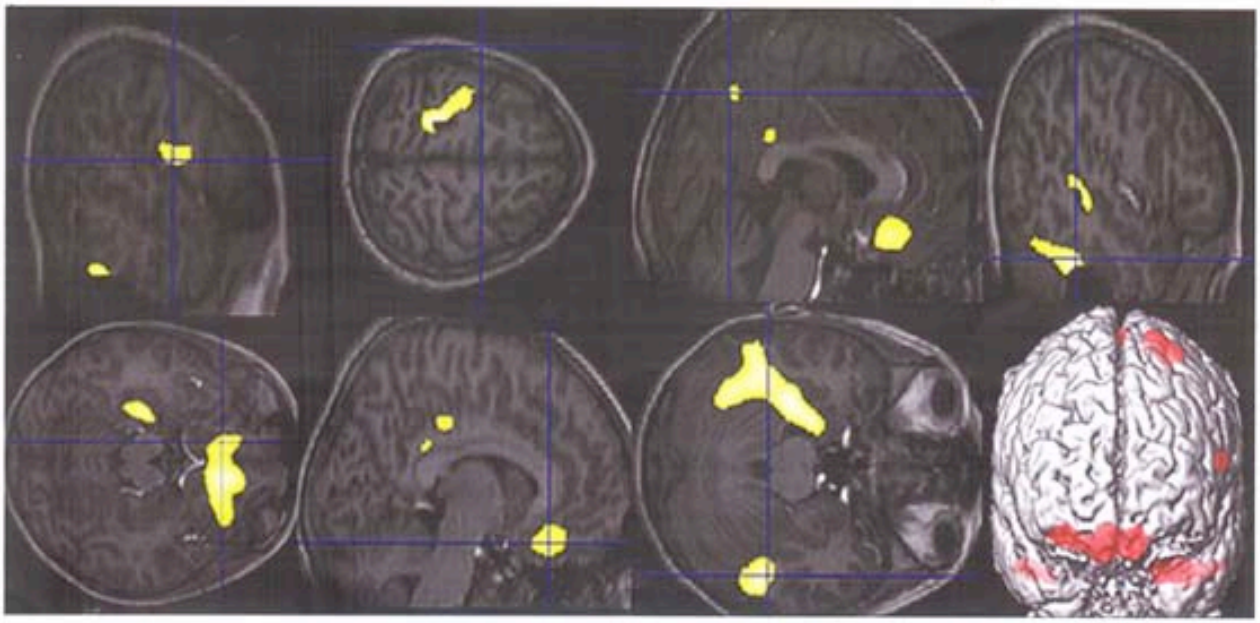


Fig. 1. Main region of decreased GM volume in patients compared to controls ($p<0.005$ FDR corrected); only clusters above 10 voxels are analysed.

Table 4
Gray matter volume decrease in ADHD children

Structure	MNI (x, y, z)	Z value	p value (FDR)-corrected	Cluster size (mm^3)
Frontal lobe				
Perirolandic areas				
L precentral (BA 6)	−22, −18, 72	4.66	0.002	
	−25, −19, 69	4.64	0.002	
	−22, −22, 71	4.58	0.002	
	−32, −14, 65	4.00	0.003	3488
L Paracentral (BA 4)	−26, −23, 68	4.68	0.002	
L Postcentral (BA 3–4)	−19, −37, 63	4.87	0.002	
	−23, −30, 65	4.20	0.002	
	−26, −28, 62	4.16	0.002	
Orbitofrontal cortex				
R rectal G. (BA 11)	10, 30, −19	4.65	0.002	
R frontal inf. orbital (BA 47)	28, 29, −14	4.42	0.002	
	32, 31, −15	4.39	0.002	8453
	33, 41, −16	3.81	0.004	
R frontal sup. orbital (BA11)	19, 27, −17	4.34	0.002	
Right cerebellum				
R cerebellum (crus 1) (BA 20)	50, −41, −30	4.64	0.002	2702
Left cerebellum				
L cerebellum (crus 1) (BA 20)	−42, −38, −32	5.10	0.002	
	−50, −42, −31	4.72	0.002	9333
L cerebellum (4–5) (BA 20)	−33, −27, −29	4.81	0.002	

L: left; R: right; Ant: anterior; Mid: middle; Post: posterior; Sup: superior; Inf: inferior; G: gyrus. Only the results that remained significant after FWE correction (0.05) are included.

middle temporal gyrus; hippocampal formation: left parahippocampal gyrus; and cerebellum: crus I bilaterally and left lobules 4–6.

The results obtained from the comparisons between ADHD subtypes showed no difference in GM or WM. These results should be interpreted with caution because of the small number of subjects belonging to the inattentive and hyperactive/impulsive subtypes of our sample.

Our ADHD children presented an average of 5.4% reduction in total brain volumes. The finding of smaller brain volumes is in agreement with other studies [8,12,13,26]. Specifically, in a recent study [13] ADHD brains were found to be, on an average, 3.2% smaller than control brains. The fact that we have used a distinct volumetric technique, and that our sample belongs to a different sociocultural and demographic area, suggests that total brain volume reduction is a consistent ADHD abnormality.

The total brain volume reduction in our sample seems to be related to a decrease in the GM segment, which is reduced by an average of 5.2%. We did not find any significant differences in the WM and CSF segments between both groups. We did not find any significant differences in the parenchimal fractions between groups. The absence of WM abnormalities is not noted in other studies [17,34,36]. The statistical power of our design allows us to detect only a significant WM differences larger than 37.8 cc. Therefore, although we actually found a reduction of 22.93 cc, we cannot take it into account because it does not reach statistical significance. However, the localization of these reductions reflects a trend towards WM in the splenium of the corpus callosum in the ADHD children, which has also been detected in other studies [42].

Regarding regional differences in the GM segment, our findings are partially consistent with those of the previous studies (see for reviews [10,16,21,31]). Our findings can be summarized in four main clusters: (a) a motor circuit including the cerebellum, the perirolandic area and the rolandic operculum, (b) the orbitofrontal cluster, (c) the left anterior/middle/posterior cingulate area and (d) the temporal lobe abnormalities.

One of the two major findings in our study has been the abnormalities in the motor circuit, including the cerebellum and sensorimotor cortices. The clusters of GM reduction in our ADHD samples included, bilaterally, the cerebellar posterior lobes and the left perirolandic area (BA areas 3–6). These findings are consistent with those of the previous studies. ADHD patients show smaller cerebellar volumes [8,12,35] even in adolescent patients [13]. Additionally, our perirolandic cluster is consistent with some previous findings of decreased volumes in the right supplementary motor area (SMA) [17] and of premotor GM reductions bilaterally in ADHD [34].

These global and regional GM reductions suggest connections between our findings with ADHD pathophysiology, though associations should be taken cautiously [27]. In general, our findings may be related to the deficits in motor control, inhibition and executive function commonly seen in ADHD [4], due to the dysfunction of cortical (frontal, prefrontal, parietal) and subcortical (limbic system, ascending reticular system and basal ganglia) circuits [9,14,32,46].

The other major GM reduction in our study has been the orbitofrontal cluster. In previous structural studies (see [21] for a review) ADHD children exhibited smaller total cerebral volume and smaller orbitofrontal cortex, with these effects greater in the right hemisphere, such as we found. The orbitofrontal abnormalities have been related to the emotionally mediated inhibitory role [2] of this area and to ADHD impulsivity behavior [25].

The abnormalities in the left anterior and middle/posterior cingulate cluster match the previous studies with ADHD abnormalities in middle [17], and posterior cingulate cortices [36]. The reduction of GM in the anterior and posterior cingulate gyrus and precuneus is a relevant finding because they belong to the midline attentional system [41,43,45].

The reduction we found in the right middle temporal gyrus is in agreement with previous studies [13], and it could be connected with functional studies [44]. As for the reduction that we found in the left parahippocampal gyrus, low birth weight children with ADHD seem to have smaller bilateral hippocampal formation than low birth weight children without ADHD [1].

Our findings might nevertheless be attributed to a more basic neurodevelopmental damage that might underlie ADHD pathology. Indeed, studies of other neurodevelopmental disorders have found similar volumentric abnormalities. For example, in preterm children, previous studies [37,38] have found decreased total cerebral volume and reductions of cerebellum, left parietal lobe, sensorimotor cortex, middle temporal areas and hippocampus. Clinical histories in our patient group showed no comorbidity of neurological damage. Hence, the possibility arises here that we might be examining cerebral regions especially sensitive to subtle neurodevelopmental damage.

We have to note that between the groups we did find differences between groups in other regions that are normally altered in ADHD, such as the caudate nuclei [12,17,39,40]. The discrepancies can be due to the technique and/or the sample. Regarding the sample, one possible explanation or the absence of caudate nuclei abnormalities could be the age range of the included subjects. In his longitudinal study, Castellanos et al. [13] found that volumetric differences in the caudate were negatively correlated with age. Therefore, it could be that if we had included only subjects with younger ages we would have found volumetric differences in caudate nuclei. Additionally, there are studies that found different patterns of asymmetry in boys and girls with ADHD [11]. These are questions to be explored in future studies.

Another issue that can be raised is the inclusion of the inattentive subtype of ADHD. Recently, some authors have suggested that inattentive type may be a distinct attentional disorder that is not a subtype of ADHD at all (e.g., [6,20,33]) while others maintain that inattentive type is a valid ADHD diagnosis [30]. In our study, no significant differences were found between ADHD subtypes in the OVBM analysis. Hence, we can conclude that, at least in our case, the neural abnormalities of all the ADHD subtypes concord.

Another consideration to be made about our sample is the possible implication of the medication. It is improbable that our findings could be attributed to the psychostimulant treatment. In other studies, ADHD GM abnormalities did not differ significantly between medicated and unmedicated patients [13].

Finally, we cannot exclude the possibility that OVBM might yield different results than other techniques. At times OVBM has been found to correlate with other manual and automatic volumetric measures [29], but there have been also discrepancies [22]. OVBM will probably be a very useful tool to explore differences in brain morphometry of different groups, but it must be complemented with other methods of analysis [15,18].

Acknowledgments

We would like to thank all the children and parents who participated in this study as well as Mercedes Riba for her collaboration, Joseph Hilferty for his editorial review, and Adolf Tobeña and Jamil Zaki for their scientific advice and revision. Susanna Carmona was supported by a FPU grant from the "Ministerio de Educación, Cultura y Deportes".

References

[1] L.J. Abernethy, M. Palaniappan, R.W. Cooke, Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight, Arch. Dis. Child. 87 (2002) 279–283.
[2] A.R. Aron, R.A. Poldrack, The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder, Biol. Psychiatry 57 (2005) 1285–1292.
[3] J. Ashburner, K.J. Friston, Voxel-based morphometry—the methods, Neuroimage 11 (2000) 805–821.
[4] R.A. Barkley, Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD, Psychol. Bull. 121 (1997) 65–94.
[5] R.A. Barkley, Attention-deficit hyperactivity disorder, Sci. Am. 279 (1998) 66–71.
[6] R.A. Barkley, The inattentive type of ADHD as a distinct disorder: what remains to be done, Clin. Psychol.: Sci. Pract. 8 (2001) 489–493.
[7] A.A. Baumeister, M.F. Hawkins, Incoherence of neuroimaging studies of attention deficit/hyperactivity disorder, Clin. Neuropharmacol. 24 (2001) 2–10.
[8] P.C. Berquin, J.N. Giedd, L.K. Jacobsen, S.D. Hamburger, A.L. Krain, J.L. Rapoport, F.X. Castellanos, The cerebellum in attention-deficit/hyperactivity disorder: a morphometric study, Neurology 50 (1998) 1087–1093.
[9] C. Büchel, M. Sommer, What causes stuttering? PLoS Biol. 2 (2) (2004) e46.
[10] F.X. Castellanos, M.T. Acosta, The neuroanatomy of attention deficit/hyperactivity disorder, Rev. Neurol. 38 (Suppl.) (2004) S131–S136.
[11] F.X. Castellanos, J.N. Giedd, P.C. Berquin, J.M. Walter, W. Sharp, T. Tran, A.C. Vaituzis, J.D. Blumenthal, J. Nelson, T.M. Bastain, A. Zijdenbos, A.C. Evans, J.L. Rapoport, Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder, Arch. Gen. Psychiatry 58 (2001) 289–295.

[12] F.X. Castellanos, J.N. Giedd, W.L. Marsh, S.D. Hamburger, A.C. Vaituzis, D.P. Dickstein, S.E. Sarfatti, Y.C. Vauss, J.W. Snell, N. Lange, D. Kaysen, A.L. Krain, G.F. Ritchie, J.C. Rajapakse, J.L. Rapoport, Quantitative brain magnetic resonance imaging in attention-deficit/hyperactivity disorder, Arch. Gen. Psychiatry 53 (1996) 607–616.

[13] F.X. Castellanos, P.P. Lee, W. Sharp, N.O. Jeffries, D.K. Greenstein, L.S. Clasen, J.D. Blumenthal, R.S. James, C.L. Ebens, J.M. Walter, A. Zijdenbos, A.C. Evans, J.N. Giedd, J.L. Rapoport, Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder, J. Am. Med. Assoc. 288 (2002) 1740–1748.

[14] R.A. Cohen, B.F. O'Donnell, Neuropsychological models of attentional dysfunction, in: R.A. Cohen (Ed.), The Neuropsychology of Attention, Plenum, New York, 1993, pp. 329–349.

[15] C. Davatzikos, Why voxel-based morphometric analysis should be used with great caution when characterizing group differences, Neuroimage 23 (2004) 17–20.

[16] S. Eliez, A.L. Reiss, Annotation: MRI neuroimaging of childhood psychiatric disorders: a selective review, J. Child Psychol. Psychiatry 41 (2000) 679–694.

[17] P.A. Filipek, M. Semrud-Clikeman, R.J. Steingard, P.F. Renshaw, D.N. Kennedy, J. Biederman, Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder and normal controls, Neurology 48 (1997) 589–601.

[18] K.J. Friston, J. Ashburner, Generative and recognition models for neuroanatomy, Neuroimage 23 (2004) 21–24.

[19] K.J. Friston, C.D. Frith, R.S. Frackowiak, R. Turner, Characterizing dynamic brain responses with fMRI—a multivariate approach, Neuroimage 2 (1995) 166–172.

[20] K.D. Gadow, D.A. Drabick, J. Loney, J. Sprafkin, H. Salisbury, A. Azizian, J. Schwartz, Comparison of ADHD symptom subtypes as source-specific syndromes, J. Child Psychol. Psychiatry 45 (2004) 1135–1149.

[21] J.N. Giedd, J.D. Blumenthal, E. Molloy, F.X. Castellanos, Brain imaging of attention deficit/hyperactivity disorder, Ann. N.Y. Acad. Sci. 931 (2001) 33–49.

[22] N.R. Giuliani, V.D. Calhoun, G.D. Pearlson, A. Francis, R.W. Buchanan, Voxel-based morphometry versus region of interest: a comparison of two methods for analyzing gray matter differences in schizophrenia, Schizophrenia Res. 74 (2005) 135–147.

[23] C.D. Good, I. Johnsrude, J. Ashburner, R.N. Henson, K.J. Friston, R.S. Frackowiak, Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains, Neuroimage 14 (2001) 685–700.

[24] C.D. Good, I.S. Johnsrude, J. Ashburner, R.N. Henson, K.J. Friston, R.S. Frackowiak, A voxel-based morphometric study of ageing in 465 normal adult human brains, Neuroimage 14 (2001) 21–36.

[25] B. Hesslinger, L. Tebartz van Elst, T. Thiel, K. Haegele, J. Hennig, D. Ebert, Frontoorbital volume reductions in adult patients with attention deficit hyperactivity disorder, Neurosci. Lett. 328 (2002) 319–321.

[26] D.E. Hill, R.A. Yeo, R.A. Campbell, B. Hart, J. Vigil, W. Brooks, Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children, Neuropsychology 17 (2003) 496–506.

[27] J.A. Hobson, Neurology, psychiatry, and neuroscience, Am. J. Psychiatry 160 (2003) 1013–1014.

[28] K.H. Krause, S.H. Dresel, J. Krause, H.F. Kung, K. Tatsch, Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography, Neurosci. Lett. 285 (2000) 107–110.

[29] M. Kubicki, M.E. Shenton, D.F. Salisbury, Y. Hirayasu, K. Kasai, R. Kikinis, F.A. Jolesz, R.W. McCarley, Voxel-based morphometric analysis of gray matter in first episode schizophrenia, Neuroimage 17 (2002) 1711–1719.

[30] B.B. Lahey, Should the combined and predominantly inattentive types of ADHD be considered distinct and unrelated disorders? Not now, at least, 1, Clin. Psychol.: Sci. Pract. 8 (2001) 494–497.

[31] J. Leo, D. Cohen, Broken brains or flawed studies? A critical review of ADHD neuroimaging research, J. Mind Behav. 24 (2003) 29–56.

[32] R.C. Miall, The cerebellum, predictive control and motor coordination, Novartis Found. Symp. 218 (1998) 272–284.

[33] R. Milich, A.C. Balentine, D.R. Lynam, ADHD combined type and ADHD predominantly inattentive type are distinct and unrelated disorders, Clin. Psychol.: Sci. Pract. 8 (2001) 463–488.

[34] S.H. Mostofsky, K.L. Cooper, W.R. Kates, M.B. Denckla, W.E. Kaufmann, Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder, Biol. Psychiatry 52 (2002) 785–794.

[35] S.H. Mostofsky, A.L. Reiss, P. Lockhart, M.B. Denckla, Evaluation of cerebellar size in attention-deficit hyperactivity disorder, J. Child Neurol. 13 (1998) 434–439.

[36] S. Overmeyer, E.T. Bullmore, J. Suckling, A. Simmons, S.C.R. Williams, P.J. Santosh, E. Taylor, Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network, Psychol. Med. 31 (2001) 1425–1435.

[37] B.S. Peterson, A.W. Anderson, R. Ehrenkranz, L.H. Staib, M. Tageldin, E. Colson, J.C. Gore, C.C. Duncan, R. Makuch, L.R. Ment, Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants, Pediatrics 111 (2003) 939–948.

[38] B.S. Peterson, B. Vohr, L.H. Staib, C.J. Cannistraci, A. Dolberg, K.C. Schneider, K.H. Katz, M. Westerveld, S. Sparrow, A.W. Anderson, C.C. Duncan, R.W. Makuch, J.C. Gore, L.R. Ment, Regional brain volume abnormalities and long-term cognitive outcome in preterm infants, J. Am. Med. Assoc. 284 (2000) 1939–1947.

[39] R. Pueyo, C. Maneru, P. Vendrell, N. Mataro, A. Estevez-Gonzalez, C. Garcia-Sanchez, C. Junque, Attention deficit hyperactivity disorder. Cerebral asymmetry observed on magnetic resonance, Rev. Neurol. 30 (2000) 920–925.

[40] A.L. Reiss, M.T. Abrams, H.S. Singer, J.L. Ross, M.B. Denckla, Brain development, gender and IQ in children. A volumetric imaging study, Brain 119 (1996) 1763–1774.

[41] K. Rubia, A.B. Smith, M.J. Brammer, B. Toone, E. Taylor, Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD, Am. J. Psychiatry 162 (2005) 1067–1075.

[42] M. Semrud-Clikeman, P.A. Filipek, J. Biederman, R. Steingard, D. Kennedy, P. Renshaw, K. Bekken, Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum, J. Am. Acad. Child Adolesc. Psychiatry 33 (1994) 875–881.

[43] J. Sergeant, The cognitive–energetic model: an empirical approach to attention-deficit hyperactivity disorder, Neurosci. Biobehav. Rev. 24 (2000) 7–12.

[44] K.M. Shafritz, K.E. Marchione, J.C. Gore, S.E. Shaywitz, B.A. Shaywitz, The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder, Am. J. Psychiatry 161 (2004) 1990–1997.

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

[46] L. Tamm, V. Menon, J. Ringel, A.L. Reiss, Event-related FMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder, J. Am. Acad. Child Adolesc. Psychiatry 43 (2004) 1430–1440.

[47] I.C. Wright, P.K. McGuire, J.B. Poline, J.M. Travere, R.M. Murray, C.D. Frith, R.S. Frackowiak, K.J. Friston, A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia, Neuroimage 2 (1995) 244–252.

1.2 Unpublished analyses/results:

Whole sample:

ADHD subtype comparisons:

In the case of study 1, ADHD subtype comparisons for the whole sample are already reported in the paper. As previously mentioned, there were no significant differences. Therefore, I shall only refer to the male sample analysis in this section.

Only male subjects:

At the moment in which this VBM analysis was performed we had a sample pool of 39 ADHD subjects and 39 healthy controls. Therefore, I was able to increasing the sample, which, in turn, allowed me a detection power similar to the one I had in the original study.

I selected 26 male ADHD and 26 male control subjects from a male pool of 27 controls and 35 ADHD. The selection criteria aimed to obtain ADHD and Control male samples matched for laterality, age and IQ-level. The final sample was composed by 13 (6 controls and 7 ADHD) new subjects and 39 (20 controls and 19 ADHD) of the subjects included in the original study. See table 5 for a full description of clinical and demographic data of the sample.

Table 5: *Demographic and Clinical data*		*ADHD*				*CONTROL*
		Inatt.	*H- I*	*Comb.*	*Total*	
N		8	5	13	26	26
Age: Mean (sd)		12.7 (sd: 2.2)	10.3 (sd: 2.9)	11.9 (sd: 2.9)	11.9 (sd: 2.8)	11.9 (sd: 3.2)
Laterality	*R*	5	4	12	21	21
	L	2	0	0	2	2
	C.D	1	1	1	3	3
Methylphenidate medication(mg/kg)		0.60 (sd: 0.064)	0.63 (sd: 0.072)	0.61 (sd: 0.04)	0.61 (sd: 0.053)	
Conners' Rating (Hyper)	*F*	18.7 (sd: 3.5)	15.5 (sd: 3.5)	16.6 (sd: 5.25)	17.2 (sd: 5.1)	
	M	19.6 (sd: 5.5)	16.6 (sd: 3.5)	20.2 (sd: 4.6)	19.4 (sd: 4.8)	
	T	19.2 (sd: 6.4)	19.3 (sd: 4.0)	22.2 (sd: 4.3)	20.6 (sd: 5.19)	

R= Right; L= Left; C.D= Cross Dominance; (sd)= Standard Deviation; Inatt= Innatentive; H-I= Hyperactive/Impulsive; Comb= Combined; mg/kg= Methilphenidate miligrams per kilogram; F= father; M= Mother; T= teacher. n= number of subjects; CI= Confidence Interval at 95%.

Global measures:

With regard to global volumetric measures I performed t-test comparisons between ADHD and controls subjects. As in the case of the original study, I found that ADHD subjects have reduced TB and GM volumes as compared to matched control children. Specifically TBV was found to be a 6.1% reduced and GM a 5.9%. No significant differences were found for WM and CSF volumes. See also table 6.

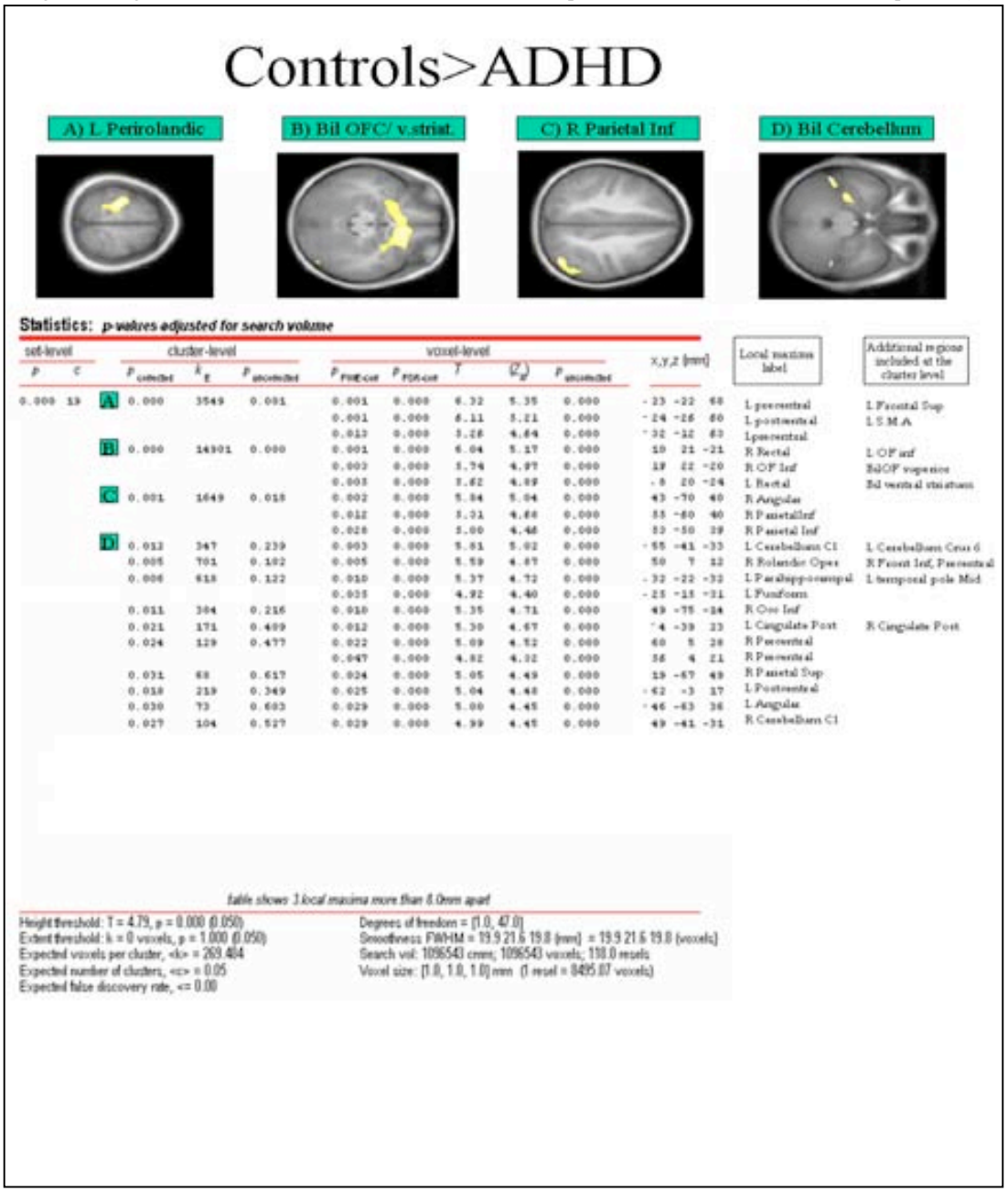
Table 6: Global volumetric measures	Mean (sd) cml		Mean difference	P	% Reduction	95% IC
	ADHD (n= 26)	CONTROLS (n= 26)				
GM	746.9 (45.4)	794.13 (45.8)	**47.1 (13.2)**	**0.001**	**5.9%**	**20.5 to 73.7 mml**
WM	342.9 (47.6)	376.25 (45.3)	24.2 (47.6)	0.079		
CSF	265.8 (25.6)	275.6 (25.3)	9.8 (7.3)	0.191		
TBV	1355.6 (97.4)	1443.5 (88.5)	**87.8 (27.1)**	**0.002**	**6.1%**	**33.1 to 142.6 mml**

(sd)= Standard Deviation; cml= Cubic Mililiters; n= number of subjects; CI= Confidence Interval at 95%.

Regional morphometric results:

Concerning regional morphometric data, I used the same analysis of covariance in which age was introduced as a nuisance variable. Results were thresholded at a p value of 0.05 FDR-corrected. Only clusters above 10 voxels were reported.

Figure 3: Regions of GM volume reduction in ADHD as compared to matched controls (t-test comparisons)

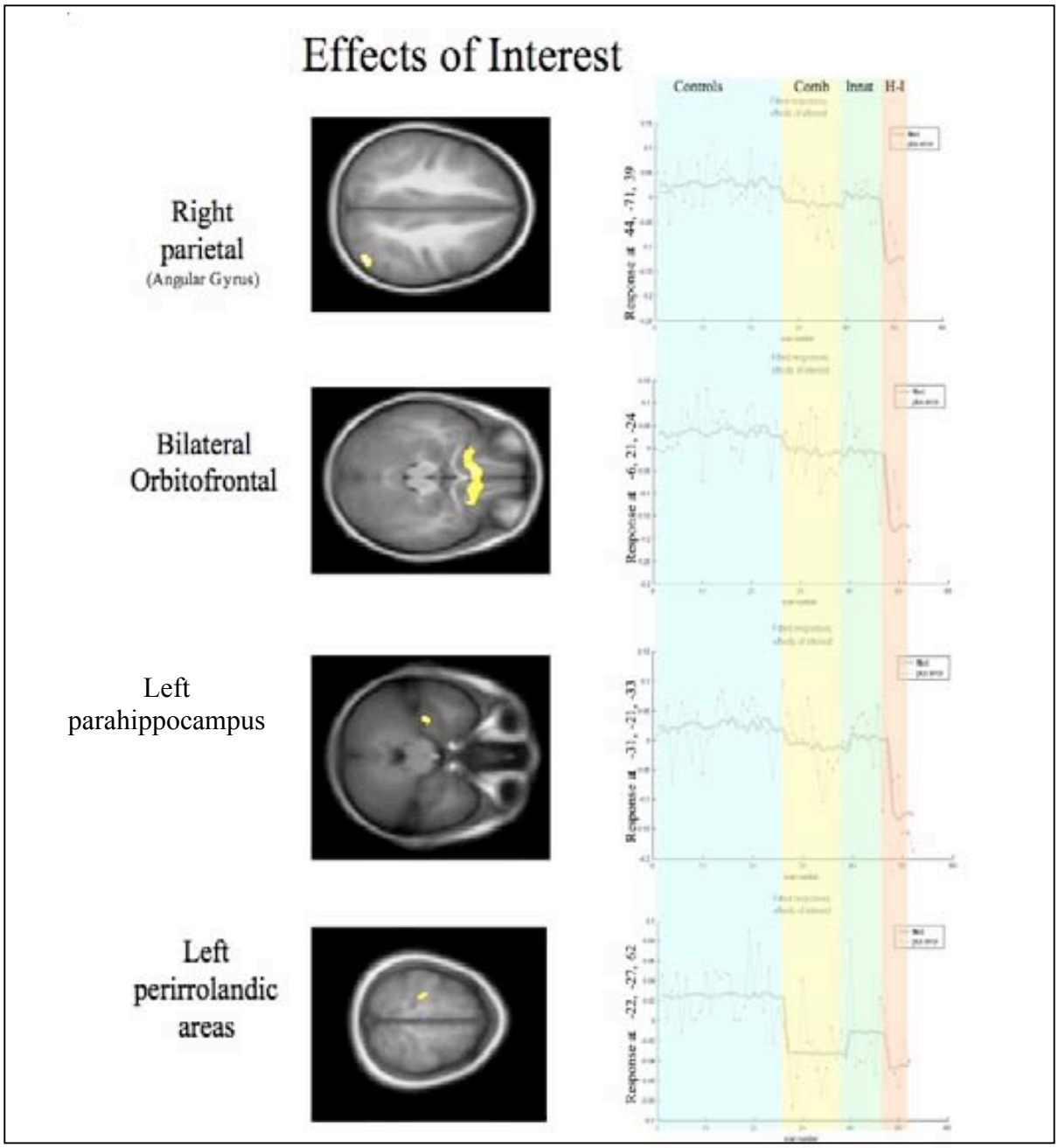


ADHD vs. Control subjects:

The result derived from the between group comparisons in the male sample coincide closely with our previous findings. Morphometric GM comparisons show that ADHD males have reduced GM volume in frontal and cerebellar regions. Specifically, I found ADHD volume reductions mainly in bilateral OF, left perirolandic, right parietal inferior and bilateral cerebellum (see figure 3). Reductions in the OFC cluster extend to a level of reaching ventral striatal regions, including AccN.

WM volume comparisons do not show any significant difference between ADHD and controls children.

Figure 4: Regions of GM volume differences between groups (F-test comparisons). Comb= ADHD-combined subtype; Innat= ADHD- inattentive subtype, and H-I= ADHD-Hyperactive/Impulsive subtype.



ADHD subtypes:

In order to see whether there were differences between ADHD subtypes, I first performed an F contrast between groups (see figure 4). GM comparisons show that groups differ in right parietal, bilateral orbitofrontal/ventral striatal regions, left parahippocampal gyrus and left precentral gyrus. Graphs reflect how these differences are especially prevalent in hyperactive impulsive children, except for the case of precentral gyrus in which combined subtype brought out the difference. Interestingly, inattentive subtype presents similar volumes as controls subjects in all these areas.

Specific t-tests were performed in order to analyze the differences between ADHD subtypes and control group. Results showed that the combined subtype, as compared to control children, have reduced GM volume in precentral gyrus. T-test comparisons between controls and ADHD/H-I subtype bring to light differences in OF/ventral striatum, parietal inferior, posterior cingulate and cerebellum. These differences although being bilateral, are more pronounced on the right side. In addition H-I subtype also presented reduced right DLPFC (see figure 5 and 6 for a full description). There were no differences between Controls and inattentive children regarding GM volume at a p level of 0.05 FDR corrected.

Figure 5: Regions of GM volume reductions in the H-I subtype as compared to control children

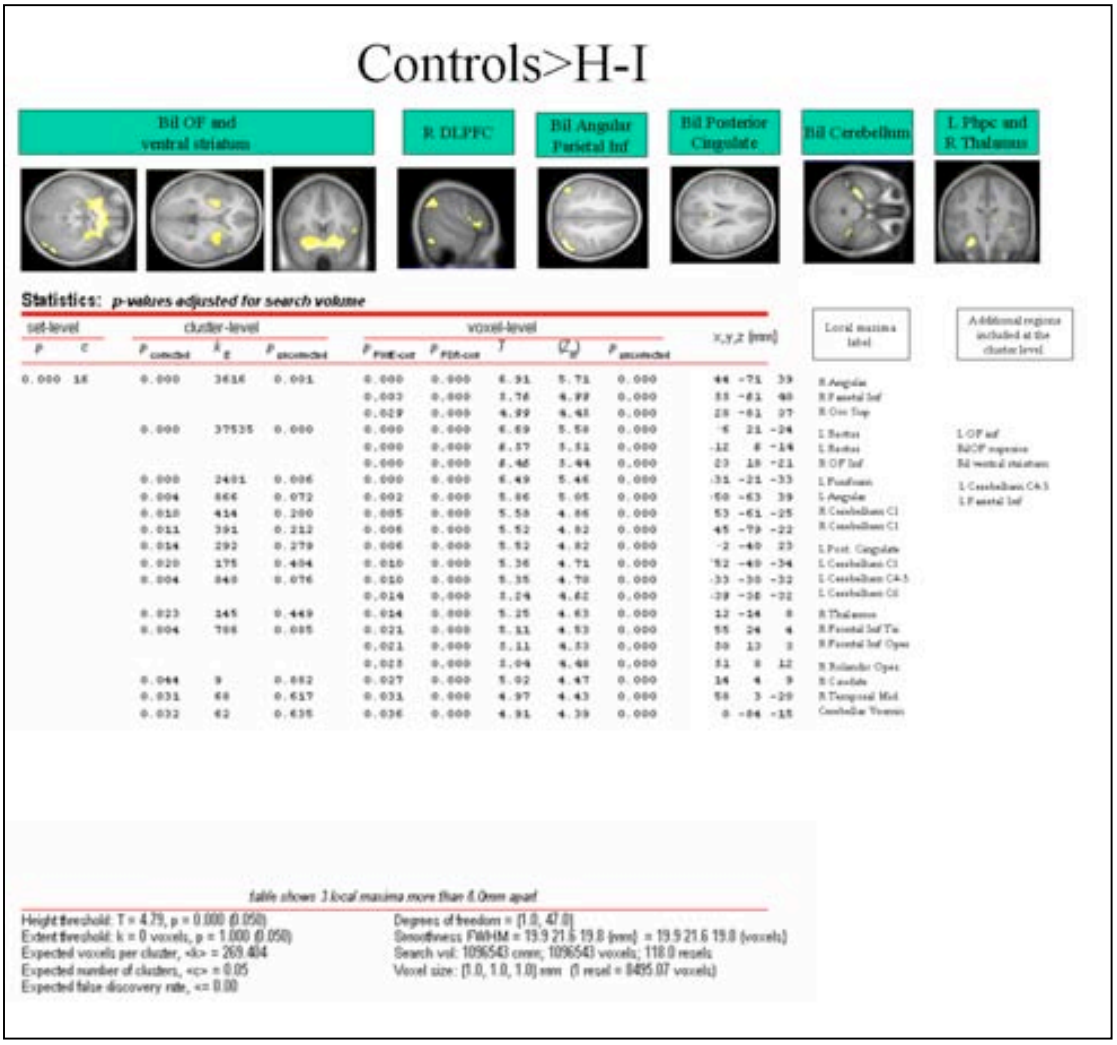
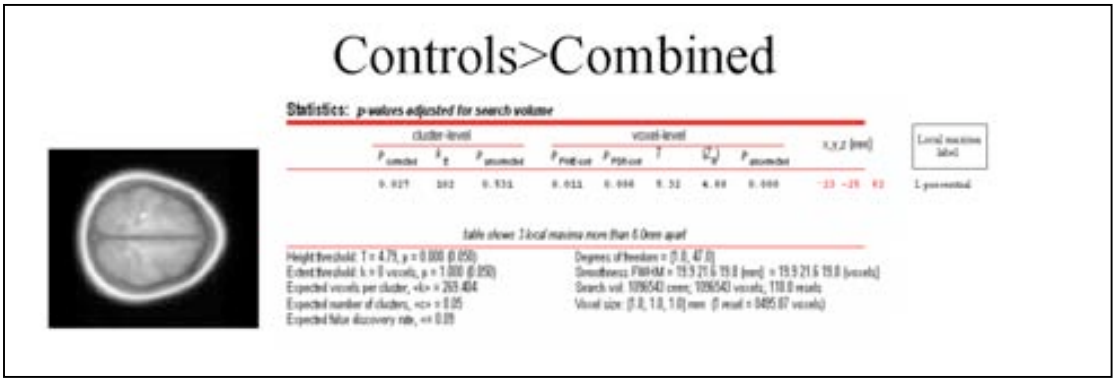


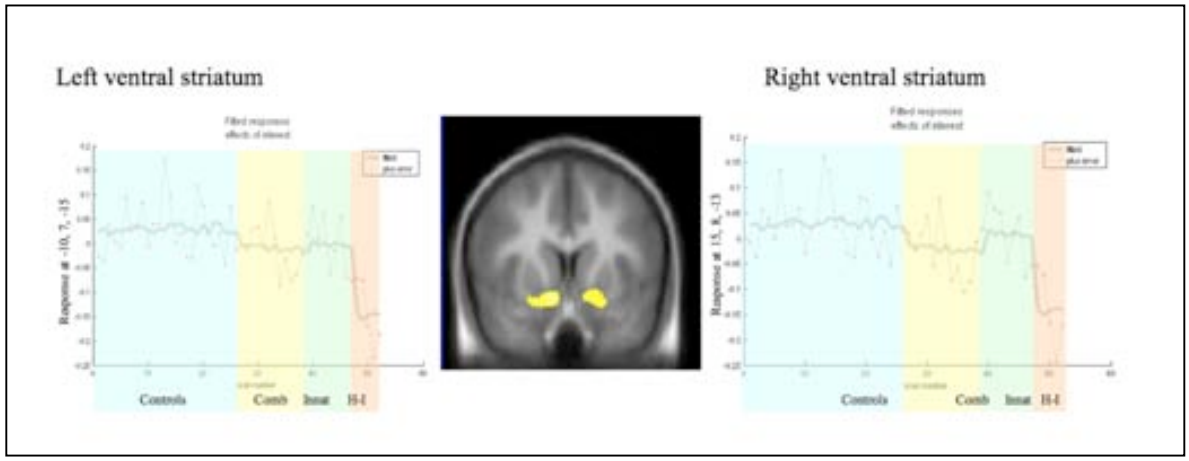
Figure 6: Regions of GM volume reductions in the combined subtype as compared to control children



Ventral Striatum:

Given the importance of ventral striatum, specifically AccN in recent ADHD theories, I aimed to study GM volume differences in this region between groups. For this purpose I performed the following additional analysis. First, using MRIcro, I created separately ROI images for right and left ventral striatum (Gunduz et al. 2002). The ROI images were based on the sample-specific template. Then, I used these ROI images as masks in the Small Volume Correction (SVC) option of SPM2. This option allowed us to perform group comparisons restricted to the ventral striatum region, and to localize the peak coordinates with maximum signal inside these regions (see figure 7). Time course of the maximum voxel signal in this coordinate was displayed in order to see the distribution of the voxel intensity between groups using the F contrast. The graph pointed to ventral striatum GM volume reductions in H-I but also combined subtype. In order to check the significance of the differences, as well as display voxel "time-courses", I lowered the threshold to p=0.005-uncorrected and performed the t-test comparisons restricted to ventral striatal area. This allows to graphically see volume differences in ventral striatum between ADHD subtypes. Results showed that, as compared to control children, right ventral striatum was reduced in combined (coordinates of local maxima= 12, 12, -15; t= 2.79) and H-I subtype (coordinates of local maxima= 15, 8, -13; t= 6.06), whilst left ventral striatum reductions were only observed in the H-I subtype (coordinates of local maxima= -10, 7, -15; t= 6.54). Innatentive children did not differ from controls in ventral striatum GM volumes.

Figure 7: Between group GM volume difference in ventral striatum



2. Study 2

2.1. Paper 1: Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder.

Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research: Neuroimaging 163 (2008) 270–278
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder

Virginia Tremols[a,b], Anna Bielsa[c], Joan-Carles Soliva[a], Carol Raheb[c], Susanna Carmona[a], Josep Tomas[c], Joan-Domingo Gispert[g], Mariana Rovira[d], Jordi Fauquet[e], Adolf Tobeña[a], Antoni Bulbena[f], Oscar Vilarroya[a,*]

[a]*Unitat de Recerca en Neurociencia Cognitiva, Departament de Psiquiatria i Medicina Legal, Universitat Autonoma Barcelona, Centre Fòrum. Hospital del Mar, Carrer Llull 410, 08019 Barcelona, Spain*
[b]*Departament de Pediatria USP Institut Universitari Dexeus, Angli 31, 08017 Barcelona, Spain*
[c]*Unitat de Paidopsiquiatria. Hospital Vall d'Hebron, Passeig de Vall d'Hebron 171, 08035 Barcelona, Spain*
[d]*CRC Corporacio Sanitaria, Barcelona, Spain*
[e]*Departament de Psicobiologia i de Metodologia de les Ciències de la Salut Universitat Autonoma Barcelona, 08193 Bellaterra, Spain*
[f]*Institut d'Atenció Psiquiàtrica, IMAS, Passeig Maritim 25-29 08003 Barcelona, Spain*
[g]*Institut d'Alta Tecnologia-Parc de Recerca Biomèdica de Barcelona, Passeig Maritim 25-29, 08003 Barcelona, Spain*

Received 3 March 2006; received in revised form 14 March 2007; accepted 22 April 2007

Abstract

The aim of the study is to present a new method for the segmentation of the caudate nucleus and use it to compare the caudate heads and bodies of an attention deficit-hyperactivity disorder (ADHD) group with those of a control group. We used a 1.5-T system to acquire magnetic resonance brain scans from 39 children with ADHD, as defined by DSM-IV TR, and 39 age, handedness and IQ matched controls. The new method for caudate head and body segmentation was applied to obtain semi-automatic volumes and asymmetric patterns. Bilateral volumetric measures of the head, body, and head-body of the caudate nuclei were compared within groups and between ADHD and control groups. Although the group factor was not significant, there were first and second order interactions. The analysis of simple effects showed that the right body and right head+body of the ADHD group was significantly smaller than in the control group, although the ADHD right caudate head was bigger. No ADHD within-group caudate differences were found. Controls showed a significantly larger left caudate head and a significantly bigger caudate right body and right head+body. Our new method for segmenting the caudate nucleus detected differential abnormalities of the right caudate head and body in the ADHD group, explaining previous heterogeneous findings in the literature.

Keywords: ADHD; MRI; Caudate nucleus; Morphometry; Volumetry

1. Introduction

The caudate nucleus is a critical brain region implicated in the pathophysiology of attention deficit-hyperactivity disorder (ADHD) (Barkley, 1997; Sergeant, 1990; Swanson et al., 1998). Structural neuro-

* Corresponding author. Tel.: +34 932 541 313; fax: +34 932 541 315.
E-mail address: oscar.vilarroya@uab.es (O. Vilarroya).

0925-4927/$ - see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2007.04.017

imaging studies have confirmed abnormalities in such a structure in ADHD patients, though with somewhat conflicting results. In caudate-nuclei morphometry studies, some authors found that ADHD populations had a smaller left caudate head (Filipek et al., 1997; Hynd et al., 1993; Semrud-Clikeman et al., 2000) in comparison with control samples. One study showed a left caudate total volume reduction (Filipek et al., 1997), while the study with the largest ADHD sample (Castellanos et al., 1996) found smaller right total caudate volumes in comparison with control samples. In intragroup comparisons, the ADHD population was found to present a right-caudate head asymmetry (right bigger than left) (Hynd et al., 1993) and total right caudate asymmetry, while the largest sample study (Castellanos et al., 1994, 1996) found a total caudate symmetry. In addition, another study (Schrimsher et al., 2002) found that a greater degree of right caudate asymmetry predicted subclinical inattentive behaviour in the general population.

Such discordant results may in part stem from methodological differences. Some studies use automatic measures, and others apply manual techniques. The studies using automatic techniques lack a standard method to segment automatically the brain structures implicated in the disorder, and the manual techniques have not provided a clear way of establishing the frontier between the caudate head and body. Besides, the samples, with the exception of those of Castellanos (Castellanos et al., 1994, 1996), Hill (Hill et al., 2003) and Durston (Durston et al., 2004) are rather small.

Two points are critical to confirm or disprove the results obtained so far in caudate nuclei. Firstly, manual measures are required to complement the automatic methods employed and, secondly, the size of the sample studied must be increased. There is nevertheless an additional point that may be more critical to detect specific abnormalities. One important difference among extant studies is between those that measure the caudate nucleus *in toto*, and those that segment the head and the rest of the nucleus. In our opinion, the measures of total caudate volumes may screen off differential abnormalities of the caudate head and body.

The fact is that the head, body and tail of the caudate nucleus seem to participate in different pathways, and hence in different functions. The caudate head is integrated in the dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate circuits of Alexander (Alexander et al., 1986). The body of the caudate is integrated in Alexander's oculomotor circuit. Functionally, the head of the caudate nucleus has been related to multi-modal information and inhibition processes. Lesions in the head of the caudate nucleus can result in sensory neglect, agitation, hyperactivity, distractibility and, in some cases, manic or schizo-affective psychosis (Aylward et al., 1996; Caplan et al., 1990; Castellanos et al., 1994; Richfield et al., 1987). In recent studies, the head of the caudate nucleus has been associated with feedback processing, while the caudate body has been implicated in successful classification learning (Seger and Cincotta, 2005).

Therefore, if the striatal pathway is dysfunctional in ADHD, and this dysfunction affects in different ways the head and the body of the caudate nucleus, then there may be morphometric abnormalities in the disorder showing a differential implication of each of these caudate areas. However, there is no extant method for segmenting the caudate head from the body. The aim of this study is to introduce a caudate segmentation method and to use it to compare the caudate heads and bodies of an ADHD group with those of a control group.

2. Methods

2.1. Participants

The study population (Table 1) included 39 children (35 boys and 4 girls) with ADHD according to DSM-IV

Table 1
Sample

	n	Sex	Age (years) mean±S.D.	Handedness[a]	Type	MPH mean±S.D.	CBCL Hyperactivity mean±S.D.
ADHD	39	Boys=35 Girls=4	10.8±2.9	R=27; L=4; CD=8	I=8 H-I=7 C=24	0.6±0.05	73.3±10.3
Control	39	Boys=27 Girls=12	11.7±2.9	R=27; L=3; CD=9	NA	NA	56.3±3.4

I=Inattention subtype; H-I=Hyperactive-impulsive subtype; C=Combined subtype. R=right-handed; L=left-handed; CD=cross-dominance. MPH (mg/kg)=methylphenidate. NA=not applicable. CBCL: Child Behavior Checklist (ages 6 to 16 years).

[a] Handedness measured with a battery that includes Piaget's Test, Head's Test and Nadine Galifret–Granjon's Test.

(referred from the Unit of Child Psychiatry at Vall d'Hebron Hospital) and 39 control subjects (27 boys and 12 girls) recruited from the community. One previous study of our group (Carmona et al., 2005) was performed with a subgroup of the present sample. Mean ages were 10.8 (S.D.: 2.9) and 11.7 (S.D.: 3), respectively. Both groups were matched for IQ level, Full Scale IQ based on the WISC-R (Wechsler, 1974) for ADHD (Verbal = 104, S.D.: 17.7; Performance = 104, S.D.: 13.6) and estimated IQ, based on WISC-R subtest, for controls (Vocabulary = 11.8, S.D.: 2.7; Block design = 11.2, S.D.: 2.9). Matching for socioeconomic status was based on a semi-structured interview that evaluated parents' marital, professional and educational status. The institutional ethics committee approved the study, and parental informed consent was obtained from all the participants.

Children with ADHD received a consensus diagnosis by a team consisting of a licensed psychologist and a psychiatrist, based on parent and teacher rating scales as well as a clinical interview systematically reviewing DSM-IV TR (American Psychiatric Association, 2000) criteria for ADHD, oppositional defiant disorder, conduct disorder, and depressive and anxiety disorders. Exclusion criteria for both the ADHD and the control groups included an IQ scores on the WISC-R (Wechsler, 1993) below 80, severe psychiatric illness (including anxiety, mood disorders, developmental disorder, dissociative disorder), brain damage, neurological illness, head trauma, deafness, blindness, severe language delay, cerebral palsy, seizures, or autism, as determined through interviews with parents. ADHD children did not present dyslexia or dyscalculia comorbidities, although some of them (23.7%) presented learning disabilities.

The patients were examined by classroom teachers and parents using questions from the Conners' Teacher and Parent Rating Scale (Conners et al., 1998a,b; Goyette et al., 1978), the Child Behaviour Checklist (CBCL) (Achenbach and Ruffle, 2000) and the Edelbrock Scale (Edelbrock, 1983). Children with ADHD were further categorized into hyperactive-impulsive, inattentive and combined subtypes using DSM-IV TR criteria at the time of original diagnosis.

All the children with ADHD were receiving stimulant medication (methylphenidate), and all were considered positive responders by their physicians (based on clinical and neuropsychological evaluations), parents and teachers; no control children were receiving any medications. No children received sustained-release amphetamines.

Control children were selected from the Traumatology Department as a sample of convenience. Two neuropsychologists excluded ADHD diagnosis in the control group. Children were included in the control group if they had no history of behavioural problems according to semi-structured interview with parents and parent behaviour rating scales (i.e., $T<70$ on subscales of the Conners' Rating Scale: Parent Version) and no significant elevations on subscales of the CBCL.

2.2. MRI acquisition

All subjects were screened for metal implants before undergoing brain MRI examination with a 1.5-T system (Signa, General Electric, Milwaukee, WI, USA). We used an FSPGR (fast spoiled gradient) T1 3D axial sequence (TR = 13.2 ms; TE = 4.2 ms; FA = 15; NEX = 1; 256 × 256 matrix; FOV = 24 cm), with 2-mm partitions and without a gap, and a FSE-PD-T2 axial sequence (TR = 3980 ms; TE = 20/100 ms; TF = 16; NEX = 2; 512 × 512 matrix; FOV = 24 cm), with 5-mm sections and a 2-mm gap.

2.3. MRI analyses

Two neuroradiologists set the axial IR (inversion recovery) T1 3D images in a plane parallel to the bicommissural plane and processed them with MRIcro (freeware: http://www.sph.sc.edu/comd/rorden/mricro.html). The regions of interest (ROI) were identified manually with MRIcro, which automatically provided each ROI volume (in voxels). The FSPGR-T1 3D sequence was used for the morphometric analysis. A measure of total brain volume for each subject was obtained with SPM2 (Wellcome Department of Imaging Neuroscience, London, United Kingdom).

2.4. Caudate segmentation method

The caudate nucleus has three components: head, body and tail. The head and body are involved in distinct fronto-subcortical circuits (Alexander et al., 1986, 1990). Although there is agreement that the head is the ovoid rostral part and the tail is its elongated, backward prolongation, the boundary between the head and body is arbitrary. Monro's interventricular foramen is used for this purpose by some authors (Duvernoy, 1991), while others have used the corpus callosum (Filipek et al., 1997) or the optic chiasm (Pineda et al., 2002). In our opinion, the main drawbacks of these methods are that they are complex (needing a thorough understanding of neuroradiology) and time-consuming, and that they do not address critical issues, such as the delimitation between the caudate and accumbens nuclei. There have also been other segmentation methods (Dreifuss et al., 2001).

However, the method that we present here has an heuristic purpose rather than an anatomical one, that is, to provide a simple, and reliable procedure for distinguishing the head from the body of the caudate nucleus.

2.4.1. Delimitation of the ROI for the head of the caudate nucleus

We defined the ROI for the head of the caudate nucleus, including all the areas presented in the axial images, according to the following criteria (see Fig. 1):

(a) The first section to be measured is the first in which the caudate nucleus can be separated from the putamen nucleus, hence, excluding the ventral striatum (Fig. 1, *a*).

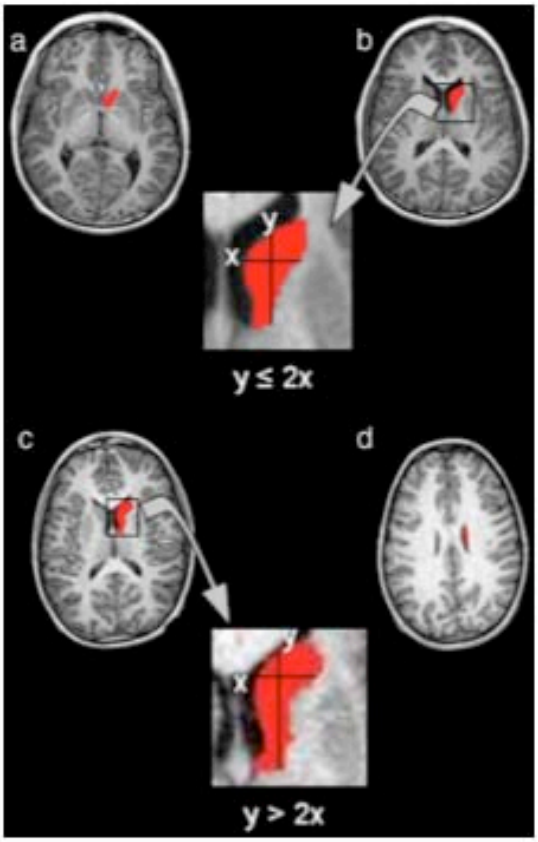


Fig. 1. Caudate head and body segmentation method: *a* shows the first section in which the caudate can be seen as distinct from the putamen; *b* presents the last section in which diameter *y* is equal to or less than two times larger than diameter *x*; *c* shows the first section in which diameter *y* is more than two times larger than diameter *x* (diameter *y* should be the larger antero-posterior diameter parallel to the interhemispheric sulcus; diameter *x* should be the larger latero-lateral diameter perpendicular to the caudate's antero-posterior diameter); *d* shows the last dorsal section in which the caudate body can be seen.

(b) The next sections to be measured should follow the ventro-dorsal direction.
(c) The last section is previous to that in which the caudate's antero-posterior diameter is more than two times larger than the medio-lateral diameter (Fig. 1, *b*).
(d) The caudate's antero-posterior diameter should be the larger antero-posterior diameter parallel to the interhemispheric sulcus (see Fig. 1, diameter *y* in the enlarged box of *b*). The medio-lateral caudate's diameter should be the larger medio-lateral diameter perpendicular to the caudate's antero-posterior diameter (see Fig. 1, diameter *x* in the enlarged box of *b*).

2.4.2. Delimitation of the ROI for the body of the caudate nucleus

We obtained the ROI for the body of the caudate nucleus according to the following criteria:

(a) The first section is that in which the caudate's antero-posterior diameter is more than two times larger than the caudate's medio-lateral diameter (Fig. 1, *c*).
(b) The next sections to be measured should follow the ventro-dorsal direction.
(c) The last dorsal section is that previous to that in which the caudate body cannot be visualized (Fig. 1, *d*).
(d) The caudate's antero-posterior diameter should be the larger antero-posterior diameter parallel to the interhemispheric sulcus (see Fig. 1, diameter *y* in the enlarged box of *c*). The medio-lateral caudate's diameter should be the larger medio-lateral diameter perpendicular to the caudate's antero-posterior diameter (see Fig. 1, diameter *x* in the enlarged box of *c*).

Measurements of the ROIs were performed by two experienced tracers. Intraclass correlation coefficients (ICC) were used to assess interrater reliability: caudate head, ICC = 0.87; caudate body, ICC = 0.89.

2.5. Statistical analyses

Differences between the groups' ROIs were analyzed with the statistical package SPSS 11.5. ROI measures in voxels were transformed into cubic millimetres (mm^3) (ROI's total number of voxels multiplied by voxel dimensions).

To determine whether or not the total caudate volume differed in the two groups, we conducted a two-way analysis of variance (ANOVA) with a between-groups

factor (diagnostic group) and a repeated measures factor (hemisphere) for the total caudate volume (dependent variable). Additionally, to investigate the differences between groups I the head and body of the caudate nucleus, we also performed a three-way ANOVA with a between-groups factor (diagnostic group) and two repeated measures factors (hemisphere and caudate region).

In order to examine the symmetry patterns, we calculated asymmetry indices (AIs) for each caudate region. The use of AI is widespread in the scientific literature of ADHD morphometric analyses, and hence they allow us to compare our results with previous findings.

We defined the AIs as follows: For the total caudate volumes, we applied the following AI (AIt), which includes right total caudate volume (RCV) and left total caudate volume (LCV):

$$\mathrm{AIt} = [((\mathrm{RCV}(\mathrm{mm}^3) - \mathrm{LCV}(\mathrm{mm}^3))/(\mathrm{RCV}(\mathrm{mm}^3) + \mathrm{LCV}(\mathrm{mm}^3))) \times 100]$$

For the head of the caudate volumes, we applied the following AI (AIh), which includes right head caudate volume (RHCV) and left head caudate volume (LHCV):

$$\mathrm{AIh} = [((\mathrm{RHCV}(\mathrm{mm}^3) - \mathrm{LHCV}(\mathrm{mm}^3))/(\mathrm{RHCV}(\mathrm{mm}^3) + \mathrm{LHCV}(\mathrm{mm}^3))) \times 100]$$

For the body of the caudate volumes, we applied the following AI (AIb), which includes right body caudate volume (RBCV) and left body caudate volume (LBCV):

$$\mathrm{AIb} = [((\mathrm{RBCV}(\mathrm{mm}^3) - \mathrm{LBCV}(\mathrm{mm}^3))/(\mathrm{RBCV}(\mathrm{mm}^3) + \mathrm{LBCV}(\mathrm{mm}^3))) \times 100]$$

To analyze eventual differences among the AIs between the two groups, we conducted a two-way ANOVA (diagnostic group and caudate region).

3. Results

The results of the two separate ANOVAs are shown in Table 2. The first ANOVA examines caudate volume as a whole, evaluating the effects of the 'group' and 'hemisphere' factors, as well as the interaction between them. When group is considered as the principal effect, the caudate volume differences between groups are not significant in the analyzed sample. However, the statistically significant interactions point to the presence of a combined or conjoint effect of some of the factors included in the analysis, justifying the interaction effects analysis in terms of conditional or simple effects. As shown in Table 2, there is a significant group-by-hemisphere interaction effect ($F=5.370$; $P=0.023$). The nature of the interaction is explored in a simple-effect analysis (Table 3), which shows a significantly decreased right total caudate volume for the ADHD group ($P=0.02$).

Table 2
Two- and three-way ANOVAs between ADHD and control caudate measures

		F statistic	(df_1, df_2)	P value
Head+body	Group	2.821	1, 76	0.097
	Hemisphere	5.687	1, 76	0.020
	Group * Hemisphere	5.370	1, 76	0.023
Head caudate nuclei vs. body caudate nuclei	Group	2.821	1, 76	0.097
	Hemisphere	5.687	1, 76	0.020
	Region	3.288	1, 76	0.074
	Group * Region	0.474	1, 76	0.493
	Group * Hemisphere	1.843	1, 76	0.179
	Group * Region * Hemisphere	10.631	1, 76	0.002

The three-way ANOVA (Table 2), in which the 'region' factor was introduced, thus distinguishing between caudate head and body, shows a significant second order interaction effect, group-by-region-by-hemisphere ($F=10.63$; $P=0.002$). The simple effect analysis, shown in Table 3, breaks down the interaction as a significantly decreased right body volume ($P=0.01$) in the ADHD group, with a moderate–high effect size ($d=0.59$). The statistical analyses did not reveal any significant effect of the different gender proportion in the samples.

Regarding the within-group comparisons, the right total caudate volume was found to be larger than the left in the control group (Table 3). Interestingly, when we take into account the head/body segmentation, the previous pattern in the control group breaks down into a left larger than right caudate head volume, and a right larger than left caudate body volume (Table 3). In other words, the caudate head and body volumes show inverse volumetric patterns in the control group, whereas the ADHD patients show no significant right/left volume differences.

Developing these findings, the AI two-way ANOVA reveals a significant group-by-region interaction effect ($F=11.039$; $P=0.001$). The simple effect analysis reveals significant differences in the head and body AIs between the two groups (see Fig. 2). In other words, an asymmetry pattern arises for the ADHD group that is is the inverse of the control pattern, namely, right asymmetry (right larger than left) for the ADHD caudate head, and left asymmetry (left larger than right) for the ADHD caudate body

Table 3
Within- and between-groups comparisons of caudate volumes

			Controls ($n=39$) Mean volume ± S.D. (mm^3)	ADHD ($n=39$) Mean volume ± S.D. (mm^3)	Mean difference (mm^3)	T	df	P value	CI (0.95) of means (mm^3)	Effect size (Cohen's d)
Caudate head+body	Right		5056 ± 613	4722 ± 713	336	2.22	76	0.02	35 to 635	0.50
	Left		4888 ± 592	4719 ± 787	169	1.07	76	0.28	−145 to 483	0.24
	Right vs. left	Mean difference	168	3						
		F	11.054	0.002						
		df_1, df_2	1, 38	1, 38						
		P value	0.001	0.962						
		CI (0.95)	67 to 269	−98 to 103						
		Effect size (Cohen's d)	0.27	0.003						
Caudate head	Right		2507 ± 715	2593 ± 930	−86	−0.45	76	0.65	−460 to 289	−0.10
	Left		2635 ± 613	2505 ± 944	130	0.72	76	0.47	−230 to 490	0.16
	Right vs. left	Mean difference	−128	88						
		F	4.086	1.968						
		df_1, df_2	1, 38	1, 38						
		P value	0.047	0.165						
		CI (0.95)	−252 to −2	−37 to 213						
		Effect size (Cohen's d)	−0.19	−0.094						
Caudate body	Right		2549 ± 685	2129 ± 736	420	2.60	76	0.01*	94 to 741	0.59
	Left		2254 ± 691	2214 ± 820	40	0.23	76	0.81	−303 to 381	0.05
	Right vs. left	Mean difference	295	−85						
		F	15.323	1.294						
		df_1, df_2	1, 38	1, 38						
		P value	<0.001	0.259						
		CI (0.95)	145 to 445	−236 to 64						
		Effect size (Cohen's d)	0.42	−0.109						

(Fig. 2). As supplementary material for the electronic version, we provide the same two- and three-way ANOVAs for the subsample of boys.

4. Discussion

The aim of this study was to introduce a method for segmenting caudate head from body, and to compare volumetric measures of both structures between a group of ADHD patients and a control group. The rationale behind this objective was that the differential implication of the caudate head and body regions must be elucidated to improve our understanding of ADHD pathophysiology.

The caudate segmentation method that we present here is anatomically coherent, and conforms to previous volumetric data. First, it captures the common anatomical understanding of the structures and, furthermore, the two caudate parts segmented, anterior and posterior, coincide with the head (rostro-ventral part) and body (dorso-posterior part) of the caudate nucleus, respectively. Moreover, our results square with previous findings in the scientific literature, backing our claim that we are measuring the same structures (total caudate) and their same main regions (head and body). In this sense, and concerning total caudate volume in the ADHD sample (left: 4.7 cm^3; right: 4.7 cm^3), our measures fall between those of Ayward et al. (1996) and those of Castellanos et al. (1996) and Filipek et al. (1997). Regarding the caudate head volume in the ADHD sample, data are still scarce. Nevertheless, our measures fall between those of Pineda et al. (2002) and those of Filipek et al. (1997).

Although the group factor in the ANOVA was not significant, there were first and second order interactions. The analysis of simple effects showed that ADHD patients present statistically significant caudate volumetric differences as compared with the control group. Besides, our method of segmentation allows us to unravel the differential implication of the caudate head and body. The right body and right head+body of the ADHD group are significantly smaller than in the control group, even if the right ADHD caudate head is larger than that of the controls. It therefore appears that

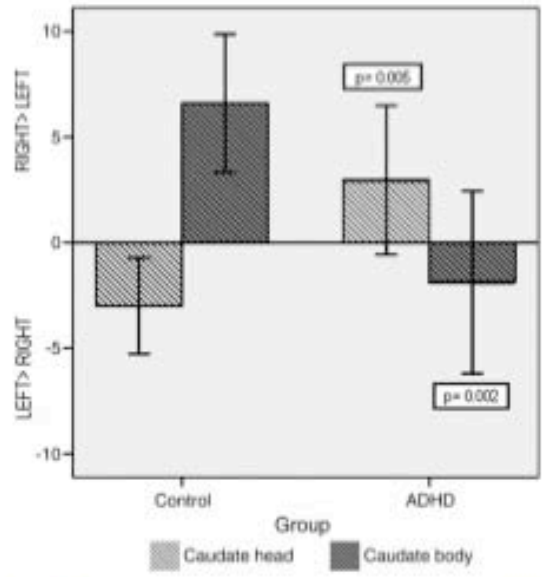


Fig. 2. Head/body caudate asymmetry indices by group and region. *P* values of between-groups comparisons are shown for caudate head ($t=-2.87$; CI 95% = −1.8 to −10.1; effect size = 0.65) and caudate body ($t=3.16$; CI 95% = 3.1 to 13.8; effect size = 0.71) measures.

the right caudate nucleus in ADHD patients is characterized by a caudate head at least as big as that of the controls, while the body of the same side is much smaller. Additionally, our method permits us to examine the asymmetry patterns of both caudate regions, and to detect an inverse asymmetry pattern in the ADHD group (right larger than left caudate head volume, and a left larger than right caudate body volume), which is actually the opposite pattern to that in the control group.

These findings are important for the study of ADHD pathophysiology for various reasons. First, our study substantially contributes to the evaluation of the caudate MR images, providing a new method for segmenting the head and body of the caudate nucleus, as well as helping to detect the differential abnormalities between these two areas. Secondly, we provide one of the largest samples in an ADHD group (39 ADHD and 39 controls) in which morphometric manual measures have been performed. Manual measures are suitable for complementing the automatic measures of other studies, because they allow the examination of MR images without the normalization processes inherent in all automatic or semi-automatic measures. As has been shown to be the case for other psychiatric conditions (Hakala et al., 2004), any conclusion about the pathophysiology of a brain-development disorder such as ADHD needs to be, at least partially, based on direct measures of brain images. Third and last, our results confirm previous data and explain some heterogeneous findings. Our total with those of Castellanos (Castellanos et al., 1996), who found a reduced right total caudate volume in the ADHD patients in the study with the biggest sample until now. Additionally, we also found a tendency towards a right-sided asymmetry of the head of the caudate nucleus and a tendency towards a reduced size of the left head of the caudate, which is concordant with findings of other studies (Hynd et al., 1993; Filipek et al., 1997; Semrud-Clikeman et al., 2000).

In sum, there seems to be a critical distinction between the abnormalities in the head and the body of the caudate nuclei of ADHD patients. Specifically, the heads of the caudate on the right side are slightly enlarged and show a right-sided asymmetry, whereas the right caudate bodies are greatly reduced and show a left-sided asymmetry in the ADHD group. The volumes of the ADHD caudate heads (enlarged) and the ADHD caudate bodies (reduced) produce a nearly symmetric total caudate. In contrast, the control groups shows a right caudate head+body asymmetry. All of these findings could account for the discrepancy in the studies where total caudate measures were considered (Castellanos et al., 1994, 1996) relative to those where the caudate head was differentiated (Filipek et al., 1997; Hynd et al., 1993; Pueyo et al., 2000). In future work, we intend to supplement our manual measures with automatic methods based on our caudate segmentation protocol. The use of automatic methods such as the voxel-based morphometry protocol, has already provided interesting results in ADHD populations (Carmona et al., 2005).

To conclude, our study provides a new method for segmenting the caudate nucleus. This method has allowed us to show that ADHD patients have striatal volumetric abnormalities in comparison with a control group, affecting in a differential way the caudate head and body. ADHD patients present a smaller right caudate body, a right caudate head asymmetry and a left caudate body asymmetry. These abnormalities confirm the role of the striatum in the pathophysiology of ADHD. Our results explain previous heterogeneous findings in the literature, and provide new and complementary methods for studying brain structures in these patients.

Acknowledgements

We thank all the children and parents who participated in this study as well as Mercedes Riba and Neus Abrines for their collaboration. We also acknowledge

the generosity of Professor F.X. Castellanos in reviewing a previous version of this report. His input has allowed us to improve the report in many ways. The junior linguist Joseph Hilferty has helped us to make the text more intelligible. Susanna Carmona was supported by a FPU grant for the "Ministerio de Educacion, Cultura y Deportes." CRC Corporacio Sanitaria received a CDTI grant for the study from the "Ministerio de Industria."

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2007.04.017.

References

Achenbach, T.M., Ruffle, T.M., 2000. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. Pediatr. Rev. 21, 265–271.

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Alexander, G.E., Crutcher, M.D., DeLong, M.R., 1990. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog. Brain Res. 85, 119–146.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. Author, Washington, DC.

Aylward, E.H., Reiss, A.L., Reader, M.J., Singer, H., Brown, J.E., Denckla, M.B., 1996. Basal ganglia volumes in children with attention-deficit hyperactivity disorder. J. Child Neurol. 11, 112–115.

Barkley, R.A., 1997. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol. Bull. 121, 65–94.

Caplan, L.R., Schmahmann, J.D., Kase, C.S., Feldmann, E., Baquis, G., Greenberg, J.P., Gorelick, P.B., Helgason, C., Hier, D.B., 1990. Caudate infarcts. Arch. Neurol. 47, 133–143.

Carmona, S., Vilarroya, O., Bielsa, A., Trèmols, V., Soliva, J.C., Rovira, M., Tomás, J., Raheb, C., Gispert, J.D., Batlle, S., Bulbena, A., 2005. Global and regional gray matter reductions in ADHD: a voxel-based morphometric study. Neurosci. Lett. 389, 88–93.

Castellanos, F.X., Giedd, J.N., Eckburg, P., Marsh, W.L., Vaituzis, A.C., Kaysen, D., Hamburger, S.D., Rapoport, J.L., 1994. Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. Am. J. Psychiatry 151, 1791–1796.

Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Vaituzis, A.C., Dickstein, D.P., Sarfatti, S.E., Vauss, Y.C., Snell, J.W., Lange, N., Kaysen, D., Krain, A.L., Ritchie, G.F., Rajapakse, J.C., Rapoport, J.L., 1996. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch. Gen. Psychiatry 53 (7), 607–616.

Conners, C., Sitarenios, G., Parker, J.D., Epstein, J.N., 1998a. The revised Conners parent rating scale (CPRS-R): factor structure, reliability, and criterion validity. J. Abnorm. Child Psychol. 26 (4), 257–268.

Conners, C., Sitarenios, G., Parker, J.D., Epstein, J.N., 1998b. Revision and restandardization of the Conners teacher rating scale (CtRS-R): factor structure, reliability, and criterion validity. J. Abnorm. Child Psychol. 26 (4), 279–291.

Dreifuss, S., Lazeyras, F.J., Andino, F., Spinelli, S.G., Delavelle, L., Seeck, J., 2001. Volumetric measurements of subcortical nuclei in patients with temporal lobe epilepsy. Neurology 57 (9), 1636–1641.

Durston, S., Hulshoff Pol, H.E., Schnack, H.G., Buitelaar, J.K., Steenhuis, M.P., Minderaa, R.B., Khan, R.S., Van Engeland, H., 2004. Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. J. Am. Acad. Child Adolesc. Psych. 43 (3), 332–340.

Duvernoy, H.M., 1991. The Human Brain: Surface, Three-Dimensional Sectional Anatomy and MR1. Springer-Verlag, Vienna.

Edelbrock, C., 1983. Problems and issues in using rating scales to assess child personality and psychopathology. Sch. Psychol. Rev. 12, 293–299.

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, 89–601.

Goyette, C.H., Conners, C.K., Ulrich, R.F., 1978. Normative data on revised Conners parent and teacher rating scales. J. Abnorm. Child Psychol. 6 (2), 221–236.

Hakala, M., Karlsson, H., Kurki, T., Aalto, S., Koponen, S., Vahlberg, T., Niemi, P.M., 2004. Volumes of the caudate nuclei in women with somatization disorder and healthy women. Psychiatry Res.: Neuroimaging 131 (1), 71–78.

Hill, D.E., Yeo, R.A., Campbell, R.A., Hart, B., Vigil, J., Brooks, W., 2003. Neuropsychology 17 (3), 496–506.

Hynd, G.W., Hern, K.L., Novey, E.S., Eliopulos, D., Marshall, R., Gonzalez, J.J., 1993. Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. J. Child Neurol. 8, 339–347.

Pineda, D.A., Restrepo, M.A., Sarmiento, R.J., Gutierrez, J.E., Vargas, S.A., Quiroz, Y.T., Hynd, G.W., 2002. Statistical analyses of structural magnetic resonance imaging of the head of the caudate nucleus in Colombian children with attention-deficit hyperactivity disorder. J. Child Neurol. 17 (2), 97–105.

Pueyo, R., Mañeru, C., Vendrell, P., Mataró, M., Estévez-González, A., García-Sánchez, C., Junqué, C., 2000. Trastornos por déficit de atención con hiperactividad. Asimetrías cerebrales observadas en resonancia magnética. Rev. Neurol. 30, 920–925.

Richfield, E., Twyman, R., Berent, S., 1987. Neurological syndrome following bilateral damage to the head of the caudate nuclei. Ann. Neurol. 22 (6), 768–771.

Schrimsher, G.W., Billingsley, R.L., Jackson, E.F., Moore, B.D., 2002. Caudate nucleus volume asymmetry predicts attention-deficit hyperactivity disorder (ADHD) symptomatology in children. J. Child Neurol. 17, 877–884.

Seger, C.A., Cincotta, C.M., 2005. The roles of the caudate nucleus in human classification learning. J. Neurosci. 25 (11), 2941–2951.

Semrud-Clikeman, M., Steingard, R.J., Filipeck, P., Biederman, J., Bekken, K., Renshaw, P.F., 2000. Using MRI to examine brain–behavior relationships in males with attention deficit disorder with hyperactivity. J. Am. Acad. Child Adolesc. Psych. 39 (4), 477–484.

Sergeant, J., 1990. The cognitive Posner MI, Peterson SE. The attention system of the human brain. Annu. Rev. Neurosci. 13, 25–42.

Swanson, J.M., Posner, M., Cantwell, D., Wigal, S., Crinella, F., Filipek, P., Emerson, J., Tucker, D., Nalcioglu, O., 1998. Attention-deficit/hyperactive disorder: symptom domains, cognitive processes and neural networks. In: Parasuramann, R. (Ed.), The Attentive Brain. MIT Press, Boston.

Wechsler, D., 1974. Manual for the Wechsler Intelligence Scale for Children—Revised. The Psychological Corporation, New York.

Wechsler, D., 1993. Escala de Inteligencia de Wechsler para niños revisada (WISC-R). TEA Ediciones, Madrid.

2.2. Previously unpublished analyses/results:

Whole sample:

Among ADHD subtype comparisons:

In order to see whether there were differences between ADHD subtypes I repeated the ANOVA comparison for total caudate, caudate regions and asymmetry indices including the three subtypes as a between group factor. Additional t-tests were also performed between inattentive vs. combined, H-I vs. combined and inattentive vs. H-I. Neither ANOVA nor t-test comparisons reported significant group differences in any of the measures. However, I performed t-test comparison between controls and each of the ADHD subtypes. Results show caudate volume reductions in combined and hyperactive subtypes as compared to controls. This difference seems to account for diminished right total caudate volume and reversed caudate-body asymmetry index (controls R>L; ADHD-comb L=R trend to L>R) in the case of the combined subtype. Interestingly, inverse caudate-head asymmetry index was also found when comparing controls with combined subtype (controls) (see table 7).

Table 7: T-test comparisons between controls and each ADHD subtype			Control Mean mm^3 (sd) N=39	Combine Mean mm^3 (sd) N= 24	Innatentive Mean mm^3 (sd) N= 8	H-I Mean mm^3 (sd) N= 7
Caudate nucleus (Head and body)	R	Mean (sd)	5056.2 (612.7)	4685,0 (778,8)	4991,4 (709,5)	4538,4 (411,3)
		P values		0.04		0.038
		M.d (SD)		371.22 (176.4)		517.8 (241.9)
		95% CI		18.3 to 724.0		30.25 to 1005.3
	L	Mean (sd)	4888,2 (592)	4680,1 (859,1)	5007,5 (737,9)	4523,5 (541,0)
		P values				
		M.d (SD)				
		95% CI				
	A.I	Mean (sd)	1,69 (3,3)	0,3160 (3,9)	-0,16 (3,4)	0,29 (2,64)
		P values				
		M.d (SD)				
		95% CI				
Caudate nucleus (Head)	R	Mean (sd)	2507,5 (715,1)	2618,5 (895,7)	2853,5 (1175,9)	2207,5 (722,8)
		P values				
		Md (SD)				
		95% CI				
	L	Mean (sd)	2634,5 (613,1)	2498,1 (987,5)	2726,6 (990,5)	2274,3 (794,5)
		P values				
		M.d (SD)				
		95% CI				
	A.I	Mean (sd)	-2,99 (6,97)	4,64 (11,25)	1,20 (6,80)	-0,7 (13,5)
		P values		0.001		
		M.d (SD)		-7.63 (2.29)		
		95% CI		-12.2 to -3.05		
Caudate nucleus (body)	R	Mean (sd)	2548,7 (685,1)	2066,4 (708,8)	2137,8 (962,8)	2330,8 (601,4)
		P values		0.01		
		M.d (SD)		482.2 (180.0)		
		95% CI		122.16 to 842.3		
	L	Mean (sd)	2253,7 (690,9)	2181,9 (874,3)	2280,8 (779,1)	2249,1 (782,9)
		P values				
		M.d (SD)				
		95% CI				
	A.I	Mean (sd)	6,60 (10,07)	-2,02 (11,77)	-6.00 (13,23)	3,41 (18,30)
		P values		0.003	0.04	
		M.d (SD)		8,6 (2.7)	12.60 (4.12)	
		95% CI		3.05 to 14.20	4.30 to 20.91	

R= Right; L= Left; A.I= Asymmetry Index; (SD)= Standard Deviation; M.d= mean difference; H-I= Hyperactive/Impulsive; 95% CI= Confidence Interval at 95%.

Male subsample:

ADHD vs Controls:

Demographic and clinical data of male subsample is described in the table 8.

Table 8: *Demographic and Clinical data*		*ADHD*				*CONTROL*
		Inatt.	*H- I.*	*Comb.*	*Total*	
N		8	7	20	35	27
Age: Mean (sd)		12.7 (sd: 2.2)	9.9 (sd: 2.4)	10.8 (sd: 3.1)	11.1 (sd: 2.9)	12.2 (sd: 3.3)
Laterality	*R*	5	5	17	27	21
	L	2	0	0	2	3
	C.D	1	2	3	6	3
Methylphenidate medication(mg/kg)		0.60 (sd: 0.064)	0.62 (sd: 0.061)	0.60 (sd: 0.04)	0.62 (sd: 0.022)	
Conners' Rating (Hyper)	*F*	18.7 (sd: 3.5)	15.3 (sd: 2.5)	16.4 (sd: 4.9)	19.5 (sd: 1.7)	
	M	19.6 (sd: 5.5)	17.6 (sd: 3.9)	19.3 (sd: 4.8)	20.5 (sd: 1.9)	
	T	19.2 (sd: 6.4)	21.7 (sd: 5.8)	21.7 (sd: 4.2)	13.0 (sd: 6.5)	

R= Right; L= Left; C.D= Cross Dominance; (sd)= Standard Deviation; Inatt= Innatentive; H-I= Hyperactive/Impulsive; Comb= Combined; mg/kg= Methilphenidate milligrams per kilogram; F= father; M= Mother; T= teacher. n= number of subjects; CI= Confidence Interval at 95%.

We repeated exactly the same statistical analyses with the male subsample. Results overlap those derived form the analyses performed with the whole sample. (See table 9 and 10)

Table 9. ANOVA of caudate measures for the male subsample.		F Statistic	(Df_1,Df_2)	P Value
Head-Body C.N.	Hemisphere	4.459	1 , 60	0.039
	Group * Hemisphere	4.849	1 , 60	0.032
Head C.N vs.Body C.N. (Region)	Hemisphere	4.459	1 , 60	0.039
	Group * Region * Hemisphere	8.737	1 , 60	0.004

C.N= Caudate nuclei, Df= degrees of freedom.

Table 10. Within and between-groups comparisons of caudate volumes in the sub-sample of boys			Controls (n=27) M ± sd (mm^3)	ADHD (n=35) M ± sd (mm^3)	Mean diff (mm^3)	T	Df	P value	CI (0.95)	E.S
C.H-B	R		5109 ±612	4742 ±720	367	2.12	60	0.04	21 to 713	0.54
	L		4934 ±509	4745 ±774	189	1.10	60	0.28	-155 to 533	0.28
	R/L	M.diff. F Df_1, df_2 P value CI (0.95) E.S	175 7.04 1 , 26 0.01 40 to 311 0.51	-3 0.005 1 , 34 0.942 -105 to 98 -0.01						
C.B	R		2548 ±795	2536 ±943	-12	-0.05	60	0.96	-440 to 463	0.01
	L		2693 ±663	2441 ±959	251	1.16	60	0.25	-181 to 684	0.29
	R/L	M.diff. F Df_1, df_2 P value CI (0.95) E.S.	-145 3.662 1 , 26 0.068 -302 to 12 -0.36	95 1.591 1 , 34 0.216 -58 to 248 -0.21						
C.H	R		2561 ±718	2205 ±727	356	1.92	60	0.06	-15 to 726	0.49
	L		2241 ±694	2304 ±806	-63	-0.32	60	0.75	-452 to 326	-0.08
	R/L	M.diff. F Df_1, df_2 P value CI (0.95) E.S.	320 10.765 1 , 27 0.005 120 to 521 0.63	-99 1.410 1 , 34 0.243 -268 to 70 -0.20						

"Right" and "Left" rows show the between-groups simple effect testing. "Right vs. Left" indicates the within-groups comparisons (in "Controls" and "ADHD" columns) between right and left hemispheres. C.H-B= caudate head and body; C.B= caudate body; C.H= Caudate head; R= Right; L= Left; s.d= Standard Deviation; E.S.= effect size; M.diff= mean difference; H-I= Hyperactive/Impulsive; 95% CI= Confidence Interval at 95%.

* It remains significant after covariation with total brain volume (Covariated mean body volume: Control, 2565 ± 687 mm^3; ADHD. 2129 ± 736 mm^3 ; Mean difference= 425 ; t statistic= 3.407; p=0.001; CI= 34.10 to 130.11; effect size= 0.61).

ADHD subtype comparisons:

As in the previous case I performed an ANOVA comparison for total caudate, caudate regions and asymmetry indices entering the subtype as between group factor. Specific t-test between inattentive vs. combined, H-I vs. combined and inattentive vs. H-I. ANOVA and t-test comparisons performed in the male sample did not report significant group differences in any of the measures. However, as in the previous case, t-test comparisons between controls and each of the ADHD subtypes were also performed.

Results show that right caudate (head-body) volume is reduced in the H-I sample as compared to controls. Reversed caudate body asymmetry index were found for the inattentive and combined subtype (controls R>L; ADHD-combined/inattentive L=R trend to L>R). In addition, combined subtype present reversed asymmetry for the head of caudate nuclei (controls L>R; ADHD-comb R=L, trend to R>L). In short, comparisons performed only in the male subsample replicate our previous findings with the whole sample, except for reduced caudate body (and subsequently caudate head+body) in the combined subtype (see table 11). Given that most of the ADHD girls belonged to the combined subtype, one cannot discard that the absence of significance would be due to reduced statistical power.

Table 11: T-test comparisons between controls and each ADHD subtype only for the male subsample			Control (n=27) Mean (sd)	Combine (n=20) Mean (sd)	Innatentive (n=8) Mean (sd)	Hyp/Imp (n=7) Mean (sd)
Caudate nucleus (Head and body)	R	Mean (sd)	5109.1 (612.1)	4713.1 (804.1)	4991,4 (709,5)	4538,4 (411,3)
		P values				0.027
		M.d (SD)				570.6 (245.9)
		95% CI				69.74 to 1071.5
	L	Mean (sd)	4933.9 (509.0)	4718.3 (854.6)	5007,5 (737,9)	4523,5 (541,0)
		P values				
		M.d (SD)				
		95% CI				
	A.I	Mean (sd)	1,65 (3,3)	0,18 (3,9)	-0,16 (3,4)	0,29 (2,64)
		P values				
		M.d (SD)				
		95% CI				
Caudate nucleus (Head)	R	Mean (sd)	2547,8 (795,4)	2524.6 (913.1)	2853,5 (1175,9)	2207,5 (722,8)
		P values				
		Md (SD)				
		95% CI				
	L	Mean (sd)	2692,8 (663,13)	2385,7 (1018,7)	2726,6 (990,5)	2274,3 (794,5)
		P values				
		M.d (SD)				
		95% CI				
	A.I	Mean (sd)	-3,51(7,72)	5.51 (12,10)	1,20 (6,80)	-0,7 (13,5)
		P values		0.003		
		M.d (SD)		-9.03 (2.89)		
		95% CI		-14.8 to -3.4		
Caudate nucleus (body)	R	Mean (sd)	2561,2 (717,8)	2188.4 (694.9)	2137,8 (962,8)	2330,8 (601,4)
		P values				
		M.d (SD)				
		95% CI				
	L	Mean (sd)	2241,1 (694.4)	2332.6 (861.6)	2280,8 (779,1)	2249,1 (782,9)
		P values				
		M.d (SD)				
		95% CI				
	A.I	Mean (sd)	6.83 (11,15)	-2.62 (10,65)	-6.00 (13,23)	3,41 (18,30)
		P values		0.005	0.031	
		M.d (SD)		9.45 (3.23)	12.84 (5.14)	
		95% CI		2.95 to 15.96	1.4 to 24.3	

3. Summary Study 1 and Study 2

Study 1.
Global and regional gray matter reduction in ADHD: A voxel-based morphometric study

Objective:

- To apply a whole-brain exploratory analysis to the study of ADHD neuroanatomy. We aimed to answer two questions:
  1. Are there global brain volume differences between ADHD and controls?
  2. Where are the differences located?

Methods:

- Sample:
  - 25 ADHD medicated children (aged 6 to 16)
    - 5 inatentive subtype,
    - 5 hyperactive/impulsive subtype
    - 15 combined subtype)
  - 25 Control children matched for age, gender and laterality.
- MRI analysis technique:
  - Automatic optimized voxel based morphometry approach.
- Statistical analysis:
  1. Global brain volume differences were analyzed using mean comparison t-test for independent samples (threshold of $p<0.05$)
  2. Regional morphometric analyses were performed using a voxel per voxel analysis of covariance the control group and the 3 ADHD subtypes. Age was included as nuisance variable. Specific t-test comparisons were performed.

Results:

1. Global brain volume reductions in the ADHD group:
   - Total brain volume was 5.4% reduced in ADHD children as compared to control children.
   - Gray matter volume was 5.2% reduced in ADHD children as compared
2. Regional morphometric analysis:
   - Reduced frontal regions (left perirolandic and bilateral orbitofrontal areas)
   - Reduced cerebellum bilaterally.
   - Reduced parietal and temporal areas

* Male analyses replicate previous findings. In addition we found regional morphometric differences among ADHD subtypes. Specifically, we found that OF and ventral striatal GM volumes were specially reduced in the H-I subtype, while combined subtypes present mainly left perirolandic reduction.

Despite the amount of literature pointing to ADHD caudate volume reduction, we did not find differences between ADHD and Control subjects using a VBM procedure. Among other factors this could be the result of methodological differences.
In fact, all the previous studies that reported Caudate volume reductions in ADHD used ROI approaches. VMB require normalizations processes while ROI analysis do not. Normalization slightly deform the structures in order to mach them to a standard template. If caudate nuclei ADHD reductions are shape-depended (ex: differences in the head but not in the body) they may be not detectable using VBM.
In order to check if ADHD children present volume reductions in specific regions of the caudate nuclei we performed the study 2, which is based on ROI approach.

Study 2:
Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder..

Objective:

- To study caudate nuclei volumes in ADHD applying a manual ROI analysis and to test a new criterion of caudate segmentation. We aimed to response to the following questions:
  1. Are there caudate volume differences between ADHD and controls?
  2. Do these differences depend on caudate region (head vs. body)?
  3. Are there right vs. left caudate asymmetry differences between groups?

Methods:

- Sample:
  - 39 ADHD medicated children (aged 6 to 16)
    - 8 innatentive subtype,
    - 7 hyperactive/impulsive subtype
    - 24 combined subtype)
  - 39 Control children.
- MRI analysis technique:
  - Manual ROI analysis: delimitation of Caudate nucleus and caudate nucleus parts (body and head) manually.
- Statistical analysis:
  1. Caudate volume differences were analyzed using two-way ANOVA with a between-groups factor (diagnosis: ADHD/controls) and a repeated measure factor (hemisphere: right/left).
  2. Head/body caudate volumes analyses were performed using a three-way ANOVA with a between-groups factor (diagnosis: ADHD/controls) and two repeated measures factors (hemisphere: right/left; and caudate region: head/body).
  3. Caudate asymmetry pattern was analyzed using paired sample t-test (right and left) for the whole caudate nuclei as well as for head and body caudate subparts. In addition, and with the main aim of comparing the results with previous studies, we also computed and asymmetry index (A.I.=((Right-left)/(Right+Left) x 100)).) for the 3 caudate measures (head, body and total). In the case of asymmetry indices, we performed two-way ANOVA with a between-groups factor (diagnosis: ADHD/controls) and a repeated measure factor (caudate region: head/body).

Results:

1. Caudate volume: Right caudate volume was found to be reduced in ADHD as compared to controls
2. Head/body caudate volumes: ADHD children have reduced right body of the caudate nuclei, but not reduced head.
3. Asymmetry Index: As compared to controls, ADHD present an inverse A.I. for the head and the body of caudate nuclei.

* Subtype: Right caudate volume reductions were specially pronounced in combined and H-I subtypes, while caudate-body asymmetry indices were mainly accounted for inattentive and combined subtypes.
* Group and subtype analyses performed with the male subsample generally overlap with our previous findings.

Main aspects of each study are concisely described here and fully explained in each of the papers. In this section I also provide unpublished results (signaled with an *). These non-reported results derive from analysis performed in a male subsample as well as from ADHD subtype comparisons, for the whole and the male sample separately. There is a full description of the unpublished data annexed at the end of each paper.

DISCUSSION:

The aim of the present dissertation was to refine and apply two complementary methods of structural neuroimaging, in order to identify the brain circuits that are altered in ADHD, as well as to relate them to different clinical ADHD subtypes and to known ADHD neuropsychological deficits.

With this in mind we performed two MRI studies comparing a group of ADHD children with a group of healthy control children. Each of the studies used a different, but complementary methodology. Study 1 uses a VBM approach, ideal for exploratory analysis, whereas study 2 uses a ROI approach that is more suitable for confirmatory analysis and has greater anatomical validity. The differential contributions of the studies presented, which represent a novelty and an improvement on previous ADHD studies, are: a) the application for the first time of a voxel-based morphometry analysis to compare ADHD children with non family-related control children; b) the design and application of a new, easy to apply, manual method of caudate nucleus segmentation.

Our results corroborate that ADHD brains are smaller than those of normal controls. Moreover, most of these reductions seem to be produced by GM deficits. In addition to this, we observed that neuroanatomical abnormalities were not only confined to fronto-striatal-cerebellar circuits, but also affect parieto-temporal and cingulate regions. We observed reduction in areas related to cognitive processes (working memory, attention and inhibition), which is coherent with "cool" neuropsychological deficits of the disorder. We also observed reduction in emotionally driven circuits, thus accounting for "hot" neuropsychological profiles. Our studies also provide a new and reliable method to measure striatal structures. This method shows caudate head and body differential abnormalities in ADHD, which explain previous heterogeneous results. Finally, we have also found deficits in sensorimotor areas, which constitute a possible indication of fine motor deficits in ADHD.

Study 1 is the first to compare ADHD children with a group of matched unrelated controls using the novel VBM methodology. According to our results, ADHD children have 5.4% reduced TBV and 5.2% reduced GM volume as compared to matched control children. These reductions are mainly located in fronto-striatal cerebellar circuits as well as in parietal, cingulate and temporal regions. Interestingly, these reductions are accentuated when comparing the sub-sample of only male subjects (see section "unpublished analyses/results"). Specifically, we found smaller GM volume in ADHD as compared to control children in left perirolandic cortices, bilateral OFC (extending to the ventral striatum), bilateral cerebellum and right parietal inferior cortex, bilateral posterior cingulate and left medial temporal lobe. With regard to subtype comparison, when using a homogeneous male-sample, we observed that OFC/ventral striatum, cerebellar and parietal GM deficits were accentuated in the H-I subtype, while left perirolandic reductions where more prominent in the combined subtype. Regarding WM volume, there were no differences between ADHD and control children.

Prior to our study, only one paper had used VBM to analyze ADHD neuroanatomy (Overmeyer et al. 2001). The study of Overmeyer compared 18 ADHD children with hyperkinetic disorder with 16 unaffected siblings. The use of siblings as control group is an interesting approach that can offer very useful information about the factors exclusively related to the manifestation of those symptoms necessary for an ADHD diagnosis. However, conclusions derived from these kind of studies present certain limitations because of the high heritability of the disorder (Faraone et al. 2005) as well as the important genetic impact on the volume of brain regions

(Durston et al. 2005). Therefore, our VBM study represents an important contribution to the neural bases of ADHD because the two samples we used are: a) relatively large; b) familiarly unrelated; and c) well-matched for gender, age and laterality.

Most of the previous studies examined ADHD brain anatomy using ROI-methods, and many of these studies reported abnormalities in caudate nuclei. However, we did not find any difference in caudate volume when we compared ADHD with control children using a VBM approach. Consequently, we decided to test if these negative results were due to methodological differences. For this reason, we analyzed caudate volume as well as caudate subparts and asymmetry indices using a ROI approach. The ROI analysis revealed that ADHD children have smaller right caudate as a result of decreased right caudate-body volume. Additionally, we examined the asymmetry patterns of both caudate regions and detected an inverse asymmetry pattern in the ADHD group (right larger than left caudate-head volumes, and left larger than right caudate-body volumes). This is an important finding because the opposite pattern has been observed in the control group. Therefore, while the right caudate-body was significantly smaller, a slight, although non-significant, increase was found for the left head of ADHD children. This head/body opposite deviations produced caudate shape differences between groups.

It is reasonable to conclude that VBM blurred these shape differences when fitting caudate nuclei into the standard stereotaxic space during the normalization step. In addition, the landmarks used to distinguish caudate-head from caudate-body could have been attenuated, not only by deformations during normalization, but also by voxel-smoothing of such a relatively small area. Interestingly, whereas right total caudate and caudate-body volumes reductions were especially prominent in the combined and H-I subtypes, inverse asymmetry indices seemed to be specially accounted for inattentive and combined subtypes.

The ROI study also represents an important advance in our knowledge of ADHD neuroanatomy. It is the study with the largest ADHD sample after the studies of Castellanos (Castellanos et al. 2001; Castellanos et al. 1994; Castellanos et al. 1996b; Castellanos et al. 2002) and Berquin (Berquin et al. 1998). In addition to the significance of the results, the relevance of the paper stems from the segmentation method. We implemented a new segmentation criterion, which not only provides a reproducible measure to distinguish between the head and the body of caudate nucleus, but also clarifies some of the discrepancies found in ADHD literature about caudate volume as will be discussed in the section about dorsal striatum.

Therefore, according to our findings, ADHD children have reduced GM volume in fronto-striatal, cerebellar, parieto-occipital, posterior cingulate and medial temporal areas. Below, I associate deficits in GM with typical ADHD cognitive deficits. The rationale comes from the evidence, provided by lesion studies, that there is a correlation between brain structural deficits and the correct functioning of particular processes (Junque and Barroso 1995). Therefore, we will discuss each of the reported regions, on the base of previous behavioral and neuroimaging findings in ADHD and normal population as well as lesion and animal studies.

1. Reductions in fronto-striatal regions:

Fronto-striatal disruptions have been extensively related to ADHD. These circuits are rich in DA transmission, which, as previously commented, is a key target of ADHD drugs.

1.1. Frontal:

Regarding frontal areas, we found that ADHD children have reduced GM volume in orbitofrontal and perirolandic cortices as compared to control children. These regions belong to the limbic and sensorimotor circuits respectively. In addition, we also found GM volume reductions in DLPFC when comparing H-I with controls. DLPFC is the cortical target of the associative frontostriatal circuit (for a full description see appendix 3).

Nearly all of the studies measuring PFC found volume reductions in ADHD. It is difficult to compare our frontal findings with previous results, especially those derived from ROI analyses, because of the high variability of the landmarks used to delimitate frontal area in each of the studies. However, the regions in which we observed frontal volume reductions generally overlap with those reported in the literature and endorse clinical and neuropsychological data.

1.1.1. ORBITOFRONTAL CORTEX:

We found OFC reductions in the ADHD children. These reductions are especially prominent in the H-I children although they are also present in the combined subtype.

There are no studies that specifically report OFC reductions in ADHD children. However, most of the studies that include the OFC when measuring prefrontal lobe, found reduced volume (see for example (Castellanos et al. 2002; Mostofsky et al. 2002). Only one study, performed in an adult sample, found volume reductions in this region in medication naïve male patients (Hesslinger et al. 2002). Interestingly, Van't Ent (van 't Ent et al. 2007) studied a population of monozygotic twins with high or low risk for ADHD, and found that the pairs concordant for high-risk of ADHD have OFC volume reductions as compared to twins concordant for low-risk of ADHD.

Go/no-go paradigms have been originally designed to elicit inhibitory control and therefore measure impulsivity. Disorders characterized by impulsive behavior show hypoactivity in OFC during no-go conditions (e.g. Vollm et al studying antisocial and borderline personality (Vollm et al. 2004) or Altshulter et al studying patients with Mania (Altshuler et al. 2005)). Interestingly, a functional neuroimaging study in ADHD children showed hypoactivity in OFC during no-go condition in the go-no go task that normalize after psychological training (Hoekzema et al. unpublished).

Impulsive behavior can be interpreted as difficulties to plan ahead and inhibit preponderant responses, but also as problems related to reward system, such as acting under the guidance of immediate instead of delayed rewards. There is evidence that the implication of OFC in impulsive behavior is specifically mediated by rewarding processes. On the one hand, functional neuroimaging studies found that OFC is involved in the selection of large delayed rewards over smaller immediate rewards. Furthermore, the authors found that activation in this area was directly associated with subjects' choices of larger delayed rewards, thus, suggesting that OFC is related to the devaluation of subjective reward value as a function of time-delay (McClure et al. 2004). On the other hand, it has been observed that patients with damage in the OFC have problems when representing, maintaining and updating reward value (Fellows 2007; Mobini et al. 2002). These problems made the patients behave on the basis of immediate rather than long-term rewards (Bechara et al. 1994). Interestingly, this is also a behavioral feature of ADHD (Sonuga-Barke 2002). Specifically, Itami and Uno (Itami and Uno 2002) observed that ADHD children perform similarly to patients

with OFC lesions during go/no-go paradigms, therefore, providing additional support for the implication of this region in ADHD.

Hence, OFC seems to be critical for representing/comparing the relative reinforcing values of stimuli as well as maintaining/updating these values in order to guide behaviour. If OFC is significantly reduced, it is possible that the reward value devalues or fades out, and, consequently, the motivational force becomes over-written by other interfering immediate rewards, resulting in stimulus-driven behaviour. According to that, hyperactivity and impulsivity symptoms can be understood as difficulties to maintain on line the reward value of stimuli. Problems keeping the expected value of rewards in mind would explain the lack of planning, and the difficulties to behave on the basis of long-term goals. As a consequence, behaviour would be guided by more immediate rewards such as those produced by self-movement perception or environmental cues.

1.1.2. DORSOLATERAL PREFRONTAL CORTEX:

There is growing evidence of functional and structural deficits in right inferior frontal gyrus in ADHD (for a review see Aron & Poldrack (Aron and Poldrack 2005) and Castellanos & Tannock (Castellanos and Tannock 2002)).

Most of the structural studies that reported PFC reductions using ROI analysis specially include inferior frontal areas in their measures (Castellanos et al. 2001; Castellanos et al. 1996b; Castellanos et al. 2002; Mostofsky et al. 2002). Moreover, whole-brain analyses found GM cortical thinning in right inferior frontal cortex in ADHD children (Sowell et al. 2003). Furthermore, Durston (Durston et al. 2004) found significant reductions in right inferior frontal cortex, not only in ADHD children, but also in their unaffected siblings. Interestingly, Casey (Casey et al. 1997) reported that right fontal cortex volume was significantly correlated with response inhibition deficits. Lesion studies also support the implication of right inferior frontal cortex in response inhibition. Moreover, it has been shown that the amount of damage in right inferior frontal cortex is positively correlated with response inhibition deficits as measured by stop-signal reaction time (SSRT; see appendix 3) (Aron et al. 2003). Concordant with these previous findings, our VBM analysis revealed GM volume deficits in DLPFC in H-I children as compared to control children. This reduction specifically affects right inferior frontal cortex.

Functional studies in healthy subjects provide support for the implication of inferior frontal gyrus in response inhibition (Aron and Poldrack 2005; Rubia et al. 2003b). With regard to functional neuroimaging in ADHD subjects, a recent meta-analysis has reported hypoactivation in right inferior frontal cortex and precentral gyrus in tasks requiring response inhibition (Dickstein et al. 2006). Additionally, reduced perfusion in right inferior frontal cortex has also been observed in drug-naïve ADHD subjects during rest (Zang et al. 2007). As a complement to structural and functional neuroimaging studies, EEG studies also found that ADHD children present an attenuation of the signal during behavioral inhibition in right frontal regions (Pliszka et al. 2000; Smith et al. 2004).

Besides deficits in inhibitory control processes, ADHD children present working memory problems. Working memory is thought to rely on DLPF regions. In particular, spatial working memory, which is one of the key neuropsychological deficits in ADHD (Nigg 2005), seems to be subserved by right DLPFC. A recent neuropsychological study (Clark et al. 2007), reported that response inhibition and spatial working memory were deficient and significantly intercorrelated in adult ADHD patient as well as in patients with right inferior frontal damage. Furthermore,

the authors observed that hyperactive impulsive subtypes were especially deficient in both tasks (Clark et al. 2007).

Finally note that, van't Ent (van 't Ent et al. 2007) observed that, while OFC deficits were genetically mediated, dorsolateral prefrontal cortex deficits seem to be more related to environmental factors. This is important because it highlights the relevance of environmental aspects in the development and maintenance of the disorder, as well as offering an anatomical substrate for them.

Therefore, our results are in line with previous reports and suggest that decreased GM volume in the right inferior frontal gyrus is related to deficits in spatial working memory and control inhibition, especially in H-I children.

1.1.3. PERIROLANDIC AREAS:

According to our findings, ADHD children have reduced GM volume in left perirolandic areas. This region seems to be specially reduced in children with combined subtype. However, when we lower the level of significance we also observe that bilateral motor and premotor cortices extending to supplementary motor area (SMA) are reduced not only in the combined subtype, but also in the inattentive subtype. It is possible that perirolandic areas are equally reduced in both subtypes, but that they do not show up at the same level of significance given the small number of subjects belonging to the inattentive subtype, as compared to those pertaining to the combined subtype.

Perirolandic areas have often been excluded from the parcelation of PFC–ROI. Only one study specifically measured motor and premotor cortices (Mostofsky et al. 2002). Mostofsky found that premotor cortex (including SMA) was reduced in a group of ADHD boys. In point of fact, the sample of Mostosfky' study was exclusively formed by children belonging to the inattentive and combined subtypes, but not H-I children. Hence, this is in the line with our findings of reduced GM in perirolandic areas specifically when comparing inattentive or combined subtypes with controls. WM abnormalities in SMA have also been observed. Specifically Ashtari (Ashtari et al. 2005), in a DTI study, reported reduced FA in right supplementary motor cortex in ADHD children.

Reduced volume in perirolandic areas could be related to fine motor deficits and/or coordination problems as well as deficits in response inhibition. Studies in control children showed up that, together with inferior frontal cortex, premotor and SMA areas are necessary for response inhibition (Simmonds et al. 2007a; Simmonds et al. 2007b).

There is empirical evidence about ADHD dysfunctions in motor areas (Courvoisie et al. 2004; Rubia et al. 2003a; Rubia et al. 2001; Yochman et al. 2006). In fact, clinical data also show that ADHD subjects benefict not only from cognitive behavioral training, but also from sensorimotor training (Banaschewski et al. 2001). Interestingly, a recent study showed that difficulties in inhibiting a preponderant motor response were especially prominent in inattentive and combined subtypes, but not in the H-I subtype (Chhabildas et al. 2001).

The fact that perirolandic areas, mainly SMA, are reduced principally in combined and inattentive subtypes suggests the possibility that this region may be related to inattention symptoms. It is known that these regions are important to integrate internal and external information. A possibility could be that GM reductions in these areas produce difficulties when integrating and updating information from the external world and this, in turn, produces a bias towards an internal focus resulting in attention deficits.

Results from functional neuroimaging studies about perirolandic alterations in ADHD are controversial. On the one hand, they endorse ADHD abnormalities in perirolandic regions. In particular, Zang, observed that, as compared to controls, ADHD children showed increased activity in left sensorimotor cortex during resting state (Zang et al. 2007). In contrast, Mostosfky (Mostofsky et al. 2006) found that ADHD children presented reduced activation of perirolandic areas during a simple finger-tapping task. This inconsistency of increased or decreased activation could be produced by different facts. For example, it is possible that the hypoactivation in perirolandic areas reported by Mostofosky (Mostofsky et al. 2006) was in fact a reflection of a smaller difference between resting and tapping condition due to an increased activity during rest in ADHD children. An additional explanation could be that the samples were differently exposed to MPH. MPH has been found to decrease perfusion in perirolandic areas (Lou et al. 1989; Schweitzer et al. 2003). In this sense, while more than half of the subjects in Mostofsky's (Mostofsky et al. 2007) study were medicated, nearly all the subjects from Zang's study (Zang et al. 2007) were medication naïve.

In summary, taken together, these studies point to abnormal functioning of the perirolandic cortex in ADHD, especially in combined and inattentive subtypes.

1.2. Striatum:

We observed reduced ventral and dorsal striatal volume in ADHD children. These reductions, mainly those of the ventral striatum, are especially prominent in H-I and combined subtypes, and nearly absent in inattentive children.

The ventral striatum is a key target of the limbic fronto-striatal circuits, and the dorsal striatum, especially caudate nucleus, constitutes the main striatal relay of the associative fronto-striatal circuit. Hence, whereas the ventral striatum is crucial for *hot* processes (such as motivation and reward), the dorsal striatum is essential for *cool* processes (such as working memory or other executive functions).

1.2.1. VENTRAL STRIATUM:

We found GM ventral striatal reductions in ADHD children. As in the case of OFC, these reductions were especially prominent in H-I children. When we focused our analysis on the region of ventral striatum, we observed bilateral reductions in the H-I children and right-sided reductions in the combined subtype. However, ventral striatum GM volume in inattentive children did not differ from controls.

Ventral striatum, especially accumbens nuclei, is the striatal relay of the limbic fronto-striatal circuit. This region receives its main cortical projections from OFC and ACC. The accumbens, together with amygdala and the hippocampus, is the target of the DA mesolimbic pathway originating in VTA. The effect of DA on the limbic circuits is related to the psychological feeling of *wanting* (Berridge 2007). This level of desiring something is necessary to direct the attentional resources and energize/motivate behavior in order to achieve the desired reward. Therefore, this region is especially important for the maintenance of responding under conditions of delayed reward (Sonuga-Barke 2005).

It has been consistently reported that ADHD children show impaired signaling during delayed rewards (Sonuga-Barke 2005). Supporting this finding, clinical observations indicate the necessity of more frequent delivery of rewards in ADHD children in order to shape their behavior. Moreover, as predicted by previous models

(Barkley et al. 2001), increased locomotor activity has been observed when delays become unavoidable (Antrop et al. 2002; Antrop et al. 2000). This latter evidence reinforces the hypothesis that hyperactivity symptoms may represent a compensatory response to a dysfunctional reward system (Castellanos and Tannock 2002).

There are no previous findings about ventral striatal abnormalities in ADHD children. However, it is important to note that none of the ROI studies in children has measured ventral striatum volume. Only one study in adult ADHD analyzed ventral striatum using a semi-automated ROI analysis (Seidman et al. 2006). Contrary to previous predictions, the authors found ventral striatal volume increase in ADHD subjects, although results were not significant ($p>0.01$). Two main factors could account for the discrepancies between Seidman's results and our results. On the one hand, there are important methodological differences. On the other hand, there are crucial sample differences, such as for example, the age of the subjects. Seidman's sample consisted of adult patients, and it could be possible that increased GM volume in ventral striatum was caused by brain plasticity mechanism directed to compensate for the initial deficits we found in child/adolescent patients.

Animal models of ADHD also support the implication of ventral striatum in the ADHD pathophysiology. In particular, it has been found that lesions in the core of AccN reduce the ability of rats to pursue large delayed rewards (Cardinal et al. 2001), Moreover, lesions in ventral striatum, have been related to H-I symptoms, but not inatention (Cardinal et al. 2001).

Finally our findings also endorse ADHD functional neuroimaging studies. It has been suggested that adolescents with ADHD show reduced DA release in ventral striatum during rest (Rosa-Neto et al. 2005). In the same line, Scheres et al (Scheres et al. 2007) observed that, as compared to controls, ADHD adolescents show reduced activation of accN during anticipation of monetary reward. Furthermore, H-I symptoms negatively correlate with ventral striatum activity. Interestingly, Shafritz, (Shafritz et al. 2004), during a task of divided attention, found that ADHD children recruited left ventral striatum in a lesser degree than control children, and that MPH increased the activation in this region.

1.2.2. DORSAL STRIATUM:

Dorsal striatum includes dorsal parts of caudate and putamen. Our VBM analysis did not reveal significant volume differences between ADHD and controls children in the dorsal parts of the striatum. However, when we focused the analysis on caudate nucleus using a manual ROI approach, we observed absolute volumetric differences in caudate volume. Specifically, we observed reduced right total caudate volume in ADHD children as compared to controls. According to our results, smaller caudate-body was responsible for this reduction. This diminution in the body of the right caudate nuclei was especially prominent in Combined and H-I subtypes.

Nearly all previous studies found significant reduction of caudate volume in ADHD (Castellanos et al. 2001; Castellanos et al. 1994; Castellanos et al. 1996b; Castellanos et al. 2002; Filipek et al. 1997; Hynd et al. 1993; Semrud-Clikeman et al. 2000), whereas only one study observed increased right caudate volume in ADHD children (Mataro et al. 1997). Reductions were either located on the left (Filipek et al. 1997; Hynd et al. 1993; Semrud-Clikeman et al. 2000) or on the right side (Castellanos et al. 1994; Castellanos et al. 1996b). Importantly, a longitudinal study observed that caudate volume reductions normalize with age (Castellanos et al. 2002).

Our findings of smaller right caudate volume are in agreement with those of Castellanos (Castellanos et al. 2001; Castellanos et al. 1994; Castellanos et al. 1996b; Castellanos et al. 2002), who also measured total caudate volume (head, and body). Our results, together with those of Castellanos, represent the only studies that used samples larger than 30 subjects per group for measuring caudate nuclei. Interestingly, the segmentation method we used also helps to clarify some of the inconsistencies in previous studies. For example, the findings of Semrud-Clikeman (Semrud-Clikeman et al. 2000) and Filipek (Filipek et al. 1997), of smaller left caudate specifically refer to the anterior parts of the nuclei, which mainly coincide with the head of the caudate according to our segmentation criterion. In our ADHD sample, the left caudate-head is slightly reduced, although not significantly, as compared to controls. Our findings are also coherent with those reported by Mataró (Mataro et al. 1997) who found increased right caudate-head in ADHD children. In this sense, we also observe a slight, yet not significant, increase in the right head of the caudate nuclei in ADHD children as compared to controls. Other studies found no differences in caudate volumes (Hill et al. 2003; Pueyo et al. 2000). However, these studies only quantified the head of the caudate (Pueyo et al. 2000) or measured sections that included part of the head and part of the body (Hill et al. 2003), therefore, blurring the differences.

Caudate nucleus is connected with PFC, inferior middle temporal gyrus, frontal eye fields, cerebellum and thalamus (Leh et al. 2007; Lehericy et al. 2004). This nucleus, especially the dorsal part, is the main striatal relay of the associative circuit; hence, it is supposed to play a key role in higher-order cognitive processes. In support of this, functional neuroimaging studies have linked caudate nucleus with EF. Activation in caudate nucleus has been reported during tasks that require strategy planning such as Tower of London (Beauchamp et al. 2003; Dagher et al. 1999; Rowe et al. 2001; van den Heuvel et al. 2003) and WCST (Monchi et al. 2001) (see annex 3). One of the key requirements for a correct planning process is the correct functioning of working memory. Caudate nucleus has been found to be active during tasks that require working memory (Manoach et al. 2003). Specifically, left caudate activity has been related to verbal working memory (Narayanan et al. 2005) whereas right caudate, especially right caudate-body, has been involved in spatial working memory (Geier et al. 2007).

As highlighted in previous sections, deficient performance in spatial working memory tasks is one of the key features of ADHD. Particularly, Nigg (Nigg 2005) observed that spatial working memory was the measure that discriminates more clearly ADHD from controls. Functional neuroimaging studies show deficits in right caudate activity in ADHD children during spatial working memory tasks (Vance et al. 2007a). In addition, abnormal caudate activity has been observed to "normalize" after behavioral (neurofeedback) training (Beauregard and Levesque 2006) and pharmacological (MPH administration) (Krause et al. 2000; Lou et al. 1984; Lou et al. 1989) treatment.

As previously said, the caudate volume reductions we found in ADHD children seem to be principally explained by smaller caudate-body. Head and body of caudate nucleus are anatomically and functionally different.

Caudate-head is strongly linked to DLPFC whereas caudate-body has denser connections with VLPFC as well as temporal and posterior areas (Alexander et al. 1986; Leh et al. 2007; Lehericy et al. 2004; Middleton and Strick 1996; Selemon and Goldman-Rakic 1985). Interestingly, it has been shown that caudate-body is also significantly connected with ACC. Specifically Rauch (Rauch et al. 2000) observed caudate-body reductions following anterior cingulotomy. Furthermore, reductions in caudate-body significantly correlate with the extension of the ACC lesion.

Obviously, there is also a functional distinction between the head and the body of caudate nucleus. Using fMRI tasks that required the deduction and application of a sequence rule, it has been observed that, while the caudate-head may support general reasoning and rule learning, caudate-body seems to be related to working memory and performance during rule application (Melrose et al. 2007; Seger and Cincotta 2005; Seger and Cincotta 2006). Using a task in which the subjects learn to categorize visual stimuli on the basis of outcome contingencies, the authors observed that activation of the head of caudate nuclei, in tandem with the ventral striatum, decreases once the categorization rule has been learned. This activation seems to be especially sensitive to feedback-reward occurring during the initial learning. In contrast, activity in caudate-body, together with putamen, increases as the stimulus-outcome contingencies were learned, and correlate positively with successful learning (Seger and Cincotta 2005). Furthermore, ACC, reported to be functionally abnormal in ADHD patients, has been consistently related to action monitoring (Kerns et al. 2004). Specifically ACC activations seem to be produced by violations in expectancy (Oliveira et al. 2007). The connectivity between ACC and caudate-body give additional support to the role of body of caudate nucleus in rule application.

Finally, we also found that, while the asymmetry pattern between caudate nuclei (as well as caudate subparts) is clearly differentiated in control children, volumetric differences between right and left sides of caudate regions do not significantly differ in the ADHD group. Moreover, when computing asymmetry indices, we observed that ADHD children lack the "normal" asymmetry pattern observed in controls. Specifically we found that the asymmetry pattern of caudate subparts in ADHD is the opposite to the one observed in normal controls. In our population of healthy children, left head of caudate is bigger than right head, whereas than left body is smaller than right body. In contrast, in our sample of ADHD children, there was a trend toward smaller left vs. right caudate-head and bigger left vs. right caudate-body.

Again, the differentiation between the head and the body of the caudate nuclei clarifies some of the previous inconsistencies regarding abnormal caudate asymmetry in ADHD population. Those studies that found the same caudate asymmetry pattern for ADHD as for control children only measured part of the head (Pineda et al. 2002) or quantified a measure that included half head and half body (Hill et al. 2003). The majority of findings point to a reverse asymmetry in ADHD. Specifically, bigger right than left caudate-head volume (Pueyo et al. 2000). In addition, it has been observed that those children that do not respond to MPH medication present a reversed asymmetry pattern of caudate nucleus, whereas children who do respond have symmetrical volumes (Filipek et al. 1997). The lack of normal asymmetry index among caudate subparts may be linked to early neurodevelopmental abnormalities (Castellanos et al. 1996b) and have been related to neuropsychological and clinical problems (Semrud-Clikeman et al. 2000). Additionally, it also could be that reversed asymmetry pattern reflects differential hemispheric specialization of the functions subserved by the caudate parts.

In conclusion, it is possible that our findings concerning reduced right caudate-body underlie the process of action monitoring and that the lack of normal asymmetry patterns between caudate parts would reflect differential hemispheric specialization of the functions subserved by these parts.

To summarize, our findings of dorsal and ventral striatal reductions provide additional support for the implication of both *cool* (working memory and action monitoring) and *hot* (reward and motivation) processes in ADHD, and, consequently,

highlight the relevance of the "dual route-model" theory (Sonuga-Barke 2003) for a comprehensive understanding of this disorder.

2. Reductions in Cerebellum:

The VBM study reveals diminished GM volume in left cerebellum in ADHD children. The reduction is located in parts of superior posterior lobule (lobule VI). When comparing control children with the subgroup of H-I children, the cerebellar reduction also affects left anterior (IV and V lobules) and bilateral superior-posterior (crus I bilaterally and lobule VI) cerebellar lobules.

The cerebellum, together with right caudate and frontal lobe, are the regions with larger GM reductions in ADHD according to a recent meta-analysis (Valera et al. 2007). Several studies in adult and childhood ADHD population have reported structural cerebellar deficits (Berquin et al. 1998; Castellanos et al. 2001; Castellanos et al. 1996b; Castellanos et al. 2002; Durston et al. 2004; Hill et al. 2003; Mostofsky et al. 1998). Indeed, in the largest study to date, the cerebellar reduction was the only finding that remained significant after adjusting for total cerebral volume (Castellanos et al. 2002). Moreover, cerebellar reduction correlated with attentional and clinical ratings (Castellanos et al. 2002), which gives additional support to the implication of this structure in ADHD pathophysiology. Likewise, the only DTI study to date also supports cerebellar abnormalities in ADHD (Ashtari et al. 2005). Specifically, ADHD children presented reduced FA values in right cerebellar peduncule, middle cerebellar peduncle and left cerebellum anterior lobule. Furthermore, FA cerebellar reductions were also found to correlate with ratings of inattention.

The cerebellum has been traditionally thought to be principally involved in motor control. However, an increasing number of studies demonstrate the implication of this structure in a wide range of cognitive and affective processes. Lesion studies, as well and functional neuroimaging studies, have shown that the cerebellum is involved in attentional shifting, emotional regulation, working memory and visuo-spatial and temporal information processing (Andreasen et al. 1999; Appollonio et al. 1993; Harrington et al. 2004; Ivry et al. 2002; Parvizi et al. 2001; Schmahmann 2004; Schmahmann and Caplan 2006; Schmahmann and Sherman 1998). It is important to note that problems in each of these domains have been observed in ADHD children (Castellanos and Tannock 2002; Nigg and Casey 2005). Moreover, it has been specifically signaled that patients with cerebellar lesions frequently mimic the behavior and cognition of ADHD patients (Bugalho et al. 2006). In support of this, various functional neuroimaging studies have reported that ADHD children show reduced metabolic activity in the cerebellum during rest (Bush et al. 2005; Gustafsson et al. 2000; Kim et al. 2002; Zang et al. 2007) as well as cerebellar hypoactivation during tasks of working memory (Valera et al. 2005) or inhibition control (Schulz et al. 2004).

Interestingly, a recent longitudinal study analyzed developmental aspects of the cerebellum in a group of ADHD and control children (Mackie et al. 2007). The study observed stable and progressive cerebellar alterations. On the one hand, stable reductions in ADHD children were observed for the superior cerebellar vermis. On the other hand, progressive reductions were found in inferior-posterior and anterior cerebellar lobules. Specifically, inferior-posterior hemispheres were found initially reduced only in a subgroup of ADHD patients classified as "worst outcome". In addition, in this group, the initial cerebellar reduction became progressively larger with age. Left anterior cerebellar lobules were found initially reduced in ADHD children regardless of the outcome, however, developmental graphs showed

significant increases in cerebellar volume with age only in the children with better outcome. To summarize, this study provides evidence for the existence of progressive cerebellar alterations in ADHD that develop differentially depending on the patients' outcome. As the authors suggest, these findings probably reflect the effects of clinical or pharmacological intervention. Regarding pharmacological intervention, it is known that the cerebellum has extensive reciprocal connections with brainstem areas in charge of NA and DA neurotransmission (Dempesy et al. 1983) both targets of MPH medication. Moreover, it has been reported that MPH increases cerebellar blood flow during rest, not only in ADHD adult (Schweitzer et al. 2003) and children (Anderson et al. 2002), but also in healthy controls (Volkow et al. 1997). Taken together, these results suggest that the cerebellum may play a key role in ADHD patients' response to MPH medication.

It has been proposed that the function of the cerebellum is to monitor and adjust input from the cerebral cortex ((Bower 1997; Parsons et al. 1997) cited by (Harrington et al. 2004)) acting as a scaling output that works to optimize sensori-motor and cognitive operation of the cerebral cortex (Mauk et al. 2000). This role is possible given the extensive connections between the cerebellum and the cerebral cortex. Frontal, parietal and ventro-medial temporal cortices are bidirectionally connected with the cerebellum via the feedfoward and feedback loops. The feedforward limb sends limbic, associative and sensorimotor information information from the cerebral cortex to the pons and, then, from the pons to the cerebellum, constituting what is known as the cortico-pontine-cerebellar circuit. The feedback limb consist of projections form the cerebellum to the thalamus and then to the cortex, forming the cerebello-thalamico-cortical projections. Feedforward and feedback limbs form a complete loop by which the cerebellum interacts with cerebral cortex (Schmahmann 2001), but these are not the only ones. Important connections have also been found between cerebellum and limbic structures such as septal nuclei, hippocampus and amygdala (Heath and Harper 1974; Schmahmann 2004). Therefore, it is possible that reduced GM volume in the cerebellum would produce deficits when adjusting and modeling fronto-striatal information, and, consequently, be related to cognitive, affective and sensorimotor dysfunctions frequently observed in ADHD patients.

3. Grey matter volume reductions in other areas:

In addition to fronto-striato-cerebellar alterations, our VBM also revealed ADHD GM volume reductions in parietal, temporal, occipital and cingulate areas. Specifically, we observed decreased GM volume in angular gyrus bilaterally, right inferior and superior parietal cortex, right occipital cortex, bilateral posterior cingulate cortex and left medial temporal lobe (including hippocampus, parahippocampal gyrus and fusiform gyrus). These areas can be grouped into two main domains: 1) reductions in areas related to posterior visuospatial attentional networks, that mainly included right parieto-occipital and posterior cingulate regions; and 2) reductions in medial temporal lobe structures, related to the limbic fronto-striatal circuits and known to be specially sensitive to be damage during early stages of brain development.

3.1. Reductions in posterior visuospatial attentional network:

3.1.1. PARIETO-OCCIPITAL:

As compared to control children, ADHD children show significant GM volume reductions in parietal cortex, principally in inferior right parietal areas, including angular gyrus. To a lesser degree, ADHD children also show GM volume reductions in right superior parietal cortex, right occipital cortex and left angular gyrus. The reductions in parieto-occipital regions are in agreement with ADHD structural and DTI (Ashtari et al. 2005) findings. In particular, regarding structural findings, Castellanos observed smaller parietal lobe volume in ADHD children (Castellanos et al. 2002). Sowell found increased cortical surface in inferior parts of parietal lobe, she also reported decreased surface in anterior parietal areas in ADHD children (Sowell et al. 2003). Moreover, Filipek (Filipek et al. 1997) also found significant volume reductions in ADHD children in their quantification of retrosplenial region, which included part of the parietal and occipital cortex. More recently, a VBM study observed right-sided fronto-striatal-parietal deficits in ADHD children (McAlonan et al. 2007) and another study reported a trend toward decreased thickness in the right parietal cortex (Shaw et al. 2006). Adult ADHD structural studies also support parietal alterations. Specifically, it has been found that adult patients with ADHD present a selective cortical thinning in right inferior parietal lobe, DLPF and anterior cingulate cortices (Makris et al. 2007). The occipital lobe has also found to be altered in ADHD children. However, whereas a cortical surface analysis reported increased occipital region (Sowell et al. 2003), other studies found occipital volume reductions (Castellanos et al. 2002; Durston et al. 2004).

The occipital cortex, in charge of basic visual processing, dorsally projects to the parietal cortex through what is known as the "where pathway". Spatial aspects of visual information (position, movement, etc) are processed in this pathway. Damage to the parietal cortex, principally in angular gyrus, produces impairment of visuospatial attention. Specifically patients with parietal lesions present hyperattention to the ipsilateral hemi-field, while neglecting the contralateral hemi-field. This symptom has been referred to as hemi-inattention and is one of the manifestations of the neglect or extinction syndrome (Heilman and Van Den Abell 1980). Based on lesion and neuropsychological studies, Posner described a posterior attentional network located in parietal lobe (Posner and Petersen 1990). Currently, functional neuroimaging studies strongly support the implication of the parietal lobe in attentional processes, especially with regard to visuospatial information. Activations in inferior and superior parietal regions have been reported in normal populations during selective (Clark et al. 2000; Kiehl et al. 2001; McCarthy et al. 1997; Menon et al. 1997; Stevens et al. 2000) and sustained (Coull et al. 1998; Lewin et al. 1996; Sunshine et al. 1997) attentional tasks. Specifically, right parieto-occipital junction, mainly the angular gyri and the inferior parts of the parietal cortex have been specially related to visuospatial attentional processes (Cabeza and Nyberg 2000; Corbetta and Shulman 2002; Duncan and Owen 2000).

Deficits in visuospatial attention could contribute to impairment in the control of attentional sources as well as influence the online manipulation of visuospatial information (Vance et al. 2007a). This may account for deficits in selective attention, sustained attention and spatial working memory, which are frequently observed in ADHD children (Nigg 2005). Moreover, it has been reported that children with ADHD show a relative inattention to the left side of the space, which offers additional support for disruptions in right inferior parietal regions (Carter et al. 1995). In the same line, functional neuroimaging studies report deficient activation in right parietal

regions in ADHD children during rest (Cho et al. 2007) and across a large number of tasks related to visuospatial attention (Booth et al. 2005; Silk et al. 2005; Tamm et al. 2006; Vance et al. 2007a; Vance et al. 2007b). Moreover, EEG studies found abnormal pattern of activation during visuospatial attentional tasks in posterior areas, probably involving parieto-occipital regions (Brandeis et al. 1998; Kemner et al. 1996; van Leeuwen et al. 1998).

As mentioned above, pharmacological studies on ADHD suggest the dysregulation of both DA and NA neurotransmittor systems (Pliszka 2005). In particular, dysfunctions in parietal attentional system are mainly modulated by noradrenergic transmission, whereas dysfunctions in frontal attentional systems are predominantly modulated by dopaminergic transmission (Pliszka et al. 1996). In addition, clinical improvement seems to be reflected also by changes in parietal regions. In this sense, a recent longitudinal study reported that ADHD reductions in right parietal cortex normalize during late adolescence, and that this normalization is only observed in the ADHD patients that present a better outcome (Shaw et al. 2006).

3.1.2. POSTERIOR CINGULATE:

We observed GM volume bilateral reductions in posterior cingulate cortex bilaterally in ADHD children. Diminished posterior cingulate regions have also been found in adolescence (Overmeyer et al. 2001) and adult ADHD patients (Makris et al. 2007). Posterior cingulate has been related to attentional processes and mental imaginery. It has been observed that posterior cingulate cortex is particularly important for attentional allocation of visuospatial attention (Mesulam et al. 2001; Rubia et al. 2007b; Small et al. 2003). Extensive connections between posterior cingulate and inferior parietal cortex have been reported in monkeys ((Mesulam et al. 1977; Morris et al. 2000) cited by (Small et al. 2003)). It has been proposed that posterior cingulate and inferior parietal cortex work interactively as components of a large network subserving spatial attention (Small et al. 2003). Various functional studies in ADHD children report reduced activation in posterior cingluate gyrus during attentional task (Rubia et al. 2007b) or other tasks that require a high load of sustained attention (Rubia et al. 1999). In addition, hypoactivity in posterior cingluate has been related to clinical severity in children (Rubia et al. 2007b) and adult ADHD patients (Ernst et al. 2003). Interestingly, posterior cingulate, together with MPFC and inferior parietal areas form an important brain network known as the default-mode network (Raichle et al. 2001; Raichle and Snyder 2007). This network is activated by default when the brain is in resting state. Attentional lapses have been related to failures to suppress the default network activity (Weissman et al. 2006). Recent studies have found altered default network in ADHD adults and adolescents mainly produced by dysfunctional communication between posterior cingulate and anterior parts of the network such as ACC and MPFC (Castellanos et al. 2007; Tian et al. 2006).

In short, reductions in parieto-occipital and posterior cingulate areas endorse behavioral, structural and functional data in ADHD patients. These regions have been extensively related to visuospatial imaginery (Cavanna 2007; Cavanna and Trimble 2006). Visuospatial processing is necessary for the correct performance in spatial working memory tasks as well as other tasks that use the location of visual stimulus to measure attention. Processes of visuospatial imaginery are, by default, swiched on in the brain during resting states. As was reported by Small (Small et al. 2003), correct connectivity between posterior cingulate and rostral areas -which are related to self-monitoring and motivational aspects- is required in order to correctly guide attentional

resources on the base of internal states and, therefore, prevent distractibility produced by external stimuli.

3.2. Medial Temporal lobe:

Our VBM analysis revealed reduced GM volume in the medial temporal lobe in ADHD children. Medial temporal lobe reductions are mainly located in left parahippocampal gyrus extending towards left hippocampus and fusiform area. Parahippocampal gyrus receives information from heteromodal association areas of the cortex and projects to the hippocampus through the perforant path. The hippocampus belongs to the limbic cortico-striatal circuit (Heimer 2003). Among others, it is connected to PFC and AccN (Heimer 2003). It has been related to novelty (Karreman and Moghaddam 1996), spatial processing (Kolachana et al. 1995) and memory encoding (Fernandez et al. 1998) (see also (Bast 2007) for a more comprehensive review). The fusiform area lies laterally to the parahippocampal gyrus. It is part of the ventral visual processing stream (also known as occipito-temporal or "what" pathway), which is related to higher order object recognition. This area is connected to the striate visual areas and projects to language-related regions. Whereas the right fusiform gyrus is specialized in face recognition (Kanwisher et al. 1997), the left fusiform gyrus has been related to lexico/semantical processing (Balsamo et al. 2006).

Animal studies suggest that middle temporal structures, specially the hippocampus, may play a relevant role in ADHD development (Levy 2004). However, few structural ADHD studies have reported abnormalities in the temporal lobe. Among them, Sowell found reduced cortical surface in anterior portions of temporal lobe whereas she observed increases in posterior portions (Sowell et al. 2003). Additionally, Castellanos (Castellanos et al. 2002) reported reduced temporal lobe volume in ADHD and observed a negative correlation between attentional problems and GM volume in frontal, temporal, caudate and cerebellar areas. More specifically, a recent surface analysis reported enlarged anterior hippocampal volume in ADHD patients (Plessen et al. 2006). Interestingly, enlarged hippocampal volume was related to fewer symptoms. The authors interpreted the increased hippocampal volume as a compensatory mechanism for a dysfunctional prefrontal-hippocampal connection. The study did not identify any significant contribution of age to the hippocampal enlargement; however, it is possible that our findings or reduced GM volume in this area may be reflecting a previous hypotrophic stage of the hippocampus.

Reduced activation in middle temporal cortex, mainly involving the hippocampus, has been observed in adult ADHD patients during decision-making (Ernst et al. 2003). In addition, hippocampal glucose metabolism has been found to be decreased in adolescent girls with ADHD during an auditory continuous performance task (Ernst et al. 1994a). In healthy populations, DA release in hippocampus has been associated with performance in working memory and attentional task (Aalto et al. 2005), both known to be deficient in ADHD patients. Furthermore, abnormal DA changes in the hippocampus have been identified after MPH administration not only in animal models of ADHD but also in adult ADHD patients (Volkow et al. 2007). Specifically, a PET study has reported lower than normal MPH induced DA changes in hippocampus and caudate in adults with ADHD as compared to controls (Volkow et al. 2007).

The significance of reduced medial temporal GM in ADHD children can be interpreted in different ways. It is possible that medial temporal lobe reductions may

reflect disruptions in the limbic fronto-striatal circuits. This would provide additional support for the theories based on dysfunctions in reward/motivational systems in ADHD. In this sense, it has been found that hippocampus strongly influences the ability of PFC to activate Acc N, and thus, modulates the limbic fronto-striatal circuit ((Grace 2001) cited by (Levy 2004)). Furthermore, it has been pointed out that hippocampus generates sustained activity in the AccN, which may maintain on line the reward aspects of a given task, and therefore motivate the subjects to stay focused for long periods (Levy 2004). An additional explanation to the reduction in medial temporal areas comes from the fact that these regions, together with basal ganglia, are especially sensitive to be damaged during early brain developmental. In this sense, it has been reported that fetuses exposed to toxins present structural abnormalities in fronto-striatal and hippocampal regions (Walhovd et al. 2007), and, interestingly, that exposure to toxics during gestation is related to ADHD development (Williams and Ross 2007). Moreover, these structures have been found altered in premature (Gimenez et al. 2004) and low birth weight children (Abernethy et al. 2002), both risk factors for ADHD development (Pinto-Martin et al. 2004). In addition, other psychiatric disorders that have been related to insults during gestation periods also show abnormalities in left medial temporal structures (e.g; Tourette (Ludolph et al. 2006), anxiety (Massana et al. 2003), dyslexia (Demonet et al. 2004) depression (Caetano et al. 2007), schizophrenia (McDonald et al. 2000), etc. It is relevant to note that there is a high prevalence of comorbidity or symptoms overlapping among these disorders and ADHD. Clinical histories in our patient group showed no diagnostic comorbidity or perinatal abnormalities. Hence, the possibility arises here that medial temporal lobe regions are especially sensitive to subtle neurodevelopmental damage. These abnormalties may be underlying symptoms that overlap the different pathologies, especially those related to dysfunctions in limbic fronto-striatal circuits.

4. Integrative model: The dual pathway model.

In summary, our findings confirm that ADHD brains are smaller, and refine this reduction by attributing it to GM reductions. We also confirm abnormalities in fronto-striatal-cerebellar circuits as well as in parietal, cingulate and temporal regions. Specifically, we observed reductions in inferior frontal cortex, dorsal striatum, inferior parietal cortex and posterior cingulate cortex; thus explaining inhibition problems, spatial working memory deficits and visuo-spatial attentional alterations. We also observed GM volume reductions in emotionally driven areas such as OFC, ventral striatum and middle temporal structures*;* thus accounting for dysfunctional delayed reward and motivational deficits. We have also found GM deficits in sensori-motor areas (specifically in perirolandic cortex and SMA) and cerebellum. On the one hand, deficits in sensori-motor areas probably reflect problems in fine motor coordination. However, the fact that these reductions were especially prominent in combined and inattentive subtypes raiser the possibility that they may be related to attentional dysfunctions. It could be hypothesized that deficits in these regions may produce a deficit when integrating and updating information from the external world and, in turn, produce a bias toward internal world focusing, thus, resulting in inattention. On the other hand, cerebellar reductions (which are extensively reported in ADHD literature) seem to be related to all cognitive, affective and sensorimotor deficits. The implication of the cerebellum in all these dysfunctions may arise from the bidirectional connections it has with the cortex as well as from its suggested role as a modulator of the flow of information between fronto-strital circuits. Finally, our findings are also the first to show caudate head and body differential abnormalities in

ADHD, which explain previous heterogeneous results, providing a new and reliable method to study striatal structures.

With the exception of perirolandic and medial temporal lobe regions, our findings were predominantly located in the right side, thus, supporting previous theories about larger right hemisphere deficits in ADHD.

All these findings can be subsumed and explained under the dual-pathway model (described in the introduction). This model proposes the implication of two distinct processes in ADHD, named *hot* (emotional) and *cool* (cognitive) processes. We found GM volume reductions in emotional and cognitive areas, therefore supporting the implication of both *hot* and *cool* functions, which agrees with most neuropsychological accounts of ADHD. As a simplification, functions such as attention, working memory, plannification or inhibition control would be ascribed to *cool* processes, whereas reward and motivational aspects would be more related to *hot* processes. However, these functions do not work independently. Haber found that information from limbic fronto-striatal circuits flows in a spiraling manner to the associative and, in turn, to the sensormotor circuit, hence, offering an anatomical explanation of how motivation can influence cognition, and, in turn, behavior (Haber 2003).

Interestingly, nearly all GM volume reductions, especially those related to emotional processes, are more prominent in H-I subtype. This is in agreement with Castellanos (Castellanos and Tannock 2002). Castellanos proposed that *hot* functions, thought to be subserved by limbic fronto-striatal circuits, are more prominent in H-I children, more preserved in combined subtypes, and relatively undisrupted in inattentive subtypes. Indeed, Scheres (Scheres et al. 2007) found a correlation between hyperactive/impulsive symptoms and hypoactivation in accN in ADHD children during a task of monetary reward anticipation.

To our knowledge this is the first time that a neuroanatomical study provides support for the existence of both cognitive and emotional dysfunctions in ADHD children. If these findings are replicated, they will constitute critical evidence for Sonuga-Barke's theory (Sonuga-Barke 2002; Sonuga-Barke 2003) about the dual route model.

CONCLUSIONS AND FUTURE DIRECTIONS:

The aim of the present dissertation was to refine and apply two complementary methods of structural neuroimaging, in order to identify the brain circuits altered in ADHD, as well as to relate them to different clinical ADHD subtypes and to known ADHD neuropsychological deficits. For that purpose, two structural MRI studies were presented and discussed: Study 1 was the first to use optimized VBM to compare ADHD children with a group of matched unrelated controls. Results show that ADHD children have reduced GM volume in areas ascribed to the emotional, cognitive and sensorimotor fronto-striatal circuits, as well as in the cerebellum, inferior parietal cortex, posterior cingulate cortex and medial temporal regions. Gray matter volume reductions in these regions fit with recent neurocognitive models that support the implication of both *cool* functions (subserved by associative fronto-striatal circuits among other brain areas) and *hot* functions (thought to be subserved specially by limbic fronto-striatal circuits) in ADHD. This is important because until date there were no structural neuroimaging studies that provide evidence of dysfunctional limbic fronto-striatal circuit in ADHD children, instead all previous anatomical studies were directed to analyze brain regions in charge of cognitive processes such as those ascribed to the associative fronto-striatal circuit. In addition, we also observed GM reductions in motor areas; thus, providing additional support for the clinical observation about deficits in coordination and motor control.

Study 2 provides a new, easy to apply, manual ROI method for segmenting and studying the caudate nucleus. This method allowed us to show that ADHD children have caudate volumetric abnormalities in comparison with controls, affecting the caudate head and body in a different way. Specifically, ADHD patients present a smaller right caudate body, right caudate head asymmetry and left caudate body asymmetry. Reduced right caudate-body volumes further support the implication of cognitive fronto-striatal circuit and the lack of normal asymmetry patterns suggests differential hemispheric specialization of caudate parts/functions.

Therefore, besides cognitive processes our results highlight the importance of focusing, experimentally and clinically, on emotional and sensorimotor processes.
In this sense, future neuroimaging studies could be directed at analyzing, anatomically and functionally, brain regions involved in emotional processes, especially ventral striatum. Transversal and longitudinal ROI analyses of ventral striatum are required in order to clarify discrepant results between child (we observed decreased volumes) and adult (which ventral striatal volume has been reported to be increased) ADHD studies.

APPENDICES

Appendix 1: Diagnostic criteria

A) Attention-Deficit Hyperactivity Disorder (DSM-IV-TR)

A. Either (1) or (2):
   1. six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
      a. often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
      b. often has difficulty sustaining attention in tasks or play activities
      c. often does not seem to listen when spoken to directly
      d. 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)
      e. often has difficulty organizing tasks and activities
      f. often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
      g. often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
      h. is often easily distracted by extraneous stimuli
      i. is often forgetful in daily activities
   2. six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

      Hyperactivity

      a. often fidgets with hands or feet or squirms in seat
      b. often leaves seat in classroom or in other situations in which remaining seated is expected
      c. often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
      d. often has difficulty playing or engaging in leisure activities quietly
      e. is often "on the go" or often acts as if "driven by a motor"
      f. often talks excessively

      Impulsivity

      g. often blurts out answers before questions have been completed
      h. often has difficulty awaiting turn
      i. often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Specify Type:

- **Attention-Deficit/Hyperactivity Disorder, Combined Type:** if both Criteria A1 and A2 are met for the past 6 months
- **Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type:** if Criterion A1 is met but Criterion A2 is not met for the past 6 months
- **Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type:** if Criterion A2 is met but Criterion A1 is not met for the past 6 months

Note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified.

Differential Diagnosis

Age-appropriate behaviors in active children; Mental Retardation; understimulating environments; oppositional behavior; another mental disorder; Pervasive Developmental Disorder; Psychotic Disorder; Other Substance-Related Disorder Not Otherwise Specified.

B) Diagnostic criteria for Hyperkinetic Disorder (ICD-10)

F90 Hyperkinetic Disorders

This group of disorders is characterized by: early onset; a combination of overactive, poorly modulated behaviour with marked inattention and lack of persistent task involvement; and pervasiveness over situations and persistence over time of these behavioural characteristics.

It is widely thought that constitutional abnormalities play a crucial role in the genesis of these disorders, but knowledge on specific etiology is lacking at present. In recent years the use of the diagnostic term "attention deficit disorder" for these syndromes has been promoted. It has not been used here because it implies a knowledge of psychological processes that is not yet available, and it suggests the inclusion of anxious, preoccupied, or "dreamy" apathetic children whose problems are probably different. However, it is clear that, from the point of view of behaviour, problems of inattention constitute a central feature of these hyperkinetic syndromes.

Hyperkinetic disorders always arise early in development (usually in the first 5 years of life). Their chief characteristics are lack of persistence in activities that require cognitive involvement, and a tendency to move from one activity to another without completing any one, together with disorganized, ill-regulated, and excessive activity. These problems usually persist through school years and even into adult life, but many affected individuals show a gradual improvement in activity and attention.

Several other abnormalities may be associated with these disorders. Hyperkinetic children are often reckless and impulsive, prone to accidents, and find themselves in disciplinary trouble because of unthinking (rather than deliberately defiant) breaches of rules. Their relationships with adults are often socially disinhibited, with a lack of normal caution and reserve; they are unpopular with other children and may become isolated. Cognitive impairment is common, and specific delays in motor and language development are disproportionately frequent.

Secondary complications include dissocial behaviour and low self-esteem. There is accordingly considerable overlap between hyperkinesis and other patterns of disruptive behaviour such as "unsocialized conduct disorder". Nevertheless, current evidence favours the separation of a group in which hyperkinesis is the main problem.

Hyperkinetic disorders are several times more frequent in boys than in girls. Associated reading difficulties (and/or other scholastic problems) are common.

Diagnostic Guidelines

The cardinal features are impaired attention and overactivity: both are necessary for the diagnosis and should be evident in more than one situation (e.g. home, classroom, clinic).

Impaired attention is manifested by prematurely breaking off from tasks and leaving activities unfinished. The children change frequently from one activity to another, seemingly losing interest in one task because they become diverted to another (although laboratory studies do not generally show an unusual degree of sensory or perceptual distractibility). These deficits in persistence and attention should be diagnosed only if they are excessive for the child's age and IQ.

Overactivity implies excessive restlessness, especially in situations requiring relative calm. It may, depending upon the situation, involve the child running and jumping around, getting up from a seat when he or she was supposed to remain seated, excessive talkativeness and noisiness, or fidgeting and wriggling. The standard for judgement should be that the activity is excessive in the context of what is expected in the situation and by comparison with other children of the same age and IQ. This behavioural feature is most evident in structured, organized situations that require a high degree of behavioural self-control.

The associated features are not sufficient for the diagnosis or even necessary, but help to sustain it. Disinhibition in social relationships, recklessness in situations involving some danger, and impulsive flouting of social rules (as shown by intruding on or interrupting others' activities, prematurely answering questions before they have been completed, or difficulty in waiting turns) are all characteristic of children with this disorder.

Learning disorders and motor clumsiness occur with undue frequency, and should be noted separately when present; they should not, however, be part of the actual diagnosis of hyperkinetic disorder.

Symptoms of conduct disorder are neither exclusion nor inclusion criteria for the main diagnosis, but their presence or absence constitutes the basis for the main subdivision of the disorder (see below).

The characteristic behaviour problems should be of early onset (before age 6 years) and long duration. However, before the age of school entry, hyperactivity is difficult to recognize because of the wide normal variation: only extreme levels should lead to a diagnosis in preschool children.

Diagnosis of hyperkinetic disorder can still be made in adult life. The grounds are the same, but attention and activity must be judged with reference to developmentally appropriate norms. When hyperkinesis was present in childhood, but has disappeared and been succeeded by another condition, such as dissocial personality disorder or substance abuse, the current condition rather than the earlier one is coded.

Differential Diagnosis :

Mixed disorders are common, and pervasive developmental disorders take precedence when they are present. The major problems in diagnosis lie in differentiation from conduct disorder: when its criteria are met, hyperkinetic disorder is diagnosed with priority over conduct disorder. However, milder degrees of overactivity and inattention are common in conduct disorder. When features of both hyperactivity and conduct disorder are present, and the hyperactivity is pervasive and severe, "hyperkinetic conduct disorder" (F90.1) should be the diagnosis.

A further problem stems from the fact that overactivity and inattention, of a rather different kind from that which is characteristic of a hyperkinetic disorder, may arise as a symptom of anxiety or depressive disorders. Thus, the restlessness that is typically part of an agitated depressive disorder should not lead to a diagnosis of a hyperkinetic disorder. Equally, the restlessness that is often part of severe anxiety should not lead to the diagnosis of a hyperkinetic disorder. If the criteria for one of the anxiety disorders are met, this should take precedence over hyperkinetic disorder unless there is evidence, apart from the restlessness associated with anxiety, for the additional presence of a hyperkinetic disorder. Similarly, if the criteria for a mood disorder are met, hyperkinetic disorder should not be diagnosed in addition simply because concentration is impaired and there is psychomotor agitation. The double diagnosis should be made only when symptoms that are not simply part of the mood disturbance clearly indicate the separate presence of a hyperkinetic disorder.

Acute onset of hyperactive behaviour in a child of school age is more probably due to some type of reactive disorder (psychogenic or organic), manic state, schizophrenia, or neurological disease (e.g. rheumatic fever).

Excludes: * anxiety disorders * mood (affective) disorders * pervasive developmental disorders * schizophrenia

F90.0 Disturbance Of Activity And Attention

There is continuing uncertainty over the most satisfactory subdivision of hyperkinetic disorders. However, follow-up studies show that the outcome in adolescence and adult life is much influenced by whether or not there is associated aggression, delinquency, or dissocial behaviour. Accordingly, the main subdivision is made according to the presence or absence of these associated features. The code used should be F90.0 when the overall criteria for hyperkinetic disorder (F90.-) are met but those for F91.- (conduct disorders) are not.

Includes: * attention deficit disorder or syndrome with hyperactivity * attention deficit hyperactivity disorder

Excludes: * hyperkinetic disorder associate with conduct disorder (F90.1)

Appendix 2: Neuropsychological task:

Continous Performance Test (CPT)

- Used to measure sustained attention.
- This test has different varieties. In general, the subjects are asked to press when a given cue appears on the screen (X, X followed by A…depending on the variant). The probability of this cue to appear is very low; only 25% of the trials are target cues. The task last around 15 minutes in which the subjects should maintain their attention. Sustained attention index is provided by a parameter known as d-prime, which combines button-press and misses in the presence of the cue.

Go-non Go

- Used as a measure of inhibition control, some versions are designed in order to measure reward and motivational processes.
- Similar to CTP, but in this case the cue that signals pressing is presented most of the time (around 80% of the trials are target cues) with the objective of creating a prepotency of responding. Pressing in the absence of the target cue is an index of poor inhibition control. Recently is has been developed a version in with correct performance is reinforced and/or punished, for example telling the child: "if you press the button when the letter A in on the screen you win 1$, but if you press when the letter B in on the screen, you loss 1 $". This new versions allows to have a index of reward and motivational aspects.

Stop Signal Task

- Used as a measure of inhibition control.
- Two stimuli are presented to the subject with the same probability of appearing. Subjects are asked to press a given key as fast as possible, which also creates a prepotency of responding. In nearly 25% of the trials a signal is presented to the subjects (e.g. a tone) indicating that they have to inhibit their response (Stoop task response suppression). Time distance between the stimuli and the tone varies, thus allowing to estimate the limits of inhibition control.

Stroop Task

- Used as a measure of inhibition control.
- The typical stroop test task consists of two condition, in both of the subjects are asked to name, as fast as possible, the ink color in which a string of letters are written. In the control conditions the string letters usually is a row of x (e.g. xxxx) written in different ink colors. The time employed during this control task gives us the index of "stroop naming speed". In the interference condition the string forms colour names (e.g. red written in green ink). Time-differences between the two conditions is an index of interference suppression mechanisms, in other words, inhibition of distractors. Given the difficulty of implementing this task in fMRI scanners because of its response system, a new version has been developed. This version is known as "Counting stroop task". During this task subject have to give a button-press response of the number of words that appear on the screen. In this case the interference condition is created by using word numbers (the word "two" written three times) and the control condition by using neutral words (the word "apple" written three times).

Posner Orienting Task:

- Presumably measures inhibition control.
- During this task the child has to fix the eyes in the center of the screen. The instruction is to press as quickly as possible when the target appear in the left or in the right side. Targets are preceded by warning cues that are either congruent or incongruent in side location. Increased reaction time during incongruent cues is though to be an index of poor inhibitory control.

Digit Span

- Used as a measure of verbal working memory.
- During this task subjects hear a series of digits they have to remember. There are different modalities with different degrees of working memory requirements. For example in some of the versions subjects hear a sequence of numbers and letters they have to return in a given order . For example, the subject hear "4kt1s5y3" and is asked to say the numbers followed by the letters ordered according to numerical and alphabetic criterion: "1345ksty").

Spatial Span:

- Used to measure spatial working memory.
- There are different variants. In one of them the experimenter touches a series of cubs in a given order and ask the subject to repeat the series.

Tower-like Tests:

- Used as a measure executive functions such as planification and spatial working memory.
- There are several varieties of this task (Tower of London, Tower of Hanoi the Stockings of Cambridge, etc). Their common element consists in that a series of discs or balls should be moved around on pegs to achieve a certain arrangement. This discs/balls cannot be moved freely, there are predetermined movements rules. Previsualization of the movements and the position of the discs/balls require spatial working memory processes.

Trail Making Test:

- Used to measure executive functions such as cognitive flexibility inferred by strategy shifting.
- During the first part of this task (Trail "A") subject have to traces a line that connects the letters following the alphabetic order (e.g. A-B-C-…). During the second part subject have to alternate letters with numbers in alphabetic and numeric order (e.g. A-1-B-2-C-3-…). Time difference between trail "B" and Trail "A" is an index of cognitive flexibility.

Wisconsin Card Sorting Test (WCST):

- Used to measure executive functions, specially cognitive flexibility inferred by strategy shifting.
- Subject has to sort a series of cards according to one of the three possible criteria (colour, number or shape). The correct sorting criterion is inferred by the feedback provided by the experimenter. Every ten cards the experimenter changes criteria without advising the child. Child must notice that the old sorting rule do not work and have to determine the new rule. The number of preservations sorting the cards according the old rule gives is indexed as preservation errors.

Choice Delay task

- Used as a measure of reward/motivational task, specifically time discounting.
- During this task subjects have to choose between large delayed rewards or smaller immediate rewards. This task gives us an index of the degree in which an objective reward value is discounted by the pass of time.

Decision Making Gambling Task

- Used as an indirect measure of reward/motivational aspects as well as other functions related to cool executive functions, such as cognitive flexibility inductive/deductive procedures.
- Subjects are presented with four decks of cards, each of them with different probabilities and amount of profits/loses. The trend toward selecting cards form one decks over the other give us an index about reward seeking against looses avoidance.

Appendix 3: Fronto-Striatal Circuits

Nearly the whole cerebral cortex projects to basal ganglia that in turn sends the information back to the cortex via thalamus. This neuronal pathway receives the name of cortico-striatal or cortico-striatal-thalamico-cortical (CSTC) circuit. When the connections are referred to frontal regions they are known as fronto-striatal circuits (FSC). These fronto-striatal connections have been traditionally related to movement control[19]. Nowadays it is known that these circuits play an important role, not only in motor processes, but also in cognitive and emotional ones.

During this section I will offer a general overview about structural and molecular aspects of basal ganglia as well as their intrinsic and cortical connections. Finally I will describe the functions of the different cortico-striatal circuits, emphasizing the recent discoveries about the flow of information among circuits.

A. The Basal Ganglia:

Basal ganglia (BG) are a set of subcortical interconnected nuclei that receive information from the cortex and send it to the brain stem or back to the cortex via thalamus (Alexander et al. 1986).

Main BG nuclei are: 1) the striatum; 2) the pallidum; 3) the substantia nigra; and 4) the subthalamic nucleus.

The striatum is the main doorway into the circuit. It receives excitatory (glutamatergic) projections from the whole cortical mantel as well as from the amygdala, hippocampus and dorsal raphe (Bolam et al. 2000). Although there is not a clear anatomical subdivision, the striatum is divided in two parts: 1) the dorsal striatum, which contains the caudate and the putamen and 2) the ventral striatum in which typically includes the accumbens nuclei (AccN). Other regions such as olfactory tubercle and Substantia Innominata have also been included as part of the ventral striatum (Heimer 2003).

The striatum projects to the output structures: 1) **the pallidum** (also referred as globus pallidus), which is divided into an external portion (GPe) and an internal portion (GPi); and 2) the **Substantia Nigra** that contains two parts: pars reticula (SNr) and pars compacta (SNpc). The former is closely related to GPi being both of them the main output structures of BG. SNpc contains dopaminergic nigrostriatal neurons that modulate the transmission within the circuit.

The **subthalamic nucleus** acts as an interface between GPe and GPi. It receives major input from the GPe (Sato et al. 2000) and projects, among other structures, to the GPi. These tonically active areas maintain an inhibitory tone over the thalamus and other projecting areas (Bevan and Wilson 1999). See also section "C. Basal Ganglia pathways".

The output structures (GPi and SNr) project: 1) back to the cortex via thalamus, thus restarting the circuit and redefining the information, and 2) to the motor pattern generators located downstream in brain stem or spinal cord (Alexander et al. 1986; Bolam et al. 2000).

[19] The idea of these circuits as being essentially involved in motor functions arises from postmortem studies in patients with motor disturbances (such as Parkinson or Huntington diseases) that revealed degeneration of BG.

B. Neurochemical aspects of Basal Ganglia:

Cortical projections to the striatum are glutamatergic and, therefore, excitatory. Projecting neurons from striatum, pallidus and SNr uses y-aminobutyric acid (GABA) as neurotransmitter and are, thus, inhibitory. Only efferent axons from the subthalamic nucleus use glutamate as neurotransmitter. Therefore, the vast majority of connections among these nuclei are inhibitory.

Under resting conditions GABAergic neurons of the striatum are inactive ((Wilson 2004) cited by (Yin and Knowlton 2006)). BG output neurons, despite being also GABAergic, have a high firing rate, thus, they are tonically inhibiting connected regions such as the ventral thalamus and the brainstem.

The neural communication of the circuit is highly modulated by DA, as proceeding from SNpc and ventral tegmental area (VTA)[20].

C. Basal Ganglia Pathways:

As mentioned, the cortical information enters the BG through the striatum. Information from the striatum then flows to the output structures (GPi and SNr) that in turn transmit the information back to the cortex and to the brainstem. There are, at least, two routes of communication between the striatum and the output structures. An additional third route, known as superdirect pathway, has also been proposed (see figure A cortico-striatal pathways).

The direct pathway connects the striatum directly to output structures such as the GPi and SNr. Specifically, when glutamate signals from the cortex reach the striatum, its GABA neurons directly inhibit the neurons of SNr and GPi which tonically inhibit the brainstem and the thalamico-cortical connections. The result of this disinhibition is the facilitation of the activity in the above mentioned target regions, i.e., the brainstem and the thalamico-cortical connections.

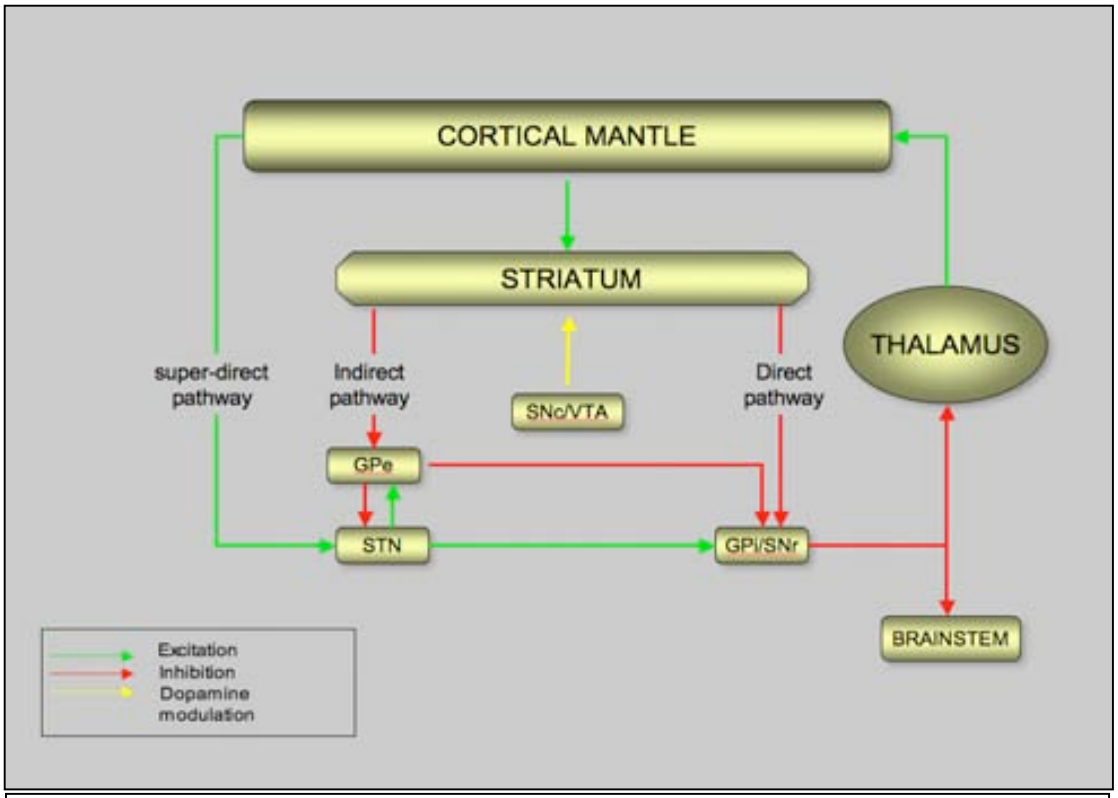
The indirect pathway also connects the stritatum with the GPi and SNr, but it does so in an indirect manner. Information from the indirect pathway is transmitted, through GABAergic neurons, from the striatum to the GPe. The GPe sends GABA projections to subthalamic nucleus that in turn send glutamatergic projections to GPi. Therefore activation of the indirect pathway results in GPi activation and, consequently, in brainstem and thalamico-cortical connection inhibition. In other words, activation of the indirect pathway (as opposed to activation of the direct one) results in maintaining the inhibition of thalamico-cortical activity as well as subcortical areas of the brainstem.

DA exerts a strong influence on the synaptic connections between these BG nuclei. Stimulation of D1 receptor by DA increases neuronal excitability, whereas D2 stimulation by DA decreases neuronal excitability. D1 receptors are mainly expressed in the striatal neurons that form the direct pathway, while D2 receptors are basically expressed in the ones that form the indirect pathway. In summary, DA facilitates corticostriatal flow of information by facilitation of the direct pathway and inhibition of the indirect pathway.

[20] To simplify, there are basically two DA pathways in the brain. The nigrostriatal pathway and the mesocorticolimbic pathway. The nigrostriatal one originates in the substantia nigra and innervates the dorsal caudate and putamen. The mesocorticolimbic originates in VTA and innervates prefrontal areas (such as OFC, ACC and DLPFC) as well as the ventral striatum, the amygdala and the hippocampus.

In addition to the above-mentioned pathways, the existence of an additional route that connects the cortex directly to the subthalamic nucleus through excitatory connections has been pointed out (Maurice et al. 1998). This has been named the superdirect route.

Figure A: Basal ganglia pathways:



Routes of communication between the cortex and the striatum. Gpe= Globus pallidus external portion; Gpi= Globus pallidus internal portion; STN= Subthalamic nuclei; SNr= Substantia Nigra pars reticula; SNc= Substantia Nigra pars compacta; VTA= Ventral Tegmental Area. (Yin and Knowlton 2006)(Adapted from Yin 2006)

D. Alexander circuits:

Based on animal studies Alexander proposed the existence of five parallel and segregated circuits: skeletomotor, oculo-motor, executive, motivational, and emotional (Alexander et al. 1986). The skeletomotor circuit begins and ends in the motor regions of the brain (motor, premotor and supplementary cortex); the occulo-motor in the frontal and supplementary eye fields; the executive in the dorsolateral prefrontal cortex; the motivational does so in the anterior cingulate cortex and the emotional, in the orbitofrontal cortex. Nowadays, instead of the above-mentioned loops, fronto-striatal connections are mainly divided into three functional circuits: the limbic, the associative and the sensorimotor circuit, dedicated to process emotional, cognitive and sensorimotor information respectively (see table A). In addition, it has been found that the circuits are not closed loops that work in an independent manner. Instead, these circuits work in a spiraling manner reentering parts of the cortex slightly displaced from the original point through spiraling thalamico-cortico-thalamic connections (Zahm 1999), and information flow from limbic to associative and to sensorimotor regions via striato-nigral-striatal connections (Haber 2003). See also figure B.

Table A: Cortico-striatal circuits

Circuit	Regions	Function
Sensorimotor	FROM: Motor: MC, PMC and SMA Sensory: S1, visual cortex… TO: Principally to posterior parts of putamen	Control of movement: Movement execution, sequence generation, motor learning Engage/Inhibit and updating motor behavior Habit formation
Associative/ Cognitive	FROM: DLPFC TO: Dorsal striatum, mainly head of caudate nucleus	Executive functions: - Working memory - Inhibition (maintaining attention) - Set-shifting - Strategy planning of goal-directed behavior - Monitoring actions - Procedural learning
Limbic/ emotional	FROM: OFC, (Hpc, Amyg) TO: Ventral striatum (AccN)	Key role in our emotional response during firsts unconditioned/conditioned stimuli. Motivate the plannification and performance of reward related behavior.

Subdivision of cortico-striatal connections into the three main circuits. It summarizes the main functions of the circuits and mention and the parts of the brain related to each of them. The label FROM refers to the regions in which the circuits are originated (mainly cortical structures) and the label TO refers to the parts of the striatum each circuit projects to. MC= motor cortex; PMC= premotor cortex; SMA= supplementary motor area; S1= primary somatosensory area; DLPFC= dorsolateral prefrontal cortex; OFC= orbitofrontal cortex; Hpc= hippocampus; Amyg= amygdala; AccN= accumbens nuclei.

E. Cortico-striatal loops:

Cortical and striatal regions are connected in a somatotopic manner. Ventral parts of the cortex projects to ventral parts of the striatum, and the same pattern can be observed in dorsal and lateral parts. These reciprocal connections are functionally and anatomically grouped into three main circuits: the sensorimotor, the associative and the limbic circuit.

The sensoriomotor circuit:
The sensoriomotor cortex (motor, premotor, SMA, and sensory regions) projects to the dorsolateral/sensoriomotor striatum (which in humans correspond to the posterior part of the putamen (Leh et al. 2007; Lehericy et al. 2004). The outputs of this circuit eventually reach the motor cortices and brainstem motor network. This circuit integrates sensory information and motor performance in order to update our action in a continuously changing environment (Dominey 1995).

Neural activity in the sensoriomotor striatum has been related to automatization of behavior and habit formation (Jog et al. 1999; Yin and Knowlton 2006). It has been reported that activity within the sensorimotor striatum does not necessary have to be goal-directed. Its activity is not directly modulated by reward expectancy; instead, it is more closely related to self-movement perception and environmental cues (Yin and Knowlton 2006). Neuroimaging studies, have reported activations of these cortical motor regions, not only during the performance of motor actions (Lehericy et al. 2005) but also when thinking of performing a specific action (Kosslyn et al. 2001; Lotze et al. 1999) or when seeing someone else performing an

action (Buccino et al. 2001). Additionally, recent fMRI studies also support the role of sensorimotor circuit in habit formation (Lehericy et al. 2005). Typical disorders related to dysfunctions in these circuits are Parkinson and Huntington Diseases.

The associative circuit:
Associative network is in charge of cognitive processes. In this circuit, information from DLPFC flows to different areas of the dorsal striatum, primarily the head of the caudate nucleus (Lehericy et al. 2004). This flow of information is believed to result in transformation of goals into actions.

This circuit has been associated with procedural learning, working memory, set-shifting and strategic planning. In rats, lesions in dorsomedial striatum (caudate in primates) or DLPFC results in impairment in goal-directed behavior, especially when tasks required delayed reward (Yin and Knowlton 2006). Therefore this network is capable of monitoring actions based on the anticipation of their consequences (Yin and Knowlton 2006). In monkeys, deactivation of the external pallidal regions that receives inputs from this network have been reported to produce attention-deficit-like behavior, with or without hyperactivity (Grabli et al. 2004). In humans, diffusion tensor imaging (DTI) studies have reported caudate connections with prefrontal cortex (PFC), inferior and middle temporal gyrus, frontal eye fields, cerebellum and thalamus. Anatomically, dorsolateral parts of PFC are linked to the head of caudate nucleus, while ventrolateral parts are connected to the body and the tail (Leh et al. 2007; Lehericy et al. 2004). Functionally, dorsolateral connections have been associated with attention monitoring and ventrolateral parts with spatial processing and memory retrieval (Kostopoulos and Petrides 2003). Activations of PFC in tandem with caudate nucleus have been observed during executive functions or other cognitive processes (Melrose et al. 2007).

The limbic circuit:
Heimer (Heimer 2003), remarked on the need to break the dichotomy between limbic system and basal ganglia, given that the structures typically considered as limbic not only have extensive projections to basal ganglia, but also share histological and embryologic characteristics with them.

Ventral parts of the striatum, mainly the AccN, receive prefrontal (from orbitofrontal cortex, medial prefrontal cortex and anterior cingulate cortex) as well as amygdalar and hippocampal projections (Heimer 2003; Lehericy et al. 2004). The AccN plays an essential role in positive and negative unconditioned responses associated with the survival of individuals (food) and species (reproductive or maternal behavior). Specifically, a region of the AccN known as the *shell* has been associated with unconditioned responses, while another part known as the *core* has been linked to conditioned responses. Initially it was thought that the role of DA in this limbic circuit was directly related to the feeling of pleasure (the *liking*). However, the effect of DA over the limbic system is currently associated with reward predicted cues, and how these cues motivate behavior. In other words, DA projections to the AccN seem to be involved in *wanting* (level of desire of something) instead of *liking* (the level of perceived hedonism), (Berridge 1996; Berridge 2000; Berridge 2007)[21].

[21] Berridge studied the differences between liking and wanting facial expression across the phylogenetic continuum (from humans to rats). His studies support the existence of two different pathways, one for *liking* and another for *wanting*. He also noted that microinjectins of GABA agonists in the nucleus AccN in rodents produce *wanting* but not *liking* facial expression.

Thus, the AccN seems to be a driving force in performing emotionally motivated actions, instead of being the center for pleasure experience, as initially thought. In human, DTI studies have also reported ventral striatum innervations from the OFC, parahipocampus and amygdala (Lehericy et al. 2004). Functional neuroimaging techniques have supported the implication of this circuit in emotionally relevant behavior (see (Knutson and Gibbs 2007) for an extensive review).

The anatomical connections between circuits allow the activity from one circuit to be propagated to the next circuit iteratively (Yin and Knowlton 2006). Consequently information form limbic circuit would interact with cognitive circuit that, in turn, would interact with the motor circuit. The flow of information within circuits also points to a hierarchical organization in which a given circuit would be considered as a particular level in a functional hierarchy. In this sense, it has been proposed that DA projections form VTA and SNpc allow that behavior control can shift from one circuit to another after practice. Specifically, it has been observed that learning new motor responses rely on the caudate and DLPFC, while well-learned responses rely on the putamen and motor cortex, thus suggesting that, with practice, goal-directed behavior becomes automatized (elicited by sensorial and motor cues) due to a shift in control from the associative network to the sensoriomotor one.

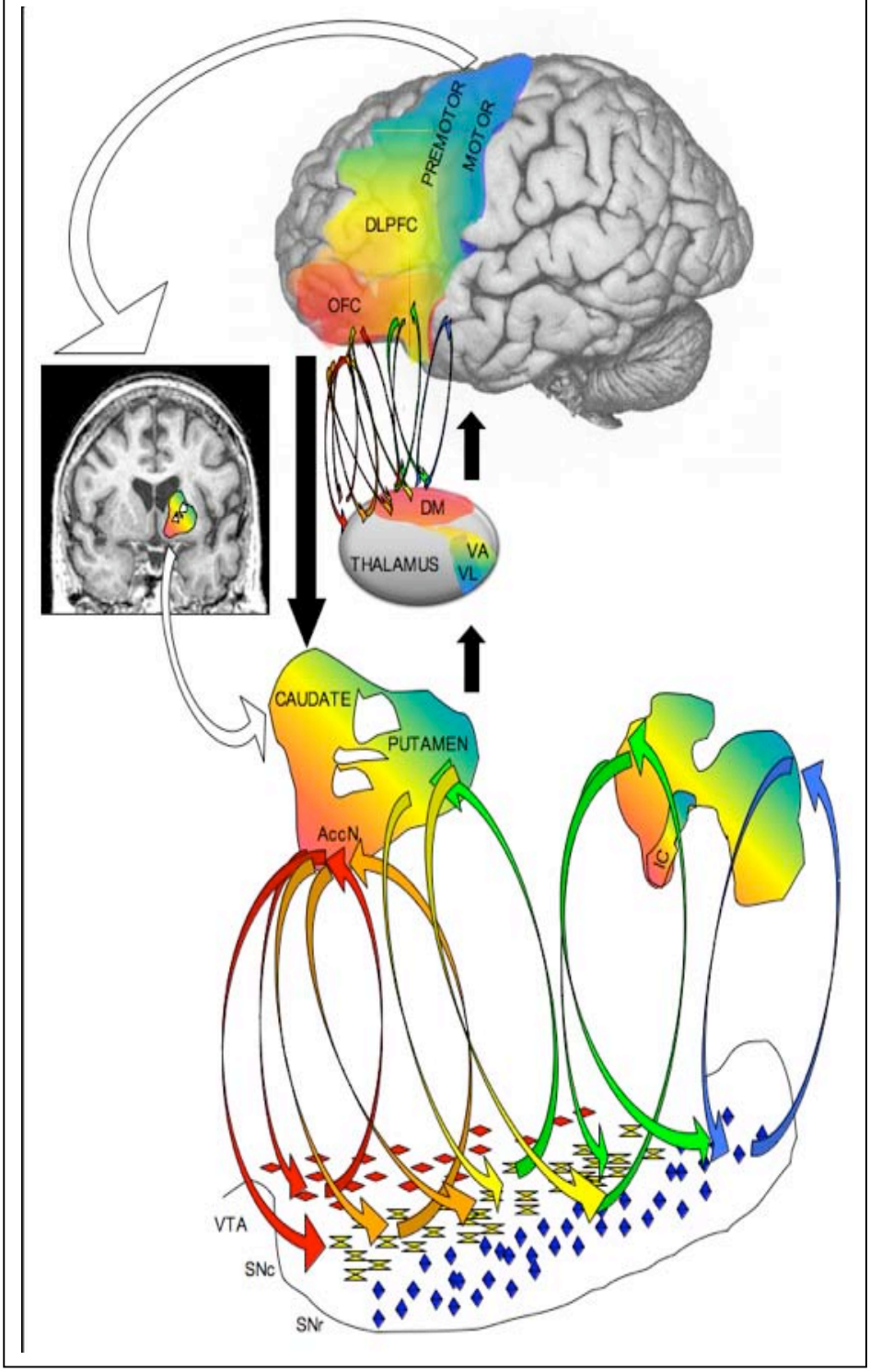
F. General function of cortico-striatal circuits:

As described in the previous paragraphs, BG are associated with movement, but also with the functions that drive movement, such as emotion and cognition. Basal ganglia operate as a gate for competing cortical signals using its complex system of inhibition-deshinibition pathways. The striatum receives cortical information from sensoriomotor, affective and cognitive fields. This information, which is highly variable *per se*, is indeed continuously changing over time. This suggests that the striatum may play an important role in the process of generating and taking into account alternative options (Bolam et al. 2000). The different pathways, and the specific effect of DA on them, make the striatum a capable structure for selecting, engaging and amplifying a response (direct route) while unselecting, suppressing or diminishing the others (indirect route) ((Mink and Thach 1993) cited by (Bolam et al. 2000)).

For example, the limbic circuit would estimate different rewards with different perceived values and would select one among the others. The representation and magnitude of the reward would be the driving force that engages cognitive/associative circuits in order to generate, choose and plan the actions necessary to achieve the reward. This planned action would then be transmitted to sensoriomotor circuits. Sensorimotor circuit will generate diverse sequence of movement and select the ones that will enable the subject to accomplish her goal.
Indeed, the information from the three circuits will be continuously shaped and updated on the bases of external and internal changes.
Thus cortico-striatal circuits would underlie the process by which the brain performs goal-directed behavior on the basis of external (sensorial) and internal (propioceptive, emotional and cognitive) information.

Berridge, K. C. Measuring hedonic impact in animals and infants: microstructure of affective taste reactivity patterns. *Neurosci Biobehav Rev* (2000) 24(2):173-98.

Figure B: Spiraling circuits



Ilustration of thalamico-cortical-thalamic and striato-nigro-striatal projections (based on Haber (Haber 2003) and Castellanos (Castellanos et al. 2006). Colors range from warm to cool gradient in the striatal thalamic and cortical regions. Warmer colors (red and orange) represent limbic functions, yellow and green correspond to associative functions, and cooler colors (blue and purple) symbolize regions with sensorimotor functions. The warmest parts of the striatum (specifically the shell of AccN) receive, among others, imput from amygdala and the hippocampus (not displayed) and OFC. DLPFC projects to caudate nuclei and central parts of the putamen. Motor and premotor areas mainly project to dorsolateral parts of putamen nuclei.
The shell of the AccN projects to the VTA and to the SNc. VTA close the loop sending projections back to the shell, but projections from SNc feed-foward to the core (orange arrow) therefore constituting the first spiral communication. Spiraling transmission continues via SNc and SNr projections in which SNS pathways projects each time to more dorsal regions. Spiraling connections has also been reported between the cortex and the thalamus (Zahm 1999)

DLPFC=Dorsolateral prefrontal cortex; OMPFC, orbital and medial prefrontal cortex; DM= Dorsomedial thalamic nuclei; VA= Ventral-anterior thalamic nuclei; VL= Ventral lateral thalamic nuclei, AccN= Accumbens nuclei; IC=internal capsule; VTA= ventral tegmental area; SNc=substantia nigra, pars compacta; SNr= substantia nigra, pars reticulata; S-N-S= striato-nigro-striatal

Appendix 4: Neuroimaging techniques:

Computed (Axial) Tomography (CT or CAT):
Computerized Tomography uses x-rays, a type of ionizing radiation. Brain image formation if based a set of algebraic equations to estimate how much x-ray is absorbed in different axes and then infer about the properties of the brain tissues.

Magnetic Resonance Imaging (MRI):
This is a non-invasive/ionizing technique. The scanner consists in a tube surrounded by an enormous circular magnet (usually of 1.5T to 3T). The magnet produces a strong magnetic field that aligns the molecules of our body (typically the protons of hydrogen). Then different radio waves are sent to the subjects. The way in which the molecules absorb and return these radio waves give us information about brain tissue, chemical properties and even brain function.

Structural Magnetic Resonance imaging (sMRI or MRI):
Different brain tissues absorb and return radio frequency in different ways. The way in which this radio frecuency is returned by each voxel give us information about tissue properties.

Diffusion Tensor Imaging (DTI):
This MRI techniques that allows to infer about WM organization and integrity. That technique is based on the magnitude and direction of water diffusion. Myelin sheath restricts the perpendicular diffusion of water, therefore making it diffuse parallel to fiber tracks. This directional dependence of water diffusion is known as anisotropy. The opposite of anisotropy is known as isotropy. In CSF water diffusion presents an isotropic distribution, which means that water moves freely without following any specific direction. Fractional anisotropy (FA) is a normalized measure of diffusion anisotropy. FA values oscillates between 0 and 1, 0 would reflect a completely isotropic distribution of water and 1 would indicated anisotropy of water diffusion therefore indicating good organization and integration of the fibers tracks.

Magnetic Resonance Spectroscopy (MRs or spectroscopy):
This MRI technique is based on the fact that different chemicals vibrate at different frequencies. This technique permits to obtain bioquimical information about brain metabolism, which, presumably, informs us about neuronal integrity and function. Although different atomic nuclei (1H, 31P, 13C, 19F, 7Li, 23Na) can be studied by spectroscopy, the most commonly used is the one based on hydrogen nuclei (1H). N-acetylaspartate (NAA), creatine and phosphocreatine (Cre), choline compounds (Cho), glutamate and glutamine (Glx), myo-inositol (mI) and gamma-amino-butyric acid (GABA) could be detected using this MRS (see appendix 5)

Functional Magnetic Resonance Imaging (fMRI):
fMRI allows us to infer about brain neuronal activity with a optimal compromise between spatial and temporal resolution. This technique is based on the fact that oxygen supply to activated neurons is overcompensated by increased perfusion, thus producing an increase in the ration of oxygenated blood (HbO) vs deoxygenated (Hb) blood in venous. Because HbO is diamagnetic while Hb is paramagnetic, changes in HbO/Hb produce changes in the magnetic properties of the voxels, therefore reflecting neuronal activity.

Electro Encephalography (EEG):
This tecnique measure the electrical acrtivity by placing electrodes in different parts of the scalp. Information proceding from this electrodes is a measure of post-synaptic potentials from the group of neurons covered by the electrodes. EEG has very good temporal resolution, but spatial resolution is less than for MRI techniques.

Magnetic Encephalography (MEG):
MEG measures electric brain activity on the base of something called SQUIDs (superconducting quantum interference devices). SQUIDS is a very sensitive device able to mesure extremely small magnetic fields, like the ones produced by brain activity. Similar to EEG concering spatial and temporal resolution, The advantatge with regard to EEG is that MEG is less affected by the conductivity profile of the brain, skull and scalp.

Single Photon Emission Computed Tomography (SPECT):
Functional neuroimaging technique requires inhalation or injection of radioactive tracers. More active regions will be need more blood, which contain is marked by the radiotracer. When radiotracers decay they emit single photon radiations, mainly gamma rays, that can be quantified by SPECT imaging thus offering an index of brain activity.

Positron Emission Tomography (PET):
As in the case of SPECT, this technique also uses radioactive material to infer about brain activity. As compared to SPECT this technique has superior spatial and temporal resolution, and it is more expensive. In the case of PET, radioactive isotopes emit positrons as they decay. These positrons are measured by PET camera.

AKNOWLEDGEMENTS:

Un par de días después de acabar la discusión fui a comer con un amigo; Juan Domingo Gispert. Caminando hacia el restaurante me hizo la pregunta que, a mis oídos, se había convertido en la canción del verano: "¿Qué?, ¿Cómo llevas la tesis?" por primera vez me alegré de oírla, sonreí, y dije "Bien, ya está casi acabada. Sólo me quedan las referencias y los agradecimientos". Cual fue mi sorpresa cuando mi amigo me respondió "¡Buff!, entonces te queda lo más difícil. Los agradecimientos son lo peor. Es lo que más me costó escribir. Piensa que, excepto el tribunal, la mayoría de personas a las que les des la tesis sólo se leerán los agradecimientos". En aquel momento no le di importancia, pero ahora, justo antes de escribirlos esa frase me persigue. Tengo tantas cosas que agradecer a tanta gente que no sé por quien empezar….Creo que la mejor manera sería hacer un pequeño recorrido que resuma mis experiencias a lo largo de estos cuatro años. Pero antes, quiero agradecer a ese amigo, Joan Domingo Gispert, por sus buenos consejos, por su ayuda práctica… y, sobretodo, por enseñarme a decir "curry sauce".

Aún recuerdo aquel acalorado día del mes Septiembre del 2003. Estaba completamente desorientada, yo diría que incluso desanimada. El verano había acabado y ya no tenía excusa para posponer más la decisión: "ya he acabado la carrera, y ahora ¿qué?: ¿quiero hacer un doctorado?, ¿quiero presentarme al P.I.R?, ¿quiero hacer un Máster?, ¿quiero estudiar otra carrera? o ¿quiero trabajar?". Con la cabeza centrifugando sobre todas estas opciones, entré en la facultad de medicina. La verdad es que no tenía ninguna intención clara, simplemente pasearme, a ver si encontraba alguna brújula que guiase un poco mi camino. Y la encontré. Fui a pedir información acerca de cursos de doctorado o másters al departamento de Psiquiatría y Medicina Legal. No había nadie en secretaria. Cuando estaba a punto de irme, la puerta del despacho contiguo se abrió: ¿Busques a algú? me dijo un hombre con acento peculiar. Más tarde descubriría que ese hombre se llamaba Adolf Tobeña. Recuerdo perfectamente la conversación: "A mi m'agrada la investigació, però també la clínica" le dije, "Perfecte. Estàs de sort, acaba de crear-se un curs de doctorat que és exactament el que busques". Su seguridad me convenció. No dudé ni un segundo de su consejo, el cual le agradezco enormemente.

El profesor Tobeña me habló del doctor Óscar Vilarroya. Nada más llegar a casa busqué más información acerca del doctorado y del tal doctor Óscar Vilarroya. Lo primero que pensé cuando vi la foto de Óscar y la innumerable cantidad de veces que su nombre aparecía en el google, fue: "¡buff! va a ser un prepotente de mucho cuidado". Nada más lejos de la realidad. Óscar no sólo es para mi un mentor, sino un buen amigo con el que he llegado a reír, llorar e incluso a discutir enfurecidamente sin que por eso se vieran afectados los cimientos de nuestra relación. Él ha sido capaz de transmitirme su inquietante interés por conocer el funcionamiento del cerebro humano. Tengo que agradecerle tantísimas cosas que ni con otro anexo podría enumerarlas. No sólo me ha abierto las puertas a un sin fin de oportunidades, sino que, lo más importante: me ha dejado caminar sola, pero siempre ha estado debajo para evitar que me cayese. Por eso, y por muchas otras cosas, Óscar se ha ganado a pulso mi confianza en él.

Gracias a Adolf y Óscar, pero sobre todo gracias a Esperanza González, me puse en contacto con el doctor Antoni Bulbena para pedirle que fuese mi director de tesis. Y allí estaba yo, delante del director del servicio de psiquiatría del Hospital del

Mar, un conocidísimo clínico y fantástico comunicador. Me sentía pequeña, incapaz de dar la talla o cumplir con sus expectativas. Hablar con él es un continuo ir y venir de ideas, tanto que en ocasiones me es difícil seguirlo. Al Doctor Bulbena le agradezco su apoyo a lo largo de estos años. Entre otros, nunca olvidaré la gran ayuda que me ofreció durante mi estancia en NY.

Así pues, con la ayuda de Óscar, Adolf y Antoni me embarqué en esta aventura que ha durado cuatro años y a lo largo de la cual he conocido personas a las que les debo mi más sincero agradecimiento.

Durante el primer año del doctorado, más que la Unitat de Recerca en Neurociencia Cognitiva, Óscar y yo formábamos el Dúo de Recerca en Neurociencia Cognitiva. Los inicios no fueron fáciles, pero estuvieron llenos de anécdotas divertidísimas e inolvidables. Virginia Trèmols, Mariana Rovira y Joan Carles Soliva, fueron los protagonistas de esta primera etapa tan llena de emociones y que ha resultado ser tan fructífera. La sinergia entre estas personas permitió que la Unitat de Recerca arrancara con fuerza. Virginia, trabajadora y siempre dispuesta a aportar su valiosísima visión clínica. Mariana, divertidísima además de gran experta en radiología y neuroanatomía cerebral, y Joan Carles, versado neurorradiólogo que además posee una gran visión práctica y un sofisticado sentido del humor. Gracias a ellos, y al resto de co-autores de los artículos presentados (Ana Bielsa, Josep Tomàs, Santiago Batlle, Carolina Raheb, Jordi Fauquet, etc…), ha sido posible realizar esta tesis.

En el segundo año entraron en escena dos personajes más, a los cuales les tengo un especial cariño: Joana Kyra Valencia y Jamil Zaki. Juntos trabajamos y aprendimos muchísimo, a la vez que pasamos momentos inolvidables, algunos incluso, podrían catalogarse de surrealistas como la invitación rogada al curso de SPM en Londres. A ambos les agradezco de corazón las vivencias compartidas tanto dentro como fuera del ambiente de trabajo

Gracias a Jamil Zaki, y a la amabilidad de mi más que admirado Doctor Andreas Olsson, tuve la oportunidad de pasar 5 meses en una de las mejores universidades del mundo: Columbia University. En ese escenario neoyorquino se desarrolló gran parte de mi tercer año de doctorado. Allí conocí a distinguidos personajes del mundo de la psicología y la neurociencia cognitiva (como al doctor Kevin Ochsner o al Doctor Tor Wager entre muchos otros). También tuve el placer de encontrarme con otros jóvenes investigadores que, seguro, en un futuro próximo llegarán tan lejos o más que sus brillantes maestros. Sumergida en ese cultivo mi interés por la investigación creció inmensurablemente. Esos 5 meses supusieron un importante punto de inflexión no sólo en mi carrera, sino también en mi crecimiento personal. Cómo ya dije en su momento "*it* changed my life in many ways".

Al volver de Nueva York…¡¡SORPRESA!!, la Unitat de Recerca en Neurociencia Cognitiva se había convertido en una verdadera Unitat. La flota había aumentado. Elseline, una espectacular e inteligentísima chica holandesa conquistó al equipo e "impuso" el Inglés como lengua oficial. A ella le agradezco especialmente que dedicase su tiempo a la lectura y revisión de la tesis. Alicia, siempre cariñosa, endulzaba las llegadas de todos. Marc, con su encantadora costumbre de visualizar y retratar a las personas como animales, se convirtió en mi compañero de asiento durante el tiempo en el que viajó con nosotros. Con él he compartido risas, cafés y tertulias. Para mi se ha convertido en un científico a admirar pero sobretodo en un amigo con el que contar. Le agradezco infinidad de cosas, entre ellas la ayuda y el consejo que me ofreció durante la redacción de la tesis así como sus acertados comentarios. Eva, una verdadera inyección de adrenalina al grupo por su alegría y vitalidad. Posee la capacidad de convertir en poesía textos de física cuántica. Para mí

ha sido, es y será mi confidente y amiga. Entre muchas otras cosas, he de agradecerle el tinte poético de estos agradecimientos.

No podría acabar este apartado sin mencionar a Joseph Hilferty y a Irina Pasqual. A Joe le doy las gracias por la corrección del inglés, por permitirme estropear sus canciones con mis coros, y, sobretodo, por ser un encanto de persona. A Irina quiero darle las gracias por su preciosa contraportada y, lo que es más importante, por llamarme *tieta Su.*

Por último, y como guinda de la sección, quiero agradecer a mi pareja por soportarme y caminar a mi lado durante todos estos años y por enseñarme a ser cada día mejor persona.

REFERENCE LIST:

Aalto, S., Bruck, A., Laine, M., et al. Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D2 receptor ligand [11C]FLB 457. *J Neurosci* (2005) 25(10):2471-7.

Abernethy, L. J., Palaniappan, M., and Cooke, R. W. Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight. *Arch Dis Child* (2002) 87(4):279-83.

Alexander, G. E., DeLong, M. R., and Strick, P. L. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* (1986) 9:357-81.

Altshuler, L. L., Bookheimer, S. Y., Townsend, J., et al. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. *Biol Psychiatry* (2005) 58(10):763-9.

Amen, D. G., and Carmichael, B. D. High-resolution brain SPECT imaging in ADHD. *Ann Clin Psychiatry* (1997) 9(2):81-6.

Anderson, C. M., Polcari, A., Lowen, S. B., et al. Effects of methylphenidate on functional magnetic resonance relaxometry of the cerebellar vermis in boys with ADHD. *Am J Psychiatry* (2002) 159(8):1322-8.

Anderson, V., Anderson, D., and Anderson, P. Comparing attentional skills in children with acquired and developmental central nervous system disorders. *J Int Neuropsychol Soc* (2006) 12(4):519-31.

Andreasen, N. C., O'Leary, D. S., Paradiso, S., et al. The cerebellum plays a role in conscious episodic memory retrieval. *Hum Brain Mapp* (1999) 8(4):226-34.

Antrop, I., Buysse, A., Roeyers, H., et al. Stimulation seeking and hyperactive behavior in children with ADHD: a re-analysis. *Percept Mot Skills* (2002) 95(1):71-90.

Antrop, I., Roeyers, H., Van Oost, P., et al. Stimulation seeking and hyperactivity in children with ADHD. Attention Deficit Hyperactivity Disorder. *J Child Psychol Psychiatry* (2000) 41(2):225-31.

Appollonio, I. M., Grafman, J., Schwartz, V., et al. Memory in patients with cerebellar degeneration. *Neurology* (1993) 43(8):1536-44.

Aron, A. R., Fletcher, P. C., Bullmore, E. T., et al. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nat Neurosci* (2003) 6(2):115-6.

Aron, A. R., and Poldrack, R. A. The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2005) 57(11):1285-92.

Artigas-Pallares, J. [Comorbidity in attention deficit hyperactivity disorder]. *Rev Neurol* (2003) 36 Suppl 1:S68-78.

Ashtari, M., Kumra, S., Bhaskar, S. L., et al. Attention-deficit/hyperactivity disorder: a preliminary diffusion tensor imaging study. *Biol Psychiatry* (2005) 57(5):448-55.

Aylward, E. H., Reiss, A. L., Reader, M. J., et al. Basal ganglia volumes in children with attention-deficit hyperactivity disorder. *J Child Neurol* (1996) 11(2):112-5.

Balsamo, L. M., Xu, B., and Gaillard, W. D. Language lateralization and the role of the fusiform gyrus in semantic processing in young children. *Neuroimage* (2006) 31(3):1306-14.

Banaschewski, T., Besmens, F., Zieger, H., et al. Evaluation of sensorimotor training in children with ADHD. *Percept Mot Skills* (2001) 92(1):137-49.

Barkley, R. A. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* (1997) 121(1):65-94.

Barkley, R. A., Edwards, G., Laneri, M., et al. Executive functioning, temporal discounting, and sense of time in adolescents with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). *J Abnorm Child Psychol* (2001) 29(6):541-56.

Bast, T. Toward an integrative perspective on hippocampal function: from the rapid encoding of experience to adaptive behavior. *Rev Neurosci* (2007) 18(3-4):253-81.

Baumgardner, T. L., Singer, H. S., Denckla, M. B., et al. Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. *Neurology* (1996) 47(2):477-82.

Beauchamp, M. H., Dagher, A., Aston, J. A., et al. Dynamic functional changes associated with cognitive skill learning of an adapted version of the Tower of London task. *Neuroimage* (2003) 20(3):1649-60.

Beauregard, M., and Levesque, J. Functional magnetic resonance imaging investigation of the effects of neurofeedback training on the neural bases of selective attention and response inhibition in children with attention-deficit/hyperactivity disorder. *Appl Psychophysiol Biofeedback* (2006) 31(1):3-20.

Bechara, A., Damasio, A. R., Damasio, H., et al. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* (1994) 50(1-3):7-15.

Becker, K., and Holtmann, M. Role of electroencephalography in attention-deficit hyperactivity disorder. *Expert Rev Neurother* (2006) 6(5):731-9.

Bellgrove, M. A., Mattingley, J. B., Hawi, Z., et al. Impaired temporal resolution of visual attention and dopamine beta hydroxylase genotype in attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2006) 60(10):1039-45.

Berger, A., Kofman, O., Livneh, U., et al. Multidisciplinary perspectives on attention and the development of self-regulation. *Prog Neurobiol* (2007) 82(5):256-86.

Berquin, P. C., Giedd, J. N., Jacobsen, L. K., et al. Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. *Neurology* (1998) 50(4):1087-93.

Berridge, K. C. Food reward: brain substrates of wanting and liking. *Neurosci Biobehav Rev* (1996) 20(1):1-25.

Berridge, K. C. Measuring hedonic impact in animals and infants: microstructure of affective taste reactivity patterns. *Neurosci Biobehav Rev* (2000) 24(2):173-98.

Berridge, K. C. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)* (2007) 191(3):391-431.

Berwid, O. G., Curko Kera, E. A., Marks, D. J., et al. Sustained attention and response inhibition in young children at risk for Attention Deficit/Hyperactivity Disorder. *J Child Psychol Psychiatry* (2005) 46(11):1219-29.

Bevan, M. D., and Wilson, C. J. Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. *J Neurosci* (1999) 19(17):7617-28.

Biederman, J., Faraone, S. V., Mick, E., et al. Clinical correlates of ADHD in females: findings from a large group of girls ascertained from pediatric and

psychiatric referral sources. *J Am Acad Child Adolesc Psychiatry* (1999) 38(8):966-75.

Biederman, J., Faraone, S. V., and Monuteaux, M. C. Differential effect of environmental adversity by gender: Rutter's index of adversity in a group of boys and girls with and without ADHD. *Am J Psychiatry* (2002a) 159(9):1556-62.

Biederman, J., Kwon, A., Aleardi, M., et al. Absence of gender effects on attention deficit hyperactivity disorder: findings in nonreferred subjects. *Am J Psychiatry* (2005) 162(6):1083-9.

Biederman, J., Mick, E., Faraone, S. V., et al. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. *Am J Psychiatry* (2002b) 159(1):36-42.

Bolam, J. P., Hanley, J. J., Booth, P. A., et al. Synaptic organisation of the basal ganglia. *J Anat* (2000) 196 (Pt 4):527-42.

Booth, J. R., Burman, D. D., Meyer, J. R., et al. Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *J Child Psychol Psychiatry* (2005) 46(1):94-111.

Bower, J. M. Control of sensory data acquisition. *Int Rev Neurobiol* (1997) 41:489-513.

Brandeis, D., van Leeuwen, T. H., Rubia, K., et al. Neuroelectric mapping reveals precursor of stop failures in children with attention deficits. *Behav Brain Res* (1998) 94(1):111-25.

Brookes, K. J., Chen, W., Xu, X., et al. Association of fatty acid desaturase genes with attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2006) 60(10):1053-61.

Buccino, G., Binkofski, F., Fink, G. R., et al. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur J Neurosci* (2001) 13(2):400-4.

Bugalho, P., Correa, B., and Viana-Baptista, M. Papel do cerebelo nas funçoes cognitivas e comportamentais: Bases científicas e moels de estudo. *Acta Med Port* (2006) 19:257-268.

Bush, G., Frazier, J. A., Rauch, S. L., et al. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biol Psychiatry* (1999) 45(12):1542-52.

Bush, G., Valera, E. M., and Seidman, L. J. Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. *Biol Psychiatry* (2005) 57(11):1273-84.

Cabeza, R., and Nyberg, L. Neural bases of learning and memory: functional neuroimaging evidence. *Curr Opin Neurol* (2000) 13(4):415-21.

Caetano, S. C., Fonseca, M., Hatch, J. P., et al. Medial temporal lobe abnormalities in pediatric unipolar depression. *Neurosci Lett* (2007) 427(3):142-147.

Cardinal, R. N., Pennicott, D. R., Sugathapala, C. L., et al. Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science* (2001) 292(5526):2499-501.

Carmona, S., Vilarroya, O., Bielsa, A., et al. Global and regional gray matter reductions in ADHD: a voxel-based morphometric study. *Neurosci Lett* (2005) 389(2):88-93.

Carter, C. S., Krener, P., Chaderjian, M., et al. Asymmetrical visual-spatial attentional performance in ADHD: evidence for a right hemispheric deficit. *Biol Psychiatry* (1995) 37(11):789-97.

Casey, B. J., Castellanos, F. X., Giedd, J. N., et al. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* (1997) 36(3):374-83.

Castellanos, F. X., and Acosta, M. T. [Syndrome of attention deficit with hyperactivity as the expression of an organic functional disorder]. *Rev Neurol* (2002) 35(1):1-11.

Castellanos, F. X., Giedd, J. N., Berquin, P. C., et al. Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* (2001) 58(3):289-95.

Castellanos, F. X., Giedd, J. N., Eckburg, P., et al. Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. *Am J Psychiatry* (1994) 151(12):1791-6.

Castellanos, F. X., Giedd, J. N., Hamburger, S. D., et al. Brain morphometry in Tourette's syndrome: the influence of comorbid attention-deficit/hyperactivity disorder. *Neurology* (1996a) 47(6):1581-3.

Castellanos, F. X., Giedd, J. N., Marsh, W. L., et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* (1996b) 53(7):607-16.

Castellanos, F. X., Lee, P. P., Sharp, W., et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *Jama* (2002) 288(14):1740-8.

Castellanos, F. X., Margulies, D. S., Kelly, C., et al. Cingulate-Precuneus Interactions: A New Locus of Dysfunction in Adult Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry* (2007).

Castellanos, F. X., Sonuga-Barke, E. J., Milham, M. P., et al. Characterizing cognition in ADHD: beyond executive dysfunction. *Trends Cogn Sci* (2006) 10(3):117-23.

Castellanos, F. X., and Tannock, R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci* (2002) 3(8):617-28.

Cavanna, A. E. The precuneuos and consciousness. *CNS Spectr* (2007) 12(7):545-52.

Cavanna, A. E., and Trimble, M. R. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* (2006) 129(Pt 3):564-83.

Chhabildas, N., Pennington, B. F., and Willcutt, E. G. A comparison of the neuropsychological profiles of the DSM-IV subtypes of ADHD. *J Abnorm Child Psychol* (2001) 29(6):529-40.

Cho, S. C., Hwang, J. W., Kim, B. N., et al. The relationship between regional cerebral blood flow and response to methylphenidate in children with attention-deficit hyperactivity disorder: comparison between non-responders to methylphenidate and responders. *J Psychiatr Res* (2007) 41(6):459-65.

Clark, L., Blackwell, A. D., Aron, A. R., et al. Association between response inhibition and working memory in adult ADHD: a link to right frontal cortex pathology? *Biol Psychiatry* (2007) 61(12):1395-401.

Clark, V. P., Fannon, S., Lai, S., et al. Responses to rare visual target and distractor stimuli using event-related fMRI. *J Neurophysiol* (2000) 83(5):3133-9.

Corbetta, M., and Shulman, G. L. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* (2002) 3(3):201-15.

Coull, J. T., Frackowiak, R. S., and Frith, C. D. Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task. *Neuropsychologia* (1998) 36(12):1325-34.

Courvoisie, H., Hooper, S. R., Fine, C., et al. Neurometabolic functioning and neuropsychological correlates in children with ADHD-H: preliminary findings. *J Neuropsychiatry Clin Neurosci* (2004) 16(1):63-9.

Dagher, A., Owen, A. M., Boecker, H., et al. Mapping the network for planning: a correlational PET activation study with the Tower of London task. *Brain* (1999) 122 (Pt 10):1973-87.

Daval, J. L., Pourie, G., Grojean, S., et al. Neonatal hypoxia triggers transient apoptosis followed by neurogenesis in the rat CA1 hippocampus. *Pediatr Res* (2004) 55(4):561-7.

Demonet, J. F., Taylor, M. J., and Chaix, Y. Developmental dyslexia. *Lancet* (2004) 363(9419):1451-60.

Dempesy, C. W., Tootle, D. M., Fontana, C. J., et al. Stimulation of the paleocerebellar cortex of the cat: increased rate of synthesis and release of catecholamines at limbic sites. *Biol Psychiatry* (1983) 18(1):127-32.

Denney, C. B., and Rapport, M. D. *Cognitive pharmacology of stimulants in children with ADHD.* , Vol. 30, 2001.

Dickstein, S. G., Bannon, K., Castellanos, F. X., et al. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *J Child Psychol Psychiatry* (2006) 47(10):1051-62.

Dominey, P. F. Complex sensory-motor sequence learning based on recurrent state representation and reinforcement learning. *Biol Cybern* (1995) 73(3):265-74.

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

Duncan, J., and Owen, A. M. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci* (2000) 23(10):475-83.

Durston, S. A review of the biological bases of ADHD: what have we learned from imaging studies? *Ment Retard Dev Disabil Res Rev* (2003) 9(3):184-95.

Durston, S., Fossella, J. A., Casey, B. J., et al. Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. *Mol Psychiatry* (2005) 10(7):678-85.

Durston, S., Hulshoff Pol, H. E., Schnack, H. G., et al. Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. *J Am Acad Child Adolesc Psychiatry* (2004) 43(3):332-40.

Durston, S., Tottenham, N. T., Thomas, K. M., et al. Differential patterns of striatal activation in young children with and without ADHD. *Biol Psychiatry* (2003) 53(10):871-8.

Ernst, M., Kimes, A. S., London, E. D., et al. Neural substrates of decision making in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* (2003) 160(6):1061-70.

Ernst, M., Liebenauer, L. L., King, A. C., et al. Reduced brain metabolism in hyperactive girls. *J Am Acad Child Adolesc Psychiatry* (1994a) 33(6):858-68.

Ernst, M., Zametkin, A. J., Matochik, J. A., et al. Effects of intravenous dextroamphetamine on brain metabolism in adults with attention-deficit hyperactivity disorder (ADHD). Preliminary findings. *Psychopharmacol Bull* (1994b) 30(2):219-25.

Ernst, M., Zametkin, A. J., Phillips, R. L., et al. Age-related changes in brain glucose metabolism in adults with attention-deficit/hyperactivity disorder and control subjects. *J Neuropsychiatry Clin Neurosci* (1998) 10(2):168-77.

Fanjiang, G., and Kleinman, R. E. Nutrition and performance in children. *Curr Opin Clin Nutr Metab Care* (2007) 10(3):342-7.

Faraone, S. V., Biederman, J., Spencer, T., et al. Diagnosing adult attention deficit hyperactivity disorder: are late onset and subthreshold diagnoses valid? *Am J Psychiatry* (2006) 163(10):1720-9; quiz 1859.

Faraone, S. V., Perlis, R. H., Doyle, A. E., et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2005) 57(11):1313-23.

Faraone, S. V., Sergeant, J., Gillberg, C., et al. The worldwide prevalence of ADHD: is it an American condition? *World Psychiatry* (2003) 2(2):104-113.

Fellows, L. K. The role of orbitofrontal cortex in decision making: A component process account. *Ann N Y Acad Sci* (2007).

Fernandez, G., Weyerts, H., Schrader-Bolsche, M., et al. Successful verbal encoding into episodic memory engages the posterior hippocampus: a parametrically analyzed functional magnetic resonance imaging study. *J Neurosci* (1998) 18(5):1841-7.

Filipek, P. A., Semrud-Clikeman, M., Steingard, R. J., et al. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology* (1997) 48(3):589-601.

Ge, Y., Law, M., and Grossman, R. I. Applications of diffusion tensor MR imaging in multiple sclerosis. *Ann N Y Acad Sci* (2005) 1064:202-19.

Geier, C. F., Garver, K. E., and Luna, B. Circuitry underlying temporally extended spatial working memory. *Neuroimage* (2007) 35(2):904-15.

Giedd, J. N., Blumenthal, J., Molloy, E., et al. Brain imaging of attention deficit/hyperactivity disorder. *Ann N Y Acad Sci* (2001) 931:33-49.

Giedd, J. N., Castellanos, F. X., Casey, B. J., et al. Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. *Am J Psychiatry* (1994) 151(5):665-9.

Gimenez, M., Junque, C., Narberhaus, A., et al. Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity. *Neuroimage* (2004) 23(3):869-77.

Good, C. D., Johnsrude, I., Ashburner, J., et al. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage* (2001a) 14(3):685-700.

Good, C. D., Johnsrude, I. S., Ashburner, J., et al. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* (2001b) 14(1 Pt 1):21-36.

Grabli, D., McCairn, K., Hirsch, E. C., et al. Behavioural disorders induced by external globus pallidus dysfunction in primates: I. Behavioural study. *Brain* (2004) 127(Pt 9):2039-54.

Grace, A. A. Psychostimulant actions on dopamine and limbic system function: relevance to the pathophysiology and treatment of ADHD. In M. V. Solanto, A. F. T. Arnsten, and F. X. Castellanos, eds., *Stimulant Drugs and ADH: Basic and Clinical Neuroscience*. Oxford University Press, 2001.

Green, L., Myerson, J., Lichtman, D., et al. Temporal discounting in choice between delayed rewards: the role of age and income. *Psychol Aging* (1996) 11(1):79-84.

Gunduz, H., Wu, H., Ashtari, M., et al. Basal ganglia volumes in first-episode schizophrenia and healthy comparison subjects. *Biol Psychiatry* (2002) 51(10):801-8.

Gustafsson, P., Thernlund, G., Ryding, E., et al. Associations between cerebral blood-flow measured by single photon emission computed tomography (SPECT), electro-encephalogram (EEG), behaviour symptoms, cognition and neurological soft signs in children with attention-deficit hyperactivity disorder (ADHD). *Acta Paediatr* (2000) 89(7):830-5.

Haber, S. N. The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat* (2003) 26(4):317-30.

Hale, T. S., Hariri, A. R., and McCracken, J. T. Attention-deficit/hyperactivity disorder: perspectives from neuroimaging. *Ment Retard Dev Disabil Res Rev* (2000) 6(3):214-9.

Harrington, D. L., Lee, R. R., Boyd, L. A., et al. Does the representation of time depend on the cerebellum? Effect of cerebellar stroke. *Brain* (2004) 127(Pt 3):561-74.

Hassani, O. K., Cromwell, H. C., and Schultz, W. Influence of expectation of different rewards on behavior-related neuronal activity in the striatum. *J Neurophysiol* (2001) 85(6):2477-89.

Heath, R. G., and Harper, J. W. Ascending projections of the cerebellar fastigial nucleus to the hippocampus, amygdala, and other temporal lobe sites: evoked potential and histological studies in monkeys and cats. *Exp Neurol* (1974) 45(2):268-87.

Heijtz, R. D., Kolb, B., and Forssberg, H. Motor inhibitory role of dopamine D1 receptors: Implications for ADHD. *Physiol Behav* (2007).

Heilman, K. M., and Van Den Abell, T. Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology* (1980) 30(3):327-30.

Heimer, L. A new anatomical framework for neuropsychiatric disorders and drug abuse. *Am J Psychiatry* (2003) 160(10):1726-39.

Hesslinger, B., Tebartz van Elst, L., Thiel, T., et al. Frontoorbital volume reductions in adult patients with attention deficit hyperactivity disorder. *Neurosci Lett* (2002) 328(3):319-21.

Hill, D. E., Yeo, R. A., Campbell, R. A., et al. Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology* (2003) 17(3):496-506.

Hoekzema, E. A., Tremols, V., Carmona, S., et al. The effect of cognitive training in ADHD children: inhibition and selective attention processes., unpublished.

Hynd, G. W., Hern, K. L., Novey, E. S., et al. Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. *J Child Neurol* (1993) 8(4):339-47.

Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R., et al. Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. *Arch Neurol* (1990) 47(8):919-26.

Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R., et al. Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. *J Learn Disabil* (1991) 24(3):141-6.

Itami, S., and Uno, H. Orbitofrontal cortex dysfunction in attention-deficit hyperactivity disorder revealed by reversal and extinction tasks. *Neuroreport* (2002) 13(18):2453-7.

Ivry, R. B., Spencer, R. M., Zelaznik, H. N., et al. The cerebellum and event timing. *Ann N Y Acad Sci* (2002) 978:302-17.

Jacobson, S. W., Carr, L. G., Croxford, J., et al. Protective effects of the alcohol dehydrogenase-ADH1B allele in children exposed to alcohol during pregnancy. *J Pediatr* (2006) 148(1):30-7.

Jin, Z., Zang, Y. F., Zeng, Y. W., et al. Striatal neuronal loss or dysfunction and choline rise in children with attention-deficit hyperactivity disorder: a 1H-magnetic resonance spectroscopy study. *Neurosci Lett* (2001) 315(1-2):45-8.

Jog, M. S., Kubota, Y., Connolly, C. I., et al. Building neural representations of habits. *Science* (1999) 286(5445):1745-9.

Junque, C., and Barroso, J. *Neuropsicologia*, 1995.

Kahn, R. S., Khoury, J., Nichols, W. C., et al. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *J Pediatr* (2003) 143(1):104-10.

Kanwisher, N., McDermott, J., and Chun, M. M. The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci* (1997) 17(11):4302-11.

Karreman, M., and Moghaddam, B. The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area. *J Neurochem* (1996) 66(2):589-98.

Kates, W. R., Frederikse, M., Mostofsky, S. H., et al. MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. *Psychiatry Res* (2002) 116(1-2):63-81.

Kelly, A. M., Scheres, A., Sonuga-Barke, E., et al. *Functional Neuroimaging of Reward and Motivational Pathways.* Wiley, 2007.

Kemner, C., Verbaten, M. N., Koelega, H. S., et al. Event-related brain potentials in children with attention-deficit and hyperactivity disorder: effects of stimulus deviancy and task relevance in the visual and auditory modality. *Biol Psychiatry* (1996) 40(6):522-34.

Kerns, J. G., Cohen, J. D., MacDonald, A. W., 3rd, et al. Anterior cingulate conflict monitoring and adjustments in control. *Science* (2004) 303(5660):1023-6.

Kiehl, K. A., Laurens, K. R., Duty, T. L., et al. Neural sources involved in auditory target detection and novelty processing: an event-related fMRI study. *Psychophysiology* (2001) 38(1):133-42.

Kieling, C., Roman, T., Doyle, A. E., et al. Association between DRD4 gene and performance of children with ADHD in a test of sustained attention. *Biol Psychiatry* (2006) 60(10):1163-5.

Kim, B. N., Lee, J. S., Cho, S. C., et al. Methylphenidate increased regional cerebral blood flow in subjects with attention deficit/hyperactivity disorder. *Yonsei Med J* (2001) 42(1):19-29.

Kim, B. N., Lee, J. S., Shin, M. S., et al. Regional cerebral perfusion abnormalities in attention deficit/hyperactivity disorder. Statistical parametric mapping analysis. *Eur Arch Psychiatry Clin Neurosci* (2002) 252(5):219-25.

Knutson, B., Adams, C. M., Fong, G. W., et al. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci* (2001a) 21(16):RC159.

Knutson, B., Fong, G. W., Adams, C. M., et al. Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* (2001b) 12(17):3683-7.

Knutson, B., and Gibbs, S. E. Linking nucleus accumbens dopamine and blood oxygenation. *Psychopharmacology (Berl)* (2007) 191(3):813-22.

Knutson, B., Westdorp, A., Kaiser, E., et al. FMRI visualization of brain activity during a monetary incentive delay task. *Neuroimage* (2000) 12(1):20-7.

Kolachana, B. S., Saunders, R. C., and Weinberger, D. R. Augmentation of prefrontal cortical monoaminergic activity inhibits dopamine release in the caudate nucleus: an in vivo neurochemical assessment in the rhesus monkey. *Neuroscience* (1995) 69(3):859-68.

Kosslyn, S. M., Ganis, G., and Thompson, W. L. Neural foundations of imagery. *Nat Rev Neurosci* (2001) 2(9):635-42.

Kostopoulos, P., and Petrides, M. The mid-ventrolateral prefrontal cortex: insights into its role in memory retrieval. *Eur J Neurosci* (2003) 17(7):1489-97.

Kotimaa, A. J., Moilanen, I., Taanila, A., et al. Maternal smoking and hyperactivity in 8-year-old children. *J Am Acad Child Adolesc Psychiatry* (2003) 42(7):826-33.

Krause, K. H., Dresel, S. H., Krause, J., et al. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. *Neurosci Lett* (2000) 285(2):107-10.

Kubicki, M., Park, H., Westin, C. F., et al. DTI and MTR abnormalities in schizophrenia: analysis of white matter integrity. *Neuroimage* (2005) 26(4):1109-18.

Kuntsi, J., Oosterlaan, J., and Stevenson, J. Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *J Child Psychol Psychiatry* (2001) 42(2):199-210.

Langleben, D. D., Austin, G., Krikorian, G., et al. Interhemispheric asymmetry of regional cerebral blood flow in prepubescent boys with attention deficit hyperactivity disorder. *Nucl Med Commun* (2001) 22(12):1333-40.

Langley, K., Holmans, P. A., van den Bree, M. B., et al. Effects of low birth weight, maternal smoking in pregnancy and social class on the phenotypic manifestation of Attention Deficit Hyperactivity Disorder and associated antisocial behaviour: investigation in a clinical sample. *BMC Psychiatry* (2007) 7:26.

Lee, J. S., Kim, B. N., Kang, E., et al. Regional cerebral blood flow in children with attention deficit hyperactivity disorder: comparison before and after methylphenidate treatment. *Hum Brain Mapp* (2005) 24(3):157-64.

Leh, S. E., Ptito, A., Chakravarty, M. M., et al. Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study. *Neurosci Lett* (2007) 419(2):113-8.

Lehericy, S., Benali, H., Van de Moortele, P. F., et al. Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. *Proc Natl Acad Sci U S A* (2005) 102(35):12566-71.

Lehericy, S., Ducros, M., Van de Moortele, P. F., et al. Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. *Ann Neurol* (2004) 55(4):522-9.

Levy, F. Synaptic gating and ADHD: a biological theory of comorbidity of ADHD and anxiety. *Neuropsychopharmacology* (2004) 29(9):1589-96.

Lewin, J. S., Friedman, L., Wu, D., et al. Cortical localization of human sustained attention: detection with functional MR using a visual vigilance paradigm. *J Comput Assist Tomogr* (1996) 20(5):695-701.

Lotze, M., Montoya, P., Erb, M., et al. Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study. *J Cogn Neurosci* (1999) 11(5):491-501.

Lou, H. C., Andresen, J., Steinberg, B., et al. The striatum in a putative cerebral network activated by verbal awareness in normals and in ADHD children. *Eur J Neurol* (1998) 5(1):67-74.

Lou, H. C., Henriksen, L., and Bruhn, P. Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. *Arch Neurol* (1984) 41(8):825-9.

Lou, H. C., Henriksen, L., Bruhn, P., et al. Striatal dysfunction in attention deficit and hyperkinetic disorder. *Arch Neurol* (1989) 46(1):48-52.

Lowe, N., Kirley, A., Hawi, Z., et al. Joint analysis of the DRD5 marker concludes association with attention-deficit/hyperactivity disorder confined to the predominantly inattentive and combined subtypes. *Am J Hum Genet* (2004) 74(2):348-56.

Ludolph, A. G., Juengling, F. D., Libal, G., et al. Grey-matter abnormalities in boys with Tourette syndrome: magnetic resonance imaging study using optimised voxel-based morphometry. *Br J Psychiatry* (2006) 188:484-5.

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

Luthman, J., Bassen, M., Fredriksson, A., et al. Functional changes induced by neonatal cerebral 6-hydroxydopamine treatment: effects of dose levels on behavioral parameters. *Behav Brain Res* (1997) 82(2):213-21.

Lyoo, I. K., Noam, G. G., Lee, C. K., et al. The corpus callosum and lateral ventricles in children with attention-deficit hyperactivity disorder: a brain magnetic resonance imaging study. *Biol Psychiatry* (1996) 40(10):1060-3.

Mackie, S., Shaw, P., Lenroot, R., et al. Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. *Am J Psychiatry* (2007) 164(4):647-55.

MacMaster, F. P., Carrey, N., Sparkes, S., et al. Proton spectroscopy in medication-free pediatric attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2003) 53(2):184-7.

Makris, N., Biederman, J., Valera, E. M., et al. Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cereb Cortex* (2007) 17(6):1364-75.

Manoach, D. S., Greve, D. N., Lindgren, K. A., et al. Identifying regional activity associated with temporally separated components of working memory using event-related functional MRI. *Neuroimage* (2003) 20(3):1670-84.

Martinussen, R., Hayden, J., Hogg-Johnson, S., et al. A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* (2005) 44(4):377-84.

Massana, G., Serra-Grabulosa, J. M., Salgado-Pineda, P., et al. Parahippocampal gray matter density in panic disorder: a voxel-based morphometric study. *Am J Psychiatry* (2003) 160(3):566-8.

Masuo, Y., Ishido, M., Morita, M., et al. Effects of neonatal 6-hydroxydopamine lesion on the gene expression profile in young adult rats. *Neurosci Lett* (2002) 335(2):124-8.

Masuo, Y., Morita, M., Oka, S., et al. Motor hyperactivity caused by a deficit in dopaminergic neurons and the effects of endocrine disruptors: a study inspired by the physiological roles of PACAP in the brain. *Regul Pept* (2004) 123(1-3):225-34.

Mataro, M., Garcia-Sanchez, C., Junque, C., et al. Magnetic resonance imaging measurement of the caudate nucleus in adolescents with attention-deficit hyperactivity disorder and its relationship with neuropsychological and behavioral measures. *Arch Neurol* (1997) 54(8):963-8.

Matochik, J. A., Liebenauer, L. L., King, A. C., et al. Cerebral glucose metabolism in adults with attention deficit hyperactivity disorder after chronic stimulant treatment. *Am J Psychiatry* (1994) 151(5):658-64.

Matochik, J. A., Nordahl, T. E., Gross, M., et al. Effects of acute stimulant medication on cerebral metabolism in adults with hyperactivity. *Neuropsychopharmacology* (1993) 8(4):377-86.

Mauk, M. D., Medina, J. F., Nores, W. L., et al. Cerebellar function: coordination, learning or timing? *Curr Biol* (2000) 10(14):R522-5.

Maurice, N., Deniau, J. M., Glowinski, J., et al. Relationships between the prefrontal cortex and the basal ganglia in the rat: physiology of the corticosubthalamic circuits. *J Neurosci* (1998) 18(22):9539-46.

McAlonan, G. M., Cheung, V., Cheung, C., et al. Mapping brain structure in attention deficit-hyperactivity disorder: a voxel-based MRI study of regional grey and white matter volume. *Psychiatry Res* (2007) 154(2):171-80.

McCarthy, G., Luby, M., Gore, J., et al. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *J Neurophysiol* (1997) 77(3):1630-4.

McClure, S. M., Laibson, D. I., Loewenstein, G., et al. Separate neural systems value immediate and delayed monetary rewards. *Science* (2004) 306(5695):503-7.

McDonald, B., Highley, J. R., Walker, M. A., et al. Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: A postmortem study. *Am J Psychiatry* (2000) 157(1):40-7.

Melrose, R. J., Poulin, R. M., and Stern, C. E. An fMRI investigation of the role of the basal ganglia in reasoning. *Brain Res* (2007) 1142:146-58.

Menon, V., Ford, J. M., Lim, K. O., et al. Combined event-related fMRI and EEG evidence for temporal-parietal cortex activation during target detection. *Neuroreport* (1997) 8(14):3029-37.

Mesulam, M. M., Nobre, A. C., Kim, Y. H., et al. Heterogeneity of cingulate contributions to spatial attention. *Neuroimage* (2001) 13(6 Pt 1):1065-72.

Mesulam, M. M., Van Hoesen, G. W., Pandya, D. N., et al. Limbic and sensory connections of the inferior parietal lobule (area PG) in the rhesus monkey: a study with a new method for horseradish peroxidase histochemistry. *Brain Res* (1977) 136(3):393-414.

Michelson, D., Faries, D., Wernicke, J., et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. *Pediatrics* (2001) 108(5):E83.

Mick, E., Biederman, J., Faraone, S. V., et al. Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. *J Am Acad Child Adolesc Psychiatry* (2002) 41(4):378-85.

Middleton, F. A., and Strick, P. L. The temporal lobe is a target of output from the basal ganglia. *Proc Natl Acad Sci U S A* (1996) 93(16):8683-7.

Mill, J., Caspi, A., Williams, B. S., et al. 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. *Arch Gen Psychiatry* (2006) 63(4):462-9.

Mink, J. W., and Thach, W. T. Basal ganglia intrisic circuits and their role in behavior. *Curr Opin Neurobiol* (1993) 3(6):950-7.

Mobini, S., Body, S., Ho, M. Y., et al. Effects of lesions of the orbitofrontal cortex on sensitivity to delayed and probabilistic reinforcement. *Psychopharmacology (Berl)* (2002) 160(3):290-8.

Monchi, O., Petrides, M., Petre, V., et al. Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *J Neurosci* (2001) 21(19):7733-41.

Moore, C. M., Biederman, J., Wozniak, J., et al. Differences in brain chemistry in children and adolescents with attention deficit hyperactivity disorder with and without comorbid bipolar disorder: a proton magnetic resonance spectroscopy study. *Am J Psychiatry* (2006) 163(2):316-8.

Morris, R., Paxinos, G., and Petrides, M. Architectonic analysis of the human retrosplenial cortex. *J Comp Neurol* (2000) 421(1):14-28.

Mostofsky, S. H., Burgess, M. P., and Gidley Larson, J. C. Increased motor cortex white matter volume predicts motor impairment in autism. *Brain* (2007) 130(Pt 8):2117-22.

Mostofsky, S. H., Cooper, K. L., Kates, W. R., et al. Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2002) 52(8):785-94.

Mostofsky, S. H., Reiss, A. L., Lockhart, P., et al. Evaluation of cerebellar size in attention-deficit hyperactivity disorder. *J Child Neurol* (1998) 13(9):434-9.

Mostofsky, S. H., Rimrodt, S. L., Schafer, J. G., et al. Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study of simple sequential finger tapping. *Biol Psychiatry* (2006) 59(1):48-56.

Mulas, F., Capilla, A., Fernandez, S., et al. Shifting-related brain magnetic activity in attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2006) 59(4):373-9.

Narayanan, N. S., Prabhakaran, V., Bunge, S. A., et al. The role of the prefrontal cortex in the maintenance of verbal working memory: an event-related FMRI analysis. *Neuropsychology* (2005) 19(2):223-32.

Nasrallah, H. A., Loney, J., Olson, S. C., et al. Cortical atrophy in young adults with a history of hyperactivity in childhood. *Psychiatry Res* (1986) 17(3):241-6.

Nigg, J. T. Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: the state of the field and salient challenges for the coming decade. *Biol Psychiatry* (2005) 57(11):1424-35.

Nigg, J. T., and Casey, B. J. An integrative theory of attention-deficit/ hyperactivity disorder based on the cognitive and affective neurosciences. *Dev Psychopathol* (2005) 17(3):785-806.

Oliveira, F. T., McDonald, J. J., and Goodman, D. Performance Monitoring in the Anterior Cingulate is Not All Error Related: Expectancy Deviation and the Representation of Action-Outcome Associations. *J Cogn Neurosci* (2007).

Overmeyer, S., Bullmore, E. T., Suckling, J., et al. Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network. *Psychol Med* (2001) 31(8):1425-35.

Overmeyer, S., and Taylor, E. Neuroimaging in hyperkinetic children and adults: an overview. *Pediatr Rehabil* (2000) 4(2):57-70.

Parsons, L. M., Bower, J. M., Gao, J. H., et al. Lateral cerebellar hemispheres actively support sensory acquisition and discrimination rather than motor control. *Learn Mem* (1997) 4(1):49-62.

Parvizi, J., Anderson, S. W., Martin, C. O., et al. Pathological laughter and crying: a link to the cerebellum. *Brain* (2001) 124(Pt 9):1708-19.

Perlman, J. M. Neurobehavioral deficits in premature graduates of intensive care--potential medical and neonatal environmental risk factors. *Pediatrics* (2001) 108(6):1339-48.

Pfefferbaum, A., Sullivan, E., Rosenbloom, M., et al. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Arch Gen Psychiatry* (1998) 55(10):905-12.

Pineda, D., Ardila, A., Rosselli, M., et al. Prevalence of attention-deficit/hyperactivity disorder symptoms in 4- to 17-year-old children in the general population. *J Abnorm Child Psychol* (1999) 27(6):455-62.

Pineda, D. A., Restrepo, M. A., Sarmiento, R. J., et al. Statistical analyses of structural magnetic resonance imaging of the head of the caudate nucleus in Colombian children with attention-deficit hyperactivity disorder. *J Child Neurol* (2002) 17(2):97-105.

Pinto-Martin, J., Whitaker, A., Feldman, J., et al. Special education services and school performance in a regional cohort of low-birthweight infants at age nine. *Paediatr Perinat Epidemiol* (2004) 18(2):120-9.

Plessen, K. J., Bansal, R., Zhu, H., et al. Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* (2006) 63(7):795-807.

Pliszka, S. R. The neuropsychopharmacology of attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2005) 57(11):1385-90.

Pliszka, S. R., Glahn, D. C., Semrud-Clikeman, M., et al. Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. *Am J Psychiatry* (2006) 163(6):1052-60.

Pliszka, S. R., Liotti, M., and Woldorff, M. G. Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biol Psychiatry* (2000) 48(3):238-46.

Pliszka, S. R., McCracken, J. T., and Maas, J. W. Catecholamines in attention-deficit hyperactivity disorder: current perspectives. *J Am Acad Child Adolesc Psychiatry* (1996) 35(3):264-72.

Posner, M. I., and Petersen, S. E. The attention system of the human brain. *Annu Rev Neurosci* (1990) 13:25-42.

Pueyo, R., Maneru, C., Vendrell, P., et al. [Attention deficit hyperactivity disorder. Cerebral asymmetry observed on magnetic resonance]. *Rev Neurol* (2000) 30(10):920-5.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., et al. A default mode of brain function. *Proc Natl Acad Sci U S A* (2001) 98(2):676-82.

Raichle, M. E., and Snyder, A. Z. A default mode of brain function: a brief history of an evolving idea. *Neuroimage* (2007) 37(4):1083-90; discussion 1097-9.

Rauch, S. L., Kim, H., Makris, N., et al. Volume reduction in the caudate nucleus following stereotactic placement of lesions in the anterior cingulate cortex in humans: a morphometric magnetic resonance imaging study. *J Neurosurg* (2000) 93(6):1019-25.

Retz, W., Rosler, M., Supprian, T., et al. Dopamine D3 receptor gene polymorphism and violent behavior: relation to impulsiveness and ADHD-related psychopathology. *J Neural Transm* (2003) 110(5):561-72.

Rhodes, S. M., Coghill, D. R., and Matthews, K. Neuropsychological functioning in stimulant-naive boys with hyperkinetic disorder. *Psychol Med* (2005) 35(8):1109-20.

Rosa-Neto, P., Lou, H. C., Cumming, P., et al. Methylphenidate-evoked changes in striatal dopamine correlate with inattention and impulsivity in adolescents with attention deficit hyperactivity disorder. *Neuroimage* (2005) 25(3):868-76.

Rowe, J. B., Owen, A. M., Johnsrude, I. S., et al. Imaging the mental components of a planning task. *Neuropsychologia* (2001) 39(3):315-27.

Rubia, K., Noorloos, J., Smith, A., et al. Motor timing deficits in community and clinical boys with hyperactive behavior: the effect of methylphenidate on motor timing. *J Abnorm Child Psychol* (2003a) 31(3):301-13.

Rubia, K., Overmeyer, S., Taylor, E., et al. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am J Psychiatry* (1999) 156(6):891-6.

Rubia, K., Smith, A., and Taylor, E. Performance of children with attention deficit hyperactivity disorder (ADHD) on a test battery of impulsiveness. *Child Neuropsychol* (2007a) 13(3):276-304.

Rubia, K., Smith, A. B., Brammer, M. J., et al. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage* (2003b) 20(1):351-8.

Rubia, K., Smith, A. B., Brammer, M. J., et al. Temporal lobe dysfunction in medication-naive boys with attention-deficit/hyperactivity disorder during attention allocation and its relation to response variability. *Biol Psychiatry* (2007b) 62(9):999-1006.

Rubia, K., Taylor, E., Smith, A. B., et al. Neuropsychological analyses of impulsiveness in childhood hyperactivity. *Br J Psychiatry* (2001) 179:138-43.

Russell, V. A. Dopamine hypofunction possibly results from a defect in glutamate-stimulated release of dopamine in the nucleus accumbens shell of a rat model for attention deficit hyperactivity disorder--the spontaneously hypertensive rat. *Neurosci Biobehav Rev* (2003) 27(7):671-82.

Sagvolden, T., Johansen, E. B., Aase, H., et al. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behav Brain Sci* (2005) 28(3):397-419; discussion 419-68.

Sagvolden, T., and Sergeant, J. A. Attention deficit/hyperactivity disorder--from brain dysfunctions to behaviour. *Behav Brain Res* (1998) 94(1):1-10.

Sato, F., Parent, M., Levesque, M., et al. Axonal branching pattern of neurons of the subthalamic nucleus in primates. *J Comp Neurol* (2000) 424(1):142-52.

Scheres, A., Milham, M. P., Knutson, B., et al. Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2007) 61(5):720-4.

Schmahmann, J. D. The cerebrocerebellar system. Anatomic substrates of the cerebellar contribution to cognition and emotion. *Int Rev NPsychiatry* (2001) 13:247-260.

Schmahmann, J. D. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci* (2004) 16(3):367-78.

Schmahmann, J. D., and Caplan, D. Cognition, emotion and the cerebellum. *Brain* (2006) 129(Pt 2):290-2.

Schmahmann, J. D., and Sherman, J. C. The cerebellar cognitive affective syndrome. *Brain* (1998) 121 (Pt 4):561-79.

Schmitz, M., Denardin, D., Silva, T. L., et al. Association between alpha-2a-adrenergic receptor gene and ADHD inattentive type. *Biol Psychiatry* (2006) 60(10):1028-33.

Schultz, W. Reward signaling by dopamine neurons. *Neuroscientist* (2001) 7(4):293-302.

Schultz, W., Dayan, P., and Montague, P. R. A neural substrate of prediction and reward. *Science* (1997) 275(5306):1593-9.

Schulz, K. P., Fan, J., Tang, C. Y., et al. Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event-related FMRI study. *Am J Psychiatry* (2004) 161(9):1650-7.

Schweitzer, J. B., Lee, D. O., Hanford, R. B., et al. A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response. *Neuropsychopharmacology* (2003) 28(5):967-73.

Seger, C. A., and Cincotta, C. M. The roles of the caudate nucleus in human classification learning. *J Neurosci* (2005) 25(11):2941-51.

Seger, C. A., and Cincotta, C. M. Dynamics of frontal, striatal, and hippocampal systems during rule learning. *Cereb Cortex* (2006) 16(11):1546-55.

Seidman, L. J., Valera, E. M., Makris, N., et al. Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. *Biol Psychiatry* (2006) 60(10):1071-80.

Selemon, L. D., and Goldman-Rakic, P. S. Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J Neurosci* (1985) 5(3):776-94.

Semrud-Clikeman, M., Filipek, P. A., Biederman, J., et al. Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum. *J Am Acad Child Adolesc Psychiatry* (1994) 33(6):875-81.

Semrud-Clikeman, M., Steingard, R. J., Filipek, P., et al. Using MRI to examine brain-behavior relationships in males with attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry* (2000) 39(4):477-84.

Shafritz, K. M., Marchione, K. E., Gore, J. C., et al. The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. *Am J Psychiatry* (2004) 161(11):1990-7.

Shaw, P., Lerch, J., Greenstein, D., et al. Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* (2006) 63(5):540-9.

Sieg, K. G., Gaffney, G. R., Preston, D. F., et al. SPECT brain imaging abnormalities in attention deficit hyperactivity disorder. *Clin Nucl Med* (1995) 20(1):55-60.

Silk, T., Vance, A., Rinehart, N., et al. Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: functional magnetic resonance imaging study. *Br J Psychiatry* (2005) 187:282-3.

Simmonds, D. J., Fotedar, S. G., Suskauer, S. J., et al. Functional brain correlates of response time variability in children. *Neuropsychologia* (2007a) 45(9):2147-57.

Simmonds, D. J., Pekar, J. J., and Mostofsky, S. H. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia* (2007b).

Small, D. M., Gitelman, D. R., Gregory, M. D., et al. The posterior cingulate and medial prefrontal cortex mediate the anticipatory allocation of spatial attention. *Neuroimage* (2003) 18(3):633-41.

Smith, J. L., Johnstone, S. J., and Barry, R. J. Inhibitory processing during the Go/NoGo task: an ERP analysis of children with attention-deficit/hyperactivity disorder. *Clin Neurophysiol* (2004) 115(6):1320-31.

Solanto, M. V. Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. *Behav Brain Res* (2002) 130(1-2):65-71.

Solanto, M. V., Abikoff, H., Sonuga-Barke, E., et al. The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. *J Abnorm Child Psychol* (2001) 29(3):215-28.

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

Sonuga-Barke, E. J. The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. *Neurosci Biobehav Rev* (2003) 27(7):593-604.

Sonuga-Barke, E. J. Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biol Psychiatry* (2005) 57(11):1231-8.

Sonuga-Barke, E. J., and Sergeant, J. The neuroscience of ADHD: multidisciplinary perspectives on a complex developmental disorder. *Dev Sci* (2005) 8(2):103-4.

Sonuga-Barke, E. J., and Taylor, E. The effect of delay on hyperactive and non-hyperactive children's response times: a research note. *J Child Psychol Psychiatry* (1992) 33(6):1091-6.

Sowell, E. R., Thompson, P. M., Welcome, S. E., et al. Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet* (2003) 362(9397):1699-707.

Stefanatos, G. A., and Baron, I. S. Attention-deficit/hyperactivity disorder: a neuropsychological perspective towards DSM-V. *Neuropsychol Rev* (2007) 17(1):5-38.

Stein, A., Campbell, E. A., Day, A., et al. Social adversity, low birth weight, and preterm delivery. *Br Med J (Clin Res Ed)* (1987) 295(6593):291-3.

Stevens, A. A., Skudlarski, P., Gatenby, J. C., et al. Event-related fMRI of auditory and visual oddball tasks. *Magn Reson Imaging* (2000) 18(5):495-502.

Sun, L., Jin, Z., Zang, Y. F., et al. Differences between attention-deficit disorder with and without hyperactivity: a 1H-magnetic resonance spectroscopy study. *Brain Dev* (2005) 27(5):340-4.

Sunshine, J. L., Lewin, J. S., Wu, D. H., et al. Functional MR to localize sustained visual attention activation in patients with attention deficit hyperactivity disorder: a pilot study. *AJNR Am J Neuroradiol* (1997) 18(4):633-7.

Swanson, J. M., Kinsbourne, M., Nigg, J., et al. Etiologic subtypes of attention-deficit/hyperactivity disorder: brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. *Neuropsychol Rev* (2007) 17(1):39-59.

Swanson, J. M., Sergeant, J. A., Taylor, E., et al. Attention-deficit hyperactivity disorder and hyperkinetic disorder. *Lancet* (1998) 351(9100):429-33.

Szeszko, P. R., Ardekani, B. A., Ashtari, M., et al. White matter abnormalities in obsessive-compulsive disorder: a diffusion tensor imaging study. *Arch Gen Psychiatry* (2005) 62(7):782-90.

Tamm, L., Menon, V., and Reiss, A. L. Parietal attentional system aberrations during target detection in adolescents with attention deficit hyperactivity disorder: event-related fMRI evidence. *Am J Psychiatry* (2006) 163(6):1033-43.

Tamm, L., Menon, V., Ringel, J., et al. Event-related FMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* (2004) 43(11):1430-40.

Teicher, M. H., Anderson, C. M., Polcari, A., et al. Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. *Nat Med* (2000) 6(4):470-3.

Tian, L., Jiang, T., Wang, Y., et al. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. *Neurosci Lett* (2006) 400(1-2):39-43.

Toft, P. B. Prenatal and perinatal striatal injury: a hypothetical cause of attention-deficit-hyperactivity disorder? *Pediatr Neurol* (1999) 21(3):602-10.

Toplak, M. E., Jain, U., and Tannock, R. Executive and motivational processes in adolescents with Attention-Deficit-Hyperactivity Disorder (ADHD). *Behav Brain Funct* (2005) 1(1):8.

Tremols, V., Bielsa, A., Soliva, J. C., et al. Differential abnormalities of the head and body of the caudate nucleus in attention deficit-hyperactivity disorder. *Psychiatry Res* (2008) 163(3):270-8.

Tripp, G., and Alsop, B. Sensitivity to reward frequency in boys with attention deficit hyperactivity disorder. *J Clin Child Psychol* (1999) 28(3):366-75.

Vaidya, C. J., Austin, G., Kirkorian, G., et al. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proc Natl Acad Sci U S A* (1998) 95(24):14494-9.

Valera, E. M., Faraone, S. V., Biederman, J., et al. Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2005) 57(5):439-47.

Valera, E. M., Faraone, S. V., Murray, K. E., et al. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biol Psychiatry* (2007) 61(12):1361-9.

van 't Ent, D., Lehn, H., Derks, E. M., et al. A structural MRI study in monozygotic twins concordant or discordant for attention/hyperactivity problems: evidence for genetic and environmental heterogeneity in the developing brain. *Neuroimage* (2007) 35(3):1004-20.

van den Heuvel, O. A., Groenewegen, H. J., Barkhof, F., et al. Frontostriatal system in planning complexity: a parametric functional magnetic resonance version of Tower of London task. *Neuroimage* (2003) 18(2):367-74.

van Leeuwen, T. H., Steinhausen, H. C., Overtoom, C. C., et al. The continuous performance test revisited with neuroelectric mapping: impaired orienting in children with attention deficits. *Behav Brain Res* (1998) 94(1):97-110.

Vance, A., Silk, T. J., Casey, M., et al. Right parietal dysfunction in children with attention deficit hyperactivity disorder, combined type: a functional MRI study. *Mol Psychiatry* (2007a) 12(9):826-32, 793.

Vance, A., Silk, T. J., and Cunnington, R. An fMRI investigation of right parietal function using a mental rotation task in pre-pubertal boys with ADHD, combined type. *Mol Psychiatry* (2007b) 12(9):793.

Volkow, N. D., Wang, G. J., Fowler, J. S., et al. Effects of methylphenidate on regional brain glucose metabolism in humans: relationship to dopamine D2 receptors. *Am J Psychiatry* (1997) 154(1):50-5.

Volkow, N. D., Wang, G. J., Newcorn, J., et al. Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* (2007) 64(8):932-40.

Vollm, B., Richardson, P., Stirling, J., et al. Neurobiological substrates of antisocial and borderline personality disorder: preliminary results of a functional fMRI study. *Crim Behav Ment Health* (2004) 14(1):39-54.

Walhovd, K. B., Moe, V., Slinning, K., et al. Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. *Neuroimage* (2007) 36(4):1331-44.

Weissman, D. H., Roberts, K. C., Visscher, K. M., et al. The neural bases of momentary lapses in attention. *Nat Neurosci* (2006) 9(7):971-8.

Williams, J. H., and Ross, L. Consequences of prenatal toxin exposure for mental health in children and adolescents: a systematic review. *Eur Child Adolesc Psychiatry* (2007) 16(4):243-53.

Wilson, C. J. *The Synaptic Organization of the Brain*. Oxford Univ. Press. , 2004.

Yin, H. H., and Knowlton, B. J. The role of the basal ganglia in habit formation. *Nat Rev Neurosci* (2006) 7(6):464-76.

Yochman, A., Ornoy, A., and Parush, S. Co-occurrence of developmental delays among preschool children with attention-deficit-hyperactivity disorder. *Dev Med Child Neurol* (2006) 48(6):483-8.

Zahm, D. S. Functional-anatomical implications of the nucleus accumbens core and shell subterritories. *Ann N Y Acad Sci* (1999) 877:113-28.

Zametkin, A. J., Liebenauer, L. L., Fitzgerald, G. A., et al. Brain metabolism in teenagers with attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* (1993) 50(5):333-40.

Zametkin, A. J., Nordahl, T. E., Gross, M., et al. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *N Engl J Med* (1990) 323(20):1361-6.

Zang, Y. F., He, Y., Zhu, C. Z., et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev* (2007) 29(2):83-91.

Zappitelli, M., Pinto, T., and Grizenko, N. Pre-, peri-, and postnatal trauma in subjects with attention-deficit hyperactivity disorder. *Can J Psychiatry* (2001) 46(6):542-8.